Selective binding of a metal ion to a protein site is a common post-translational modification and is the basis for generating proteins that are involved in, for example, catalysis, selective metal transport, or metal-dependent transcription factors. In a step towards the larger challenge of understanding the role of metals in biomaterials, here we address selective metal binding in the KcsA K+ ion-channel protein. Selectivity depends on both ion-protein interactions and the hydration of ions in the aqueous phase; we will discuss each of these in turn.

Ion-residue interactions are strong on a thermal energy scale and it is common to study ion-protein interactions within a local neighborhood, the binding site, around the ion. We adopt this strategy and express the excess chemical potential of the ion as a function of the various coordination states of the ion in the site. The simulation data interpreted within this framework leads to the finding that the coordination state that is most relevant to the thermodynamics of the ion is also one for which the binding site is least distorted. Further, selectivity arises due to contributions beyond the mean-field to the excess chemical potential of the ion; these fluctuation contributions depend sensitively on the excess internal energy of the binding site and highlight the role of chemistry of ligands in selectivity. By contrasting the results with those for a semi-synthetic analog of KcsA and valinomycin, a small ionophore, we elucidate the essential role of the bulk protein in selectivity and the conditions under which a local model of selectivity is suitable.

We next consider hydration of ions in the bulk aqueous phase on the basis of multi-state models. For the monovalent ions that we have studied, we find that only a subset of water molecules in the first hydration shell of the ion sense the chemical type of the ion. Further, these core-water molecules tend to attenuate the interaction of the ion with the rest of the medium, and thus the higher coordination states of the ion more sensitively reflect density fluctuations of the solvent medium at the size scale of the observation volume. The relevance of this development to the question of coordination states in selective binding of ions to biological molecules in indicated.