Supporting Information for

Poisson–Boltzmann versus Size-modified Poisson–Boltzmann Electrostatics Applied to Lipid Bilayers

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I. A BRIEF DESCRIPTION OF THE SMPBE FORMULATION

Assume that the system contains M ion species; their radii are $r_1, \ldots, r_M$ and their "linear sizes" are $a_1, \ldots, a_M$. The volume of ion i is $v_i = a_i^3 = 4\pi r_i^3/3$. The ion concentrations at location $\boldsymbol{x}$, $\boldsymbol{x}$ is a vector, are $c_1(\boldsymbol{x}), \ldots, c_M(\boldsymbol{x})$. Similarly, the size, volume and concentration of the solvent molecule are denoted as r_0, a_0, v_0 and $c_0(\boldsymbol{x})$. With the above definitions, we have:

$$c_0(\boldsymbol{x}) = v_0^{-1}\left[\lambda - \sum_{i=1}^{M} v_i c_i(\boldsymbol{x})\right] \tag{1}$$

Where $\lambda = 0.64$ is the maximum packing fraction for randomly placed uni-sized spheres; it is used here as a reasonable approximation.

The way the ion sizes are incorporated into the PBE formulation is through the construction of the phenomenological lattice gas free energy of the system:

$$F(c_1, \ldots, c_M) = \int \left\{\frac{1}{2}\sum_{i=1}^{M} q_i c_i \psi + \frac{1}{2} Q\psi\right\} dV + \int \left\{\frac{1}{\beta}\sum_{i=0}^{M} c_i[\ln(v_i c_i) - 1] - \sum_{i=1}^{M} \mu_i c_i\right\} dV \tag{2}$$

Where q_i is the charge of the ith ion species, $\psi = \psi(\boldsymbol{x})$ is the local electrostatic potential, $Q = Q(\boldsymbol{x})$ is the local fixed-charge density from the biomolecule, $\beta^{-1} = k_B T$, k_B is the Boltzmann constant, T is the temperature and μ_i is the chemical potential for ion species i. Both integrations are over all space. The first term is the potential energy term and the second is the entropy term.

At equilibrium, the free energy should be minimized. If c_is are considered as the only independent variables in Eq. (2), Eq. (2) can be minimized with respect to each c_i constrained by the Poisson equation. After minimization, the following equation is obtained:

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$$\frac{v_i}{v_0}\ln(v_0 c_0) - \ln(v_i c_i) = \beta(q_i\psi - \mu_i) \tag{3}$$

In the bulk phase, Eq. (3) gives $\mu_i = \beta^{-1}\ln\left[(v_i c_i^{bulk})/(v_0 c_0^{bulk})^{\frac{v_i}{v_0}}\right]$, where μ_i is a function of the bulk ion concentrations. Plugging μ_i back into Eq. (3) for non-bulk regions gives:

$$c_i(\boldsymbol{x}) = \left[\frac{c_0(\boldsymbol{x})}{c_0^{bulk}}\right]^{\frac{v_i}{v_0}}\left[c_i^{bulk} e^{-\beta\psi}\right] \tag{4}$$

Plugging Eq. (4) into Eq. (1) will result in an equation containing c_0 as the only unknown:

$$v_0 c_0(\boldsymbol{x}) + \sum\nolimits_{i=1}^{M}\left\{v_i\left[\frac{c_0(\boldsymbol{x})}{c_0^{bulk}}\right]^{\frac{v_i}{v_0}}\left[c_i^{bulk} e^{-\beta\psi}\right]\right\} - \lambda = 0 \tag{5}$$

where c_0, as the root of the equation, can be solved by numerical methods like the Newton's method. Once c_0 is obtained, all of the c_is can be calculated from Eq. (4). Eq. (4) is called the size-modified Boltzmann distribution as it contains the Boltzmann distribution term, $c_i^{bulk} e^{-\beta\psi}$, and a multiplicative correction term modeling the ion-size effects. The SMPBE is a PBE with the Boltzmann distribution term substituted by the size-modified Boltzmann distribution term in Eq. (4).

II. THE SMPBE ROUTINE IN APBS

For each SMPBE calculation, a 3-dimentional finite difference grid is created covering the biomolecule and its surrounding solvent region. The electrostatic potential $\psi(\boldsymbol{x})$ and ion concentrations $c_i(\boldsymbol{x})$, where $\boldsymbol{x}$ represents each grid point, are solved iteratively. The calculation starts with an initial guess of $\psi(\boldsymbol{x})$, which is uniformly zero. This initial guess is used in Eq. (5) as the input to solve for $c_0(\boldsymbol{x})$, which gives the $c_i(\boldsymbol{x})$s through Eq. (4). With the $c_i(\boldsymbol{x})$s, the potential is updated by solving the Poisson equation:

$$\nabla^2\psi(\boldsymbol{x}) = Q(\boldsymbol{x}) + \sum\nolimits_{i=1}^{M} q_i c_i(\boldsymbol{x}) \tag{6}$$

This process goes on iteratively until the maximum relative difference between the ψ obtained from two consecutive iteration steps is below an acceptable error. And the resulting ψ and c_i will be considered as the converged solution.

The SMPBE routine in APBS can be easily used by adding the following keywords into the APBS input file:

```
smpb1 step {step} eps {eps}
```

`{step}` is the step size of the Newton's method, which is used to solve the SMPBE. `{step}` is a number between 0 and 1. The smaller the `{step}`, the more numerically stable, but slower, the method and vice versa. `{esp}` is the value that the maximum relative difference of the electrostatic potentials among all grid points between two consecutive Newton iteration steps have to go below for the confirmation of convergence. Mathematically, this convergence criterion is given by:

$$max\left(\left|\frac{\psi^k(\boldsymbol{x}) - \psi^{k-1}(\boldsymbol{x})}{\psi^{k-1}(\boldsymbol{x})}\right|\right) < \texttt{\{esp\}}$$

where $\psi^k(\boldsymbol{x})$ is the electrostatic potential at grid point $\boldsymbol{x}$ in step k. In this work, `{step}` is set to be 0.01 or smaller, `{esp}` is set to be 0.01.

III. THE MD SIMULATION SETTINGS

The equilibration for the MD simulations use the default steps generated by CHARMM-GUI Membrane Builder. The production simulation conditions are: NPT ensemble with constant temperature set at 300K by the Langevin thermostat with damping coefficient 1/ps and constant pressure set at 1atm by the Nose-Hoover Langevin piston barostat with oscillation period 50fs and oscillation decay time 25fs. The simulation time step is 2fs. All the bonds involving hydrogen atoms are fixed, non-bonded interactions are subjected to cut-off at 12Å. Periodic boundary conditions are applied on all sides of the simulation box. Particle Mesh Ewald (PME) method is used to calculate the electrostatic forces in the system.

The convergence of the MD simulations are determined by two criteria, the convergence of the area per lipid value and the convergence of the number of ions bound to the lipid bilayer surface. The number of ions bound is calculated by counting the total number of ions within $|z|$=25Å (z is defined in Figure S1).

IV. APBS INPUT FILE EXAMPLE

```
read
    mol pqr lipid.pqr
end
elec name lipid_bilayer
    mg-auto
    dime        161 161 193
    cglen       100 100 120
    fglen       70 70 90
    cgcent      0 0 0
    fgcent      0 0 0
    mol         1
    npbe
    bcfl        mdh
    pdie        2.00
    sdie        78.54
    srfm        smol
    chgm        spl4
    sdens       10.00
    swin        0.30
    temp        300
    calcenergy total
    write       pot dx potential_file
    write       conc dx concentration_file
    srad        1.4
    smpb1       step 0.01 eps 0.01
    ion         charge  1 conc 0.13 radius 1.4
    ion         charge -1 conc 0.13 radius 2.3
end
quit
```

V. OTHER SUPPORTING FIGURES

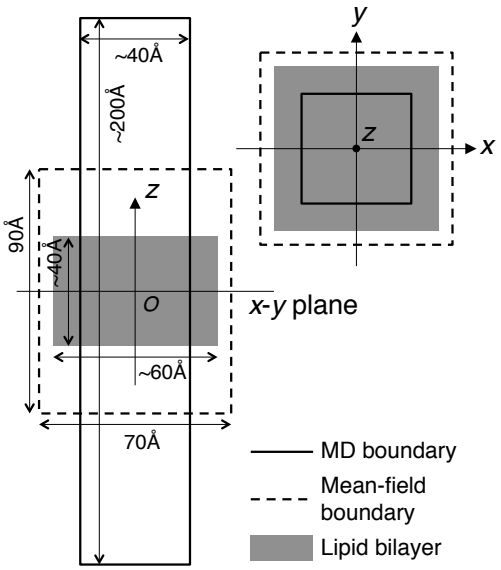

Figure S1. The dimensions of the lipid bilayer systems used in the MD simulations and the mean-field calculations. The *x* and *y* dimensions of the lipid bilayers are always equal.

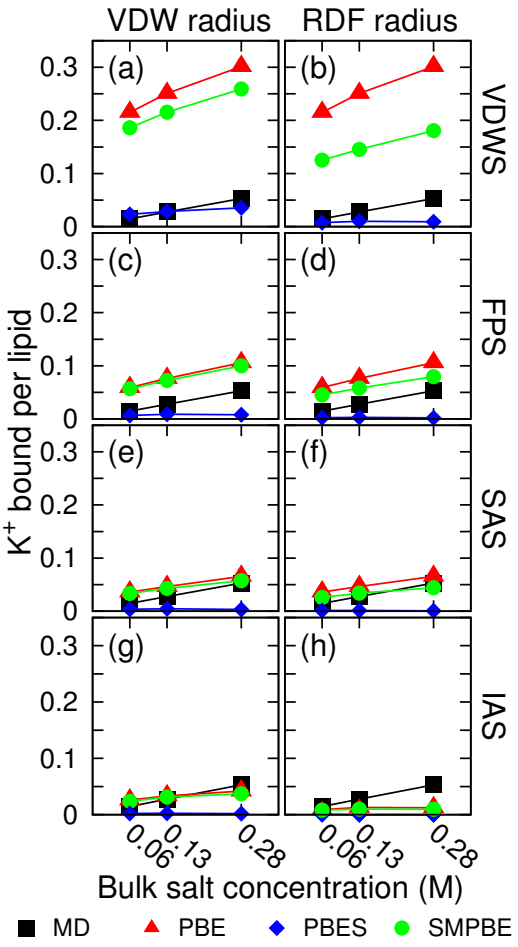

Figure S2. The number of K^+ bound per POPC molecule at three KCl bulk concentrations (systems 4 to 6 in Table 1). MD: molecular dynamics; PBE: nonlinear Poisson-Boltzmann equation (without Stern layer); PBES: PBE with Stern layer; SMPBE: size-modified Poisson-Boltzmann equation (without Stern layer). Subfigures (a) to (h) use eight different parameter sets; each is a combination of a molecular surface (VDWS, FPS, SAS, IAS, see Figure 1) and an ion radius set (VDW radius, RDF radius, see Table 2).

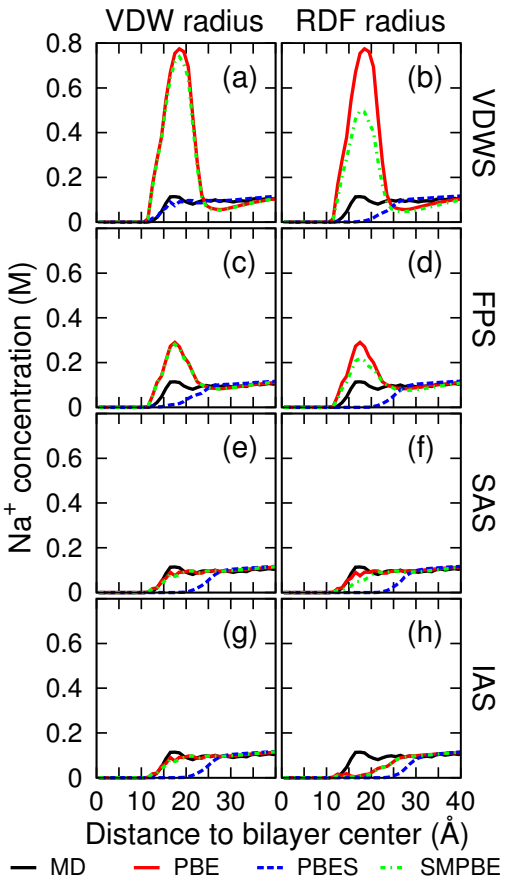

Figure S3. The Na^+ distribution along the perpendicular direction to a POPC lipid bilayer surface (system 2 Table 1). MD: molecular dynamics; PBE: nonlinear Poisson-Boltzmann equation (without Stern layer); PBES: PBE with Stern layer; SMPBE: size-modified Poisson-Boltzmann equation (without Stern layer). Subfigures (a) to (h) use eight different parameter sets; each is a combination of a molecular surface (VDWS, FPS, SAS, IAS, see Figure 1) and an ion radius set (VDW radius, RDF radius, see Table 2).

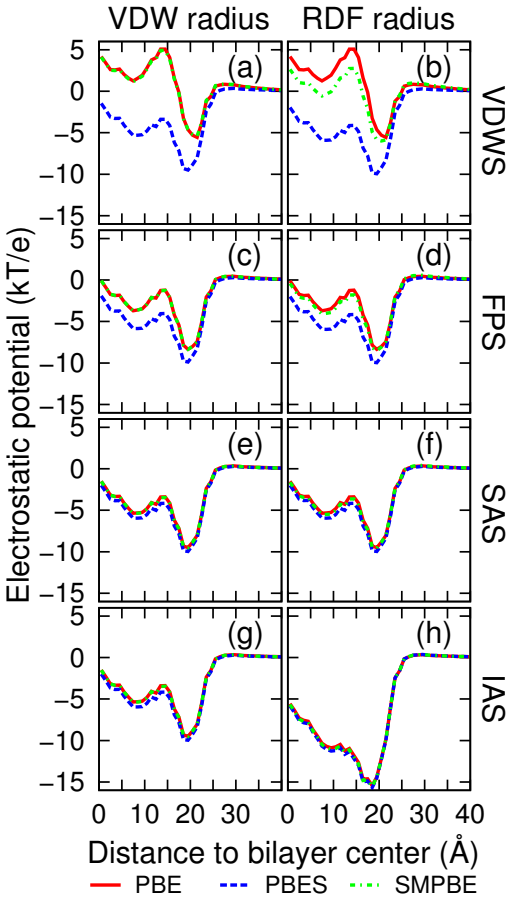

Figure S4. The electrostatic potential along the perpendicular direction to a POPC lipid bilayer surface (system 2 Table 1). PBE: nonlinear Poisson-Boltzmann equation (without Stern layer); PBES: PBE with Stern layer; SMPBE: size-modified Poisson-Boltzmann equation (without Stern layer). Subfigures (a) to (h) use eight different parameter sets; each is a combination of a molecular surface (VDWS, FPS, SAS, IAS, see Figure 1) and an ion radius set (VDW radius, RDF radius, see Table 2).

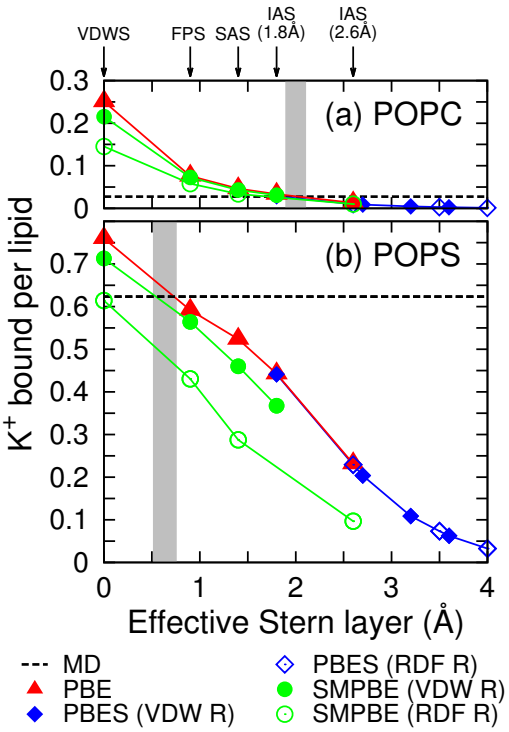

Figure S5. The number of K^+ bound per lipid as a function of the "effective Stern layer thickness", the minimum distance between the VDWS and the "molecular surface" used for each calculation. (a) KCl of bulk concentration 0.13M outside of the POPC bilayer, system 5 in Table 1. (b) KCl of bulk concentration 0.17M outside of the POPS bilayer, system 8 in Table 1. VDW R and RDF R are shorthand for VDW radius and RDF radius. Gray shades mark where the mean-field calculations using VDW radius agree with MD.