

5 Classical Molecular Dynamics (MD) Simulations with Tinker

In this set of exercises, you will be briefly introduced to the concept of classical force fields and molecular dynamics via propagation of atomic positions in time. You will learn how to create molecules (methylcyclohexane) using the `MOLDEN` chemical editing program and you will minimise, solvate and finally run molecular dynamics simulations on these structures to obtain separate trajectories for each.

5.1 Classical Molecular Dynamics

The extensive computational demand of electronic structure elucidation implies that an exact (fully quantum mechanical) description and time-propagation of even modestly sized molecular systems is in practice impossible. Although systems that comprise about 10^3 atoms are nowadays routinely described using approximate quantum mechanical (such as state-of-the-art Kohn-Sham Density Functional Theory) or semi-empirical methods, the computational demand of explicitly treating electrons in even larger systems such as biomolecules (10^5 atoms and more) becomes untractable all too quickly.

Fortunately, for such systems it is frequently sufficient to use a classical approximation to accurately reproduce supramolecular properties, such as the folding of a protein or the structure of a liquid. Classical approximations typically scale better with system size, and they therefore allow both for large systems and long simulation times to be taken into account. Here, atoms are treated as effective point charges with mass, instead of nuclei with explicit electrons. The classical approach makes use of a parameterised force field (or classical potential energy function), which is an approximation of the quantum-mechanical potential energy surface due to the electronic and nuclear potential, as a function of nuclear position. Such classical force fields typically work well under the following assumptions:

- a) The Born-Oppenheimer approximation is valid.
- b) The electronic structure is not of interest.
- c) The temperature is modest.
- d) There is no bond breaking or forming.
- e) Electrons are highly localised.

5.1.1 Classical Approximation: Basic Features

In the classical approximation, one describes positions and momenta of all the atomic nuclei:

$$\mathbf{r}^N = \{x^1, y^1, z^1, \dots, x^N, y^N, z^N\} \quad (1)$$

$$\mathbf{p}^N = \{p_{x1}, p_{y1}, p_{z1}, \dots, p_{xN}, p_{yN}, p_{zN}\}, \quad (2)$$

where each position and all momenta are known simultaneously. One microstate is then characterised by a set of the $3N$ positions $\{\mathbf{r}^N\}$ and $3N$ momenta $\{\mathbf{p}^N\}$ for a total of $6N$ degrees of freedom, such that the notation $\{\mathbf{p}_m^N, \mathbf{r}_m^N\}$ defines a particular microstate m . For any microstate, one can calculate the total energy as a sum of the kinetic $T(\{\mathbf{p}^N\})$ and potential $V(\{\mathbf{r}^N\})$ terms. The Hamiltonian of a classical system then becomes:

$$\mathbf{H}(\{\mathbf{p}^N\}, \{\mathbf{r}^N\}) = \mathbf{T}(\{\mathbf{p}^N\}) + \mathbf{V}(\{\mathbf{r}^N\}), \quad (3)$$

where the kinetic term is simply:

$$\mathbf{T}(\{\mathbf{p}^N\}) = \sum_i^N \frac{|\mathbf{p}_i|^2}{2m_i}. \quad (4)$$

Interactions between atoms are then described by a potential energy function $\mathbf{V}(\{\mathbf{r}^N\})$ that depends solely on the positions of all atoms $\{\mathbf{r}^N\}$. A key part of describing time evolution of a molecular system classically is then the definition of the potential energy function $\mathbf{V}(\{\mathbf{r}^N\})$. In fact, the functional form of $\mathbf{V}(\{\mathbf{r}^N\})$ is often chosen by examining the various modes by which atoms interact according to a quantum mechanical treatment of the molecular system and patching simple, often first-order theoretical expressions for these modes together. These modes can also be fitted to experimental (and/or quantum mechanical calculations of) model compounds such that the force field reproduces selected properties of a database of representative test structures.

$\mathbf{V}(\mathbf{r}^N)$ can be mainly decomposed into the following components:

$$\mathbf{V}(\{\mathbf{r}^N\}) = \mathbf{V}_{bonded}(\{\mathbf{r}^N\}) + \mathbf{V}_{non-bonded}(\{\mathbf{r}^N\}), \quad (5)$$

where $\mathbf{V}_{bonded}(\{\mathbf{r}^N\})$ and $\mathbf{V}_{non-bonded}(\{\mathbf{r}^N\})$ correspond to intermolecular and intramolecular potentials respectively. Intramolecular interactions typically include bond stretching, bond angle bending and bond torsional modes, while intermolecular interactions include dispersion and coulombic potentials. These are discussed in more detail below.

5.1.2 Intramolecular Interactions

Intramolecular interactions occur through bonds between atoms, the three most well known being bond stretching (vibration), bond angle bending and bond torsional modes. These are illustrated in Figure 1.

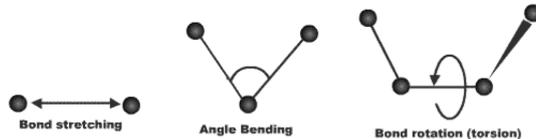


Figure 1: Depiction of the 2, 3, and 4-centre intramolecular forces.

Bond Stretching An accurate description of bond stretching that well-describes the intramolecular behaviour is the empirical Morse potential:

$$V_B(d) = D_e[1 - e^{-a(d-d_0)}]^2, \quad (6)$$

where d is the length of the bond, a is a constant, d_0 is the equilibrium bond length, and D_e is the well-depth minimum. Typically this form is not used, as it requires three parameters per bond and is somewhat expensive to compute in simulation due to the exponential. Since the energy scales of bond stretching are relatively high, bonds rarely deviate significantly from the equilibrium bond length, thus one can use a second-order Taylor expansion around the energy minimum:

$$V_B(d) = \alpha(d - d_0)^2, \quad (7)$$

where α is a constant. This form treats bond vibrations as harmonic oscillations, and thus atoms cannot be dissociated. Figure 2 provides a depiction of both the Morse potential and the corresponding harmonic approximation.

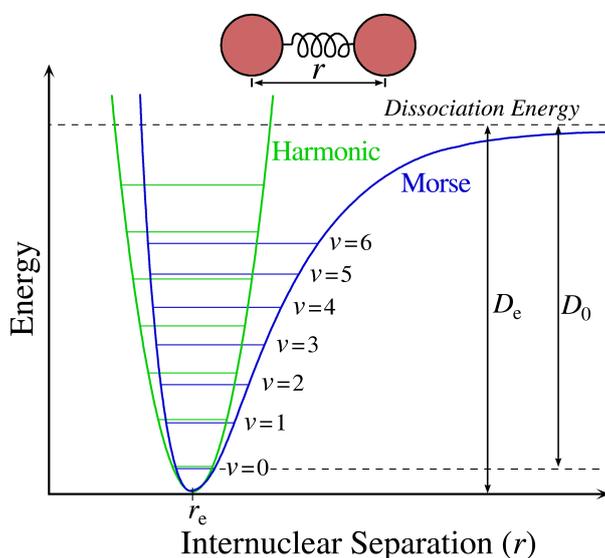


Figure 2: Depiction of a Morse and harmonic potential used to approximate chemical bonds.

Bond Angle Bending This term accounts for deviations from the preferred hybridisation geometry (e.g sp^3). Again, a common form is the second-order Taylor expansion about the energy minimum:

$$V_A(\theta) = b(\theta - \theta_0)^2, \quad (8)$$

where θ is the bond angle between three atoms, b is a constant and θ_0 is the equilibrium bond angle.

Bond Torsions These interactions occur among four atoms and account for rotational energies along bonds. Unlike the previous terms, torsional modes are "soft" such that energies are often not so high as to only allow small deviations from an equilibrium structure. Torsional modes are frequently modeled with the following expression:

$$V_T(\omega) = \sum_{n=0}^N c_n [1 + \cos(n\omega - \gamma)], \quad (9)$$

where ω is the torsional angle, n and c_n are summation index and coefficients respectively, and γ is an additional dihedral-dependent parameter. A depiction of $V_T(\omega)$ is provided in Figure 3.

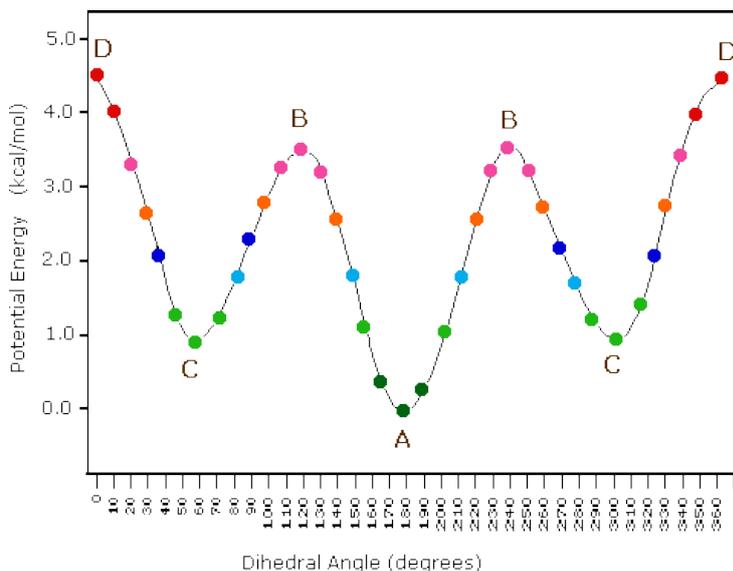


Figure 3: A typical dihedral potential used in classical force fields.

5.1.3 Intermolecular Interactions

Intermolecular interactions apply to any atoms that are not bonded, either within the same molecule or between different molecules.

These interactions are described using a pairwise decomposition of the energy. Formally one can decompose the potential energy function into interactions involving single atoms, pairs of atoms, triplets of atoms and so forth:

$$\mathbf{V}(\{\mathbf{r}^N\}) = \sum_{i=1}^N \mathbf{v}_1(\mathbf{r}_i) + \sum_{i=1} \sum_{j=i+1} \mathbf{v}_2(\mathbf{r}_{ij}) + \sum_{i=1} \sum_{j=i+1} \sum_{k=j+1} \mathbf{v}_3(\mathbf{r}_{ij}, \mathbf{r}_{ik}, \mathbf{r}_{jk}) + \dots \quad (10)$$

It is convenient to truncate this expansion beyond pairwise interactions as the computational expense of adding additional terms scales as $O(N^k)$, where k is the number of bodies interacting. This truncation is performed at the expense of certain polarization effects which can lead to subtle deviations away from experimental results. The resulting effective pair potential is given by:

$$\mathbf{V}(\{\mathbf{r}^N\}) = \sum_{i=1}^N \mathbf{v}_1(\mathbf{r}_i) + \sum_{i=1} \sum_{j=i+1} \mathbf{v}_{eff}(\mathbf{r}_{ij}). \quad (11)$$

Electrostatics Interactions between charges (partial or formal) are modeled using Coulomb's law:

$$\mathbf{V}_c(\mathbf{r}_{ij}) = \frac{q_i q_j}{4\pi\epsilon_0 \mathbf{r}_{ij}}, \quad (12)$$

for which the atoms i and j are separated by distance \mathbf{r}_{ij} . The partial charges are given by q_i and q_j while ϵ_0 denotes the free space permittivity.

London Dispersion Forces Correlations between instantaneous electron densities surrounding two atoms gives rise to an attractive potential:

$$\mathbf{V}_{ld}(\mathbf{r}_{ij}) \propto \mathbf{r}_{ij}^{-6}, \quad (13)$$

and is a component of the Van der Waals force, which contains other forces including dipole-dipole (Keesom force), permanent dipole-induced dipole (Debye force) and London dispersion forces. A depiction of London dispersion and Coulombic forces can be seen in Figure 4.

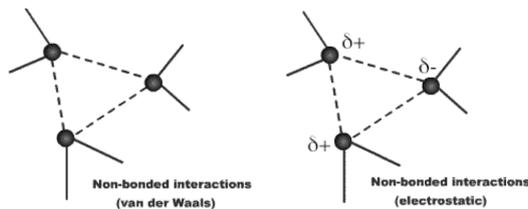


Figure 4: Depiction of London dispersion and Coulombic forces.

Excluded Volume Repulsion When two atoms approach and their electron densities overlap, they experience a steep increase in energy and a corresponding strong repulsion. This occurs due to the Pauli principle: two electrons are forbidden to have the same quantum number. At moderate inter-nuclear distances, this potential has the approximate form:

$$\mathbf{V}_{evr}(\mathbf{r}_{ij}) \propto e^{-c\mathbf{r}_{ij}}, \quad (14)$$

where c is a constant. To alleviate computational complexity this can be successfully modeled by a simple power law that is much more convenient to compute:

$$\mathbf{V}_{evr}(\mathbf{r}_{ij}) \propto \mathbf{r}_{ij}^{-m}, \quad (15)$$

where m is greater than 6.

Lennard-Jones Potential An effective method to model both the excluded volume and London dispersion forces is to combine them into a single expression, which Lennard-Jones proposed in the following pairwise interaction:

$$\mathbf{V}(\mathbf{r}_{ij}) = 4\epsilon_{ij} \left[\left(\frac{\mathbf{r}_{ij}}{\sigma} \right)^{-12} - \left(\frac{\mathbf{r}_{ij}}{\sigma} \right)^{-6} \right] \quad (16)$$

where ϵ and σ are atom-dependent constants. The factor of 12 is used for the repulsive term simply because it is convenient to square the attractive \mathbf{r}_{ij}^{-6} term.

5.2 The Atomic Force Field

A bare-minimum force field can now be constructed as a simple addition of individual contributions to the approximation of the potential energy surface:

$$\begin{aligned} \mathbf{V}(\{\mathbf{r}^N\}) = & \sum_{bonds,i} \alpha_i (d_i - d_{i,0})^2 + \sum_{angles,j} \beta_j (\theta_j - \theta_{j,0})^2 + \sum_{torsions,k} \left[\sum_n c_{k,n} (1 + \cos(\omega_k n + \gamma_k)) \right] \\ & + \sum_i \sum_{j < i} \frac{q_i q_j}{4\pi\epsilon_0 \mathbf{r}_{ij}} + 4\epsilon_{ij} \left[\left(\frac{\mathbf{r}_{ij}}{\sigma_{ij}} \right)^{-12} - \left(\frac{\mathbf{r}_{ij}}{\sigma_{ij}} \right)^{-6} \right]. \quad (17) \end{aligned}$$

5.2.1 Force Field Parameterisation and Transferability

The minimal force field in section 5.2 contains a large number of parameters:

$$\alpha_i, d_{i,0}, \beta_j, \theta_{j,0}, c_{k,n}, \gamma_k, q_{i,j}, \epsilon_{ij}, \sigma_{ij},$$

which must be chosen, depending on the kind of atoms involved and their chemical environment (e.g an oxygen-bound carbon behaves differently to a nitrogen-bound carbon), for every single type of bond, angle, torsion, partial charge and repulsive/dispersive interaction. In fact, all modern force fields typically contain more functions than the minimal and hence this results in a huge set of adjustable parameters that define a particular force field. Classical force fields are an area of active research, and are continually and rigorously developed and improved by a number of different research groups. Values for these parameters are typically taken from a combination of electronic structure calculations of small model molecules, and also experimental data. The inclusion of experimental data tends to improve accuracy because it fits bulk phases rather than the very small systems ab initio simulations can treat and as a result, the majority of force fields are semi-empirical.

5.3 Time Evolution

Given the potential for atomic interaction in section 5.2, the force acting upon the i th atom is determined by the gradient with respect to atomic displacements:

$$\mathbf{F}_i = -\nabla_{\mathbf{r}_i} V(\mathbf{r}_1, \dots, \mathbf{r}_N) = -\left(\frac{\partial V}{\partial x_i}, \frac{\partial V}{\partial y_i}, \frac{\partial V}{\partial z_i}\right). \quad (18)$$

Using Newton's equations of motion one can then achieve propagation of atomic positions in time, using some time step Δt :

$$\mathbf{a}_i(r_i, t) = \frac{\mathbf{F}_i(\mathbf{r})}{m_i}, \quad (19)$$

$$\mathbf{v}_i(t + \Delta t) = \mathbf{v}_i(t) + \mathbf{a}_i(t)\Delta t, \quad (20)$$

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \mathbf{v}_i(t)\Delta t. \quad (21)$$

5.3.1 The Position-Verlet Algorithm

The potential energy $U(\mathbf{r}_1, \dots, \mathbf{r}_N)$ is a function of the positions ($3N$) of all atoms in the system. Due to the complicated nature of this function and the large number of atoms typically modeled in classical systems, there is no analytical solution to the equations of motion, and hence these must be solved numerically. The most common numerical solutions to integrating the equations of motion are called finite difference methods. First, the positions, velocities and accelerations can be approximated by a Taylor series expansion:

$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + \mathbf{v}(t)\Delta t + \frac{1}{2}\mathbf{a}(t)\Delta t^2 + \dots, \quad (22)$$

$$\mathbf{v}(t + \Delta t) = \mathbf{v}(t) + \mathbf{a}(t)\Delta t + \frac{1}{2}\mathbf{b}(t)\Delta t^2 + \dots, \quad (23)$$

$$\mathbf{a}(t + \Delta t) = \mathbf{a}(t) + \mathbf{b}(t)\Delta t + \dots, \quad (24)$$

where \dots denotes higher order derivatives of $\mathbf{r}(t)$. One can then propagate the position function forwards and backwards in time, yielding:

$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + \mathbf{v}(t)\Delta t + \frac{1}{2}\mathbf{a}(t)\Delta t^2, \quad (25)$$

$$\mathbf{r}(t - \Delta t) = \mathbf{r}(t) - \mathbf{v}(t)\Delta t + \frac{1}{2}\mathbf{a}(t)\Delta t^2, \quad (26)$$

$$(27)$$

and by summing these the position-Verlet is obtained:

$$\mathbf{r}(t + \Delta t) = 2\mathbf{r}(t) - \mathbf{r}(t - \Delta t) + \mathbf{a}(t)\Delta t^2, \quad (28)$$

while the subtraction of the Taylor series for $\mathbf{r}(t + \Delta t)$ and $\mathbf{r}(t - \Delta t)$ yields:

$$\mathbf{v}(t) = \frac{\mathbf{r}(t + \Delta t) - \mathbf{r}(t - \Delta t)}{2\Delta t}. \quad (29)$$

5.3.2 The Velocity-Verlet Algorithm

The position-Verlet algorithm uses positions and accelerations at time t , and the positions from time $t - \Delta t$ to calculate new positions at time $t + \Delta t$. The position-Verlet algorithm does not use velocities explicitly, and as such it is straightforward to implement and requires minimal storage space. However, this form of the Verlet algorithm is not self-starting, i.e it requires two time steps before propagation can take place, and as such is heavily dependent on initial starting conditions. A modification to the above is the velocity-Verlet:

$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + \mathbf{v}(t)\Delta t + \frac{1}{2}\mathbf{a}(t)\Delta t^2, \quad (30)$$

$$\mathbf{v}(t + \Delta t) = \mathbf{v}(t) + \frac{1}{2}(\mathbf{a}(t + \Delta t) + \mathbf{a}(t))\Delta t, \quad (31)$$

which is self-starting and additionally minimises round-off errors.

5.4 Conformers in Solution: axial-methylcyclohexane and equatorial-methylcyclohexane

Despite the emergence of large chemical information resources such as PubChem, finding molecular structures that are suitable starting points for computational modeling can be a challenge. Therefore, in this exercise session you will learn the basics of how to obtain a simple classical molecular dynamics trajectory from scratch using **Tinker**: building molecules, defining force fields, minimisation, solvation and finally production MD. You will begin by creating two structures in `.xyz` format of axial-methylcyclohexane and equatorial-methylcyclohexane respectively, shown in Figure 5. The following guide provides a tutorial for axial-methylcyclohexane only.

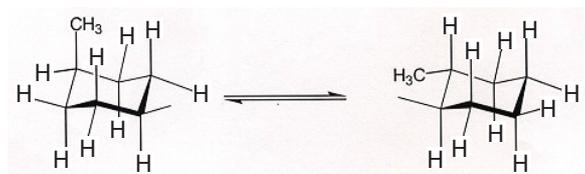


Figure 5: Structures of axial-methylcyclohexane and equatorial-methylcyclohexane. These conformers of methylcyclohexane are stable in solution due to the non-negligible energetic barriers of ring flipping at ambient temperatures.

5.4.1 Building the Structures with MOLDEN

There are a multitude 3D molecular structure builders available, but for these exercises we will use MOLDEN. This tool provides the ability to read and write molecular structures from various file formats. Type the following to open MOLDEN:

```
molden
```

and click on **ZMAT Editor** (it is advisable to do this in the **Ball & Stick** drawing mode).

5.4.2 ZMAT Editor: Building methylcyclohexane

Building H₂ Click on **Add Line** in the **ZMAT Editor**, select hydrogen and then click somewhere in your **MOLDEN** window. You will see a single hydrogen atom appear. Next, repeat the process and instead of clicking within the **MOLDEN** window, click on the first hydrogen to create a H₂ molecule. This will be your starting point for building methylcyclohexane.

Building axial-methylcyclohexane You will substitute the first hydrogen to produce your desired structure. This is necessary since you will take a shortcut to create cyclohexane. Click on the first hydrogen (1st atom in the **ZMAT Editor**), click on **Substitute atom by Fragment** and select **CycloHexane**. This will substitute your H₂ molecule with

cyclohexane, however the dihedral of the now substituted hydrogen will be incorrect. You will need to modify the dihedral of this hydrogen (4th atom in the ZMAT Editor) from its current value to 120. Once you have done this the MOLDEN window will show a cyclohexane molecule, from which you may create the conformers of methylcyclohexane. Click on one of the axial hydrogens such that it is marked with a red ball, and by selecting **Substitute atom by Fragment** again, you can substitute this atom by a -CH₃ group to produce the axial-cyclohexane structure.

Assigning Atom Types Tinker requires that atom types are specified in the .xyz file such that the correct parameters for vibrational, angular, torsional and other contributions to the force field can be properly assigned. For this you must make sure the ZMAT Editor window is closed. Within the Molden Control panel, click on FF to modify atom attributes. Under the Force Field label, select Tinker MM3 and click OK. You can now save this file as a tinker .xyz file by selecting Write, then Tinker and choosing the file name a-methylcyclohexane.xyz.

You can now perform the same procedure to create the equatorial-methylcyclohexane structure. You can either start from scratch by clicking New Z-mat from the ZMAT Editor window or you can modify the structure by deleting and adding atoms with Delete Line and Add Line respectively.

Adding and Removing Atoms You can add and remove atoms from the ZMAT Editor by clicking Add Line and Delete Line respectively. Upon clicking Add line, you can then specify which atom type you wish to add. If you are creating a new bond, you must first specify the atom you wish the new atom to be bonded to, followed by the atom it forms an angle with and finally the atom with which it forms a dihedral. Specifying these atoms is simply done by clicking in the appropriate order. To delete atoms, click on an atom in the MOLDEN (or in the ZMAT Editor) window and then click Delete Line. You can also modify bond lengths, angles and dihedrals explicitly by modifying the values within the ZMAT Editor. If you wish to delete a Z-matrix and start over, simply click New Z-mat.

5.4.3 Minimisation: Specifying the Force Field

Before you begin any form of calculation with Tinker, you must create a basic .key file which Tinker will use to obtain system and simulation specific information. For this exercise you only need to specify that you wish to use the MM3 force field. In your terminal type the following command:

```
echo "parameters /path-to-mm3/mm3.prm" > molecule.key
```

5.4.4 Minimisation: Gas Phase

The structure created by MOLDEN is not the exact minimum energy conformer, in fact, this is impossible to guess without explicit knowledge of all bond lengths, angles and

dihedrals. To perturb the molecular structure to its nearest minimum, we can use the `minimize` program within Tinker as follows:

```
/opt/tinker/minimize molecule.xyz -k molecule.key 0.01
```

which will minimise the structure with the MM3 force field supplied in the `molecule.key` file, using a root mean squared (RMS) value of 0.01 as the stopping criteria for the convergence test. This command will produce a file called `molecule.xyz_2`, which you can rename appropriately with the command:

```
mv molecule.xyz_2 min_molecule.xyz.
```

5.4.5 Energy Decomposition

You can use the Tinker program `Analyze` to analyse force field related properties. Here it is interesting to analyse the individual contributions to the total energy, as well as discern the overall relative stability of a given molecule in its current configuration and environment. You can use `Analyze` as follows:

```
/opt/tinker/analyze min_molecule.xyz -k molecule.key
```

and select option E to look at the total potential energy and the individual components that contribute to it.

5.4.6 Solvation

To solvate the molecules in a water, you can use the `waterbox.xyz` file from the previous exercise.

You can soak your minimised molecule with the `xyzedit` program as follows:

```
/opt/tinker/xyzedit min_molecule.xyz -k molecule.key
```

and choosing option #18 to add the contents of `waterbox.xyz` to surround your molecule. This will produce a solvated system called `min_molecule.xyz_2` which you can rename to something more meaningful with the following command: `mv min_molecule.xyz_2 solv_molecule.xyz.`

Since the water molecules for the previous exercise did not use the MM3 force field, you will need to modify their atom types accordingly. This can be performed by loading the `solv_molecule.xyz` file into `MOLDEN` and selecting the correct force field as before. Save this file to something appropriate, e.g `solv_molecule_mm3.xyz.`

5.4.7 Molecular Dynamics

To run the simulation use the following command:

```
nohup /opt/tinker/dynamic solv_molecule_mm3.xyz -k molecule.key  
5000 1.0 0.1 2 298.0 &
```

This command specifies that you wish to perform molecular dynamics upon the `molecule.xyz` system using parameters defined within the `molecule.key` file. The additional parameters passed by command-line are:

- a) Number of steps: 5000.
- b) Time step length: 1.0 femtoseconds.
- c) Record the output coordinates at every 0.1 picosecond.
- d) Sample the canonical ensemble (Option 2).
- e) Temperature held constant at 298.0K.

And finally the output of the simulation is piped to the file `nohup.out` which you can track the progress of by typing the following command:

```
tail -10 nohup.out
```

where the `-10` flag will make `tail` print the last 10 lines of the `nohup.out` file to your terminal.

5.4.8 Creating the Trajectory

The above dynamics will produce 50 snapshots of the system, saved in the files named 'solv_molecule_mm3.001...solv_molecule_mm3.050'. These files contain the coordinates of the trajectory at every 0.1 picosecond. To visualise this trajectory, you must first compile them together into a single archive using the following program:

```
/opt/tinker/archive
```

You will be asked to enter the name of the coordinate archive file. Enter 'solv_molecule_mm3' and then '1' to indicate that you are compressing a set of frames. you will now need to enter the frames over which the dynamics was recorded, so enter '001 050'. This will produce a `solv_molecule_mm3.arc` file which can be loaded into VMD:

```
vmd solv_molecule_mm3.arc
```

5.4.9 Creating the Trajectory: Modifications

If the `solv_molecule_mm3.arc` file produced above does not load into VMD immediately, it will need a small amount of editing. Open the file in `vi` as follows:

```
vi solv_molecule_mm3.arc
```

and type the following command:

```
:%s/ 24.662000.*\n//ge
```

and press enter. Note that there are 4 spaces between the first / and the numeral 2. This command will remove the second line (containing simulation box information) from every frame in the archive.

5.5 Exercises

5.5.1 Time Evolution

- Derive the form of $\mathbf{r}(t + \Delta t)$ in the velocity-Verlet (equation 30). **Hint:** solve equation 29 for $\mathbf{r}(t - \Delta t)$, and use equations 28 and 25.
- Derive the form of $\mathbf{v}(t + \Delta t)$ in the velocity-Verlet (equation 30). **Hint:** recast equations 29 and 28 to a timestep Δt in the future, and use the result obtained above.

5.5.2 Conformer Preparation

Create initial starting structures for both conformers of methylcyclohexane and minimise them in the gas phase. Use the **Analyse** program to investigate the main components of the total potential energy for the initial and minimised (gas phase) structures for both conformers of methylcyclohexane.

- For one of the minimised conformers, provide the entire Tinker `.xyz` in your report and comment upon the main differences between this and a standard `.xyz` file. Why are these differences important for using **Tinker**?
- Include images of both the initial and minimised structures in your report.
- Tabulate the potential energy components in your report, including the total energy for both the initial and minimised structures. Which components change the most during the minimisation process?
- What are the largest contributions to the potential energy, which molecule is more stable (in the gas phase) and why?

Note: You can visualise Tinker `.xyz` files in VMD by loading them as new molecules, and selecting the Tinker format.

5.5.3 Running Classical Molecular Dynamics

Solvate the minimised molecules separately and perform molecular dynamics of both systems for a total duration of 50ps, with the MM3 force field. Using the Tinker **archive** program, create a trajectory from the MD and visualise it in **VMD**.

- a) Include a frame from the MD simulation within your report.
- b) From one of your trajectories, tabulate the following averages in your report: the $\text{H}_3\text{C}-\text{CH}_2-\text{C}_5\text{H}_9$ bond length, one of the $\text{CH}_3-\text{CH}_2-\text{C}_5\text{H}_9$ angles and one of the $\text{H}-\text{CH}_2-\text{CH}_2-\text{C}_5\text{H}_9$ dihedrals. Do the averages you have computed correspond to those in the `mm3.prm` file? Why?
- c) Plot the $g(r)$ functions (using 'name O' as both selection criteria) for both solvated conformers and include the $g(r)$ graphs in your report. Comment upon why these graphs have such a significant 2nd solvation shell, versus that of the pure water you simulated in exercise 4.

Note: You can track changes in a given property (bond, angle or dihedral) with VMD. First open the **Mouse** menu from the **VMD Main** window, and select the appropriate property from the **Label** item. Your mouse has now changed into label mode, and from here you can select the appropriate atoms. Once you have selected the correct atoms, click the **Labels...** item from the **Graphics** menu option in the **VMD Main** window. Select **Bonds**, **Angles** or **Dihedrals** from the drop-down menu, and go to the **Graph** tab. Here you can choose to **Graph...** the data over the course of the trajectory, or save the data as a `.dat` file, from which you can calculate the average.