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Using osmotic pressure simulations to test potentials for ions

Colin Gillespie[a] and Scott T. Milner *[b]

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This paper presents a new method to simulate the osmotic pressure of an ionic solution. Previous simulation methods confine ions between walls, and the osmotic pressure is inferred from the force required to maintain this confinement. In this work, we impose a harmonic potential on the ions to form a nonuniform concentration profile in the solution. As this profile arises from the force balance of the harmonic potential with the osmotic pressure, it can be used to determine the osmotic pressure across the entire concentration profile. This method can be performed without specialized programming, making it accessible to the general user. Using our method, we find that standard potentials for Na^+ and Cl^- ions need adjustments to be consistent with experimental osmotic pressure at high concentrations.

1 Introduction

Understanding the behavior of ions and ionic solutions is important across a wide range of topics, from biology to colloid science to electrochemistry. Simulating ionic solutions as they interact with biomolecules, colloidal particles, and electrochemical interactions provides an important source of physical insight and complements experimental results.

In general, simulation potentials are tuned to reproduce liquid state properties. Potentials such as the Optimized Potential for Liquid Simulations (OPLS) have been tuned to reproduce liquid densities, boiling points, and heats of vaporization.[1] The analogous quantity to validate potentials for ions is the osmotic equation of state, *i.e.*, the osmotic pressure as a function of concentration. Physically, osmotic pressure is the force per area exerted by solutes confined by semipermeable membranes, and varies with the concentration of the solution.

Hamer and Wu have published a collection of osmotic and activity coefficient for electrolyte solutions.[2] Experimental data was collected using a variety of techniques based on colligative properties, including freezing-point depression, vapor-pressure lowering, and isopiestic equilibrium. Detailed descriptions of the techniques can be found in their paper. This data collection serves as an excellent source to validate simulation results, allowing us to tune ion potential parameters.

For concentrated ionic solutions, the osmotic pressure depends delicately on the apparent size of ions, represented in the potential by the short-range repulsion. Too much short-range repulsion gives too high an osmotic pressure at high concentrations, as ions increasingly repel each other; too little short-range repulsion gives too low an osmotic pressure, as ions of opposite signs tend to cluster under Coulomb attraction. Therefore, adjusting the apparent size of ions is a potent way to adjust the osmotic equation of state.

Most published osmotic pressure simulation methods confine ions in some way between repulsive walls and measure the force on those barriers. The first such approach, developed by Luo and Roux, uses two flat-bottom harmonic potentials to confine ions.[3,4] The potentials confine the ions by applying a linear opposing force when the ions pass beyond the start of the potential. The osmotic pressure is obtained as the time average force from the potential divided by the area. Unfortunately, the flat bottomed harmonic potential is not available in most simulation software, and thus requires specialized coding which makes this method inconvenient for general use.

The second approach simulates a confined system with no explicit semi-permeable membrane, using Gibbs ensemble Monte Carlo methods.[5] In the simulation, solute particles are exchanged between a pure solvent compartment and a mixture compartment until equilibrium is obtained. The osmotic pressure for the system is calculated from the chemical potential. However, this approach also requires specialized software, limiting its usefulness.

The third approach uses a physical membrane constructed in the simulation. Raim and Srebnik used a polyamide membrane that was impermeable to ions while impeding the flow of solvent molecules.[5] The pressure difference across the barrier at equilibrium gives the osmotic pressure. In a related approach, Murad and Prowles used a molecular membrane that was invisible to solvent molecules, while remaining completely

[a] *326 Crestview Circle, Media, PA, USA. E-mail: colinhgillespie@gmail.com; Tel: +1-610-809-3706*
[b] *Penn State University, Department of Chemical Engineering, University Park, PA, USA. E-mail: stm9@psu.edu*

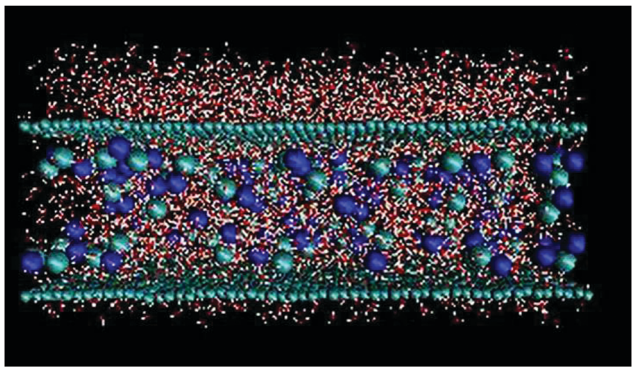

Fig. 1 A typical configuration of a 2.50 M NaCl solution confined between graphene-like sheets invisible to water. The Na^+ (blue spheres) and Cl^- (cyan spheres) ions tend to order near the confining membranes.

impermeable to the solute.[6] This method did not require additional coding outside general simulation software.

While measuring osmotic pressure by confining ions can be effective, there are several inherent issues with this simulation archetype. Each simulation gives osmotic pressure only at a single concentration. Therefore, to measure the osmotic equation of state, separate simulations must be performed at a series of concentrations.

Furthermore, the impenetrable barrier imposed on the ions leads to ordering at the wall and non-uniform concentration profiles. Fig. 1 is a rendering of a frame of a simulation using confinement, in which ordering of the ions near the boundary membranes is evident. The resulting ion distributions are shown in Fig. 2. The nonuniform ion concentration raises complications in determining the effective concentration of the bounded region.

In this work, we present a new method, in which we measure the osmotic equation of state over a wide range of concentration in a single simulation. In brief, the method works by placing the ions in a harmonic potential. This potential leads to an nonuniform equilibrium concentration profile, as sketched in Fig. 3. In equilibrium, each slice of the concentration profile can be regarded as stationary under the sum of three forces: the

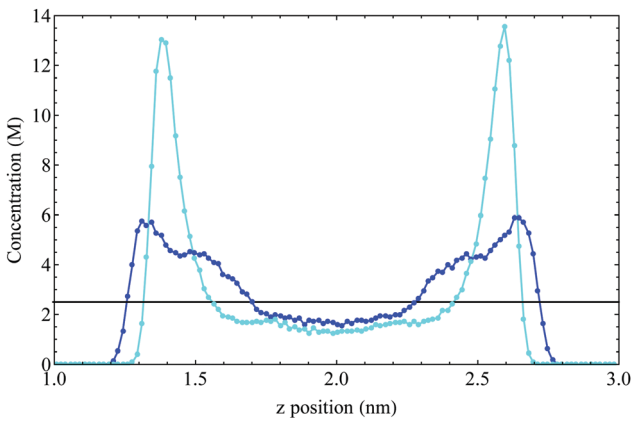

Fig. 2 A plot of the concentration profiles of Na^+ (blue) and Cl^- (cyan) ions compared to the target concentration (black) in a simulation of 2.50 M NaCl between confining sheets.

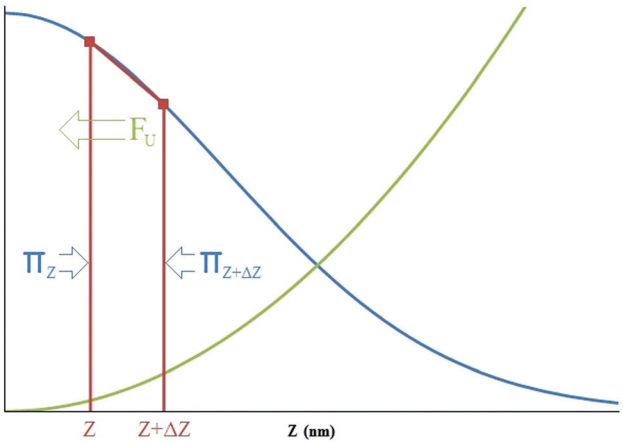

Fig. 3 Sketch of the new method. Potential (green) results in nonuniform ion concentration (blue). Each slice of solution (red) is acted on by harmonic force F_U, and osmotic pressure Π from left and right.

gradient of the external potential, and the osmotic pressure on the two sides of the slice, which differ slightly because of the nonuniform concentration. By analyzing this balance of forces, we can infer the osmotic pressure everywhere in the system from the measured concentration profile.

2 $\Pi(\phi)$ by harmonic confinement

Ions in a harmonic potential exhibit a nonuniform concentration profile at equilibrium. This nonuniform profile arises from the balances of forces exerted on the solution by the external harmonic potential and internal forces. Consider the balance of forces on a thin slice from z to $z + \Delta z$ (see Fig. 3). The force exerted on the slice by the potential U is:

$$F_U = \phi(z)\frac{dU(z)}{dz}\Delta z \quad (1)$$

where $\phi(z)$ is the total ion concentration at height z. (By design, the imposed potential acts equally on both species of ions.)

The force exerted on each slice by the osmotic pressure depends on the concentration of each neighboring slice. A solution with higher concentration exerts a higher osmotic pressure onto its surroundings than one with a lower concentration. The difference in concentration from the two adjacent slices produces a net force on a given slice:

$$F_\Pi = \frac{d\Pi(z)}{dz}\Delta z \quad (2)$$

When the system is in equilibrium, the sum of the osmotic and gravitational forces on each slice must vanish. The same conclusion can be reached by the device of inserting massless, semipermeable membranes between each successive slice of the concentration profile. Inserting the membranes changes nothing about the equilibrium configuration, but allows us to identify the forces acting throughout the fluid. Each membrane supports the weight of the suspension in the slice immediately above, and is acted on by the slightly different osmotic

pressures in the slices above and below. The sum of the forces acting on each membrane must evidently vanish.

By the above arguments, the change in the osmotic pressure across a thin slice is then proportional to the change in the harmonic potential multiplied by the concentration of the slice.

$$\frac{d\Pi(z)}{dz} = -\phi(z)\frac{dU(z)}{dz} \quad (3)$$

This allows the osmotic pressure of the simulation to be inferred from the concentration profile and the imposed harmonic potential.

2.1 Simulation setup

We chose NaCl for the first salt to simulate. Sodium cations and chlorine anions are ubiquitous; high quality data on NaCl osmotic pressure is readily available; and both cation and anion are single atoms, so that the simulation potentials describing ion interactions are particularly simple.

Our all-atom molecular simulations were performed with the simulation package GROMACS, using the OPLS potentials.[7–10] GROMACS has a wide range of options for imposing forces on atoms in solutions, referred to as "pull code" options. One such option imposes a force onto a target atom or molecule that depends linearly on the distance from a chosen origin. By choosing the origin at the center of the simulation, we create an external harmonic potential centered in the system.

While there is no hard limit on the number of pulls that can be enabled, each ion pull option must be individually defined in two places. Each ion needs its own individual group defined in the system index (.ndx) file, and pull options for each group must be defined in the molecular dynamics parameters (.mdp) file. The pull code options have the form shown in Table 1. (To produce these long and repetitive files, we used two bash shell scripts.)

When building a new simulation, a balance must be struck between processing time and data quality. Increasing the size or length of a simulation increases the quality of the data collected at the cost of additional computational power and time required. To achieve this balance, there are four parameters to be considered: the size of the system, the strength of the harmonic potential, the number of ions, and the length of the simulation.

The size of the system determines the number of ions and water molecules that can be placed in the solution. More ions means better statistics for the concentration profile. However, a simulation with twice the number of atoms takes twice as long to run with the same computational resources.

Table 1 Pull code options for a harmonic potential

pull	=	yes
pull-ngroups	=	160
pull-ncoords	=	160
pull-group1-name	=	ion1
pull-coord1-type	=	umbrella
pull-coord1-geometry	=	direction-periodic
pull-coord1-vec	=	0 0 1
pull-coord1-groups	=	0 1
pull-coord1-origin	=	2.491 2.491 2.491
pull-coord1-dim	=	N N Y
pull-coord1-k	=	3.250
pull-group2-name	=	ion2
	...	

For this work, we used two different system sizes, one a 2.5 nm cube, the other a 5 nm cube. By carefully choosing the system parameters, with the same concentration profile as a function of scaled position. If the profiles produced are not the same, this would indicate the presence of finite-size effects.

The spring constant of the harmonic potential controls how rapidly the potential varies along the z axis. If the harmonic potential is too strong, then the ions will predominately gather in the center. This would waste computational power, as the edges of the system would consist only of water. If the harmonic potential is too weak, the resulting concentration profile will not cover a large enough range, and will not become dilute at the boundary, preventing the simulation from achieving its goal.

Therefore, we want to choose a spring constant to produce a concentration profile that approaches zero only at the boundary of the system. This ensures that the space is fully utilized, while maintaining the ability to measure osmotic pressure across the full concentration profile. We chose the spring constant such that the energy difference between the maximum of the harmonic potential and the boundary of the potential is equal to $4kT$, where k is the Boltzmann constant and T is the absolute temperature. This makes the concentration at the boundary approximately e^{-4} times the maximum concentration, giving us a large range for the concentration profile.

For the small system, this gives a spring constant K of 13 kJ mol^{-1} nm^{-2}. Since the large system is twice as large in each direction, the equivalent spring constant for the large system is four times smaller, or 3.25 kJ mol^{-1} nm^{-2}. This produces the same harmonic potential curve in each system when measured on a scaled z axis.

The number of ions in the solution determines the maximum concentration that the solution can reach for a given simulation size. After initial testing, the small system was taken to contain 10 of each ion. The large system contained 80 of each ion, as the volume is eight times that of the small system.

When the three parameters are chosen in this manner, the concentration profile for the large and small systems plotted on a scaled z axis are indeed the same, as shown in Fig. 4. The concentration profiles were averaged with their mirror images, taking advantage of symmetry to improve the accuracy of the measurements. Note that the concentration nicely approaches zero far away from the center of the box.

By comparing the concentration profiles of the small and large systems, with correspondingly stronger and weaker harmonic potentials (with K equal to 13 and 3.25 kJ mol^{-1} nm^{-2} respectively), we can assess the extent of finite-size effects on our simulation protocol. We may expect that if our system were too small, and the concentration profile varied too rapidly with respect to molecular scales, our analysis of the osmotic pressure balance would begin to fail. Because the two profiles in Fig. 4 are nearly identical, we have confidence that our simulation system, though small, is large enough for our purposes.

Our simulations were performed with periodic boundary conditions in all three directions. The imposed harmonic

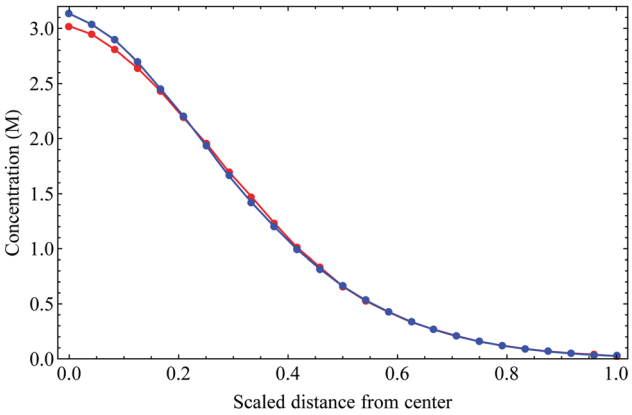

Fig. 4 Ion concentration verses scaled z position for small (red) and large (blue) systems.

potential is defined with respect to the nearest distance along z to the center of the box, so that the potential is continuous at the system boundary in z. The periodic boundary conditions allow us to dispense with any vacuum interfaces or walls that would tend to collect ions, as was observed for the ionic solutions confined between semipermeable membranes.

The simulation run time must be chosen large enough to give good statistics for the concentration profile, from which the osmotic pressure is calculated. After initial experimentation, we simulated the small system for 80 ns and the large system for 10 ns. With this choice, simulations with large and small systems produced concentration profiles with comparable accuracy, as the eightfold increase in the ions in the larger system is compensated by the eightfold increase in run time for the smaller system. Indeed, both runs then use comparable computational resources, so there is little reason to prefer one over the other.

2.2 Analysis

The osmotic pressure of the simulation is calculated from the force balance:

$$\frac{\mathrm{d}\Pi}{\mathrm{d}z} = -\phi\frac{\mathrm{d}U(z)}{\mathrm{d}z} \tag{4}$$

The harmonic potential takes the form:

$$U(z) = \frac{1}{2}Kz^2 \tag{5}$$

where z is centered in the system, and K is the spring constant. Substituting the harmonic potential into the force balance gives:

$$\frac{\mathrm{d}\Pi}{\mathrm{d}z} = -\phi Kz \tag{6}$$

We measure the concentration profile as a sequence of equally spaced z values, so we discretize the force balance as

$$\frac{\Delta\Pi}{\Delta z} = -\phi Kz \tag{7}$$

Solving for the increment in osmotic pressure across a given slice Δz gives

$$\Pi_2 = \Pi_1 + \phi Kz(\Delta z) \tag{8}$$

where Π_1 is the osmotic pressure closer to the boundary of the system.

Since ϕ and z are given at the endpoints of each interval Δz, their average value is taken to give the final form of the equation as:

$$\Pi_2 = \Pi_1 + \frac{\phi_2 + \phi_1}{2}\,\frac{z_2 + z_1}{2}K\Delta z \tag{9}$$

This equation allows for the stepwise calculation of the osmotic pressure given an initial value. This value is calculated at the edge of the system, where the ion concentration approaches zero and ideal behavior can be assumed, with an osmotic pressure given by Π = RMT.

2.3 Results

To test the potential parameters for Na^+ and Cl^- ions, the osmotic equation of state for NaCl solutions was determined using the new method, and compared to experimental data.[2]

In Fig. 5, the simulation results for the small (red) and large (blue) systems lie well below experimental data (black) for concentrations above 0.5 M. This indicates that the simulated ions are too much attracted to each other, tending to cluster at higher concentrations, thus reducing the osmotic pressure.

2.3.1 Tuning the simulation potentials. To counteract the deviation of the simulated osmotic pressure from the data, we need to prevent the ions from clustering so much. Of course, we should not change the ionic charge. Rather, we strengthen the repulsive part of the Lennard-Jones interaction between Na^+ and Cl^- ions. The Lennard-Jones potential is the sum of repulsive and attractive terms:

$$V = V_\mathrm{A} + V_\mathrm{R} = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \tag{10}$$

To increase the repulsive force while maintaining the same attractive force, we find new σ and ε values such that

$$V_\mathrm{R}(\sigma',\varepsilon') = (1 + X)V_\mathrm{R}(\sigma,\varepsilon) \tag{11}$$

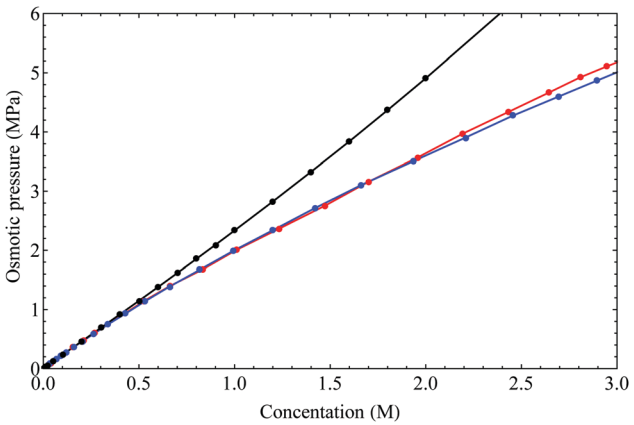

Fig. 5 Experimental data (black) *vs.* simulation data for small (red) and large (blue) systems using default OPLS parameters for Na^+ and Cl^-.

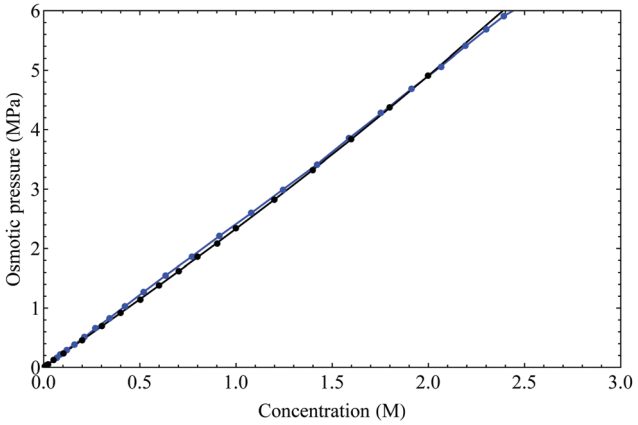

Fig. 6 Simulated osmotic pressure *vs.* solution concentration solution with modified potential parameters (blue) compared to experimental data (black).

$$V_A(\sigma',\varepsilon') = V_A(\sigma,\varepsilon) \tag{12}$$

where X is the fractional increase in the repulsive potential. This gives:

$$\sigma' = \sqrt[6]{(1+X)}\sigma \tag{13}$$

$$\varepsilon' = \frac{\varepsilon}{1+X} \tag{14}$$

A 20 percent increase in repulsive potential between Na^+ and Cl^- ions above the standard OPLS value for their Lennard-Jones interactions gives osmotic pressure results that closely match the experimental data, as shown in Fig. 6. The corresponding increase in repulsive radius σ is very modest (3 percent). Note that we only adjusted the interactions between Na^+ and Cl^-, overriding the default mixing rule that determines all cross-interactions from the LJ parameters for each species. We have not changed the ion–water interactions in any way. As a result, in our simulations both species of ions have hydration shells of reasonable size, before and after the adjustment.

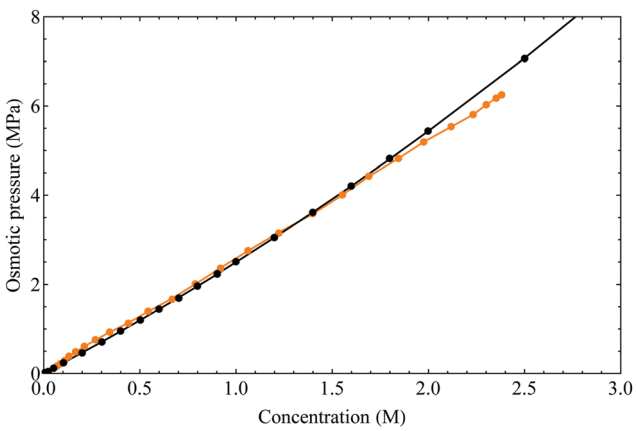

Fig. 7 Simulation results for osmotic pressure *vs.* concentration for sodium acetate (orange) compared to experimental data (black).

As a second example, a particularly important ionic group for biomolecules is the carboxylic acid anion, COO^-. To study the potential for this ion, we investigate sodium acetate, $Na^+CH_3COO^-$. If we correctly capture the osmotic pressure of this salt, we may be confident that we properly model the carboxylic acid groups in charged polymers and biomolecules.

Fig. 7 presents osmotic pressure results for sodium acetate compared to experimental data, using the same system size, ion count, and spring constant as the large NaCl simulations. In this case, the unmodified OPLS force field for these ions, without any adjustments, produced results close enough to experiment to be usable in simulation even at high concentrations.

3 Conclusions

In this paper, we presented a new method to simulate the osmotic pressure of ionic solutions. The method works by placing the ions in a harmonic potential, which induces a nonuniform concentration profile. By analyzing the equilibrium balance of osmotic and external forces, we can measure the osmotic pressure across a wide concentration range.

The method exploits the ability to impose external potentials available in leading simulation platforms such as GROMACS, and so requires no specialized coding.

Previous simulation approaches effectively confine ions between walls, and measure the force on the walls. This works, but provides only one value of osmotic pressure at one ion concentration. To measure one point accurately by such method takes about as much computer time as our method takes to obtain the entire osmotic pressure curve from 20 mM to 2 M. To generate such a curve with previous confinement methods would require 10–20 simulations, and thus take 10–20 times as long.

Additionally, for previous confinement simulations, it is problematic to determine the appropriate concentration of the confined solution. Boundary effects of the confining wall lead to strong local perturbations of the concentration near the wall. In contrast, harmonic confinement eliminates boundaries from the system, ensuring that there is no wall effect on the ion distribution.

One important application of reliable and convenient simulations of the osmotic equation of state is in validating simulation potentials for ionic solutions. Simulations of aqueous ions are important for biomolecules, colloidal particles, and electrochemical interfaces. In all these instances, charged surfaces may attract counterions, leading to local concentrations well in excess of average solution concentrations, possibly as high as several molar in a thin nanoscale layer. If the simulation potential is not accurate for such concentrated ions, ions will cluster too much or too little onto charged surfaces, leading to qualitatively incorrect results and predictions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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