Robust Optimization of Electrostatic Interactions Between Biological Molecules

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Summary

We have developed a computationally efficient method for optimizing electrostatic interactions between biological molecules such as proteins. These optimizations offer valuable insights into the means by which molecules recognize one another, binding their targets tightly and yet not binding other molecules. Drug design processes can also be guided by biomolecule electrostatic optimization. Although the optimization approach was originally described almost ten years ago, its applications have been relatively few in number; one of the most important limiting factors has been the significant amount of required computer time. Our previous work had demonstrated the viability of a much faster approach, which unfortunately suffered from occasional numerical instabilities. Our results this year demonstrate how to stabilize this approach and thereby open up several important avenues for studying molecular recognition processes.

The inside of a cell is a crowded environment, consisting of a complex mixture of thousands of proteins, DNA, RNA, and other molecules, all of which are surrounded by millions of water molecules and mobile ions. Life, as we know it, simply could not exist if the biological molecules all interacted strongly with one another. Instead, the vast majority bind to only a small number of other kinds of molecules. In biology, the mechanisms underlying the specificity of binding events are commonly termed *molecular recognition* processes.

Our research focuses on the electrostatic aspects of molecular recognition. Most bonds between atoms are "asymmetric;" that is, the atoms do not share their bonded electrons equally. As a result, most biomolecules contain a distribution of charge distinct to their chemical species. As two molecules approach one another, these distributions interact increasingly strongly, and the interaction between the charge distributions can have a strong impact on whether the molecules bind or not.

Predicting the strength of the electrostatic interactions between two molecules is a challenging task, because the surrounding solvent molecules are in constant motion, interacting with the biomolecules as well as each other. We use one popular and well-tested model that approximates these interactions using continuum electrostatic theory in which the molecular charge distributions are modeled with discrete point charges, and the electrostatic potential satisfies a linear partial differential equation (PDE). Under reasonable assumptions, the molecular charge distributions contribute

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quadratically to the overall binding free energy. When designing a drug, one considers the target charge distribution to be fixed, and then the electrostatic component of the binding energy is a function with a unique *global* optimum. Calculating "optimal charge distributions" has allowed the design of tighter-binding drugs and the analysis of protein—protein interactions. Because these optimizations require a great amount of computer time, however, the application of the charge optimization method has been limited.

Several years ago, we introduced a more efficient method for solving charge optimization problems, which unfortunately suffered from numerical instabilities. This year, we have stabilized the optimization technique by reformulating the PDE problems to allow us to rapidly approximate how different charges affect the energy. These approximations allow the design of penalty functions that help the optimizer avoid charge distributions that are physically unreasonable, but numerically favorable given the inherent inaccuracies introduced by solving the PDE on a computer with limited memory. Our latest results agree well with other optimization techniques and analyses (see Figure 2).

The regularization method highlights a subtle but vital aspect of numerical simulation. There exist multiple approaches for simulating the electrostatic problem, which are equivalent in most respects but significantly different in their capability to be solved approximately. Applied mathematics research is central to resolving questions of this type.

Our current research focuses on characterizing the electrostatic properties of small molecules that bind optimally to their target proteins, and the inverse problem of characterizing the target proteins. The answers to these questions will be important for therapeutic drug research, for the design of advanced biochemical probes, and for engineering cells for bioremediation and energy storage.

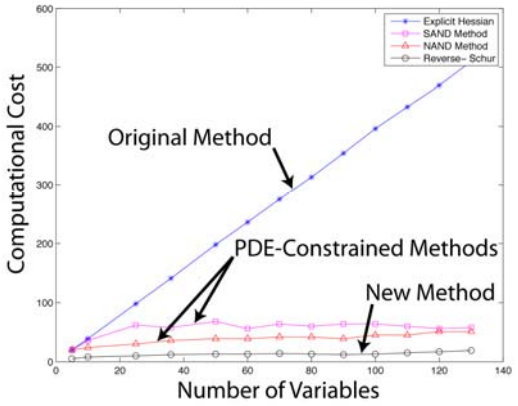

Figure 1. The new optimization technique outperforms other available methods.

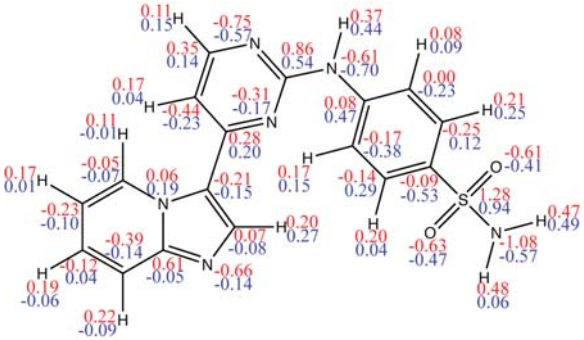

Figure 2. The designed charges of a small-molecule inhibitor closely match the charges derived from ab initio quantum mechanical simulations; this indicates that the inhibitor is nearly optimal.

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