New and Notable

The Iso-Competition Point, a New Concept for Characterizing Multivalent versus Monovalent Counterion Competition, Successfully Describes Cation Binding to DNA

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Counterion condensation theory has a long and successful record of explaining the experimental and simulated data obtained for polymer polyelectrolytes and their counterions (Manning and Ray, 1998). Despite its success over nearly the past 20 years, it has been criticized as being far too primitive a description of polyelectrolyte systems: a charged rod of infinite length immersed in a salt solution at zero concentration. Nevertheless, in recent years there have been a number of reports independently validating some of the equations resulting from counterion condensation theory using mathematical analysis of the Poisson-Boltzmann equation, which provides a more detailed description of counterion binding (Manning and Ray, 1998). The durability of counterion condensation theory attests to its power to explain polymer polyelectrolyte-salt interactions simply.

Arguably the most important biological polyelectrolyte is DNA. There is a long history of successful application of counterion condensation theory to DNA as a polyelectrolyte in a single or two species salt solution. However, there have been few practical physical insights provided by simple counterion condensation theory in such studies. In the spirit of making counterion condensation theory more widely applicable, Li and Marx's paper in this issue has finally accomplished this goal (Li and Marx, 1999). It describes the competitive binding of multivalent cations versus monovalent cations to a DNA polyion, through an exhaustive numerical study of Manning's two-variable counterion condensation theory to which the constraint of monovalent (1) to multivalent (Z) charge neutralization equivalence ($\theta_1 = Z\theta_z$) has been added. Part of the original contribution here is the authors' definition of the critical concept of the iso-competition point (ICP). ICP_z is the Z-valent cation concentration at which monovalent cations neutralize the same phosphate charge level as do the Z-valent cations, under a fixed ionic strength condition. With the ICP representing the boundary point separating the two DNA phosphate neutralization regimes, one dominated by monovalent cations, the other by multivalent cations, the numerical simulations of ICP allow the overall cation competition binding environment to be simplified conceptually in a single parameter. The authors have carried out extensive simulations that reveal a number of interesting dependencies. The effect of ionic strength I on ICP_z for a Z-charged multivalent cation is $ICP_z = A_z I^Z$, where A_z is a constant. This was observed for divalent, trivalent, and tetravalent cation simulations, which compared well with the authors' previous experimental data. Over 2–3 logs' concentration of ICP_{di}, ICP_{tri}, and ICP_{tetra} values are presented versus the total charge neutralization level on DNA. The critical collapse point (CCP) is the trivalent cation concentration at which point DNA undergoes a conformational transition to a condensed, largely toroidal shape (Marx and Ruben, 1983). ICP_{tri} and CCP_{tri} are presented in relation to ionic strength and to each other. The authors employ a unique icon graphic to visualize the two separate DNA charge neutralization regions delineated by the ICP boundary.

One of the attractive features of these simulations and the ICP concept is that they can be utilized in the design of experiments, the interpretation of experiments, or both. To illustrate the promise of this approach, the authors present a number of complete sets of simulations, over 4.5 logs multivalent concentration, of two cation species competition systems, the monovalent/divalent and the monovalent/trivalent, where monovalent cation concentrations have been fixed at the buffer values of the authors' previously published experimental results (Li et al., 1998). For gel electrophoresis or other experiments involving DNA in the presence of multivalent/monovalent cation competition systems, at or in the range of these monovalent concentrations, these simulations could provide valuable experimental design or interpretive guidance. For the former, simulations would allow experimenters to design their specific cation environment (i.e., dominant in monovalent or multivalent cation binding) before doing experiments. As a practical example of the latter, in another report (Li et al., 1997), the authors measured the mobility reductions (μ/μ_o) observed for λ-DNA-*Hind*III fragments ranging from 23.13 to 2.027 kb, due to interactions with varying concentrations of Ca^{2+} (0–40 μM) in Tris-borate buffer. They observed the normalized mobility reduction to be shifted by a small amount $\Delta(\mu/\mu_o)$ relative to the Manning counterion condensation predicted value. The $\Delta(\mu/\mu_o)$ values were found to be a function of DNA length and the ion environment. Interestingly, the $\Delta(\mu/\mu_o)$ values were observed to be significant only where the divalent cation began to dominate the DNA phosphate neutralization, near the calculated ICP_{di}. Here, it is clear that the value of simulating the exact cation environment in this two-cation system allows for an interpretation of the data that would otherwise be impossible.

Li and Marx have performed carefully crafted simulations to implement counterion condensation theory. They have successfully applied cation binding in a two-component system to their DNA experimental data, demonstrating agreement and producing easily accessible new methods. This paper presents useful concepts in utilizing counterion condensation theory as well as quantitative measures such as the

iso-competition point, ICP, and the critical collapse point, CCP, that can predict or explain experimental results.

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