A Simple Molecular Dynamics Lab To Calculate Viscosity as a Function of Temperature

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S *Supporting Information*

ABSTRACT: A simple molecular dynamics experiment is described to demonstrate transport properties for the undergraduate physical chemistry laboratory. The AMBER package is used to monitor self-diffusion in *n*-hexane. Scripts (available in the Supporting Information) make the process considerably easier for students, allowing them to focus on the simulations and their meaning. Mean-squared displacements are determined as a function of simulation time for 250 ps in a small simulation box at a variety of temperatures. From these, the Einstein–Smoluchowski and Stokes–Einstein relationships are used to determine the viscosity, which can be directly compared to literature values. The needed trajectories can be calculated in less than 1 h and analyzed in a second hour, leaving a third hour for further explorations as appropriate.

KEYWORDS: *Upper-Division Undergraduate, Physical Chemistry, Laboratory Instruction, Computer-Based Learning, Alkanes/Cycloalkanes, Molecular Mechanics/Dynamics, Transport Properties*
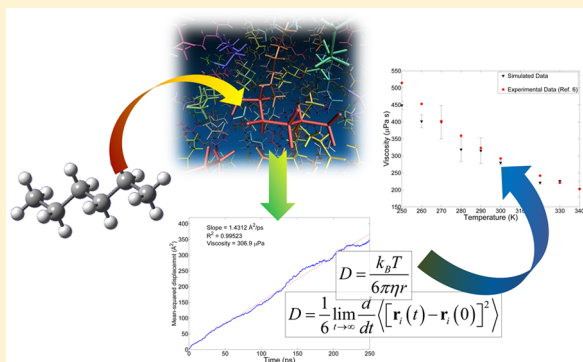
■ INTRODUCTION

Although molecular dynamics (MD) simulations[1] have become ubiquitous in chemistry and biology research,[2] student access to such simulations has historically been somewhat limited. As MD simulations rose to prominence at the turn of the millennium, two early exercises were published in this *Journal*. One focused on the interaction between two water molecules,[3] while the other explored the fundamental algorithms using a generic three-particle system.[4] Because of the somewhat complicated nature of preparing the necessary input files for MD, and the computational resources required to perform them, larger simulations have been slower to receive classroom attention. Recently, a handful of authors have begun incorporating MD simulations into chemistry curricula, primarily as tools for understanding the nature of intermolecular forces,[5] or the structure of liquids.[6,7] Many of the more recent advances have been summarized as part of an overview chapter on computational chemistry (from a POGIL perspective).[7] Such simulations can provide visualization for difficult topics, and have been used in both General[8] and Physical Chemistry[5] courses. Experiments and exercises have been described that calculate intermolecular interactions,[5] hydrogen bonding,[9] radial distribution functions,[6] and solvent effects.[10] While examples of molecular mechanics calculations (on single molecules) exist,[11] particularly for biochemistry, the use of classical approaches there is intended more for rapid structure calculations than as a mechanism of modeling the full behavior of bulk solutions. Even so, a recent report[10] using mixed quantum/classical methods has also described a

laboratory investigating the impact of solvent molecules on the structure of individual molecules, with clear connections to organic and biomolecule structure and reactivity. Each of these exercises illuminates some aspect of the atomistic effects which molecular dynamics simulations model so well, even without the incorporation of complicated quantum computations. In keeping with a Physical Chemistry Laboratory course philosophy that emphasizes modeling of bulk-observable effects, we sought a molecular dynamics simulation that was simple to complete, but would emphasize the statistical approach of constructing phenomena from molecular interactions. Transport phenomena were an ideal ground for this exploration. Several laboratories ranging from direct classical measurements,[12,13] to modern optical techniques,[14] to virtual experiments[15] have been previously presented to measure viscosity and its effects. This provides students with a range of experimental methods for directly observing viscosity, but we are aware of no reports of calculation from molecular-level simulations, apart from qualitative descriptions.[16] We propose that a discussion of Einstein and Smoluchowski's relationships between mean-squared displacement and diffusion coefficient,[17,18] along with the Stokes–Einstein relationship for viscosity, can be an excellent way to cover such simulations in a physical chemistry course while simultaneously allowing students to visualize a molecular perspective on self-diffusion

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in liquids. In this computational experiment, students simulate a common organic solvent (*n*-hexane) using commercially available molecular dynamics software. We show that, with prepackaged scripts, meaningful simulations can be performed in a single laboratory period with modest computational resources. This exercise exposes students to the methods used by modern simulation techniques while reinforcing a connection between intermolecular interactions and bulk behavior. It is intended for students in a junior-level physical chemistry course, but could easily be adapted for an accelerated general chemistry course (one designed, for example, specifically for chemistry majors), or expanded for a more advanced simulations course.

■ EXPERIMENTAL PROCEDURES

A full set of Student and Instructor Notes, including all scripts referenced, are included in the Supporting Information. Procedures listed here are amended based on input following student performance of the laboratory exercise in fall, 2014. The students involved were five upper-division, ACS-certified chemistry majors in a physical chemistry course. The exercise was the final lab in the first semester of the two-semester sequence at a large regional comprehensive university in the southeastern United States. The course centers on quantum mechanics, molecular structure, spectroscopy, and statistical mechanics, including transport properties and kinetic molecular theory. All calculations were performed on the Western Kentucky University High Performance Computer (HPC) in a single, 3 h laboratory session. The WKU HPC consists of three head nodes available for different research and instructional purposes. The head node used here has 128 nodes; each node consists of two Intel Xeon E5640 units for a total of eight processors with 24 MB of memory running on each node at 2.66 GHz.

Software Packages and Scripts

To reduce the logistical burden of performing molecular dynamics simulations, shell scripts that accomplish many of the basic tasks involved were distributed to students. The scripts (available in the Supporting Information) were made available through the course site. Each student uploaded them to their executable directory in their remote account on our server. By this point in the semester, students in our course had extensive experience working with Linux command structures and file transfer, so limited instruction was required. The students did not have previous experience with molecular dynamics simulations, but had performed several quantum computational chemistry laboratory experiments during the semester. The AMBER 14 suite,[19] including AMBERTools utilities, was used to perform these calculations. A protein data bank (.pdb) file was downloaded from a publicly available location and solvated using packmol, and calculations were run using Sander. Scripts and other input files (see Supporting Information) were designed to be edited by students as necessary to reflect their specific assignment.

Calculations of Density and Box Size

Students were assigned a temperature in advance of class, and directed to literature references[20−22] to find the experimentally measured density and viscosity of *n*-hexane at that temperature. On the basis of the literature density, they were asked to calculate (prior to class) the size of the simulation box needed to contain 128 *n*-hexane molecules at their assigned temperature. This information is needed as part of the solvation input file. One of the first steps in the experimental procedure is to modify the solvation input file with the appropriate box size. This process enforces for students (a) typical number densities in liquids near room temperature; (b) the finite nature of molecular dynamics simulations, coupled with the concept of periodic boundary conditions; and (c) the temperature dependence of bulk properties. It also acclimatizes them to the units used for simulations (lengths in Å, for example). Simulation boxes consistent with the density of hexane near room temperature are approximately 30 Å on a side. Students must enter simulation box size by adjusting the last line of the SolvateHexane.inp file, replacing all three of the nonzero numbers with the side length. The script tleapScript.tls is used to generate parameter-topology (.prmtop) and input-coordinates (.inpcrd) files, which can then be used as inputs for the MD engine to perform the simulation.

Simulation Details

Each student edited the temperatures in two files provided before jobs were submitted to the server. This was done both in the heating.in and production.in files, which contain the temperatures and other variables for the simulation. Our simulations used the general AMBER force field (GAFF)[23] without modification, with a step size of 1 fs. Many other authors have used a variety of more tailored force fields for simulation of similar systems,[24,25] but our experience was that the general AMBER force field was adequate for our purposes. The main simulation script (AMBER14_SIMULATE) was run without student editing, but was instructive for students to view, as it calls the other scripts in order, from minimization to heating to production. The minimization lines use SHAKE to initialize the input file. The heating section brings the temperature of the simulation box from 0 K to the desired temperature, varying from student to student between 250 and 340 K, all within the liquid range for *n*-hexane, by coupling to an external bath through Langevin dynamics[26] with a collision frequency of 2 ps^{-1}. Following heating (which requires only about 2 ps of simulation time), the system continued to thermally equilibrate for a total of 150 ps. The output of this file was used as the input for a production run (the script runs them sequentially, one automatically beginning upon the completion of the previous). Production runs of 250 ps in the NVT ensemble by coupling to an external bath through the Berendsen[27] thermostat provide ample data for the calculation of the self-diffusion coefficient. The combined process of heating and production required less than 1 h of laboratory time for each student when distributed over eight processors (i.e., a single node was occupied per student). While the simulations were running, students were asked to reflect on the scripts and processes they had just undergone, and were posed a series of discussion questions to allow them to explore each of the steps in detail. This served both to review the logistical details and to develop script analysis skills. Because many students enter physical chemistry courses with limited programming experience, such simple scripts can cleanly reinforce that computer code is nothing more than a series of directions, some of which may simply be setting the variables for a simulation. The basics of molecular dynamics engines, including the velocity−Verlet algorithm,[28] were also discussed. This information, with the Einstein−Scholuchowski and Stokes−Einstein relations, were covered in the lab procedures provided to students through the course site (also provided in the Supporting Information).

Data Visualization

Students downloaded their trajectories from the remote server, then visualized them using the VMD software package.[29] Each student viewed single snapshots in time of the full simulation, and assembled the trajectories as molecular movies. They were encouraged to explore VMD on their own, and a paragraph describing the trajectories was required as part of the laboratory report. Typical student responses noted vibrations within molecules as well as the motion of molecules relative to one another without instructor prompting. Most noted the disappearance of molecules which exit the box at one face, and its reappearance on the other side of the box (periodic boundary conditions), but a class discussion on this topic was helpful. By highlighting a single molecule, students were able to observe its diffusion relative to the other molecules in the simulation. Further details are available in the Instructor Notes.

Next, a set of quantitative analyses were performed with the AMBERTools ptraj utility (incorporated into the script ptrajrunner.sh). These analyses included plots of potential, kinetic, and total energy as well as temperature over time. Students were asked to comment on the stability of each, and to explain why the temperature increased over time. Typical student responses correctly identified that, even after the target temperature was reached, 100 ps or more of simulation time was used. A few students correctly identified that, although the correct average kinetic energy could be achieved quickly, the remaining time is needed to ensure that a Boltzmann distribution of energies is achieved. Further discussion on that matter during the laboratory period is likely warranted on this topic, as it reinforces the idea that dominant configuration will naturally be achieved in any ensemble, but is not the only way to attain a particular temperature.

Finally, the mean-squared displacement was plotted as a function of time. Because the Einstein and Smoluchowski relation,[17,18]

$$D = \frac{1}{6} \lim_{t \to \infty} \frac{\mathrm{d}}{\mathrm{d}t} \langle [\mathbf{r}_i(t) - \mathbf{r}_i(0)]^2 \rangle \tag{1}$$

connects diffusion coefficient, D, with the limit of the slope of the mean-squared displacement (MSD, given by $\langle [r_i(t) - r_i(0)]^2 \rangle$), students readily calculated D based on a plot of MSD as a function of time. The computational results are well-fit to a linear function, and provided values consistent with experimental results without concern for the long-time limitation, which is reached so rapidly that fitting only part of the curve does not improve results. Once students had calculated D, it was a trivial matter to use the well-known Stokes−Einstein relation,

$$D = \frac{k_B T}{6 \pi \eta r} \tag{2}$$

to determine the viscosity, η, of n-hexane, which was directly compared to experimental values. Each student was asked to calculate based on a diffuser radius, r (not to be confused with the position vector $\mathbf{r}_i$), of 3 Å for n-hexane. In fact, it is straightforward to use the .pdb file (with molecular visualization software) to estimate the value. This could be done before lab begins as an exercise, and would allow students to become accustomed to the VMD software on their own prior to its use in the laboratory. Alternatively, estimates could be made based on molecular geometry considerations using average bond lengths, or other approximations.

■ COMPUTATIONAL RESULTS

Because MD simulations are inherently stochastic, it is worth assessing the variability in results which could be expected between simulations. To do this, we have used our scripts to run simulations from 10 different starting distributions (assigned at random by the solvation algorithm). Typical results for the MSD as a function of time during the production run at 300 K are shown in Figure 1. The values for η calculated
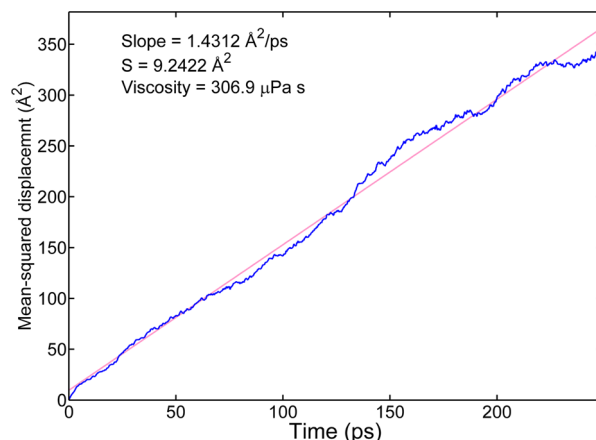
Figure 1. Typical data from a 250 ps simulation of n-hexane at 300 K using the standard AMBER force field. The slope of the mean-squared displacement as a function of time is used to calculate the viscosity of the liquid. Errors are characterized by the standard deviation of the residuals (S).

from the slope of this and similar plots averaged 296.5 μPa s, with a standard deviation of 20.8 μPa s. The range of values determined was thus about ±10% of the value of the calculated viscosity, so that reproducibility should not be an issue in performing this lab, but will be enough to reinforce with students that, for molecular dynamics calculations with a randomly seeded initial distribution, a series of different calculations with the same parameters will yield different values. Longer simulation times might improve variability, but given that the data in Figure 1 "hop" between domains with similar slope, it is more likely that a larger simulation (more molecules) would be more effective at reducing statistical variance between simulations.

A comparison of the values for viscosity (assuming a radius of 3.0 Å) at different temperatures is provided in Figure 2. In their
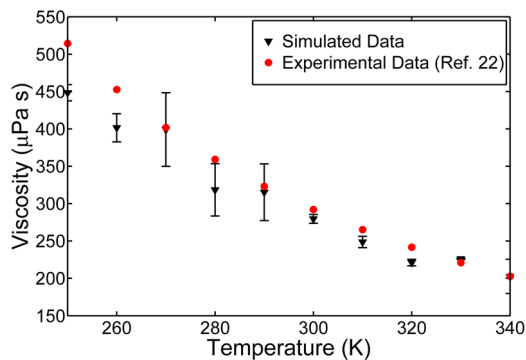
Figure 2. Viscosity results as a function of temperature (black triangles). Students may address deviations from literature data from ref 22 (red circles) with respect to the molecular force field used.

reports, students are asked to compile a similar plot by sharing data. The calculated values are within 15% of the experimental values[22] in all cases. Students can show that the agreement could be reduced slightly by adjusting the radius from the suggested 3 Å, but should note that such adjustments represent unphysical precision for a nonspherical diffuser. In the data shown, three simulations were performed at each temperature; the average is shown, with error bars that represent standard deviations. Once students have performed a single simulation, and discussed the procedure and results, it is productive to ask them to perform the calculation twice more. This reinforces the procedures, but also allows them to see that, even though the results are computational, each run yields a different result because the initial distribution is generated by seeding the random number generator to the time and date. For deeper investigation, students could be asked to account for the decrease in agreement at low temperatures relative to the literature data (which are also computational, but are in much better agreement with experiment). This offers the opportunity to review the concept of a molecular force field and to relate it to intermolecular forces as a function of temperature.

The simulations described here have been designed to be as straightforward as possible while still providing experimentally meaningful diffusion information. As such, we have neglected an important simulation detail: NVT-ensemble calculations using thermostats such as the Berendsen used here do not conserve momentum. As such, the mean-squared displacement calculated in the data shown is not a rigorously physical representation of self-diffusion. One possible means to address this with students (assuming they are prepared to deal with the subtle differences between different ensembles) is to equilibrate the simulations using an NVT ensemble, then, taking the output of this file and run a production period in the NVE ensemble. The value of $\langle[\mathbf{r}_i(t) - \mathbf{r}_i(0)]^2\rangle$ is then calculated based on the more rigorous NVE period. Data collected in this way are included as part of the Instructor Notes in the Supporting Information; differences between those results and the ones presented above were within the error bars discussed in that section. The simulations collected in the NVE ensemble require slightly longer computational time to complete because the total simulation time (even if the NVT equilibration period is only 250 ps, followed by 250 ps of NVE production time) is approximately 60% longer compared to the NVT production described above.

It is worth noting that, while our experiments were performed on a high-performance computer, we did not take advantage of the possibility of massive parallelization. Even so, the time to perform the calculations was well within a normal laboratory period, even considering the need to modify scripts and visualize and analyze trajectory data. Students in courses with particular emphasis on computational chemistry could assign the composition of the scripts (in full or in part) rather than asking students to edit them. The simulations could be performed on nearly any server designed for scientific analysis without significantly increasing the total time to perform them. In fact, for those working without direct access to such resources, a distributed network such as XSEDE could be used to perform these calculations.[30] The computational resources available through XSEDE are similar or superior to our own computational cluster in terms of hardware specifications, but the queueing process may prevent calculations being edited and submitted on the same day they are analyzed, which could be mitigated by splitting the lab across lab periods in different

weeks. As an alternative, we have also provided a sample trajectory in the Supporting Information which could be visualized in VMD. Self-diffusion could be evaluated using a variety of freely available software at the discretion of the instructor.

■ CONCLUSIONS

While many chemists, particularly biochemists, use molecular dynamics simulations in their research, coverage of MD in the standard curriculum remains less common. By introducing the basics of MD theory, viewing simulated trajectories, and analyzing composite data derived from those trajectories, students gain an appreciation for connecting molecular interactions with bulk properties. This connection is particularly informative for transport phenomena such as diffusion and viscosity, because the simulations allow students to see directly the motion of molecules relative to one another. This picture provides a clearer understanding of mean-squared displacement, which serves as an excellent introduction to other correlation functions, many of which are also readily calculated from MD simulations. Some comparison of eq 1 with, for example, the Kubo−Green relations[31,32] (which makes use of velocity autocorrelation functions instead of mean-squared displacement) can be accomplished to demonstrate diffusion from a different perspective. The calculation of viscosity from a computational molecular simulation would dovetail very well to popular experiments using Ostwald viscometers to measure the temperature dependence of viscosity for simple solvents. Such simulations are particularly useful for courses which, like ours, emphasize corroboration of experimental results with computational simulations.

■ HAZARDS

No hazards are associated with this experiment.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00587.

    Scripts (ZIP)
    Production (ZIP)
    Heat (ZIP)
    Output (ZIP)
    Instructor notes (PDF, DOCX)
    Student notes (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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