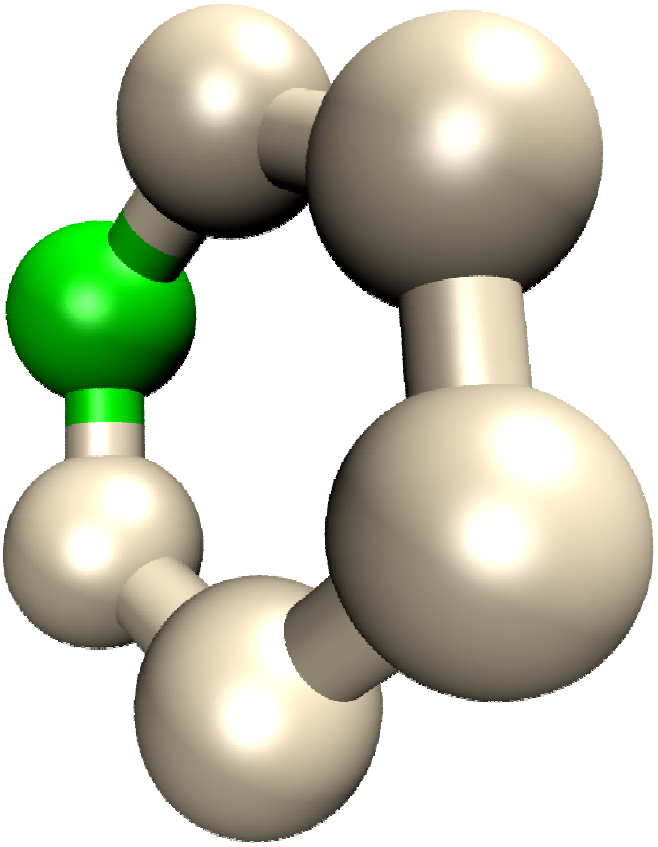

User's Manual

Release 0.4

January 30, 2009

Website: SimTK.org/home/zephyr

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Acknowledgments

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Table of Contents

List of Tables

No table of figures entries found.

List of Figures

List of Examples

1 Overview

1.1 Introduction to Molecular Dynamics

Researchers are increasingly using molecular dynamics (MD) simulations to model molecular motion and help expand our knowledge and understanding of biology. Examples of how MD simulations have been used include:

- Providing hypotheses for biological phenomena that cannot currently be observed experimentally and guiding new experiments [1, 2, 3]
- Identifying which engineered molecules would be stable or would bind with another molecule [3]
- Augmenting information provided by static structures, i.e., from x-ray crystallography [4]

The potential uses for MD simulations are exciting, but getting started can be overwhelming and time-consuming. OpenMM Zephyr was designed to get researchers running MD simulations quickly.

1.2 What is OpenMM Zephyr?

OpenMM Zephyr is a freely downloadable application with a graphical user interface that allows users to easily run the OpenMM version of GROMACS, a widely used MD package. The OpenMM version speeds up the GROMACS simulations, so that more complex molecules and/or longer processes can be simulated. Read more about OpenMM and how to take full advantage of it in Section 1.3.

OpenMM Zephyr leads the user through the basic steps required to set up and run a simulation, and also to visualize the simulation results using VMD, a popular molecular visualization program. [Explain what is hard about learning to run MD simulations in general?] Throughout the process, the specific GROMACS (and VMD?) commands being

used are displayed, enabling users to teach themselves how to use the command-line GROMACS package to run more (complex?) simulations.

1.3 What is OpenMM?

OpenMM is a freely downloadable, high performance, extensible library that allows molecular dynamics simulations to run on high performance computer architectures, such as computer clusters and graphics processing units (GPUs). This makes it more reasonable to simulate complex molecules and/or longer processes. Performance speed ups of over 100X have been achieved in some cases using OpenMM. [5]

1.3.1 Running OpenMM on GPUs

Version 1.0 of OpenMM enables fast MD simulations on NVIDIA and ATI GPUs. GPUs are computer chips designed for generating computer graphics. Their parallel design makes them also very useful for speeding up a variety of other applications, including MD simulations.

To take advantage of these speed-ups, though, your computer needs to be equipped with one of the supported GPU cards:

Supported NVIDIA GPUs:
http://www.nvidia.com/object/cuda_learn_products.html

Supported ATI GPUs:
http://ati.amd.com/technology/streamcomputing/requirements.html

Your computer does not need one of these GPU cards to run OpenMM Zephyr, but your simulations will not run as fast.

1.3.2 More information about OpenMM

You can learn more about the OpenMM project at http://simtk.org/home/openmm.

1.4 Conventions Used in this Document

1.5 References

[1] PE Marszalek, et al., “Mechanical unfolding intermediates in titin molecules,” Nature, 1999 Nov 4; 402(6757):100-103.

[2] HD Herce, AE Garcia, “Molecular dynamics simulations suggest a mechanism for translocation of the HIV-1 TAT peptide across lipid membranes,” PNAS, 2007; 104:20805-20810

[3] PM Kasson, VS Pande, “Structural basis for influence of viral glycans on ligand binding by influenza hemagglutinin,” Biophysical Journal, 2008; 95:L48-L50.

[4] DS Glazer, RJ Radmer, RB Altman, “Combining molecular dynamics and machine learning to improve protein function recognition,” Pac Symp Biocomput, 2008; 332-343.

[5] MS Friedrichs, P Eastman, V Vaidyanathan, M Houston, S Legrand, AL Beberg, DL Ensign, CM Bruns, VS Pande, “Accelerating Molecular Dynamic Simulation on Graphics Processing Units,” Journal of Computational Chemistry, in press.

2 Installation

2.1 Prerequisites

In order to run OpenMM Zephyr, you need a computer that runs Windows XP or Windows Vista. Linux and MacOS will be supported in the future.

You will also need to install Tcl/Tk (see Section 2.1.1). And if you wish to use the visualization capabilities of OpenMM Zephyr, you will need to install VMD (see Section 2.1.2).

To take advantage of GPU accelerated molecular dynamics you must have a supported GPU (see section 1.3.1). Further, for Nvidia GPUs you must have CUDA version 2.0 installed, and for ATI GPUs you must have CAL and Brook installed [Links needed]. It might be helpful to verify that CUDA or Brook are working by running some GPU test programs.

2.1.1 Installing Tcl/Tk version 8.5

OpenMM Zephyr requires Tcl/Tk, version 8.5. You can download this version for free from http://www.activestate.com/activetcl/ (Figure 1).

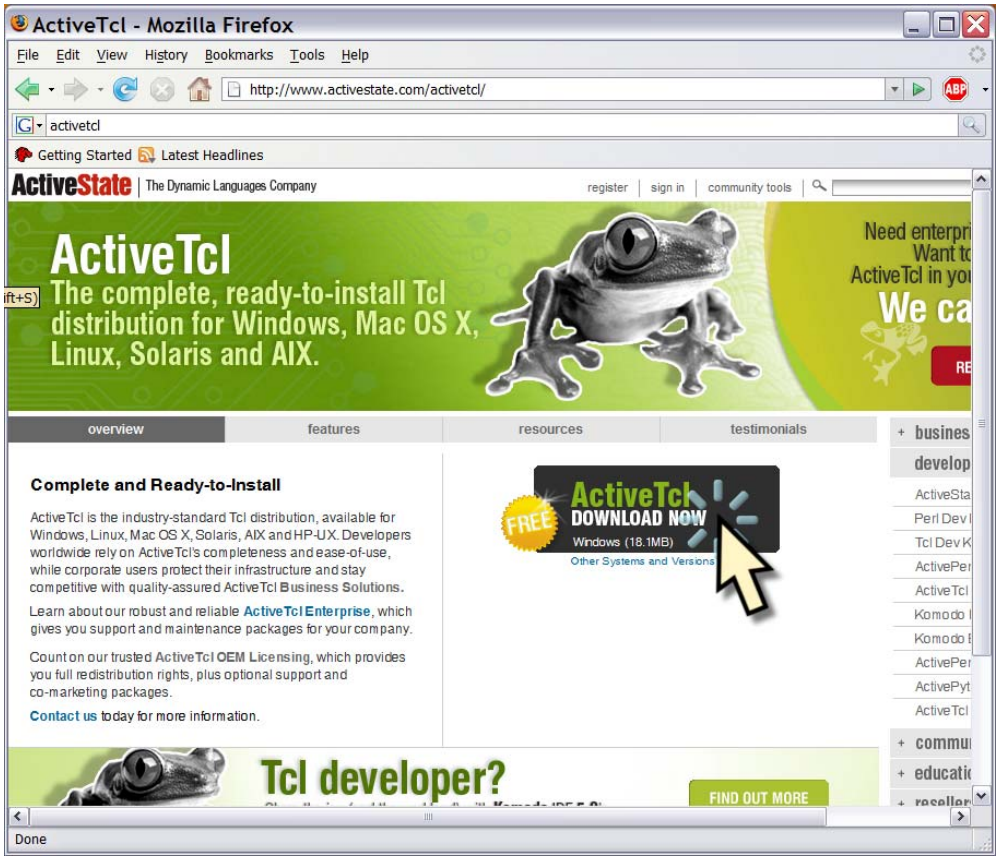


Figure 1: Website for downloading Tcl/Tk

From the website, click on the "Download Now" button. A dialog window will appear asking if you want to "Run" or "Save" the program. If you do not see the dialog window, make sure your pop-up blocker has been disabled. Click on "Save" and note where you save the program!

Double-click on the program you just downloaded to install it. You may get a "Security Warning" that the "publisher could not be verified." Go ahead and click "Run." Follow the directions that appear on the screen to complete the installation.

2.1.2 Installing VMD (optional but recommended)

OpenMM Zephyr also uses the molecular visualization program VMD. If you do not intend on visualizing the MD simulation results within OpenMM Zephyr, you do not need to install VMD. However, to take full advantage of OpenMM Zephyr, it is recommended that you install VMD.

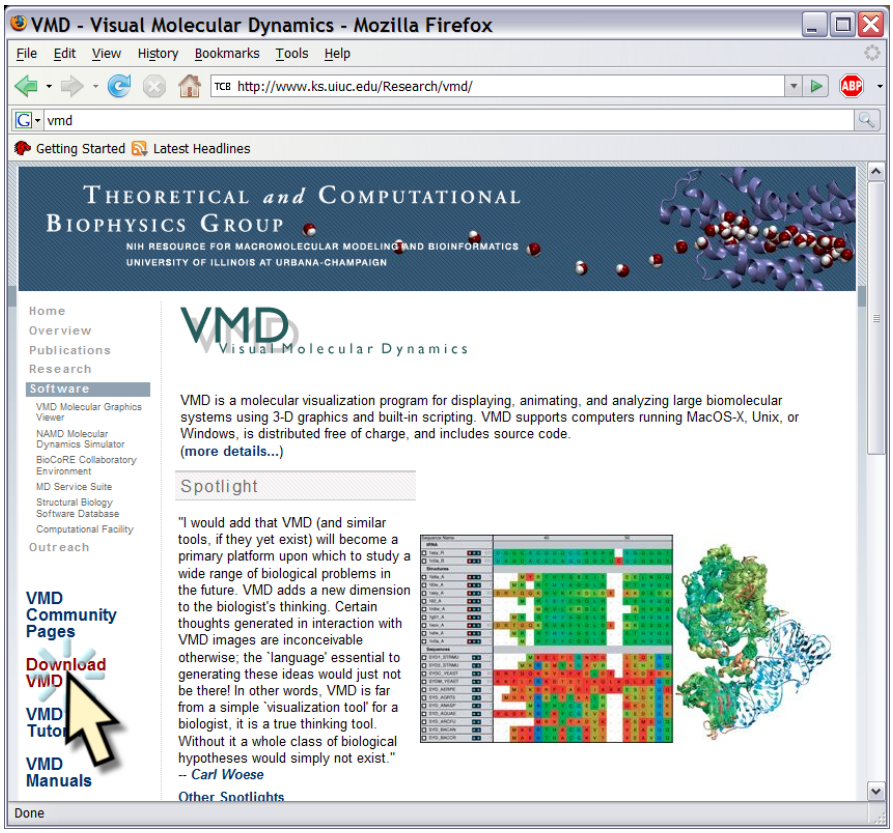


Figure 2: Download VMD from the University of Illinois

VMD can be downloaded for free from http://www.ks.uiuc.edu/Research/vmd/. Click on the "Download VMD" link in the left-hand column (Figure 2). You will be taken to another webpage, listing all the different versions of VMD. Select the Windows OpenGL distribution of the most recent version.

You will be taken to a registration/login window. Provide a username and password, and accept the license agreement that appears.

A dialog window will then appear asking if you want to "Run" or "Save" the program. If you do not see the dialog window, make sure your pop-up blocker has been disabled. Click on "Save" and note where you save the program!

Double-click on the program you just downloaded to install it. You may get a "Security Warning" that the "publisher could not be verified." Go ahead and click "Run." Follow the directions that appear on the screen to complete the installation.

2.1.3 Installing GPU software

If you intend to use GPU accelerated molecular dynamics, install CUDA (for Nvidia GPUs) or CAL and Brook (ATI GPUs), and test them before running Zephyr. [More detail is needed here]

2.2 Getting OpenMM Zephyr

2.2.1 Download OpenMM Zephyr

OpenMM Zephyr can be freely downloaded from https://simtk.org/home/zephyr. From the main project page, click on the "Downloads" link in the left-hand column (Figure 3).

You will be taken to the Downloads webpage. Click on the link for InstallOpenMMZepher.exe. If you are not already logged in to Simtk.org, you will be asked to log in (or register). You will then be asked to describe how you plan to use this software. Provide a description and then click "Download Now."

A dialog window will appear asking if you want to open or save this file. Click "Save" and note where you save the file!

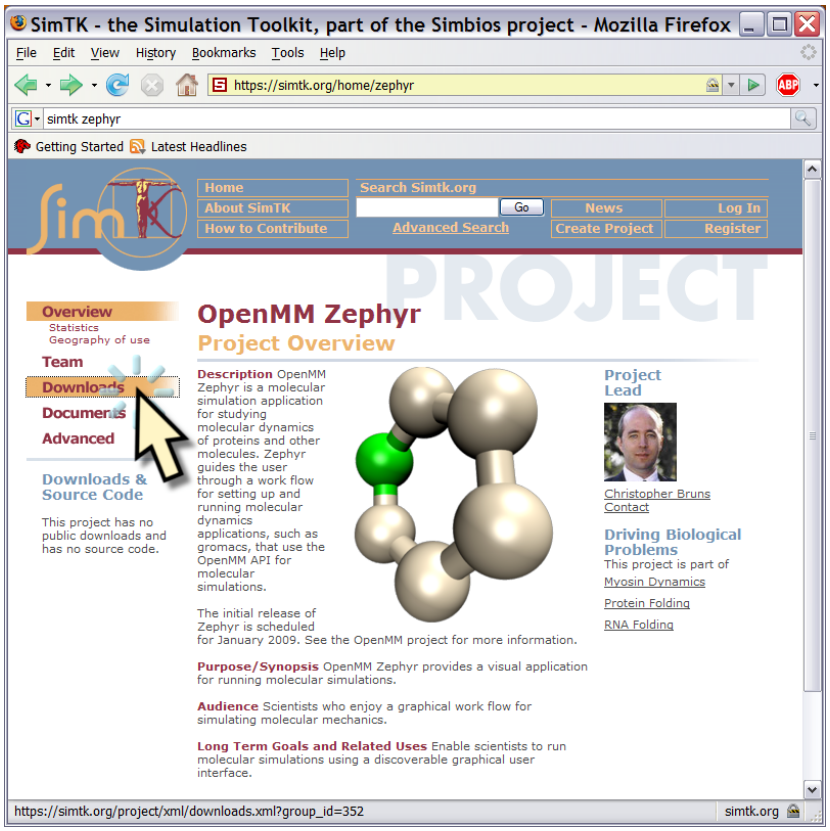


Figure 3: OpenMM Zephyr can be downloaded from Simtk.org

2.2.2 Install OpenMM Zephyr application

Save the InstallOpenMMZephr.exe program to your computer and then double click to run the installer.

When you install OpenMM Zephyr, you will be asked where to save all the files. You can save the files anywhere you like on your computer. However, **the path name for the installed files must not contain any spaces.** This is a limitation of the version of gromacs used as the basis for OpenMM Zephyr. For a Windows computer, a good place to save the files is to C:\Zephyr.

Installing Zephyr to "My Documents" will not work. You will be able to extract the files to that location but will not be able to run OpenMM Zephyr from there. ***Remember: the path for the OpenMM Zephyr files must not contain any spaces.***

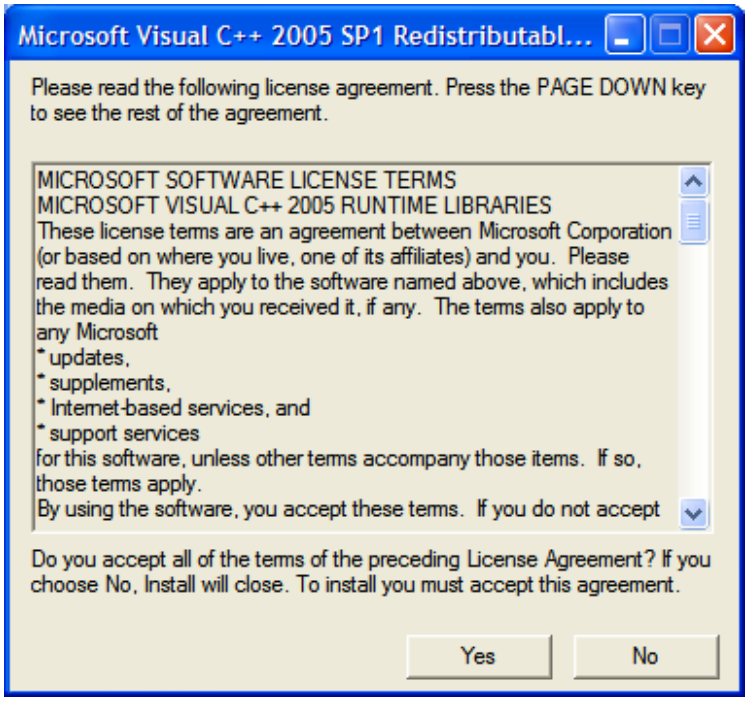


Figure 4: The Zephyr installer installs some required Microsoft software libraries. Click "Yes" to install these libraries.

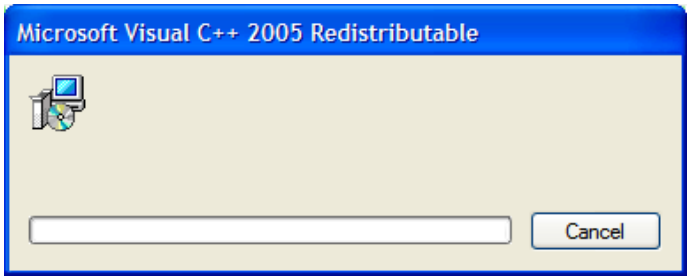


Figure 5: Sometimes the installation of the Microsoft libraries takes a while. Please be patient.

If you have successfully installed Zephyr, you should see the following files and directories:

- **OpenMMZephyr:** This is the OpenMM Zephyr application. Double-click on this to start the program.

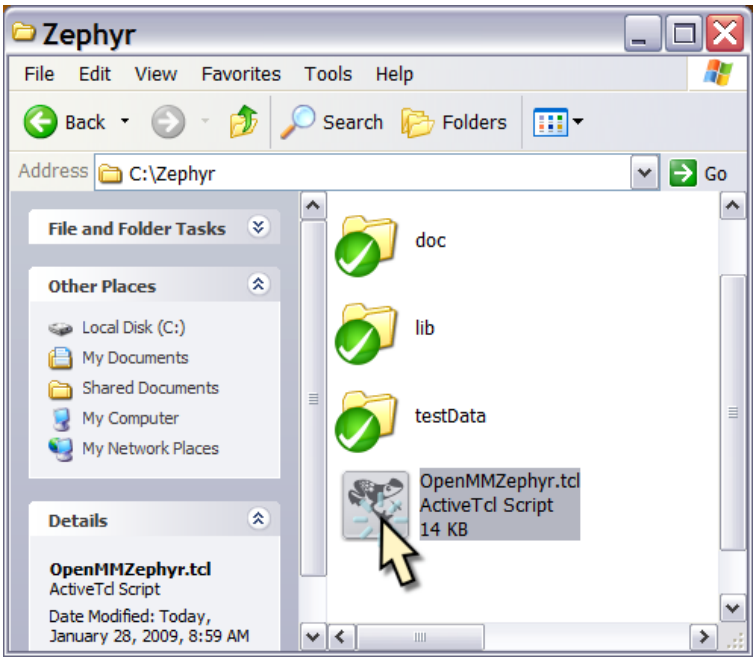
- **doc:** This directory contains the documentation files
- **simulations:** By default, the outputs of our simulations will be saved to this directory
- **testData:** This directory contains example data files to use for starting the example simulations

You will also see three other directories (**bin**, **images**, and **lib**), which provide files used behind the scenes by the OpenMM Zephyr program.

3 Running a Simulation

3.1 Launching OpenMM Zephyr

To start OpenMM Zephyr, double-click the OpenMMZephyr.tcl file. The window shown in Figure 7 appears.



6 Launch Zephyr by double clicking the OpenMMZephyr.tcl icon

Note the series of tabs near the top of the window: Molecules, Parameters, (Idle) (grayed out), VMD console (grayed out), About. The order of the tabs guides you in setting up and running the simulation:

1. Choose a molecule to simulate (the Molecules tab) – See Section 3.2
2. Set the simulation parameters (the Parameters tab) – See Section 3.3
3. Run the simulation (simulation progress shown in the third tab) – See Section 3.4
4. If desired, visualize the simulation results in VMD (the VMD tab) – See Section 3.6

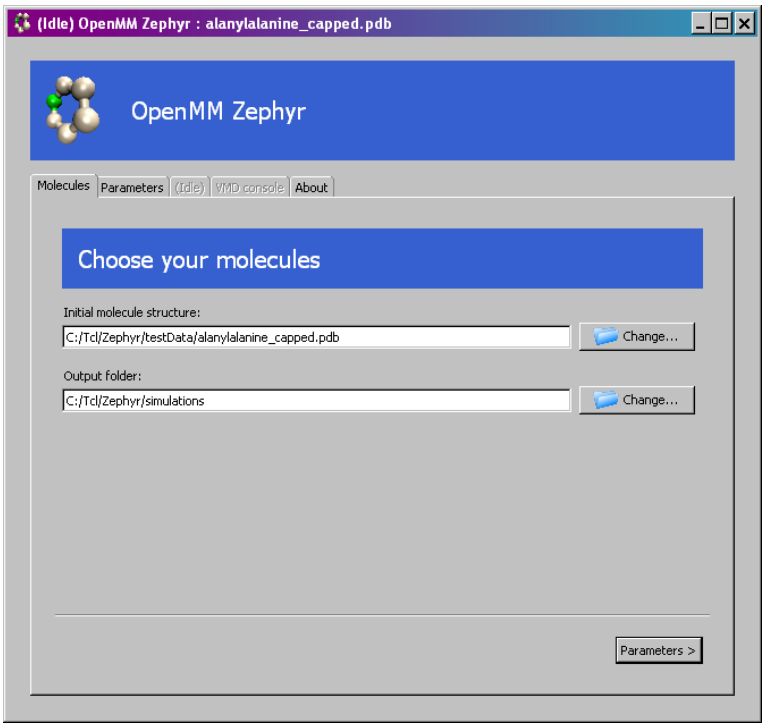


Figure 7: OpenMM Zephyr application

3.2 Choose a Molecule

Molecular simulations need an initial molecular structure to start the simulation. To choose the molecule you wish to simulate, click on the **Molecules** tab. Click the **Change...** button next to the field for **Initial molecule structure** to select the file describing the molecular structure. You can also type in the file name.

3.2.1 Finding PDB molecular structure files

http://www.rcsb.org/pdb/home/home.do

3.2.2 Preparing a PDB file for loading into Zephyr

Using a text editor, change some residue names and atom names for gromacs Amber96 force field. http://chemistry.csulb.edu/ffamber/.

- rename protein “LYS” residues to “LYP”
- For first residue of chain, prepend residue name with “N” for proteins, or “5” for DNA or RNA

- For final residue of chain, prepend residue name with “C” for proteins, or “3” for DNA or RNA
    - rename final protein residue atom name “O” to “OC1”
    - rename final protein residue atom name “OXT” to “OC2”
- [many other rules – see example PDB files for help]

3.2.3 Supported molecular structure files

3.2.4 What kind of information is in these molecular structural files?

3.3 Select Location for Output Files

Molecular simulations produce what are called “molecular trajectories” or just “trajectories.” By definition, a trajectory is the path of a moving body through space. However, in a molecular simulation, many bodies (atoms) are moving through space, so an intuitive way to capture all the information is to save snapshots of the molecule throughout the simulation. At the end of a simulation, you (typically?) end up with a set of molecular structure files, each representing a time point along the molecular trajectory.

What OpenMM Zephyr saves is....[Explain what files are actually saved....]

To select the location for these output files, click on the **Molecules** tab. Click the **Change...** button next to the field for **Output folder** to select the folder for the output files. You can also type in the name of the folder.

3.4 Run Simulation

3.4.1 Simulations are in implicit solvent

No water molecules are used in the simulation. [Explicit solvent simulations are possible using gromacs command line tools]

3.4.2 Time scale of simulation

Proteins fold in microseconds to hours. Time steps are femtoseconds. Even with 100x speed up the time requirements for folding are staggering. Even with GPUs, simulations are less than one microsecond per day.

3.5 Examples

3.5.1 Polyalanine

Should form into an alpha helix if part of an alpha helix is already there. A completely extended structure might take a long time to start forming an alpha helix.

3.5.2 Villin head piece

One of the fastest folding proteins known. Still takes at least microseconds to fold.

3.6 Watch the Trajectory with VMD

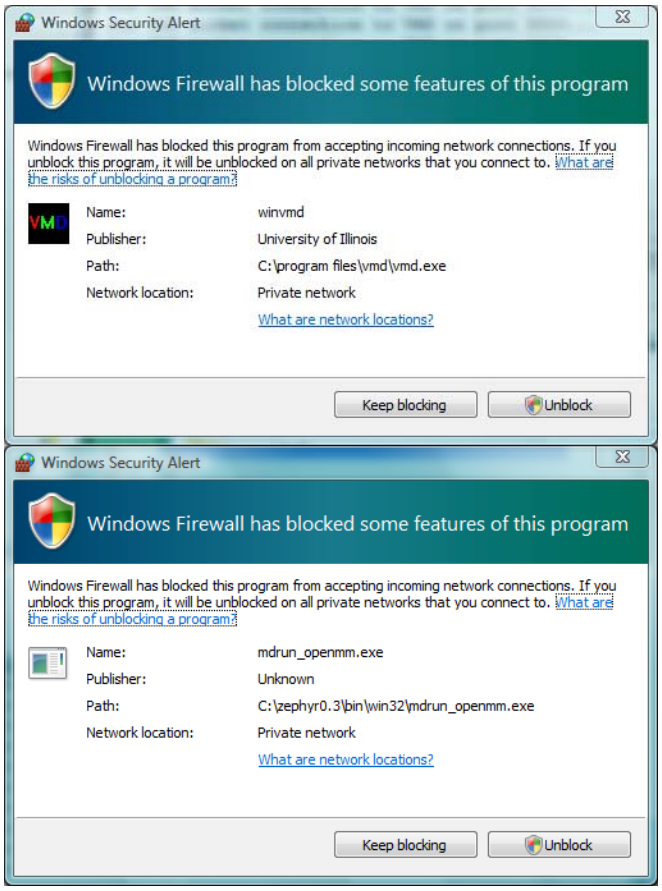


Figure 8: Click "Unblock" to grant permission for Zephyr and VMD to communicate through TCP sockets.

[Put screenshot of “unblock?” dialog that may come up when trying to connect to VMD]

3.7 Final Simulation Results

3.7.1 Saving a trajectory from VMD

[]

3.7.2 Saving a final structure from VMD

[]

3.7.3 Contents of simulation output directory

[output mdp parameters]
[log files]

3.7.3.1 Cleaning up when the output directory gets too full

[remove #*# files]

3.8 Stopping a simulation

Press the "Cancel" button in the Status panel to halt a running simulation. (This actually works in Zephyr 0.3 and later. For earlier versions, you must also kill the mdrun processes with the task manager).

4 Troubleshooting

4.1 Why is my simulation going so slowly?

If the VMD view of the simulation is changing very slowly, try decreasing the interval for VMD updates, and restarting the simulation. This will result in a smoother display in the VMD window.

Appendix A

References

Friedrichs; Eastman; Vaidyanathan; Houston; LeGrand; Beberg; Ensign; Bruns; Pande (2009) Accelerating Molecular Dynamic Simulation on Graphics Processing Units. J. Comp. Chem. in press

Hess, B., Kutzner, C., van der Spoel, D. and Lindahl, E. (2008)
GROMACS 4: Algorithms for Highly Efficient, Load-Balanced, and Scalable Molecular Simulation J. Chem. Theory Comput., 4, 435-447

Humphrey, W., Dalke, A. and Schulten, K., (1996) "VMD - Visual Molecular Dynamics", J. Molec. Graphics, vol. 14, pp. 33-38.