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Modeling Salt Dependence of Protein-Protein Association: Linear vs Non-Linear Poisson-Boltzmann Equation

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Abstract. Proteins perform various biological functions in the cell by interacting and binding to other proteins, DNA, or other small molecules. These interactions occur in cellular compartments with different salt concentrations, which may also vary under different physiological conditions. The goal of this study is to investigate the effect of salt concentration on the electrostatic component of the binding free energy (hereafter, salt effect) based on a large set of 1482 protein-protein complexes, a task that has never been done before. Since the proteins are irregularly shaped objects, the calculations have been carried out by a means of finite-difference algorithm that solves Poisson-Boltzmann equation (PB) numerically. We performed simulations using both linear and non-linear PB equations and found that non-linearity, in general, does not have significant contribution into salt effect when the net charges of the protein monomers are of different polarity and are less than five electron units. However, for complexes made of monomers carrying large net charges non-linearity is an important factor, especially for homo-complexes which are made of identical units carrying the same net charge. A parameter reflecting the net charge of the monomers is proposed and used as a flag distinguishing between cases which should be treated with non-linear Poisson-Boltzmann equation and cases where linear PB produces sound results. It was also shown that the magnitude of the salt effect is not correlated with macroscopic parameters (such as net charge of the monomers, corresponding complexes, surface and number of interfacial residues) but rather is a complex phenomenon that depends on the shape and charge distribution of the molecules.

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Key words: Poisson-Boltzmann equation, electrostatics, protein-protein complexes, salt-dependence of binding energy, finite-difference Poisson-Boltzmann method.

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1 Introduction

The electrostatic potential in media containing mobile charged particles obeys the Poisson-Boltzmann equation [1–3]. Examples of such media include colloidal systems [4, 5], macromolecules [1, 2, 6, 7], and membranes [8–10] in a physiological liquid with a non-zero concentration of mobile ions (non-zero ionic strength, I). While in the case of simple geometry, it is possible to obtain an analytical solution of the Poisson-Boltzmann equation, most of the practical cases do not fall into this category. This is especially true in the case of biological macromolecules in solution with a non-zero ionic strength that represents a system with multiple dielectric regions separated by irregularly shaped boundaries. Solving the Poisson-Boltzmann equation in this case requires numerical techniques such as finite-difference methods [11–13].

Modelling the interactions of biological macromolecules in a solution containing mobile ions is an important task that allows for an understanding of the mechanisms of protein-protein binding [14–16]. Among the forces driving the association of macromolecules, the electrostatic force is primarily affected by the ion "atmosphere" and thus at the first order of approximation, the salt dependence of the binding free energy could be considered purely electrostatic in origin (see Ref. [17] for detailed discussion). Therefore, calculating the change of the electrostatic binding free energy component as a function of the ionic strength provides a good estimate of the sensitivity of protein-protein interactions to the concentration of mobile ions.

It was shown in the past that the binding free energies associated with the formation of macromolecular complexes are generally extremely sensitive to ionic strength. For example, the binding of proteins to nucleic acids and to the surface of membranes containing anionic phospholipids exhibits a strong salt dependence that has been extensively studied both experimentally and theoretically [9, 18, 19]. The underlying principles are well-understood, and the calculated salt dependence of binding free energies based on the non-linear Poisson-Boltzmann equation (NLPB) are generally in remarkable agreement with experimental measurements. The salt-dependence of protein-protein interactions has also been studied experimentally [20–23], and it has generally been found that increases in ionic strength weaken binding affinities. The linear Poisson-Boltzmann equation (LPB) has been applied with considerable success on calculations of protein-protein binding free energies [14, 24] and on studying the salt dependence of the association rate constant [15, 25]. However, systematic studies of the salt effect on the binding free energy of protein-protein complexes using LPB and NLPB on a large scale of examples are absent from the scientific literature.

From the electrostatic standpoint, biological systems can be grouped into two categories: (a) systems with entities carrying large net charge such as protein-DNA/RNA and protein-membrane complexes and (b) systems that generally do not carry a large net charge such as protein-protein complexes. Nucleic acid or phospholipids have a large and fairly uniform negative charge density which results in a large accumulation of positively charged counter-ions in the vicinity of DNA/RNA [18,26] and phospholipid mem-