

# INTRODUCTION TO CONTINUUM ELECTROSTATICS, WITH MOLECULAR APPLICATIONS

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## Introduction

Ideas from the macroscopic world have long been translated to the microscopic world of molecules. Examples include mechanics, fluid dynamics, and electrostatics. It is sometimes said that such applications often succeed better than have any right to, given the extrapolation of size scales. Classical electrostatics in particular provides intuitive insights that help us to reason about the properties of molecules. It also allows quantitative or at least semi-quantitative predictions of such properties, depending upon the nature of the problem, the availability of adequate parameters, etc.

These notes discuss the basics of continuum electrostatics and its application to classically described molecular systems. I have tried to stick with Standard International (SI) units here, but multiple systems of units and notation are frequently used in classical electrostatics, and there may be a few inadvertent deviations. The equations have been checked, but not with a fine-toothed comb. Please feel free to call any apparent errors to my attention: [gilson@umbi.umd.edu](mailto:gilson@umbi.umd.edu).

## Electrostatics without Dielectrics; i.e., in Vacuum

Classical electrostatics takes on its simplest form when it considers only charges *in vacuo*. Such a system is described by Poisson's equation in the following form:

$$\begin{aligned} -\nabla \cdot \nabla \phi(\mathbf{r}) &= \frac{\rho(\mathbf{r})}{\epsilon_0} \\ \mathbf{E}(\mathbf{r}) &= -\nabla \phi(\mathbf{r}) \end{aligned} \quad (1)$$

Here  $\phi(\mathbf{r})$  and  $\rho(\mathbf{r})$  are, respectively, the electrostatic potential and the charge density as a function of position, and  $\mathbf{r}$  is the Cartesian coordinates of a point in space. For a point-charge,  $\rho(\mathbf{r})$  has the form of a  $\delta$ -function. The permittivity of free space,  $\epsilon_0$ , is a physical constant whose numerical value can be found in textbooks. Equation 1 is in SI units: Joules, Coulombs, meters. Intuitively, this equation says that charges are the source of electrical field, since  $-\nabla \cdot \nabla \phi(\mathbf{r})$  represents the divergence of the  $\mathbf{E}$  field (figure 1). Solutions of Equation 1 yield the familiar Coulomb's law.

The useful superposition principle can be deduced from Equation 1. This states that the total electrostatic field produced by a system of charges is the arithmetic sum of the fields produced by the individual charges. Thus, the field is the superposition of the individual fields. This holds for charges in vacuum and, often to good approximation, for charges in or near atoms and molecules, as discussed below.

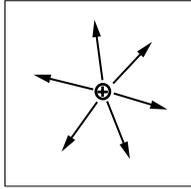


Figure 1: Field lines diverging from a positive charge *in vacuo*.

### Electrostatic energy

The electrostatic energy of a system of charges  $Q$  usually is taken to mean the electrostatic work required to form the system from an infinitely dispersed and thus non-interacting distribution of charge. Mathematically, this work can be expressed as a charging integral of the form

$$U = \int_0^Q \phi(q) dq. \quad (2)$$

That is, the work of adding an infinitesimal charge  $dq$  to the distribution depends upon the potential, which increases in magnitude as charge is added. The work of forming the complete charge distribution  $Q$  is the integral of this infinitesimal work. Because  $\phi$  is proportional to charge – i.e., the system is linear – this integral can be rewritten as

$$U = \int_0^Q (Cq) dq = \frac{1}{2} CQ^2 \quad (3)$$

where  $\phi = Cq$  and it is assumed for convenience that each charge increment is spread smoothly across the entire system.

### Point charges

Because the electrostatic potential at a point-charge is infinite, the work required to form a point-charge is infinite. This infinite “self-energy” of a point-charge might appear to be problematic in molecular models that represent atomic charges as point-charges. In fact, however, it is not a problem so long as the infinite self-energy of the point-charges remains fixed; i.e., so long as the charges do not increase or decrease, contact any other point-charges, or come into direct contact with a medium of different dielectric constant. (Any of these changes would produce a physically meaningless infinite change in energy.) If these restrictions are observed, the infinite self-energies of atomic charges remain fixed, and charges will contribute to energy changes only through interactions among charges and between charges and dielectric media.

We thus begin by considering the (finite) interaction energy of two point-charges *in vacuo*. Solving the Poisson Equation (Equation 1) yields Coulomb’s Law:

$$U(r_{12}) = \frac{q_1 q_2}{4\pi\epsilon_0 r_{12}} \quad (4)$$

where  $r_{12}$  is the distance between charges  $q_1$  and  $q_2$ . This equation can also be written in what might be called “Biochemical Units”:

$$U(r_{12}) = \frac{332q_1 q_2}{r_{12}} \quad (5)$$

where the energy is now in kcal/mol, charge is in electron-charges, and distance is in Angstroms. This “interaction energy” is the work of bringing the two charges together from infinite separation. If the force between the charges is attractive, the work is negative in sign; if the force is repulsive, the work is positive in sign. More generally, the force is negative the derivative (gradient) of the energy. Thus, the force on charge 2 due to charge 1 is

$$F_2 = \frac{q_1 q_2}{4\pi\epsilon_0 r_{12}^2} \quad (6)$$

directed along the line from charge 1 to charge 2. The force on charge 1 is equal and opposite (Figure 2). These energies and forces can also be described in terms of fields. Thus, the interaction of charges 1 and 2 can be written as

$$\begin{aligned} U(r_{12}) &= q_2 \phi_1(\mathbf{r}_2) \\ \phi_1(\mathbf{r}_2) &= \frac{q_1}{4\pi\epsilon_0 r_{12}} \\ r_{12} &\equiv |\mathbf{r}_2 - \mathbf{r}_1| \\ \mathbf{F} &= q_2 \mathbf{E}_1(\mathbf{r}_2) \\ \mathbf{E}_1(\mathbf{r}_2) &= \frac{q_1}{4\pi\epsilon_0 r_{12}^2} \mathbf{d} \\ \mathbf{d} &\equiv \frac{\mathbf{r}_2 - \mathbf{r}_1}{r_{12}} \end{aligned} \quad (7)$$

Here  $\phi_1(\mathbf{r}_2)$  is the potential produced by charge 1 at the location of charge 2 ( $\mathbf{r}_2$ ) and  $\mathbf{d}$  is a unit vector directed from charge 1 to charge 2. One can precompute the field produced by charge 1 and use it to evaluate the interaction energy of any added charge with atom 1 and the force on it. (See Appendix for a more formal description of the force and electric field in this case.)

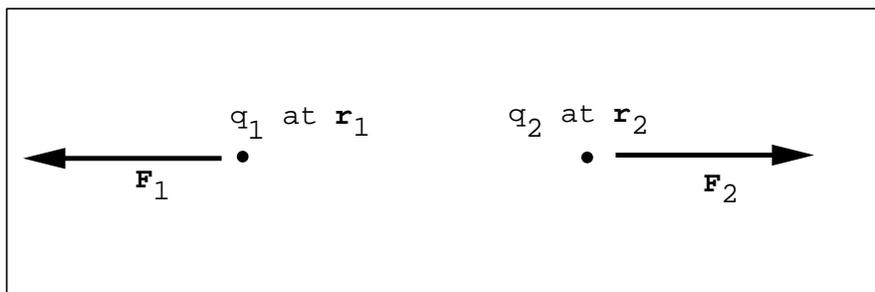


Figure 2: Forces acting on two point-charges of like sign *in vacuo*.

## Charge-distributions

Charges can be conceived of as concentrated at points, but more generally they are distributed over surfaces or through volumes. The potential generated by a general charge-distribution  $\rho(\mathbf{r})$  in vacuum is

$$\phi(\mathbf{r}) = \frac{1}{4\pi\epsilon_0} \int \frac{\rho(\mathbf{r}_1)}{|\mathbf{r} - \mathbf{r}_1|} d\mathbf{r}_1 \quad (8)$$

The self-interaction energy of such a charge-distribution is given by

$$U = \frac{1}{8\pi\epsilon_0} \int \int \frac{\rho(\mathbf{r}_1) \rho(\mathbf{r}_2)}{|\mathbf{r}_2 - \mathbf{r}_1|} d\mathbf{r}_1 d\mathbf{r}_2 \quad (9)$$

This energy is relative to that when the charges are dispersed to infinitesimal density through space  $\rho = 0$ . It can also be expressed in terms of an energy density (Equation 10). The additional factor of  $\frac{1}{2}$  in Equation 9 corrects for double counting of the charge-charge interactions in the double integral.

## Electrostatic field energy

It is sometimes helpful to consider electrostatic energy not in terms of charging integrals or charge-charge interactions, but rather in terms of the energy stored in the electrostatic field  $\mathbf{E}$  that the charges generate. In vacuum, the field energy is

$$U = \frac{\epsilon_0}{2} \int \mathbf{E}^2(\mathbf{r}) d\mathbf{r} \quad (10)$$

From the principle of superposition, the fields generated by multiple charges in vacuum can be added together to get the total field. Thus, for our two point-charges,  $\mathbf{E} = \mathbf{E}_1 + \mathbf{E}_2$ , and the energy can be written as:

$$\begin{aligned} U &= \frac{\epsilon_0}{2} \int [\mathbf{E}_1(\mathbf{r}) + \mathbf{E}_2(\mathbf{r})]^2 d\mathbf{r} \\ &= \epsilon_0 \int \left[ \frac{1}{2} \mathbf{E}_1^2(\mathbf{r}) + \frac{1}{2} \mathbf{E}_2^2(\mathbf{r}) + \mathbf{E}_1(\mathbf{r}) \mathbf{E}_2(\mathbf{r}) \right] d\mathbf{r} \end{aligned} \quad (11)$$

The three terms here correspond, respectively, to the infinite self-energies of charges 1 and 2 plus their interaction energy. The integral of the interaction term over all space can be shown to yield Coulomb's Law (Equation 4).

## Electrostatics in a Uniform Dielectric Medium

The electrostatic interactions among charges in a uniform medium (gas, liquid, or solid) are usually weakened relative to those for the same charges in vacuum. Often to a good approximation, the field is reduced everywhere by a constant factor known as the dielectric constant  $D$ .

For a charges in a medium of uniform dielectric constant, the following form of the Poisson equation is appropriate:

$$-\nabla \cdot \nabla \phi(\mathbf{r}) = \frac{\rho(\mathbf{r})}{\epsilon_0 D} \quad (12)$$

It is apparent that the potentials that result from this equation are just  $\frac{1}{D}$  of their values in vacuum for the

same charge distribution  $\rho(\mathbf{r})$ . Energies are reduced by the same factor. For example, for two point-charges,

$$U(r_{12}) = \frac{q_1 q_2}{4\pi D \epsilon_0 r_{12}}$$

or, in Biochemical Units,

$$U(r_{12}) = \frac{332 q_1 q_2}{D r_{12}} \quad (13)$$

Note that the dielectric constant is often symbolized by  $\epsilon$  instead of  $D$ .

### The Physical Basis of Dielectric Screening

An atom or molecule in an externally imposed electric field develops a nonzero net dipole moment (Figure 3); if the molecule already has a nonzero dipole moment, the field increases it further. The magnitude of a dipole moment is a measure of charge separation. (Thus, an electron and proton separated by 1 Angstrom possess a dipole moment of 1 electron-Angstrom (or, in SI units,  $1.65 \times 10^{-29}$  Coulomb-meters.) Thus, the atoms or molecules in a material develop dipole moments when the material is exposed to an electrical field. The field generated by these induced dipoles runs against the inducing field. As a consequence, the overall field is weakened, as expected for a dielectric medium.

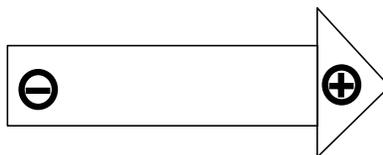


Figure 3: Diagram of a simple dipole. By convention, the arrowhead is at the positive charge.

Figure 4 illustrates how a dielectric medium weakens the field due to a positive charge. The dipoles induced in the material are aligned with the inducing field. The charges at the heads and tails of the induced dipoles cancel each other except at the surface of the inducing charge. This leaves a net surface charge that produces a field opposite to that of the inducing charge (Figure 4).

A dipole moment is a vector because it has a direction. (By convention, the arrow points from negative to positive, as shown in Figure 3.) In a material, the dipole moment per unit volume is a vector field known as the polarization vector  $\mathbf{P}(\mathbf{r})$ . In many materials, the polarization is proportional to the inducing field over a wide range of inducing fields  $\mathbf{E}(\mathbf{r})$ , and the constant of proportionality is the susceptibility  $\chi$ :  $\mathbf{P}(\mathbf{r}) = \chi \mathbf{E}(\mathbf{r})$ . When this proportionality holds, the dielectric response is said to be linear.

There are two chief ways that an atom or a molecule can develop a dipole moment in response to an inducing field: electronic polarization and orientational polarization. Electronic polarization occurs when the inducing field shifts the positively charged nucleus of an atom in the direction of the inducing field and the negatively charged electrons in the opposite direction (Figure 5, left), creating a dipole. Every atom can be polarized in this way. Electronic polarization rises linearly with the inducing field up to very high field strengths.

Orientational polarizability is limited to molecules that have significant permanent dipole moments; i.e., molecules that have a dipole moment even in the absence of an inducing field. Water is a good example of such a molecule. In the absence of an inducing field, a water molecule in liquid water tumbles randomly due

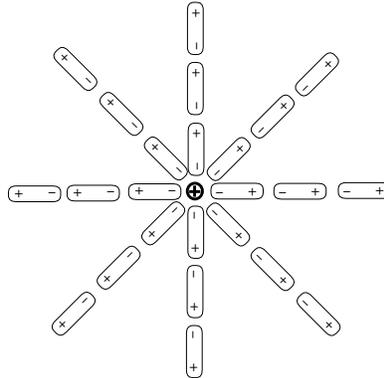


Figure 4: Positive charge in a dielectric medium induces dipoles that produce an effective negative surface charge that opposes the inducing field.

to thermal motion. As a consequence, its time-averaged dipole moment is zero. (Remember that the dipole moment is a vector.) However, in the presence of an electrical field, the tumbling of the molecule is biased in the direction of the field (Figure 5, right), leading to a nonzero time-averaged dipole moment along the field. The permanent dipole moments of some molecules with biochemically relevant functional groups are given in Table 1.

The average dipole moment of a tumbling dipole in an inducing field is given by the Langevin function. This function is linear for weak fields but saturates as the field becomes very strong: once a dipole is fully aligned with the field, its average dipole moment can increase no more. Note that the work of aligning an isolated, thermally agitated dipole is purely entropic because the internal energy of the system does not depend upon the orientation of the dipole.

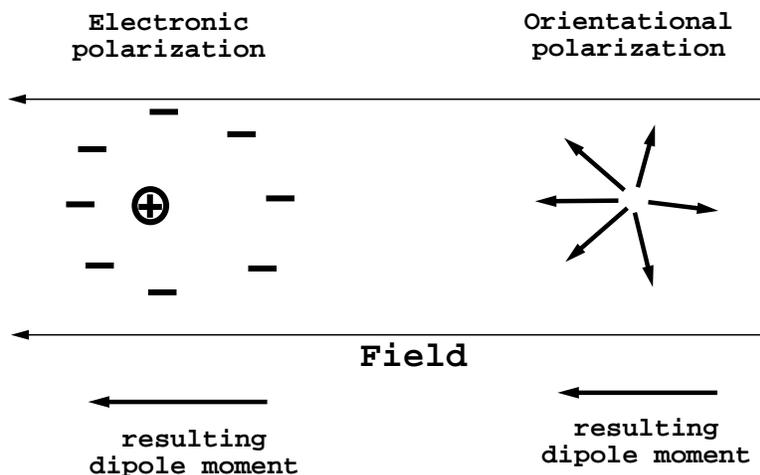


Figure 5: Left: Electric field displaces an atom's nucleus with respect to its electron cloud, creating a nonzero dipole moment. Right: Electric field biases a thermally randomized polar molecule to form a non-zero time-averaged dipole moment.

By itself, electronic polarization in condensed media gives dielectric constants of  $\sim 1.5 - 2.5$ ; e.g.,

hexane 1.9; benzene 2.3). This is actually very large, in the sense that it drops electrostatic field energies by a factor of two relative to vacuum. Adding orientational polarizability gives much larger dielectric constants, such as that of water which is about 80. Note, however, that raising the dielectric constant from 2 all the way to infinity, and thus lowering the energy to zero, produces no more change in the energy than going from 1 (vacuum) to 2 (just electronic polarization). The largest possible dielectric constant is found in an electrical conductor: fields inside a conductor are zero and the dielectric constant is  $\infty$  because electrons in the conduction band redistribute freely in response to an applied field.

Molecule	Dipole moment
Water	1.9
Ethanol	1.7
Acetic acid (neutral)	1.7
Acetone	2.88
Acetamide	3.8

Table 1: Gas-phase dipole moments (Debye) of representative molecules. (1 Debye = 0.2 electron-Angstroms =  $3.3 \times 10^{-30}$  C-m). These dipole moments rise somewhat in solution because the permanent dipoles induce a reaction field that further polarizes the molecule by factors of roughly 1.1 - 1.5. (See Bottcher.)

We have discussed the fact that a dielectric medium weakens an applied field. However, it is evident that the local electric fields inside materials are far from zero. The field that is weakened is actually the average field, where the averaging takes place over the smallest volumes that still contain enough induced dipoles to make the averaging meaningful. The local fields in a material are strong and are complex in form. The statistical thermodynamic theory of the dielectric response links the average field with the local field. This theory, which is associated with the names Clausius, Mossotti, Debye, Onsager, Kirkwood, and Frohlich, forms the basis of computer simulations aimed at computing dielectric constants and is beautifully presented in Bottcher's book (see below). The temperature- and frequency-dependence of the dielectric response are also interesting topics but are beyond the scope of these introductory notes.

## The Work of Polarization

It takes work to shift electrons or orient dipoles. This can be seen by a hypothetical thermodynamic process in which a charge  $q$  is built up from  $q_i = 0$  to a final charge of  $q_f$  near a polarizable object which could be a single molecule or a macroscopic dielectric body (Figure 6). For a linear response, the reaction field back at the inducing charge is proportional to  $q$  and is of opposite sign:

$$\begin{aligned} \phi &= C q \\ C &< 0 \end{aligned} \tag{14}$$

The work of charging from  $q = 0$  to  $q_f$  is then

$$W_1 = \int_0^{q_f} \phi dq$$

$$\begin{aligned}
&= \int_0^{q_f} C q dq \\
&= \frac{C}{2} q_f^2 \\
&= \frac{1}{2} \phi_f q_f < 0
\end{aligned} \tag{15}$$

where  $\phi_f$  is the back potential at  $q$  at the end of the charging process. (We ignore the self-energy of the inducing charge  $q$ .) Note that the charging work equals, not the charge times the potential, but only half of this quantity. The missing work is the energy cost of polarizing the polarizable object. This can be seen clearly by fixing the polarization in its final state and discharging  $q$  back to zero (Figure 6). The back potential is fixed at  $\phi_f$  during this process, so the work is:

$$W_2 = \int_{q_f}^0 \phi_f dq = -\phi_f q_f > 0 \tag{16}$$

The charge is now zero again, and the work of returning to the initial state is the work of allowing the polarization to relax to zero again. This quantity is obtained by closing the thermodynamic cycle:

$$\begin{aligned}
0 &= W_1 + W_2 + W_3 \\
W_3 &= \frac{1}{2} \phi_f q_f < 0
\end{aligned} \tag{17}$$

Thus, the work of releasing the frozen polarization is favorable, implying that setting up the polarization in step 1 was unfavorable. This is as expected; if the work of polarization in the absence of an inducing field were negative, the object would polarize spontaneously. (Such materials do exist; they are known as ferroelectrics.)

What is the nature of this work (free energy) cost of polarization? This depends upon the nature of the polarizable object. If the only source of polarization is electronic, then the energy is purely enthalpic. If orientational polarization plays a role, then there is an entropic component. In most cases, the free energy of polarization combines enthalpic and entropic contributions.

## Continuum Electrostatics at the Molecular Level

We now extend the concept of a macroscopic dielectric constant to the microscopic size scale. The polarization response of a molecule is considered from the molecular frame of reference; thus, the molecule does not rotate so its overall orientational polarizability does not contribute to its dielectric response. Rather, molecular motions will be included explicitly via simulations methods like molecular dynamics, Monte Carlo, etc. For small molecules like water, ethanol, etc., only the electronic polarizability contributes to the dielectric response, and one can readily determine a macroscopic dielectric constant that, when allowed to fill the inside of the molecule, reproduces experimentally observed molecular polarizabilities. Typical values are 1.5-2.5. If the molecule is in vacuum, it is surrounded by a medium of dielectric constant of 1; if it is in water, it is surrounded by a medium of dielectric constant 80. Thus, we are no longer dealing with systems of uniform dielectric constant, but rather with systems with dielectric boundaries or even more complex inhomogeneities. The electrostatics of such systems will be discussed below, but we first turn to the dielectric constant of a protein in solution.

The dielectric constant of a protein clearly has contributions from electronic polarization, so its dielectric

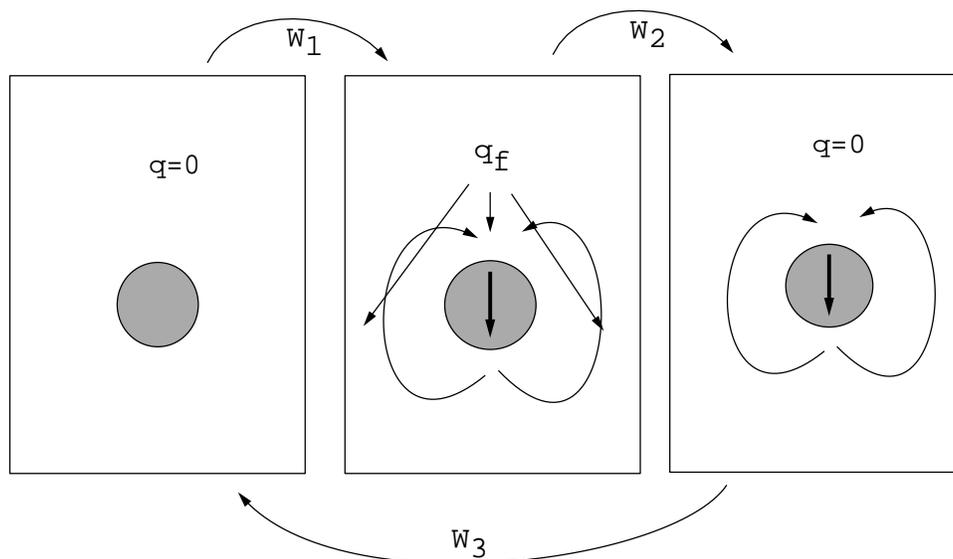


Figure 6: Thermodynamic cycle to analyze the work of polarization. Charge and polarization start at 0 (left). The object becomes polarized when the charge is changed to  $q_f \neq 0$ , with work  $W_1$ . The charge is then reduced to 0 again but the object is left polarized ( $W_2$ ). Finally, the polarization is allowed to relax to zero in the absence of any external charge ( $W_3$ ).

constant must be at least 1.5-2.5. The issue of orientational polarization is more complex. First, it is inappropriate to include dipole moment fluctuations that result from the overall tumbling of the protein in the lab frame because these do not contribute the polarization for a viewer in the molecular frame of reference. Including this polarizability contribution is appropriate only if one is interested in evaluating the dielectric constant of a solution contain dissolved protein; i.e., in evaluating the dielectric increment due to the protein. Second, if one aims to simulate the internal motions of a protein in detail via molecular dynamics, for example, then any reorientation of dipolar groups within the protein are included explicitly in the simulation and should not be included as contributions to the polarizability of the protein.

However, if one is modeling a protein as rigid, then the reorientation of internal groups does contribute to the dielectric constant. The relevant groups are the polar side chains and, most importantly, the main-chain amides. The latter are dominant because of their number and magnitude. For example, there are about 60 neutral polar side-chains in Ribonuclease A, with dipole moments of 1.8 - 3.8 D, and about 120 main-chain amides, all with dipole moments of 3.8 D (Figure 7). I used normal mode calculations to compute the mobility of these groups and used this result with Kirkwood-Frohlich theory to obtain a computed protein dielectric constant of about 2-5. Subsequently, detailed dynamics simulations have obtained similar results for the interior of a protein. Simulations that have obtained larger values have included the motions of charged side-chains, which are not dipoles, or of water molecules, which are not part of the protein; or have included the rotation of the protein as a whole which, as noted above, is more appropriate for a dielectric increment than for the dielectric constant of a protein as a material. Measurements show the dielectric constants of dried protein films and powders to range from 2.5 -3.5, but one may well question the relevance of these values to hydrated proteins, which are expected to be more flexible.

It is worth noting that typical empirical force fields use a dielectric constant of 1 to compute charge-charge interactions. Thus, any modulation of electrostatic interactions by electronic polarizability must be

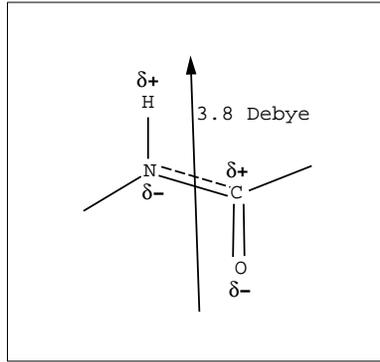


Figure 7: Dipole moment of the protein main-chain amide group.

implicit in other terms. For well-hydrated molecules, this may not be a problem because the orientational polarizability of water makes up for the lack of explicit electronic polarizability. However, the neglect of electronic polarization is likely to be a significant problem in the protein interior, where orientational polarizability probably cannot compensate.

### Dielectric Boundaries

A system consisting of a protein or other molecule in water is not well described by a uniform dielectric constant because there is a sudden change in dielectric constant at the surface of the protein. This boundary can be modeled as a step-function change in dielectric constant, although more detailed models have also been explored. The electrostatics are now significantly more complex than when the dielectric constant is uniform (previous section). The relevant form of the Poisson equation is:

$$-\nabla \cdot [D(\mathbf{r})\nabla\phi(\mathbf{r})] = \frac{\rho(\mathbf{r})}{\epsilon_0} \quad (18)$$

Now the space-varying dielectric constant  $D(\mathbf{r})$  is operated on by the divergence ( $\nabla \cdot$ ). As a consequence, a dielectric discontinuity can serve as a source of  $\mathbf{E}$ -field lines even if there are no source charges there ( $\rho = 0$ ). In effect, a field across a dielectric boundary induces a surface charge remote from any source charges. These surface charges act as new field sources. Figure 8 illustrates this phenomenon for an idealized slab of dielectric in a uniform applied field (Figure 8).

More generally, dielectric boundaries can influence fields in large and sometimes unexpected ways. Let us begin by considering the classic and analytically solvable case of a charge  $q$  in a medium of low dielectric constant  $D_1$  near a planar boundary with a medium of high dielectric constant  $D_2$  (Figure 9). A layer of surface charge  $\sigma$  forms at the boundary. Its net charge is

$$q' = \int \sigma dA = \frac{D_1 - D_2}{D_1 + D_2} q \quad (19)$$

If  $D_2 > D_1$ , as for a protein in water, the surface charge is opposite in sign to  $q$ . The influence of this surface charge in region 1 is equivalent to that of a point-charge  $q'$  placed opposite  $q$  in region 2:

$$\phi_1(\mathbf{r}) = \frac{q}{4\pi\epsilon_0 D_1 r} + \frac{q'}{4\pi\epsilon_0 D_1 r'} \quad (20)$$

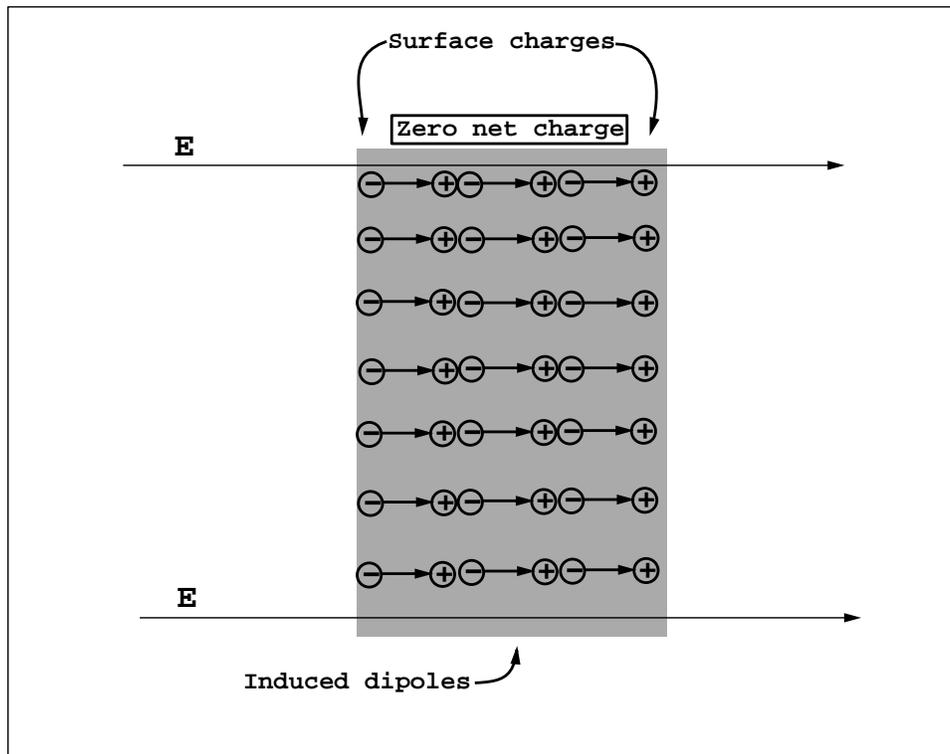


Figure 8: Formation of surface charge at the boundaries of a dielectric block in an electric field  $\mathbf{E}$ . The field induces dipoles within the material. The positive “heads” and negative “tails” of the dipoles cancel except at the surfaces.

Charge  $q$  is attracted toward the surface charge it induces through the reaction field of the surface charge. This “image-charge force” is the same force that causes an electrostatically charged balloon to cling to the ceiling.

The potential due to the image charge also causes the “effective dielectric constant”  $D_{\text{eff}}$  for interactions of other charges with  $q$  to be greater than or equal to  $D_1$  and to vary with position. When  $q$  is near the boundary and one looks at the potential somewhere far away but still near the boundary,  $D_{\text{eff}}$  approaches  $(D_1 + D_2)/2$ . When the charge is far from the boundary and one looks at the potential somewhere else far from the boundary,  $D_{\text{eff}}$  goes to  $D_1$ . It can be shown that the effective dielectric constant for a charge at site  $a$  producing a potential at site  $b$  equals that for a charge at site  $b$  producing a potential at site  $a$ .

Qualitatively similar results are obtained when the boundary is spherical (Figure 10). Note that the effective dielectric constant for two interacting charges is not controlled by the dielectric constant of the material directly between them, but by the entirety of their dielectric environment. More complex behaviors are also possible, including the “lightning rod” or “focussing” effect observed in superoxide dismutase (Figure 11).

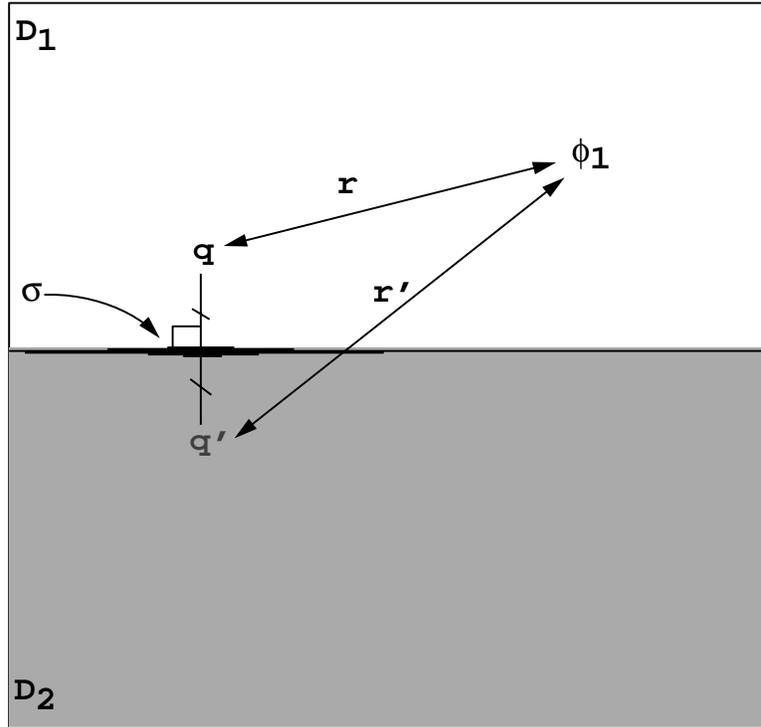


Figure 9: Charge  $q$  near a planar boundary between regions of dielectric constant  $D_1$  and  $D_2$ . The effect of the induced surface charge  $\sigma$  on the potential  $\phi_1$  in region 1 is equivalent to that of an image charge  $q'$  directly across from  $q$ .

### Electrostatic Forces for a Non-Uniform Dielectric Constant

We usually think of electrostatic forces as being given by

$$\mathbf{F} = q\mathbf{E} \quad (21)$$

However, this is not the whole story when there are dielectric boundaries. Consider the case of a spherical molecule containing an off-center charge and immersed in water (Figure 12). There must be some force other than  $q\mathbf{E}$ , or the molecule would be a perpetual motion machine. A hint as to what is going on can be obtained by the classical picture of a parallel plate capacitor with a block of dielectric partly inserted into the gap. The block is pulled into the gap because this lowers the field energy. Put differently, the charges on the plates polarize the block and attract the induced dipoles. Something similar is happening with our eccentric molecule (Figure 12): the high dielectric solvent is trying to get closer to the charge, and the resulting force or pressure exactly balances the force on the charge. Thus, the force on the molecule is the sum of a  $q\mathbf{E}$  force and a dielectric boundary force:

$$\mathbf{F} = q\mathbf{E} + \mathbf{F}_{dbf} \quad (22)$$

For the whole of a molecule in the absence of an external field, the net force must come to zero, but the forces on each atom need not balance. Interestingly, the formula for dielectric boundary pressure is not quite so simple as the product of field and surface charge density; see the Suggested Reading for more information.

The dielectric boundary force increases with the strength of the field at the dielectric boundary. One im-

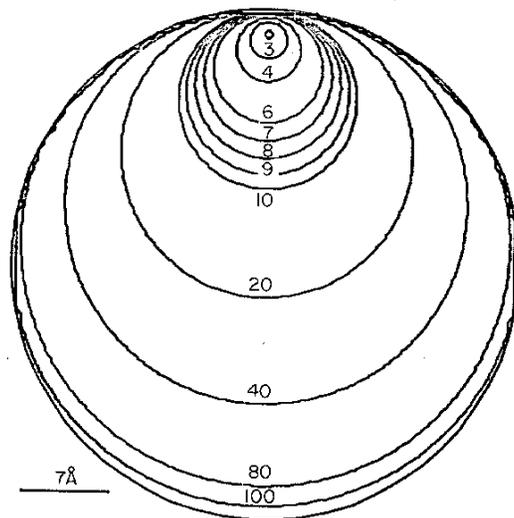


Figure 10: Contour plot of effective dielectric constants for the potential produced by a point charge (small circle near top) 2 Angstroms from the surface of a hypothetical spherical protein of dielectric constant 2 in water ( $D=80$ ) with no dissolved electrolyte. (From JMB 183:503,1985.)

plication is that low-dielectric molecules in water will be repelled by charges because the boundary pressure is greater on the side near the charge than on the opposite side, as illustrated in Figure 13.

### Electrostatic Solvation

We just noted that a charge in water will tend to push away a low-dielectric body. Put differently, the charge is pulling in high-dielectric water to solvate itself better. One can use concepts from continuum electrostatics to think about and model solvation. The classic example of this is the Born ion, a point-charge in a spherical cavity of radius  $a$  (Figure 14). The work of transferring this object from a medium of dielectric constant  $D_1$  to  $D_2$  is, lapsing into Biochemical units,

$$W_{el} = \frac{332q^2}{2a} \left( \frac{1}{D_2} - \frac{1}{D_1} \right) \quad (23)$$

For transfer from vacuum to water,  $D_1 = 1$ ,  $D_2 \approx 80$ . For simple monovalent ions, such as sodium, potassium and chloride, whose effective cavity radii  $a$  run about 1.5 - 2.5 Å, hydration energies range from about -100 to -50 kcal/mol. Minor adjustment of these radii within a reasonable range allows one to reproduce experimental solvation energies quite well. Note that doubling the charge quadruples the solvation free energy; and indeed, divalent cations are far more strongly hydrated than monovalent ions, with solvation energies of several hundred kcal/mole. Note, also, that because the high-dielectric solvent never actually contacts the point-charge at the center of the sphere,  $W_{el}$  remains finite. From a physical standpoint, what is happening here is that the charge within the molecular cavity polarizes the solvent, the polarized solvent produces a reaction potential  $\phi_{RF}$  at the charge, and the charge interacts with this field.

One can think in the same way about the electrostatic solvation of more complex compounds including

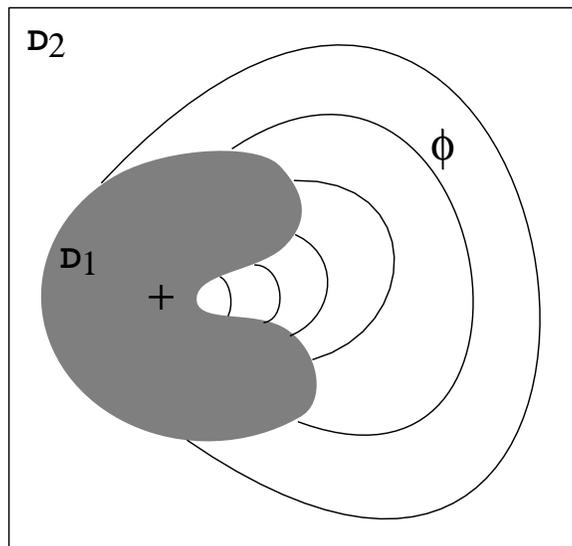


Figure 11: Diagram of “focusing” of the electric field of a positive charge by a concavity in the surface of a protein.

ones that are not ions. For example, Figure 15 shows a model for computing the electrostatic solvation energy of ethanol. Note that, for transfer from vacuum to water,  $W_{el}$  is always negative because the solvent always reduces the fields weaker from their vacuum values, and the electrostatic energy is given by an integral of the field squared (Equation 11).

The “total electrostatic energy”  $G_{el}$  of a molecule in water is the sum of the Coulombic interactions of its atoms via the internal dielectric constant of the molecule ( $D_{int}$ ), and its solvation energy. If the molecule changes conformation, its electrostatic energy changes due to both the Coulombic and the solvation terms.

$$G_{el} = \sum_{i>j} \frac{q_i q_j}{4\pi\epsilon_0 D_{int}} + \frac{1}{2} \sum_i q_i \phi_{RF} \quad (24)$$

where, again,  $\phi_{RF}$ , is the reaction field potential at the charge. The electrostatic energy in this expression is best viewed as a free energy, because the work of polarizing the solvent can include not only enthalpic but also entropic contributions. This point, as well as the origin of the factor of  $\frac{1}{2}$  in the solvation term, is discussed in the section entitled The Work of Polarization.

Of course, solvation is not just electrostatic. There are van der Waals interactions between the solute and solvent, as well as entropic and enthalpic contributions resulting from changes in water structure. The latter are often lumped as the hydrophobic effect. A complete solvation model can be assembled by thinking about the process illustrated in Figure 16. One first forms a molecule-shaped cavity in the solvent, which has van der Waals and hydrophobic interactions with the solvent. The work of forming this nonpolar cavity is termed  $W_{np}$  and is often estimated as linear in the solvent-accessible surface area of the solute. One then moves the charges into this cavity, gaining the electrostatic part of the solvation free energy that we have just been discussing,  $W_{el}$ . Then  $W_{solvation} = W_{np} + W_{el}$ , and the total energy of a molecule as function of conformation can be written as the sum of its internal energy computed via a force-field like CHARMM or AMBER and a solvation energy computed with the present approach. The application of these ideas to proteins and other biomolecules to study properties like folding and binding energetics is discussed below.

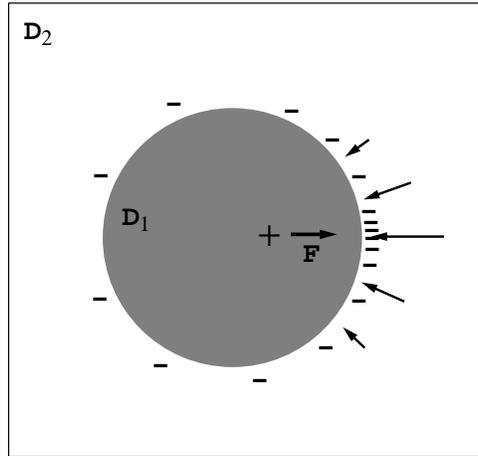


Figure 12: Diagram of a low-dielectric molecule in water and containing an off-center positive charge. The charge induces a negative surface charge at the boundary and is attracted to this induced charge. The arrows indicate the pressure of the high-dielectric solvent, which produces a net force equal and opposite to the reaction field force on the positive charge.

### Mobile Ions and the Poisson-Boltzmann Equation

Up to now, we've been solving the Poisson equation in various forms and the only field sources on the right-hand-side have been the charges described in  $\rho$ . These are typically point charges from an empirical force field, though could use charge densities measured by X-ray crystallography or calculated with *ab initio* quantum mechanics. However, when the solution contains a dissolved electrolyte, such as sodium chloride, there can be more field sources on the right-hand-side of the equation. Consider a cationic lysine side-chain in an aqueous sodium chloride solution. The positive potential generated by the lysine tends to repel sodium ions and attract chlorides, producing an "atmosphere" of net negative charge. This charge atmosphere weakens or "screens" the positive potential produced by the lysine. In general, a dissolved electrolyte weakens electric fields. This is why experimentalists test whether binding is driven by electrostatic interactions by seeing whether it diminishes with increasing ionic strength.

This redistribution of the electrolyte is the focus of Debye-Huckel theory. This theory uses the Boltzmann factor of dissolved ions in the local electrostatic potential ( $e^{-\beta\phi(\mathbf{r})q_i}$ ) to estimate the increase or decrease in the local concentration ( $c(\mathbf{r})$ ) of the ions relative to their bulk concentration ( $c_{bulk}$ ) For example,

$$c_{Na}(\mathbf{r}) = c_{Na,bulk} e^{-\beta\phi(\mathbf{r})q_{Na}} \quad (25)$$

Of course,  $\phi$  is itself influenced by the redistribution of sodium and chloride, so the potentials and concentrations must be solved for self-consistently. Applying this idea to the case of an electrolyte with  $N$  types of ion each having charge  $q_i$  and concentration  $c_i$  yields the (nonlinear) Poisson-Boltzmann:

$$-\epsilon_o \nabla \cdot [D(\mathbf{r}) \nabla \phi(\mathbf{r})] = \rho^f(\mathbf{r}) + \sum_{i=1}^N q_i c_{i,bulk}(\mathbf{r}) e^{-\beta q_i \phi(\mathbf{r})} \quad (26)$$

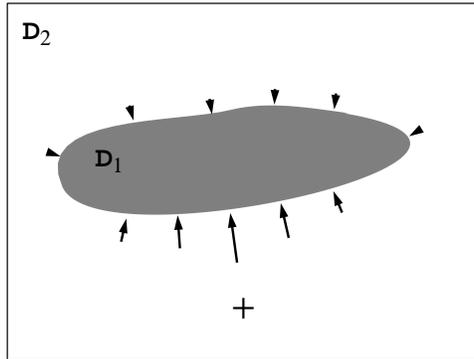


Figure 13: Unbalanced dielectric boundary pressure repels a a low-dielectric object in a high-dielectric solvent from a charge.

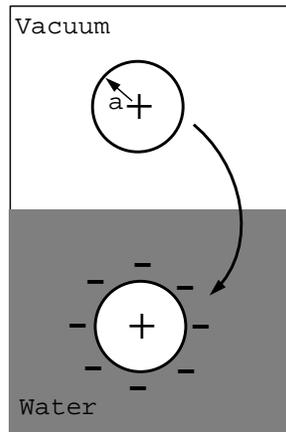


Figure 14: The Born ion. A spherical ion of radius  $a$  is transferred from vacuum to water. In water, the induced polarization creates a surface charge and thus a reaction field that stabilizes the ion.

Although this is not made explicit in the formula, note that the bulk ion concentrations depend upon position because they are zero inside the solute and they have the bulk solution values outside.

The potentials this yields do not vary linearly with the source charges  $\rho^f$ , so many of the appealing properties of linear systems discussed above do not apply (see below). It is also hard to solve this equation numerically. Fortunately, there is a linearizing approximation that is often well-justified. One writes a Taylor series expansion of the Boltzmann factor and uses only terms up to first order in  $\phi$ . This is a good approximation so long as the exponent is near zero, which holds best for monovalent electrolytes, weak source charges, and high ionic strengths. The resulting linearized Poisson-Boltzmann equation is:

$$\begin{aligned}
 -\epsilon_0 \nabla \cdot [D(\mathbf{r}) \nabla \phi(\mathbf{r})] &= \rho^f(\mathbf{r}) + \epsilon_0 D(\mathbf{r}) \kappa^2(\mathbf{r}) \phi(\mathbf{r}) \\
 \kappa^2 &\equiv \frac{\beta}{D\epsilon_0} \sum_1^N c_{i,bulk} q_i^2 \\
 &= \frac{2}{D\epsilon_0 kT} I
 \end{aligned} \tag{27}$$

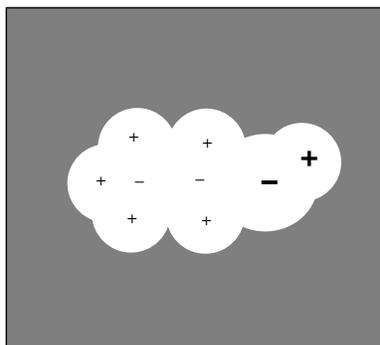


Figure 15: Electrostatic model of a molecule of ethanol in solvent. Each aliphatic hydrogen and carbon atom possesses a small central charge, while the hydroxyl group is more polar.

where  $I$  is the ionic strength. Again, it is implicit that  $I$  and  $\kappa$  are zero inside the solute.

For a point-charge in solution, the mobile ions redistribute to produce an damping of the potential, relative to Coulomb's law, that is exponential with distance:

$$\phi(r) = \frac{q}{4\pi D \epsilon_0 r} e^{-r/r_{Debye}} \quad (28)$$

where  $r_{Debye} = \kappa^{-1}$ , the Debye length, is the characteristic distance of the exponential screening. The Debye length decreases as ionic strength increases. For physiologic ionic strength – about 150 mM – the Debye length of 8 Å leads to marked damping of Coulombic interactions. An electrolyte dissolved in water also tends to strengthen the solvation of charges, but this effect is small compared to the powerful solvating effect of water itself.

The linearized Poisson-Boltzmann Equation (LPBE) possesses convenient mathematical properties that the full nonlinear Poisson-Boltzmann Equation (PBE) lacks. First, the electrostatic field generated by a collection of charges equals the sum of the fields of the individual charges; that is, the fields are superposable. Fields are not superposable in the full PBE because the degree of ionic screening varies nonlinearly with potential. Second, the electrostatic energy of a system of charges  $q_i$  retains the same simple form as for charges in vacuum or in a linear dielectric medium:  $U = \frac{1}{2} \sum_i q_i \phi_i$ . Again, this expression does not hold for the full PBE because the electrostatic potential is no longer proportional to the charge. (See also Equation 3.)

The electrostatic forces in a system described by the linearized Poisson-Boltzmann equation include an additional contribution from the pressure of ions at the molecular interface– an ionic boundary force:

$$\mathbf{F} = q\mathbf{E} + \mathbf{F}_{dbf} + \mathbf{F}_{ibf} \quad (29)$$

Formulae for this force are in the literature, but it is always weak in aqueous systems and can safely be neglected in most cases.

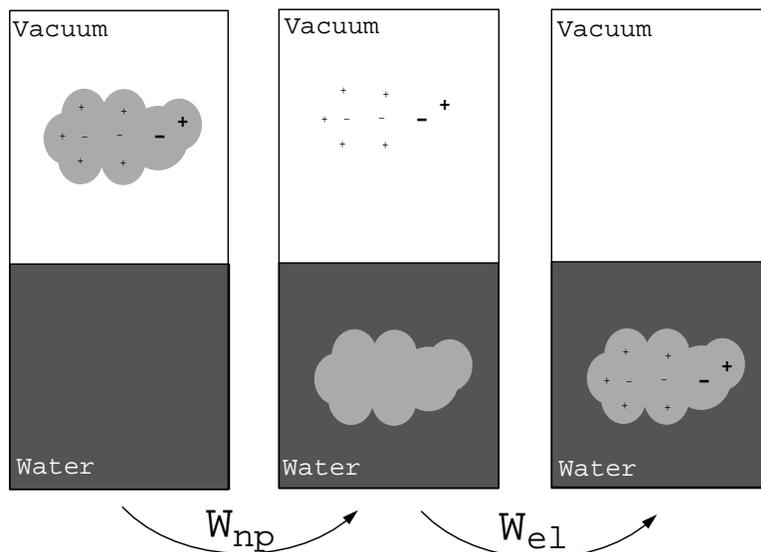


Figure 16: Two-step hydration process, illustrated for ethanol. Step 1 is formation of a molecule-shaped cavity in the solvent ( $W_{np}$ ) and Step 2 is the transfer of the molecular charges into the cavity ( $W_{el}$ ), a step analogous to solvation of a Born ion.

### Solving the Linearized Poisson-Boltzmann Equation

In order to address problems in molecular electrostatics, we need a method to solve the linearized Poisson-Boltzmann equation for various distributions of atomic charges, dielectric boundaries, and ionic strengths. We can no longer rely on the analytic solutions that are available for planar boundaries and spherical molecules, but must resort to numerical methods. Such methods convert the linear Poisson-Boltzmann equation from a continuous partial differential equation into discretized problems described by systems of linear equation that can be solved by matrix methods. Several numerical methods are available, and there are also variants of each method.

The *boundary element method* tessellates the dielectric boundary between the interior and exterior of the molecule and solves for the surface charge at each flat boundary element. An advantage of boundary element methods over methods that discretize volume (such as finite differences), is that the number of discrete elements tends to be smaller, because a surface is 2-dimensional while volume is 3-dimensional. On the other hand, it is not trivial to tile a complex molecular surface. Also, boundary element methods are not well suited for dielectric media that vary smoothly with position, rather than having sharp boundaries.

The finite difference method discretizes space into a cubic lattice, typically. (The grid as a whole can be rectangular, however.) Electrostatic potentials, charges, and mobile charges are defined at the grid points, while the dielectric constant also exists on the grid lines (Figure 17). The divergence of the field  $\epsilon \nabla \phi$  is computed by finite differences. The condition to be satisfied at each grid point is:

$$\phi_i = \frac{\sum_1^6 \epsilon_o D_j \phi_j + q_i/h}{\sum_1^6 \epsilon_o D_j + \epsilon_o D_i \kappa_o^2 h^2} \quad (30)$$

where  $h$  is the length of one grid-line, the  $i$  subscript implies a grid point of interest and  $j = 1, 6$  indexes the 6 neighboring grid points or the grid lines joining grid point  $i$  with grid point  $j$ . There is one of these

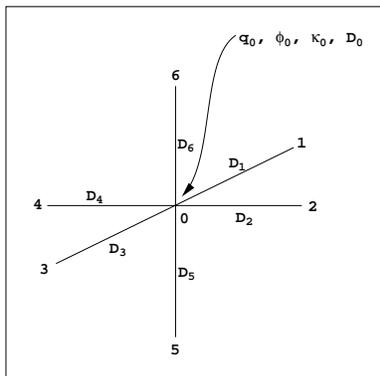


Figure 17: One finite-difference grid point and its 6 neighbors. Charge, potential and ionic strength (or  $\kappa$ ) are defined on the grid points. Dielectric constant is defined on the grid lines. For simplicity, the central grid point is given the subscript 0 here and in Equation 30.

equations for each grid point, and each equation involves the potentials at neighboring grid point. This is a big system of linear equation that can be represented in matrix notation and and solved for  $\phi$  at all grid points by various matrix methods. The potential at any off-grid location can then be obtained by trilinear interpolation from the 8 nearest grid points.

Grid points at the edge of the grid are special because they are missing some neighbors. They are dealt with by assigning them fixed, estimated potentials at the beginning of the calculation (boundary conditions). So long as the edge of the grid is in the solvent region at some distance from any solutes, a good compromise between accuracy and speed is to compute the boundary potentials as the sum of the Debye-Huckel screened potentials due to each of the solute charges (see Equation 28). (Setting the grid potential to 0 can lead to noticeable errors if one is doing high-precision calculations and if the boundary is only a few Angstroms from any solute charges.)

Before one can solve for the potential, it is necessary to set up grid representations of  $\rho$ ,  $\kappa$  and  $\epsilon$ . Atomic point-charges can be placed by distributing them on the 8 grid points of the box it occupies; UHBD uses a trilinear method that preserves the location of the center of charge. The distribution of the mobile charges in the solvent electrolyte is defined by another grid that is set to zero for the molecular interior and 1 for the exterior where the electrolyte can penetrate. Here the “exterior” typically extends one ion-radius beyond the van der Waals radii of the solute atoms. This increment keeps the mobile ions from overlapping with the solute, and forms an ion-excluding region of high dielectric constant that is known, in double-layer theory, as the Stern layer. Because each grid point is associated with 3 grid lines, and dielectric constant is defined on the grid lines, there are 3 dielectric grids: one each for the x-, y- and z-directed grid lines. The dielectric constant is typically set according to whether the center of a grid line is inside or outside the Richards molecular surface of the solute. UHBD also allows grid branches that cross this boundary to be assigned dielectric constants between the interior and exterior dielectric constants. This “smoothing” step represents the position of the boundary more accurately.

With the finite difference method, an electrostatic solvation energy can then be computed as an energy change when solvent is added to the system:

$$W_{el} = \frac{1}{2} \sum_i q_i (\phi_S(\mathbf{r}_i) - \phi_{NS}(\mathbf{r}_i)) \quad (31)$$

Here the  $S$  and  $NS$  subscripts imply potentials computed in the presence and absence of the solvent. These potentials can be obtained by running separate finite difference calculations with and without solvent, though other approaches also exist. It is worth emphasizing that this equation requires calculating potentials at the atomic charges that are generating the potentials. These potentials are not physically meaningful on their own; they depend upon the grid location and spacing. However, *differences* in these potentials can be meaningful, as in Equation 31.

## Electrostatics and molecular modeling

The ideas and methods described above can be used to estimate the difference in energy between two conformations of a molecule in solution or between the bound and unbound states of two molecules. Here we focus on conformational change; the application to binding is completely analogous.

In the present model, the change in internal plus solvation energy when a molecule changes conformation can be written as:

$$\Delta G = \Delta U_{int} + \Delta W_{np} + \Delta W_{el} \quad (32)$$

where the three terms on the right hand side are, respectively, the change in internal energy, the change in the nonpolar solvation energy, and the change in electrostatic solvation energy. The first term may be estimated by direct application of an empirical force field, such as CHARMM or AMBER, to the two conformations. The second term may be estimated via the change in the molecular surface area due to the conformational change; other methods may also be applicable. The third term may be estimated by using finite difference Poisson-Boltzmann calculations to evaluate  $W_{el}$  for the molecule in the initial and final conformations (Equation 31), and taking the difference to obtain  $\Delta W_{el}$ .

To date, applications of this approach have yielded reasonable and even promising results. On the other hand, the results are sensitive to the precise conformations examined. This is not unexpected because molecular properties are averages over multiple thermally accessible conformations, and research groups are exploring methods of combining conformational sampling with the present model. One approach is to use the present implicit solvation model within molecular dynamics simulations. Algorithms have been developed for computing the atomic forces associated with the linearized Poisson-Boltzmann equation and are currently being tested and optimized for use in molecular dynamics.

## Thinking About Molecular Electrostatics

Here are some ideas and methods that I have found helpful and/or interesting.

### The effective dielectric constant

It is incorrect to assume that the electrostatic interaction of two charges is controlled by the dielectric constant of the material along a line joining the two charges. In reality the electrostatic field is strongly influenced by the complete distribution of dielectric media near the charges, as highlighted by the contours of effective dielectric constant shown in Figure 10. This is because the solvent polarization induced by a solute charge effectively weakens the charge's interaction with other charges in all directions.

### The balance between solvation and Coulombic interactions

The total electrostatic interaction energy of two charged atoms in water is the sum of their direct Coulombic interaction (calculated with their internal dielectric constant) and their solvation energies. These two quan-

ties change in opposite directions as the charges move together, and the balance between them accounts for dielectric screening. Consider two ions of opposite sign. When they are far apart, they do not interact and they are strongly solvated. As they move together, the field they produce together gradually diminishes, going to zero when the charges are at the same place. As their combined field becomes weaker, they polarize the solvent less and less and so are less strongly solvated; their electrostatic solvation energy becomes less negative. At the same time, their Coulombic interaction becomes more negative. The partial cancellation of the Coulombic attraction by the weakening interaction with solvent explains the screening of the net charge-charge interaction by the dielectric medium.

### **Computing the interaction of one charge with many others**

One sometimes wishes to evaluate the interaction between many charges  $j = 1, N$  in a protein and a single charged atom  $i$ , such as an ionizable site in an enzyme active site. The slow way to do this is to carry out  $N$  separate finite-difference calculations, one for each atom  $j$  charged and everything else neutral, and to look at the potential each charge produces at site  $i$ ; the interaction energy is then  $\phi_j(\mathbf{r}_i) q_i$ . The fast – and equivalent – way is to charge group  $i$  and use a single finite-difference calculation to look at the potential it produces at all  $N$  of the other groups. The interaction energies will then be  $\phi_i(\mathbf{r}_j) q_j$ ; and it can be shown that these interaction energies are exactly the same as those computed by the “slow” method. Note that the same approach can be used if  $i$  and  $j$  are groups of charges.

### **Helix macrodipoles**

In an alpha-helix, the backbone amides of the protein all point from the C- toward the N-terminus. As a consequence, the total dipole moment of a helix of  $N$  residues is roughly  $3.8N$  Debyes. It has been argued that the large dipole moment of an alpha helix can produce correspondingly large electrostatic fields. This is only partly true. In fact, the overall field of a long alpha-helix macrodipole is approximately equal to that produced by one charge of about 0.5 proton-charges at the N-terminus of the helix, and another of about -0.5 protons at the C-terminus. This is because neighboring amide dipoles inside the helix pretty well cancel each other, leaving only the N- and C-terminal charges uncanceled. The field produced by a charge of 0.5 is nontrivial, but its field does not rise linearly with the length (net dipole moment) of the helix: once the C-terminus is far from the N-terminus, the helix fields do not change much. Consider a dipole made of an electron at the North pole of the Earth and a proton at the South pole. The dipole moment is enormous (about  $10^{18}$  Debye), but the fields at the termini are only those of unit charges.

### **Validity and applicability of continuum electrostatics at the molecular level**

In a sense, continuum electrostatics should not work well at the molecular size-scale. It treats water as a smooth continuum, rather than as a granular molecular liquid with specific hydrogen-bonding preferences. It also ignores dielectric saturation – the inability of a dielectric medium to polarize more and more with an increasing field. Nonetheless, experience has shown that continuum electrostatics applies well enough at the molecular size scale to give useful insights and quantitative or semi-quantitative results. This probably results in part from time-averaging of the thermally agitated solvent, and also from fortunate cancellations of errors. For example, it has been suggested that dielectric saturation is often balanced by electrostriction – an increase in the density of water in regions of high field strength.

It is still difficult to judge the accuracy of continuum electrostatics in detail because any comparison with experiment requires not only a solvation model, but also a set of atomic charges, cavity radii, van der Waals terms, etc.; and the success of a model depends upon the interplay of all of its parts. In this respect, continuum electrostatics is not much different from other molecular modeling techniques.

The ability of continuum electrostatics to reproduce measured solvation energies has been encouraging. Further tests on binding and folding for macromolecular systems are appropriate, but such systems are also very challenging because they have so many degrees of freedom. For macromolecules, it is often difficult to interpret the results of a test purely in terms of the validity of the energy model, because the results may be determined by inadequate conformational sampling. Smaller systems, such as host-guest pairs, whose conformations can be more thoroughly sampled, may be particularly useful for further evaluating models of molecular energetics.

### **Running Finite Difference Poisson-Boltzmann Calculations**

Here are a few pointers on the execution of actual calculations. The focus is on UHBD, the program with which I am currently most familiar, but many of these considerations apply to other implementations as well.

#### **Dielectric cavity radii**

The question of atomic parameters is perennial in molecular modeling. For continuum electrostatics, a central issue is the size of the dielectric cavity to assign to each atom (see Figure 16). For a typical empirical force field, such as CHARMM, a good approximation is to set the dielectric cavity radius of each atom type to  $R_{min}$  or  $\sigma/2$ , where these are the usual van der Waals parameters. (Note that  $R_{min}$  does not equal  $\sigma/2$ , but it is close.) Some force fields, such as at least one version of OPLS, do not assign any van der Waals interactions to polar hydrogens. In such cases, the hydrogen lies very near the edge of the cavity defined by whatever atom it is bound to. This is problematic because a charge so close to a dielectric boundary demands a very fine finite-difference grid if the results are to be properly converged. This problem can be removed, and good solvation energies can still be obtained, if polar hydrogens are assigned a dielectric cavity radius of 1 to 1.2 Å. Ideally, one should adjust the radii so that calculated solvation energies for sample molecules match experiment.

#### **Grid size and spacing**

If one wishes to view potential contours or field lines around a protein, the finite difference grid must extend far enough into the solvent that the estimated boundary potentials are accurate enough that they do not distort the field. (See previous section on Solving the Linearized Poisson-Boltzmann Equation.) A reasonable grid should probably be at least 1.5 times as long as the protein in each dimension. For solvation energies, the grid can fit more snugly without changing the results more than a few percent; say about 1.25 the size of the solute.

For viewing field contours and lines around protein, a grid spacing of 0.5 - 1.0 Å is usually adequate. For solvation energies to be fully converged, a grid spacing of about 0.2 - 0.3 Å is recommended for the current version of UHBD. These fine spacings ensure that several grid lines separate any atomic charge from the dielectric boundary.

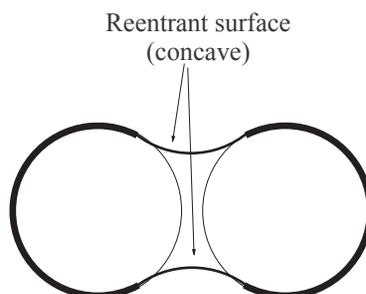


Figure 18: Two spherical atoms (thin line) along with their solvent contact surface (thick line) and their reentrant surface (medium line).

### Molecular surfaces and dielectric boundaries

UHBD can set the dielectric boundary of a molecule to either the van der Waals surface or the Richards molecular surface. (The latter includes contact and reentrant surface.) The two surface definitions yield similar solvation energies for small molecules. However, for proteins, the two surfaces are very different: the van der Waals surface produces cracks and crevices all through the protein, while the molecular surface envelopes the protein smoothly. Using the van der Waals surface to define the dielectric boundary thus effectively allows high dielectric solvent to penetrate deep into the protein, into sites where a water molecule could not fit. The molecular surface is therefore normally considered to be more realistic.

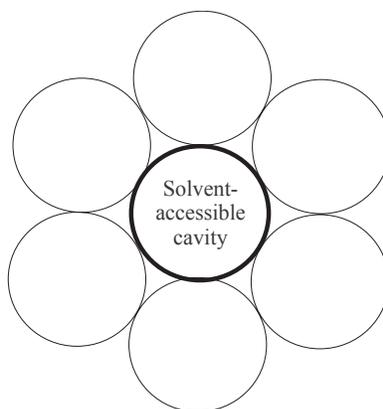


Figure 19: Six spherical atoms (thin lines) forming a cavity (thick line) just large enough for one solvent molecule. An infinitesimal inward motion of one atom into the cavity will obliterate the cavity in a discontinuous fashion.

On the other hand, using the molecular surface as the dielectric boundary between the molecular interior and exterior (see above) produces certain problems in the calculation of atomic forces. First, it was not immediately obvious how the dielectric boundary pressure on areas of reentrant surface (Figure 18) should be applied to the atoms of the solute. However, it would appear that this problem has now been solved. Second, the molecular surface does not always change continuously with changes in atomic position: a solvent-accessible (high-dielectric) cavity within the solute can suddenly cease to be solvent-accessible (become low-dielectric) when a solute atom moves an infinitesimal distance (Figure 19). As a consequence,

the electrostatic solvation energy varies discontinuously and is not differentiable; i.e., the electrostatic solvation force is not well-defined. It is not yet clear how serious this problem is; there may well be ways of overcoming it through minor changes to the model.

## Suggested Reading

The following books and papers provide greater detail on many of the topics presented above. This is not an attempt to document all of the important contributions to this area, but a personal bibliography of relevant materials that I have found particularly useful or that reflect my own understanding of the field.

- THEORY OF ELECTRIC POLARIZATION, 2ND EDITION, VOLUME 1: DIELECTRICS IN STATIC FIELDS. C.J.F. BOTTCHER, O.C. VAN BELLE, P. BORDEWIJK AND A. RIP. ELSEVIER, AMSTERDAM, 1973. Clearly written and relatively nonmathematical synthesis of a complex literature.
- ELECTROMAGNETIC THEORY. J.A. STRATTON, MCGRAW-HILL, NEW YORK, 1941. Excellent reference book for mathematical aspects and especially for treatment of forces in media with dielectric discontinuities.
- AN INTRODUCTION TO STATISTICAL THERMODYNAMICS. T.L. HILL, DOVER, NEW YORK, 1986. Excellent introductory text with a helpful chapter on Debye-Huckel theory and the Poisson-Boltzmann equation.
- CALCULATION OF THE TOTAL ELECTROSTATIC ENERGY OF A MACROMOLECULAR SYSTEM: SOLVATION ENERGIES, BINDING ENERGIES, AND CONFORMATIONAL ANALYSIS. M.K. GILSON & B. HONIG, PROTEINS: STRUCTURE, FUNCTION AND GENETICS, 4:7-18, 1988. Describes the use of finite difference solutions of the Poisson-Boltzmann equation for computing electrostatic solvation energies.
- THE DIELECTRIC CONSTANT OF A FOLDED PROTEIN. M.K. GILSON & B. HONIG, BIOPOLYMERS 25:2097-2119, 1986. Early calculation of the dielectric constant of a protein. Outlines the problem and describes application of Kirkwood-Frohlich theory.
- ENERGETICS OF CHARGE-CHARGE INTERACTIONS IN PROTEINS. M.K. GILSON & B. HONIG, PROTEINS: STRUCTURE, FUNCTION AND GENETICS, 3:32-52, 1988. Uses finite-difference Poisson-Boltzmann method to survey the strength of charge-charge interactions in sample proteins, and provides comparisons with experiment.
- CALCULATION OF THE ELECTRIC POTENTIAL IN THE ACTIVE SITE CLEFT DUE TO ALPHA-HELIX DIPOLES. J. WARWICKER & H.C. WATSON. J.MOL.BIOL. 157:671-679, 1982. Early finite-difference solution of the Poisson equation for a biological macromolecule.
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- COMPUTATION OF ELECTROSTATIC FORCES ON SOLVATED MOLECULES USING THE POISSON-BOLTZMANN EQUATION. M.K. GILSON, M.E. DAVIS, B.A. LUTY AND J.A. MCCAMMON, J. PHYS. CHEM. 97:3591-3600, 1993. Variational analysis of and numerical calculation of atomic forces for the Poisson-Boltzmann equation by the method of finite differences.

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## Appendix

The force on point-charge 2 due to point-charge 1 is the gradient of the energy with respect to the position of charge 2; in vacuum:

$$\begin{aligned}
 \mathbf{F}_2(\mathbf{r}_2) &= -\frac{q_1 q_2}{4\pi\epsilon_0} \nabla_{\mathbf{r}_2} \left( \frac{1}{r_{12}} \right) \\
 &= -\frac{q_1 q_2}{4\pi\epsilon_0} \left( \frac{\partial}{\partial x_2} \mathbf{i} + \frac{\partial}{\partial y_2} \mathbf{j} + \frac{\partial}{\partial z_2} \mathbf{k} \right) \frac{1}{\sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}} \\
 &= \frac{q_1 q_2}{4\pi\epsilon_0 r_{12}^3} ((x_2 - x_1)\mathbf{i} + (y_2 - y_1)\mathbf{j} + (z_2 - z_1)\mathbf{k})
 \end{aligned} \tag{33}$$

Electric field generated by charge 1 at site 2:

$$\begin{aligned}\mathbf{F}_2(\mathbf{r}_2) &= q_2 \mathbf{E}_1(\mathbf{r}) \\ \mathbf{E}_1(\mathbf{r}_2) &= \frac{q_1}{4\pi\epsilon_0 r_{12}^3} ((x_2 - x_1)\mathbf{i} + (y_2 - y_1)\mathbf{j} + (z_2 - z_1)\mathbf{k})\end{aligned}\quad (34)$$

where

$$r_{12} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}\quad (35)$$