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Accurate pKa Computation Using Matched Interface and Boundary (MIB) Method Based Poisson-Boltzmann Solver

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Abstract. The pK_a values are important quantities characterizing the ability of protein active sites to give up protons. pK_a can be measured using NMR by tracing chemical-shifts of some special atoms, which is however expensive and time-consuming. Alternatively, pK_a can be calculated numerically by electrostatic free energy changes subject to the protonation and deprotonation of titration sites. To this end, the Poisson-Boltzmann (PB) model is an effective approach for the electrostatics. However, numerically solving PB equation is challenging due to the jump conditions across the dielectric interfaces, irregular geometry of the molecular surface, and charge singularities. Our recently developed matched interface and boundary (MIB) method treats these challenges rigorously, resulting in a solid second order MIBPB solver. Since the MIBPB solver uses Green's function based regularization of charge singularities by decomposing the solution into a singular component and a regularized component, it is particularly efficient in treating the accuracy-sensitive, numerous, and complicated charge distributions from the pK_a calculation. Our numerical results demonstrate that accurate free energies and pK_a values are achieved at coarse grid rapidly. In addition, the resulting software, which pipelines the entire pK_a calculation procedure, is available to all potential users from the greater bioscience community.

AMS subject classifications: 92C40, 35J66

Key words: pKa, acid dissociation constant, Poisson-Boltzmann, finite difference, charge singularity.

1 Introduction

The acid dissociation constant K_a is a quantitative measure of the strength of an acid in solution, which is usually written as a quotient of the equilibrium concentrations as

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$$K_a = \frac{[H^+][A^-]}{[HA]},$$

where [HA], [A^-], and [H^+] are concentrations of the acid, its conjugate, and proton in mol/L. The value $pK_a = -\log_{10} K_a$ is the co-logarithm of acid dissociation constant, which measures the tendency for a group to give up a proton. The smaller the value of pK_a, the more likely the acid is going to lose a proton, i.e. the stronger the acid is. Since proteins are chains of amino acids, the protonation or deprotonation of the titration sites (strongly polar amino acids) plays significant roles in binding affinities, enzymatic activities, and structural properties [1].

Since pK_a values are of significance to many biomolecular processes, their accurate measurement/calculation are practically important. For a short review, pK_a values can be measured by the following approaches.

Titration graph of acid-base reaction. The Henderson-Hasselbach equation shows $pH = pK_a + \log_{10}\left(\frac{[A^-]}{[HA]}\right)$. Thus pK_a=pH when [HA]=[A^-], which happens at half way of the titrant needed for reaching the equivalence point, i.e. the pH for which the site is 50% occupied. For a simple acid (e.g. the acetic acid), we can trace the pH during the titration process while adding base and then locate the pK_a on the titration curve.

NMR spectra. For proteins, however, pK_a of a titration site on a particular residue is hard to measure with acid-base reaction. NMR spectra in terms of chemical shifts are thus recorded as a function of pH [2,3]. The information of the chemical shift can indicate at which pH value the interested site is half-way protonated, and the corresponding pH is the desired pK_a.

Computer simulation. Since pK_a is associated with the thermodynamics of the acid dissociation [4], its values can also be predicted theoretically assisted with computer simulations. Various theoretical methods have been reported in literature including 1) Poisson-Boltzmann (PB) model [5–16], 2) Molecular Dynamics (MD) [17], 3) Monte Carlo (MC) method [18], 4) QM/MM (ab initio QM for the titratable residue and MM for the rest of the protein environment) [19], and 5) Empirical approaches [20,21].

We will focus on the PB model based pK_a computation, which assumes that the protonation or deprotonation asserts limited effect to the protein structure, and it is the titration states that bring the changes in electrostatic free energies. Under this assumption, one molecular structure is used for all titration states. The pK_a computation amounts to numerically solve PB equation for many times with different charge distributions, while repeatedly uses the same protein structure related information such as interface, mesh, elements, etc. This calls for an efficient and accurate PB solver.

However, numerically solving PB equation is challenging due to the jump conditions across the dielectric interface, irregular geometry of the molecular surface, and charge singularities. Although numerous PB solvers have been developed in the literature, the Matched Interface and Boundary method based Poisson-Boltzmann (MIBPB)