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Electrical interactions in the cell: Asymmetric screening in a watery antiverse

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Abstract

The problem of electrostatics in biomolecular systems presents an excellent opportunity for cross-disciplinary science and a context in which fundamental physics is called for to answer complex questions. Due to the large density in biological cells of charged biomacromolecules such as protein factors and DNA, it is challenging to understand quantitatively the electric forces in these systems. Two questions are especially puzzling. First, how is it that such a dense system of charged molecules does not simply aggregate in random and non-functional ways? Second, since some mechanism apparently prevents such aggregation, how is it that binding of biomolecules still occurs so reliably? Recognizing the role of water as a universal solvent in living systems is key to understanding these questions. We present a simplified physical model in which water is regarded as a medium of high dielectric constant that nevertheless exhibits the key features essential for answering the two questions presented. The answer to the first question lies in the strong screening ability of water, which reduces the energy scale of the electrostatic interactions. Furthermore, our model reveals the existence of asymmetric screening, a pronounced asymmetry between the screening for a system with like charges and that for a system with opposite charges, and this provides an answer to the second question.

I. INTRODUCTION

It is widely believed that exposure to examples and applications deepens understanding of the core principles of physics. Topics in biology comprise a growing area of interdisciplinary science and provide ample opportunities for the application of physical principles.¹ The mechanics and thermodynamics of molecular machines and macromolecules² and the thermodynamics of evolution^{3,4} are some of the biological topics to appear in this journal recently. Electrical interactions are often a prominent feature of biological systems,^{5–7} and have therefore received considerable attention. Here we present an application of electrostatics to biomolecular interaction in the hope of illuminating important principles of both physics and biology.

In order to provide context for why electrical interactions are important in the operation of cells, we ask the following question: How crowded is a cell? In order to get a quick estimate

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of how much solvent a protein is surrounded by on average, take textbook⁸ values for the volume of a eukaryotic cell ($4 \times 10^{-9} \text{ cm}^3$) and the protein mass fraction (0.18) in a eukaryotic cell, and assume that the rest of the mass is water, thereby providing an upper bound for the amount of water per protein. A typical cell will be more crowded. A simple calculation reveals that a typical protein of mass $m_p = 50,000 \text{ u}$ will have a radius of about $24 \text{ \AA}$. [The density of water is 1 g/cm^3 and the average density⁹ of protein is $\rho_p = 1.43 \text{ g/cm}^3$ ($0.86 \text{ u/\AA}^3$). Because the volume of a roughly spherical protein will be

$v_p = 4\pi R_p^3/3 = m_p/\rho_p$, where R_p is the protein radius and m_p is the protein mass, one can solve to get $R_p = (3m_p/4\pi\rho_p)^{1/3}$.] On the other hand, the total volume of the cell divided by the average number of proteins in the cell leads to a separation distance of about $92 \text{ \AA}$ between two nearby proteins (assuming uniform distribution of proteins). Experimental studies of *E. coli* find comparable levels of crowding.¹⁰ Therefore, the average distance between the surfaces of two adjacent proteins is the separation between two protein centers (about $92 \text{ \AA}$) minus twice the typical protein radius (about $24 \text{ \AA}$), leading to a value of about $44 \text{ \AA}$. Goodsell has created visual representations with accurate scale of the crowded interior of cells.¹¹

Now we know that the cell is crowded—it is a dense mixture of charged heteropolymers and smaller molecules in a solution of water and ions. The operation of a cell relies on the mobility of the molecules. In particular, consider the proteins. It is understood that hydrophobic amino acids tend to reside away from the surface of proteins while charged or polar amino acids tend to reside near the surface. Consequently, one might expect so many non-functional electric interactions that proteins would by chance form many random clumps rather than reliably functional complexes (i.e. groups of proteins or RNA that assemble by means of secondary bonds and perform some distinct biological function). Is the problem as dire as just described? If so, how can this system possibly work?

Evidently the electrical interactions are kept under control. The question is, how is this done? A satisfactory answer can only come from the most basic laws of electrostatic interactions, namely, Maxwell's equations (for the specific case of static charges). As is often the case, this is easier said than done. However, it is possible to accomplish this goal. One finds that a proper accounting of all electrostatic interactions between all fixed charges (permanent partial charges including dipoles and higher-order moments of the charge distribution) and induced charges (water with its high dielectric constant is key in creating these) leads both to an overall reduction of the energy scale (ordinary screening) and to a general enhancement of repulsion due to an asymmetry between the repulsion of like charges and the attraction of opposite charges (asymmetric screening). The key factor in generating the induced charges responsible for this effect is the high dielectric constant of the miraculous solvent water, a material that has gotten a lot of attention but whose crucial role in enabling life has not yet been qualitatively and quantitatively encapsulated and thus has been under-appreciated.

II. A SIMPLE MODEL OF BIOMOLECULAR BINDING

It has long been recognized that in systems with inhomogeneous dielectric properties the laws of electromagnetism imply the existence of forces that tend to move objects with

relatively high dielectric constant into regions of relatively high electric field strength.^{12–15} The typical textbook example is that of a dielectric slab being sucked into a parallel-plate capacitor. It is energetically favorable for the dielectric material to move to a region of high field. In the context of biochemistry, water with its high dielectric constant plays the role of the dielectric slab in the capacitor example, and the charged biopolymers play the role of the capacitor plates. Unlike the capacitor plates, however, the charged biopolymers are also mobile. A qualitative sense of the physics involved can be gleaned from Figs. 1 and 2, which show sketches of the electric field lines in vacuum (or air) and water respectively. The electrical interactions in the presence of a high-dielectric-constant medium rearrange both the solvent and the molecules. Since most of our everyday experience involves air rather than water as the “solvent” medium, it is possible to be misled by intuition. In particular, a quantitative examination of a simple model system will demonstrate a rather surprising feature: the attractive interaction of opposite charges is severely suppressed as compared to the repulsive interaction of like charges—hence the term “asymmetric screening.”

The goal of this section is to illustrate the application of classical electrostatics to biomolecular interaction with minimal mathematical complexity, while still exhibiting the essential biological and physical features such as asymmetric screening. As such, it is hoped that this analysis will be suitable for advanced undergraduates. Returning to the textbook example of a parallel-plate capacitor drawing a slab of high dielectric material into the interplate region, one can imagine placing a single charge behind each plate (now non-conducting), immersing the plates in an unlimited reservoir of high dielectric fluid, and allowing the plates to move along the plate normal. This situation corresponds to the case of two molecules, each with an embedded charge, sufficiently close to each other so that the surfaces can be taken to be planar, and it has been examined in detail.¹⁶ As mentioned earlier, the actual cellular environment of such biomolecules includes not just the solvent (water) but also a certain concentration of ions (e.g., Ca^{2+}). In some instances, the presence of ions can lead to qualitatively different behavior.¹⁷ In the present situation, however, this would not be expected. Instead, one would expect the presence of ions simply to enhance the effectiveness of the solvent as a screening medium, reducing somewhat the overall energy scale without qualitatively changing the physical behavior.

As a model system, consider a region that has uniform thickness $2d$ in the z -direction, extends to infinity in the x and y directions, and is filled with dielectric fluid with dielectric constant ϵ_i (see Fig. 3). The regions on each side of the fluid are occupied by a half-space of dielectric with dielectric constant ϵ_e . Embedded rigidly within each of the half-spaces is a single point charge a fixed distance s from the interface with the slab. The line joining the two charges q_1 and q_2 is normal to both interfaces between the slab and the surrounding regions. The origin is located half way between the two point charges and the positive z -axis is oriented so it passes through point charge q_1 .

For $\epsilon_i \gg \epsilon_e$ (a reasonable assumption given that $\epsilon_i \approx 80$ for water and $\epsilon_e \approx 4$ for protein), this system can represent a simplified model of the close approach of two molecules with embedded charges in a water solution. In particular, the fluid could be a thin layer of water between two molecules that might (or might not) form a complex.

Although a clever application of the method of images (as will be clear later) or a surface charge method would provide paths to a solution, for the rather symmetric geometry under consideration, separation of variables in cylindrical coordinates (ρ, ϕ, z) offers the most straightforward method of solution for the potential Φ . The boundary conditions are:

1. $\Phi \rightarrow 0$ as $z \rightarrow \pm \infty$;
2. Φ is continuous at $z = \pm d$;
3. $\epsilon \frac{\partial \Phi}{\partial z}$ is continuous at $z = \pm d$.

A solution of Laplace's equation will be needed in each region and the potential of a point charge will be needed in the half spaces to form a solution of Poisson's equation.

The relevant general solution of Laplace's equation has Bessel functions in the radial coordinate ρ , exponentials in the z coordinate, and trigonometric functions in the angular coordinate ϕ so that¹⁸

$$\Phi = \sum_{m=0}^{\infty} \int_0^{\infty} J_m(k\rho) [a(k)e^{kz} + b(k)e^{-kz}] [c(m)\sin m\phi + d(m)\cos m\phi] dk. \quad (1)$$

By azimuthal symmetry, only the $m = 0$ term is needed and the general solution of Laplace's equation becomes

$$\Phi = \int_0^{\infty} J_0(k\rho) [a(k)e^{kz} + b(k)e^{-kz}] dk. \quad (2)$$

In the two outer regions we need to add to the solution of Laplace's equation the potential of a point charge located at $\rho' = 0$ and $z' = \pm(d+s)$ to create a solution to Poisson's equation. The appropriate form of the point charge potential is¹⁹

$$\Phi_{pc}(\rho, z) = \frac{q}{\epsilon(\rho'=0, z') \sqrt{\rho^2 + (z - z')^2}} = \frac{q}{\epsilon(\rho'=0, z')} \int_0^{\infty} e^{-k|z-z'|} J_0(k\rho) dk. \quad (3)$$

Combining Eqs. (2) and (3) and using boundary condition 1 in the two outer regions leads to the potentials in the upper, lower, and middle regions, given respectively by

$$\Phi_1 = \int_0^{\infty} B_1(k) e^{-kz} J_0(k\rho) dk + \frac{q_1}{\epsilon_e} \int_0^{\infty} e^{-k|z-d-s|} J_0(k\rho) dk, \quad (4)$$

$$\Phi_2 = \int_0^{\infty} A_2(k) e^{kz} J_0(k\rho) dk + \frac{q_2}{\epsilon_e} \int_0^{\infty} e^{-k|z+d+s|} J_0(k\rho) dk, \quad (5)$$

$$\Phi_0 = \int_0^{\infty} [A_0(k) e^{kz} + B_0(k) e^{-kz}] J_0(k\rho) dk. \quad (6)$$

Application of the remaining boundary conditions leads to algebraic equations for B_1 , A_0 , B_0 , and A_2 that can be solved to obtain

$$B_1(k) = e^{k(d-2s)} \frac{e^{ks}(\varepsilon_i + \varepsilon_e)(\varepsilon_i - \varepsilon_e)q_1 - e^{k(4d+s)}(\varepsilon_i - \varepsilon_e)(\varepsilon_i + \varepsilon_e)q_1 + 4e^{k(2d+s)}\varepsilon_i\varepsilon_eq_2}{-\varepsilon_e(\varepsilon_i - \varepsilon_e)^2 + e^{4kd}\varepsilon_e(\varepsilon_i + \varepsilon_e)^2}, \quad (7)$$

$$A_0(k) = 2e^{k(d-2s)} \frac{e^{k(2d+s)}(\varepsilon_i + \varepsilon_e)q_1 + e^{ks}(\varepsilon_i - \varepsilon_e)q_2}{-(\varepsilon_i - \varepsilon_e)^2 + e^{4kd}(\varepsilon_i + \varepsilon_e)^2}, \quad (8)$$

$$B_0(k) = 2e^{k(d-2s)} \frac{e^{ks}(\varepsilon_i - \varepsilon_e)q_1 + e^{k(2d+s)}(\varepsilon_i + \varepsilon_e)q_2}{-(\varepsilon_i - \varepsilon_e)^2 + e^{4kd}(\varepsilon_i + \varepsilon_e)^2}, \quad (9)$$

$$A_2(k) = e^{k(d-2s)} \frac{4e^{k(2d+s)}\varepsilon_i\varepsilon_eq_1 - e^{k(4d+s)}(\varepsilon_i + \varepsilon_e)(\varepsilon_i - \varepsilon_e)q_2 + e^{ks}(\varepsilon_i - \varepsilon_e)(\varepsilon_i + \varepsilon_e)q_2}{-\varepsilon_e(\varepsilon_i - \varepsilon_e)^2 + e^{4kd}\varepsilon_e(\varepsilon_i + \varepsilon_e)^2}, \quad (10)$$

The full potential that solves our problem is then obtained by substituting these coefficients into Eqs. (4)–(6).

To understand what happens in the biological system, we need to compute the energy and then find the force that pushes the charged half-spaces together or apart. The energy in a system with both free and induced charges is

$$U = \frac{1}{2} \int \rho_f(\vec{r}) \Phi(\vec{r}) d\vec{r}, \quad (11)$$

where ρ_f is the free charge density—the point charges in our case—and Φ is the full potential. In the case at hand, we have a discrete distribution of free charges so the integral becomes a sum

$$U = \frac{1}{2} \int \rho_f(\vec{r}) \Phi(\vec{r}) d\vec{r} = \frac{q_1}{2} \Phi'_1(\rho=0, z=d+s) + \frac{q_2}{2} \Phi'_2(\rho=0, z=-d-s), \quad (12)$$

where Φ' indicates that the term in the potential that would create an infinite self-energy has been excluded. Using our solution for the potential, we find

$$U = \frac{4q_1q_2\varepsilon_i}{(\varepsilon_i + \varepsilon_e)^2} \int_0^\infty \frac{e^{-k(2d+2s)}}{1 - \alpha^2 e^{-4kd}} dk + \frac{(q_1^2 + q_2^2)\alpha}{2\varepsilon_e} \int_0^\infty \frac{e^{-2ks}(e^{-4kd} - 1)}{1 - \alpha^2 e^{-4kd}} dk, \quad (13)$$

where $\alpha = (\varepsilon_i - \varepsilon_e)/(\varepsilon_i + \varepsilon_e)$. All of the integrals are of the same form and can be evaluated using

$$\int_0^\infty \frac{e^{-ck}}{1 - a^2 e^{-bk}} dk = \sum_{n=0}^\infty \frac{a^{2n}}{c + bn}. \quad (14)$$

This result is obtained by expanding the denominator in a geometric series and integrating term by term. The final expression for the energy is therefore

$$U = \frac{4q_1 q_2 \varepsilon_i}{(\varepsilon_i + \varepsilon_e)^2} \sum_{n=0}^{\infty} \frac{\alpha^{2n}}{2d + 2s + 4dn} + \frac{(q_1^2 + q_2^2)}{2\varepsilon_e} \sum_{n=0}^{\infty} \alpha^{2n+1} \left(\frac{1}{4d + 2s + 4dn} - \frac{1}{2s + 4dn} \right). \quad (15)$$

This energy can be interpreted as the collective effect of an infinite set of image charges, and as mentioned the method of images could have been used to arrive at this result. However, the image method would not be available for more complicated geometries.

Since we imagine the internal layer to be water that can be drawn into or squeezed out of the region between the two molecules, we are interested in how the system behaves as the separation $2d$ varies. Therefore, the force that is of interest has magnitude

$$F = \frac{1}{2} \frac{\partial U}{\partial d}, \quad (16)$$

where positive (negative) values means the molecules are being pushed apart (together). Evaluating the derivative of U gives

$$F = \frac{4q_1 q_2 \varepsilon_i}{(\varepsilon_i + \varepsilon_e)^2} \int_0^{\infty} e^{-k(2d+2s)} k \frac{1 + \alpha^2 e^{-4kd}}{(1 - \alpha^2 e^{-4kd})^2} dk + \frac{(q_1^2 + q_2^2)}{\varepsilon_e} \alpha (1 - \alpha^2) \int_0^{\infty} \frac{e^{-k(2s+4d)} k}{(1 - \alpha^2 e^{-4kd})^2} dk. \quad (17)$$

In interpreting the results, we will temporarily adopt the custom of some biologists who choose to decompose the electrical interaction into various parts. It should be remembered, however, that in terms of actual physics the electrical force is a single unified entity. The decomposition can be represented by the equation

$$F = F_C + F_S + F_P, \quad (18)$$

where F_C is called the Coulomb interaction, F_S is called the solvation, and F_P is called the joint polarization. The term “Coulomb interaction” is used to refer only to the direct interaction of the free charges and the induced charge located right at the location of the free charges as if the charges were in an infinite water solution. The term “solvation” refers to the portions of the electrostatic energy that arise from the interaction of each individual charge with the solvent; these are the q_1^2 and q_2^2 terms (as opposed to the $q_1 q_2$ term). This effect exists even when there is only one charge and has been understood in simple geometries since Born.²⁰ The remainder of the electrical interaction does not have a customary name, probably because it is often difficult to calculate properly. Here we refer to it as the “joint polarization” term because it is a polarization effect that arises from both charges, as opposed to the solvation term that arises from a single charge. Together, solvation and joint polarization produce an effect we call *asymmetric* screening because the screening effect is highly asymmetric with respect to changing the sign of one of the charges.

Figure 4 shows a dimensionless force F/F_w , where $F_w = (q_1 q_2) / [\varepsilon_i (2s + 2d)^2]$, between the two nearby molecules as a function of the dimensionless separation d/s between the charges, using $|q_1| = |q_2| = 1$, $\varepsilon_i = 80$, and $\varepsilon_e = 1$. The ordinate F/F_w is the ratio of the actual force to

the force that would be obtained if the two charges were embedded in an infinite water medium. This quantity therefore reflects the degree to which the actual force deviates from the more basic and intuitive result for point charges in an infinite medium. The most obvious feature of this graph is that the attractive force between opposite charges is dramatically suppressed compared to the repulsive force between like charges, a result of solvation and joint polarization both opposing the bare Coulomb interaction in the case of opposite charges. One can see from Fig. 4 that while the Coulomb and joint polarization forces both change sign when going from like charges to unlike charges, the solvation force remains exactly the same—the fact that the solvation force remains repulsive in both situations is at the heart of this asymmetric screening.

In the case of like charges, all three elements of the force are repulsive at very small separations, while at slightly larger (and more interesting) separations the bare Coulomb and solvation portions of the force still act repulsively but are somewhat attenuated by the joint polarization. While solvation is the main correction to the bare Coulomb force at small separations, joint polarization is the main correction at larger separations.

Caution must be used when interpreting the results at very small separation. Suppose that the length s at which the point charges q_1 and q_2 are embedded in their respective molecules is comparable to the size of an amino acid (about 10 Å). Even though the mathematical results are correct at all separations, the model is not relevant to biology if the solvent layer is a fraction of a water molecule in thickness. Therefore, when considered as a model of biomolecular binding, the region $d/s < 1/2$ should be disregarded as it is not biologically accessible.

Importantly, the behavior of this simple model of biomolecular interaction is actually quite general and is by no means restricted to the simplified geometry examined here. The present model is the limit of two spheres quite close to each other with charges embedded near the surface. With the help of a surface charge method²¹ that is both direct and intuitive, it is possible to demonstrate the same behavior for the more general spherical geometry.²² As in the present model, the exact calculation of the electrical interactions shows that repulsive forces are enhanced compared to attractive forces, which are markedly suppressed. And, of course, numerical methods can be employed for systems lacking symmetry.

III. WATER SAVES THE DAY

Electrostatic interactions should be considered in a unified framework. The arbitrary separation of electrostatic effects into several terms only makes accurate calculations harder, not easier. Still, given that there are several portions of the electrostatic interaction that are sometimes thought of separately, it is of some conceptual benefit to learn how they arise from Maxwell's equations and to see how they manifest themselves in biological contexts.

As mentioned above, a cell consists of many charged biomolecules crowded together in a polar solvent. In particular, a cell has a high density of charged biopolymers. The most obvious portion of the electrical force is the interaction of the bare partial charges without any polarization or dielectric response. This is sometimes rather misleadingly referred to as the Coulomb interaction. In fact, it is the Coulomb interaction of only a handful of the

physical charges in the system. This portion of the electrostatic force leads to the paradox mentioned in the first section. On first inspection, these interactions would seem likely to cause the entire cell to seize up.

However, another relatively well-known aspect of the electrostatic interaction, namely regular dielectric screening, lowers the binding energy for all of the bare interactions between partial charges. For example, a pair of charges of magnitude e (the electron charge) separated by a nanometer has electrostatic energy $U = 1.43 \text{ eV} = 57k_B T$ (at room temperature) while the same system in an infinite water medium ($\epsilon \approx 80$) has $U = 1.8 \times 10^{-2} \text{ eV} = 0.7k_B T$. This effect is not very intuitive because most of our experience is at the macroscopic scale in which air is the usual medium; the effect is then not noticeable. The presence of water acts to reduce the interaction energy down to the scale of thermal energy. Nevertheless, if two macromolecules have several pairs of matching charges near their surfaces, their cumulative effect can still be quite large, thereby allowing binding to occur.

The example above demonstrates that asymmetric screening is more subtle than regular dielectric screening and has vital implications for cellular processes. While regular dielectric screening helps prevent random binding and aids the movement of molecules around the cell, the additional effect of asymmetric screening allows the attractive interactions that bind complexes or fold proteins to have their effect.

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FIG. 1. Two biomolecules with equal and opposite charges in vacuum: (a) small separation and (b) larger separation. When the separation is larger more of the high-field area is in vacuum; thus, the configuration in (a) is energetically more favorable and there is an attractive force.

FIG. 2.

Two biomolecules with equal and opposite charges in water: (a) small separation and (b) larger separation. When the separation is larger more of the high-field area is in the high-dielectric solvent; thus, the configuration in (b) is energetically more favorable and there is a repulsive force.

FIG. 3.

The model analyzed in this paper consists of two point charges q_1 and q_2 symmetrically placed on the z -axis. The point charges are embedded rigidly in a medium with dielectric constant ϵ_e and are separated by a layer of high-dielectric-constant fluid ($\epsilon_i > \epsilon_e$) of variable thickness $2d$, symmetrically placed with respect to the xy -plane. The point charges are a distance s from the fluid layer.

FIG. 4.

The total force and its constituent parts between two half-spaces with charges fixed within them and separated by a variable region of high-dielectric material sandwiched between them. The force is parallel to the z -axis; positive (negative) values represent repulsion (attraction). The calculations are for $|q_1| = |q_2| = 1$, $\epsilon_i = 80$, and $\epsilon_e = 1$. Thick lines are for charges equal in sign, while thin lines are for charges opposite in sign. The curves for the solvation force are identical and therefore appear as one. Applicability of the calculation to molecular contact requires a layer of water at least a couple of molecules thick. Therefore, attention should be restricted to the region for which $d/s > 0.5$.