Desmond User's Guide
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D. E. Shaw Research

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Preface

Intended audience

This guide is intended for computational scientists using Desmond to prepare configuration and structure files for molecular dynamics simulations. It assumes a broad familiarity with the concepts and techniques of molecular dynamics simulation.

Prerequisites

Desmond runs on Intel based Linux systems with Pentium 4 or more recent processors; running CentOS 5.4 (RHEL5) or later. Linux clusters can be networked with either Ethernet or InfiniBand. To build the source code, Desmond is known to work with gcc Version 4.5.1 and glibc Version 2.5. Certain python scripts require a recent version of Python; we recommend Version 2.7.1 or greater. This guide assumes that someone has prepared the Desmond executable for you, either by installing a binary release or by building the executable.

Preliminary support is provided for Windows 7, 64 bit, using the Microsoft Visual Studio 2010 compiler. Desmond using MPI is not supported under Windows.

Format conventions

Command lines appear in a `typewriter` font; in some cases, **bolding** draws your attention to a particular part of the command:

```
desmond --include equil.cfg
```

Placeholders intended to be replaced by actual values are obliqued:

```
desmond --tpp 4 --restore checkpoint_file
```

Configuration file examples also appear in a typewriter font:

```
mdsim = {
  title = w
  last_time = t1
  checkpt = { ... }
  plugin = { ... }
}
```

Configuration files are divided into sections, which can in turn contain other sections; parameters occur at all levels. When discussed in the context of their particular section, configuration parameters appear by name in a typewriter font, thus: plugin. When discussed outside of the context of their sections, however, configuration parameters appear as a keypath, in which the name of each enclosing section appears in order from outermost to innermost, separated by periods. For example, `force.nonbonded.far.sigma` refers to the `sigma` configuration parameter in the `far` subsection of the `nonbonded` subsection of the `force` section of the configuration file.

About the equations

The equations in this document are concerned with scalars, vectors, and matrices of various sorts. To help clarify the type of a quantity, equations in this manual use the following conventions:

- An upper or lowercase letter without bolding or arrows, such as A or a, is a scalar.
- An arrow over a variable, such as $\vec{A}$ or $\vec{a}$, indicates three variables as a three-dimensional vector.
- A boldfaced lowercase letter, such as $\mathbf{a}$, is a vector of unspecified dimension, with a_i indicating the i^{th} element of the vector.
- A boldfaced uppercase letter is a matrix of unspecified dimensions, though usually 3×3, with A_{ij} being the element of row i and column j in matrix $\mathbf{A}$.

Certain quantities that are $3n$ dimensional vectors, such as $\mathbf{r}$, the positions of n particles, are indexed differently. The manual does not use r_i to refer to one of its $3n$ components, but instead $\vec{r}_i$ denotes the i^{th} three-dimensional vector in r, which is the position of the i^{th} particle in this case.

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Chapter 1

Key Concepts

This chapter explains the basic ideas underlying Desmond and describes how Desmond fits into a workflow.

1.1 What is Desmond?

Desmond is a suite of computer programs for carrying out molecular dynamics simulations. Such simulations model the motion of a collection of atoms—a chemical system—over time, according to the laws of classical physics.

A collection of atoms representing such real-world components as a protein molecule in water undergoing a structural change, or a drug molecule interacting with a protein. Desmond models solvents such as water explicitly, as individual water molecules.

The chemical system exists in a thermodynamic environment, which represents the conditions under which the simulation is carried out. This environment mimics the experimental conditions: whether the temperature or pressure is regulated, for example, or whether the system is isolated so that it cannot exchange energy with its environment. The chemical system occupies a three-dimensional volume of space of a specified size, and each atom is generally represented by a particle at a specific position in that space. Motion is simulated in discrete *timesteps* like the frames of a film. From one step to the next, a tiny slice of time goes by, and atom positions update accordingly. Atoms move; time advances; atoms move again. Frame by frame, the simulation builds a movie: for example, a microsecond in the life of a protein.

How the atoms move—in which direction? by how much?—is determined by:

- the initial atom positions and velocities,
- the thermodynamic environment, and
- a molecular mechanics force field.

The molecular mechanics force field is a set of functions and parameters that describe the potential energy of the interactions between the particles in a chemical system.

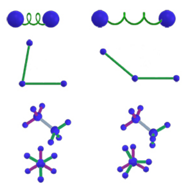


Figure 1.1: The various kinds of bonded forces.

In addition to its position, each particle has an associated charge and atomic number, as well as a list of the bonds that it participates in. Using this information, the force field models the forces exerted on each particle by every other particle, thus determining each particle's acceleration.

Simulations such as Desmond's that use the laws of classical physics can only approximate full quantum mechanical reality. They bow to the limits of computer performance: solving the full set of quantum mechanical equations would take far too long. Though merely an approximation, integrating Newton's laws of motion for so many particles still means a great many computations for each step forward. Molecular dynamics simulations therefore face a dilemma:

For accurate results, the simulation timestep must be short enough to capture the vibrational frequency of the atoms you're modeling. Yet the shorter the timestep, the less simulated time you can compute in a practical period of clock time.

To enhance performance as much as possible, Desmond implements a variety of features. Some, such as an algorithm used to minimize interprocessor communication, are built into Desmond and require no action on your part. Others require you to specify their use; for example, you can run Desmond in parallel, using as many processes as your parallel environment can support. Spreading the many computations among many processes can yield a significant increase in speed.

Still other performance features, however, don't make sense for every simulation; therefore, part of configuring a simulation is to set them as you require. In order to make most effective use of Desmond, then, you'll need to learn certain details about the way it works. Where relevant, such performance issues are noted below and throughout the manual.

In addition to the simulations described above, Desmond has the ability to perform Gibbs free energy simulations, which compute the change in free energy of a chemical system as it evolves from one state to another. These are described in detail in Chapter 8.

1.1.1 Forces

The total force on a particle is the sum of bonded and nonbonded forces. A bonded force is a force due to two or more atoms that are chemically bound. Bonded forces are of at least three kinds:

stretch Depends on the distance between the centers of two atoms sharing a bond.

bend Depends on the angle between two bonds shared by one atom with two other atoms.

torsion Depends on the torsion angle between two planes each defined by a group of three atoms where two of the atoms are shared between the groups. A normal torsion is defined by a sequentially connected set of four atoms, and an improper torsion has a more general relationship among its atoms.

In addition, some force fields define other bonded terms.

Nonbonded force is the sum of two forces: electrostatic and van der Waals. Both kinds of nonbonded forces are a function of the distance between the two atoms.

In principle, electrostatic and van der Waals forces must be computed between every pair of atoms in the system. In practice, however, the magnitude of van der Waals forces falls off rapidly with distance, becoming negligible between pairs of atoms separated by more than a certain distance, referred to as the *cutoff radius*. Therefore, the simulation can restrict van der Waals calculations to only nearby atoms, thus improving performance by reducing the number of computations Desmond must perform.

The cutoff radius cannot be used to limit electrostatic interactions, however, without seriously compromising accuracy. Instead, the electrostatic interactions are split into those between particles within the cutoff radius, and those between more distant particles. Modified electrostatic interactions are computed explicitly for the closer particle pairs, while the distant particle pairs are computed according to a more efficient method, thus further improving performance.

Interactions between pairs of particles separated by less than the cutoff radius are called *nonbonded near interactions* or more briefly the near interactions. They comprise both van der Waals forces and the short-range electrostatic forces.

Electrostatic forces between pairs of particles separated by more than the cutoff radius are referred to as nonbonded far interactions or far interactions. Instead of computing each pair wise interaction explicitly, Desmond computes far interactions more efficiently in Fourier space, thus:

1. The application maps charges from particles to nearby grid points needed for the Fourier transform: charge-spreading.

2. Using this charge density, it determines the nonbonded far potential at each mesh point via Fourier space techniques.

3. It calculates the resulting forces on the particles from the results at the nearby grid points: force interpolation.

Even with optimizations such as the Fourier space computation, far interactions are expensive to compute. Because the overall force these interactions exert on a particle varies more slowly in time than other interactions, you can configure Desmond to compute them less often to further accelerate the computation; this is discussed below in Section 1.1.6.

1.1.2 Particles

Desmond represents each atom in the chemical system as a particle. (Special cases for molecules such as water are discussed below; see the discussion of “pseudoparticle” on page 4.)

The particle:

- models key real-world aspects of an atom: its mass, charge, position, and velocity;
- participates in bonds of specified types; and
- can be a member of one or more groups.

You can assign particles to groups for various purposes:

- To understand how energy is distributed throughout the system, particles can belong to different energy groups.
- To control the temperature of subsets of particles independently, particles can belong to different temperature groups.
- To restrain them to a predetermined position relative to another particle group or to the simulation coordinate system, particles can belong to a center-of-mass group.
- To hold them motionless in the simulation, particles can belong to the frozen group.
- To define a ligand, used in free energy simulations, particles can belong to the ligand group.

1.1.3 Force fields

A force field is a model of the potential energy of a chemical system. It’s a set of functions and parameters used to model the potential energy of the system, and thereby to calculate the forces on each particle.

To accurately simulate different kinds of systems, Desmond supports several variants of the Amber, CHARMM, and OPLS-AA force field models; see Table 4.1.

To more accurately simulate the behavior of water or other molecules, certain force fields add electrostatic or van der Waals interaction sites located where no atom is. Desmond implements these as *pseudoparticles*. Desmond supports the most common kinds of pseudoparticles, including those needed for common water models such as SPC, TIP3P, TIP4P, and TIP5P. See details in Section 5.4.2. Like particles, pseudoparticles have a mass, charge, position, and velocity; however, their mass is often zero.

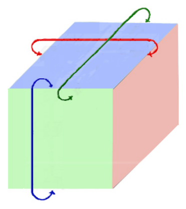


Figure 1.2: The global cell is a three dimensional parallelpiped with periodic boundary conditions.

1.1.4 Space

The volume of space in which the simulation takes place is called the *global cell*. A three-dimensional volume of space containing the chemical system. This volume is ordinarily visualized as a three-dimensional rectangular box, though Desmond can simulate other shapes.

The simulation can change dimensions in the course of running—for example, to satisfy a requirement for a constant pressure.

Positions within the global cell are specified in x, y, z coordinates.

Desmond employs a technique known as periodic boundary conditions to wrap each face of the global cell to its opposite face. That is, particles that move leftwards out of the global conditions cell appear to be moving in at a corresponding spot on the right-hand face, and vice versa; particles that move out the top appear to enter at the bottom, and vice-versa; and finally, particles that move out the front appear at the back, and vice-versa. Thus, you can picture your simulation as an arbitrarily large space tiled by the global cell repeating periodically.

Because the global cell tiles the simulation volume, it must be a shape that can tile a three-dimensional space without gaps, such as a parallelepiped, a hexagonal prism, or a truncated octahedron.

The global cell also has specified dimensions. It must be large enough that the molecule of interest doesn't interact with its counterparts—its periodic images—in other repetitions of the global cell.

When you run a simulation in parallel, Desmond apportions the work among processes by breaking the global cell into smaller boxes. Therefore, how you configure the global cell can have a significant effect on how efficiently your simulation runs in parallel. Details of these parallelization parameters, and related ones, are discussed in Section 3.2.

1.1.5 Time

The simulation begins at a specified reference time and advances by timesteps. The time at which the simulation begins.

Ordinarily, a simulation begins at time 0.0, but it need not. For example, if you wish to use the output of one simulation as the input for the next, thus effectively continuing a simulation, you can specify a reference time equal to the time at which the previous simulation finished.

Starting with the initial chemical system, Desmond:

1. computes forces on each particle based on all the other particles in the system, and
2. moves the particles according to the results of these computations.

This sequence, forming the basis of the timestep, is repeated again and again. The period of simulated time computed between each update of the particle positions. The action of the force field on the atoms is a continuous function of position and time which the simulation samples at regular intervals. Thus, the timestep is analogous to the resolution of an image in pixels, or the sampling rate of an analog to digital converter. And like those, it presents trade-offs—too long a timestep sacrifices accuracy; too short, performance.

For accurate results, the timestep must be short enough to resolve the highest frequency vibrations present in your system sufficiently for the timestepping scheme you are using. For typical Desmond simulations, timesteps around 1 to 2 femtoseconds (fs) are sufficient. To allow larger timesteps in common situations, Desmond also provides constraints, discussed in Section 1.1.6.

1.1.6 Dynamics

The action of the force field on the particles is described by a differential equation that Desmond integrates—numerically solves—at every timestep, thus computing a new position and velocity for every particle in the system. The differential equation is based on the laws of Newtonian mechanics applied to particles in the system, but modeling some physical systems requires augmenting the differential equations. Desmond implements three broad categories:

- Ordinary differential equations that hold certain measures constant—Verlet constant volume and energy, Nosé-Hoover constant volume and temperature, MTK constant pressure and temperature, and Piston constant enthalpy.
- Stochastic differential equations that hold certain measures constant and in which one or more of the terms is a stochastic process—Langevin constant volume and temperature, and Langevin constant pressure and temperature.
- Ordinary differential equations coupled to feedback control systems that keep a certain measure within a certain range—Berendsen constant temperature, and Berendsen constant temperature and pressure.

The particular algorithm that Desmond uses to solves the differential equation is called the *integrator*. Integrators are described in detail in Section 7.2. Desmond allows you to specify other aspects of the motion in your simulation, as well. For example, if you're using certain integrators, you may wish to remove the center-of-mass motion of the chemical system.

Even with optimizations such as the Fourier space computation, far interactions are expensive to compute. They also change more slowly in time than the other forces. For many simulations, then, you can improve performance by configuring Desmond to compute the far interactions less often—for example, on alternating timesteps. The integrator still computes the near interactions every timestep, but it skips the far-range computations half the time, weighting the results accordingly to compensate for not including them at every timestep.

Typically, near interactions vary at a rate intermediate between bonded forces and far interactions. Given their often dominant computational expense, Desmond also allows these to be scheduled less often. Desmond allows timestep scheduling as follows:

- Bonded forces are computed at every timestep. This is then called the *inner timestep*.
- Nonbonded near forces can be computed at every nth timestep, as configured.
- Nonbonded far forces can be computed at the same interval as nonbonded near forces, or a multiple of it. This is then called the *outer timestep*.

Timestep scheduling appears as a configuration parameter called *RESPA*, an acronym that stands for reference system propagator algorithm.

Constraints among particles let you lengthen the timestep by not modeling the very fastest vibrations; the integrator moves these constrained particles in unison. A variety of geometries can be constrained this way:

- a fan of 1–8 particles, each bonded to a central particle, such as the three hydrogen atoms connected to a carbon atom in a methyl group; and,
- three particles arranged in a rigid triangle, such as a water molecule.

These constraints are described in detail in Chapter 6.

When you prepare your structure file, you specify the types of constraints, if any, and the atoms involved in them. When you configure your simulation, you can specify how precisely to compute the constraints. Whether and how to use constraints depends on simulation specific factors or the force field you're using.

1.2 Using Desmond

Desmond is a suite of computer programs. It uses a standard format for input—structure (DMS) files—-and an open format for output—trajectory files, or frame files. So you can also use other applications with Desmond, both public domain and commercial.

1.2.1 Input

Desmond requires two files for input: a structure file that defines the chemical system, and a configuration file that sets simulation parameters.

The structure file specifies what to simulate, the initial state of the system: the size of the global cell; the particles it contains, their positions and other properties; the force fields to employ; and possibly other details.

Structure files are also called *DMS* files (file name suffix `.dms` for DESRES Molecular System).

The configuration file specifies how you want to simulate the chemical system: the reference temperature and pressure, if any; the integrator to use; the length of the timestep; the fineness of the grid to use for charge-spreading; how many processes to assign to a given dimension of the global cell; and possibly many other such parameters. By using different configuration files with the same structure file, you can run different simulations.

1.2.2 Applications and scripts

Desmond consists of three main applications and several companion Python scripts:

mdsim The application that performs the molecular dynamics simulation.

minimize The application that prepares the molecular dynamics simulation, if necessary, by minimizing energetic strains in the system so that they don't destabilize the simulation at the first few steps.

vrun The application used to analyze framesets output by `mdsim`.

Viparr The Python script that adds force field information to the structure file.

build_constraints The Python script that adds constraint information to the structure file.

1.2.3 Output

Timestep by timestep, an atom traces a path through the global cell as the simulation advances.

The path that molecules take through the global cell is the trajectory. Trajectories are writ ten out in a set of files representing a time series, like the frames of a movie.

Each frame is a file containing the positions and velocities of all the particles and pseudoparticles in the chemical system at that particular timestep. In addition to particle positions and velocities, frames can include system characteristics such as its total energy, temperature, volume, pressure, and dimensions of the global cell.

You can configure Desmond to output frames—typically at an interval corresponding to a multiple of the outer timestep, when nonbonded far interactions are computed.

A time-ordered series of frame files representing the dynamics of the chemical system for the specified time period. Framesets are ordinarily the meaningful unit of analysis for `vrun` or other analysis applications such as VMD.

1.2.4 Workflow

The following typical workflow illustrates the roles of Desmond's three main applications, as well as those of other cooperating applications:

1. Prepare the structure file. Typically, start with a Protein Data Base (`.pdb`) file and produce a DMS file.

   (a) Depending on its contents, and the manner in which it was created, it may need some repair of artifacts (e.g. due to x-ray crystallography). Maestro is one tool that can do this; others also exist. Maestro or a comparable application outputs a structure file typically containing:

   the solute proteins, ligands, or other molecules of interest; and

   the solvent water; and often ions such as sodium, potassium, or chloride to ensure that the overall chemical system is neutral with respect to charge. (A charge-neutral system is desirable for computing long-range electrostatic interactions.)

   The structure file contains all particle and bond information, but has as yet no information about the force field describing the interactions between particles.

   (b) To add the force field information, the structure file is input to Viparr.

   You specify the force field you wish to use, and Viparr outputs a structure file with the force field information added. It can access a set of databases specifying the required force terms for the various molecules in the chemical system. Viparr reads the structure file and appends the necessary force terms in a separate section of the file.

   You now have a structure file that defines the particles and forces in your simulation.

   (c) If you wish to use constraints in your simulation, you now run `build_constraints`. By default, the script constrains the bond length of all bonds involving hydrogen atoms, as well as the angle in all water molecules. The out put is a new structure file with the constraint terms added. You now have a structure file that describes the particles and forces in your simulation, as well as any constraints you wish to apply.

2. The simulation still needs to be configured, which involves specifying the values of parameters in a configuration file. The simplest way is to start with an existing con figuration file and edit it.

   Chapter 2 provides an overview of configuring the simulation. For details about specific configuration file parameters, see the chapters that discuss the applicable configuration file sections.

3. Most simulations now require that the energy of the system be equilibrated so that initial forces between atoms are small. One way to do this is to `minimize` the potential energy of the system. Desmond provides two means of doing this. The

first is by Brownian motion, through the use of the `brownie_NVT` or `brownie_NPT` integrators, or by gradient minimization, through the `minimize` application. You may not need to use equilibrated if your system was prepared with care to avoid energetic strains, or if it has already been equilibrated with another tool.

On the other hand, depending on how the structure file was obtained, you may wish to use `minimize` even if you don't intend to run `mdsim`, in order to rectify strange conformations resulting from the homology model, or undesired artifacts resulting from x-ray crystallography.

To minimize the energy of the system, the structure file and associated configuration file are input to `minimize`, which changes the atom positions slightly as needed. It then outputs another structure file but does not change the configuration file.

4. The new structure and the configuration file are now input to `mdsim`, which executes the simulation (possibly for days or weeks), writing the results as frame files at the configured intervals of simulated time.

   Analyze the results

5. The frameset and configuration file can now be input to `vrun`, which analyzes the results according to the manner specified in the configuration. For example, you can specify that `vrun` print the energy of the system for each frame, or the forces on each particle at each frame.

Other tools such as VMD, a freely available visualization application, can be used to analyze results in addition to, or instead of, `vrun`.

1.2.5 Customizing Desmond

Desmond modularizes its functionality in the form of extensions.

An *extension* is a software module that implements a discrete set of capabilities, compiled separately so that it can be added to, or removed from, an existing application. The capabilities are further divided logically into units of functionality called *plugins*. As it runs, the Desmond executable calls plugins as specified in the configuration file for its application. In this way you can execute the functions that you need while skipping those that you don't. Each Desmond application has a main loop which it repeats: one step in the minimization process, one simulation timestep, or one trajectory frame loaded. Plugins can be called during this loop to perform their work repeatedly as the simulation unfolds. For example, the plugin `eneseq` computes system energy, temperatures, pressures, and other data, breaking down the energy into various categories, then writes the result to the specified output file. For example, `randomize_velocities` reinitializes the velocities of the particles in the simulation according to the Boltzmann distribution for a specified temperature, something you may wish to do once, at the start of the simulation. On the other hand, trajectory writes all particle positions to the specified output file at specified intervals, which you probably wish to do more than once, but less often than at every timestep.

The main loop plugins are configured in the section of the configuration named after the application being run (e.g. `mdsim` or `remd`). Not all plugins are active in the main loop. Some plugins provide integrators and additional force terms. They are either partly or wholly configured in these sections of the configuration.

Plugins provided with Desmond are described in Section 2.6.

Desmond already has most or all the functionality required for typical molecular dynamics simulations, but you can extend this functionality by writing your own plugins to, for example, support new force field terms, add new integrators, or apply arbitrary steering forces to the simulation, all without recompiling the Desmond executable. Implement the functionality you need as a plugin; then specify the parameters for your plugin in the configuration file. Other requirements are discussed in Chapter 10.

Chapter 2

Running Desmond

This chapter explains the basics of working with configuration files; describes how to invoke the various Desmond applications, including in parallel; and describes how to configure Desmond applications and built-in plugins, as well as the optional profiling mechanism.

2.1 About configuration

Desmond reads configuration parameters from a configuration file, specified on the command line.

The simplest way to configure a simulation is to copy one of the sample configuration files provided and edit it. See the `README.txt` file for the location of these files. For those who wish to edit extensively or create their own, configuration file syntax is described in Appendix B.

Configuration files are divided into sections, with the configuration information for a given application going into the section named for that application. In addition, other sections configure other aspects of the simulation, such as the global cell, the force field, constraints (if any), and the integrator. The same configuration file can apply to any Desmond application.

Configuration file sections are:

```
app = mdsim|remd|minimize|vrun|...
boot = { file = p } # the structure file
global_cell = { ... }
force = { ... }
migration = { ... }
integrator = { ... }
profile = { ... } # for debugging
mdsim = { ... }
vrun = { ... }
minimize = { ... }
remd = { ... }
```

Each application reads a particle system and a force field from a structure file located at the path p, the details of which can be found in Chapter 4. The structure file defines the global cell dimensions, initial particle properties, and the specific parameters of the force field.

Many Desmond objects share the following configuration idiom:

```
object = {
  first = t_f
  interval = t_i
    ...
}
```

This describes the pattern of activity of the object, acting only at specific times, the first time at t_f and thereafter periodically with period t_i. Setting $t_i = 0$ causes the object to act at every opportunity after t_f.

Note: The application might modify t_f and t_i slightly from their configuration values to make them a multiple of the current timestep.

Setting t_f to `inf` meaning infinity (see Appendix A) declares that the activity never occurs; but beware: some plugins use the Boolean parameter `write_last_step` that when set causes output to occur at the end of the simulation regardless.

2.2 Invoking Desmond

Desmond applications are invoked from the command line by the `desmond` executable. Use the `--include` to specify the configuration file. For example, to invoke `desmond` with the configuration file `equil.cfg`:

Example 2.1

```
desmond --include equil.cfg
```

As indicated above, the configuration specifies the application and the structure file, as in:

Example 2.2

```
app = mdsim
boot = {
  file = /path/to/my/input.dms
}
```

The `--cfg` option allows you to append additional configuration information to the command line. It's often used to specify the structure file. For example, to invoke `desmond` with the structure file `/path/to/my/input.dms`:

Example 2.3

```
desmond --include equil.cfg --cfg boot.file=/path/to/my/input.dms
```

This has the same effect as the line from the configuration file above.

Note: Use quotation marks around the parameter to `--cfg` if it contains any special characters (such as spaces) that are interpreted by the shell.

You can specify multiple configuration files; this can be useful for configuring a simulation in a modular way. For example, you might choose to have alternative integrator configurations in two files named `nve.cfg` and `ber_nvt.cfg`, with other configuration parameters in the base configuration file in `base.cfg`. Then, for a simulation in which you intend to use the Verlet constant volume and energy integrator, you'd invoke:

Example 2.4

```
desmond --include base.cfg --include nve.cfg --cfg boot.file=input.dms
```

Whereas, for a simulation in which you intended to use the Berendsen constant volume and temperature integrator, the command line would instead be:

Example 2.5

```
desmond --include base.cfg --include ber_nvt.cfg --cfg boot.file=input.dms
```

You cannot specify multiple structure files. The `--include` and `--cfg` arguments are evaluated in order, and the last specified name for the structure file overrides any previous ones.

The `--tpp` command line option sets the number of threads per process. If your application is to run on a processor with multiple cores, you may benefit by setting this value to other than its default of one. Otherwise, the command line can omit it. The `--cpc` command line option sets the number of cores per physical chip and as a side effect ties Desmond threads to processor cores. If `--cpc N`, where `N` ≥ 1, is used master and worker threads are bound to processor cores. If `--spin 1` or `--spin 2` is used, a faster but more processor intensive thread idle strategy using spin-locks is employed. When 1, foreground threads will spin, and background threads will sleep; when 2, all worker threads will spin.

Note: If you run more than one Desmond job on a multiprocessor node, make sure that `--cpc` is set to 0, otherwise Desmond processes in the different jobs will use the same core resulting in significant performance degradation.

Note: When running on an interactively used workstation and with more than one Desmond thread, it is better to set `--spin 0`.

For example, to start a Desmond application with four threads per process:

Example 2.6

```
desmond --tpp 4 --include example.cfg --cfg boot.file=input.dms
```

Note: Under most circumstances, it's best to run `desmond` with one thread per process and one process per processor core.

Each application logs its configuration at startup, so users can observe the net result of the configuration options. This includes displaying a list of the loaded plugins with full paths, so that you can see all the code that Desmond can access. (Plugins are described in Section 2.6.)

Table 2.1 lists the full set of supported options. All command line options have the same effect for all applications except `--restore`, which pertains to the `mdsim` and `remd` applications only, enabling them to start from a checkpoint file. It is an error to provide a command line option that is not recognized by Desmond or one of its components. Command line options can be given in any order.

argument	**description**
`--tpp` N	Sets the number of threads per process. Defaults to 1.
`--cpc` N	Gives the number of cores per physical chip. Defaults to 0.
`--spin` N	Sets the worker thread idle strategy. Defaults to 0. If 1 or 2 then use spin-lock based idle strategies. Sets the name of the communications plugin to use for parallel jobs.
`--destrier` name	Defaults to serial.
`--include` file name	Adds configuration information from the given file. Can be given any number of times.
`--cfg` string	Adds configuration information from the given string. Can be given any number of times.
`--restore` file	Restarts the `mdsim` or `remd` applications from a checkpoint. Because these applications are expected to run for long periods of time, during which hardware might fail, they can be set to produce a checkpoint file periodically, from which you can restart

Table 2.1: Desmond command line options

Restoring from a checkpoint

You can configure the `mdsim` or `remd` applications to create a checkpoint file at regular intervals as it runs. When you wish `desmond` to start from a checkpoint file created during an earlier run, use the restore flag to specify the file name.

For example, to restore from a checkpoint:

```
desmond --tpp 4 --restore checkpoint_file
```

Note: To avoid an application error, set the `--tpp` and other thread specific flags the same way it was set for the original simulation. `desmond` must initialize the parallel environment before it can read the checkpoint file.

You need not specify other configuration options; they've been saved. When restoring from a checkpoint file, only certain options can be changed from the configuration of the original simulation: `last_time` (see Section 2.4.1 and Section 2.4.2), `checkpt.interval` (see Section 2.4.1), and certain plugin options (for example, the `name` and `interval` for `eneseq` and `trajectory`).

2.2.1 Using plugins

Desmond applications use certain plugins for various diagnotics and interventions. Plugins can be implemented as part of an application (called *built-in plugins*), or in external files (called *extensions*).

Desmond locates extensions (files containing plugins) by means of either of two environment variables DESMOND_PLUGIN_PATH and DESRES_PLUGIN_PATH. You can specify more than one path to search for plugins by separating them with colons, as in:

Example 2.7

```
DESMOND_PLUGIN_PATH=/this/is/the/first/path:/this/is/the/second
```

The line above specifies two directories, which are searched for plugins in the given order. Many plugins are compiled with Desmond already and are therefore available to all its applications; these are discussed in Section 2.6. In addition, you can implement your own plugins, or use those developed by third parties. Extending Desmond's functionality in this way is discussed in Chapter 10.

Each application has a main loop, consisting of one minimization or simulation step (`mdsim`, `remd`, and `minimize`) or processing one trajectory frame (`vrun`). You can configure a plugin to run once at the beginning of a simulation, or periodically at an interval of one or more steps.

Each application's plugin section of the configuration contains a `list` under the key `plugin` that gives the names of main loop objects to create.

For example, the plugins to call when the `mdsim` application runs appear in a list like the one below:

```
mdsim = {
  plugin = {
    list = [ key1 ... keyn]
    key1 = {
      type= type1
      ...
    }
    ...
    keyn= {
      type= typen
      ...
    }
    ...
  }
}
```

The key names appearing in the plugins list are arbitrary (though, for a given section, they must be unique). For each key, key$_i$, Desmond creates a main loop object of type type$_i$. The remainder of the table under key$_i$ contains the object's configuration:

```
mdsim = {
  plugin = {
    list = [ my_status ]
    my_status = {
      type=status
      first=0
      interval=1
    }
  }
}
```

In this case, the `mdsim` application will create an object of type `status`, which is set to run every picosecond.

Note: Main loop plugin objects are evaluated in the order in which they're listed in the configuration. In certain circumstances, listing plugins in a different order can yield different results: for example, if your simulation calls both the `randomize_velocities` and `eneseq` plugins. Because `randomize_velocities` generally changes the kinetic energy of the system, different kinetic energies and temperatures are reported if the `randomize_velocities` plugin is listed before `eneseq` rather than after—the dynamics of the system will be the same, but the reported temperatures will be different. Section 2.6 describes the built-in main loop plugins.

2.3 Running Desmond in parallel

Desmond can be run either in serial or in parallel, in environments ranging from laptops to large Linux clusters. High-performance parallel systems consist of nodes connected together in a network, containing one or more processors each of which consisting of one or more processor cores or cores. In the following we will frequently refer to processor cores as processors where confusion is unlikely.

When you run Desmond in parallel, specify the number of Desmond processes you want to run according to the particulars of your parallel environment.

You can run Desmond in parallel—that is, run multiple Desmond processes—and also run each process with multiple threads (using the `--tpp` command line parameter). In order to run Desmond in multi-threaded mode efficiently, you'll need to request as many total processor cores as the total number of threads. For example, if you are running on a system with 8 processors cores per node, and specify 2 processes per node, then you should set the `--tpp` parameter no larger than 4. The details of selecting the number of nodes and processes per node are system dependent and are not discussed further. When running a simulation in parallel, Desmond processes exchange the information by means of a parallel communication interface (typically, MPI), implemented with a plugin called a *destrier*. That implementation is registered under a symbol (normally, either `mpi` or `serial`) by which it can be selected by giving an application the destrier flag:

Example 2.8

```
desmond --destrier mpi --tpp 1 --include example.cfg
```

Without the `--destrier` flag, a Desmond application defaults to serial. The details of Desmond installations and parallel environments vary, but a plugin containing a destrier implementation in a file named `destrier.so`, and registered as `mpi`, must either be built-in (that is, compiled as part of the Desmond executable), or located in an extension specified by the path given in your `DESMOND_PLUGIN_PATH` environment variable.

`--destrier serial`: runs Desmond applications with a single process. This gives you a means to check your code and find any other problems while your installation creates a usable parallel environment.

`--destrier mpi`: uses the MPI destrier variant, a common parallel programming specification, implemented as a library of C, C++, or Fortran functions.

`--destrier other`: You can create your own destrier plugin by modifying the examples provided for the serial and mpi plugins. Register the resulting plugin under the name of your choice, supplying that name as the argument to the `--destrier` parameter.

The parallel environment is initialized before checkpoint information is read. Therefore, if you're restoring from a checkpoint, the `--destrier` flag must be set in the same way it was when you started the original simulation.

Note: The `mpi` destrier plugin requires Open MPI version 1.4.3 or later. If you wish to use a different parallel communication interface, you'll need to compile your own plugin.

2.4 Configuring Desmond applications

The main Desmond applications are `mdsim`, `minimize`, `remd`, and `vrun`, as described in Section 1.2.2. Configuration parameters for each of these applications are described below.

2.4.1 mdsim

`mdsim` is Desmond's main molecular dynamics simulation code. It's configured as shown in:

```
mdsim = {
  title = w
  last_time = t1
  plugin = { ... }
  checkpt = { ... }
}
```

name	**description**
`title`	A short string to include in various output files—by default, "(no title)". [*string*]
`last_time`	Time at which to stop the simulation, in picoseconds, relative to the reference time given as part of the global cell configuration (see Section 3.2). [*time*]
`plugin`	Description of the main loop plugins to call during simulation. See Using plugins. [*configuration*]
`checkpt`	Checkpoint configuration. See Checkpointing. [*Configuration*]

Table 2.2: Parameters for mdsim

Checkpointing

Because `mdsim` can run for a long time, during which hardware can fail, checkpointing allows you to restart a simulation from a backup file called a *checkpoint*. A checkpoint file is a snapshot of the entire state of the computation and can therefore be quite a large file. However, because their purpose is to restart an interrupted simulation, checkpoint files can be discarded after the simulation completes. Desmond checkpoints are designed such that the state of a simulation restarted from checkpoint is bitwise identical to the state of simulation at the point when the checkpoint file is written.

Configuration information for checkpointing appears as shown in:

```
checkpt = {
   first = $t_f$
   interval = $t_i$
   name = $p$
   write_first_step = $b_f$
   write_last_step = $b_1$
}
```

Setting `checkpt = none` shuts off checkpointing.

A checkpoint is written at simulation time t_f and thereafter with a period t_i or at the wall clock interval t_w as measured from the start of each invocation of the simulator. The output file name convention is followed for the checkpoint files; see Section 2.5.

You can cause `mdsim` to write a checkpoint file initially and finally by setting b_i and b_f respectively to `true`.

name	**description**
`first`	First time to create a checkpoint. [*time*]
`interval`	Periodic interval at which to create checkpoints. [*time*]
`wall_interval`	Periodic interval at which to create checkpoints; wall clock time in units of seconds. [*time*]
`name`	Output `filename` to use for the checkpoint files. [*filename*]
`write_first_step`	Whether to write a checkpoint file before the first step is taken. [*Boolean*]
`write_last_step`	Whether to write a checkpoint file after the last step is taken. [*Boolean*]

Table 2.3: Parameters for checkpointing

2.4.2 remd

The `remd` application in Desmond implements the replica exchange protocol, sometimes known as parallel tempering. The number of replicas that can be simulated is limited only by the number of processors available and that an equal number of processors must be assigned to each replica. The only restriction on the replicas themselves is that they must all have the same number of particles. Thus, `remd` can be used for the usual temperature exchange method, as well as exchanges between systems with different Hamiltonian parameters.

`remd` runs as a single parallel application, just like `mdsim` and `vrun`, producing a single checkpoint file if checkpointing is enabled. Each replica runs as a normal simulation, with swaps of coordinates taking place as specified by the user through the configuration. When an exchange is attempted between two replicas, the usual Metropolis criterion is applied to determine if the exchange should be accepted or accepted, according to the fol lowing prescription: with

$$Q = (\beta_1 U_{11} + \beta_2 U_{22} - \beta_1 U_{12} - \beta_2 U_{21}) + (\beta_1 P_1 - \beta_2 P_2)(V_1 - V_2)\,, \qquad (2.1)$$

where rand_N is a random variate on $(0, 1]$, U_{ij} is the potential energy of replica i in the Hamiltonian of replica j, P_i is the instantaneous pressure of replica i, V_i is instantaneous volume of replica i, and β_i is the inverse temperature of replica i. If $Q > 0$ accept the exchange, or if $Q < -20$ reject it, otherwise accept the exchange if $\mathrm{rand}_N < \exp(Q)$.

An example `remd` configuration is shown in following Example; all parameters are required. The parameters are summarized in Table 2.4.

Example 2.9

```
remd = {
  title = w
  last_time = t1
  checkpt = { ... }
  plugin = { ... }
  first = tf
  interval = $t_i$
  seed = $s$
  exchange_type = neighbors|random
  cfg = [ $c_1$ ... $c_r$ ]
}
```

name	description
title	A short string to include in various output files. Optional—by default, "(no title)". [*string*]
last_time	Time at which to stop the simulation, in picoseconds, relative to the reference time given as part of the global cell configuration (see Section 3.2). [*time*]
checkpt	Checkpoint configuration. See Checkpointing. [*configuration*]
plugin	See Using plugins. [*configuration*]
first	Time of first exchange attempt [*Time*]
interval	Time between exchange attempts [*Time*]
type	Either exchanges only between neighboring replicas or exchanges between any pair of replicas [*neighbors /random*]
seed	random number seed for the Metropolis criterion [*Integer*]
cfg	configuration overrides for each replica [*List of configurations*]

Table 2.4: Parameters for remd

Exchanges are attempted starting at chemical time given by first, and at intervals of interval thereafter. If type is `neighbors`, then on each exchange attempt, all replicas will attempt an exchange with either of their neighbors in a linear order with 50% probability, and accept based on the Metropolis criterion above. If type is `random`, then only two out of all replicas will attempt an exchange, but those two replicas could be any of the replicas in the ensemble. Exchanges are implemented by swapping the positions of a pair of replicas. If an exchange is accepted, the velocities of the replicas are rescaled to the temperature of the host replica; otherwise, the positions are simply swapped back. Thus, in any replica, the temperature and Hamiltonian will stay the same, but the dynamics will be discontinuous as new coordinates are swapped in via exchanges.

The `cfg` configuration in `remd` serves two purposes. First, the number of entries in the list, r, serves to specify how many replicas are to be run in the simulation. Second, each entry in `remd.cfg` overrides the configuration for the corresponding replica, in the same way that the cfg command line option overrides a setting for an `mdsim` run. For example,

Example 2.10

```
cfg = [
  {integrator.temperature.T_ref=300       plugin.eneseq.name=0.ene}
  {integrator.temperature.T_ref=303.3333  plugin.eneseq.name=1.ene}
```

```
    {integrator.temperature.T_ref=306.6667  plugin.eneseq.name=2.ene}
    {integrator.temperature.T_ref=310       plugin.eneseq.name=3.ene}
  ]
```

has four replicas: replica 0 will see a configuration with the integrator temperature set to 300, replica 1 will get a temperature of 303.3333, and so forth. Also in this example, a plugin variable is overridden on a per replica basis. Overrides to the `remd` section itself should not qualified with the prefix `remd.` as one would have expected.

2.4.3 remd-graph

The `remd-graph` app driver is a generalization of the `remd` driver intended to give advanced users more control over the set of possible exchanges in the network of replicas. The configuration for `remd-graph` is identical to that of `remd`, except that the `type` and `cfg` sections are replaced by a new section called `graph`:

Example 2.11

```
remd-graph.graph = {
  edges = [
    { type=linear     nodes=[T1 T2 T3] }
    { type=all-to-all nodes=[T1 T4 T5] }
    ...
  ]
  T1 = { ... }
  T2 = { ... }
  T3 = { ... }
  T4 = { ... }
  T5 = { ... }
}
```

The `graph` section of the `remd-graph` config must contain an `edges` section, which is a list of edge declarations. Each edge declaration has two fields: `nodes`, which is a list of symbolic replica names, and `type`, which specifies how those replicas are connected. In an edge declaration of type `linear`, edges are created between the nodes that are neighbors in the corresponding `nodes` list; for type `all-to-all`, edges are created between all nodes in the declaration. The set of all edges is the union of the edges in all the declarations. In our example, we have edges `T1-T2` and `T2-T3` coming from the first declaration, and edges `T1-T4`, `T1-T5`, and `T4-T5` coming from the second declaration, for a total of five edges.

The number of replicas in the simulation is given by the number of unique node names in the edges declarations. For each name, the `graph` section may also contain config overrides, keyed to the name of the replica.

Once the set of edges is established, `remd-graph` performs replica exchange by selecting an edge at random from the full set of edges.

2.4.4 minimize

`minimize` performs steepest descent minimization followed by LBFGS minimization. Configuration parameters are shown in following example; all parameters are optional; the defaults should be adequate for most systems.

```
minimize = {
  migrate_interval = i
  m = m
  maxsteps = s_max
  tol = τ
  stepsize = l
  switch = g
  sdsteps = s_0
  debug = d
  dt =  t
  plugin = { ... }
}
```

`minimize` requires an integrator section, even though all parameters in that section are ignored during the calculation. We recommend that you use the same configuration for minimization and dynamics, appending the minimize section to the `mdsim` configuration discussed above.

`minimize` handles constraints differently from `mdsim`; for a discussion, see Section 4.2.3.

name	**description**
`plugin`	See Using plugins. [*configuration*]
`migrate_interval`	Number of minimization steps between each migration event. Optional—by default, 1. [Integer > 0]
`m`	Number of state vectors to use during L-BFGS minimization. Optional—by default, 3. [Integer > 0]
`maxsteps`	Maximum number of steps to iterate. Optional—by default, 200. [*Integer*]
`tol`	Stopping tolerance for gradient norm. Optional—by default, 1.0. [Energy/Length > 0]
`stepsize`	Norm of first step. Optional—by default, 0.005. [Length > 0]
`switch`	Minimum gradient before switching to L-BFGS. Optional—by default, 100.0. [*Energy/Length* > 0]
`sdsteps`	Minimum number of initial steepest descent steps. Optional—by default, 0. [*Integer*]
`debug`	Debug level. Optional—by default, 0. If debug=1, Desmond prints additional minimization information. [*Integer*]
`dt`	A fake time scale for the minimize step. Optional—by default, 1.0. [*time* > 0]

Table 2.5: Parameters for minimize

2.4.5 vrun

The `vrun` application is used to analyze structure files and trajectories. It loads successive trajectory frames (written by `mdsim` or per-replica frames written by `remd`) and triggers plugins to act on those frames.

Configuration information is shown in:

```
vrun = {
  title = w
  plugin = { ... }
  input = bootfile | frameset
  frameset = {
    name = p
    first = t_f
    interval = t_i
    last_time = t_1
  }
}
```

Loads a configuration, or sequence of configurations, given by the set of frames from a trajectory file. p is expected to be a path to a frameset, a trajectory output. If not given, then the initial configuration is processed as loaded.

name	**description**
`plugin`	See Using plugins. [*configuration*]
`title`	A string to be included in various output files. Optional—by default, "(no title)". [*string*]
`input`	Input mode: either 'frameset' or 'bootfile'. [*String*]
`frameset.name`	Path to the input trajectory. Optional. [*filename*]
`frameset.first`	Start processing frames after this chemical time. [*time*]
`frameset.interval`	Skip this much chemical time between frames. [*time*]
`frameset.last_time`	Stop processing after this chemical time. [*time*]

Table 2.6: Parameters for vrun

2.5 Naming output files

Output files are created according to a format string having terms that are expanded on a per-file basis. These terms are of the form `@`X, where X is a single character; they expand as listed in Table 2.7

Term	Expands to
`@B`	A boot timestamp: a date string, resolved to the second, taken from the start time of one of the parallel processes.
`@S`	A sequence number: an integer, starting at zero and incrementing each time this `filename` is expanded, producing an ordered sequence of files rather than overwriting the same file.
`@P`	The UNIX process ID of the process writing the file, as a hexadecimal integer.
`@R`	The rank—a unique identifier within a parallel run—of the process writing the file.
`@FS`	The result of passing S to strftime.
`@@`	The `@` character.

Table 2.7: Terms for naming output files

For example, if you wish to write an output file several times during a run, the `filename` `my_output-@S` creates a sequence of files named `my_output-0`, `my_output-1`, and so on. The last-used value of the sequence number is saved in the checkpoint file. To ensure that unique files are created with each Desmond run, give files names such as: `my_output-@B`, thus causing each to be named with a unique timestamp. (If the runs are expected to take less than one second to complete, unique file names would require a different strategy; perhaps: `my_output-@B-@P`.)

A `filename` can encode the current date and time in various formats. For example, you can use a file name of the form `my_output-@F{%Y-%m-%d}` to name a file according to current date: `my_output-2010-04-23`. You could name your checkpoint file in this way if you wanted to ensure that no more that one checkpoint file is written per day. Plugins that periodically update an output file—for example, `eneseq`, `compute_forces`, `energy_groups`, and `gibbs.output`—can use an empty string as a `filename`; in this case, data is written to the standard output. However, `maeff_output` and `checkpt` require real file names.

2.6 Configuring the built-in plugins

Desmond is compiled with various plugins, which are therefore available to all Desmond applications. These plugins offer a range of commonly useful functionality; configuration information for them all is discussed below.

2.6.1 anneal

The Desmond `anneal` plugin periodically updates the temperature setting of the `anneal` integrator during an `mdsim` run. The anneal integrator is actually a thin shell around any other Desmond integrator. Hence, there are two places in the configuration that need to be changed in order to use the `anneal` plugin.

Integrator setup

The integrator section of the configuration normally has the following form:

```
integrator = {
  type = name
  name = { ... }  # integrator-specific options
  # ... other non-specific integrator options
}
```

In order to enable the `anneal` plugin, the above should be changed as follows:

Example 2.12

```
integrator = {
  type = anneal
  anneal = { type = name
             name = { ... } } # integrator-specific options
  # ... other integrator options
}
```

This wraps whatever integrator *symbol* was asking for inside the anneal integrator and thereby makes it responsive to requests for temperature changes.

Plugin setup

Within the application specific `plugin` section, the following specifies the component of annealing that schedules the temperature changes:

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = anneal
    first = t0
    interval = δ
    schedule = {
      time = [ t1 t2 ... tN ]
      value = [ T1 T2 ... TN ]
    }
  }
}
```

t_0: first time to reset the thermostat temperature

δ: interval between thermostat resets. There is a small performance cost to resetting the thermostat, so its recommended that the delta be set no smaller than the natural thermalization time of the system, typically on the order of 1 ps.

`schedule`: When the plugin is invoked, as specified by `first` and `interval`, a target temperature is computed based on the current chemical time t. If $t < t_1$, no action is taken. If $t \geq t_N$, the target temperature will be T_N, the last temperature in values. Otherwise, the target temperature is computed by linearly interpolation between the time points t_i, t_{i+1} that bracket the current time:

$$T = T_i + (T_{i+1} - T_i)\frac{(t - t_i)}{(t_{i+1} - t_i)} \tag{2.2}$$

For example, the following schedule would heat a system from 0 to 500 K during the first 20 ps, then cool it to 300 K during the subsequent 80 ps, and maintain it at 300 K thereafter:

Example 2.13

```
mdsim.plugin.key.schedule = {
    time = [ 0 20 100 ]
    value = [ 0 500 300 ]
}
```

2.6.2 Biasing Force

The `BiasingForce` plugin can be used to restrain two groups of atoms within a chemical system with respect to each other, in displacement, distance, and/or orientation. It can also be used to restrain the position and orientation of a group of atoms within the molecular system with respect to the simulation box. Unlike most plugins, its configuration is given in the `force` section of the configuration (note below).

```
force.term = {
  list = [ ... key ... ]
  key = {
    type = BiasingForce
    cm_moi = [ {
      groups          = [ $A$ $B$ ]
      displace_coeff  = [  $k_x$ $k_y$ $k_z$  ]
      displacement    = [  $x_0$ $y_0$ $z_0$  ]
      distance_coeff  =  $k_d$
      distance        =  $R_0$
      orient_coeff    = [  $\omega_1$ $\omega_2$ $\omega_3$  ]
      Euler_angles    = [  $\theta_0$ $\phi_0$ $\psi_0$  ]

      use_lab_frame_for_displacement = Boolean
      pull_displacement = [  $v_x$ $v_y$ $v_z$  ]
      pull_distance     =  $v_d$
      pull_Euler        = [  $\frac{d\theta}{dt}$ $\frac{d\phi}{dt}$ $\frac{d\psi}{dt}$  ]
    } # Multiple biasing potentials, supplied as a list, can be applied.
```

quantity	unit
$t0$	picosecond
k_x, k_y, k_z	kcal·mol^{-1} · Å^{-2}
x_0, y_0, z_0	Å
k_d	kcal·mol^{-1} · Å^{-2}
R_0	Å
ω_1, ω_2, ω_3	kcal·mol^{-1}
θ_0, ϕ_0, ψ_0	degree (*not radian*)
v_x, v_y, v_z	Å·picosecond^{-1}
v_d	Å·picosecond^{-1}
$\frac{d\theta}{dt}$, $\frac{d\phi}{dt}$, $\frac{d\psi}{dt}$	degree·picosecond^{-1}

Table 2.8: Units of the parameters in biasing force.

```
      ... ]
      output = {
        first = t_f
        interval = t_i
        name = filename
      }
      t0 = t0
    }
    ... # Other force terms
  }
```

The units of the parameters in the configuration are given in Table. 2.8.

The biasing force in the above configuration will restrain particles in `cm_moi` group B with respect to particles in `cm_moi` group A. Group A consists of all atoms whose `grp_bias` property is set to the integer value A; Group B those set to the integer value B (see Chapter 4). The allowed values of `grp_bias` are 0, 1, 2, and 3 and by default all particles in the chemical system are in center of mass group 0. If $A = -1$, however, `BiasingForce` will restrain group B with respect to the simulation box.

The `BiasingForce` plugin works by imposing the following restraining potential on the molecular system:

$$\begin{aligned} E_{\text{biasing}} &= \frac{\kappa_x}{2}(\vec{R}_{AB} \cdot \vec{q}_{A1} - x)^2 + \frac{\kappa_y}{2}(\vec{R}_{AB} \cdot \vec{q}_{A2} - y)^2 + \frac{\kappa_z}{2}(\vec{R}_{AB} \cdot \vec{q}_{A3} - z)^2 \\ &+ \frac{\kappa_d}{2}(R_{AB} - R)^2 \qquad (2.3) \\ &+ \frac{\omega_1}{2}((\mathcal{G}\vec{q}_{B1}) \cdot \vec{q}_{A1} - 1)^2 + \frac{\omega_2}{2}((\mathcal{G}\vec{q}_{B2}) \cdot \vec{q}_{A2} - 1)^2 + \frac{\omega_3}{2}((\mathcal{G}\vec{q}_{B3}) \cdot \vec{q}_{A3} - 1)^2 \end{aligned}$$

where R_A (R_B) is the center of mass of group A (B), $R_{AB} = (x_{AB}, y_{AB}, z_{AB}) = R_B - R_A$, $q_{A\alpha}, \alpha = 1, 2, 3$ ($q_{B\alpha}$) are the principal axis of group A (B), and $\mathcal{G}$ is the rotational matrix that will superimpose the q_B's onto q_A's when B is in the relative orientation with respect to A, as specified by the Euler angles (θ, ϕ, ψ).

In E_{biasing}, the first three terms restrain the relative displacement between the centers of mass of groups B and A, to the desired displacement (x, y, z). The term in the second line restrains the scalar center-of-mass distance R_{AB} of the two groups A and B and R is the target displacement. The three terms in the third line restrain the relative orientations of the particles in group B with respect to those in group A.

If the parameters `pull_displacement` are set to 0, the desired displacement—(x, y, z) in Equation 2.3—are taken to be (x_0, y_0, z_0) in the configuration, and they will not change in the course of the simulation. But if they are not zero, the biasing force will be used to pull the two groups from the initial positions at the specified rates $v = (v_x, v_y, v_z)$, and the target displacement, $R(t)$, at time t is given by

$$\vec{R}(t) = (x(t), y(t), z(t)) = \vec{R}_{AB}(0) + \vec{v}\,t \tag{2.4}$$

where $R_{AB}(0)$ is the initial displacement between A and B at the beginning of the simulation.

The same convention applies to `pull_distance` and `pull_Euler`.

The parameter `use_lab_frame_for_displacement` is false by default. If it is set to true, the displacement between groups B and A will be measured in the reference frame of the simulation box, and will not be projected onto the reference frame formed by the principal axes of group A. Namely, the three terms in the first line of Equation 2.3 are replaced in this case by

$$\frac{\kappa_x}{2}(x_{AB} - x)^2 + \frac{\kappa_y}{2}(y_{AB} - y)^2 + \frac{\kappa_z}{2}(z_{AB} - z)^2 \tag{2.5}$$

A maximum of 4 `cm_moi` groups can be defined for a chemical system. Because the center-of-mass and moment-of-inertia are computed for these groups of atoms in order to apply the biasing potential, the user must avoid imposing the biasing potential upon a group of atoms that can wrap around the periodic box since in this case, the center-of-mass and the moment-of-inertia are ill-defined. There is a limit of 4 biasing potentials in the `cm_moi` list of the `force.BiasingForce` configuration.

The user can monitor the action of the biasing potential from the data written at the specified time intervals to the output file. The header in the output file reports the number of atoms in each `cm_moi` group; the user should verify that these match the intended grouping. Following this is a header line that labels each column of the subsequent data. Each row of data corresponds to one moment in time, beginning with the properties of the first `cm_moi` group, followed by those of the ensuing groups. The data reported are as follows:

xci, yci, zci, where i = 0, 1, . . . : the center-of-mass coordinates of the i^{th} `cm_moi` group in units of Å.

p1xi, p1yi, p1zi : the unit vector of the first principal axis of the i^{th} `cm_moi` group.

p2xi, p2yi, p2zi, p3xi, p3yi, p3zi : the unit vectors of the second and third principal axes of the ith `cm_moi` group.

I1i, I2i, I3i : the diagonal moment-of-inertia tensor of the ith `cm_moi` group, corresponding to the principal axes in the same order. They are in units of amu × $\mathring{A}^2$.

From these data together with the parameters in the biasing potential configuration, it is straightforward to compute the energy contributions from the biasing potential at each recorded moment.

name	**description**
`cm_moi`	Biasing force definition for a list of cm_moi groups [*List*]
`groups`	The groups to restrain [*List*]
`displace_coeff`	Force coefficients for displacement restraints [*List of 3 Energy/Length*^{2}]
`displacement`	Relative displacement between the two groups [*List of 3 Lengths*]
`distance_coeff`	Force coefficient for distance restraint [*Energy/Length*^{2}]
`distance`	Distance between the two groups [*Length*]
`orient_coeff`	Force coefficients for orientational restraints [*List of 3 Energies*]
`Euler_angles`	Euler angles between the two groups [*List of 3 Degrees*]
`use_lab_frame_for_displacement`	If true, the displacement between the groups are measured in the reference frame of the simulation box [*Boolean*]
`pull_displacement`	Velocity of pulling in displacement [*List of 3 Length/Time*]
`pull_distance`	Velocity of pulling in distance [*Length/Time*]
`pull_Euler`	Velocity of pulling in orientation [*List of 3 Degree/Time*]
`t0`	The time to begin apply pulling, as specified by pull_displacement, pull_distance, and pull_Euler. *This is not to be confused with the biasing force itself, which is applied from the beginning of the simulation.* [*Time*]
`output.first`	The time to write the first biasing results [*Time*]
`output.interval`	The interval at which to write the biasing results [*Time*]
`output.name`	The name of the file to which to write the energy estimates [*Filename*]

Table 2.9: Parameters for BiasingForce

2.6.3 e_bias

The `e_bias` plugin applies a constant electric field with the direction and magnitude given by `E_applied`. The `schedule` subsection can be set to `none`; if so, the field remains constant over time; otherwise, it's scaled by the values given in `schedule.value`.

```
    force.term = {
```

```
    list = [ ... key ... ]
    key = {
      type = e_bias
      E_applied = [Ex Ey Ez] # Applied field in kcal/mol/A/e
      schedule = {
        time = [ t1 t2 ... tN ]  # Times in picosecond
        value = [ S1 S2 ... SN ]
      }
    }
    ... # other force terms
  }
```

With `e_bias`, a particle carrying charge q experiences a force

$$\vec{F} = (qE_x(t), qE_y(t), qE_z(t))$$

where the electric field at time t is given by

$$E_\alpha(t) = E_\alpha S(t) \text{ for } \alpha = x, y, z$$

The time-dependent scaling factor $S(t)$ is determined by the schedule. If `schedule=none`, then $S(t) = 1$ for all t. Otherwise, $S(t)$ at time t is given by piecewise linear interpolation:

$$S(t) = \begin{cases} S_i + (S_{i+1} - S_i)\frac{t-t_i}{t_{i+1}-t_i} & \text{if } t \in [t_i, t_{i+1}) \\ S_1 & \text{if } t < t_1 \\ S_N & \text{if } t \geq t_N \end{cases} \tag{2.6}$$

`e_bias` is often used to model electric potentials across membranes.

name	**description**
`E_applied`	Applied electric field in kcal/mol/Å/e [*List of 3 Energy/Length/ElectronCharge*]
`schedule.time`	Times at which scale factors are specified [*List of Times*]
`schedule.value`	Scale factors to apply at corresponding times. Same length as schedule.time list [*List of Scalars*]

Table 2.10: Parameters for e_bias

2.6.4 energy_groups

Periodically writes energy to the output file *p*, broken down both by the *energy group property* of the particles and the *Hamiltonian category* of the potential energy term. (Energy groups are assigned in the structure file, while the string identifiers of various Hamiltonian categories are set by their computational pipelines.)

Additionally, the 3×3 instantaneous pressure tensor and the nonbonded correction energy are printed if specified. The nonbonded correction energy is the sum of the nonbonded tail correction and the electrostatic self-energy correction (see sections 5.3.2 and 5.4.1).

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = energy_groups
    first = $t_f$
    interval = $t_i$
    name = $p$
    options = [ pressure_tensor corr_energy self_energy ]
  }
}
```

The output format is a sequence of ascii blocks of plain text. Each block begins with a line of the form

```
time=$t$ en=$\varepsilon_v$ E_p=$\varepsilon_p$ E_k=$\varepsilon_k$ E_x=$\varepsilon_x$ P=$P$ V=$V$
```

giving the chemical time, the raw potential, the potential, kinetic, and extended energies, as well as the pressure and volume. The raw potential energy is potential energy without the electrostatic self-energy or the nonbonded tail corrections.

What follows is then a break down of the raw potential energy by energy group. The kinetic energy is broken down into the kinetic energy per group. The potential energies are broken down (by column) according to their interacting pairs of groups and (by row) their Hamiltonian category.

name	**description**
`first`	First time for this action. [*Time*]
`interval`	Time between actions. [*Time*]
`name`	The output file name. [*String*]
`options`	Whether to print pressure tensor (pressure_tensor), the correlation energy (corr_energy), and/or the self energy (self_energy) [*List of strings*]

Table 2.11: Parameters for energy_groups

2.6.5 compute_forces

The `compute_forces` plugin Writes a per-particle listing of forces to an output trajectory frameset *p*. It is primarily useful for diagnostics.

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = compute_forces
    first = $t_f$
    interval = $t_i$
    name = p
    mode = m
  }
}
```

name	description
first	First time for this action. [*Time*]
interval	Time between actions. [*Time*]
name	The directory name of the trajectory frameset. [*String*]
mode	append/noclobber/clobber, see discussion in Table 2.19 [*String*]

Table 2.12: Parameters for compute_forces

2.6.6 eneseq

The `eneseq` plugin Writes energy, temperatures, pressures, and other summary data to an output file. Configuration information is given in:

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = eneseq
    first = $t_f$
    interval = $t_i$
    sync_io = $b_s$
    name = p
  }
}
```

The energy is broken down into components and printed in columns of the `eneseq` file indexed by simulation time (column `time`):

conserved The sum of potential, kinetic, and extended system energy. For many integration methods, this quantity is asymptotically conserved as the simulation timestep goes to 0 and serves as a check on the correctness of the trajectory (column `E`).

potential The value of $U(\mathbf{r})$ (column `E_p`).

kinetic The value of $K(\mathbf{p}) = \sum_i \|p_i\|^2/(2m_i)$ (column `E_k`).

extended The energy associated with the extended variables of the dynamical system being integrated (column `E_x`).

force correction The value of $-\delta_t^2 \sum_i \|\vec{f_i}\|^2/(8m_i)$, where $\vec{f_i}$ is the force on particle i. Because its addition to the energy gives an exactly (up to arithmetic) conserved quantity in systems where the potential is purely harmonic integrated with velocity Verlet, this quantity is sometimes of technical interest (column `E_f`).

The `eneseq` plugin also reports pressure `P`, volume `V` and temperature `T`, as well as a temperature for each temperature group identified in the structure file `T_N`.

The header of the `eneseq`, excerpted with a few columns below, gives the number of particles `N_atoms`, the number of degrees of freedom `N_dof`, the total charge `q_i` and squared charge `q_i`, together with other sometimes pertinent information.

```
# 5dhfr production parameters
# Simulation started on Wed May 19 15:36:52 2010

# sum_i q_i = -10.999998, sum_i q_i^2 = 7582.727781
# N_atoms = 23558
# N dof =  70674 ( 70674 )
# n_pressure_grp = 23558
# n_frozen_atoms = 0

# 0:time (ps)  1:E   (kcal/mol)  2:E_p (kcal/mol)  3:E_k (kcal/mol) ...
        0.000   -7.24497189e+04   -7.24497189e+04    0.00000000e+00 ...
        0.050   -7.39533259e+04   -8.30207059e+04    9.06738003e+03 ...
```

Note: Not all integration schemes have a conserved energy. Details are discussed in Chapter 7.

Note: When performing initial velocity thermalization, place this plugin before the `eneseq` plugin on the list of plugin names.

name	**description**
`first`	First time for this action. [*Time*]
`interval`	Time between actions. [*Time*]
`name`	The output file name. [*String*]

Table 2.13: Parameters for eneseq

2.6.7 maeff_output

The `maeff_output` plugin writes a structure file in the deprecated *Maestro* file format using current simulation coordinates. It preserves non-coordinate information from the structure file. Configuration information is given in:

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = maeff_output
```

```
      first = $t_f$
      interval = $t_i$
      name = $p$
      write_last_step = $b_1$
      periodicfix = $b_p$
    }
  }
```

name	description
first	First time for this action. [*Time*]
interval	Time between actions. [*Time*]
name	The output file name. [*String*]
write_last_step	Whether to write a structure file at the last step. [*Boolean*]
periodicfix	Whether to wrap atom positions across periodic boundaries to minimize bond lengths. [*Boolean*]

Table 2.14: Parameters for maeff_output

2.6.8 posre_schedule

The posre_schedule plugin scales the strength of position restraints according to a time schedule. It is useful for slowly turning off position restraints during a simulation. The following Example shows the configuration:

Example 2.14

```
  app.plugin = {
    list = [ ... key ... ]
    key = {
      type = posre_schedule
      schedule = {
        time = [ $t_1$ $t_2$ ... $t_N$ ]
        value = [ $S_1$ $S_2$ ... $S_N$ ]
      }
    }
  }
```

name	description
time	Times at which scale factors are specified. [*List of Times*]
value	(must be same Scale factor to apply to position restraints. Required. length as time list) [*List of Scalars*]

Table 2.15: Parameters for posreschedule

The scale factor S used at time t is given by piecewise linear interpolation as in Equation 2.6.

For example, if a schedule has time points `[1 10]` and values `[1.0 0.0]`, then the scale factor will be 1.0 for times before 1 ps, 0.0 for times after 10 ps, and in between, the scale factor will decrease linearly.

2.6.9 pprofile

The `pprofile` plugin computes pressure profiles, which gives the surface tension in a molecular system as a function of the z coordinate. Pressure profile analysis can give insight into the role of the lipid environment on embedded proteins. Configuration of the `pprofile` plugin is shown in the Example.

Example 2.15

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = pprofile
    first = t_f
    interval = t_i
    eval_interval = t_e
    nslabs = N
    name = p
    include = [ ... ] # optional
    exclude = [ ... ] # optional
  }
}
```

name	**description**
`first`	first output time [*Time*]
`interval`	interval between outputs [*Time*]
`eval_interval`	time interval between virial calculations [*Time*]
`nslabs`	number of simulation cell partitions [*Integer*]
`name`	frameset output directory [*String*]
`include`	if present, include only the given force terms in the virial calculation [*List of strings*]
`exclude`	if present, do not include the given force terms in the virial calculation; it is an error to specify both `include` and `exclude` in the same pprofile instance [*List of strings*]

Table 2.16: Parameters for pprofile

At each application, the `pprofile` plugin divides the simulation cell into a number of slabs parallel to the z axis. Contributions to the pressure from particles located within each slab are computed, where each particle's position is wrapped to the central global cell. These values are output to a frameset.

The time between pressure profile calculations can be specified; in addition, the time between profile output can be given separately, in which case the average of the values collected over the preceeding interval will be written.

Output frameset contains the following fields:

- `FORMAT`: the string "PPROFILE_V1".
- `CHEMICALTIME`: the simulation time at which the data was written.
- `NSLABS`: the number N of partitions of the simulation cell.
- `NEVALS`: the number of virial evaluations that have been averaged to compute the data in the frame.
- `UNITCELL`: the global cell dimensions at the current time.
- `CORRECTION`: the x, y, and z diagonal components of the long range correction to the pressure from the nonbonded tail correction (see Section 5.3.2).
- `kinetic`: $3N$ doubles listing the x, y, and z diagonal components of the pressure for each slab due to particle kinetic energy.
- *`C`*: $3N$ doubles listing the x, y, and z diagonal components of the pressure for each slab due to interactions in Hamiltonian category C.
- `total`: $3N$ doubles listing the x, y, and z diagonal components of the pressure for each slab (totaled over categories and kinetic).

Some force components, especially `far_terms`, are expensive to compute and vary slowly with time. One can improve the efficiency of the pressure profile calculation by instantiating the `pprofile` plugin twice, with one instance evaluating the non-`far_terms` components relatively frequently, and the other instance evaluating the `far_terms` components relatively infrequently. For example:

Example 2.16

```
app.plugin = {
  list = [ ... slow fast ... ]

  slow = {
    type = pprofile
    first = 0
    interval = 10
    eval_interval = 0.2
    nslabs = 8
    name = pp-slow.dtr
```

```
      include = [far_terms]
    }

    fast = { # fast
      type = pprofile
      first = 0
      interval = 10
      eval_interval = 0.01
      nslabs = 8
      name = pp-fast.dtr
      exclude = [far_terms]
    }
  }
```

2.6.10 randomize_velocities

The randomize_velocities plugin periodically thermalizes velocities. Configuration is shown in:

```
  app.plugin = {
    list = [ ... key ... ]
    key = {
      type = randomize_velocities
      first = t_f
      interval = t_i
      seed = s
      temperature = T
    }
  }
```

You can use this plugin to perform initial velocity randomization, by setting the value of first to zero, interval to infinity, and temperature to the desired temperature. The plugin can also serve as a rough implementation of an Andersen thermostat.

name	description
first	First time for this action. [*Time*]
interval	Time between actions. [*Time*]
seed	Seed for the random number generator. [*Integer*]
temperature	The target temperature. [*temperature*]

Table 2.17: Parameters for randomize_velocities

2.6.11 remove_com_motion

The remove_com_motion plugin periodically removes net center of mess motion from the system velocities. Configuration is shown in:

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = remove_com_motion
    first = $t_f$
    interval = $t_i$
  }
}
```

Although most systems in their exact mathematics have no net center of mass motion, numerical implementations might have nonzero motion. Most dynamical systems do not explicitly remove center of mass motion. This plugin will periodically subtract off any net center of mass motion from the system.

name	**description**
`first`	First time for this action. [*Time*]
`interval`	Time between actions. [*Time*]

Table 2.18: Parameters for remove_com_motion

2.6.12 trajectory

The `trajectory` plugin writes trajectory data using current simulation coordinates. It is configured as shown in the Synopsis.

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = trajectory
    first = $t_f$
    interval = $t_i$
    name = $d$
    write_velocity = $b_v$
    mode = $m$
    periodicfix = $b_p$
    center = [ $c_1$ ... $c_m$ ]
    glue = [ $g_1$ ... $g_n$ ]
    write_last_step = $b_l$
  }
}
```

Data is written as a set of frames in the directory, d, (following output file naming conventions; see Section 2.5), with individual frames written as files within that directory as described in Section 11.

The `periodicfix`, `center`, and `glue` options together describe how simulation coordinates should be preprocessed before being written to the frameset. If `periodicfix` is turned off and no centering or glue is applied, all atom coordinates are wrapped to the central unit cell, irrespective of bonds between atoms. This makes visualization and trajectory analysis difficult. The `periodicfix` option instructs Desmond to re-wrap atoms so that no bond is longer than half the length of of any global cell vector. Note that the bonds considered are those of the `bond` section of the structure file, not the `stretch_harm` or any other force field terms. The `glue` option extends the list of bonds supplied by the structure file with fictitious bonds that can improve the wrapping behavior. For example, if a protein is composed of four disconnected monomers that nevertheless stay non-covalently bound to each other during a simulation, it will be desirable to keep them together during wrapping. Without glue, however, if one monomer strays close to the edge of the periodic cell, it will be wrapped to the other side while the other three monomers remain where they are. To correct this behavior, one could use a glue configuration of the form `glue=[ [n1 n2 n3 n4] ]`, where each `n` is from a different monomer. This would create fictitious bonds $n1 - n2$, $n1 - n3$, and $n1 - n4$. Note that it is important to choose particles for the glue that are as close as possible to each other in the input structure.

After the bond fixing step, the centering step is performed if any particles in the `center` configuration have been specified. A single translation is applied to the entire system in order to bring the geometric center of the center atoms to the origin.

The last transformation applied to the coordinates, assuming `periodicfix` is enabled, is to take connected sets of atoms and translate each set as a group so that their geometric centers are located within the central unit cell. Here, again, the definition of connected use both the input structure bonds as well as bonds supplied by glue.

name	**description**
`first`	First time for this action. [*Time*]
`interval`	Time between actions. [*Time*]
`name`	The output directory name for the frameset. [*String*]
`write_velocity`	Whether to include velocity information in output frames. [*Boolean*]
`mode`	Open mode for the frameset. **‘append’** open for append, **‘noclobber’** open for writing, fails if the directory exists, and **‘clobber’** open for writing, recursively deleting the directory if it exists [*String*]
`periodicfix`	Whether to wrap atom positions across periodic boundaries to minimize bond lengths. [*Boolean*]
`center`	Set of atoms specified by *global ids* (GIDs) whose coordinates should be used to center trajectory frames. Requires `periodicfix` to be true. [*List*]
`glue`	A list whose elements are lists of GIDs; each GID list is to be kept together during centering and `periodicfix` application. Requires `periodicfix` to be true. [*List of lists*]
`write_last_step`	Whether to write a frame at the last step. [*Boolean*]

Table 2.19: Parameters for trajectory

2.6.13 status

The `status` plugin periodically outputs to the log the simulation speed in terms of simulation time per unit of wall clock time, and at the end of the simulation writes a cumulative speed. It’s configured as shown in:

```
app.plugin = {
  list = [ ... key ... ]
  key = {
    type = status
    first = t_f
    interval = t_i
    verbose = b_v
  }
}
```

name	description
`first`	First time for this action. [*Time*]
`interval`	Time between actions. [*Time*]
`verbose`	Print out running cumulative speed information. Optional—by default, false. [*Boolean*]

Table 2.20: Parameters for status

2.7 Configuring optional sections

Certain sections of the configuration can be omitted entirely. One such section is the profile section, which can sometimes be useful for debugging and tuning performance.

2.7.1 profile

Each Desmond application can generate a runtime profile of time spent in various activities, output at the end of the run, thus helping you to tune your simulation for best performance. These activities usually correspond to functions, families of related functions, or blocks of code dedicated to a particular task.

This feature is primarily to assist developers; the activities are described by short names that are somewhat self-explanatory.

The profile section is optional. If omitted, no profile is generated. Profile configuration is given in:

```
profile = {
  show_tree = $b_t$
  show_flat = $b_f$
  min_calls = $c_{\min}$
  max_depth = $d_{\max}$
}
```

Two profile views can be output: a *tree view* and a *flat view*, both analogous to the output of the well-known profiler `gprof`.

The tree view gives times for various activities in a hierarchy, since activities can contain sub-activities (or children). The accumulated time for each activity is the total time spent in that activity and its children. An activity can occur in more than one place in the hierarchy.

The flat view removes the hierarchy and lists one line per activity, accumulating times spent in an activity which may be the result of different parent activities. Additionally, the time printed for the flat view is given as the difference between the time spent in that activity and the total time spent in the children of that activity, and hence the total time in the flat view should be roughly equal to the total runtime of the application, minus some startup and shutdown overhead.

The Boolean variables b_t and b_f control which views are presented. By default, both are true.

To control the complexity of the output, users can pick a maximum depth of the tree view, d_{max}, and a minimum number of occurrences, c_{min}, below which the activity is not reported. (For example, most initialization activities occur just once, so $c_{\mathrm{min}} = 2$ suppresses them.)

When profiling a simulation run in parallel, profile prints the profile for process 0. If the simulation is sufficiently load-balanced, this is representative of the whole computation.

name	**description**
`max_depth`	Maximum depth of the tree view. Optional—by default infinite [*Integer*]
`min_calls`	Minimum number of occurrences to report. Optional—by default 1 [*Integer*]
`show_tree`	Whether to display the tree view. Optional—by default, true. [*Boolean*]
`show_flat`	Whether to display the flat view. Optional—by default, true. [*Boolean*]

Table 2.21: Parameters for profile

Chapter 3

The Global Cell

This chapter discusses Desmond's parallelization strategies and describes how to configure the global cell.

3.1 Parallelization

As described in Section 1.1.4, the global cell is Desmond's representation of the space occupied by the chemical system. It fills an infinite volume by tiling the space periodically with repetitions of the global cell.

To parallelize the computations, Desmond decomposes the work spatially. Therefore, configuring the global cell appropriately requires an understanding of several of Desmond's parallelization mechanisms.

The global cell is divided into regular three-dimensional volumes called *boxes*. Each box is assigned to a single Desmond process, which maintains the information describing each particle located within that box.

Note: For an efficiently parallelized simulation in Desmond, we recommend no more than one process (one box) per processor.

The box encompassing the volume of space in which a particle is located is called its *home box*. The home box determines which process owns the particle—that is, maintains its mass, charge, position, velocity, and other associated data.

Interactions between particles can cross box boundaries, of course; communication across box boundaries can be necessary for other reasons, too. This means that communication must occur between processes. Interactions that require communication between processes have a strong effect on how well your simulation performs in parallel—how much it can take advantage of the multiple processes available to it. Communication between processes is necessary to resolve two common situations:

- A particle near the face of a box is bonded with a particle in a neighboring box, or close enough to it that the electrostatic or van der Waals forces between them are computed explicitly—that is, within the cutoff radius (see page 3).

- A particle that was not originally inside the cutoff radius drifts inside it from one timestep to the next.

To ensure that a given process can access all the data it needs to compute such interactions, Desmond copies data for any particle that's outside the home box, but within a given distance of its edge. Such copies are called *clones*, and this distance is the clone radius.

For example, if particle A near the edge of its home box A participates in a bond with particle B just outside home box A, then process A has access to data associated with both particles: A, which it owns; and B, which it clones. Because each face of the global cell wraps to its opposite, particles are also cloned when they are close enough to particles on the opposite face of the global cell, as well as the edges of their home box. If you're running Desmond serially (a single process), the home box equals the global cell, and this is the only manifestation of clones in the simulation. In the example illustrated in Figure 3.1, either process could, in principle, compute the AB interaction. In Desmond, the process that does so is the one whose home box contains the midpoint between the two particles. After computing forces on the clone, it sends the result to process B, which sums A's result with its own before computing B's new position and velocity.

More generally, the process that computes an interaction of a group particles is the one whose home box contains the (unweighted) midpoint of that group.

At the end of a timestep, after new particle positions are computed, some particles will have moved out of their previous home boxes into neighboring ones. *Migration* is the process by which particles are reassigned to the processes responsible for their new home boxes.

You can configure Desmond to migrate particles every time it updates particle positions—at each inner timestep—a setting called *eager migration.* However, during migration, processes need to exchange a lot of data, so it's desirable to minimize its occurrence.

Lazy migration lets you avoid some communication overhead by reassigning particles to home boxes less often than every time particle positions are updated. Position updates can then occur without migration. (The migration schedule is described in Section 3.3.)

But if particles aren't reassigned to new processes every time positions are updated, then inevitably, between migration events, some particles will approach each other and drift within the cutoff radius. Then the near interactions between the pair will have to be calculated.

How often this happens depends on the size of the cutoff radius, and how volatile the simulation is: the faster particles move, the more often pairs of particles will end up in separate home boxes.

For efficiency, Desmond maintains a list—the pairlist—of particle pairs that might need to be used to evaluate the effects of nonbonded near interactions. The pairlist must contain particle pairs that are now outside the cutoff radius, but might approach each other closely enough to interact in upcoming timesteps, before the next migration.

Instead of the cutoff radius, therefore, the pairlist contains particle pairs separated

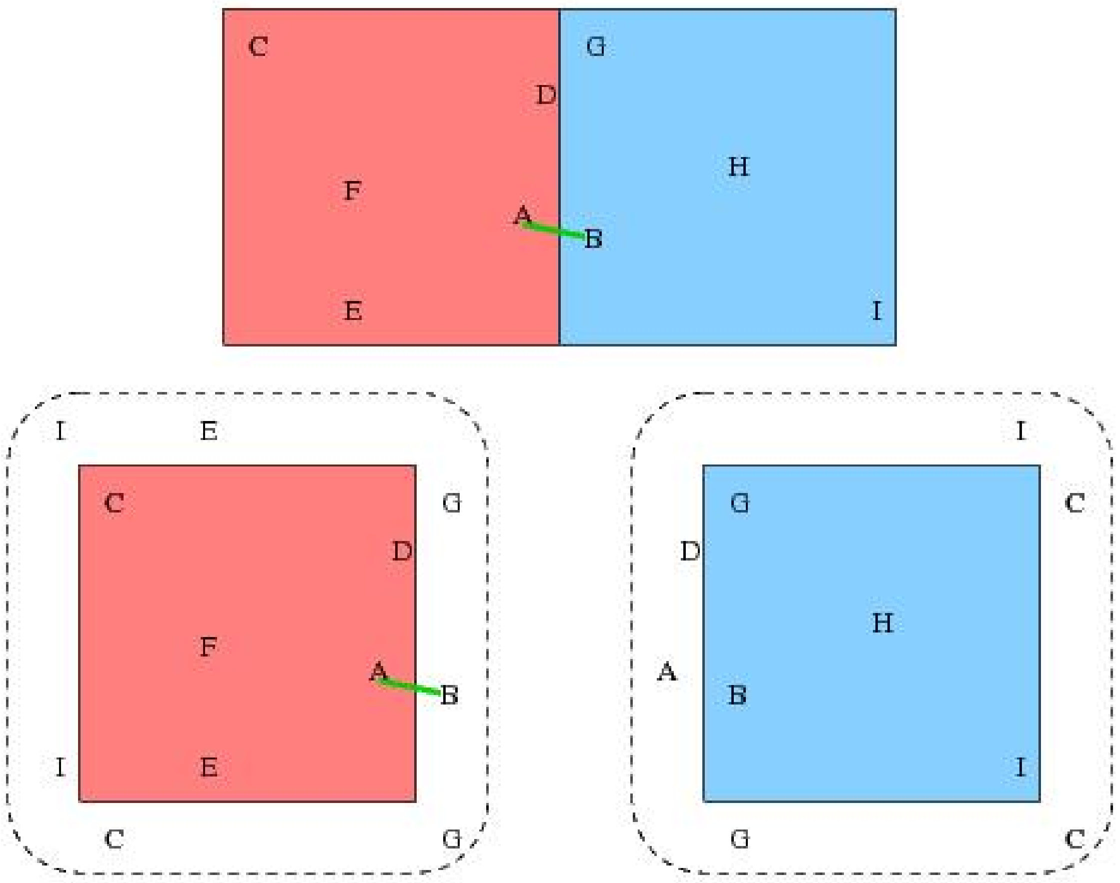


Figure 3.1: An 2D illustration with nine particles, labeled A through I, in a 2x1 global cell partitioned between two processes into two homeboxes. Below, per process views of space with copies of remote and local particles in each processes clone buffer. The interaction between A and B is computed on the process containing their midpoint.

by less than the *lazy radius*. The lazy radius sets the maximum distance of all pairs of particles included in the pairlist at the time of its assembly (the most recent migration).

The lazy radius is determined implicitly from the *margin* parameter, Δ, by $R_{\text{lazy}} = R_{\text{cut}} + \Delta$. If no particle has moved a distance more than $\Delta/2$ since the last update, the pairlist still contains all pairs of particles within R_{cut} of each other. In typical simulations it is highly unlikely that particles move faster than 50 Å/ps (by a probabilistic argument involving the number and masses of all particles, based on the Maxwell-Boltzmann distribution), hence $\Delta \geq 50t_i$, where t_i is the interval between migrations, is sufficient to ensure correct calculations. Because $R_{\text{lazy}} \geq R_{\text{cut}}$, additional work (roughly of order $O(R_{\text{cut}}^2\Delta)$) is needed to iterate over uninteresting pairs for near interactions, so, for good performance, you must strike a balance. A typical value used is $\Delta = 0.625$ Å with a pairlist update every 12 fs, though this can miss pairs occasionally. The pairlist is updated at each migration event.

The cutoff radius is a therefore key factor in setting the correct lazy radius, and the lazy radius in turn is a key factor in setting the clone radius, in particular. For correct pairlist assembly $R_{\text{lazy}} \leq R_{\text{clone}}$.

To determine which process computes an interaction between two particles, Desmond uses the midpoint method: it's the process whose home box contains the midpoint between the two. If the midpoint of a pair of particles within the lazy radius lies in a particular home box, then in order for both particles (owned and cloned) to be accessible to the appropriate process, the clone radius must be at least half of the lazy radius. While the clone radius is set as part of configuring the global cell, the cutoff and lazy radii are specified in the force section of the configuration; for details, see Chapter 5.

Note: When migrating eagerly ($t_i = 0$), one can set $\Delta = 0, R_{\text{cut}} = 2 \cdot R_{\text{clone}}$.

Note: Ordinarily, near interactions restrict the size of the clone radius more than any other consideration. For all restrictions on the size of the clone radius, see Appendix C. For setting these three radii, the following rule of thumb is useful for most simulations:

1. Choose the cutoff radius R_{cut}.
2. Choose the margin Δ.
3. Set the clone radius R_{clone} to half of $R_{\text{lazy}} = R_{\text{cut}} + \Delta$.

3.2 Configuration

Configuring the global cell involves setting:

- the reference time, and
- the clone radius.

In addition, if you're running Desmond in parallel, you can also:

- specify how you wish to partition the global cell among the processes, and
- provide an estimate of average particle density per homebox.

These parameters are discussed below. The global cell's section in the configuration file appears as shown in the following Synopsis, Configuring the global cell:

```
global_cell = {
  reference_time = $t_r$
  r_clone = $R_{\text{clone}}$
  partition = [ $n_1$ $n_2$ $n_3$ ]
  margin = $\Delta$
  est_pdens = $d$
}
```

The global cell is centered at the origin, with edge vectors given by the *lattice vectors*, $\vec{a}$, $\vec{b}$, $\vec{c}$, read from the structure file. This is described Section E.1.1.

The global cell is responsible for the time coordinate, t, initialized to t_r. The integers n_1, n_2, n_3 specify how the global cell is partitioned among processes, with each process assigned a home box:

- n_1 is the number of processes along the X axis of the global cell.
- n_2 is the number of processes along the Y axis of the global cell.
- n_3 is the number of processes along the Z axis of the global cell.

By definition, then, $n_1 n_2 n_3$ is the total number of Desmond processes.

Note: The number of processes along each axis may be constrained by the requirements of the nonbonded terms if a discrete Fourier transform is used to implement Ewald summation (see Section 5.4); if not, it outputs an error message and halts.

Assuming a homogeneous particle density throughout the global cell, it's most efficient if the relative number of boxes along each axis is as close as possible to the relative proportions of the global cell, so that each box is as close as possible to a cube. This minimizes the surface-to-volume ratio of each box. A surface represents a boundary between boxes, so a minimal surface minimizes interprocessor communication. For example, for a relatively homogeneous system with dimensions 90 Å $\times$ 90 Å $\times$ 50 Å running on 32 processes, a partition of $n_1 = 4$, $n_2 = 4$, $n_3 = 2$ is most efficient.

If you'd like Desmond to set the number of processes assigned to a given axis, then instead of setting it explicitly set the corresponding parameter to zero. To allow Desmond to determine how to partition the global cell along all three axes, therefore, set n_1, n_2, n_3 to 0, 0, 0. Desmond can nearly always determine an efficient global cell partitioning.

When the global cell isn't a rectangular volume, Desmond issues a warning. For example, a hexagonal prism has X and Y vectors of the same length, but the Z axis could be any length. In this case, if you set n_1, n_2, n_3 to 0, 0, 0, Desmond generates a partition, but prints: Automatic partitioning is untested for global cells with off-diagonal boxes. If you see this warning, check the partitioning to ensure that it meets the criteria discussed above.

The margin, Δ, is a user provided upper bound on the maximum distance any particle will move between migration steps events. Certain data structures within Desmond (such as pairlists) will rely on Δ to be faithful.

To tune various internal parameters for best performance, Desmond needs an estimate of particle density `est_pdens` per home box. By default, Desmond sets d by computing an average density from the structure file. For most simulations, it's safe to omit `est_pdens`, in which case Desmond uses its default. However, if the density of particles in the system is highly inhomogeneous, set d to:

- the maximum number of particles that could exist in a single home box,
- multiplied by the number of home boxes,
- divided by the volume of the global cell.

Configuring the global cell is summarized in:

name	**description**
`reference_time`	Start time for the simulation. [*Time*]
`r_clone`	Radius of particle / home box visibility. [*Length* > 0]
`margin`	A user-promised maximum displacement of any particle between migration events. [*Length* > 0]
`partition`	Number of process subdivisions along each axis. Optional; by default, 0,0,0—meaning that Desmond sets them. [*List of three Integers*]
`est_pdens`	Average number of particles per unit volume. Optional; by default, computed from the structure file. [1/length$^3 > 0$]

Table 3.1: Parameters for global cell

3.3 Migration

Migration is configured as shown in:

```
migration = {
  first = t_f
  interval = t_i
}
```

Desmond partitions particles across processors by a spatial decomposition. As such, when particle positions change, home box ownership must be recalculated and interprocess communication must occur to make each process aware of new particles in its view. This is called *migration*. Since it is a significant computational and communicative task, which need not be performed at every position update, this task is scheduled independently of position changes. The parameters t_f and t_i set the time for the first migration update and the interval of time between later migration update.

name	**description**
`first`	Approximate amount of time of the first migration. [$Time \geq 0$]
`interval`	Approximate amount of time between subsequent migrations. [$Time \geq 0$]

Table 3.2: Parameters for migrate

Chapter 4

Preparing a structure file

Starting with version 2.4, Desmond switched the format of its structure file from *Maestro* to a new format called DMS. The DESRES Molecular Structure (DMS) file format is a set of schemas for storing coordinate and forcefield information about a single biomolecular system in an SQLite-format database. SQLite[13] is a in-process library that implements a self-contained, serverless, zero-configuration, transactional SQL database engine. The code for SQLite is in the public domain and is thus free for use for any purpose, commercial or private.

Note: Section E provides additional information on the format and contents of MAE files.

SQLite reads and writes directly to ordinary disk files. A complete SQLite database with multiple tables, indices, triggers, and views, is contained in a single disk file. The database file format is cross-platform—it is portable between 32- and 64-bit systems, between big- and little-endian architectures, and between Unix and Windows operating systems.

All data in a DMS file lives in a flat list of two-dimensional tables. Each table has a unique name. Columns in the tables have a name, a datatype, and several other attributes, most importantly, whether or not the column is the primary key for the table. Rows in the tables hold a value for each of the columns. Table names, column names, and datatypes are case-preserving, but case-insensitive: thus “pArTiCLE” is the same table as “particle”, and “NAME” is the same column as “name”.

For more about the DMS format, see Appendix D.

There are two main ways to prepare a DMS file for Desmond. The first method is to convert an existing MAE file and all its forcefield data to DMS using the `mae2dms` tool described below. The second method is to construct a DMS file containing just the minimal set of molecular structure information, and build a forcefield for that structure using Viparr.

4.1 Converting a Desmond 2.0/2.2 structure file

If you already have an MAE file, prepared either with `viparr.py` from Desmond 2.0/2.2 or with Schrodinger's `Maestro` tool, you can convert to to DMS using `mae2dms`. `mae2dms` preserves all forcefield information, including bonded terms, vdw tables energy and temperature groups, constraints, cmap tables, and position restraints. Force field terms that were present and supported in Desmond 2.2 should be properly handled by `mae2dms`; any forcefield type that was not present in Desmond 2.2 is not likely to be recognized and converted.

Alchemical MAE files require special attention. Before running `mae2dms`, run the `prep_alchemical_mae` program on the MAE file. This program interprets the `fepio_fep` sections of the MAE file and converts the MAE file to a form more amenable to conversion to DMS format.

Once you have successfully converted a forcefield-containing MAE file to DMS, you are ready to begin equilibration and minimization.

4.2 Preparing a Desmond DMS file

Preparing a DMS file from scratch can be divided into four main steps. First a DMS file must be constructed that contains all the atoms and bonds in the structure, including ions, waters, protons, etc., along with a specification of the global cell. Second, this DMS file serves as the input to Viparr, which adds forcefield information. Third, the `build_constraints` program is used to constrain bonds between hydrogen and heavy atoms. Finally, additional atom properties may be specified in order to perform specialized tasks such as energy group analysis or biasing force application.

4.2.1 Constructing an input DMS file for Viparr

The simplest method for preparing an input DMS file for Viparr is to use `VMD`. `VMD` provides a number of tools for building structures in `psf/pdb` format. Once you have a molecule in `VMD` containing the full set of atoms and bonds, you can write out the structure in DMS format using the `dms` file plugin.

Alternatively, a DMS file may be produced by any tool that can write to the SQLite file format. The input DMS file for Viparr must contain `particle`, `bond`, and `global_cell` tables. The `particle` table must contain at a minimum the `anum` column for atomic number; `resid`, `resname`, `chain`, and `segid` columns will also be used if provided to distinguish residues from each other. See Appendix D for the specification of these columns and tables.

Viparr uses atomic numbers and bond structure (graph isomorphism) to match residues to templates. Thus if you have nonstandard atom or residue PDB names, you do not need to modify them, and you do not need to be concerned about the atom and residue names used in the force field. You can, however, modify atom and residue names for your own purposes, if you wish. In particular, Viparr identifies the N- and

C-terminus versions of the residues correctly, as well as protonated and deprotonated versions of a residue, even if you do not identify them as such.

4.2.2 Running Viparr

Once you have a complete structure in DMS format, use Viparr to add forcefield information. The command line for running Viparr is:

```
viparr input.dms output.dms [-d ffdir]* [-f ffname]*
```

Here, `ffdir` is path to a forcefield directory, and `ffname` is the the subdirectory of `$VIPARR_FFDIR` containing a forcefield directory. The available force fields are listed in Table 4.1.

Multiple forcefields can be provided; this allows one, for example, to use either tip3p or tip4p with the charmm27 forcefield by specifying `-f charmm27 -f tip3p` or `-f charmm27 -f tip4p`, respectively, as command line options. When multiple force fields match a given residue in the structure, the *first* forcefield takes precedence. All specified force fields must have consistent van der Waals combining rules; water models can be used with any force field. When a bond exists between two residues, both residues must be matched by exactly one of the specified force fields.

Force field name	Description
amber03	Amber
amber94	Amber
amber96	Amber
amber99	Amber
amber99SB	Amber
charmm27	CHARMM 27
charmm22nocmap	CHARMM 22 without CMAP terms
charmm31	CHARMM 31
oplsaa_impact_2001	OPLS-AA 2001
oplsaa_impact_2005	OPLS-AA 2005
spc	Water model
spce	Water model
tip3p	Water model
tip3p_charmm	Water model
tip4p	Water model
tip4pew	Water model
tip5p	Water model

Table 4.1: Force fields built into Viparr

4.2.3 Adding constraints

Like other force field terms, constraint terms must be specified explicitly; in this way, Desmond is unlike other molecular dynamics applications that infer the existence of constraints based on molecular topology and configuration options. You add constraints to a structure file using the `build_constraints` program provided with Desmond.

Note: Viparr does not update the constraint tables in a dms file, so if you use Viparr to update a structure file that included constraints, you'll need to add the constraints again.

`build_constraints` examines a structure file for atom groups of the following forms:

AHn An atom other than hydrogen, bonded to n hydrogen atoms.

HOH An oxygen atom bonded to two hydrogen atoms and no other atoms.

Desmond's implementation of constraints is described in Chapter 6.

The atom identities are determined from the atomic number of each atom, while the bonds are determined from the `bond` table. `build_constraints` then constructs a new `constraints` table (replacing any existing table by that name) and populates it with the detected constraint groups.

By default, the stretch and angle force terms corresponding to groups that are constrained by the constraint groups are also modified: the `constrained` column of `stretch_harm` and `angle_harm` records is set to 1. This is done because evaluating forces on constrained groups is wasted effort: the constrained lengths and angles are not allowed to change. However, the constrained bonds and angles cannot be completely removed from the structure file, because the `minimize` application does not currently evaluate constraint terms, but instead evaluates the forces in the constrained bond and angle terms.

The `mdsim` application, on the other hand, ignores the constrained bond and angle terms, and prints a message at startup indicating how many terms have been ignored.

4.2.4 Running the build_constraints program

To run `build_constraints`:

```
build_constraints [options] input.dms output.dms
```

The options are:

-k Leave constrained bonds and angle terms unmodified rather than setting their `constrained` column to 1.

-x C Don't build any constraints of type C.

Chapter 5

Calculating Force and Energy

This chapter provides a high-level overview of configuring force fields; then discusses the computations involved in, and how to configure, the various interactions. It also describes additional off-atom interaction sites.

5.1 Configuring force fields

Force fields are configured as shown in:

```
force = {
  bonded = {
    exclude = [ ... ] # optional
    include = [ ... ] # optional
  }
  virtual = {
    exclude = [ ... ] # optional
    include = [ ... ] # optional
  }
  constraint = {
    exclude = [ ... ] # optional
    include = [ ... ] # optional
    ...
  }
  nonbonded = { ... } # vdW and es
  term = { ... } # force plugins
  ignore_com_dofs = b_i
}
```

Molecular force fields approximate the total potential energy of a chemical system as a sum of the form:

$$U = U_{\text{bonded}} + U_{\text{vdW}} + U_{\text{es}} \tag{5.1}$$

These are the bonded, van der Waals, and electrostatic terms, respectively.

The bonded term arises from the covalent bond structure of the molecules. This term includes stretch terms involving two particles connected by a bond, angle terms involving three particles connected by two bonds, and dihedral (torsion) terms involving four particles connected by a chain of three bonds.

During startup, Desmond scans the records in the `bond_term` table and creates a corresponding bonded force term. The names of these terms are printed to the log by Desmond during startup. The `bonded.include` and `bonded.exclude` configurations allow you to override the set of bonded terms that will be created. These entries are lists, and are empty by default. A value of "*" in `bonded.exclude` will turn off all bonded force terms. Putting the name of a specific term in `bonded.exclude` will turn off just that term. Putting the name of the term in `bonded.include` will override `bonded.exclude` and ensure that the force term gets evaluated. Similarly for the `include` and `exclude` lists in `virtual` (records from the `virtual_term` table) and `Constraint` (records from the `constraint_term` table).

The van der Waals and electrostatic terms are known as nonbonded terms because they include all pairs of particles in the system that are not bonded. More precisely, they include all pair interactions that are not explicitly excluded by the force field. Many force fields also define a scaling for the 14 (that is, atoms separated by three bonds) van der Waals and electrostatic interactions, called *partial 14* interactions. This is a scaling to reduce the strength of these interactions since they are correlated with the bonded terms. In Desmond, these 14 interactions are implemented in the same way as bonded interactions and it is simplest to think of them in this way. (For example, their interactions are not subject to a distance cutoff, and they are treated as bonded terms in multiple timestepping integration.)

Equation 5.1 can now be refined:

$$U = U_{\text{bonded}} + \sum_{(i,j)\in N} U_{\text{vdW}} + \sum_{(i,j)\in N} q_i q_j \operatorname{erfc}(r_{ij}/\sqrt{2}\,\sigma)/r_{ij} \quad (5.2)$$

$$+ \sum_{(i,j)} q_i q_j \operatorname{erf}(r_{ij}/\sqrt{2}\,\sigma)/r_{ij} - \sum_{(i,j)\notin N} q_i q_j \operatorname{erf}(r_{ij}/\sqrt{2}\,\sigma)/r_{ij} \quad (5.3)$$

where N is the set of pairs that are non-excluded pairs. The term U_{bonded} includes the partial-14 interactions. The second term is the van der Waals term and the remaining three terms comprise the electrostatic term. The near nonbonded terms (2) and (3) for pairs in N are calculated together in the same cutoff-limited compute kernel in Desmond and is called the nonbonded near calculation. The far nonbonded term (4) is computed by means of the PME or k-GSE algorithms. Finally, the term (5) represents the far exclusion, which subtracts the far term contribution of excluded pairs.

Most molecular dynamics force fields have the property that the dynamics they produce has no net center of mass translation. Hence, the degrees of freedom of the system are effectively reduced by 3. The flag `ignore_com_dofs` causes 3 to be subtracted from any appropriate degree of freedom counters within Desmond (such counters are used by some integrators and by some output diagnostics). Changing this flag would, for example, alter reported simulation temperatures obtained by dividing kinetic energy by degrees of freedom. For large systems, its effects become negligible.

name	**description**
`bonded.exclude`	bonded terms to turn off. Optional—by default, empty [*List of names*]
`bonded.include`	bonded terms which must be turned on (overrides exclude). Optional—by default, empty [*List of names*]
`virtual.exclude`	virtual terms to turn off. Optional—by default, empty [*List of names*]
`virtual.include`	virtual terms which must be turned on (overrides exclude). Optional—by default, empty [*List of names*]
`constraint.exclude`	constraint terms to turn off. Optional—by default, empty [*List of names*]
`constraint.include`	constraint terms which must be turned on (overrides exclude). Optional—by default, empty [*List of names*]
`nonbonded`	configuration of the nonbonded forces. Can be set to `none` for no nonbonded forces. [*configuration*]
`term`	configuration of a set of special force terms provided typically by a general force plugin. [*configuration*]
`ignore_com_dofs`	A user assertion that, at least up to exact arithmetic, the dynamics do not have any net center of mass motion. [*Boolean*]

Table 5.1: Parameters for force

5.1.1 Force terms

This section is a specification of force term plugins similar in layout to the application specific `plugin` section.

```
force.term = {
  list = [ ... key ... ]
  key = {
    type = type
    ... # term specific configuration options
  }
}
```

Examples of such terms that we have seen so far are `BiasingForce`, described in Section 2.6.2 and `e_bias`, described in Section 2.6.3.

5.2 Bonded, pair, and excluded interactions

This section describes the built-in bonded term objects that can be used in a Desmond application, specified by records in the `bond_term` table of the DMS file.

name	**type**	**description**
r0	FLOAT	equilibrium separation (LENGTH)
fc	FLOAT	force constant (ENERGY / LENGTH^2)
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
constrained	INTEGER	if nonzero, constrained; default 0

Table 5.2: Schema for `stretch_harm`. Stretch terms that overlap with constraints should have the constrained field set to 1. Applications that evaluate constraint terms need not evaluate `stretch_harm` records that are marked as constrained.

Stretch terms

The vibrational motion between two atoms (i, j) is represented by a harmonic potential as:

$$V_s(r_{ij}) = f_c(r_{ij} - r_0)^2 \tag{5.4}$$

where f_c is the bond force constant in units of Energy/Length^2 and r_0 is the equilibrium bond distance. Terms in `stretch_harm` are evaluated using this potential.

These terms are in the `stretch` Hamiltonian category.

Angle terms

The angle vibration between three atoms (i, j, k) is evaluated as:

$$V_a(\theta_{ijk}) = f_c(\theta_{ijk} - \theta_0)^2 \tag{5.5}$$

where f_c is the angle force constant in Energy/Radians^2 and θ_0 is the equilibrium angle in radians. Beware, the explicit use of the θ_{ijk} angle will introduce discontinuities in the potential at $\theta_{ijk} = \pm\pi$. Terms in `angle_harm` are evaluated using this potential.

These terms are in the `angle` Hamiltonian category.

Proper dihedral terms

Desmond implements two functional forms for calculating proper and improper torsion potential terms. The first is:

$$V_t(\phi_{ijkl}) = f_{c0} + \sum_{n=1}^{6} f_{cn} \cos(n\phi_{ijkl} - \phi_0) \tag{5.6}$$

where $f_{c0} \ldots f_{c6}$ are dihedral angle force constants in units of Energy and ϕ_0 is the equilibrium dihedral angle in radians. The ϕ angle is formed by the planes $p0$–$p1$–$p2$ and $p1$–$p2$–$p3$. Terms in `dihedral_trig` are handled by this potential function.

These terms are in the `dihedral` Hamiltonian category.

name	**type**	**description**
theta0	FLOAT	equilibrium angle (DEGREES)
fc	FLOAT	force constant (ENERGY / DEGREE^2)
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
p2	INTEGER	3rd particle
constrained	INTEGER	constrained if nonzero; default 0

Table 5.3: Schema for `angle_harm`. The $p0$ particle forms the vertex. Angle terms that overlap with constraints should have the constrained field set to 1. Applications that evaluate constraint terms need not evaluate `angle_harm` records that are marked as constrained.

name	**type**	**description**
phi0	FLOAT	phase (DEGREES)
fc0	FLOAT	order-0 force constant (ENERGY)
fc1	FLOAT	order-1 force constant (ENERGY)
fc2	FLOAT	order-2 force constant (ENERGY)
fc3	FLOAT	order-3 force constant (ENERGY)
fc4	FLOAT	order-4 force constant (ENERGY)
fc5	FLOAT	order-5 force constant (ENERGY)
fc6	FLOAT	order-6 force constant (ENERGY)
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
p2	INTEGER	3rd particle
p3	INTEGER	4th particle

Table 5.4: Schema for the `dihedral_trig` table.

name	type	description
phi0	FLOAT	equilibrium separation (DEGREES)
fc	FLOAT	force constant (ENERGY / DEGREE$\hat{2}$)
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
p2	INTEGER	3rd particle
p3	INTEGER	4th particle

Table 5.5: Schema for the `improper_harm` table.

Improper dihedral terms

The second dihedral functional form is:

$$V_t(\phi_{ijkl}) = f_c(\phi_{ijkl} - \phi_0)^2 \tag{5.7}$$

where f_c is the dihedral angle force constant in units of Energy/radians^2 and ϕ_0 is the equilibrium dihedral angle in radians. The ϕ angle is formed by the planes $p0$–$p1$–$p2$ and $p1$–$p2$–$p3$. Terms in `improper_harm` are handled by this potential function.

The harmonic dihedral term given in Eq 5.7 can lead to accuracy issues if f_c is too small, or if initial conditions are poorly chosen due to a discontinuity in the definition of the first derivative with respect to i in ϕ_{ijkl} near $\phi_0 \pm \pi$.

These terms are in the `improper` Hamiltonian category.

CMAP torsion terms

CMAP is a torsion-torsion cross-term that uses a tabulated energy correction. It is found in more recent versions of the CHARMM forcefield. The potential function is given by:

$$V_c(\phi, \psi) = \sum_{n=1}^{4} \sum_{m=1}^{4} C_{nm} \left(\frac{\psi - \psi_L}{\Delta_\psi} \right)^{n-1} \left(\frac{\phi - \phi_L}{\Delta_\phi} \right)^{m-1} \tag{5.8}$$

where C_{nm} are bi-cubic interpolation coefficients derived from the supplied energy table, ϕ is the dihedral angle formed by particles $p0 \ldots p3$, and ψ is the dihedral angle formed by particles $p4 \ldots p7$. The grid spacings are also derived from the supplied energy table. Terms in `torsiontorsion_cmap` are handled by this potential function.

The `cmap` tables for each term can be found in `cmapN`, where `N` is a unique integer identifier for a particular table (multiple `cmap` terms in `torsiontorsion_cmap` can refer to a single `cmapN` block). The format of the `cmap` tables consists of two torsion angles in degrees and an associated energy. `cmap` tables must begin with both torsion angles equal to -180.0 and increase fastest in the second torsion angle. The grid spacing must be uniform within each torsion coordinate, but can be different from the grid spacing in other torsion coordinates. More information can be found in [1].

These terms are in the `cmap` Hamiltonian category.

name	**type**	**description**
phi	FLOAT	phi coordinate (DEGREES)
psi	FLOAT	psi coordinate (DEGREES)
energy	FLOAT	energy value (ENERGY)

Table 5.6: Schema for the each of tables holding the 2D `cmap` grids. The CHARMM27 forcefield uses six `cmap` tables, which have names `cmap1`, `cmap2`, . . . , `cmap6` in DMS.

name	**type**	**description**
cmap	INTEGER	name of cmap table
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
p2	INTEGER	3rd particle
p3	INTEGER	4th particle
p4	INTEGER	5th particle
p5	INTEGER	6th particle
p6	INTEGER	7th particle
p7	INTEGER	8th particle

Table 5.7: Schema for the `torsiontorsion_cmap` table.

name	type	description
fcx	FLOAT	X force constant in ENERGY/LENGTH^2
fcy	FLOAT	Y force constant in ENERGY/LENGTH^2
fcz	FLOAT	Z force constant in ENERGY/LENGTH^2
p0	INTEGER	restrained particle
x0	FLOAT	x reference coordinate
y0	FLOAT	y reference coordinate
z0	FLOAT	z reference coordinate

Table 5.8: Schema for the `posre_harm` table.

name	type	description
p0	INTEGER	1st particle
p1	INTEGER	2nd particle

Table 5.9: Schema for the `exclusion` table.

Position restraint terms

Particles can be restrained to a given global coordinate by means of the restraining potential:

$$V_r(x, y, z) = \frac{1}{2}(f_{cx}(x - x_0)^2 + f_{cy}(y - y_0)^2 + f_{cz}(z - z_0)^2) \tag{5.9}$$

where f_{cx}, f_{cy}, f_{cz} are the force constants in Energy/Length^2 and x_0, y_0, z_0 are the desired global cell coordinates (units of Length). Terms in `posre_harm` are evaluated using this potential.

These terms are in the `posre` Hamiltonian category.

Exclusions

Exclusion terms in `exclusion` are used to prevent calculation of certain non bonded interactions at short ranges. The excluded interactions are typically those that involve particles separated by one or two bonds, as these interactions are assumed to be adequately modeled by the stretch and angle terms described above.

Desmond requires that $p0 < p1$ for each term, and every $p0$, $p1$ pair should be unique.

Exclusions are in the `far_exclusion` Hamiltonian category.

Pair 12–6 terms

Pair terms in `pair_12_6_es` allow for modifying the normally calculated nonbonded interactions either by scaling the interaction energy, or by specifying new coefficients

name	**type**	**description**
aij	FLOAT	scaled LJ12 coeff in ENERGY LENGTH^{12}
bij	FLOAT	scaled LJ6 coeff in ENERGY LENGTH^{6}
qij	FLOAT	scaled product of charges in CHARGE^{2}
p0	INTEGER	1st particle
p1	INTEGER	2nd particle

Table 5.10: Schema for the `pair_12_6_es` table.

to use for a particular pair. This partial or modified energy is calculated in addition to the normally calculated interaction energy.

The functional form of the pair potential is:

$$V_p(r_{ij}) = \frac{a_{ij}}{r_{ij}^{12}} + \frac{b_{ij}}{r_{ij}^{6}} + \frac{q_{ij}}{r_{ij}} \tag{5.10}$$

The a_{ij}, b_{ij}, and q_{ij} coefficients are specified in the `pair_12_6_es` table.

Pair terms contribute the van der Waals interaction to the `pair_vdw` Hamiltonian category and the electrostatic interaction to `pair_elec`.

Flat-bottomed harmonic well

Desmond supports a variant of the usual harmonic stretch, angle, improper, and position restraint terms in which a region of the potential near the equilibrium position is flat. In addition, the flat-bottomed harmonic stretch term supports specification of an interaction between groups of particles, where the force acting on the particles is based on the distance between the geometric centers of the particles in the respective groups. A given particle can participate in multiple groups. The flat-bottomed harmonic stretch term also differs from the other potentials in that it transitions from a harmonic to a linear potential at large separation. All flat-bottomed potentials transition to the harmonic region with a continuous first derivative; i.e., forces are everywhere continuous.

The Hamiltonian categories of the flat-bottomed terms are, correspondingly, `stretch_fbhw`, `angle_fbhw`, `improper_fbhw`, and `posre_fbhw`.

5.3 Van der Waals and electrostatic interactions

The nonbonded forces are configured as shown in:

```
force.nonbonded = {
  n_zone = $n_z$
  sigma = $\sigma$
  r_cut = $R_{\text{cut}}$
  near = {
```

name	**type**	**description**
lower	FLOAT	lower bound for flat-bottomed region in LENGTH
upper	FLOAT	upper bound for flat-bottomed region in LENGTH
sigma	FLOAT	width of harmonic region in LENGTH for $r >$ *upper*
beta	FLOAT	slope of linear region in ENERGY/LENGTH
fc	FLOAT	overall proportionality constant in ENERGY/LENGTH^2
group1	INTEGER	tag for first group with specified parameters
group2	INTEGER	tag for second group with specified parameters

Table 5.11: Schema for the `stretch_fbhw` table.

name	**type**	**description**
p0	INTEGER	particle id
group	INTEGER	group for given particle

Table 5.12: Schema for the `stretch_fbhw_term` table.

name	**type**	**description**
fc	FLOAT	force constant in ENERGY/RADIANS^2
theta0	FLOAT	equilibrium angle in DEGREES
sigma	FLOAT	half-width of flat-bottomed region in DEGREES
p0	INTEGER	first particle
p1	INTEGER	second particle
p2	INTEGER	third particle

Table 5.13: Schema for the `angle_fbhw` table.

name	**type**	**description**
fc	FLOAT	force constant in ENERGY/RADIANS^2
phi0	FLOAT	equilibrium improper dihedral angle in DEGREES
sigma	FLOAT	half-width of flat-bottomed region in DEGREES
p0	INTEGER	first particle
p1	INTEGER	second particle
p2	INTEGER	third particle
p3	INTEGER	fourth particle

Table 5.14: Schema for the `improper_fbhw` table.

name	type	description
fc	FLOAT	force constant in ENERGY/LENGTH^2
x0	FLOAT	equilibrium x coordinate in LENGTH
y0	FLOAT	equilibrium y coordinate in LENGTH
z0	FLOAT	equilibrium z coordinate in LENGTH
sigma	FLOAT	radius of flat-bottomed region in LENGTH
p0	INTEGER	restrained particle

Table 5.15: Schema for the `posre_fbhw` table.

```
    type = near-type
    ...
  }
  far = {
    type = far-type
    ...
  }
}
```

Van der Waals interactions decay rapidly with distance, whereas electrostatic interactions are split into a rapidly decaying part (near) and a slowly decaying part (far). Near nonbonded interactions are computed by summing them over all pairs (except the excluded ones) within a distance R_{cut} of each other. Far electrostatic interactions are computed by an Ewald summation technique specified in the far configuration (see Section 5.4) and a sum over certain designated electrostatic correction terms.

The electrostatic potential is decomposed as:

$$\frac{q_i q_j}{r_{ij}} = q_i q_j \text{erfc}(r_{ij}/\sqrt{2}\sigma)/r_{ij} + q_i q_j \text{erf}(r_{ij}/\sqrt{2}\sigma)/r_{ij} \tag{5.11}$$

where q_i and q_j are the charges of particles i and j, and erf(r) and erfc(r) are the error function and the complementary error function, respectively. The term involving erfc falls off quickly with distance; it is usually computed by an interpolating function, truncated to 0 for $r_{ij} > R_{\text{cut}}$. The erf term is essentially the far interaction. The value of σ is typically chosen such that erfc$(r/\sqrt{2}\,\sigma)$ is small at the cutoff radius R_{cut} (a common choice is $\sigma = R_{\text{cut}}/(3\sqrt{2}$ which assumes erfc$(3) = 2.209 \times 10^{-5}$ is sufficiently small).

Note: Setting $\sigma = \infty$ makes erfc $= 1$ and erf $= 0$, so that the electrostatic potential is computed entirely as a cutoff pairwise interaction; users operating in this regime should consider setting `nonbonded.far` to `none`.

Because the nonbonded forces are partitioned into near (van der Waals and electrostatic) and far (electrostatic) components, they share a number of arguments in common, such as the splitting parameter, σ and the near cutoff radius R_{cut}.

name	description
`r_cut`	Distance at which near interactions vanish. [*Length* > 0]
`n_zone`	Number of polynomial regions for potential interpolation functions. [*Integer* > 0]
`sigma`	Electrostatic splitting parameter. [*Length* > 0]
`near`	Configuration for the near nonbonded. Can be set to `none`. [*configuration*]
`far`	Configuration for the far nonbonded. Can be set to `none`. [*configuration*]

Table 5.16: Parameters for nonbonded

5.3.1 Near interactions

```
force.nonbonded.near = {
  type = default|table|force-only
  taper = none|shift|c1switch|c2switch
  r_tap = R_tap
  average_dispersion = ν # optional
}
```

`nonbonded.near.type` specifies the method used to compute nonbonded near interactions. Some of these methods are built-in and some are provided by extensions. The built-in ones:

default van der Waals using a tuned Lennard-Jones computational pipeline and an interpolating function for electrostatics.

table an alternate implementation providing greater flexibility at the expense of performance by using interpolating functions for both.

force-only similar to the default, but without energy evaluations. Provides increased performance.

Where energies do not need to be calculated you can achieve significantly greater performance by using the `force-only` form of the nonbonded interaction. This form of the nonbonded interaction cannot be used where energies need to be evaluated as with the `energy_groups` plugin.

`table` is an alternative to default which employs an interpolation scheme for both van der Waals and electrostatic computations. This allows a tapering method to be applied to all near nonbonded interactions. This is computationally slower.

The Lennard-Jones 12–6 potential between two particles is:

$$V_{LJ}(r_{ij}) = \frac{a_{ij}}{r_{ij}^{12}} + \frac{b_{ij}}{r_{ij}^{6}} \tag{5.12}$$

where $r_{ij} = \|r_i - r_j\|$ is the distance between two particles i and j. Coefficients a_{ij} and b_{ij} depend on the types of the particles i and j. Desmond reads per-particle van der Waals properties, a_i and b_i for particle i, and constructs a_{ij} and b_{ij} by a function of the per-particle coefficients called a *combining rule* (specified in the structure file).

Each near nonbonded potential function (electrostatic or van der Waals), $\phi(r)$, is truncated by a cutoff to $\phi = 0$ for $r > R_{\text{cut}}$. If R_{cut} is selected too aggressively $R_{\text{cut}} < 9$, then discontinuities in ϕ at $r = R_{\text{cut}}$ can have detrimental effects on the simulation.

For those potential functions that are computed by a piecewise polynomial interpolation function (for the `default` near term this is only the electrostatic potential), you can alleviate this detrimental effect somewhat by choosing a tapering strategy, where the potential ϕ, being approximated by $\tilde{\phi}$, is first replaced with a function ϕ_T and $\tilde{\phi}$ constructed to approximate ϕ_T, instead. Three strategies are available for constructing ϕ_T: shift,

$$\phi_T(r) = \phi(r) - \phi(R_{\text{cut}}) \tag{5.13}$$

which vertically shifts the function so that $\phi_T(r) = 0$ for $r = R_{\text{cut}}$, `c1switch` and `c2switch`,

$$\phi_T(r) = (1-x)^2(1+2x)\phi(r) \tag{5.14}$$

$$\phi_T(r) = (1-x)^3(1+3x+6x^2)\phi(r) \tag{5.15}$$

respectively, for $R_{\text{tap}} \le r < R_{\text{cut}}$ where $x = (r - R_{\text{tap}})/(R_{\text{cut}} - R_{\text{tap}})$, and $\phi_T(r) = \phi(r)$ for $r < R_{\text{tap}}$.

In practice, tapering is not usually necessary for typical cutoff values ($R_{\text{cut}} = 10$Å is typical).

Piecewise polynomial interpolation is used as an approximation for some potentials in the near term (which ones dependent on the kind of near term chosen). The interpolation is actually a piecewise cubic spline interpolation $\tilde{\phi}$ of ϕ constructed as function of r^2, interpolating through points of the form $r^2 = R_{\text{cut}}^2 m/n_z$, where $0 \le m \le n_z$. As such, the accuracy of the approximation is controlled through n_z (set by the parameter `n_zone`). Although a simple error bound is difficult to express for general ϕ, for power-law potentials, $\phi \propto r^{-C}$ for some C, the relative error of approximation is roughly given by

$$\left|\frac{\tilde{\phi}(r) - \phi(r)}{\phi(r)}\right| \sim \frac{C(C+2)(C+4)(C+6)}{4^4 4!}\left(\frac{R_{\text{cut}}^2}{n_z r^2}\right)^4.$$

The relative error of $\tilde{\phi}$ decreases with the fourth power of n_z and increases with the fourth power of C (using interpolation to compute van der Waals potentials, hence, would require a much greater n_z). Meanwhile, increasing n_z increases the size of the table of spline coefficients (as well as the size of the linear system numerically solved to set those coefficients).

The near nonbonded force calculation skips over excluded pairs, if any. Additionally, for all excluded pairs (i, j), a far exclusion calculation subtracts the contribution from the potential term $q_i q_j \text{erf}(r_{ij}/\sqrt{2}\,\sigma)/r_{ij}$, and its associated force from the energy and the forces. Like the near nonbonded terms, this function is evaluated by a cutoff interpolation

name	**type**	**description**
sigma	FLOAT	VdW radius in LENGTH
epsilon	FLOAT	VdW energy in ENERGY

Table 5.18: Schema for the **vdw_12_6** nonbonded type, with the functional form $V = a_{ij}/|r|^{12} + b_{ij}/|r|^6$, where a_{ij} and b_{ij} are computed by applying either the combining rule from `nonbonded_info` or the value from `nonbonded_combined_param` to obtain σ and ϵ, then computing $a_{ij} = 4\epsilon\sigma^{12}$ and $b_{ij} = -4\epsilon\sigma^6$.

function. Because the calculation is cut off for large r, in practice the distance between excluded pairs of particles is always within a sensible R_{cut}.

name	**description**
`taper`	Tapering strategy to use. [*none/shift/c1switch/ c2switch*]
`r_tap`	Distance at which to begin the tapering strategy. [*Length* $\leq r_{\text{cut}}$]
`average_dispersion`	Correction factor for long-range van der Waals interactions. Optional—by default, calculated. [Length$^6 > 0$]

Table 5.17: Parameters for near

For both `default` and `table`, the van der Waals contributions are in the `nonbonded_vdw` Hamiltonian category, while the near electrostatic contributions are in `nonbonded_elec`. (`force-only` contributes to no category, and this is debatably a bug.)

5.3.2 Nonbonded tail corrections

The truncation of van der Waals forces to a cutoff neglects the energy of the r^{-6} term over the volume beyond $r > R_{\text{cut}}$. This term decays as R_{cut}, and thus can be significant enough to warrant a tail correction term to the total energy of the system (as well as an associated correction to the pressure). The tail correction represents an averaged r^{-6} interaction between particles outside of R_{cut} from each other. The term depends on the number of particles in the system, the average dispersion, and the current system volume, the precise form depending on the means by which the term has been tapered.

none

$$U_{\text{tail}} = -\frac{2\pi}{3}\nu\frac{N^2}{V}\frac{1}{R_{\text{cut}}^3} \tag{5.16}$$

shift

$$U_{\text{tail}} = -\frac{4\pi}{3}\nu\frac{N^2}{V}\frac{1}{R_{\text{cut}}^3} \tag{5.17}$$

c1switch or c2switch

$$U_{\text{tail}} = -\frac{2\pi}{3}\nu\frac{N^2}{V}\frac{1}{R_{\text{tap}}^3}\left(1 - 3\int_0^1 \frac{\alpha t(x)}{(1+\alpha x)^4}dx\right) \tag{5.18}$$

where $\alpha = R_{\text{tap}}/R_{\text{cut}} - R_{\text{tap}}$ and $t(x) = (1-x)^2(1+2x)$ or $t(x) = (1-x)^3(1+3x+6x^2)$ correspond to `c1switch` or `c2switch` respectively.

The average dispersion, ν, is used to calculate energy and virial corrections due to cutoff in the van der Waals interactions whenever such interactions are present in the force field and used by the selected nonbonded type. If omitted, Desmond calculates ν based on the van der Waals terms and the atom types in the system.

5.4 Nonbonded far interactions

The nonbonded far electrostatic forces are configured as shown in:

```
force.nonbonded.far = {
  type = gse|pme
  n_k = [ kx ky kz ]
  transform = c2c|r2c|r2c_2round|auto # optional
  keep_nyquist = bn # optional
  ... # gse or pme specific options
}
```

The far interactions are computed by using an Ewald mesh calculation. The built-in methods support both smooth particle mesh Ewald (PME) and k-space Gaussian split Ewald (k-GSE) according to the `type` parameter. In these methods, particle charges are spread onto a three-dimensional Cartesian mesh and a Poisson equation is solved on this mesh. The resulting potentials are used to compute the forces and energy of each particle. The Poisson equation is solved efficiently using fast Fourier transforms.

The splitting parameter, σ, first referenced in Section 5.3, determines the far electrostatic potential:

$$V_{\text{far}} = \frac{q_i q_j}{r_{ij}}\text{erf}(r_{ij}/(\sqrt{2}\,\sigma)) \tag{5.19}$$

Both methods compute the sum of far interactions for all pairs of particles, including those pairs that are excluded. Thus it is necessary to subtract the portion of the energy and forces due to the exclusions with a far exclusion computation.

The Ewald mesh dimensions are specified as the number of subdivisions k_i along the axes of the global cell. The spacing of mesh points along the $\vec{a}$ axis, for example, is $\|\vec{a}\|/k_1$. A mesh spacing between 0.6 Åand 1.5 Åusually gives a good balance between accuracy and efficiency. The subdivisions are required to be integers of the form $k_i = 2^a 3^b 5^c 7^d$ (for nonnegative integers a, b, c, and d) that are also multiples of the global cell partition along the corresponding axes (see Chapter 3); the smallest such integer that provides a suitable mesh spacing is recommended.

The Fourier c2c and r2c differ in their efficiency depending on the underlying networking hardware. Since the type of the network is not available to Desmond, the user is responsible for picking the correct value of transform. For low-latency networks such as available with InfiniBand, we have found that setting `transform=c2c` gives the best performance at high levels of parallelism, with `transform=r2c` performing better at low levels of parallelism and `transform=r2c-2round` at very low levels. For high-latency networking hardware such as Gigabit Ethernet, setting `transform=r2c` has been found to give good performance in most cases. The default setting of `transform=auto` uses a heuristic method to set the value according to the above advice, but the user is still responsible for ensuring that this selection is optimal for his situation. Almost never should it be required to set `keep_nyquist=true`, since the amplitude of the farfield electrostatics should be small at the Nyquist frequency and if it is not signals a problem with the configuration of the simulation.

Additional parameters particular to the method type are also specified in this configuration section, as described below.

name	**description**
`type`	Type of Ewald summation method to use. [*gse/pme*]
`n_k`	Number of fourier mesh points along each global cell axis. [*List of Integers* > 0]
`transform`	`c2c`: complex-to-complex transform, `r2c/r2c-2round` variants of real-to-complex transform. Optional—by default `auto`. [*c2c/r2c/r2c_2round/auto*]
`keep_nyquist`	If true keep Nyquist value in transform, default is false. [*Boolean*]

Table 5.19: Parameters for far

Both PME and GSE nonbonded far computations are in the `far_terms` Hamiltonian category.

Particle mesh Ewald

Particle-mesh Ewald computations are configured as shown in:

```
force.nonbonded.far = {
  type = pme
  ... # common options
  order = [ o_x o_y o_z ]
}
```

For PME, point charges are spread to the mesh by convolving them with cardinal B-spline functions (scaled to the mesh dimensions) in real space and then sampled on the mesh. The Fourier transform then implements a spectral convolution with a kernel. Finally, forces and energies are accumulated using another B-spline convolution in real space. The spectral convolution kernel is that of a Gaussian charge density of width deconvolved twice by the B-spline functions.

It is necessary to choose an order for the B-splines i, for each dimension. Orders of 4–7 are supported. As a balance between accuracy and efficiency, order 5 (quartic interpolation) is recommended for most applications.

name	**description**
`order`	Order of interpolation along each axis. [*List of Integers:* $4 \leq$ integer ≤ 7]

Table 5.20: Parameters for pme

For more information, see [4].

Gaussian split Ewald

Gaussian split Ewald computations are configured as shown in:

```
force.nonbonded.far = {
  type = gse
  ... # common options
  sigma_s = σ_s
  r_spread = R_spread
}
```

k-GSE spreads the point charges by a real-space convolution with a Gaussian of width σ_s, sampling the result on the mesh. The mesh charges are spectrally convolved with a kernel by means of the Fourier transform. The forces and energies are then accumulated using another real-space convolution by a Gaussian of width s. The spectral convolution kernel is a Gaussian of width $k = -2\sigma_s$, which is a Gaussian of width deconvolved twice by a Gaussian of width s. Because the charge-spreading and force and energy-accumulation steps are done in real space with a localized (but not compactly supported) function, a cutoff, R_{spread}, is used to truncate the Gaussian to zero. Experiments have shown that spreading the charge onto more than 250 mesh points does not significantly improve accuracy.

Thus R_{spread} is typically selected to contain a sphere of approximately 250 mesh points; for example:

$$R_{\text{spread}} = h \left(\frac{250}{4\pi/3} \right)^{\frac{1}{3}} \tag{5.20}$$

where h is the smallest mesh spacing along any axis. The value of σ_s is then chosen such that $\operatorname{erfc}(r/\sqrt{2}\,\sigma_s)$ is small at the radius R_{spread}.

name	description
`sigma_s`	Bandwidth parameter for Gaussian charge density interpolation. [0 < Length < $\sigma/\sqrt{2}$]
`r_spread`	Cutoff parameter for Gaussian charge density interpolation. [$Length > 0$]

Table 5.21: Parameters for gse

For more information, see [11].

Note: Normally, the GSE is not used in Desmond simulations.

5.4.1 Electrostatic self-energy correction

The Gaussian spreading of point charges creates non-physical self interaction energies, where a point charge interacts with itself. To remove these contributions a self-energy correction is added to the potential.

$$U_{\text{self}} = -\left(\frac{1}{\sqrt{2\pi}}\frac{q_2}{\sigma} + \pi\frac{q_1^2}{\sigma^{-2}V}\right) \tag{5.21}$$

where $q_2 = \sum_i q_i^2$ and $q_1 = \sum_i q_i$ with the sums taken over all the particles in the system. The first term is simply the interaction of a Gaussian cloud with itself. The second term, which is only relevant for systems that are not charge-neutral, is an additional interaction between a Gaussian cloud and a uniform background charge of density $\rho = q_1/V$. This background charge, in non-neutral simulations, is required to cancel the non-zero contributions from the system charges, which would otherwise cause the Ewald sum to blow up.

5.4.2 Virtual sites

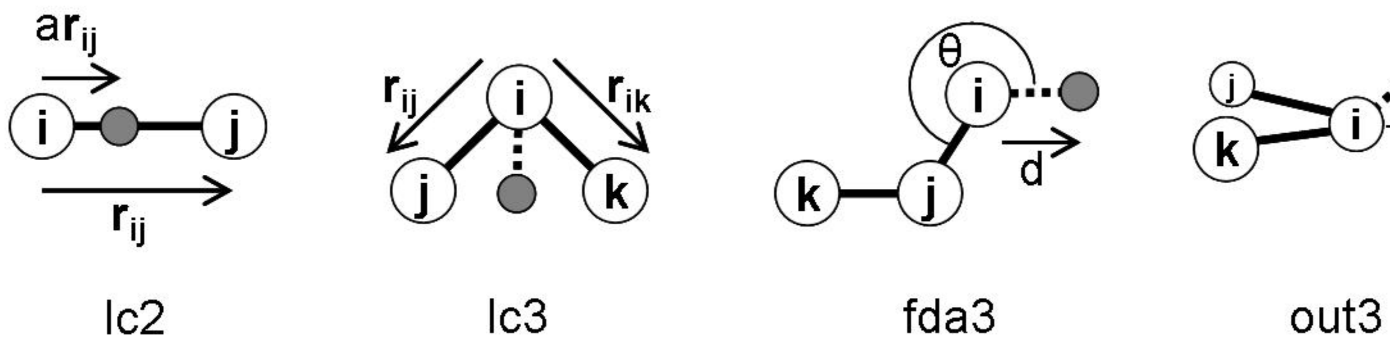
Virtual sites, a form of pseudoparticle, are additional off-atom interaction sites that can be added to a molecular system. These sites can have charge or van der Waals parameters associated with them; they are usually massless. The TIP4P and TIP5P water models are examples that contain one and two off-atom (virtual) sites, respectively. Because these sites are massless, it is necessary to redistribute any forces acting on them to the particles used in their construction. (A consistent way to do this can be found in [6].) The virial in most cases must also be modified after redistributing the virtual site force.

The types of virtual site placement routines are described below.

lc2 virtual site

The lc2 virtual site is placed some fraction a along the vector between two particles (i, j).

$$\vec{r}_v = (1 - c_1)\vec{r}_i + c_1\vec{r}_j \tag{5.22}$$



name	type	description
c1	FLOAT	coefficient 1
p0	INTEGER	pseudoparticle id
p1	INTEGER	parent atom i
p2	INTEGER	parent atom j

Table 5.22: Schema for `virtual_lc2` records, in which pseudoparticle $p0$ is placed at the fractional position $c1$ along the interpolated line between $p1$ and $p2$.

name	type	description
c1	FLOAT	coefficient 1
c2	FLOAT	coefficient 2
p0	INTEGER	pseudoparticle id
p1	INTEGER	parent atom i
p2	INTEGER	parent atom j
p3	INTEGER	parent atom k

Table 5.23: virtual_lc3

lc3 virtual site

The lc3 virtual site is placed some fraction a and b along the vectors between particles (i, j) and (i, k) respectively. The virtual particle lies in the plane formed by (i, j, k).

$$\vec{r}_v = (1 - c_1 - c_2)\vec{r}_i + c_1\vec{r}_j + c_2\vec{r}_k \tag{5.23}$$

fdat3 virtual site

The fdat3 virtual site is placed at a fixed distance d from particle i, at a fixed angle θ defined by particles (v, i, j) and at a fixed torsion ϕ defined by particles (v, i, j, k).

$$\vec{r}_v = \vec{r}_i + a\vec{r}_1 + b\vec{r}_2 + c\vec{r}_2 \times \vec{r}_1 \tag{5.24}$$

where $\vec{r}_1$ and $\vec{r}_2$ are unit vectors defined by

$$\vec{r}_1 \propto \vec{r}_j - \vec{r}_i \tag{5.25}$$

$$\vec{r}_2 \propto \vec{r}_k - \vec{r}_j - (\vec{r}_k - \vec{r}_j) \cdot \vec{r}_1\vec{r}_1 \tag{5.26}$$

The coefficients a, b and c above are defined as $a = d\cos(\theta)$, $b = d\sin(\theta)\cos(\phi)$ and $c = d\sin(\theta)\sin(\phi)$.

out3 virtual site

The out3 virtual site can be placed out of the plane of three particles (i, j, k).

$$\vec{r}_v = \vec{r}_i + c_1(\vec{r}_j - \vec{r}_i) + c_2(\vec{r}_k - \vec{r}_i) + c_3(\vec{r}_j - \vec{r}_i) \times (\vec{r}_k - \vec{r}_i) \tag{5.27}$$

name	**type**	**description**
c1	FLOAT	d coefficient
c2	FLOAT	θ coefficient
c3	FLOAT	ϕ coefficient
p0	INTEGER	pseudoparticle id
p1	INTEGER	parent atom i
p2	INTEGER	parent atom j
p3	INTEGER	parent atom k

Table 5.24: virtual_fdat3

name	**type**	**description**
c1	FLOAT	coefficient 1
c2	FLOAT	coefficient 2
c3	FLOAT	coefficient 3
p0	INTEGER	pseudoparticle id
p1	INTEGER	parent atom i
p2	INTEGER	parent atom j
p3	INTEGER	parent atom k

Table 5.25: virtual_out3

Chapter 6

Constraints

This chapter describes the constraints available to eliminate the fastest vibrational motions and how to configure them.

By applying constraints that eliminate the fastest vibrational motions, simulations can be run using longer timesteps—typically 2 or 2.5 fs instead of 1 fs. Constraints are configured as shown in:

```
force.constraint = {
  tol = δ
  maxit = m
  use_reshake = b_r
  use_Reich = b_R

  exclude = [ ... ] # optional
  include = [ ... ] # optional
}
```

Constraints fix the distances between pairs of particles according to a topology of rigid rods:

$$||r_i - r_j|| = d_{ij} \tag{6.1}$$
$$||r_k - r_l|| = d_{kl} \tag{6.2}$$
$$\ldots \tag{6.3}$$

The topologies that can be constrained are:

AHn n particles connected to a single particle, with $1 \leq n \leq 8$.

HOH three mutually connected particles.

The schemas in the DMS file for `AHn` and `HOH` constraints are shown in Tables 6.1 and 6.2, respectively.

A constrained particle is no longer free; each such particle has $3 - m/2$ degrees of freedom, where m is the number of independent constraints involved; for example, a

name	**type**	**description**
r1	FLOAT	A-H1 distance
r2	FLOAT	A-H2 distance
...		
rN	FLOAT	A-HN distance
p0	INTEGER	id of parent atom
p1	INTEGER	id of H1
p2	INTEGER	id of H2
...		
pN	INTEGER	id of HN

Table 6.1: Schema for `constraint_ah1`, `constraint_ah2`, etc. records corresponding to `AHn`-type constraints on the lengths of the bonds between a single parent atom and `n` child atoms.

name	**type**	**description**
theta	FLOAT	H-O-H angle in DEGREES
r1	FLOAT	O-H1 distance
r2	FLOAT	O-H2 distance
p0	INTEGER	id of heavy atom (oxygen)
p1	INTEGER	id of H1
p2	INTEGER	id of H2

Table 6.2: Schema for `constraint_hoh` records, corresponding to rigid water.

pair of particles having only one distance constraint between them has five degrees of freedom. Constraints thus affect the calculation of the instantaneous temperature and pressure, which depend on the number of degrees of freedom. Constraints are implemented in Desmond by the M-SHAKE algorithm, iteratively obtaining corrections to particle positions (as well as secondary corrections to momenta). The implementation is controlled by two parameters, a relative tolerance, δ, and a maximum iteration count, m. Iteration ceases if each particle-pair distance is within a factor of $1 + \delta$ of its constrained distance. A value of $\delta = 10^{-8}$ is suitable for most simulations. The convergence rate is high enough that usually fewer than five steps are needed. In the event that the constraint iteration fails, Desmond prints a warning to the simulation log.

Regardless of the precision (single or double) used for the atomic coordinates, the M-SHAKE implementation performs its calculations in double precision. If the atomic coordinates are in single precision, some error is inevitably introduced when these M-SHAKE results are converted to atomic coordinates, which could, in principle be recovered at the next M-SHAKE update. This cumulative error is recovered by employing a novel algorithm we call *reshake*, at the cost of additional arithmetic.

An alternative constraint algorithm for water constraints, since the constrained molecule is a rigid body. An algorithm due to Reich [10] derives a fixed rigid motion approximation to the constrained motion, generally needing fewer arithmetic operations to preserve constraints to full precision.

name	**description**
`exclude`	constraint terms to turn off. Optional—by default, empty [*List of names*]
`include`	constraint terms which must be turned on (overrides exclude). Optional—by default, empty [*List of names*]
`tol`	Relative tolerance for the constraint algorithm. [Real > 0]
`maxit`	Maximum number of iterations to use in the constraint algorithm. [Integer > 0]
`use_Reich`	employ Reich's rigid motion constraint algorithm. Optional–by default true. [*Boolean*]
`use_reshake`	Compensate for double to single precision rounding effects. Optional—by default true. [*Boolean*]

Table 6.3: Parameters for constraint

6.1 Single precision resolution and constraints

The degree to which a set of distance constraints can possibly be satisfied is a function of the resolution of the representation of particle positions. When the atomic coordinates are represented by single precision numbers, there is some possibility that numerical errors, coming from constraints with poor position resolution, can accumulate during the course of the simulation.

step/size	10 Å	20 Å	30 Å	40 Å	60 Å	80 Å
2.0 fs	-0.08(0.44)	0.01(0.19)	0.03(0.13)	-0.04(0.10)	-0.04(0.11)	0.02(0.07)
1.0 fs	-0.25(0.47)	0.01(0.27)	-0.09(0.17)	-0.07(0.14)	-0.46(0.14)	-1.22(0.07)
0.5 fs	-0.10(0.55)	-0.57(0.28)	-1.97(0.26)	-4.58(0.62)	-14.21(0.48)	-31.06(0.62)
0.25 fs	-1.7(2.3)	-14.3(2.3)	-42.0(3.2)	-80.6(1.3)	-166.6(2.1)	-238.6(3.0)

Table 6.4: Influence of finite precision resolution and timestep on energy drift

Particle positions are represented in a local coordinate system whose origin depends on the owning process. The dimensions of that local cell are proportional to the distances, along Cartesian axes, between representable positions in real space, and thus inversely proportional to resolution. Thus, when the dimensions of the local cell increase, by running on larger systems or with fewer processors, the resolution decreases.

Time resolution is also relevant. Clearly, the more time steps used for a given simulated time, the more space resolution errors accumulate, but empirically, the relationship is not as linear as this rationale suggests (see below). In terms of an overall energy drift, more constraint errors manifest as a negative (downward) drift in conserved energy. In fact, should one see a substantial negative energy drift, one should suspect constraint accuracy.

In order to guide users away from such problems, we have made a table of the energy drifts (in Kelvin/ns) which result from the simulation of a cubic cell of water at standard density for various local cell sizes and (inner) timesteps. For each size and step, ten NVE simulations were run with random initial velocities (drawn from a Maxwell-Boltzmann distribution at 300 K). All force interactions were shut off and the constraint convergence tolerances were set very stringently (twelve M-SHAKE iterations always), and thus the simulation is purely that of free motion of rigid water molecules, the only possible source of energy being the resolution errors from the constraint calculations. The simulations were run for 25 ps of simulated time. With the first 5 ps discarded, the total (kinetic) energy profile of each simulation was fit to a line and the drift reported is the mean slope of the ten simulations (standard deviation in parentheses). For larger time steps and smaller box sizes, the simulation energy profiles resembled unbiased random walks and fit poorly to lines, as indicated by standard deviations which are larger than their means in these regimes.

Although real simulations will include interactions and other molecules, we believe that for simulations where water is the solvent, running at typical temperatures, Table 6.4 captures the ballpark drift contribution one can expect to see from constraint resolution issues.

Chapter 7

Dynamics

This chapter summarizes the basic concepts of particle dynamics and describes how to configure the migration interval, timestep scheduling, pressure, and temperature. It also describes each of the available dynamical systems, and how to configure them.

7.1 Particles and mechanics

Molecular systems are collections of particles evolved by some variant of the dynamics of Newtonian mechanics. Newtonian mechanics can be summarized by a few conserved quantities (usually a scalar with units of energy and a probability density). Certain variations to the equations of motion can be used to control certain macroscopic parameters of the system; for example, the volume of cell or the temperature of the particles. This section reviews basic mechanical and statistical concepts of particle motion; later sections describe these different kinds of dynamics.

7.1.1 Particles

The basic data describing each particle are its position and momentum vectors, r and p, and a set of (usually) fixed particle properties ranging from the parameters of certain particle interactions (charge, mass, van der Waals radius) to discrete parameters indicating membership in some group or another (for example, this particle is part of a ligand and this particle is not).

Given a set of particles, the kinetic energy is:

$$K(\mathbf{p}) = \sum_{i=1}^{N} \|\vec{p}_i\|^2/(2m_i) \tag{7.1}$$

where m_i is the mass of the particle i. A force field refers to a potential energy function $U(\mathbf{r}) = U(\vec{r}_1, \ldots, \vec{r}_N)$, which makes the total energy, E, of the particles:

$$E(\mathbf{r},\mathbf{p}) = \sum_{i=1}^{N} \|\vec{p}_i\|^2/(2m_i) + U(\mathbf{r}) \tag{7.2}$$

A basic problem of molecular dynamics is the time-integration of the Newton equations of motion,

$$\dot{\vec{r}}_i = \vec{p}_i/m_i \tag{7.3}$$

$$\dot{\vec{p}}_i = -\nabla_{\vec{r}_i}U(\mathbf{r}) = F_i(\mathbf{r}) \tag{7.4}$$

whose exact solutions conserve $E(\mathbf{r}, \mathbf{p})$.

In Desmond, particles are placed in the global cell with periodic boundary conditions. This means that long-range interactions (for example, electrostatic interactions) are, in principle, summed over all periodic images of the global cell, making the potential energy properly a function of both $\mathbf{r}$ and the 3×3 matrix $\mathbf{B} = [\vec{a}, \vec{b}, \vec{c}]$, where $\vec{a}$, $\vec{b}$, and $\vec{c}$ are the *lattice vectors* of the cell. Usually this dependence on $\mathbf{B}$ is suppressed, unless variations in the cell shape need to be considered.

7.1.2 Chemical systems

In addition to the energy of the particles, a number of other macroscopic properties of the system are of interest, particularly pressure and temperature. These quantities are only properly defined in reference to very large systems with ergodic dynamics, aver aged over statistically significant lengths of time. However, instantaneous microscopic versions of these quantities can be defined.

The instantaneous temperature, T, of a group of particles is given by:

$$\frac{1}{2}k_BT = \frac{1}{N_f}\sum_i \|\vec{p}_i\|^2/(2m_i) \tag{7.5}$$

where k_B is the Boltzmann constant and N_f counts the number of degrees of freedom of the particles (for N free particles $N_f = 3N$). The instantaneous pressure is given by $P = \mathrm{Tr}\,\{\mathbf{P}\}\,/3$, the average of the main diagonal components of the 3×3 tensor:

$$\mathbf{P}(\mathbf{r}, \mathbf{p}, \mathbf{B}) = |\mathbf{B}|^{-1}\left(\sum_i \left(\vec{p}_i\vec{p}_i/m_i - \nabla_{\vec{r}_i}U(\mathbf{r}, \mathbf{B})\vec{r}_i^{\,t}\right) - \nabla_{\mathbf{B}}U(\mathbf{r}, \mathbf{B})\mathbf{B}^t\right) \tag{7.6}$$

Variations of the Newton equations are often made through additional ordinary or stochastic variables coupled dynamically to the positions and momenta or via feedback control interventions which adjust the positions and momenta. These variations are typically designed to ensure certain statistical properties of the macroscopic quantities.

7.2 Integrator

Simulation dynamics are specified in a section named integrator, in which one specifies the conditions for evolving the system forward in time. The integrator is configured as shown in:

```
integrator = {
  dt =  δt
  respa = { ... }
  pressure = { ... }
  temperature = { ... }
  type = key   # dynamics type
  key = { ... } # specific options
}
```

The type value specifies the dynamical system defining the system's evolution (see Section 7.6). Additionally, the type value is used as a key for any additional parameters that the selected system requires.

δ_t is the amount of simulated time between particle position updates. Every position update is:

$$\vec{r_i}(t+\delta_t) = \vec{r_i}(t) + \vec{p_i}(t+\delta_t/2)\delta_t/m_i \tag{7.7}$$

followed by a modification to account for any constraints (see Section 6).

Because Desmond supports multiple timestepping, the full timestep, Δ_t, between successive simulation steps might not be δ_t but instead some integer multiple of it. δ_t is sometimes called the inner timestep and $\Delta_t = n\delta_t$ is called the outer timestep.

name	**description**
`dt`	The time length of a position update step. [*Time* > 0]
`respa`	breakdown of the integrator timestep. [*configuration*]
`pressure`	configuration of the system pressure. [*configuration*]
`temperature`	configuration of the system temperature. [*configuration*]
`type`	Type of dynamical system to integrate. [*Symbol*]

Table 7.1: Parameters for integrate

7.3 RESPA

Timestep scheduling is configured as shown in:

```
integrator.respa = {
  near_timesteps  = $i_n$
  far_timesteps   = $i_f$
  outer_timesteps = $i_o$
}
```

Most Desmond integrator types (and force configurations) support a splitting of the force field into three computational categories with separate scheduling of each. The divisions are bonded, nonbonded near (van der Waals and short-range electrostatic interactions), and nonbonded-far (long-range electrostatic interactions). Additionally, certain dynamical events, typically corresponding to the dynamics of extended variables, such as a thermostat, occur outside of a complete NVE step.

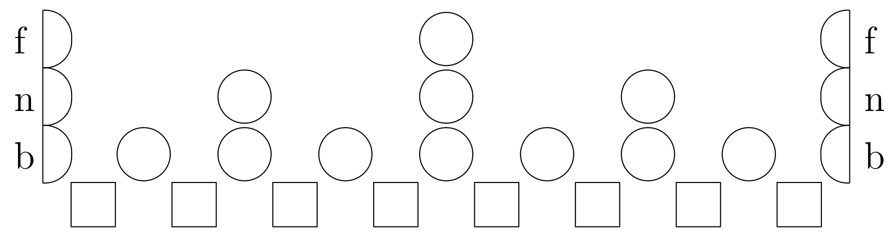


Figure 7.1: A schematic representation of a $(i_n, i_f, i_o) = (2, 4, 8)$ RESPA schedule. Stacks of circles represent momentum updates with bonded, near, and far force components. Squares represent position updates.

The scheduling of these different categories is controlled by these values. During the course of a simulation, positions and momenta are updated according to the velocity Verlet algorithm:

$$\begin{aligned}
\vec{p}_i(t + \delta_t/2) &= \vec{p}_i(t) + \vec{f}_i(t)\delta_t/2 && (7.8)\\
\vec{r}_i(t + \delta_t) &= \vec{r}_i(t) + \vec{p}_i(t + \delta_t/2)\delta_t/m_i && (7.9)\\
\vec{p}_i(t + \delta_t) &= \vec{p}_i(t + \delta_t/2) + \vec{f}_i(t + \delta t)\delta_t/2. && (7.10)
\end{aligned}$$

The force is split into three components $\mathbf{f}(t) = \mathbf{f}^b(t) + \mathbf{f}^n(t) + \mathbf{f}^f(t)$, where each of $\mathbf{f}^b$, $\mathbf{f}^n$, and $\mathbf{f}^n$ is computed every δ_t, $i_n\delta_t$, and $i_f\delta_t$ units of time based on the current value of $r(t)$ for i_f phases of time repeated i_o/i_f times for a total of i_o phases, or an outer time step of $\Delta_t = i_o\delta_t$. It is required that i_n divide i_f and that i_f divide i_o.

Another way to think of this is that (unless otherwise specified) each full time step is built from a sequence of i_o position updates interspersed with momentum updates. Each position update is identical and takes the form of Equation 7.9. Each momentum update takes the form of Equation 7.8 using the weighted combination $f_i(t) = \mathbf{f}^b(t) + o_i i_n \mathbf{f}^n(t) + o_f i_f \mathbf{f}^f(t)$ where the o_q are both 1 for the first step and thereafter $o_q = 1$ every i^q steps and 0 otherwise. If there are no outer step dynamics, and $i_o = k i_f$ then the full integration step is equivalent to the concatenation of k the integration steps one obtains with $i_o = i_f$. We illustrate a $(i_n, i_f, i_o) = (2, 4, 8)$ schedule in Figure 7.1.

Multiple timestepping is effectively disabled by setting $i_n = i_f = i_o = 1$, which makes the force and extended dynamics purely a function of current position, $\mathbf{f}(t) = \mathbf{f}(\mathbf{r}(t))$, and not the phase of time.

name	description
`near_timesteps`	The number of position updates per nonbonded near force calculation. [*Integer* > 0*, divides far_timesteps*]
`far_timesteps`	The number of position updates per nonbonded far force calculation. [*Integer* > 0*, divides the outer_timesteps*]
`outer_timesteps`	The number of position updates per application of additional "outer step" dynamics. [*Integer* > 0]

Table 7.2: Parameters for respa

7.4 Pressure

Some dynamical systems change the unit cell vectors of the global cell, thus changing the size and possibly the shape of the cell during the integration to realize a constant pressure ensemble. The `pressure` section gives the parameters for such systems.

Pressure is configured as shown in:

```
integrator.pressure = {
  isotropy = isotropic|semi_isotropic|anisotropic|constant_area
  max_margin_contraction = $c_{\max}$
  P_ref = $P_0$
  tension_ref = $t_{33}$
}
```

isotropy constrains the changes allowed for the global cell:

isotropic The cell scales uniformly along all three axes.

semi-isotropic The X and Y axes scale uniformly, while the Z axis scales independently.

anisotropic The cell scales independently along all three axes.

constant area The cell scales along its Z axis only.

As the cell changes shape, its clone radius changes as well. If the new radius is less than a factor of $c_{\max}$ times the old radius, certain lazily updated quantities (such as particle pairlists) are immediately recomputed. P_0 and t_{33} are parameters that appear in the equations of certain dynamical systems. Their roles in those systems are described in Section 7.6.

name	**description**
`isotropy`	The allowed class of cell changes. [*Symbol*]
`max_margin_contraction`	The amount of relative contraction beyond which all particle ownerships must be recalculated. [*Real*]
`P_ref`	The reference pressure for the cell. [*Pressure* > 0]
`tension_ref`	The reference tension for the cell. Optional—by default, 0. [*Pressure*Length* > 0]

Table 7.3: Parameters for pressure

7.5 Temperature

Each particle in a structure file is assigned a property called its *temperature group*. The following synopsis shows how to assign reference temperatures to sets of temperature groups:

```
integrator.temperature = {
  T_ref = T
  T_groups = [ {
    T_ref = T_1
    groups = [g_1 ... ]
  } ... {
    T_ref = T_k
    groups = [g_k ... ]
  } ]
}
```

The reference temperature T is taken as the temperature of any component in the system which does not have some other temperature assignment that overrides it. For nearly all uses this is the only variable that needs to be set. However, for certain exceptional applications it is possible to assign alternative temperatures to system components (what this means physically is the province of the user). It is also sometimes desirable, in systems sampling from contant temperature ensembles to assign separate thermostats (or no thermostat) to subsets of the particles. The `T_groups` section is an optional means for exercising this fine control. The elements of the `T_groups` list correspond to logically distinct thermostats that apply to the temperature groups listed in `groups` and these groups can be assigned their own reference temperatures, T_j. Subsequent sections in this chapter will be written at this finer level of control and use $\chi(i)$ to denote the element of temperature in which the i^{th} particle's temperature group occurs (in other words, $\chi(i) = j$ means particle i is governed by thermostat j in temperature- controlled simulations). We set $\chi(i) = 0$ when the group is not assigned a reference temperature.

Note: Desmond prints a warning if some particles in the simulation have not been assigned a reference temperature.

name	**description**
`T_ref`	The global reference temperature. [*Temperature* > 0]
`T_groups[i].T_ref`	The reference temperature for thermostat i. Optional– defaults to the global reference temperature. [*Temperature* > 0]
`T_groups[i].groups`	The temperature groups regulates by thermostat i. [*List of Integers* ≥ 0]

Table 7.4: Parameters for temperature

7.6 Dynamical systems

Three kinds of dynamical systems are available in Desmond:

- ordinary differential equations (ODEs) with certain energy and measure-conserving properties,
- stochastic differential equations (SDEs) with invariant measures, and
- stochastic differential equations coupled to feedback control systems

This section describes the supported systems in a mathematically exact and unconstrained form, omitting the details of the integration method and the complexities of incorporating constraints.

A simulation is evolved according to a dynamical system specified by the integrator.type variable, which is a name. This name selects the system to be used and is also treated as a key in the integrator section under which the parameters for the specified system can be found.

7.6.1 V_NVE: Verlet constant volume and energy

The `V_NVE` dynamical system is configured as shown in:

```
integrator.V_NVE = {}
```

No parameters are needed. The system is the ODE:

$$\dot{\vec{r}_i} = \vec{p}_i/m_i \tag{7.11}$$

$$\dot{\vec{p}_i} = -\nabla_{\vec{r}_i} U(\mathbf{r}) \tag{7.12}$$

which conserves the scalar:

$$H_o(\mathbf{r}, \mathbf{p}) = \sum_i \|\vec{p}_i\|^2/(2m_i) + U(\mathbf{r}) \tag{7.13}$$

and the phase space density (differential form):

$$\Omega_0 = \prod_i d^3\vec{r}_i d^3\vec{p}_i \tag{7.14}$$

where $d^3\vec{r}_i$ and $d^3\vec{p}_i$ are the volume elements of the position and momentum of particle i. Thus, the trajectory, if ergodic, is expected to sample uniformly from a surface of constant $H_0(\mathbf{r}, \mathbf{p})$.

7.6.2 NH_NVT: Nosé-Hoover constant volume and temperature

The `NH_NVT` dynamical [7] system is configured as shown in:

```
integrator.NH_NVT = {
  thermostat = {
    mts = m
    tau = [τ1 ...  τn ]
  }
}
```

This system supplies a thermostat using a Nosé-Hoover chain (with extended system variables) for each of the elements of the `integrator.temperature` list (the length of which must match that of the thermostat list). For each thermostat and each τ_i parameter, a pair of variables ζ_i, ν_i) is introduced for a total of $2nk$ additional variables (k being the number of thermostats). The dynamics are given by the ODE:

$$\dot{\vec{r}}_i = \vec{p}_i/m_i \tag{7.15}$$

$$\dot{\zeta}_i^j = \nu_i^j/w_i^j \tag{7.16}$$

$$\dot{\vec{p}}_i = -\nabla_{\vec{r}_i} U(\mathbf{r}) - \vec{p}_i \nu_1^{\chi(i)}/w_1^{\chi(i)} \tag{7.17}$$

$$\dot{\nu}_1^j = \sum_{i|\chi(i)=j} \|\vec{p}_i\|^2/m_i - C_1^j - \nu_1^j \nu_2^j/w_2^j \tag{7.18}$$

$$\dot{\nu}_i^j = (\nu_i^j)^2/w_{i-1}^j - C_i^j - \nu_i^j \nu_{i+1}^j/w_{i+1}^j \tag{7.19}$$

$$\dot{\nu}_n^j = (\nu_n^j)^2/w_{n-1}^j - C_n^j \tag{7.20}$$

where $w_i^j = C_i^j(\tau_i)^2$ with $C_1^j = k_B T_j N_j$ and $C_{i>1}^j = k_B T_j$, where N_j is the number of degrees of freedom of the governed particles j. Recall from Section 7.5 that $\chi(i)$ denotes the thermostat which governs particle i.

This system preserves the scalar:

$$H(\mathbf{r}, \zeta, \mathbf{p}, \nu) = H_0(\mathbf{r}, \mathbf{p}) + \sum_{ij} (\nu_i^j)^2/(2w_i^j) + \sum_{ij} C_i^j \zeta_i^j \tag{7.21}$$

and the phase space density:

$$\Omega = \exp\left(\sum_j (k_B T_j)^{-1} \sum_i C_i^j \prod_{ij} d\zeta_i^j d\nu_i^j\right) \Omega_0 \tag{7.22}$$

In particular, if $T_1 = \ldots = T_k = T$, then the density,

$$\Omega' = \exp\left(-(k_B T)^{-1}\left(H_0(\mathbf{r}, \mathbf{p}) + \sum_{ij} (\nu_i^j)^2/(2w_i^j)\right)\right) \prod_{ij} d\zeta_i^j d\nu_i^j \Omega_0 \tag{7.23}$$

is preserved. Hence, the trajectories of these equations, if ergodic, sample (r, p) from the canonical ensemble with temperature T.

The current numerical implementation of the ODE updates each Nosé-Hoover chain as a separate step from the governed position and momentum variable updates. Because these updates are inexpensive, they can be done multiple times, m, with a smaller timestep proportionate to $1/m$, for higher accuracy. In practice, we usually set $m = 2$.

name	**description**
`thermostat.mts`	The number of discrete updates within the chain. Required. [*Integer* > 0]
`thermostat.tau`	The time constants determining the length and masses of the chain variables. [*List of Time* > 0]

Table 7.5: Parameters for NH_NVT

7.6.3 L_NVT: Langevin constant volume and temperature

The `L_NVT` dynamical system is configured as shown in:

```
integrator.L_NVT = {
  thermostat = {
    tau = τ
    seed = s
  }
}
```

It supplies a thermostat using the Langevin method for all of the elements of the `integrator.temperature` list.

This dynamical system adds a damping term and a stochastic force to the atoms. The amount of stochastic force used is a function of the T_j for the j^{th} thermostat, while the damping $1/\tau$ is uniform across all thermostats. The mean collision time for water, roughly 1/62 ps, is often used for τ.

The dynamics are given by the SDE:

$$\dot{\vec{r}}_i = \vec{p}_i/m_i \tag{7.24}$$
$$\dot{\vec{p}}_i = -\nabla_{\vec{r}_i}U(\mathbf{r}) - (\vec{p}_i + \sigma_i\dot{\vec{S}}_i(t))/\tau \tag{7.25}$$

where each component of the random vector $\vec{S}(t)$ is a standard Wiener process, $W(t)$, having the probability density:

$$Prob(w \le W(t) \le w + dw) = \frac{1}{\sqrt{2\pi t}}\exp(-w^2/(2t))dw \tag{7.26}$$

and $\sigma_i = \sqrt{2m_i k_B T_j \tau}$ where particle i is in the j^{th} thermostat (temperature T_j). The Wiener distribution is seeded by s.

Although this SDE does not have a conserved scalar, it does have an invariant phase space density, given by:

$$\Omega = f(\mathbf{r}, \mathbf{p}) \prod_i d^3\vec{r}_i d^3\vec{p}_i \tag{7.27}$$

where f satisfies the PDE:

$$0 = \sum_i \left(\frac{1}{m_i}\vec{p}_i \cdot \nabla_{\vec{r}_i} f - \nabla_{\vec{r}_i} U(r) \cdot \nabla_{\vec{p}_i} f + \left(\nabla_{\vec{p}_i} \cdot (\vec{p}_i f) + \frac{1}{2}\sigma_i^2 \nabla_{\vec{p}_i}^2 f \right) / \tau \right) \tag{7.28}$$

If $T_1 = \ldots = T_k = T$, then:

$$f = \exp(-H_0(\mathbf{r}, \mathbf{p})/(k_B T)) \tag{7.29}$$

Thus, the trajectories of this system are expected to produce samples from the canonical ensemble with temperature T.

In Desmond, the net energy (or *heat*) subtracted by the stochastic portions of the SDE are accounted for in the extended variable energy term, which results in a conserved energy useful for diagnostic purposes.

name	**description**
`thermostat.tau`	The decay time (inverse damping constant) of the particle momenta. [*Time* > 0]
`thermostat.seed`	The random number seed for normally distributed random variables. [*Integer*]

Table 7.6: Parameters for L_NVT

7.6.4 Piston_NPH: constant pressure and enthalpy

The Piston_NPH dynamical system is configured as shown in:

```
integrator.Piston_NPH = {
  barostat={
    tau = τ_p
    T_ref = T_b # optional
  }
}
```

This is the simplest dynamical system that changes the cell according to a conservative dynamics. More complex systems that change the cell have many similarities with Piston_NPH and share its definitions.

Usually energy is the conserved quantity, but in this case the conserved quantity is enthalpy.

To describe the equations of motion in Piston_NPH, recall the definition $\mathbf{B} = [\vec{a}, \vec{b}, \vec{c}]$, a 3×3 matrix with the system's unit cell vectors as columns; the volume of the system is the determinant $|\mathbf{B}|$.

Since changes in the global cell affect long-range interactions, we expose the dependence of the potential function on **B**, writing $U(\mathbf{r}, \mathbf{B})$ for the potential energy (and writing $H_0(\mathbf{r}, \mathbf{B}, \mathbf{p}) = \sum_i \|p_i\|^2/(2m_i) + U(\mathbf{r}, \mathbf{B})$). The dynamics of the cell are expressed through some number of new scaling variables, $s_1, \ldots, s_d$, and their relative momenta, $\eta_1, \ldots, \eta_d$, depending on the `pressure.isotropy`. For a given isotropy, we define the maps **B**, **A**, and **a** (**a** is the adjoint of **A**), as shown in Equation 7.31 through Equation **??**:

Isotropic

$$\mathbf{B}(s_1) = \begin{pmatrix} s_1 & 0 & 0 \\ 0 & s_1 & 0 \\ 0 & 0 & s_1 \end{pmatrix} [\vec{a}, \vec{b}, \vec{c}] \tag{7.30}$$

$$\mathbf{A}(\eta_1) = \begin{pmatrix} \eta_1 & 0 & 0 \\ 0 & \eta_1 & 0 \\ 0 & 0 & \eta_1 \end{pmatrix} \tag{7.31}$$

$$\mathbf{a}\begin{pmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{pmatrix} = m_{11} + m_{22} + m_{33} \tag{7.32}$$

Semi-isotropic

$$\mathbf{B}(s_1, s_2) = \begin{pmatrix} s_1 & 0 & 0 \\ 0 & s_1 & 0 \\ 0 & 0 & s_2 \end{pmatrix} [\vec{a}, \vec{b}, \vec{c}] \tag{7.33}$$

$$\mathbf{A}(\eta_1, \eta_2) = \begin{pmatrix} \eta_1 & 0 & 0 \\ 0 & \eta_1 & 0 \\ 0 & 0 & \eta_2 \end{pmatrix} \tag{7.34}$$

$$\mathbf{a}\begin{pmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{pmatrix} = \begin{pmatrix} m_{11} + m_{22} \\ m_{33} \end{pmatrix} \tag{7.35}$$

Anisotropic

$$\mathbf{B}(s_1, s_2, s_3) = \begin{pmatrix} s_1 & 0 & 0 \\ 0 & s_2 & 0 \\ 0 & 0 & s_3 \end{pmatrix} [\vec{a}, \vec{b}, \vec{c}] \tag{7.36}$$

$$\mathbf{A}(\eta_1, \eta_2, \eta_3) = \begin{pmatrix} \eta_1 & 0 & 0 \\ 0 & \eta_2 & 0 \\ 0 & 0 & \eta_3 \end{pmatrix} \tag{7.37}$$

$$\mathbf{a}\begin{pmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{pmatrix} = \begin{pmatrix} m_{11} \\ m_{22} \\ m_{33} \end{pmatrix} \tag{7.38}$$

Constant area

$$\mathbf{B}(s_1) = \begin{pmatrix} 1 & 0 & \\ 0 & 1 & 0 \\ 0 & 0 & s_1 \end{pmatrix} [\vec{a}, \vec{b}, \vec{c}] \tag{7.39}$$

$$\mathbf{A}(\eta_1) = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \eta_1 \end{pmatrix} \tag{7.40}$$

$$\mathbf{a} \begin{pmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{pmatrix} = m_{33} \tag{7.41}$$

The ODE for the Piston_NPH dynamical system is:

$$\dot{\vec{r}_i} = \vec{p_i}/m_i + \mathbf{A}(\eta)\vec{r_i}/W \tag{7.42}$$

$$\dot{s}_i = \eta_i s_i/W \tag{7.43}$$

$$\dot{\vec{p}_i} = -\nabla_{\vec{r}_i} U(\mathbf{r}, \mathbf{B}(\mathbf{s})) - (1 + 1/N_g)\mathbf{A}(\eta)\vec{p_i}/W \tag{7.44}$$

$$\dot{\eta} = \mathbf{a}\left((\mathbf{P}(\mathbf{r}, \mathbf{p}, \mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \vec{p_i}\vec{p_i}^t/m_i \right) \tag{7.45}$$

where:

$$\mathbf{P}_0(\mathbf{B}) = (P_0 - \mathrm{Tr}\left\{\mathbf{T}\mathbf{B}^{-1}\right\})\mathbf{I} + (\mathbf{T}\mathbf{B}^{-1})^t \tag{7.46}$$

with P_0 given by the `pressure.P_ref` parameter and

$$T = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & t_{33} \end{pmatrix} \tag{7.47}$$

with t_{33} given by `the pressure.tension_ref` parameters. The barostat mass, W, is given by $W = (3N_g + d)k_B T_b \tau_p^2$, where N_g is the number of constraint terms (or molecular groups) of the system and d is the number of independent η variables. This system is not thermostated, so the roles of T_b and τ_p are redundant for this system. However, other systems use the same barostat framework and do apply a thermostat to the barostat.

This system preserves the scalar:

$$H_p(\mathbf{r}, \mathbf{s}, \mathbf{p}, \eta) = H_0(\mathbf{r}, \mathbf{B}(\mathbf{s}), \mathbf{p}) + \sum_i \eta_i^2/(2W) + \left(P_0 - \mathrm{Tr}\left\{\mathbf{T}\mathbf{B}(\mathbf{s})^{-1}\right\}\right)|\mathbf{B}(\mathbf{s})| \tag{7.48}$$

and the phase space density (by isotropy type):

isotropic

$$\Omega_p = s_1^2 ds_1 d\eta_1 \Omega_0 \tag{7.49}$$

semi-isotropic

$$\Omega_p = s_1 \prod_{j=1}^{d} ds_j d\eta_j \Omega_0 \tag{7.50}$$

anisotropic

$$\Omega_p = \prod_{j=1}^{d} ds_j d\eta_j \Omega_0 \tag{7.51}$$

constant area

$$\Omega_p = ds_1 d\eta_1 \Omega_0 \tag{7.52}$$

Like a V_NVE simulation, the exact trajectory, if ergodic, is expected to sample from a surface of constant $H_p(\mathbf{r}, \mathbf{s}, \mathbf{p}, \eta)$, weighted by Ω_p.

name	**description**
`tau`	Used to set the mass. [*barostat.Time* > 0]
`barostat.T_ref`	Equilibrium temperature (used to set the mass). Optional–defaults to the global reference temperature. [*Temperature* > 0]

Table 7.7: Parameters for Piston_NPH

7.6.5 MTK_NPT: Martyna-Tobias-Klein, constant pressure and temperature

The `MTK_NPT` dynamical system [8] is configured as shown in:

```
integrator.MTK_NPT = {
  barostat = {
    tau = $\tau_p$
    T_ref = $T_b$
    thermostat = {
      mts = $m^b$
      tau = [ $\tau_1^b$ ... $\tau_n^b$ ]
    }
  }
  thermostat = {
    mts = $m^1$
    tau = [ $\tau_1$ ... $\tau_n$ ]
  }
}
```

The Martyna-Tobias-Klein dynamical system is a combination of Piston_NPH (see Section 7.6.4) and NH_NVT (see Section 7.6.2) dynamics. There is also an additional Nosé-Hoover chain, with n_b additional pairs of variables (ζ_i^b, ν_i^b) that govern the barostat degrees of freedom. To include this chain in sums or products over chains, treat the index of the sum or product as ranging over the numbers $1, \ldots, k$ (for the particle Nosé-Hoover chains) and the letter b.

The ODE for this system is

$$\begin{aligned}
\dot{\vec{r}_i} &= \vec{p}_i/m_i + \mathbf{A}(\eta)\vec{r}_i/W && (7.53)\\
\dot{s}_i &= \eta_i s_i/W && (7.54)\\
\dot{\zeta}_i^j &= \nu_i^j/w_i^j && (7.55)\\
\dot{\vec{p}_i} &= -\nabla_{\vec{r}_i}U(\mathbf{r},\mathbf{B}(\mathbf{s})) - (1+1/N_g)\mathbf{A}(\eta)\vec{p}_i/W - \vec{p}_i\nu_1^{\chi(i)}/w_1^{\chi(i)} && (7.56)\\
\dot{\eta} &= \mathbf{a}\left((\mathbf{P}(\mathbf{r},\mathbf{p},\mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \vec{p}_i\vec{p}_i^t/m_i\right) - \eta\nu_1^b/w_1^b && (7.57)\\
\dot{\nu}_1^{j\neq b} &= \sum_{i|\chi(i)=j} \|\vec{p}_i\|^2/m_i - C_1^j - \nu_1^j\nu_2^j/w_2^j && (7.58)\\
\dot{\nu}_1^b &= \sum_i \eta_i^2/W - C_1^b - \nu_1^b\nu_2^b/w_2^b && (7.59)\\
\dot{\nu}_i^j &= (\nu_{i-1}^j)^2/w_{i-1}^j - C_i^j - \nu_i^j\nu_{i+1}^j/w_{i+1}^j && (7.60)\\
\dot{\nu}_n^j &= (\nu_{n-1}^j)^2/w_{n-1}^j - C_n^j && (7.61)
\end{aligned}$$

where $C_1^b = k_BT_bd$ and $C_{i>1}^b = k_BT_b$, where d is the number of independent variables in the barostat (according to its isotropy type) and $w_i^j = C_i^j(\tau_i^j)^2$. (Note: the astute reader may observe that our equations vary from the original MTK equations in the handling of the $1/N_g$-terms in the $\dot{\vec{p}_i}$ and $\dot{\eta}$ equations.)

Recalling the definitions of the invariant scalar and phase space density from Piston_NPH (see Section 7.6.4), the above ODE preserves the scalar:

$$H(\mathbf{r},\mathbf{s},\zeta,\mathbf{p},\eta,\nu) = H_p(\mathbf{r},\mathbf{s},\mathbf{p},\eta) + \sum_{ij}(v_i^j)^2/(2w_i^j) + \sum_{ij} C_i^j\zeta_i^j \tag{7.62}$$

and the phase space density:

$$\Omega = \exp\left(\sum_j (k_BT_j)^{-1}\sum_i C_i^j\zeta_i^j\right)\prod_{ij} d\zeta_i^j d\nu_i^j \Omega_p \tag{7.63}$$

In particular, if $T_1 = \ldots = T_k = T_b = T$, then the density shown below is preserved:

$$\Omega' = \exp\left(-(k_BT)^{-1}\left(H_p(\mathbf{r},\mathbf{s},\mathbf{p},\eta) + \sum_{ij}(\nu_i^j)^2/(2w_i^j)\right)\right)\prod_{ij} d\zeta_i^j d\nu_i^j \Omega_p \tag{7.64}$$

name	description
`barostat.tau`	Used to set the mass (see Piston_NPH). [*Time* > 0]
`barostat.T_ref`	Equilibrium temperature (see Piston_NPH and NH_NVT). Optional—defaults to the global reference temperature. [*Temperature* > 0]
`barostat.thermostat`	Description of the barostat chain (see NH_NVT). [*Nosé-Hoover chain*]
`thermostat`	Description of the particle thermostat (see NH_NVT). [*Nosé-Hoover chain*]

Table 7.8: Parameters for MTK_NPT

7.6.6 L_NPT: Langevin constant pressure and temperature

The L_NPT dynamical system is configured as shown in:

```
integrator.L_NPT = {
  barostat = {
    tau = τp
    T_ref = Tb
    thermostat = {
      tau = τb
      seed = sb
    }
  }
  thermostat = {
    tau = τ
    seed = s
  }
}
```

The Langevin constant pressure and temperature dynamical system [5] is a combination of the L_NVT (see Section 7.6.3) stochastic dynamics and Piston_NPH (see Section 7.6.4). An additional stochastic differential equation governs the barostat degrees of freedom.

The SDE for this system is:

$$\dot{\vec{r}_i} = \vec{p_i}/m_i + \mathbf{A}(\eta)r_i/W \qquad (7.65)$$

$$\dot{s}_i = \eta_i s_i/W \qquad (7.66)$$

$$\dot{\vec{p}_i} = -\nabla_{\vec{r}_i} U(\mathbf{r}, \mathbf{B}(\mathbf{s})) - (1 + 1/N_g)\mathbf{A}(\eta)\vec{p_i}/W - (\vec{p_i} + \sigma_i \dot{\vec{S}}(t))/\tau \qquad (7.67)$$

$$\dot{\eta} = \mathbf{a}\left((\mathbf{P}(\mathbf{r}, \mathbf{p}, \mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \vec{p}_i\vec{p}_i^t/m_i \right) - (\eta + \sigma_b \dot{\mathbf{S}}(t))/\tau_b \qquad (7.68)$$

where each of the components of the vectors $\mathbf{S}$ and $\vec{S}_i$ is a standard Wiener process and $\sigma_b = \sqrt{2Wk_BT_b\tau_b}$.

Although this SDE does not have a conserved scalar, it does have an invariant phase space density, given by:

$$\Omega = f(\mathbf{r}, \mathbf{s}, \mathbf{p}, \eta)\Omega_p \tag{7.69}$$

where f satisfies the PDE:

$$\begin{aligned}
0 \;=\; & \sum_i \left(\frac{1}{m_i}\vec{p}_i + \mathbf{A}(\eta)\vec{r}_i/W\right) \cdot \nabla_{\vec{r}_i} U(r) \\
& + \sum_i (1 + 1/N_g)\left(\mathbf{A}(\eta)\vec{p}_i/W\right) \cdot \nabla_{\vec{p}_i} f \\
& + \sum_i \left(\nabla_{\vec{p}_i} \cdot (\vec{p}_i f) + \frac{1}{2}\sigma_i^2 \nabla_{\vec{p}_i}^2 f\right)/\tau \\
& + \mathbf{a}\left((P(r, s, B(s)) - P_0(B(s)))|B(s)| + \frac{1}{N_g}\sum_i \vec{p}_i\vec{p}_i^{\,t}/m_i\right) \cdot \nabla_\eta f \\
& + \sum_i \eta_i s_i/W \nabla_{s_i} f + ((\nabla_\eta \cdot (\eta f) + \frac{1}{2}\sigma_b^2 \nabla_\eta^2 f))/\tau_b
\end{aligned}$$

If $T_1 = \ldots = T_k = T_b = T$, then:

$$f = \exp(-H_p(\mathbf{r}, \mathbf{s}, \mathbf{p}, \eta)/(k_B T))) \tag{7.70}$$

is the invariant phase space density.

As with L_NVT, the energy (or *heat*) added or subtracted by the stochastic portions of the SDE are accounted for in the extended variable energy term, resulting in a conserved energy useful for diagnostic purposes.

name	**description**
`barostat.tau`	Used to set the mass (see Piston_NPH). [*Time* > 0]
`barostat.T_ref`	Equilibrium temperature (see Piston_NPH and L_NVT). Optional–defaults to the global reference temperature. [*Temperature* > 0]
`barostat.thermostat`	Description of the thermostat of the barostat (see L_NVT). [*Langevin parameters*]
`thermostat`	Description of the thermostat for the particles (see L_NVT). [*Langevin parameters*]

Table 7.9: Parameters for L_NPT

7.6.7 Ber_NVT: Berendsen constant volume and temperature

The Ber_NVT dynamical system [3] is configured as shown in:

```
integrator.Ber_NVT = {
  tau = τ
```

```
    min_velocity_scaling = $s_{\min}$
    max_velocity_scaling = $s_{\max}$
  }
```

Berendsen constant volume and temperature simulations do not sample microstates according to their probability distribution in a canonical ensemble. Instead, this dynamics keeps the kinetic energy of the system close to the average kinetic energy in the corresponding canonical ensemble by means of feedback control. It can be used to equilibrate a system in short simulations.

It is recommended that Berendsen integrators be run with the net center of mass motion periodically removed from the system to prevent certain long-term degenerate behaviors.

The instantaneous temperature, T_j^*, of the atoms governed by thermostat j (with reference temperature T_j) is related to their kinetic energy by:

$$K_j = \sum_{i|\chi(i)=j} \|\vec{p}_i\|^2/(2m_i) = \frac{1}{2}N_j k_B T_J^* \tag{7.71}$$

where N_j is the number of degrees of freedom of thermostat j.

In a Berendsen constant volume and temperature simulation, the particle velocities are rescaled at each full timestep, Δt, to bring the instantaneous temperature T_j^* closer to the target temperature T_j: if $T_j^* > T_j$, the particle velocities are scaled down; if the $T_j^* < T_j$, the particle velocities are scaled up. Velocities are rescaled gradually, according to a linear rate given by τ.

$$\Delta T_j^* = \frac{\Delta_t}{\tau}(T_j - T_j^*) \tag{7.72}$$

To elaborate, scaling the particle velocities by s_j scales the kinetic energy and instantaneous temperature by s_j^2, thus $\Delta T{*}_j = (s_j^2 - 1)T_j^*$ serves to determine s_j. However, such a procedure tends to be unstable unless the center of mass motion of the entire system is simultaneously removed. With the mass and velocity of each thermostat defined by:

$$M_j = \sum_{i|\chi(j)=j} m_i \tag{7.73}$$

and

$$M_j\vec{V}_j = \sum_{i|\chi(j)=j} \vec{p}_i/m_i \tag{7.74}$$

The velocity of the system, after rescaling, is:

$$\vec{V}(\mathbf{s}) = \frac{1}{M}\sum_j s_j M_j \vec{V}_j \tag{7.75}$$

where $M = \sum_j M_j$. The new particle momenta are given by:

$$\vec{p}_i^{\text{new}} = s_{\chi(i)}\vec{p}_i - m_i\vec{V}(s) \tag{7.76}$$

where s is determined by solving the following nonlinear equation:

$$\Delta K_J = s_j^2 K_j - s_j M_j \vec{V}_j \cdot \vec{V}(\mathbf{s}) + \frac{1}{2} M_j \|\vec{V}(\mathbf{s})\|^2 - K_j = \frac{\Delta_i}{\tau}\left(\frac{1}{2} k_B T_j N_j - K_j\right) \tag{7.77}$$

name	**description**
`tau`	Relaxation time. [*Time* > 0]
`min_velocity_scaling`	Minimum factor for scaling particle velocities in one timestep. [$0 <$ *Real* < 1]
`max_velocity_scaling`	Maximum factor for scaling particle velocities in one timestep. [$1 <$ *Real*]
`thermostat`	Description of the thermostat for the particles (see NH_NVT). [*List of Langevin parameters*]

Table 7.10: Parameters for Ber_NVT

7.6.8 Ber_NPT: Berendsen constant temperature and pressure

The Ber_NPT dynamical system is configured as shown in:

```
integrator.Ber_NPT = {
  barostat = {
    tau = $\tau_p$
    kappa = $\kappa$
    min_contraction_per_step = $s^p_{\min}$
    max_expansion_per_step = $s^p_{\max}$
  }
  tau = $\tau$
  min_velocity_scaling = $s_{\min}$
  max_velocity_scaling = $s_{\max}$
}
```

Just as a Berendsen NVT simulation does not sample according to canonical distributions, a Berendsen NPT simulation does not sample according to probability distributions in isothermal-isobaric equilibrium ensemble. It employs feedback control systems which try to keep the instantaneous temperature and pressure close to their reference values. Temperature control is carried out similarly to `Ber_NVT`; we discuss only the pressure control here.

Pressure control is performed by scaling the dimensions of the cell at each full timestep Δ_t. If the instantaneous scalar pressure $P = \mathrm{Tr}\{\mathbf{P}\}/3$ is greater than the target pressure P_0, the cell is expanded to release the extra pressure; if $P < P_0$, the cell is contracted to build up pressure. The scaling is done gradually, according to a given parameter, κ, which estimates of the compressibility of the system:

$$\kappa = \frac{1}{|\mathbf{B}|}\frac{\partial |\mathbf{B}|}{\partial P} \tag{7.78}$$

and a relaxation time τ_p:

$$\Delta P = \frac{\Delta_t}{\tau_p}(P_0 - P) = -\frac{\Delta|\mathbf{B}|}{|\mathbf{B}|}\frac{1}{\kappa} \tag{7.79}$$

In the isotropic case, this is achieved by scaling each axis of the global cell by a factor s, given by:

$$s = \left(1 - \kappa(P_0 - P)\frac{\Delta_t}{\tau_p}\right)^{\frac{1}{3}} \approx 1 - \frac{1}{3}\kappa(P_0 - P)\frac{\Delta_t}{\tau_p} \tag{7.80}$$

More generally (for non-isotropic cases), we scale B to $B(s)$, where s satisfies:

$$\mathbf{a}(\mathbf{A}(\mathbf{s}))= \mathbf{a}\left(\mathbf{I} - \frac{\kappa\Delta_t}{3\tau_p}(P_o\mathbf{I} - \mathbf{P})\right) \tag{7.81}$$

and the forms of **a**, **A**, and **B** are determined by the isotropy.

Note: Berendsen is not expected to work with constant area isotropy.

To avoid changing the box dimensions too much in a single step, each scaling factor s is constrained to $s_{\text{min}} < s < s_{\text{max}}$.

name	**description**
`barostat.tau`	Relaxation time for Berendsen pressure control. [$Time > 0$]
`barostat.kappa`	Estimated compressibility of the system. [$Pressure^{-1} > 0$]
`barostat.min_contraction_per_step`	Minimum factor for scaling the box in one timestep. [$0 < Real < 1$]
`barostat.max_expansion_per_step`	Maximum factor for scaling the box in one timestep. [$1 < Real$]
`tau`	Relaxation time. [$Time > 0$]
`min_velocity_scaling`	Minimum factor for scaling particle velocities in one timestep. [$0 < Real < 1$]
`max_velocity_scaling`	Real maximum factor for scaling particle velocities in one timestep. [$1 < Real$]

Table 7.11: Parameters for Ber_NPT

7.6.9 Brownian motion integrators

```
integrator.brownie_NVT = {
  thermostat = {
    seed = i
  }
  delta_max = Δmax
}
integrator.brownie_NPT = {
  thermostat = {
    seed = i
  }
  barostat = {
    thermostat = {
      seed = $i_b$
    }
    tau = $\tau_p$
    T_ref = $T_b$
  }
  delta_max = $\Delta_{\max}$
}
```

Desmond provides two Brownian dynamics integrators whose primary purpose is to equilibrate systems which might be in high potential energy configurations due to system preparation artifacts, `brownie_NVT` and `brownie_NPT`. They differ in that the latter will sample global cell dimensions as well as particle positions.

Mathematically, the dynamics of these integrators are no different from that of the corresponding Langevin integrators (`L_NVT` and `L_NPT`) of Sections 7.6.3 and 7.6.6 in the limit as $\tau = \tau_b \to 0$. In this limit, all inertial information is lost and the equations proceed as either `V_NVE` or `Piston_NPH` dynamics with particle and piston momenta being sampled independently from Maxwell-Boltzmann distributions.

While it is possible to obtain the mathematical behavior of these integrators by taking $\tau = \tau_b \to 0$ in previously discussed integrators, obtaining samples from the same stationary distribution, the Brownian dynamics integrators have been modified to stabilize the equilibration process from starting points with very large potential energies (and forces). Specifically, all particle and piston velocities are *clipped* so that no particle is displaced by more than a length of $\Delta_{\max}$ in any direction on position update. We typically set $\Delta_{\max} = 0.1$Å. This additional safety feature prevents run-away particles or a collapsing/exploding global cell during the initial steps of the simulation and becomes superfluous later.

As per the corresponding Langevin integrators, the Brownian dynamics integrators track the net heat transferred from the stochastic processes in their extended variable energies, which creates a useful conserved diagnostic quantity. The velocity clipping process (which removes kinetic energy from the system) is not accounted for, and will cause the diagnostic quantity and extended variable energy to increase when clipping takes place.

name	**description**
`delta_max`	maximum displacement of any particle position per step. [*Length*> 0]
`thermostat.seed`	random seed for normally distributed random variables of the particles. [*Integer*]
`barostat.thermostat.seed`	random seed for normally distributed random variables of the global cell. [*Integer*]

Table 7.12: Parameters for brownian

7.6.10 The Multigrator integrator

```
integrator.Multigrator = {
  nve = {
    type = none | Verlet | PLS
  }
  thermostat= {
    type = Langevin | NoseHoover
    timesteps = $n_T$
    Langevin = {
      tau = $\tau$
      seed = $s$
    }
    NoseHoover = {
      mts = $m$
      tau = [ $\tau_1$ ... $\tau_n$ ]
    }
  }
  barostat = {
    type = MTK
    timesteps = $n_B$
    MTK = {
      T_ref = $T_b$
      tau = $\tau_p$
      thermostat = {
        type = none | Langevin | NoseHoover
        Langevin = {
          tau = $\tau_b$
          seed = $s_b$
        }
        NoseHoover = {
          mts = $m^b$
          tau = [ $\tau_1^b$ ...$\tau_{n_b}^b$ ]
        }
```

```
            }
          }
        }
      }
```

The multigrator is an integrator developed in-house to allow greater flexibility in the design of the integration step, combining the features of the dynamical system and stochastic integrators. It also allows the user the option of carrying out thermostat and barostat updates less frequently than once per outer RESPA timestep, reducing the performance overhead of extended system dynamics.

The integration update steps vary periodically with a full period of n_B updates spanning a chemical time of $n_B\delta_t$. Every update contains a full *NVE step*, which updates positions and momentum to approximate the solution of

$$\dot{\vec{r}_i} = \vec{p}_i/m_i \tag{7.82}$$

$$\dot{\vec{p}_i} = -\nabla_{\vec{r}_i}U(\mathbf{r}). \tag{7.83}$$

according to the selected `nve.type` and the `integrator.respa` schedule (only certain RESPA schedules are currently compatible with the multigrator: 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:2:2, 1:3:3, 1:4:4, 1:2:4, and 1:3:6) (Note: the `none` NVE type performs no position or momentum changes). For every sequence of n_T inner NVE steps, a pair of *thermostat* steps are added to the beginning of the first and to the end of the last such that the full sequence is an NVT step spanning a chemical time of $n_T\delta_t$. Every n_B inner NVE steps, or n_B/n_T NVT steps, a pair of *barostat* steps are added to the beginning of the first and the end of the last such that the full sequence is an NPT step spanning a chemical time of $n_B\delta_t$.

The `Verlet` NVE type performs a standard RESPA integrator step, splitting the force field into weighted components according to the schedule (see Section 7.3). The `PLS` is similar to Verlet in that it creates an integrator step from momentum and position updates similar to a RESPA step, but the weights of the force components and individual time increments of each update have been somewhat modified such that true harmonic motions are approximated to higher order than $\propto \delta_t^2$. The `PLS` steps are generally less stable than the analogous `Verlet` steps, see below.

The timescales of the steps employed for thermostat and barostat updates are independent of n_B, n_T, and the RESPA schedule. Each pair of steps of a given type updates its associated variables by an approximation to a differential equation evolved, as described below, for a total time equal to an inner timestep, δ_t. In the limit as $\delta_t \to 0$, a multigrator configuration that corresponds to one of the previous integrators (`NH_NVT`, `MTK_NPT`, `L_NPT`, etc.) approaches the results of that integrator with barostat τ parameters multiplied by n_B and thermostat τ parameters multiplied by n_T.

The `Langevin` thermostat steps evolve the $\mathbf{p}$ variables according to

$$\dot{\vec{p}_i} = -(\vec{p}_i + \sigma_i\dot{\vec{S}_i}(t))/(n_B\tau), \tag{7.84}$$

where each component of the random vector $\vec{S}(t)$ is a standard Wiener process.

The `NoseHoover` thermostat steps add Nosé-Hoover chains consisting of 2 extended variables (ζ_i^j, ν_i^j) for each τ_i^j, governing the particles of thermostat j, and evolve them and the $\mathbf{p}$ variables according to

$$\begin{aligned}
\dot{\zeta}_i^j &= \nu_i^j / w_i^j && (7.85)\\
\dot{\vec{p}}_i &= -\vec{p}_i \nu_1^{\chi(i)} / w_1^{\chi(i)} && (7.86)\\
\dot{\nu}_1^j &= \sum_{i|\chi(i)=j} \|\vec{p}_i\|^2/m_i - C_1^j - \nu_1^j \nu_2^j / w_2^j && (7.87)\\
\dot{\nu}_i^j &= (\nu_i^j)^2 / w_{i-1}^j - C_i^j - \nu_i^j \nu_{i+1}^j / w_{i+1}^j && (7.88)\\
\dot{\nu}_n^j &= (\nu_n^j)^2 / w_{n-1}^j - C_n^j && (7.89)
\end{aligned}$$

where $w_i^j = C_i^j (n_T \tau_i^j)^2$ with $C_1^j = k_B T_j N_j$ and $C_{i>1}^j = k_B T_j$, where N_j is the number of degrees of freedom of the governed particles j.

To have no thermostat set `thermostat = none`.

The only type of barostat supported is `MTK` (to have no barostat set `barostat = none`). The `MTK` type introduces extended variables $\mathbf{s}$ and η (as described in Section 7.6.4), and add an extended variable energy equal to $\sum_i \eta_i^2/(2W) + \left(P_0 - \mathrm{Tr}\left\{\mathbf{T}\mathbf{B}(\mathbf{s})^{-1}\right\}\right)|\mathbf{B}(\mathbf{s})|$. The `MTK` barostat's velocities, η, can be thermostated by one of `Langevin` or `NoseHoover` (to have no thermostat set `barostat.thermostat = none`).

Without a thermostat the `MTK` barostat steps evolve the $\mathbf{r}, \mathbf{p}, \mathbf{s}, \eta$ variables as a Martyna-Tobias-Klein barostat without its Nosé-Hoover chain,

$$\begin{aligned}
\dot{\vec{r}}_i &= \mathbf{A}(\eta)\vec{r}_i / W && (7.90)\\
\dot{s}_i &= \eta_i s_i / W && (7.91)\\
\dot{\vec{p}}_i &= -\left(1 + 1/N_g\right) \mathbf{A}(\eta)\vec{p}_i / W && (7.92)\\
\dot{\eta} &= \mathbf{a}\left((\mathbf{P}(\mathbf{r}, \mathbf{p}, \mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \frac{\vec{p}_i \vec{p}_i^t}{m_i} \right) && (7.93)
\end{aligned}$$

The barostat mass, W, is given by $W = (3N_g + d) k_B T_b (n_B \tau_p)^2$,

With the `Langevin` thermostat, the barostat steps evolve the $\mathbf{r}, \mathbf{p}, \mathbf{s}, \eta$ variables as a Langevin piston,

$$\begin{aligned}
\dot{\vec{r}}_i &= \mathbf{A}(\eta)\vec{r}_i / W && (7.94)\\
\dot{s}_i &= \eta_i s_i / W && (7.95)\\
\dot{\vec{p}}_i &= -\left(1 + 1/N_g\right) \mathbf{A}(\eta)\vec{p}_i / W && (7.96)\\
\dot{\eta} &= \mathbf{a}\left((\mathbf{P}(\mathbf{r}, \mathbf{p}, \mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \frac{\vec{p}_i \vec{p}_i^t}{m_i} \right) - (\eta + \sigma_b \dot{\mathbf{S}}(t))/(n_B \tau_b) && (7.97)
\end{aligned}$$

where each of the components of the vectors $\mathbf{S}$ and $\vec{S}_i$ is a standard Wiener process and $\sigma_b = \sqrt{2 W k_B T_b \tau_b}$.

With the `NoseHoover` thermostat, the barostat steps add two variables (ζ_j^b, ν_j^b) for each τ_j^b and evolve them and the $\mathbf{r}, \mathbf{p}, \mathbf{s}, \eta$ variables as a Martyna-Tobias-Klein piston,

$$\begin{aligned}
\dot{\vec{r}_i} &= \mathbf{A}(\eta)\vec{r}_i/W && (7.98)\\
\dot{s}_i &= \eta_i s_i/W && (7.99)\\
\dot{\zeta}_i^j &= \nu_i^j/w_i^j && (7.100)\\
\dot{\vec{p}_i} &= -\left(1+1/N_g\right)\mathbf{A}(\eta)\vec{p}_i/W && (7.101)\\
\dot{\eta} &= \mathbf{a}\left((\mathbf{P}(\mathbf{r},\mathbf{p},\mathbf{B}(\mathbf{s})) - \mathbf{P}_0(\mathbf{B}(\mathbf{s})))|\mathbf{B}(\mathbf{s})| + \frac{1}{N_g}\sum_i \frac{\vec{p}_i\vec{p}_i^t}{m_i}\right) - \eta\nu_1^b/w_1^b && (7.102)\\
\dot{\nu}_1^b &= \sum_i \eta_i^2/W - C_1^b - \nu_1^b\nu_2^b/w_2^b && (7.103)\\
\dot{\nu}_i^j &= (\nu_{i-1}^j)^2/w_{i-1}^j - C_i^j - \nu_i^j\nu_{i+1}^j/w_{i+1}^j && (7.104)\\
\dot{\nu}_n^j &= (\nu_{n-1}^j)^2/w_{n-1}^j - C_n^j && (7.105)
\end{aligned}$$

where each of the components of the vectors $\mathbf{S}$ and $\vec{S}_i$ is a standard Wiener process and $\sigma_b = \sqrt{2Wk_BT_b\tau_b}$.

name	**description**
`nve.type`	the type of NVE step. [*none*/*Verlet*/*PLS*]
`thermostat.type`	the type of thermostat step. [*Langevin*/*NoseHoover*]
`thermostat.timesteps`	Number of innermost time steps per full thermostat step. [*Integer*> 0 *a multiple of the outer RESPA timesteps*]
`barostat.type`	the type of barostat step. [*MTK*]
`barostat.thermostat.type`	thermostat type of the barostat step. [*Langevin*/*NoseHoover*]
`barostat.timesteps`	Number of innermost time steps per full barostat step. [*Integer*> 0 *a multiple of the thermostat timesteps*]

Table 7.13: Parameters for Multigrator

The particular parameters for the various kind of thermostat and barostat steps are discussed in sections on other integrators.

Stability of the PLS and Verlet inegrators

Although the PLS NVE steps have accuracy advantages over Verlet NVE steps for integrating harmonic motion as well as advantages in reproducing certain thermodynamic statistics, they can have decreased stability (the maximum δ_t for which the simulation does not *blow up*) in comparison.

Linear stability theory can be carried out analytically, by integrating a harmonic oscillator and looking for modes which positive exponential growth, but such analysis is not useful in making stability comparisons for schemes where the force field has been split into various components active in different phases (any component may contain the hypothetical harmonic potential). Instead, we have carried out an empirical analysis on a test system (5dhfr), comparing the results of Verlet and PLS at different RESPA schedules. The maximum δ_t reported is the value of `integrator.dt` for which the simulation, judging by a sudden increase in energy drift, began to become unstable.

method-schedule	max δ_t (fs)	fraction of Verlet111	fraction of Verlet
Verlet 1,1,1	3.7	1.00	1.00
Verlet 1,2,2	3.1	0.84	1.00
Verlet 2,2,2	2.0	0.54	1.00
Verlet 1,3,3	2.3	0.62	1.00
Verlet 3,3,3	1.3	0.35	1.00
Verlet 1,4,4	1.7	0.46	1.00
PLS 1,1,1	3.7	1.00	1.00
PLS 1,1,2	2.3	0.62	0.62
PLS 1,1,3	2.7	0.73	0.73
PLS 1,1,4	2.5	0.68	0.68
PLS 1,2,2	2.3	0.62	0.74
PLS 1,3,3	2.3	0.62	1.00
PLS 1,3,6	1.5	0.41	0.65
PLS 1,2,4	2.1	0.57	0.68
PLS 1,4,4	1.7	0.46	1.00

Table 7.14: Empirical estimation of the maximum δ_t before the onset of instability for various types of NVE step. The last two columns give the fraction of each method's δ_t relative to that of Verlet 1,1,1 and to Verlet with the same schedule.

7.6.11 The Concatenator integrator

```
integrator.Concatenator = {
  sequence = [ {
    name=key_1
    type=type_1
    time=T_1
  } ... {
    name=key_n
    type=type_n
    time=T_n
  } ]
  key_1={ ... }
  ...
  key_n={ ... }
}
```

The concatenator is a means to alternate different integrator types for various periods of time in a cyclic sequence. The `sequence` parameter specifies the integrator types, *type*$_i$, to be run for periods of time, T_i. The sequence is treated cyclically, starting over from the first one after the last one finishes. The configuration section for each integrator is given by an arbitrary key name, *key*$_i$, in the remainder of the concatenator configuration.

For example, if one wished to alternately employ `L_NVT` and `V_NVE` for periods of 100 ps and 500 ps each, one configures this integrator as follows:

Example 7.1

```
integrator.Concatenator = {
  sequence = [ {
    name=firstone
    type=L_NVT
    time=100
  } {
    name=secondone
    type=V_NVE
    time=500
  } ]
  firstone = {
    thermostat = {
      tau = τ
      seed = s
    }
  }
  secondone = {}
}
```

A typical application would be to have one integrator function as an equilibration, or initialization, of the second integrator.

name	**description**
`sequence[i].type`	The type of integrator i in the sequence, e.g. `V_NVE`, `MTK_NPT`, etc. [*string*]
`sequence[i].time`	Length of time for which to run integrator i in the sequence. [*time*]
`sequence[i].name`	Arbitrary key name, *key*$_i$, for the integrator specific configuration information for integrator i in the sequence. [*string*]
key$_i$	The integrator specific configuration section for the particular integrator type of integrator i in the sequence. [*configuration*]

Table 7.15: Parameters for mdsim

Chapter 8

Free Energy Simulations

This chapter explains the concepts necessary to configure ligand-binding and alchemical free-energy simulations and those using the Bennett acceptance ratio method, as well as describing how to prepare a structure file for free energy simulations.

8.1 Configuring free energy simulations

Free energy simulations are configured as shown in:

```
force.term = {
  list = [ ... key ... ]
  key = {
    type = alchemical|binding
    alpha_vdw = α
    window = i_w
    output = {
      first = t_f
      interval = t_i
      name = filename
    }
    weights = { ... }
  }
}
```

The free energy F of a thermodynamic system with Hamiltonian H is related to the partition function Z of the corresponding ensemble by:

$$F = -k_B T \ln(Z_H) \tag{8.1}$$

where k_B is the Boltzmann constant and T is the temperature and Z_H is the partition function for the Hamiltonian H. The free energy is not an average of some quantity over the phase space; therefore it can not be computed from molecular dynamic simulations or other importance sampling techniques. Fortunately, what matters in problems of chemistry and biology is the relative free energy: the difference between two systems acting through different Hamiltonians. This difference in free energy can be expressed as an ensemble average and is thus amenable to computation by importance sampling.

Consider two systems with different Hamiltonians H_0 and H_1. In the canonical ensemble at temperature T, the free-energy difference between the two systems is:

$$\begin{aligned} F &= F_1 - F_0 = -k_B T \ln(Z_0/Z_1) && (8.2)\\ &= -k_B T \ln \int Z_0^{-1} e^{-\beta H_1(\mathbf{r})} \prod_i d^3\vec{r}_i && (8.3)\\ &= -k_B T \ln \int Z_0^{-1} e^{-\beta H_0(\mathbf{r})} e^{\beta(H_0(\mathbf{r})-H_1(\mathbf{r}))} \prod_i d^3\vec{r}_i && (8.4)\\ &= -k_B T \ln \left\langle e^{\beta(H_0(\mathbf{r})-H_1(\mathbf{r}))} \right\rangle_0 && (8.5)\end{aligned}$$

where $d^3\vec{r}_i$ is the volume elements of the position of particle i.

This equation suggests that, at least in theory, we can compute ΔF by sampling $\mathbf{r}$ according to the canonical distribution $e^{-\beta H_0(x)}$ and computing the average of $e^{\beta(H_0(x)-H_1(x))}$. In practice, we use better estimators, such as the Bennett acceptance ratio (BAR) method (see Section 8.1), to compute ΔF because of its lower statistical variance.

The variance in the computed ΔF is small only when the two Hamiltonians are similar such that the two systems overlap significantly in phase space. In order to compute ΔF when H_0 and H_1 are very different, we introduce $n-1$ interpolating Hamiltonians, H_λ, where $\lambda \in \{i/n : 0 \le i \le n\}$, between H_0 and H_1, such that each pair of adjacent Hamiltonians is similar enough that the corresponding systems overlap significantly in phase space. This family of Hamiltonians therefore provides a smooth and gradual transition from the initial state H_0 to the final state H_1.

To compute the free energy difference between H_0 and H_1, n independent simulations are run for each $\lambda = i_w/n$. Each such simulation computes a pair of energy differences, $(w^{(i_w,+)}, w^{(i_w,-)})$, where $w^{(i_w,+)} = H_{(i_w+1)/n} - H_{i_w/n}$ and $w^{(i_w,-)} = H_{(i_w-1)/n} - H_{i_w/n}$, sampled at a prescribed time interval t_i. The free energy differences between the associated consecutive pair of H_λ is then estimated from the $(w^{(i_w,+)}, w^{(i_w,-)})$ samples using the Bennett acceptance ratio method. These estimates $W^{(i_w,\pm)}$ are written to the output file by the name specified in `force.gibbs.output.name` in the format shown in:

$$\begin{array}{ccc} t_f & W_0^{(i_w,-)} & W_0^{(i_w,+)} \\ t_f + t_i & W_1^{(i_w,-)} & W_1^{(i_w,+)} \\ & \cdots & \\ t_f + m t_i & W_m^{(i_w,-)} & W_m^{(i_w,+)} \end{array} \qquad (8.6)$$

Combining two outputs from simulation i_w and i_w+1, we can estimate the free energy difference $\Delta F_{i_w/n,(i_w+1)/n}$ between systems $H_{i_w/n}$ and $H_{(i_w+1)/n}$. The desired free energy difference between H_0 and H_1 is then given by $\Delta F = \Delta F_{0,1/n} + \cdots + \Delta F_{(n-1)/n,1}$.

name	description
`type`	The type of free energy simulation to run. [*alchemical/binding*]
`alpha_vdw`	The parameter in the softcore potential. [*Real* ≥ 0]
`window`	Selecting the values to use in this simulation. [*Integer* $\in \{0, 1, \ldots, n\}$]
`output.first`	The time to write the first energy difference value. [*Time* ≥ 0]
`output.interval`	The interval at which to write the energy difference estimates. [*Time* ≥ 0]
`output.name`	The name of the file to which to write the energy estimates. [*Filename*]

Table 8.1: Parameters for FEP

Bennett acceptance ratio method

Consider a simulation under Hamiltonian H_a and another under H_b, both at temperature T. N_a samples of $W^{(+)} = H_b(\mathbf{r}) - H_a(\mathbf{r})$ are accumulated in the former simulation and N_b of $W^{(-)} = H_a(\mathbf{r}) - H_b(\mathbf{r})$ in the latter. The free energy difference between systems a and b is estimated by solving the following nonlinear equation for ΔF:

$$\sum_{i=1}^{N_a} \frac{1}{1 + \frac{N_a}{N_b}\exp(\beta(W_i^{(+)} - \Delta F))} - \sum_{j=1}^{N_b} \frac{1}{1 + \frac{N_a}{N_b}\exp(\beta(\Delta F + W_j^{(-)}))} = 0 \tag{8.7}$$

Charles Bennett (see [2]) first demonstrated that this solution provides the minimum-variance estimate of ΔF. Two decades later, Michael Shirts et al. (see [12]) proved that it is also the maximum-likelihood estimator of ΔF.

The Bennett acceptance ratio method is implemented in the script `bennett.py`. It is tailored to work with output files of the above form.

Binding free energy simulations

```
force.term.key = {
  type = binding
  ...
  weights = {
    es = [C_0 C_1/n ... C_1]
    vdw = [v_0 v_1/n ... v_1]
  }
}
force.nonbonded.near = {
  type=binding:softcore
  ... # same parameters as default
}
force.nonbonded.far = {
  type=binding:pme|binding:gse
  ... # same parameters as pme or gse
}
```

Binding free energy simulations compute the free energy of adding a molecule (called the *ligand*) to the chemical system. Effectively, this free energy is the difference between:

- the system in which the ligand is fully interacting with the rest of the system, and
- the system in which the ligand is not interacting at all with the rest of the system.

Denoting the ligand degrees of freedom by $\mathbf{r}_L$ and those of the rest of the system by $\mathbf{r}_S$, the Hamiltonian of the system can be separated into three components:

$$H(\mathbf{r}) = H_L(\mathbf{r}_L) + H_S(\mathbf{r}_S) + V(\mathbf{r}_L, \mathbf{r}_S), \tag{8.8}$$

where H_L and H_S are the Hamiltonians of the ligand and the rest in isolation and V is the interaction potential between the particles of the ligand and the rest.

We introduce a family of interpolating Hamiltonians:

$$H_\lambda(\mathbf{r}) = H_L(\mathbf{r}_L) + H_S(\mathbf{r}_S) + V_\lambda(\mathbf{r}_L, \mathbf{r}_S), \tag{8.9}$$

such that $V_0(\mathbf{r}_L, \mathbf{r}_S) = 0$ and $V_1(\mathbf{r}_L, \mathbf{r}_S) = V(\mathbf{r}_L, \mathbf{r}_S)$.

At present, Desmond handles only the most common case where ligand molecules do not have covalent interactions with the rest of the system. In terms of a classical force field, this means that the interaction between the ligand and the rest of the system consists of nonbonded (van der Waals and electrostatic) interactions only. Desmond uses the following form for the interaction potential V_s:

$$V_\lambda(\mathbf{r}_L, \mathbf{r}_S) = \sum_{i\in L, j\in S} f_{v_\lambda}(\|\vec{r}_i - \vec{r}_j\|; \epsilon_{ij}, \sigma_{ij}, \alpha) + C_\lambda \sum_{i\in i, j\in s} \frac{q_i q_j}{\|\vec{r}_i - \vec{r}_j\|} \tag{8.10}$$

where f_v is the following softcore potential governed by parameter α:

$$f_v(r; \epsilon, \sigma, \alpha) = 4v\epsilon \left(\left(\frac{\sigma^6}{\alpha(1-v)^2\sigma^6 + r^6} \right)^2 - \frac{\sigma^6}{\alpha(1-v)^2\sigma^6 + r^6} \right), \tag{8.11}$$

where ϵ_{ij} and σ_{ij} are the usual Lennard-Jones parameters. The soft-core potential is used so that the energy difference $W^{(i_w,+)}$ is always bounded for $v = 0$, even when non-ligand atoms are infinitesimally close to the ligand atoms.

In theory, the path of changing (v, C) from $(0, 0)$ to $(1, 1)$ should not affect the computed ΔF, because free energy is a state variable, independent of history and determined only by the thermodynamic state. Practically, however, the choice of the (v, C) path affects both the convergence and the stability of simulations. Most importantly, when the ligand and the rest of the system interact through the softcore potential (that is,

$v \neq 1$), non-ligand atoms can overlap with ligand atoms in space, causing the Coulombic interaction between their partial charges to diverge, unless this electrostatic interaction has been turned off (that is, $C = 0$). Hence, it is always necessary to turn off Coulombic interactions before turning off Lennard-Jones interactions.

An example of a sensible λ schedule for a binding free energy simulation is given in:

```
weights = {
  vdw = [0.00 0.25 0.50 0.75 1.00 1.00 1.00 1.00 1.00]
  es  = [0.00 0.00 0.00 0.00 0.00 0.25 0.50 0.75 1.00]
}
```

To carry out ligand-binding free energy simulations, you must specify which atoms in the system belong to the ligand by setting `grp_ligand` for these atoms to 1, and for all other atoms to 0 in the structure file.

name	**description**
`weights.vdw`	parameterizes intermediate Lennard-Jones interactions. [*List of* $0 \leq$ *Reals* ≤ 1]
`weights.es`	parameterizes intermediate electrostatic interactions. [*List of* $0 \leq$ *Reals* ≤ 1]

Table 8.2: Parameters for binding FEP

Alchemical free energy simulations

Alchemical free energy simulations are configured as shown in:

```
force.term.key = {
  type = alchemical
  ...
  weights = {
    bondA = [$b_0^A$ $b_{1/n}^A$ ... $b_1^A$]
    bondB = [$b_0^B$ $b_{1/n}^B$ ... $b_1^B$]
    qA = [$c_0^A$ $c_{1/n}^A$ ... $c_1^A$]
    qB = [$c_0^B$ $c_{1/n}^B$ ... $c_1^B$]
    vdwA = [$v_0^A$ $v_{1/n}^A$ ... $v_1^A$]
    vdwB = [$v_0^B$ $v_{1/n}^B$ ... $v_1^B$]
  }
}
force.nonbonded.near = {
  type=alchemical:softcore
  ... # same parameters as default
}
```

In alchemical free energy simulations, a part of the system (called A) is changed into something else (called B). In this transformation, some atoms change their Lennard-Jones parameters and partial charges, and some bonded interactions change their parameters. We introduce a family of interpolating potential functions parameterized by λ and $(v^A, v^B, c^A, c^B, b^A, b^B)$. The potential function of H_λ is the sum of electrostatic, softcore Lennard-Jones, and bonded terms

$$V_\lambda(\mathbf{r}) = V_\lambda^{\text{elec}}(\mathbf{r}) + V_\lambda^{\text{vdw}}(\mathbf{r}) + V_\lambda^{\text{bond}}(\mathbf{r}). \tag{8.12}$$

The interpolating electrostatic interaction is computed using partial charges linearly interpolated between A and B. In other words, it is computed using the charges:

$$q_i = c_\lambda^A q_i^A + c_\lambda^B q_i^B \tag{8.13}$$

(the alchemical charges, q^A, q^B are taken from the structure file). The Lennard-Jones interactions for a pair of atoms, i and j, changing their combined Lennard-Jones parameters from $(\epsilon_{ij}^A, \sigma_{ij}^A)$ to $(\epsilon_{ij}^B, \sigma_{ij}^B)$, the following intermediate potential is used:

$$V_\lambda^{\text{vdw}}(\vec{r}_i, \vec{r}_j) = f_{v_\lambda^A}(\|\vec{r}_i - \vec{r}_j\|, \epsilon_{ij}^A, \sigma_{ij}^A) + f_{v_\lambda^B}(\|\vec{r}_i - \vec{r}_j\|, \epsilon_{ij}^B, \sigma_{ij}^B) \tag{8.14}$$

where f is the softcore potential defined in Equation 8.11. The intermediate bonded interactions are the linear interpolations between the interactions with parameters in A and B:

$$V_\lambda^{\text{bond}}(\mathbf{r}) = b_\lambda^A V_A^{\text{bond}}(\mathbf{r}) + b_\lambda^B V_B^{\text{bond}}(\mathbf{r}) \tag{8.15}$$

where the A state and B state bonded interactions, V_A^{bond} and V_B^{bond}, are taken from the structure file. Arguably, alchemical *partial 14* terms (see Section 5.1) should transform according to the $v^{\{A,B\}}, c^{\{A,B\}}$ and adopt the soft-core functional form of Equation 8.11. Within a DMS file, users can select this version by replacing their `alchemical_pair_12_6_es` terms with identically parameterized `alchemical_pair_softcore_es` terms.

Although the path of changing V_λ from V_0 to V_1 should not, in theory, affect the outcome of the free energy calculation, in practice, the choice of λ path determines the precision of calculated ΔF, as well as the stability of the simulations. For instance, if an atom has different Lennard-Jones parameters in states A and B, at intermediate v_λ, it is interacting with other atoms through the soft-core potential. Unlike the Lennard-Jones potential that rises steeply to infinity as the inter atomic distance r decreases to zero, the soft-core potential remains bounded for $r = 0$.This means that other atoms can be infinitesimally close to this atom. If the concerned atom has a nonzero partial charge, infinite electrostatic energy results; therefore, it's important to turn off the partial charges on mutating atoms before changing their Lennard-Jones interactions. Here is a sensible schedule of alchemical transformation:

```
weights = {
  bondA = [1.00 1.00 1.00 0.75 0.50 0.50 0.50 0.25 0.00 0.00 0.00]
  bondB = [0.00 0.00 0.00 0.25 0.50 0.50 0.50 0.75 1.00 1.00 1.00]
  qA    = [1.00 0.75 0.50 0.25 0.00 0.00 0.00 0.00 0.00 0.00 0.00]
```

```
    qB    = [0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.25 0.50 0.75 1.00]
    vdwA  = [1.00 1.00 1.00 1.00 0.75 0.50 0.25 0.00 0.00 0.00 0.00]
    vdwB  = [0.00 0.00 0.00 0.00 0.25 0.50 0.75 1.00 1.00 1.00 1.00]
}
```

name	**description**
`lambda.vdwA`	values to parameterize the Lennard-Jones interactions in the A state. [*List of* $0 \leq$ *Real* ≤ 1]
`lambda.vdwB`	values to parameterize the Lennard-Jones interactions in the B state. [*List of* $0 \leq$ *Real* ≤ 1]
`lambda.chargeA`	values to scale the partial charges in A state. [*List of* $0 \leq$ *Real* ≤ 1]
`lambda.chargeB`	values to scale the partial charges in B state. [*List of* $0 \leq$ *Real* ≤ 1]
`lambda.bondedA`	values to scale the bond terms in A state. [*List of* $0 \leq$ *Real* ≤ 1]
`lambda.bondedB`	values to scale the bond terms in B state. [*List of* $0 \leq$ *Real* ≤ 1]

Table 8.3: Parameters for alchemical

Chapter 9

Enhanced Sampling and Umbrella Sampling

9.1 Introduction

9.1.1 Who should read this chapter?

This document is intended to provide all the information needed for a Desmond user to perform umbrella sampling and metadynamics using the enhanced sampling plugin. Basic understanding of the theory of umbrella sampling and metadynamics is assumed. Though the information in this document will be of interest to developers, the primary developer documentation is the Doxygen comments in the source code.

9.1.2 Enhanced sampling functionality

The enhanced sampling plugin is capable of performing umbrella sampling for potentials that can be expressed as functions of the coordinates of a subset of particles, expressed as VMD selections. To support complex potentials, a simple interpreter for symbolic expressions has been developed. The interpreter allows the user to specify the potential using a set of primitive operations, such as norm and arithmetic operators, which will be transformed into a Desmond configuration file. The advantage of symbolic expressions is that the user needs only to specify the potential, and the force associated with the potential will be calculated automatically. The expressions may also include more complex primitives, such as RMSD computation, that specialize the expressions to handle common chemistry potentials. It is expected that the number of available chemistry-specific primitives will grow as awkward or frequently-used constructs are identified.

Metadynamics is supported through the same interpreter as umbrella sampling, and the collective coordinates needed for metadynamics are specified using the same symbolic expressions. The metadynamics coordinates may also be arbitrary functions of the particle positions, so long as they are expressible using the expression primitives. Support for metadynamics is provided through the `meta` keyword in the symbolic expressions, and umbrella sampling may be used in conjunction with metadynamics (e.g. to provide "walls" to bound the collective coordinates).

It is important to understand that whether being used for umbrella sampling or metadynamics, the action of the enhanced sampling plugin is always applied at the outer RESPA timestep. For a discussion of how Desmond applies plugins see the Desmond User's Guide.

9.2 Using the Enhanced Sampling Plugin

9.2.1 Workflow

Enhanced sampling potentials must be specified using the imperative *m-expression* syntax described below. The user will then run the `enhsamp` program to transform the potential description into an *s-expression* form suitable to use as a Desmond configuration file. The `enhsamp` is also responsible for resolving VMD atom selections using a Maestro structure file specified in its command line arguments.

A typical usage of the enhanced sampling plugin is given below.

```
edit enh.pot                                         # write potential file
enhsamp structure-file.dms enh.pot > enh.ark         # run parser
mdsim --include desmond-config.ark --include enh.ark  # launch Desmond
```

The output of the enhsamp program is a valid Desmond configuration file, and including the enhsamp output with a standard Desmond configuration file is all that is required to use the enhanced sampling plugin. The structure file used with Desmond must be the same as the structure file given to the enhsamp program.

9.2.2 Output format

By default, the only output generated is the chemical time and the value of the enhanced sampling potential. The user may specify additional output using the `print` function in symbolic expressions. This allows the user to print the value of an arbitrary expression to aid in debugging and interpreting results. Because of looping and other constructs in the symbolic expressions, the amount of output generated may not be the same every time the interpreter is called. In addition, if `print` is called within a loop, a large amount of output may be generated on each step. For these reasons, a structured output format is used instead of column output. This output occurs only every `interval` picoseconds to a file whose name is given by the `name` parameter.

Each line of output represents one evaluation of the enhanced sampling plugin and is of the format `[[`*`name1 value1`*`] [`*`name2 value2`*`] ...]`. Each value is a list of floating point numbers.

9.2.3 Example configuration

The following is an example of a simple configuration that creates a harmonic potential between atoms with GIDs 10 and 20.

```
declare_output( name     = "cvseq",  # output file
                first    = 0.0,      # first output occurs at time 0.0 ps
                interval = 0.020 );  # output every 0.020 ps

p = atomsel("index 10 20");  # select the needed particles
7.5 * dist(p[1], p[0])^2;    # compute the potential
```

The syntax of this m-expression code is explained below.

9.3 Interpreter

This section documents the m-expression syntax and semantics. The complete function reference is given in Appendix F.

9.3.1 Syntax

Potentials are specified in the interpreter using an imperative syntax. The program is divided into a header where global declarations are made, and a body where executable statements are written. Both the header and the body are semicolon-separated lists of statements, and the header is distinguished from the body only by the type of statements allowed in each section. In the example configuration above, the only header statement was the `declare_output` statement, and the rest of the statements constituted the body.

Each statement in the body is either an assignment or an expression. Each assignment is a variable name, followed by an equal sign, and then an expression. Each variable may only be bound once (i.e. this is a single assignment language), and later references to the variable use the stored value of the variable. The only exception to the single binding rule is if the variables are at different scopes, as explained below.

Expressions are written in a style similar to C or Python. Functions are called by writing the function name followed by a comma-separated list of arguments enclosed by parentheses. The binary operators $+$, $-$, $*$, $/$, and ^ are available, and they obey the normal precedence rules. Unary negation is indicated by writing a negative sign at the front of an expression. Importantly, the subtraction operator does not perform a minimum image computation. See the section 9.3.6 for more information. Array subscripts are indicated by using the syntax $a[i]$, where both the array and the index may be arbitrary expressions. Array subscripts have higher precedence than the binary arithmetic operators.

Expressions may indicate conditionals with the notation

`if` *`condition`* `then` *`positive-branch`* `else` *`nonpositive-branch`*

Note that `if` returns a value and may be used in expressions. The condition must be a single number, and the positive branch is used if that number is greater than zero. An example is

```
interaction = if time() - 10
                 then k * x^2  # if time > 10, use harmonic potential
                 else 0;       # otherwise, use zero potential
```

The unneeded branch is not executed.

The only looping construct in the m-expression language is the `series` expression, which sums its body over a set of iterators. As an example, the following series computes the sum of all harmonic pairwise interactions between sets of particles `a` and `b`.

```
s = series (i=0:length(a), j=0:length(b))
      k * dist(a[i], b[j])^2;
```

Each iterator is specified as

```
     iter_name = lower_bound:upper_bound
```

and the iteration is carried out for all integers i where *lower_bound* $\leq i <$ *upper_bound*.

Expression blocks and scoping are available. Blocks are indicated by wrapping a sequence of statements in braces, and blocks may appear anywhere within expressions. The only requirement is that the last statement in a block must be an expression and not an assignment. The value of the block is then the value of its last statement. Each block introduces a nested scope so that assignments made within a block are only available inside the block and shadow assignments made outside the block. An example that uses blocks is the following all-pairs interaction.

```
s = series (i=0:length(a), j=0:length(b)) {
      r = dist(a[i], b[j]);
      if r - 5
         then {
           r2 = (r-5)^2;
           k * r2;
         } else {
           0;
         };
    };
```

Note that the entire body of the enhanced sampling program is treated as if it is wrapped in a block.

Integer and floating point literals may be used in the normal manner. Some functions take strings as arguments. This is a special behavior, and strings do not exist anywhere else within the interpreter.

9.3.2 Interpreter values

All values within the interpreter are arrays of *germs*. A germ is a double-precision value and its differential. The differentials are not manipulated directly by the user; instead, every function uses the differentials of its arguments to compute the differential of its return value. In this way, the force associated with the user-specified potential is computed automatically.

Numeric literals in a symbolic expression are converted internally to arrays of length 1 with zero differential.

Some functions take an integer argument. Since there are no integers in the interpreter, a length one array should be used instead. The element of this array will be rounded to get an integer, and the differential of the germ will be discarded. If a function requires a particle identifier, then this should be a reference to a particle obtained by the `atomsel` function.

9.3.3 Static Variables

The interpreter has the ability to retain the value of certain variables for use on later time steps. The variables that should be preserved for future time steps are declared in the header with the `static` keyword. The type (array length) of each static variable must be specified in parentheses after the variable name. Static variables can be read like any other variable, but storing values in static variables must be done with the `store` function. The first argument to the store function is the variable name, while the second argument to the function is the value to be stored. It is important to note that the action of `store` is delayed, and *the values of static variables do not change until the end of the time step.* For this reason, all references to a static variable on the same time step will give the same value, regardless of stores executed on that time step. By the next time step, any stores will have had their effect and changed the value of the static variable. If a variable is referenced before a value has been stored in it, then the value of the variable will be a zero array of the correct length. For the purpose of derivative computation, the derivative of a static variable is always zero, even if the value stored had a nonzero derivative.

As an example of two uses of static variables, the following potential restrains a particle to its initial location and prints the displacement vector of the particle on this time step.

```
static x0(3), x_last(3);

k = 10;
p = atomsel("index 10");
x = pos(p[0]);

store(x_last, x);
print("x_diff", min_image(x-x_last));

if time()
   then {
     k * norm2(min_image(x-x0));
   }
```

```
else {
  store(x0, x);
  0;
};
```

Note that the printed difference will not make sense for the initial step because static variables are initialized with zeros.

9.3.4 Function classes

There are four classes of functions which differ in the way they evaluate their arguments. The classes are Normal, Threaded, Binary Threaded, and Special Forms. Unless otherwise noted, arguments are evaluated in left-to-right order.

Normal functions evaluate all their arguments before the function body is entered. After the arguments are evaluated, the function executes with the value of the arguments.

Threaded functions take exactly one argument and compute their return value element-wise over the elements of their argument. For example, if `cos` is applied to an array of angles, the result is an array of cosine values in the same order as the input array. This behavior should be familiar to users of software packages like `MATLAB`.

Binary Threaded functions take exactly two arguments, and represent an underlying function of two scalar arguments. If the two arguments to the Binary Threaded function are the same length, then the n-th element of the return value is the underlying binary function applied to the n-th elements of each of the two arguments. For example, `a+b` is just the element-wise sum of `a` and `b`. If a binary threaded function has an argument of length 1, then that argument is paired with each of the elements of the other argument. For example, the return value of `a*5` is the array whose n-th element is 5 times the n-th element of `a`. The behavior of Binary Threaded functions is similar, but not identical, to `MATLAB`'s treatment of addition.

Special Forms evaluate some or all their arguments in a non-standard manner. The output statement `print` is an example. The documentation for these functions explain their argument evaluation rules.

9.3.5 Functions

Below is a list of the available functions with brief descriptions of their behavior. Full descriptions of the functions are available in Appendix F.

`*`	multiplication
`+`	addition
`-`	subtraction
`/`	division
`^`	raise to integer power
`acos`	arccosine
`angle`	cosine of angle for 2 vectors

`angle_gid`	cosine of angle for 3 particles
`angle_gid_radians`	angle of 3 particles (unstable for angles near 0 or π)
`angle_radians`	angle of 2 vectors (unstable for angles near 0 or π)
`array`	create array
`atan2`	arctangent for two arguments
`center_of_geometry`	center of geometry for a group of particles
`center_of_mass`	center of mass for a group of particles
`cos`	cosine
`cross`	cross product
`delta`	min-image vector between two particles
`dihedral`	cosine and sine of dihedral angle for 3 vectors
`dihedral_gid`	cosine and sine of dihedral angle for 4 particles
`dihedral_gid_radians`	dihedral angle for 4 particles (problematic for angles near $\pm\pi$)
`dihedral_radians`	dihedral angle for 3 vectors (problematic for angles near $\pm\pi$)
`dist`	min-image distance between two particles
`dot`	dot product
`exp`	exponent
`length`	array length
`log`	logarithm
`mass`	mass of particle in amu
`meta`	metadynamics
`min_image`	minimum image of vector
`mod`	modulus
`norm`	norm of vector
`norm2`	squared norm
`pos`	lookup particle position
`pos_inner_prod`	weighted sum of particles positions
`pow`	positive base raise to arbitrary power
`print`	create output
`rmsd`	RMS displacement from model structure
`sign`	sign function with sign(0) = +1
`sin`	sine
`sqrt`	square root
`store`	store value for use at a later time step
`sum`	sum an array
`time`	chemical time

9.3.6 Periodic Images

The interpreter does not distinguish between vectors representing atom coordinates and arbitrary length-3 arrays, and the user is responsible for considering periodic images when computing collective variables. In particular, the code `pos(gid[2]) - pos(gid[1])` will *not* compute the minimum image displacement due to wrapping of periodic coordinates. The function `min_image` will compute the minimum image of an arbitrary length-3 array for the current simulation box. As a convenience, the functions `delta` and `dist` cover the most common coordinate differences that are needed. They are defined as follows.

```
delta(gid2, gid1) == min_image( pos(gid2) - pos(gid1) )
dist(gid2, gid1) == norm( min_image( pos(gid2) - pos(gid1) ) )
```

For algorithms that operate on widely separated parts of the protein, such as center of mass, the user is strongly encouraged to consider carefully how periodic images will be handled. Note that functions like the Enhanced Sampling implementation of RMSD have carefully specified behavior with respect to periodic images, and the user should review this behavior to ensure that the correct periodic images are chosen.

9.4 Metadynamics

Metadynamics is a free energy perturbation method which enhances sampling of the underlying free energy space by biasing against previously-visited values of user-specified collective variables. The biasing is achieved by dropping kernels (only Gaussian kernels have been implemented) at the current location of the simulation in the phase space of the collective variables. This history-dependent potential encourages the system to explore new values of the collective variables, and the accumulation of potential allows the system to cross potential barriers much more quickly than would occur in standard dynamics.

9.4.1 Usage

The enhanced sampling plugin implements metadynamics by using the `declare_meta` header to define the accumulator for the history-dependent potential and using the `meta` function to compute the potential for the interpreter. Each call to `declare_meta` creates an independent kernel accumulator, which does not share kernels with any other accumulator. The accumulators are indexed in the order that they are declared. The parameters to `declare_meta` are as follows.

dimension: defines the dimension of the collective variable space, which must be a positive integer.

cutoff: If the collective variables in the current configuration are more than cutoff number of kernel widths away from the center of a kernel, the kernel is not computed. If the cutoff is 0.0, an infinite cutoff is used.

first: determines the first time at which a Gaussian is added.

interval: determines the time between Gaussian drops. A value of 0.0 indicates that a Gaussian is dropped on every time step.

name: If non-empty, this gives the name of the kernel sequence file, which logs every kernel added to the simulation. See below.

initial: If non-empty, gives the location of a file containing kernels to be added at the beginning of a simulation. See below.

All kernels that are added to the simulation are logged to the kernel sequence file, where each kernel is described by the time it was added, its height, and its widths. Lines that begin with a hash, `#`, are comments. This same format may be used to define an initial kernels file, which is loaded at Desmond boot. The logged kernels can be used to initialize a new simulation with the metadynamics potential produced by a previous simulation or to start the simulation with a potential defined by an arbitrary kernel mixing model. When the kernels are loaded, the time values are required but are ignored in the computation—all initial kernels are used, regardless of the current value of chemical time. All initial kernels are written to the kernel sequence file before any new kernels are written.

The syntax of the `meta` keyword is

`meta(`*`meta_acc`*`, `*`height_width`*`, `*`collective_vars`*`)`

where *meta_acc* is an integer that references a member of the set of metadynamics accumulators, *`height_width`* is an array of height and widths to use for newly-inserted kernels, and *`collective_vars`* is an expression for the collective variables. The length of the collective variables array is equal to the dimension of the accumulator, and the length of the *`height_width`* array is one more than the dimension of the accumulator. The height is the value of the kernel at its center. The *`height_width`* array is only evaluated when a kernel is added to the potential.

9.4.2 Metadynamics example

An example configuration for a simple metadynamics simulation is given below. This configuration file biases the inter-atomic distance of the atoms given by GIDs 0 and 1.

```
# define the accumulator
declare_meta( dimension = 1,         # only one collective variable
              cutoff    = 9,         # in units of widths
              first     = 0.0,       # begin dropping immediately
              interval  = 0.200,     # wait 0.2 picoseconds between drops
              name      = "kerseq",  # log kernels to kerseq
              initial   = "" );      # no initial kernel file

p = atomsel("index 0 1");

meta(0,                    # use accumulator 0
     array(0.2, 0.1),      # height is 0.020 kcal/mole, width is 0.1 A
     dist(p[1], p[0]));    # coordinate is distance between atoms 0 and 1
```

More examples of metadynamics can be found in the next section.

9.5 Examples

The following sections give examples of enhanced sampling configurations to illustrate the uses of the enhanced sampling plugin.

9.5.1 Center of mass restraint

This example shows the use of an umbrella potential to harmonically restrain the center of mass for a group of particles. In this example, the masses of all particles are assumed to be the same.

```
declare_output( name = "cvseq", first = 0.0, interval = 0.1 );
spring = 1.0;
center = array(4.0, 5.0, 6.0);
p = atomsel("index 21 22 23 25 26 29");

sum_val = series( i=0:length(p) ) {
            diff = pos(p[i]) - center;
            norm2(min_image(diff));
         };

disp2 = sum_val / length(p);

print("sqr_disp", disp2);
spring * disp2;
```

9.5.2 Metadynamics for a dihedral angle

This example demonstrates the use of metadynamics on dihedral angles. In this case, the sine and cosine of the angle are biased to avoid the derivative singularities associated with inverse trigonometry.

Biasing angles based on sine and cosine can be understood in the following way. For a Gaussian centered at $\sin(\phi)$ and $\cos(\phi)$ with width w, we have

$$\exp\left(-\frac{(\sin(\theta)-\sin(\phi))^2}{2w^2}-\frac{(\cos(\theta)-\cos(\phi))^2}{2w^2}\right)=\exp\left(\frac{\cos(\theta-\phi)-1}{w^2}\right).$$

In the case that the width is small, this function is approximately a Gaussian in the angles with width w. This function differs only by normalization from the normal distribution on the circle, also known as the von Mises distribution.

```
declare_meta( dimension=2,        # for sine and cosine
              cutoff = 9,         # in units of widths
              first = 0.0,        # begin dropping immediately
              interval = 0.200,   # wait 0.2 picoseconds between drops
              name = "kerseq",    # log kernels to kerseq
              initial = "" );     # no initial kernel file

p = atomsel("index 14 15 16 17");

# height is 0.2 and widths are both 0.1
meta(0, array(0.2, 0.1, 0.1), dihedral_gid(p[0], p[1], p[2], p[3]));
```

9.5.3 Well-tempered metadynamics

This example will use well-tempered metadynamics to demonstrate metadynamics with dynamically varying heights. For well-tempered metadynamics, the height of a Gaussian added at time t is given by $h_0 e^{-\frac{V_t(x)}{kT_1}}$ where h_0 is the initial height, $V_t(x)$ is the metadynamics potential at the center position, and T_1 is a user-specified temperature. Since the metadynamics potential must be known before the Gaussian is added, a small trick is used. To evaluate the metadynamics potential without changing the potential, metadynamics is called with a height of 0.0. In this case, Gaussian kernels are added by this evaluation, but they do not contribute to the potential. They are, however, present in the kernel sequence file.

```
declare_meta( dimension=1, cutoff = 9, first = 0.0, interval = 0.200,
              name = "kerseq", initial = "" );

p   = atomsel("index 0 1");

h_0 = 0.020;  # initial height of gaussians
w   = 0.1;    # width of gaussians
kT1 = 2.4;    # sampling temperature

cv  = dist(p[1], p[0]);   # collective variable is interatomic distance

meta(0,
     array(h_0 * exp( meta(0, array(0,0), cv) / -kT1 ), w),
     cv)
```

9.5.4 Metadynamics with a wall

This example demonstrates the use of a wall to prevent metadynamics from driving the collective coordinates too far. The form of this wall is

$$\frac{h_{\text{wall}}}{1+\exp(\frac{x_0-c}{w_{\text{wall}}})},$$

where h_{wall} is the wall height, x_0 is the location of the wall, c is the collective variable, and w_{wall} is the width of the wall. The wall potential is added as an umbrella potential to the enhanced sampling symbolic expression.

```
declare_meta( dimension=1, cutoff = 9, first = 0.0, interval = 0.200,
              name = "kerseq", initial = "" );

p  = atomsel("index 0 1");

cv     = dist(p[1], p[0]);  # collective variable
x0     = 14;                # wall location
w_wall = 0.2;               # wall width
h_wall = 1000;              # wall height

wall = h_wall / (1 + exp( (x0-cv)/w_wall ));

wall + meta(0, array(0.2, 0.1), cv);
```

Chapter 10

Extending Desmond

This chapter provides a sketch for implementing extensions for Desmond. Full technical specifications are difficult to accomplish or keep current in a document removed from the source files. Hence, this chapter can only provide an outline and some pointers for further information.

10.1 Implementation

Desmond's built-in plugins are compiled with the application itself, but you can include your own plugins in the application by implementing them in an extension, a shared library (.so file) which is dynamically linked into an application at runtime. All plugins for Desmond must be organized into extensions.

You can create an extension with nothing more than GNU make. To create an extension:

- Put the root of the Desmond tree (containing the plugins subdirectory) into the include path, and add `#include <Desmond/Desmond.hxx>` to the top of the extension's header file.
- Compile and link the plugin as a shared library, without linking against any Desmond libraries. Be sure to compile and link with `-fPIC` (required in Linux when loading shared libraries).
- Other compiler flags and preprocessing directives may have to be set in accordance with the particulars of the Desmond installation. This may require recording the flags passed to Desmond during installation, unfortunately.
- Extensions are loaded into Desmond with `RTLD_GLOBAL`, so place all classes defined by the extension into either an anonymous namespace, or a namespace unique to your development environment.
- If you wish to checkpoint your simulation, all API subclasses must be serializable. These classes need to follow conventions layed out in `base/desmond_src/util/desurrection`.

factory (in namespace Desmond)	description
`MainPlugin::factory()`	main-loop plugins
`Integrator::factory()`	integration algorithms
`Hamiltonian::factory()`	force terms
`App::abstract_driver::factory()`	Application type (e.g. mdsim, remd)

Table 10.1: List of some of Desmond's factories and their call signatures.

10.1.1 Plugin interface

Desmond provides a number of APIs which can be extended to provide additional functionality, following the *abstract factory pattern.* These APIs take the form of abstract C++ classes, which are subclassed to create the new functionality, and extensible factories that can construct instances of these classes. When an extension is loaded the plugins in the extension add new concrete types in the extension to various factories in Desmond. The most common factories are listed in Table 10.1.

10.2 Running your plugin

If your plugin resides in a separately compiled extension, Desmond must find it and load it before it can be used. When Desmond starts, it searches for extensions by parsing the environment variable `DESMOND_PLUGIN_PATH` and searching for shared libraries created according to the compilation guidelines outlined in Section 10.1.

Extensions are loading immediately after the Desmond executable starts. Desmond processes extensions in three steps:

1. Desmond reads the extension's type, description, boot, and halt methods. This information is created by a static instance of the `desres::plugin::declaration` class. When Desmond loads the extension, it examines this information and checks to see if a plugin of that type has already been loaded; if it has, this plugin is not used, the declaration is ignored. In this manner, the plugins of all extensions in the `DESMOND_PLUGIN_PATH` are loaded and examined. Desmond then unloads any extensions who contributed no plugins and calls the boot method of each plugin declaration.

2. Among other thing, a plugin's boot method typically registers a concrete subclass of some interface class with an abstract factory under some *name*, so that this subclass can be produced by the factory as directed by the configuration or the structure file.

3. At some point in the parsing of the configuration file or the structure file, a string identifying the subclass by its abstract type and registered *name* will direct an instance of the subclass to be created through the appropriate factory.

When Desmond shuts down, the steps occur in reverse:

1. Desmond calls the halt method, as given in the plugin declaration, for each booted plugin; and
2. Desmond unloads the shared libraries.

Chapter 11

Trajectory Format and Analysis

Desmond writes time sampled data into trajectory collections. These collections are stored in the file system and are called *framesets*. These trajectories are a series of *frames* that represent snapshots of the simulation a various times. Each frame has a collection of simulation data. The data contains (at a minimum) information about chemical time, the unit cell, atom positions and atom velocities.

11.1 Structure of frameset directories

Framesets are stored in standard file system directories. At the top level of the directory are the `timekeys` file, the `metadata` file, a `clickme` file, and the `not hashed` directory which holds the `.ddparams` file. The frame data is held in frame files of the form `frame`*XXXXXXXXX* which are either at the top level (normally) or under a nest of numbered subdirectories.

The `timekeys` file contains version information, the number of frames contained in each frame file, and a map into the frame files. The number of total frames in the frameset is $\texttt{sizeof}((\mathit{timekeys}) - 12)/24$.

The `metadata` file is a frame file, but rather than containing time centered data, it contains data common to all frames in a trajectory. The `metadata` file may contain an empty frame. Typical fields in this file include `TITLE` and `INVMASS`.

The `clickme` file is an artifact of selecting files in a GUI browser like VMD. The file browser won't allow a user to select a directory, rather it clicks through to the underlying files. Selecting the `clickme` file results in VMD actually selecting the enclosing directory.

Very large framesets (100's of thousands of frames) can exceed directory files storage limits, so framesets can use a `DeepDir` hierarchical subdirectory structure to get around that limit. The `.ddparams` file contains two ASCII integers, `ndir1` and `ndir2`, that describe a two-level subdirectory system. `ndir1` is the number of directories at the top level while `ndir2` is the number of directories at the second level. For typical framesets, these numbers are 0 and 0 (i.e. framefiles are stored directly under the top level directory).

Desmond frames contain the following fields:

FORMAT	char[*]	WRAPPED_V_2 (FLT = float) or DBL_WRAPPED_V_2 (FLT = double)
CREATOR	char[*]	DESMOND
VERSION	char[*]	Desmond version
ELAPSED	double	wallclock from start
TITLE	char[*]	Title from configuration
PROVENANCE	char[*]	Build source info
BUILDCLASS	char[*]	real or double (will match FORMAT)
KERNEL	char[*]	e.g. linux
PROCESSOR	char[*]	e.g. x86_64
ISROGUE	uint32	1 for releases, 0 for internal builds
CHEMICALTIME	double	simulation time in picoseconds
ENERGY	double	in kcal/mole
POT_ENERGY	double	in kcal/mole
KIN_ENERGY	double	in kcal/mole
EX_ENERGY	double	in kcal/mole
FORCE_ENERGY	double	in kcal/mole
TEMPERATURE	double	in Kelvin
VOLUME	double	in cubic angstroms
PRESSURE	double	in Bar
PRESSURETENSOR	double[9]	in Bar
TEMPERATURE_PER_GROUP	double[ngroups]	in Kelvin
DEGREES_OF_FREEDOM	double	dimensionless
DEGREES_OF_FREEDOM_PER_GROUP	double[ngroups]	dimensionless
CHARGE_SUM	double	electron charge
CHARGE_SQUARED_SUM	double	electron charge squared
POSITION	FLT[3*natoms]	in Ångströms
VELOCITY	FLT[3*natoms]	in Ångströms/picosecond
UNITCELL	FLT[9]	Unit cell shift vectors as Ax,Bx,Cx, Ay,By,Cy, Az,Bz,Cz

11.2 Soft catenation option

Multiple frameset directories can be *soft catenated* by listing the directory pathnames in a STK file (ess-tee-kay) (file name suffix `.stk`) file separated by newlines. Tools like the Python `frameset` tools (see below), the VMD trajectory reader, and `molfile` can read STK files anywhere a DESRES trajectory file (DTR, file name suffix `.dtr`) is expected.

11.3 Command line tools for framesets

Frameset files have internal binary structure and are difficult to interpret manually. The frameset library includes some programs that allow users to inspect, view, and correct framesets.

11.3.1 fsdump

`fsdump` is used to look at the times, fields, and data contained in every frame in a frameset. Command line options control begin/end frames, which fields are viewed, and the maximum number of items in each field to view.

Example 11.1
```
$ fsdump [--begin=n] [--end=n] [--match=xxx] [--matchnot=xxx]
      [--max=n] [--hexfloat] [--json] framesetdir framesetdir ...
```

The `--begin` option defaults to frame 0, `--end` defaults to -1 (negative indices count from the back, so the -1th frame is the last frame, -2nd is second to last frame, etc. . .).

The `--match` and `--matchnot` options signify fields to pick or fields to skip. You may use multiple `--match` options together. So, to select only the potential and kinetic fields of a frameset, run:

Example 11.2
```
$ fsdump  --match=POT_ENERGY --match=KIN_ENERGY foobar.dtr
```

The `--max` option is used to trim very long output fields if you simply want to see a truncated view of a field. So, for example, `--max=12` will allow you to see the first 3 position triples.

By default, `float`s and `double`s are printed in decimal using default formats that, while they use a sufficient number of digits, can not precisely represent all the bits of precision stored internally in the frame. Using the `--hexfloat` option will print the floating point values in `%a` (hex) format that, while not easily readable, does perfectly represent all bits of precision in the `double` and `float` values.

The `--json` option creates `json` (Javascript object notation) compatible output that can be fed into any standard json reader. While slightly less readable, `json` output is easier to machine parse.

11.3.2 framedump

The `framedump` command works just like `fsdump`, but works on a single frame file. The command can be used to examine the common fields in the *metadata* frame file, for instance.

Example 11.3

```
$ framedump  [--begin=n] [--end=n] [--match=xxx] [--matchnot=xxx]
   [--max=n] [--hexfloat] [--json] framefile framefile ...
```

11.3.3 fstime

`fstime` lists the number of frames and the last time contained in a frameset directory.

Example 11.4

```
$ fstime framesetdir
105 10.5
```

11.3.4 fskeycheck

Occasionally, frameset files can be corrupted on disks. The `fskeycheck` tool will check the integrity of the timekeys and frame files. Using the `--fix` option will output a new timekeys file (in the current working directory) that truncates any bad frames. The frameset can be updated by replacing the original timekeys file with the newly generated one.

Example 11.5

```
$ fskeycheck [--fix] framesetdir
```

11.3.5 rebuild_timekeys

The information in the `timekeys` file is redundant. It is used to make a quick association between times and the bytes that represent the associated frames in the frame files. If the `timekeys` file is corrupt, broken, or missing, the `rebuild_timekeys` tool will scan all the frame files and create a new `timekeys` file in the current working directory.

Example 11.6

```
$ rebuild_timekeys  framesetdir
```

11.4 Python tools for trajectories and framesets

Command line tools are useful for a quick look at the data contained in trajectories, but it is difficult to write analysis tools from the text tools or the raw format itself. Desmond provides a library of C++ and Python tools to access frame data.

The Python modules make it easy to write high performance scripts to analyze trajectory data. The data are accessible via `numpy` arrays.

11.4.1 framesettools module for direct access

The `framesettools` module allows Python scripts access to the raw field data contained in the frames of a frameset. Desmond can write either its floating point positition data in a bitwise precise internal form or a simpler to access floating point form.

In its simplest form, Python framesets provide a frame iterator and `numpy` array access to data fields.

Example 11.7

```
import framesettools

fs = framesettools.FrameSet('myframeset.dtr')

print 'myframeset has', len(fs), 'frames from time', fs.times()[0],
      'to'fs.times()[-1]

# assumes a normal WRAPPED_V_2 Desmond trajectory
for frame in fs:
   x = frame.POSITION[0:3]
   print '  ',frame.CHEMICALTIME,'atom 0 has position',x
```

Users can also write (`'w'`), overwrite (`'w!'`), or extend (`'a'`) trajectories. By default, framesets opened in write mode will fail if the file already exists (Use `'w!'` if you wish to rewrite an existing frameset). Here is a sample program that will randomize positions.

Example 11.8

```
import framesettools
import random

fs = framesettools.FrameSet('foobar.dtr')
out = framesettools.FrameSet('output.dtr','w')
for frame in fs: # This iterates over all the frames
     pos = frame.POSITION # This is a 1-D (3*natoms) numpy array
     delta = [random.gauss(0,.1) for i in range(len(pos))]
     pos += delta
     out.push_back(frame,frame.CHEMICALTIME)
```

An example that writes out all the `ENERGY` fields:

Example 11.9

```
import framesettools
import random

fs = framesettools.FrameSet('foobar.dtr')
out = framesettools.FrameSet('output.dtr','w')
```

```
for frame in fs:
    print 'AT TIME',frame.CHEMICALTIME
    for attr in frame: # This iterates over the labels
        if attr.endswith('ENERGY'):
            print '  ',attr,getattr(frame,attr)
```

FrameSet attributes and methods	
`name`	file name used to open this frameset
`size`	number of frames in a frameset (also `len(fs)`)
`[index]`	get index'th frame
`hierarchicalName( filename )`	`DeepDir` hierarchical name of `filename`
`framefile(frameindex)`	path to `filename` holding the `frameindex`'th frame
`frameinfo(frameindex)`	`framefile, filesize, time, offset, framesize` of `frameindex`'th frame. `framefile` is the file (of size `filesize` bytes) holding the frame at `time`. The `framesize` serialized bytes for this frame are at position `offset` within the file.
`fileinfo(frameindex)`	`filepath, offset, framesize, first, lastp1, filesize` of the `frameindex`'th frame. `filepath` is the full path name to the file that contains frame `index`. `offset` is the starting bytes of the frame in the file. `framesize` is the size (in case there are varible length frames in a file). `first` is the lowest frame number contained in the same file. `lastp1` is 1 plus the highest frame number contained in the file (`lastp1` itself is not included in the file). `filesize` is the size of the file.
`metainfo()`	path to metadata frame file
`time(frameindex)`	Time associated with the `frameindex`'th frame
`times()`	`numpy` array of times associated with all frames
`rewind(time)`	For a writeable frameset, truncate any times after time
`nearest(time)`	Return frame object with associated time x where abs($x -$ `time`) is minimal
`le(time)`	Return frame object with largest associated time x where $x <=$ `time`
`lt(time)`	Return frame object with largest associated time x where $x <$ `time`
`ge(time)`	Return frame object with smallest associated time x where $x >=$ `time`
`gt(time)`	Return frame object with smallest associated time x where $x >$ `time`
`push_back(frame,t)`	Append frame to a writeable frameset. Time must be greater than previous last time entered.
`meta()`	Get the metaframe. On writeable framesets, changes here will be flushed to disk on closing.

Frame attributes and methods	
`__labels__`	list of all field names
`__endianism__`	endianism of the data in this frame (integer)
`__machineEndianism__`	endianism of this machine (integer)
`__sameendianism__`	true iff endianism of this frame matches machine endianism (Boolean)
`__has__(fieldname)`	true iff frame has an attribute `fieldname` (Boolean)
`__knowsType__(typename)`	true iff frame understands named C type (Boolean)
`__framesize__()`	Number of bytes required for serialization
`__serialize__()`	string serialization
`__type__(fieldname)`	C type name for this field (string)
`__count__(fieldname)`	Number of elements in this field
`__elementsize__( fieldname)`	Size of individual elements in the named field
`__nbytes__(fieldname)`	Number of bytes used to hold a field

11.4.2 generictrajectory module for simplified access

The generic trajectory module provides an interface to the unified trajectory reader object. We use this reader object to open any of the variety of trajectory files (and trajectory-like files) that are supported by Desmond. The module provides `Trajectory` and `Frame` types.

Not all frameset based trajectories have convenient `POSITION` and `VELOCITY` fields. Frames with the `FORMAT` field set `to WRAPPED_V_2` for `DBL_WRAPPED_V2` will have those fields, but frames in other formats will not. To simplify access, the `generictrajectory` module understands all Desmond formats and auto-converts frames into Python objects with `position`, `velocity`, `box`, `title`, and `time` attributes. Position and velocity are `numpy` arrays of `double[natoms][3]`, box is `double[3][3]`, `title` is a Python string, and `time` is a Python `float` (C `double`).

The generictrajectory frames are similar to the full frameset frames above, but have only the fixed attributes listed. These Frame objects are, however, pickleable.

The `generictrajectory` trajectory objects also have simplified time accessors. For instance you can access and iterate from frames based on their times, for example. To look at all frames whose times are between 20.5 and 30.5

Example 11.10
```
from generictrajectory import *

T = Trajectory('/path/to/somewhere.dtr')
for frame in T.at_time_ge(20.5):
   if frame.time > 30.5: break
   # process frame ...
```

The iterators can be accessed via the `at_time_near`, `at_time_lt`, `at_time_le`, `at_time_gt`, `at_time_ge` methods.

11.4.3 molfile module

The `molfile` module is a Python interface to the set of file I/O plugins that are included with the program VMD, developed at the University of Illinois. The Python interface provides methods for creating, loading and saving molecular structures and coordinates to all the file formats supported by VMD.

Below is a synopsis of how to perform common tasks using `molfile`.

Example 11.11

```
import molfile

# Reading a structure file:

reader = molfile.mae.read('/path/to/foo.mae')

# Iterating through the frames in a file:

for frame in molfile.dtr.read('/path/to/foo.dtr').frames():
    function( frame.pos, frame.vel, frame.time, frame.box )

# Random access to frames (only dtr files support this currently):

f27 = molfile.dtr.read('/path/to/foo.dtr').frame(27) # 0-based index

# Convert an mae file to a pdb file:

input=molfile.mae.read('foo.mae')
output=molfile.pdb.write('foo.pdb', atoms=input.atoms)
output.frame(input.frames().next())
output.close()

# Write every 10th frame in a dtr to a trr:

input=molfile.dtr.read('big.dtr')
output=molfile.trr.write('out.trr, natoms=input.natoms)
for i in range(0,input.nframes, 10):
    output.frame( input.frame(i) )
output.close()
```

All data is read to and from `molfile` objects in terms of a small number of classes defined within the module:

- `Atom`: Represents fixed particle attributes; i.e. no position or velocity! Atoms hold references to other atoms through their bonds member; use Atom.addbond and Atom.delbond to change the bond topology.

- `Frame`: Data from a single timestep. Contains position, velocity, unit cell, and physical time.

- `Plugin`: For each supported file type, e.g., 'pdb', 'mae', 'trr', there is a `Plugin` object with that name in the module. A `Plugin` can be queried for its capabilities using its `can_*` methods. Nearly all plugins can read files, but only some can write. Use the `Plugin.read` method to create a `Reader`, and `Plugin.write` to create a `Writer`. Some plugins, e.g., 'psf', read only structure data (atoms), while others, e.g., 'dtr', read only coordinate data (frames). If you try to read atoms from a 'dtr', or frames from a 'psf', you'll get an error.

- `Reader`: A `Reader` is a handle to an open file. Use the `atoms` member to fetch the atomic structure from the file, assuming it exists. To access frames, there are two methods. `Reader.frames()` returns a `FrameIter` object for iteration over frames. `FrameIter` has two methods: the usual `next()` method which returns a `Frame`, and `skip(n=1)`, which advances the iterator by `n` frames without (necessarily) reading anything. `FrameIter` is a very poor iterator: once a frame has been read or skipped, it can't be loaded again; you have use a brand new `Reader`. `Reader.frame(n)` — returns the nth frame (0-based index). Currently only the 'dtr' plugin supports this method.

- `Writer`: Writers are initialized with a path and either an array of Atoms or an atom count. If the Writer supports structure writing, Atoms must be provided; if the `Writer` only writes frames, either one will do. If the writer supports frame writing, `Writer.frame(f)` appends frame `f` to the end of the file. `Writer.close()` will be invoked when the Writer goes out of scope, but it's not a bad idea to invoke it explicitly.

Finally, there is a `guess_filetype(path, default=None)` function in the `molfile` module which returns a `Plugin` based on the file name, or the default if none found.

molfile object properties and methods	
Atom.altloc	PDB altloc value
Atom.anum	atomic number
Atom.bfactor	temperature factor
Atom.bonds	set of bonded neighbor atoms
Atom.chain	chain name
Atom.charge	charge in e
Atom.insertion	PDB insertion value
Atom.mass	mass in AMU
Atom.name	atom name
Atom.occupancy	PDB occupancy
Atom.radius	a vdw radius value
Atom.resid	PDB residue id
Atom.resname	residue name
Atom.segid	segment name
Atom.type	VMD atom type
Atom.addbond(atom)	add bond between self and atom
Atom.delbond(atom)	remove bond between self and atom
Frame.box	unit cell vectors as ROWS of 3x3 matrix
Frame.pos	positions as rows of Nx3 matrix
Frame.time	physical time
Frame.vel	velocities as rows of Nx3 matrix
Frame.__init__(natoms)	new Frame with given number of atoms
Frame.moveby(x,y,z)	shift the positions by the given amount
Frame.select(inds)	new Frame with selected atoms
Reader.atoms	copy of the atoms in the structure
Reader.natoms	number of atoms
Reader.nframes	number of frames; -1 if not known
Reader.topology	bond neighbor list
Reader.frame(i)	Frame at index i
Reader.frames()	iterator over frames
Writer.natoms	number of atoms in output file
Writer.path	path of output file
Writer.close()	close the writer
Writer.frame(f)	write Frame f
Plugin.can_read	can create a Reader
Plugin.can_write	can create a Writer
Plugin.name	name of the plugin
Plugin.prettyname	pretty name
Plugin.version	(major, minor) version
Plugin.read(path)	new Reader for given path
Plugin.write(path, ...)	new Writer for path; supply natoms or atoms

Appendix A

Units

This appendix explains how numbers provided as configuration parameters are interpreted.

Many configuration parameters are real numbers that are interpreted as dimensioned quantities. Desmond code uses the 2002 CODATA adjustment for units as given by the National Institute for Standards [9]. For a given dimension, Desmond always uses the same kind of units:

- Time is in picoseconds (ps).
- Length is in Ångströms (Å).
- Energy is in (thermochemical) kilocalories per mole.
- Pressure is in Bar.
- Temperature is in degrees Kelvin (K).
- Charge is in multiples of the absolute electron charge.

Boolean values are either true or false.

Integers are assumed to be in the range of two's complement 32bit representations.

Real-valued quantities can be given in decimal or scientific 'e' notation. ±`infinity` and ±`inf` are also recognized real values, as is ±`nan`. See strtod(3) for a full description of the acceptable values for real-valued quantities.

Appendix B

Configuration syntax

This appendix describes the configuration file syntax.

All Desmond applications are configured by means of command line options or configuration file parameters according to a uniform syntax. The command line options can be summarized and stored in plain text files, called *configuration files*, which represent a summary of the state of the configuration. This is discussed in Section 2.2.

This appendix describes configuration file syntax in formal terms and provides additional examples.

In Backus-Naur Form (BNF), a configuration is:

```
CONFIG -> KEYVAL *
KEYVAL -> key = VALUE
VALUE -> {CONFIG} |[VALUE*] |"atom"| ?
```

The terminals are:

key A valid key name—a string consisting of alphanumerical and underscore characters with a nonnumerical leading character.

atom An arbitrary string

? A nil value. Not commonly used.

The keys of a `CONFIG` are assumed to be distinct and its `KEYVAL` terms are considered unordered.

A configuration is therefore a table of atoms, lists, and more tables. Because of this tree structure, leafs and subtrees can be referenced by a path starting from the root.

```
KEYPATH -> key INDEX *
INDEX -> [number] |. key
```

A *key* indexes a table. A subscript, `[ number ]`, accesses a zero-based list. This is identical to the member/vector indexing notation used in many programming languages. A subscript expression of the form `[+]` can be used in assignments.

A *keypath* is a path to a configuration parameter. For example, `force.nonbonded.far.sigma` is a keypath referring to the sigma configuration parameter in the far subsection of the nonbonded subsection of the force section of the configuration file.

Note: The internal data structure used to implement configurations is called *ark*, and error messages referring to it most likely indicate either bad syntax or missing values. In addition, a configuration can include comments. A comment starts with a `#` mark and continues until the end of the line.

When producing a configuration with either the `--include` and `--cfg` options (discussed in Section 2.2, the contents of files (for the former) and string arguments (for the latter) are concatenated and parsed as a single text, with comments removed.

The text is parsed according to a more complex grammar:

```
CONFIG -> KEYVAL *
KEYVAL -> KEYPATH = VALUE/KEYPATH CONFIG/INCLUDE
KEYPATH -> key INDEX *
INDEX -> [number] |. key
VALUE -> {CONFIG}| [VALUE*] |QATOM|?
QATOM -> "atom"|'atom'|`atom`|atom
INCLUDE -> ! include QATOM
```

`QATOM` Resolves to either a quote-delimited string using any of the standard quotation marks, or a bare string—a sequence of characters containing no white space or syntactic tokens. Within a quote-delimited string, internal quotes can be escaped with a backslash as per the common convention.

The `KEYVAL` terms are interpreted in the order given; later terms can have affects on previous terms.

The `KEYPATH` term expands to a key which can be extended by a list (`[number]`) or table (.key) indexes. New lists or tables are created when necessary to accommodate these indexes. The `KEYPATH` term resolves to a (possibly newly created) subtree of the configuration. An assignment, `KEYPATH = VALUE`, obliterates the previous subtree, if any, and replaces it with the expansion of the `VALUE` term. A list `KEYPATH` term can be extended with an assignment of the form `KEYPATH[+] = VALUE`. An enclosure, `KEYPATH { CONFIG }`, changes the subtree to an empty table, unless it is already a table, and merges the two tables by appending to the subtree's table the `KEYVAL` terms of the `CONFIG`. This is analogous to the behavior of namespaces in C++.

An `INCLUDE` term expands into the text of the file indicated by the `QATOM` in its production rule, with comments removed. This text is presumed to be a `CONFIG` term and its sequences of `KEYVAL` terms are inserted into the stream of terms in which the text is included. Inclusion is properly nested: an included file can include other files, referring to it by paths relative to itself. The `--include FILE` command line option is equivalent to `--cfg '!include FILE'`.

Table B.1 summarizes the information above:

	Terms	Definitions
Terminals	**atom**	A string, bare or quoted (any of the three standard quotation marks—single or double quotation marks, or backticks), with internal quotes escaped with the \ character.
	nil	written as `?`.
Combinations	**table**	An unordered set of (key,value) pairs with distinct keys written: `{key1=value1 key2=value2 ...keyN=valueN}` A key is an alphanumeric unquoted string that can also include underscores.
	list	A sequence of values written: `[value1 value2 ...valueN]` Syntax does not require that the values of a list be of similar type, though for clarity, we recommend following this convention.

Table B.1: Summary of terms

Examples using enclosure and keypaths are given the next section.

B.1 Examples

Below is an example of a configuration file.

Example B.1

```
title='this is an example' # an atom, quoted string
pi =3.14159 # an atom, bare string
file=myDoc.txt # an atom, bare string
matrix=[ [1 0 0] [0 1 0] [0 0 1] ] # a list (of lists)
options={
  verbose=yes
  Nsteps=100
  vec=[1 2 3] #  a table
}
```

This configuration could be given to a Desmond application with either the `--include` or `--cfg` options as follows.

Example B.2

```
desmond --include config_file
```

or:

Example B.3

```
desmond --cfg "title='this is an example' \
             pi =3.14159 file=myDoc.txt \
             matrix=[ [1 0 0] [0 1 0] [0 0 1] ] \
             options={ verbose=yes Nsteps=100 vec=[1 2 3]}"
```

The first of these reads a file named `config_file`, which we assume holds the contents of the example. The second gives the contents of the previous example as a string.

Configuration flags can be combined arbitrarily:

Example B.4

```
desmond --include config_file --cfg "last_time=10.0"
```

which is equivalent to the following configuration text:

Example B.5

```
title=this is an example
pi =3.14159
file=myDoc.txt
matrix=[ [1 0 0] [0 1 0] [0 0 1] ]
options={
  verbose=yes
  Nsteps=100
  vec=[1 2 3]
}
last_time=10.0
```

Repeated key assignments override previous ones. In the following Example, both assignments have the effect of producing the configuration `X="2"`.

Example B.6

```
desmond --cfg 'X=1 X=2'
desmond --cfg 'X=1' --cfg 'X=2'
```

Through keypaths, elements of a configuration can be individually overridden from the command line

Example B.7

```
desmond --include config_file --cfg 'matrix[2]=[1 1 1]
  options.verbose=no'
```

which results in a configuration equivalent to:

Example B.8

```
title='this is an example'
pi =3.14159
file=myDoc2.txt
matrix=[ [1 0 0] [0 1 0] [1 1 1] ]
options={
  verbose=no
  Nsteps=100
  vec=[1 2 3]
}
```

The enclosure syntax can be used to extend a table.

Example B.9

```
desmond --include config_file --cfg ’options {verbose=no Nsteps=50 }’
```

which results in a configuration equivalent to:

Example B.10

```
title=’this is an example’
pi =3.14159
file=myDoc2.txt
matrix=[ [1 0 0] [0 1 0] [1 1 1] ]
options={
  verbose=no
  Nsteps=50
  vec=[1 2 3]
}
```

Conversely, an assignment such as in the next Example results in the configuration shown in

Example B.11

```
desmond --include config_file --cfg ’options={ verbose=no Nsteps=50 }’
```

Example B.12

```
title=’this is an example’
pi =3.14159
file=myDoc2.txt
matrix=[ [1 0 0] [0 1 0] [1 1 1] ]
options={
  verbose=no Nsteps=50
}
```

Appendix C

Clone Radius Restrictions

This appendix provides the full set of restrictions on the size of the clone radius, for those who need more than the practical guidelines given in Chapter 3.

The clone radius must be chosen large enough to ensure that a process can access all the particles it needs to compute force interactions. There are, however, also practical limits on the size of the clone radius. This Appendix collects all the restrictions placed on the clone radius.

For correct pairlist reconstruction, Desmond requires

$$2R_{\text{clone}} \geq R_{\text{lazy}} = R_{\text{cut}} + \Delta, \tag{C.1}$$

(recall that R_{cut} is a parameter in `force.nonbonded` and Δ is `global_cell.margin`). This is normally how the clone radius is chosen; it is set to half of the lazy radius (plus a small fudge factor of about 10^{-6} to allow for roundoff error).

To correctly compute bonded interactions and constraints, R_{clone} should be large enough that every such group of bonded or constrained particles fit within some sphere of radius R_{clone}. When a violation of this condition would prevent correct computation Desmond halts with an error. For practical values of the cutoff radius ($R_{\text{cut}} \leq R_{\text{lazy}} \leq 2 \cdot R_{\text{clone}}$), R_{clone} should be large enough to guarantee that each process has all the particles it requires for bonded force and constraint calculations.

For far electrostatic force calculations, there are additional restrictions on the clone radius. These restrictions are usually weaker than the above, but are included for completeness.

In the case of PME,

$$R_{\text{clone}} \geq \frac{1}{2}\sqrt{(h_x(\sigma_x - 1))^2 + (h_y(\sigma_y - 1))^2 + (h_z(\sigma_y - 1))^2} + \frac{\Delta}{\sqrt{2}} \tag{C.2}$$

where h_i is the Ewald mesh spacing in the i^{th} direction, Δ is the margin defined in on page 48. and ω_i is the PME interpolation order in the i^{th} direction.

In the case of k-GSE,

$$R_{\text{clone}} \geq R_{\text{spread}} + \frac{\Delta}{\sqrt{2}} \tag{C.3}$$

where R_{spread} is the k-GSE spreading radius.

It is generally not necessary and is inefficient to choose the clone radius larger than what the above restrictions require. There are also upper limits to the size of the clone radius. These come from the parallelization of the global cell and particle image tracking, which does not allow greater than nearest neighbor communications or certain kinds of self-overlapping clone regions. First, because Desmond communicates only with immediately adjacent boxes during migration, the clone radius cannot be larger than the box dimension in any direction, in other words,

$$R_{\text{clone}} < L_i \tag{C.4}$$

where L_i is the home box dimension in the i^{th} direction. This condition may restrict how many processes you can use to parallelize your chemical system. At low levels of parallelism, if a dimension i has been partitioned into only two boxes, then we have the more strict limitation

$$R_{\text{clone}} < \frac{3}{4} L_i \tag{C.5}$$

because clone regions cannot overlap. Finally, if a dimension i has not been partitioned at all

$$R_{\text{clone}} < \frac{1}{4} L_i \,. \tag{C.6}$$

These restrictions have been phrased in terms of a Cartesian global cell. For a triclinic cell, the concerns are analogous, though the mathematical conditions more difficult to summarize.

Appendix D

DMS file format

All data in a DMS file lives in a flat list of two-dimensional tables. Each table has a unique name. Columns in the tables have a name, a datatype, and several other attributes, most importantly, whether or not the column is the primary key for the table. Rows in the tables hold a value for each of the columns. Table names, column names, and datatypes are case-preserving, but case-insensitive: thus “pArTiCLE” is the same table as “particle”, and “NAME” is the same column as “name”.

Of the five datatypes available in SQLite, DMS uses three: INTEGER, a signed 64-bit int; FLOAT, a 64-bit IEEE floating point number; and TEXT, a UTF8 string. In addition, any value other than a primary key can be NULL, indicating that no value is stored for that row and column. A NULL value is allowed in the DMS file but might be regarded as an invalid value by a particular application; for example, Desmond make no use of the atomic number column in the particle table, but Viparr requires it.

Because DMS is used to store dimensionful quantities, we must declare a system of units. The units in DMS, summarized in Table D.1, reflects a compromise between an ideal of full consistency and the reality of practical usage; in particular, the mass unit is amu, rather than an algebraic combination of the energy, length, and time units.

In addition to tables, DMS files may contain stored queries known as views. A view combines data from one or more tables, and may apply a predicate as well a sorting criterion. How this is actually done in SQL will be obvious to database afficiandos; for this specification it suffices to note that a view looks just like a table when reading a DMS file, so the views will be described in terms of the data in their columns, just as for

TIME	picosecond
CHARGE	electron charge
LENGTH	Angstrom
ENERGY	thermochemical kcal/mol
MASS	atomic mass unit (amu)

Table D.1: DMS system of units

name	**type**	**description**
id	INTEGER	unique particle identifier
anum	INTEGER	atomic number
x	FLOAT	x-coordinate in LENGTH
y	FLOAT	y-coordinate in LENGTH
z	FLOAT	z-coordinate in LENGTH

Table D.2: Schema for the `particle` table.

name	**type**	**description**
p0	INTEGER	1st particle id
p1	INTEGER	2nd particle id
order	FLOAT	bond order

Table D.3: Schema for the `bond` table.

tables. Importantly, views cannot be written to directly; one instead updates the tables to which they refer.

D.1 Molecules

The DMS file contains the identity of all particles in the structure as well as their positions and velocities in a global coordinate system. The particle list includes both physical atoms as well as pseudoparticles such as virtual sites and drude particles. The most important table has the name `particle`; all other tables containing additional particle properties or particle-particle interactions refer back to records in the `particle` table. References to particles should follow a naming convention of $p0$, $p1$, $p2$, ... for each particle referenced.

Particles

The `particle` table associates a unique *id* to all particles in the structure. The ids of the particles must all be contiguous, starting at zero. The ordering of the particles in a DMS file for the purpose of, e.g., writing coordinate data, is given by the order of their ids. The minimal schema for the `particle` table is given in Table D.2.

Bonds

The `bond` table specifies the chemical topology of the system. Here, the topology is understood to be independent of the forcefield that describes the interactions between particles. Whether a water molecule is described by a set of stretch and angle terms,

name	type	description
id	INTEGER	vector index (0, 1, or 2)
x	FLOAT	x component in LENGTH
y	FLOAT	y component in LENGTH
z	FLOAT	z component in LENGTH

Table D.4: Schema for the `global_cell` table.

or by a single constraint term, one would still expect to find entries in the `bond` table corresponding to the two oxygen-hydrogen bonds. Bonds may also be present between a pseudoatom and its parent particle or particles; these bonds aid in visualization.

The $p0$ and $p1$ values correspond to an id in the `particle` table. Each $p0$, $p1$ pair should be unique, non-NULL, and satisfy $p0 < p1$.

The global cell

The global_cell table specified in Table D.4 specifies the dimensions of the periodic cell in which particles interact. There shall be three records, with *id* 0, 1, or 2; the primary key is provided since the order of the records matters, and one would otherwise have difficulty referring to or updating a particular record in the table.

Additional particle properties

Additional per-particle properties not already specified in the `particle` table should be added to the particle table as columns. Table D.5 shows the schema for the additional properties expected and/or recognized by Desmond and by Viparr.

D.2 Forcefields

A description of a forcefield comprises the functional form of the interactions between particles in a chemical system, the particles that interact with a given functional form, and the parameters that govern a particular interaction. At a higher level, interactions can be described as being *local* or *nonlocal.* Local particle interactions in DMS are those described by a fixed set of n-body terms. These include bonded terms, virtual sites, constraints, and polar terms. Nonlocal interactions in principle involve all particles in the system, though in practice the potential is typically range-limited. These include van der Waals (vdw) interactions as well as electrostatics.

Local particle interactions

In order to evaluate all the different forces between particles, a program needs to be able to find them within a DMS file that may well contain any number of other auxiliary tables. The DMS format solves this problem by providing a set of "metatables"

name	**type**	**description**
mass	FLOAT	Desmond: particle mass in MASS
charge	FLOAT	Desmond: particle charge in CHARGE
vx	FLOAT	Desmond: x-velocity in LENGTH/TIME
vy	FLOAT	Desmond: y-velocity in LENGTH/TIME
vz	FLOAT	Desmond: z-velocity in LENGTH/TIME
nbtype	INTEGER	Desmond: nonbonded type
grp_temperature	INTEGER	Desmond: temperature group
grp_energy	INTEGER	Desmond: energy group
grp_ligand	INTEGER	Desmond: ligand group
grp_bias	INTEGER	Desmond: force biasing group
resid	INTEGER	Viparr: residue number
resname	TEXT	Viparr: residue name
chain	TEXT	Viparr: chain identifier
name	TEXT	Viparr: atom name
formal_charge	FLOAT	Viparr: format particle charge
occupancy	FLOAT	pdb occupancy value
bfactor	FLOAT	pdb temperature factor

Table D.5: Optional particle properties that may be added as additional columns in the particle table.

metatable name	description
`bond_term`	Interactions representing bonds between atoms, including stretch, angle, and dihedral terms, as well as 1-4 pairs and position restraints.
`constraint_term`	Constraints on bonds and/or angles involving a reduction in the number of degrees of freedom of the system.
`virtual_term`	Similar to a constraint; a set of parameters describing how a pseudoparticle is to be positioned relative to a set of parent atoms.
`polar_term`	Similar to a virtual site; a set of parametere describing how a pseudoparticle moves relative to its parent atoms.

Table D.6: Metatables for local particle interactions.

name	**type**	**description**
name	TEXT	name of the table for an interaction form

Table D.7: Schema for the `bond_term`, `constraint_term`, `virtual_term`, and `polar_term` tables described in Table D.6.

containing the names of force terms required by the forcefield as well as the names of the tables in which the force term data is found. The force terms are placed into one of four categories: bonded terms, constraints, virtual sites, polar terms. Table D.6 shows the names and descriptions of those tables. The first four tables, all of which refer to local particle interactions, have the same schema shown in Table D.7. Each row in any of these four metatables corresponds to a unique functional form, documented in later sections.

Each table name corresponding to the values in the local term metatables is the designated string for a particular functional form. The required columns for these tables is given in the next section. Note that creators of DMS files are free to implement the schema as an SQL view, rather than as a pure table; a reader of a DMS file should not assume anything about how the columns in the table name have been assembled.

Nonbonded interactions

The functional form for nonbonded interactions, as well as the tables containing the interaction parameters and type assignments, are given by the fields in the `nonbonded_info` table, shown in Table D.8.

There should exactly one record in the `nonbonded_info` table. Like the local interaction tables described by Table D.7, the `name` field indicates the functional form of the nonbonded interaction type. If the particles have no nonbonded interactions, *name*

name	**type**	**description**
name	TEXT	nonbonded functional form
rule	TEXT	combining rule for nonbonded parameters

Table D.8: Schema for the `nonbonded_info` table.

name	**type**	**description**
param1	INTEGER	1st entry in `nonbonded_param` table
param2	INTEGER	2nd entry in `nonbonded_param` table
coeff1	FLOAT	first combined coefficient
...		other combined coefficients...

Table D.9: Schema for the `nonbonded_combined_param` table. Only `param1` and `param2` are required; the remaining columns provide the interaction-dependent coefficients.

should have the special value `none`.

The parameters for nonbonded interactions will be stored in a table called `nonbonded_param`, whose schema depends on the value of `name` in `nonbonded_info`. All such schemas must have a primary key column called `id`; there are no other restrictions.

The `nbtype` column in the `particle` table gives the nonbonded type assignment. The value of the type assignment must correspond to one of the primary keys in the `nonbonded_param` table.

Typically, the parameters governing the nonbonded interaction between a pair of particles is a simple function of the parameters assigned to the individual particles. For example, in a Lennard-Jones functional form with parameters *sigma* and *epsilon*, the combined parameters are typically the arithmetic or geometric mean of *sigma* and *epsilon*. The required approach is obtained by the application from the value of `rule` in `nonbonded_info`.

For the interaction parameters that cannot be so simply derived, a table called `nonbonded_combined_param` may be provided, with a schema shown in Table D.9. Like the `nonbonded_param` table, the schema of `nonbonded_combined_param` will depend on the functional form of the nonbonded interactions, but there are two required columns, which indicate which entry in `nonbonded_param` are being overridden.

D.3 Alchemical systems

Methods for calculating relative free energies or energies of solvation using free energy perturbation (FEP) involve mutating one or more chemical entities from a reference state, labeled “A”, to a new state, labeled “B”. DMS treats FEP calculations as just another set of interactions with an extended functional form. In order to permit multiple independent mutations to be carried out in the same simulation, a “moiety” label is

name	type	description
p0	INTEGER	alchemical particle id
moiety	INTEGER	moiety assignment
nbtypeA	INTEGER	entry in nonbonded_param for A state
nbtypeB	INTEGER	entry in nonbonded_param for B state
chargeA	FLOAT	charge in the A state
chargeB	FLOAT	charge in the B state

Table D.10: Schema for the `alchemical_particle` table .

name	type	description
r0A	FLOAT	equilibrium separation in A state
fcA	FLOAT	force constant in A state
r0B	FLOAT	equilibrium separation in B state
fcB	FLOAT	force constant in B state
p0	INTEGER	1st particle
p1	INTEGER	2nd particle
moiety	INTEGER	chemical group

Table D.11: Schema for `alchemical_stretch_harm` records, corresponding to alchemical harmonic stretch terms with a functional form given by interpolating between the parameters for states A and B.

applied to each mutating particle and bonded term.

Alchemical particles

Any particle whose charge or nonbonded parameters changes in going from state A to state B, is considered to be an alchemical particle and must have a moiety assigned to it. The set of distinct moieties should begin at 0 and increase consecutively. The set of alchemical particles, if any, should be provided in a table called `alchemical_particle` shown in Table D.10.

Bonded terms

Alchemical bonded terms are to be treated by creating a table analogous to the non-alchemical version, but replacing each interaction parameter with an "A" and a "B" version. An example is given in Table D.11. As a naming convention, the string "alchemical_" should be prepended to the name of the table.

Constraint terms

No support is offered for alchemical constraint terms at this time. If particles A, b, and c are covered by an AH2 constraint in the A state, and particles A, d, and e are covered by an AH2 constraint in the B state, then the set of constraint terms in the alchemical DMS file should include an AH4 constraint between A and b, c, d and e.

Virtual sites

No support is offered for alchemical virtual sites at this time.

Polar terms

No support is offered for alchemical polar terms at this time.

Appendix E

Legacy Applications: Preparing a Maestro structure file

As discussed in Section 1.2.1, Desmond requires two files for input: a structure file that defines the chemical system, and a configuration file that sets simulation parameters. The details of setting configuration parameters are described in Chapter 2. This chapter describes how Desmond prior to version 2.4 specified the structure file.

E.1 Format

A structure file—also known as a Maestro file or `MAE` file, file name suffix `.mae`—is organized as a set of nested blocks. Each block has a set of attributes and can contain other blocks. Some blocks, called *arrays* or *indexed-blocks*, contain multiple records. Blocks start and end with curly braces: { }. Within each block, attribute names are listed first, followed by `:::`, and finally the values of those attributes. A typical structure file starts with an unnamed block, as shown in:

Example E.1

```
{
  s_m_m2io_version
  :::
  2.0.0
}
```

The unnamed block specifies the version of the format of the structure file and is other wise not used. The unnamed block is followed by one or more connection tables. These are called `f_m_ct` blocks, or simply `ct` blocks:

Example E.2

```
f_m_ct {
  s_m_title
  r_chorus_box_ax
```

```
    r_chorus_box_ay
    r_chorus_box_az
    :::
    "this is the title"
    25.0
    0.0
    0.0
    m_atom[2] {
      i_m_mmod_type
      r_m_x_coord
      r_m_y_coord
      r_m_z_coord
      :::

      1 0.326 0.704 0.726
      2 1 -0.431 1.245 1.295
      :::
    }
  }
```

The `ct` block in the previous Example shows four attributes, plus an array block called `m_atom`. The attributes are `m_title`, `chorus_box_ax`, `chorus_box_ay`, and `chorus_box_az`.

The array block called `m_atom` has three attributes and two records. The attribute names are prepended by `s_`, `r_`, or `i_`, depending on whether the corresponding value is a string (text), real number, or integer, respectively.

Note: In the discussion below, these prefixes are ordinarily excluded.

Attributes names also encode the owner of the attribute—that is, the name of the application responsible for managing that quantity. For example, the attribute name prefix `m_` indicates that Maestro is responsible for managing that attribute. In an array, each record has a one-based index, followed by values for the attributes of the block, one for each record. The size of the array block is given by the number in square brackets after the name. In the Example above, the value corresponding to `chorus_box_ax` is 25.0, and the `m_x_coord` attribute takes on the values of 0.326 and -0.431 in the first and second `m_atom` records, respectively.

Note: Two kinds of `ct` blocks exist: full or partial, indicated by the respective name components `f_` and `p_`. Partial blocks contain only attributes and values that override the corresponding values in the preceding full block. Desmond makes no use of this feature.

You can think of each `ct` block as containing a complete description of a chemical system and the interaction between its particles. Desmond reads all the `ct` blocks in a structure file and simulates them together in one chemical system, with two exceptions:

- `ct` blocks with the attribute `ffio_ct_type` equal to `full_system` are not included in the simulation. Such `ct` blocks are used by Maestro for visualization.

- ct blocks corresponding to alchemical stages are combined into a single block before being loaded into the simulation. More about preparing structure files for alchemical simulations can be found in Section E.2.

E.1.1 Global cell

Desmond carries out simulations in a three-dimensional region of space called the global cell, described in Section 1.1.4. The dimensions of the global cell are specified by the three shift vectors $\vec{a}$, $\vec{b}$, and $\vec{c}$, which together determine the shape of the global cell. These shift vectors are specified in the ct attributes given in Table E.1.

Global cell component	Attribute
X component of a vector	r_chorus_box_ax
Y component of a vector	r_chorus_box_ay
Z component of a vector	r_chorus_box_az
X component of b vector	r_chorus_box_bx
Y component of b vector	r_chorus_box_by
Z component of b vector	r_chorus_box_bz
X component of c vector	r_chorus_box_cx
Y component of c vector	r_chorus_box_cy
Z component of c vector	r_chorus_box_cz

Table E.1: Global cell specification

Note: Each ct block in a structure file must contain the same global cell specification as every other ct block in that file, if any.

E.1.2 Particles and pseudoparticles

After loading the structure file, Desmond scans the ct blocks looking for particles to include in the simulation. Each ct block must contain one or more atoms; depending on the force field to be used, it can also contain pseudoparticles representing additional charge sites. (Pseudoparticles are described in general in Section 1.1.3; specific implementations are described in Section 5.4.2.) The atoms in a ct block are specified by the records in the m_atom array. Pseudoparticles, if any, are given by the records in the ffio_pseudo array within the ffio_ff subblock of the ct block.

Each atom and pseudoparticle record can contain any number of attributes; however, Desmond reads only:

- the positions and velocities using the attributes listed in Table E.2, and
- a set of integer-valued properties ffio_grp_name. Desmond makes use of energy, temperature, cm_moi, ligand, and frozen groups, described in Section 1.1.2.

particle property	`m_atom` attribute	`ffio_pseudo` attribute
X position	`m_x_coord`	`ffio_x_coord`
Y position	`m_y_coord`	`ffio_y_coord`
Z position	`m_z_coord`	`ffio_z_coord`
X velocity	`ffio_x_vel`	`ffio_x_vel`
Y velocity	`ffio_y_vel`	`ffio_y_vel`
Z velocity	`ffio_z_vel`	`ffio_z_vel`

Table E.2: Initial particle position and velocity specification

Particles are loaded into Desmond in the order in which they appear in the structure file. Within a given `ct`, all atoms are injected, followed by all pseudoparticles, if any. This is also the order in which the particles appear in trajectory output. For alchemical systems, the order is that of the internally constructed alchemically combined `ct` block

E.1.3 Force field sections

Bonded and nonbonded interactions between particles are determined by the contents of the force field section of the structure file. Desmond requires that each `ct` block (except the `full_system` block) contain a sub-block named `ffio_ff`, containing at least two sub-items:

- an array block called `ffio_sites`, whose attributes are summarized in Table E.3, and
- a string attribute named `ffio_comb_rule`, the value of which specifies how Lennard-Jones interactions are computed.

Site property	`ffio_sites` attribute
particle type (ATOM or PSEUDO)	`ffio_type`
charge (units of e)	`ffio_charge`
mass (atomic units)	`ffio_mass`
van der Waals type (string key)	`ffio_vdwtype`

Table E.3: Particle properties obtained from ffio sites block

Note: The value of `ffio_comb_rule` must be same for all `ct` blocks.

All other interactions are determined by additional subsections of the `ffio_ff` block. For example, two-body stretch harmonic stretch terms are found in a subblock called `ffio_bonds`, and van der Waals interactions are specified by the VDW type and by a subblock called `ffio_vdwtypes`.

Note: Because the Maestro file format is designed to be extensible, many other interaction types are possible; consult the documentation for the specific force terms you wish to employ to determine which structure file records contribute to those terms.

Note: The Maestro file is sometimes referred to as a MaeFF file when it has force field parameter assignments present. The Maestro Desmond system builder tool will output MaeFF files with the file name suffix `.cms`.

Note: The DMS file can not be directly converted into a MAE file. A workaround is to use VMD to convert a DMS file to a MAE file. This conversion will not include force field parameters present in the DMS file, however. Force field parameters can be added to the MAE file using versions of Viparr provided with Desmond 2.2

E.2 Preparing the structure file for Free Energy Simulations

Structure file preparation in general is discussed in Chapter E. The sections below describe additional steps needed to prepare a structure file for ligand-binding free energy simulations and for alchemical free energy simulations.

E.2.1 Ligand-binding free energy simulations

To prepare the structure file for ligand_binding free energy simulations, specify the atoms that belong to the ligand. To do so, set the `ffio_grp_ligand` field in the `m_atoms` records to 1 for the ligand atoms, and to 0 for other atoms.

The following Example shows an excerpt from a structure file for simulating the solvation free energy of methanol, highlighting the `ffio_grp_ligand` field. The first `ct` block describes the solute—methanol, having all the atoms in its `ffio_grp_ligand` set to 1. The second `ct` block describes the solvent—water, having all the atoms in its `ffio_grp_ligand` set to 0.

Example E.3

```
... # lines omitted
f_m_ct {
  ... # lines omitted
  s_ffio_ct_type
  :::
  ... # lines omitted
  solute
  m_atom[6] {
    i_m_mmod_type
    r_m_x_coord
    r_m_y_coord
    r_m_z_coord
    s_m_pdb_atom_name
    i_m_atomic_number
    i_ffio_grp_ligand
    :::
    13     -0.683143 -0.071748 0.090914 "C1" 6 1
```

```
          2 16    0.463103 0.750632 -0.140535 "O2" 8 1
          3 41   -1.138147 -0.383230 -0.876254 "H3" 1 1
          4 41   -1.450629 0.486326 0.674057   "H4" 1 1
          5 41   -0.403379 -0.990407 0.655399 "H5" 1 1
          6 42    0.858372 0.916697 0.724639   "H5" 1 1
          :::
        }
        ... # lines omitted
      }
      f_m_ct {
        ... # lines omitted
        s_ffio_ct_type
        :::
        ... # lines omitted
        solvent
        m_atom[2484] {
          i_m_mmod_type
          r_m_x_coord
          r_m_y_coord
          r_m_z_coord
          s_m_pdb_atom_name
          i_m_atomic_number
          i_ffio_grp_ligand
          :::
          1 16   -7.429789 -7.792630 4.945186 "OW" 6 0
          2 42   -6.709420 -8.366949 4.498097 "HW1" 1 0
          3 42   -7.200478 -6.819860 4.736009 "HW2" 1 0
          ... # lines omitted
          :::
        }
      }
```

E.2.2 Alchemical free energy simulations

The structure file used for alchemical free energy simulations consists of the following components:

- original_ct (system in state A)
- perturbed_ct (system in state B)
- environment_ct's

The original_ct contains the unperturbed version of the molecule in the alchemical transformation, and the perturbed_ct contains what the original_ct becomes. They both contain `ffio` information to describe the force field parameterization in their respective states. They also both contain FEPIO information specific to alchemical free energy simulation.

The environment_ct's are component CTs or multicomponent CTs that do not undergo alchemical transformation. These CTs have only `ffio` information, but not FEPIO information.

CT-level MMFEPIO properties

Both the original_ct and the perturbed_ct must contain a user-specified name for the FEP transformation, and whether it corresponds to the original or the perturbed state.

Property name	Description
s_fepio_name	Arbitrary name used to distinguish the original perturbed pair from other pairs.
i_fepio_stage	1 for the original ct; 2 for the perturbed ct.

Table E.4: CT level MMFEPIO properties

The fepio_fep block

The perturbed CT has an fepio_fep block to indicate how atoms and interactions map from the original_ct onto the perturbed_ct. The top-level properties in the fepio_fep block are shown in Table E.5:

Property name	Description
s_fepio_name	Should be the same as the s_fepio_name used in the original_ct.
i_fepio_stage	Normally 1, indicating transformation from the ct with s_fepio_stage = 1 to the ct with s_fepio_stage = 2.

Table E.5: fepio_fep properties

Inside fepio_fep block are the following blocks:

- fepio_atommaps
- fepio_bondmaps
- fepio_anglemaps
- fepio_dihedralmaps
- fepio_exclmaps
- fepio_pairmaps

fepio_atommaps

This indexed block maps the alchemically transformed atoms. Specifically, it maps the atom number from the original_ct onto the perturbed_ct.

Property name	Description
i_fepio_ai	The atom index in the original_ct being mapped
i_fepio_aj	The atom index in the perturbed_ct being mapped.

Table E.6: fepio_atommaps properties

For atoms in the original_ct (i_fepio_ai) that map onto dummy atoms in the perturbed_ct (that is, that disappear in the perturbed_ct), `i_fepio_aj` is set to 1. For atoms in the perturbed_ct that map onto dummy atoms in the original_ct, we assign atom numbers `i_fepio_ai` counting from -(the number of real atoms in the original_ct + 1). For instance, if ten real atoms are in the original_ct, these dummy atoms are numbered i_fepio_ai = -11, -12, and so on.

fepio_bondmaps

This indexed block maps the bond potentials from the original_ct onto the perturbed_ct.

Property name	Description
i_fepio_ti	Bond potential number in original_ct. Negative bond number indicates a bond involving at least one dummy atom.
i_fepio_tj	Bond potential number in perturbed_ct. Negative bond number indicates a bond involving at least one dummy atom.
i_fepio_ai	The first atom in the bond in original_ct. Negative atom numbers can appear here, by the same convention as in atommaps.
i_fepio_ai	The second atom in the bond in orignal_ct. Negative atom numbers can appear here, by the same convention as in atommaps.

Table E.7: fepio_bondmaps properties

fepio_anglemaps

This indexed block maps the angle potential from original_ct onto perturbed_ct.

Property name	Description
i_fepio_ti	Angle potential number in original_ct. Negative angle numbers indicate an angle involving at least one dummy atom; 0 indicates that this potential should disappear in the corresponding ct.
i_fepio_tj	Angle potential number in perturbed_ct. Negative angle numbers indicate an angle involving at least one dummy atom; 0 indicates that this potential should disappear in the corresponding ct.
i_fepio_ai	The first atom in the angle in original_ct. Negative atom number can appear here, by the same convention as in atommaps.
i_fepio_aj	The second atom in the angle in orignal_ct. Negative atom number can appear here, by the same convention as in atommaps.
i_fepio_ak	The third atom in the angle in orignal_ct. Negative atom number can appear here, by the same convention as in atommaps.

Table E.8: fepio_anglemaps properties

fepio_dihedralmaps

This indexed block maps the dihedral angle potentials from original_ct onto perturbed_ct.

Property name	Description
i_fepio_ti	Dihedral potential number in original_ct. Negative dihedral numbers indicate a dihedral involving at least one dummy atom; 0 indicates that this potential should disappear in the corresponding ct.
i_fepio_tj	Dihedral potential number in perturbed_ct. Negative dihedral numbers indicate a dihedral involving at least one dummy atom; 0 indicates that this potential should disappear in the corresponding ct.
i_fepio_ai	The first atom in the dihedral in original_ct. Negative atom number can appear here, by the same convention as in atommaps.
i_fepio_aj	The second atom in the dihedral in orignal_ct. Negative atom number can appear here, by the same convention as in atommaps.
i_fepio_ak	The third atom in the dihedral in orignal_ct. Negative atom number can appear here, by the same convention as in atommaps.
i_fepio_al	The fourth atom in the dihedral in orignal_ct. Negative atom number can appear here, by the same convention as in atommaps.

Table E.9: fepio_dihedralmaps properties

fepio_exclmaps

This indexed block maps the exclusions from original_ct onto perturbed_ct.

Property name	Description
i_fepio_ti	Exclusion number in original_ct. Negative exclusion number indicates that this exclusion does not exist in the original ct, and it involves at least one dummy atom.
i_fepio_tj	Exclusion number in perturbed_ct. Negative exclusion number indicates that this exclusion does not exist in the perturbed ct, and it involves at least one dummy atom. If both i_fepio_ti and i_fepio_tj are -1, this exclusion does not exist in either the original or perturbed ct, and is an extra exclusion to prevent dummy atoms in original_ct from interacting with dummy atoms in perturbed_ct.
i_fepio_ai	The first atom in the exclusion in original_ct. Negative atom numbers can appear here, by the same convention as in atommaps.
i_fepio_aj	The second atom in the exclusion in orignal_ct. Negative atom numbers can appear here, by the same convention as in atommaps.

Table E.10: fepio_exclmaps properties

fepio_pairmaps

This indexed block maps the pairs from original_ct onto perturbed_ct.

Property name	Description
i_fepio_ti	Pair number in original_ct. Negative exclusion number indicates a pair involving at least one dummy atom.
i_fepio_tj	Pair number in perturbed_ct. Negative exclusion number indicates a pair involving at least one dummy atom.
i_fepio_ai	The first atom in the pair in original_ct. Negative atom numbers can appear here, by the same convention as in atommaps.
i_fepio_aj	The second atom in the pair in orignal_ct. Negative atom numbers can appear here, by the same convention as in atommaps.

Table E.11: fepio_pairmaps properties

The next Example shows an excerpt from a structure file for an alchemical free energy simulation in which a methyl group in ethane vanishes and is replaced by another methyl group.

The first `ct` block describes the original ethane molecule, and the second `ct` block describes the ethane molecule with one methyl group replaced by another—albeit identical—methyl group. The second `ct` block contains the fepio_fep section that details the mapping of the second molecule onto the first one.

The third `ct` block describes the solvent, in which the transformation takes place from the ethane in the first `ct` block to the ethane in the second.

Example E.4

```
...
f_m_ct {
  ...
  s_fepio_name
  i_fepio_stage
  :::
  ...
  ethane_to_ethane
  1
  m_atom[8] {
    ... # lines omitted
  }
  ffio_ff {
    ... # lines omitted
  }
}
... # lines omitted
f_m_ct {
  ...
  s_fepio_name
  i_fepio_stage
  :::
  ethane_to_ethane
  2
  m_atom[8] {
    ... # lines omitted
  }
  ffio_ff {
    ... # lines omitted
  }
  fepio_fep {
    s_fepio_name
    i_fepio_stage
    :::
    ethane_to_ethane
    1
    fepio_atommaps[13] {
      i_fepio_ai
      i_fepio_aj
      :::
      1 1 1
      2 2 2
      3 3 3
      4 4 -1 # The 4, 5, 6, 7, and 8th atoms in state A
      vanish and become dummy atoms in state B
      5 5 -1
      6 6 -1
      7 7 -1
      8 8 -1
      9 -9 4 # The 4, 5, 6, 7, and 8th atoms in state B don't
      exist and are dummy atoms in state A
      10 -10 5
      11 -11 6
      12 -12 7
      13 -13 8
      :::
    }
    fepio_bondmaps[12] {
      i_fepio_ti
      i_fepio_tj
      i_fepio_ai
      i_fepio_aj
      :::
      11112
      22213
      3 3 -1 1 4 # The bond between atoms 1 and 4 in state A
      does not exist in state B, but will not be changed
      ... # lines omitted
    }
    fepio_anglemaps[23] {
      i_fepio_ti
      i_fepio_tj
      i_fepio_ai
      i_fepio_aj
      i_fepio_ak
      :::
      1 1 -1 6 5 1 # The angle between atoms 6-5-1 in state A does
      not exist in state B, but will not be changed
      2 2 0 7 5 1 # The angle between atoms 7-5-1 in state A does
      not exist in state B, and will vanish
      ... # lines omitted
    }
    fepio_dihedmaps[18] ...
    fepio_exclmaps[78] ...
    fepio_pairmaps[36] ...
  }
}
f_m_ct {
    ...
    s_ffio_ct_type
    :::
    ... # lines omitted
    solvent
    m_atom[915] {
      s_m_pdb_atom_name
      s_m_pdb_residue_name
      s_m_chain_name
      i_m_residue_number
      r_m_x_coord
      r_m_y_coord
      r_m_z_coord
      i_m_atomic_number
      :::
      1 " OWS" SOL X 2 5.690000 12.750000 11.650000   8
      2 " HWS" SOL X 2 4.760000 12.680000 11.280001   1
      3 " HWS" SOL X 2 5.800000 13.639999 12.090000   1
      4 " OWS" SOL X 3 15.549999 15.110001 7.030000   8
      5 " HWS" SOL X 3 14.980000 14.950000 7.840000   1
      6 " HWS" SOL X 3 14.960001 15.210000 6.230000   1
      ... # lines omitted
    }
    ... # lines omitted
  }
```

Appendix F

Enhanced sampling function reference

Name: *
Class: Binary Threaded
Arguments:

- a, array
- b, array

Return: $a * b$ computed element-wise by the binary threading rules
Additional:

Name: +
Class: Binary Threaded
Arguments:

- a, array
- b, array

Return: $a + b$ computed element-wise by the binary threading rules
Additional:

Name: -
Class: Binary Threaded
Arguments:

- a, array
- b, array

Return: $a - b$ computed element-wise by the binary threading rules
Additional:

Name: /
Class: Binary Threaded
Arguments:

- a, array

- b, array

Return: a/b computed element-wise by the binary threading rules
Additional:

Name: ˆ
Class: Binary threaded
Arguments:

- a, array
- b, integer

Return: a^b performed element-wise by the binary threading rules
Additional: Note that b will be rounded to get an integer. If this is not the desired behavior, then pow should be used instead.

Name: acos
Class: Threaded
Arguments:

- a, array

Return: the element-wise arccosine of a
Additional: note that this function is not numerically stable for arguments near +1 or -1

Name: angle
Class: Normal
Arguments:

- a, 3-element array
- b, 3-element array

Return: The cosine of the angle between a and b
Additional: This function does not return the angle directly due to numerical issues that arise due to the periodicity of angles. In particular, inverse trigonometric functions often have singularities in their derivatives.

Name: angle_gid
Class: Normal
Arguments:

- p1, particle
- p2, particle
- p3, particle

Return: The cosine of the angle of $p1$, $p2$, and $p3$
Additional: This function does not return the angle directly due to numerical issues that arise due to the periodicity of angles. In particular, inverse trigonometric functions often have singularities in their derivatives.

Name: angle_gid_radians

Class: Normal
Arguments:

- p1, particle
- p2, particle
- p3, particle

Return: Angle of a and b in radians. Result is in the range $[0, pi]$.
Additional: This function is not safe to use if the angle is near 0 or π because the derivative of this function diverges. It is preferable to use the function "angle" when possible.

Name: angle_radians
Class: Normal
Arguments:

- a, 3-element array
- b, 3-element array

Return: Angle of a and b in radians. Result is in the range $[0, pi]$.
Additional: This function is not safe to use if the angle is near 0 or π because the derivative of this function diverges. It is preferable to use the function "angle" when possible.

Name: array
Class: Normal
Arguments:

- An arbitrary number of array arguments

Return: the concatenation of all arguments
Additional: This function is useful for the creation of data arrays. For example, [array 1.0 2.0 3.0 4.0] is a 4-element array because scalar literals are 1-element arrays.

Name: atan2
Class: Binary Threaded
Arguments:

- y, array
- x, array

Return: arctangent of y/x computed according to the binary threading rules with the quadrants chosen according to the signs of x and y. The range of this function is $[-\pi, \pi]$.
Additional: The derivative of this function does not capture the discontinuity of the function at $\pm\pi$. If the angle crosses $\pm\pi$, there can be a discrete change in the potential without a corresponding derivative divergence. This can cause energy drift in the simulation. The user is advised to exercise caution if using atan2 in enhanced sampling potentials.

Name: center_of_geometry
Class: Normal
Arguments:

- gids, array of gids

Return: center of geometry with periodic image handling
Additional: To compute the center of geometry with periodic image ambiguities, the following convention is used. The minimum image displacement of each GID is calculated with respect to the previous GID in the gids array. The location of a particle for the purposes of the center of geometry is then the sum of all these minimum image displacements for each adjacent pair in the gid array going back to the first particle. The user must guarantee that each adjacent pair in the position_gid array is less than 1/2 of the unit cell apart. If this condition is violated, then particles may be wrapped to the wrong side of the cell, distorting the center of geometry.

Name: center_of_mass
Class: Normal
Arguments:

- gids, array of gids

Return: center of mass with periodic image handling
Additional: To compute the center of mass with periodic image ambiguities, the following convention is used. The minimum image displacement of each GID is calculated with respect to the previous GID in the gids array. The location of a particle for the purposes of the center of mass is then the sum of all these minimum image displacements for each adjacent pair in the gid array going back to the first particle. The user must guarantee that each adjacent pair in the position_gid array is less than 1/2 of the unit cell apart. If this condition is violated, then particles may be wrapped to the wrong side of the cell, distorting the center of mass.

Name: cos
Class: Threaded
Arguments:

- a, array

Return: the element-wise cosine of a
Additional:

Name: cross
Class: Normal
Arguments:

- a, 3-element array
- b, 3-element array

Return: the cross product of a and b
Additional:

Name: delta
Class: Normal
Arguments:

- gid1, particle
- gid2, particle

Return: the minimum image displacement from particle gid1 to particle gid2
Additional:

Name: dihedral
Class: Normal
Arguments:

- a, 3-element array
- b, 3-element array
- c, 3-element array

Return: A 2-element array. The first element is the cosine of the dihedral angle of vectors a, b, and c, and the second element is the sine of the dihedral angle.
Additional:

Name: dihedral_gid
Class: Normal
Arguments:

- p1, particle
- p2, particle
- p3, particle
- p4, particle

Return: A 2-element array. The first element is the cosine of the dihedral angle for particles $p1$, $p2$, $p3$, and $p4$, and the second element is the sine of the dihedral angle.
Additional:

Name: dihedral_gid_radians
Class: Normal
Arguments:

- p1, particle
- p2, particle
- p3, particle
- p4, particle

Return: Dihedral angle in radians for particle $p1$, $p2$, $p3$, and $p4$. Result is in the range $[-\pi, \pi]$.
Additional: This function is based internally on atan2. Please see the documentation for atan2 for more information. In particular, this function is discontinuous when the dihedral angle is near $\pm\pi$, and the derivative of the function does not describe this singularity. This can cause significant energy drift when the dihedral angle crosses $\pm\pi$. Users are advised to exercise caution when using dihedral_gid_radians. It is preferable to use the function "dihedral_gid" when possible.

Name: dihedral_radians

Class: Normal
Arguments:

- a, 3-element array
- b, 3-element array
- c, 3-element array

Return: Angle in radians for vectors a, b, and c. Result is in the range $[-\pi, \pi]$.
Additional: This function is based internally on atan2. Please see the documentation for atan2 for more information. In particular, this function is discontinuous when the dihedral angle is near $\pm\pi$, and the derivative of the function does not describe this singularity. This can cause significant energy drift when the dihedral angle crosses $\pm\pi$. Users are advised to exercise caution when using dihedral_radians. It is preferable to use the function "dihedral" when possible.

Name: dist
Class: Normal
Arguments:

- gid1, particle
- gid2, particle

Return: the minimum image distance from particle gid1 to particle gid2
Additional:

Name: dot
Class: Normal
Arguments:

- a, array
- b, array of the same length as a

Return: the dot product of a with b
Additional:

Name: exp
Class: Threaded
Arguments:

- a, array

Return: the element-wise exponent of a
Additional:

Name: length
Class: Normal
Arguments:

- a, array

Return: the number of elements in a
Additional:

Name: log
Class: Threaded
Arguments:

- a, array

Return: the element-wise logarithm of a
Additional:

Name: mass
Class: Threaded
Arguments:

- a, array of gids

Return: the element-wise mass of a
Additional:

Name: meta
Class: Special Form
Arguments:

- mid, integer index of a metadynamics accumulator, zero-indexed
- array of the gaussian height followed by the gaussian widths
- array of the collective variables

Return: the metadynamics potential at the current location in the collective variables
Additional: Note that the height and the widths of the gaussian may be an arbitrary expression, and the height and widths expression is only evaluated when a gaussian is added to the potential. On each gaussian addition, the height, width, and center of the resulting gaussian is written to a file as specified in the declare_meta statement in the header of the potential.

Name: min_image
Class: Normal
Arguments:

- a, 3-element array

Return: the minimum image of a with respect to the unit cell
Additional:

Name: mod
Class: Binary Threaded
Arguments:

- a, array
- b, array

Return: $\mathrm{mod}(a, b)$ computed element-wise by the binary threading rules. Answer is between 0 and b, including 0 and excluding b.
Additional:

Name: norm
Class: Normal
Arguments:

- a, array

Return: Magnitude(norm) of *a*. Equivalent to [sqrt [norm2 $a]]
Additional:

Name: norm2
Class: Normal
Arguments:

- a, array

Return: the dot product of *a* with itself
Additional: note that if a is a scalar, this is simply the square of the scalar

Name: pos
Class: Normal
Arguments:

- gid, particle

Return: the position of the particle whose GID is given by gid
Additional:

Name: pos_inner_prod
Class: Normal
Arguments:

- gids, array of gids
- weigths, array, same length as gids

Return: sum from i=0 to length(gids) of weights[i]*pos(gids[i]) after periodic image correction
Additional: This function is useful for computing center of mass, center of geometry and dipole moments. To compute the inner product with periodic image ambiguities, the following convention is used. The minimum image displacement of each GID is calculated with respect to the previous GID in the gids array. The location of a particle for the purposes of the inner product is then the sum of all these minimum image displacements for each adjacent pair in the gid array going back to the first particle. The user must guarantee that each adjacent pair in the position_gid array is less than 1/2 of the unit cell apart. If this condition is violated, then particles may be wrapped to the wrong side of the cell, distorting the inner product.

Name: pow
Class: Normal
Arguments:

- a, array of positive numbers
- b, length-1 array

Return: a^b performed element-wise
Additional: If a is not positive, the result is undefined.

Name: print
Class: Special Form
Arguments:

- printname, string
- a, array

Return: returns its argument a
Additional: print is used to log values from the interpreter to a file. printname is used to control the name associated with output from this print statement, and the value of a is sent to the output. The output file and frequency is controlled by the name, first, and interval parameters specified in the declare_output header. The output side-effect occurs only on the rank 0 process.

Name: rmsd
Class: Normal
Arguments:

- model, array of the model coordinates. This argument should be of the form [x_1 y_1 z_1 x_2 y_2 ...], and the length of the array must be three times the length of position_gids.
- position_gids, array of particles
- weights, array of the length as the position_gids array. This argument is optional and if omitted, all particles have the same weight. The gradient of the RMSD with respect to weights is ignored.

Return: Minimum RMS distance between the positions described by position_gids and the structure described by model. The minimum is taken of all possible affine transformations of the model.
Additional: To compute RMSD with periodic image ambiguities, the following convention is used. The minimum image displacement of each GID is calculated with respect to the previous GID in the position_gids array. The location of a particle for the purposes of RMSD is then the sum of all these minimum image displacements for each adjacent pair in the position_gid array going back to the first particle. The user must guarantee that each adjacent pair in the position_gid array is less than 1/2 of the unit cell apart. If this condition is violated, then particles may be wrapped to the wrong side of the cell, distorting the RMSD. Note that the derivatives of the model configuration and the weights are not considered in computing the derivative of the RMSD. Model coordinates are not wrapped in any way.

Name: sign
Class: Threaded
Arguments:

- a, array

Return: For each element x of a, returns +1 if $x >= 0$, -1 if $x < 0$, and x otherwise. Sign is computed element-wise.
Additional:

Name: sin
Class: Threaded
Arguments:

- a, array

Return: the element-wise sine of a
Additional:

Name: sqrt
Class: Threaded
Arguments:

- a, array

Return: the element-wise square root of a
Additional:

Name: store
Class: Special Form
Arguments:

- storename, see description
- a, array

Return: returns its argument a
Additional: This operation stores its second argument under the name given by the first argument. The storename must be declared in a "static" statement of the enhanced sampling configuration, and the length of the array a must be the same as the length declared in the static statement. Note that the store does not actually occur until the end of the potential evaluation, so that the stored value is not accessible until the next potential evaluation.

Name: sum
Class: Normal
Arguments:

- a, array

Return: the sum of the elements of a
Additional:

Name: time
Class: Normal
Arguments:

- None

Return: the chemical time for this step
Additional:

Appendix G

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G.2 Licensed Companion Software

Desmond and its related software makes use of several software packages prepared by organizations and individuals outside of D. E. Shaw Research. We include here the licensing terms for two of those packages.

G.2.1 Boost C++ Libraries

Desmond 3.x uses Boost version 1.45.0, available from the Boost website `http://www.boost.org`, under the terms of the Boost Software License, Version 1.0.

```
Boost Software License - Version 1.0 - August 17th, 2003

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G.2.2 SunPro Error Function

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G.2.3 ANTLR

The directory `src/port/export/antlr3` contains run-time files from the ANTLR version 3.1.3 distribution. The entire distribution is available from the URL: `http://www.antlr.org`

```
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G.2.4 Standard C compliant headers — stdint.h and inittypes.h

The Windows version of Desmond makes use of two headers files developed by Alexander Chemeris.

inttypes.h license

```
// ISO C9x compliant inttypes.h for Microsoft Visual Studio
// Based on ISO/IEC 9899:TC2 Committee draft (May 6, 2005) WG14/N1124
//
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```

stdint.h license

```
// ISO C9x compliant inttypes.h for Microsoft Visual Studio
// Based on ISO/IEC 9899:TC2 Committee draft (May 6, 2005) WG14/N1124
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