Efficient Optimization of Electrostatic Interactions Between Biomolecules

Jaydeep P. Bardhan, Michael D. Altman, Jacob K. White, Bruce Tidor

***Abstract*— We present a PDE-constrained approach to optimizing the electrostatic interactions between two biomolecules. These interactions play important roles in the determination of binding affinity and specificity, and are therefore of significant interest when designing a ligand molecule to bind tightly to a receptor. Using a popular continuum model and physically reasonable assumptions, the electrostatic component of the binding free energy is a convex, quadratic function of the ligand charge distribution. Traditional optimization methods require exhaustive pre-computation, and the expense has precluded a full exploration of the promise of electrostatic optimization in biomolecule analysis and design. In this paper we describe an approach in which the electrostatic simulations and optimization problem are solved simultaneously; unlike many PDE-constrained optimization frameworks, the proposed method does not incorporate the PDE as a set of equality constraints. This *co-optimization* approach can be used by itself to solve unconstrained problems or those with linear equality constraints, or in conjunction with primal–dual interior point methods to solve problems with inequality constraints. Model problems demonstrate that the co-optimization method is computationally efficient and that it can be used to solve realistic problems.**

I. INTRODUCTION

The electrostatic interactions between biomolecules can play important roles in determining binding affinities and specificities [1]–[3]. Methods for estimating these interactions are therefore important computational tools [1], [4]. The task of estimation is challenging because electrostatic interactions are long-range and involve many solvent water molecules around the biomolecules of interest. Computational approaches that treat the solvent explicitly, such as Monte Carlo or molecular dynamics methods [5]–[9] are often prohibitively expensive, and therefore implicit solvent models [10] based on macroscopic, continuum electrostatic theory are frequently used [1], [3], [11], [12]. Frequently, these models treat the solvent and solute as homogeneous dielectric media and the solute charge distribution is treated as a set of discrete point charges.

The estimated electrostatic energies are frequently useful in molecular design efforts, in which one often wishes to design a molecule, called a *ligand*, that can bind a specified target, or *receptor*, with high affinity and specificity. Binding free energies between candidate ligands and the target can be estimated using quite sophisticated methods (see, for example, [13]). However, for computational expediency the relative free energies of binding are often modeled much more simply as sums of electrostatic and non-electrostatic terms [14]. In these simpler models, the non-electrostatic interactions between molecules are extremely short-ranged, and not particularly variable with respect to the types of atoms at the interface. Consequently, shape complementarity at the binding site is thought to be necessary but not sufficient for achieving tight binding. In contrast, the electrostatic forces between molecules are long-range and can have significant effects on the binding interaction. Therefore, one promising approach for improving computational molecular design methodologies is to identify a ligand charge distribution, or multiple distributions, that have optimal electrostatic interactions with the target. Such knowledge may suggest regions of design space that will have a relatively high density of compounds that would be predicted to bind tightly.

A rigorous optimization theory, based on linear-response theory, has been developed to identify optimal charge distributions for molecular design and analysis [15]–[18]. Lee and Tidor were the first to investigate the possibility of optimizing a ligand molecule's charge distribution for binding to a target receptor [15]. They based their study on analytically solvable spherical geometries and a multipole representation of the ligand charge distribution. A series of papers by Kangas and Tidor extended the optimization theory [16]–[18], demonstrating that the ligand-dependent component of the binding free energy is a convex quadratic function of the ligand charges for more general molecular geometries and charge distributions. A number of groups have applied and explored the theory in contexts ranging from cation-binding studies to protein–protein interface redesign [19]–[29]. A notable validation of the charge optimization approach was reported by Mandal and Hilvert [30], who modified a known inhibitor of *B. subtilis* chorismate mutase to verify the charge-optimization analysis of Kangas and Tidor [22]. The modified ligand yielded the expected improvement over the original and represented the tightest binder measured to date [30].

Despite these promising results, however, exploitation of

This work was supported by the National Institutes of Health (GM065418), by the Singapore-MIT Alliance, and by the National Science Foundation. J. P. Bardhan gratefully acknowledges support from a Department of Energy Computational Science Graduate Fellowship and a Wilkinson Fellowship in Scientific Computing funded by the Mathematical, Information, and Computational Sciences Division Subprogram of the Office of Advanced Scientific Computing Research, Office of Science, U. S. Dept. of Energy, under Contract DE-AC02-06CH11357.(jbardhan@mcs.anl.gov)

J. P. Bardhan is with the Mathematics and Computer Science Division of Argonne National Laboratory.

M. D. Altman is with the Department of Chemistry, Massachusetts Institute of Technology.

J. K. White is with the Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology.

B. Tidor is with the Biological Engineering Division and the Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology.

the electrostatic optimization framework has been somewhat hampered by the computational expense of setting up the optimization problem. The Hessian matrix, which completely describes the curvature of the objective function, requires an expensive pre-computation whose cost scales linearly with the number of optimization variables. This paper presents an approach to solving these optimization problems without explicitly calculating the Hessian matrix. This approach, which we call co-optimization, resembles some PDE-constrained optimization methods such as that of Biros *et al.* [31], but differs significantly from previously presented strategies. The next section provides background on biomolecule electrostatics, a method for numerical simulation of electrostatic problems, and the electrostatic optimization theory. Section III describes the new coupled optimization/simulation method and contrasts it with the traditional approach and other PDE-constrained optimization techniques. Section IV presents a set of numerical results demonstrating the computational efficiency of the new method and its application to a realistic molecular design problem. Section V summarizes the paper and discusses areas for future work.

II. BACKGROUND

A. A Mixed Discrete–Continuum Electrostatic Model

One model for studying biomolecule electrostatics is shown in Figure 1. Space is divided into two regions by the surface Ω: the biomolecule interior (region I) and the solvent exterior (region II). Region I is a homogeneous dielectric with low permittivity ε_I, which is typically between 2 and 4 [3]. The biomolecule charge distribution is modeled as a set of n_c discrete point charges located at the atom centers, with the i^{th} charge at r_i and having value $q_{L,i}$. The electrostatic potential $\varphi(r)$ satisfies a Poisson equation in this region. The solvent region is a homogeneous dielectric with high permittivity ε_{II}, which is usually approximately that of bulk water. The potential in this region is assumed to obey either the Laplace equation (in non-ionic solutions) or the linearized Poisson–Boltzmann equation (in dilute ionic solutions) [3]. The potential and the normal displacement field are continuous at the interface [32] and the potential satisfies regularity conditions at infinity [33]. The presence of the charges polarizes the high-dielectric solvent and the polarization produces a *reaction potential* at the charge locations; one needs to calculate these potentials in order to evaluate the electrostatic energy of the system. Representing the biomolecule as a union of van der Waals spheres and rolling a probe sphere over this union allows the interface Ω between the regions to be defined as the set of points closest to the union that the probe sphere surface can reach [34]. This is called the solvent-excluded, or molecular, surface.

B. Numerical Simulation of Electrostatics

The coupled PDE system described in Section II-A can be solved using any of a variety of numerical techniques: finite-difference, finite-element, and boundary-element methods have all been used [11], [33], [35]–[43]. We demonstrate the co-optimization approach using a simple integral-equation formulation specialized to non-ionic solutions and the boundary-element method (BEM) [40], [41], [44]–[46]. Several other formulations allow treatment of dilute ionic solutions [33], [42], [43], [47]; for clarity, however, we present only the simplest formulation.

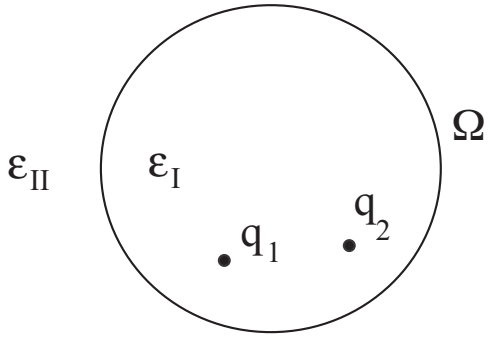

Fig. 1. Mixed discrete-continuum electrostatics model.

Consider the unbound ligand molecule. An induced surface charge $\sigma_{p,u}(r)$ forms at the dielectric boundary Ω in response to the ligand charge distribution. The charge distribution satisfies the second-kind integral equation

$$\frac{\varepsilon_I+\varepsilon_{II}}{2\varepsilon_I(\varepsilon_I-\varepsilon_{II})}\sigma_{p,u}(r)+\int\!\!\!\!\!\!-_{\Omega}\frac{\partial}{\partial n(r)}\frac{\sigma_{p,u}(r')dA'}{4\pi\varepsilon_I||r-r'||} = -\frac{\partial}{\partial n(r)}\sum_{i=1}^{n_c}\frac{q_{L,i}}{4\pi\varepsilon_I||r-r_i||}, \quad (1)$$

where the subscript u denotes the unbound geometry, $\int\!\!\!\!\!\!-$ denotes the principal value integral, and $n(r)$ denotes the normal direction at r on the surface, which is defined to point outward into solvent. This integral equation may be derived by replacing region II with a medium of permittivity ε_I and forcing the electric field discontinuity across the same boundary to match the field discontinuity of the original two-dielectric problem [40], [46], and can be written in operator form as

$$A_2\sigma_{p,u}=A_1q_L, \quad (2)$$

where q_L is the vector of partial atomic charges and A_2 and A_1 are linear operators.

The *reaction potential* at the i^{th} ligand charge location r_i induced by solvent polarization in response to the charges q_L may then be found by calculating the potential induced by $\sigma_{p,u}(r)$:

$$\varphi_u^{REAC}(r_i)=\int_{\Omega}\frac{\sigma_{p,u}(r')dA'}{4\pi\varepsilon_I||r_i-r'||}, \quad (3)$$

which in operator form is written

$$\varphi_u^{REAC}=A_3\sigma_{p,u}, \quad (4)$$

where A_3 is the linear operator that maps the surface charge distribution to the reaction potentials.

One can solve (1) numerically by defining a set of basis functions on the surface such that the unknown surface variable $\sigma_{p,u}(r)$ can be reasonably well approximated as a scaled sum of the basis functions. A finite-dimensional

square linear system is formed by forcing the integral to satisfy a carefully chosen set of constraints [45], [46]. The resulting matrix equation $Ax = b$ is dense, unlike linear systems produced by finite-difference or finite-element methods. To eliminate the prohibitive $O(n^2)$ memory requirement and $O(n^3)$ time costs associated with dense LU factorization or dense Krylov methods, Krylov methods such as GMRES [48] are used in conjunction with approximate algorithms such as the fast multipole [49], [50], precorrected-FFT [51], or FFTSVD [52], which can rapidly compute the required dense matrix–vector products. The combination of Krylov methods, effective preconditioners, and fast algorithms allow solution of the dense BEM systems in linear or near-linear time and memory [53].

C. Biomolecule Electrostatic Optimization Theory

Combining (2) and (4) allows the reaction potentials at the ligand charge locations to be written explicitly as a linear function of the charge values:

$$\varphi_u^{REAC} = A_3 A_2^{-1} A_1 q_L. \tag{5}$$

The electrostatic free energy due to the reaction field, which is $\frac{1}{2} q_L^T \varphi_u^{REAC}$ [32], is therefore a quadratic function of the charge distribution q_L. The mapping $L_u = A_3 A_2^{-1} A_1$ is symmetric and positive definite.

The quantity to be optimized is the electrostatic component of the binding free energy, which is the difference in electrostatic free energies between the bound and unbound states. The ligand is assumed to be rigid, and the ligand charge values are assumed to be the same in the bound and unbound states. The bound-state electrostatic free energy is a sum of four components: the reaction energies associated with the receptor and ligand charges, the energy associated with the interaction of the ligand charges with the receptor-charge-induced reaction field, and the Coulombic interaction between the ligand and receptor charge distributions. The receptor charge distribution is assumed to be fixed, and therefore the first term is independent of the ligand charge distribution and can be dropped from the objective function. The third and fourth terms can be grouped into a single vector c, and then the bound-state ligand-dependent free energy can be written as

$$\Delta G_{bound} = \frac{1}{2} q_L^T B_3 B_2^{-1} B_1 q_L + c^T q_L = \frac{1}{2} q_L^T L_b q_L + c^T q_L, \tag{6}$$

where B_1, B_2, and B_3 denote the operators for the bound-state electrostatics problem. The component of the electrostatic binding free energy that is dependent on the ligand charges is thus

$$\Delta\Delta G = \frac{1}{2} q_L^T L_b q_L - \frac{1}{2} q_L^T L_u q_L + c^T q_L. \tag{7}$$

It has been shown that this quadratic function of q_L is convex for many physically reasonable bound- and unbound-state geometries [17]. Equality constraints are usually applied to ensure that the total ligand charge has a particular integer value [15], [19], [21], and in addition inequality constraints are often imposed so that the computed charges are limited in magnitude [21]. The resulting unconstrained or constrained quadratic programs can be solved using standard techniques once the matrices L_b, L_u, and the vector c have been calculated.

III. COUPLING SIMULATION AND OPTIMIZATION

A. Co-optimization is a "Reverse-Schur-Complement" Method

The essential idea of the co-optimization approach is that the Hessian's Schur-complement structure can be exploited to solve the optimization problem without explicit calculation of the Hessian. A simple example demonstrates the approach. The linear system

$$A_3 A_2^{-1} A_1 x = b, \tag{8}$$

where $A_1 \in \Re^{n\times k}$, $A_2 \in \Re^{n\times n}$, and $A_3 \in \Re^{k\times n}$, with $n > k$, has the same solution x as the linear system

$$\begin{bmatrix} 0 & A_3 \\ -A_1 & A_2 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} b \\ 0 \end{bmatrix}, \tag{9}$$

where we have introduced the auxiliary variable y. Because the original system (8) is the Schur complement of (9), we say that co-optimization is a reverse-Schur-complement method.

The Hessian structure in (7) is a difference of two reverse Schur complements, and the optimal solution q_L^* to the unconstrained problem may therefore be found by solving the linear system

$$\begin{bmatrix} 0 & B_3 & -A_3 \\ -B_1 & B_2 & \\ -A_1 & & A_2 \end{bmatrix} \begin{bmatrix} q_L^* \\ \sigma_{p,b} \\ \sigma_{p,u} \end{bmatrix} = \begin{bmatrix} -c \\ 0 \\ 0 \end{bmatrix}. \tag{10}$$

Optimization with sum-of-charge or other linear equality constraints of the form $A_c q_L = b$ have solutions that satisfy a linear relation for their optimality (Karush-Kuhn-Tucker, or KKT conditions [54]), such as

$$\begin{bmatrix} L_b - L_u & A_c^T \\ A_c & \end{bmatrix} \begin{bmatrix} q_L^* \\ \lambda^* \end{bmatrix} = \begin{bmatrix} -c \\ b \end{bmatrix}, \tag{11}$$

and this block system can be transformed similarly.

B. Primal–Dual Interior-Point Methods and Co-optimization

Primal–dual interior-point methods represent an extremely powerful and efficient approach to solving inequality-constrained quadratic programs [55]. The electrostatic optimization problems with linear inequality constraints can be transformed into the standard quadratic program

$$\begin{aligned} \text{minimize} \quad & \frac{1}{2} x^T L x + x^T c \\ \text{subj. to} \quad & Ax = b \\ \text{and} \quad & x \geq 0. \end{aligned} \tag{12}$$

This program has optimality conditions that are nonlinear in the primal variables x, the Lagrange multipliers λ, and the dual slacks s. Primal–dual interior-point methods find an optimal solution using a modified form of the Newton–Raphson method that preserves positivity of the primal

variables and dual slacks at every iteration by biasing the Newton–Raphson updates so that the pairwise products $x_i s_i$ remain approximately equal. The k^{th} update is calculated by solving a linear system such as

$$\begin{bmatrix} L_b - L_u & -A_c^T & -I \\ A_c & 0 & 0 \\ S^k & 0 & X^k \end{bmatrix} \begin{bmatrix} \Delta x^k \\ \Delta \lambda^k \\ \Delta s^k \end{bmatrix} = -F(x^k, \lambda^k, s^k) + \begin{bmatrix} 0 \\ 0 \\ \sigma \mu e \end{bmatrix}, \quad (13)$$

where $F(x,\lambda,s)$ is the nonlinear function whose zeros are optimal solutions when $(x,s) \geq 0$ and $x_i s_i = 0 \forall\, i$, S^k is the diagonal matrix with $S^k_{ii} = s^k_i$, X^k is defined similarly with the entries of x^k along the diagonal, e is a vector of all ones, and $\mu = x^{k,T} s^k / n$ where n is the number of primal variables. This linear system can also be expanded using two reverse Schur complements to be solved using an implicit representation of the Hessian matrix.

Explicit-Hessian techniques can easily be adapted using regularization schemes [20], because the eigendecomposition is readily computed. However, regularization in the co-optimization is somewhat more subtle, and is a subject of current research [56]. The results reported in Section IV-A rely on penalizing the eigenvectors corresponding to the smallest eigenvalues of an approximate Hessian, which is computed as $\hat{L} = B_3 P_{B_2} B_1 - A_3 P_{A_2} A_1$, where P_{B_2} and P_{A_2} denote the preconditioners for the bound- and unbound-state BEM simulations.

C. Comparison to Other Techniques

1) Traditional Optimization Method: Until the co-optimization method was developed, electrostatic optimization problems were typically solved by explicitly calculating the Hessian one column at a time. The i^{th} column is calculated by setting the i^{th} ligand charge to 1 and all others to zero, simulating the bound and unbound states, with a null receptor charge distribution in the bound state, and subtracting the calculated potentials at the ligand charge locations. The computational expense required for this approach grows linearly with the number of charges and must be fully paid before optimization can begin [19], [29].

2) An Alternative Implicit-Hessian Approach: An alternative to the co-optimization approach might be to solve the KKT or biased Newton–Raphson equations using a nested Krylov method. Each Krylov iteration to solve (11) would then require simulation of the bound and unbound states. It can be difficult to precondition the outer Krylov method effectively, and in the worst case may require as much or more computation than that required to compute an explicit Hessian [57].

3) PDE-Constrained Optimization: The co-optimization technique differs markedly from other approaches to PDE-constrained optimization (see, for instance, references [31], [58], [59]) in one important respect: in co-optimization, the PDE constraints are not introduced formally into the mathematical program as constraints. In most PDE-constrained approaches, such as that of Biros and Ghattas [31], [58], the PDE variables are added as variables to the optimization problem, and the PDE itself becomes an equality constraint. The Schur preconditioner presented by Biros and Ghattas allows efficient solution of the resulting system. In contrast, in a co-optimization method one first writes down the linear system to be solved and assumes the ability to form the Hessian–vector product. The KKT equations—or the primal–dual interior-point Newton–Raphson equations—are then transformed using the reverse Schur complement. It is possible that the co-optimization approach works only in very restricted circumstances, such as the selection of an optimal distribution given a fixed basis set.

IV. COMPUTATIONAL RESULTS

In this section we first present a set of simple examples to demonstrate the superior scaling of the co-optimization method relative to the explicit-Hessian method [57], [60]. The examples are similar to those described in Lee and Tidor's initial work on electrostatic optimization [15]. In addition, a problem with realistic geometries and charge distributions has been optimized successfully and the co-optimization results validated against the traditional approach [57].

A. Spherical Geometries

Figure 2 is an illustration of the ligand and ligand–receptor complex, which are spheres of 8 and 32 Å, respectively. The ligand binds to the receptor such that the ligand center is at (0, 0, 24) if the center of the complex is the origin. The receptor has 200 charges placed at random locations inside the complex, subject to the constraints that charges were all separated by at least 2.5 Å and at least 1 Å away from the ligand and receptor surfaces. The receptor charge values were chosen randomly from a uniform distribution between -0.85 and +0.85 times the electron charge. Twelve sets of ligand charges were generated. The sets varied in size from 4 to 120 charges and placed at random locations in the ligand sphere, subject to the constraints that no charges be placed within 2.5 Å of one another or within 1 Å of the ligand surface.

Each of the resulting twelve objective functions was minimized without constraints. Figure 3 is a plot of the computational expense required to solve the unconstrained problems using the implicit-Hessian method and using a standard method in which the Hessian is calculated explicitly. For each of the optimization methods, the total number of GMRES iterations required for solution was counted and used as a cost metric. For all of these problems, the bound-state and unbound-state geometries each consisted of 1810 spherical boundary elements [61], the FFTSVD [52] algorithm was used to compress the BEM operators, and preconditioned GMRES was run to a tolerance of 1e-5. A diagonal preconditioner was employed for the BEM simulations; the co-optimization preconditioner was a product of four block matrices that would exactly invert the co-optimization matrix (10) if the BEM preconditioner were exact [56]. A 10 kcal/mol/e^2 penalty was assessed for exploring

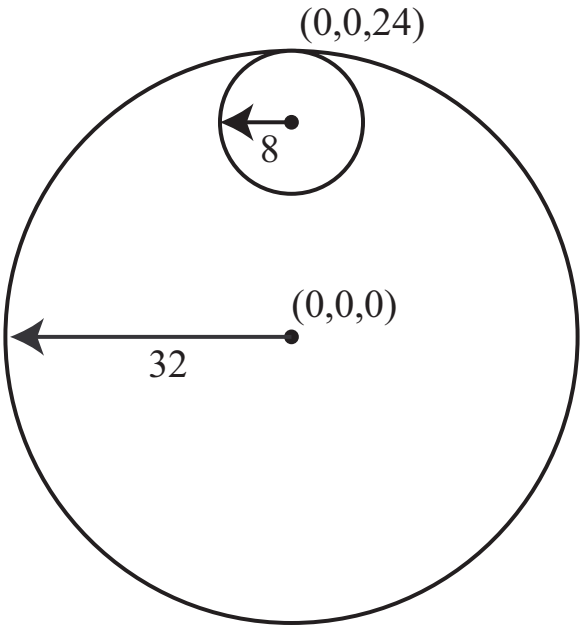

Fig. 2. Dielectric boundaries of the model problems. The ligand is a sphere with radius 8 Å centered at $x = 0, y = 0, z = 24$ Å. The ligand–receptor complex is a sphere of radius 32 Å centered at the origin. All units are Å.

eigendirections corresponding to eigenvalues less than 1e-2 in magnitude.

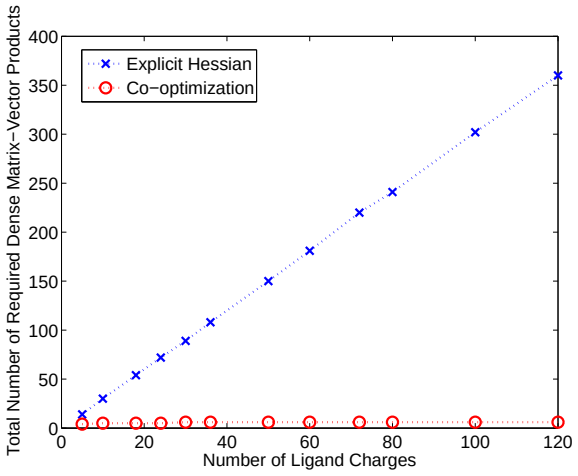

Fig. 3. Computational expense required to solve unconstrained optimization problems using explicit-Hessian calculation and the co-optimization technique.

B. A Realistic Example: Chorismate Mutase and an Inhibitor

The first large-scale implementation of the co-optimization method was based on the pFFT++ boundary-element method and the PETSc scientific computing libraries [51], [62], [63]. This implementation was used to find the optimal charge distribution in a transition-state analog inhibitor of the enzyme chorismate mutase from *E. coli* [57], imposing linear equality and linear inequality constraints. The optimal charges computed using the Hessian-implicit primal–dual method closely matched those computed by explicitly calculating the Hessian using a finite-difference method; Figure 4 is a plot of the computed charge distributions. The inhibitor contains 26 charges to be optimized. Each primal–dual step required the solution of a linear system of dimension greater than 130,000 by preconditioned GMRES [48].

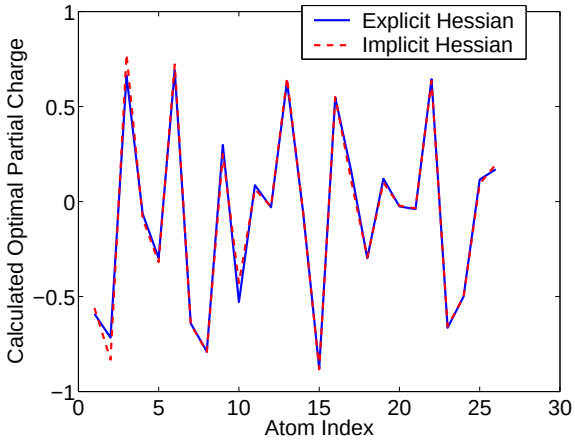

Fig. 4. Primal–dual interior-point methods, used with co-optimization, allow accurate computation of optimal charges [57].

V. DISCUSSION

This paper has described biomolecule electrostatic optimization and presented an efficient PDE-constrained approach to solve these problems. Unlike many other PDE-constrained optimization techniques, the present approach does not introduce the PDE into the optimization problem as a set of equality constraints. Numerical results illustrate that the method's computational cost grows very slowly as a function of the number of optimization variables and that both unconstrained and constrained problems can be solved using co-optimization. A realistic example demonstrates the viability of the approach for solving problems in biomolecule analysis and design.

Although this paper has presented a co-optimization method built on boundary-element methods to solve the underlying PDE, no conceptual difficulties preclude the use of other numerical methods such as the finite-difference or finite-element methods. Such techniques might decrease the overall time required to set up the linear system of equations to be solved, especially because forming the compressed BEM operator can be expensive. Fast direct methods [64], [65] may offer significant advantages for some types of optimization problems, particularly when multiple binding geometries are being studied. Ultimately, however, the total computational cost of co-optimization depends critically on the availability of efficient methods for solving the transformed KKT (or biased Newton–Raphson) equations.

Numerous questions about co-optimization remain to be studied. A detailed convergence analysis has yet to be presented; the relationship between co-optimization and

other PDE-constrained methods is being examined more thoroughly; finally, it is possible that electrostatic co-optimization may offer even better efficiency in other types of QP solvers such as active-set methods [66]. Work in these areas continues, and in addition the co-optimization methods presented here are being applied to study new problems in drug design.

NOTICE

REFERENCES

[1] K. A. Sharp and B. Honig, "Electrostatic interactions in macromolecules: Theory and applications," *Annual Review of Biophysics and Biophysical Chemistry*, vol. 19, pp. 301–332, 1990.

[2] F. B. Sheinerman, R. Norel, and B. Honig, "Electrostatic aspects of protein–protein interactions," *Current Opinions in Structural Biology*, vol. 11, pp. 153–159, 2000.

[3] B. Honig and A. Nicholls, "Classical electrostatics in biology and chemistry," *Science*, vol. 268, pp. 1144–1149, 1995.

[4] C. Tanford and J. G. Kirkwood, "Theory of protein titration curves I. General equations for impenetrable spheres," *Journal of the American Chemical Society*, vol. 59, pp. 5333–5339, 1957.

[5] V. Lounnas, B. M. Pettitt, L. Findsen, and S. Subramaniam, "A microscopic view of protein solvation," *Journal of Physical Chemistry*, vol. 18, pp. 7157–7159, 1992.

[6] J. A. McCammon and S. C. Harvey, *Dynamics of Proteins and Nucleic Acids*. Cambridge: Cambridge University Press, 1987.

[7] C. L. Brooks, III, M. Karplus, and B. M. Pettitt, "Proteins: A theoretical perspective of dynamics, structure and thermodynamics," *Adv. Chem. Phys.*, vol. 71, pp. 1–249, 1988.

[8] A. Jean-Charles, A. Nicholls, K. Sharp, B. Honig, A. Tempczyk, T. F. Hendrickson, and W. C. Still, "Electrostatic contributions to solvation energies: Comparison of free energy perturbation and continuum calculations," *Journal of the American Chemical Society*, vol. 113, pp. 1454–1455, 1991.

[9] S. W. Rick and B. J. Berne, "The aqueous solvation of water: A comparison of continuum methods with molecular dynamics," *Journal of the American Chemical Society*, vol. 116, pp. 3949–3954, 1994.

[10] B. Roux and T. Simonson, "Implicit solvent models," *Biophysical Chemistry*, vol. 78, pp. 1–20, 1999.

[11] J. Warwicker and H. C. Watson, "Calculation of the electric potential in the active site cleft due to alpha-helix dipoles," *Journal of Molecular Biology*, vol. 157, pp. 671–679, 1982.

[12] J. D. Madura, J. M. Briggs, R. C. Wade, M. E. Davis, B. A. Luty, A. Ilin, J. Antosiewicz, M. K. Gilson, B. Bagheri, L. Ridgway-Scott, and J. A. McCammon, "Electrostatics and diffusion of molecules in solution: Simulations with the University of Houston Brownian Dynamics program," *Computer Physics Communications*, vol. 91, pp. 57–95, 1995.

[13] H.-J. Woo and B. Roux, "Calculation of absolute protein–ligand binding free energy from computer simulations," *Proceedings of the National Academy of Sciences of the USA*, vol. 102, no. 19, pp. 6825–6830, 2004.

[14] B. Honig, K. Sharp, and A. S. Yang, "Macroscopic models of aqueous solutions: Biological and chemical applications," *Journal of Physical Chemistry*, vol. 97, no. 6, pp. 1101–1109, 1993.

[15] L.-P. Lee and B. Tidor, "Optimization of electrostatic binding free energy," *Journal of Chemical Physics*, vol. 106, pp. 8681–8690, 1997.

[16] E. Kangas and B. Tidor, "Optimizing electrostatic affinity in ligand–receptor binding: Theory, computation, and ligand properties," *Journal of Chemical Physics*, vol. 109, pp. 7522–7545, 1998.

[17] ——, "Charge optimization leads to favorable electrostatic binding free energy," *Physical Review E*, vol. 59, no. 5, pp. 5958–5961, 1999.

[18] ——, "Electrostatic specificity in molecular ligand design," *Journal of Chemical Physics*, vol. 112, pp. 9120–9131, 2000.

[19] L. T. Chong, S. E. Dempster, Z. S. Hendsch, L.-P. Lee, and B. Tidor, "Computation of electrostatic complements to proteins: A case of charge stabilized binding," *Protein Science*, vol. 7, no. 1, pp. 206–210, 1998.

[20] L.-P. Lee and B. Tidor, "Optimization of binding electrostatics: Charge complementarity in the barnase-barstar protein complex," *Protein Science*, vol. 10, pp. 362–377, 2001.

[21] ——, "Barstar is electrostatically optimized for tight-binding to barnase," *Nature Structural Biology*, vol. 8, pp. 73–76, 2001.

[22] E. Kangas and B. Tidor, "Electrostatic complementarity at ligand binding sites: Application to chorismate mutase," *Journal of Physical Chemistry*, vol. 105, pp. 880–888, 2001.

[23] T. Sulea and E. O. Purisima, "Optimizing ligand charges for maximum binding affinity. A solvated interaction energy approach," *Journal of Physical Chemistry B*, vol. 105, no. 4, pp. 889–899, 2001.

[24] ——, "Profiling charge complementarity and selectivity for binding at the protein surface," *Biophysical Journal*, vol. 84, no. 5, pp. 2883–2896, 2003.

[25] P. A. Sims, C. F. Wong, and J. A. McCammon, "Charge optimization of the interface between protein kinases and their ligands," *Journal of Computational Chemistry*, vol. 25, no. 11, pp. 1416–1429, 2004.

[26] D. F. Green and B. Tidor, "Escherichia coli glutaminyl–tRNA synthetase is electrostatically optimized for binding of its cognate substrates," *Journal of Molecular Biology*, vol. 342, no. 2, pp. 435–452, 2004.

[27] ——, "Design of improved protein inhibitors of HIV-1 cell entry: Optimization of electrostatic interactions at the binding interface," *Proteins: Structure, Function, and Bioinformatics*, vol. 60, pp. 644–657, 2005.

[28] K. A. Armstrong, B. Tidor, and A. C. Cheng, "Optimal charges in lead progression: A structure-based neuraminidase case study," *Journal of Medicinal Chemistry*, vol. 49, pp. 2470–2477, 2006.

[29] M. K. Gilson, "Sensitivity analysis and charge-optimization for flexible ligands: Applicability to lead optimization," *Journal of Chemical Theory and Computation*, vol. 2, no. 2, pp. 259–270, 2006.

[30] A. Mandal and D. Hilvert, "Charge optimization increases the potency and selectivity of a chorismate mutase inhibitor," *Journal of the American Chemical Society*, vol. 125, no. 19, pp. 5598–5599, 2003.

[31] G. Biros and O. Ghattas, "Parallel Lagrange–Newton–Krylov–Schur methods for PDE-constrained optimization. Part I: the Krylov–Schur solver," *SIAM Journal of Scientific Computing*, vol. 27, no. 2, pp. 687–713, 2005.

[32] J. D. Jackson, *Classical Electrodynamics*, 3rd ed. Wiley, 1998.

[33] A. H. Juffer, E. F. F. Botta, B. A. M. van Keulen, A. van der Ploeg, and H. J. C. Berendsen, "The electric potential of a macromolecule in a solvent: A fundamental approach," *Journal of Computational Physics*, vol. 97, no. 1, pp. 144–171, 1991.

[34] F. M. Richards, "Areas, volumes, packing, and protein structure," *Annual Review of Biophysics and Bioengineering*, vol. 6, pp. 151–176, 1977.

[35] I. Klapper, R. Hagstrom, R. Fine, K. Sharp, and B. Honig, "Focusing of electric fields in the active site of Cu-Zn superoxide dismutase: Effects of ionic strength and amino-acid modification," *Proteins: Structure, Function, Genetics*, vol. 1, pp. 47–59, 1986.

[36] M. K. Gilson and B. Honig, "Calculation of the total electrostatic energy of a macromolecular system: Solvation energies, binding energies, and conformational analysis," *Proteins: Structure, Function, Genetics*, vol. 4, pp. 7–18, 1988.

[37] W. Rocchia, E. Alexov, and B. Honig, "Extending the applicability of the nonlinear Poisson–Boltzmann equation: Multiple dielectric constants and multivalent ions," *Journal of Physical Chemistry B*, vol. 105, pp. 6507–6514, 2001.

[38] M. J. Holst, "Multilevel methods for the Poisson–Boltzmann equation," Ph.D. dissertation, Univ. of Ill. at Urbana-Champaign, 1993.

[39] N. A. Baker, D. Sept, M. J. Holst, and J. A. McCammon, "Electrostatics of nanoysystems: Application to microtubules and the ribosome," *Proceedings of the National Academy of Sciences of the USA*, vol. 98, pp. 10 037–10 041, 2001.

[40] P. B. Shaw, "Theory of the Poisson Green's-function for discontinuous dielectric media with an application to protein biophysics," *Physical Review A*, vol. 32, no. 4, pp. 2476–2487, 1985.
[41] R. J. Zauhar and R. S. Morgan, "A new method for computing the macromolecular electric-potential," *Journal of Molecular Biology*, vol. 186, no. 4, pp. 815–820, 1985.
[42] B. J. Yoon and A. M. Lenhoff, "A boundary element method for molecular electrostatics with electrolyte effects," *Journal of Computational Chemistry*, vol. 11, no. 9, pp. 1080–1086, 1990.
[43] D. M. Chipman, "Solution of the linearized Poisson–Boltzmann equation," *Journal of Chemical Physics*, vol. 120, no. 12, pp. 5566–5575, 2004.
[44] R. J. Zauhar and R. S. Morgan, "The rigorous computation of the molecular electric potential," *Journal of Computational Chemistry*, vol. 9, no. 2, pp. 171–187, 1988.
[45] J. Tausch, J. Wang, and J. White, "Improved integral formulations for fast 3-D method-of-moment solvers," *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, vol. 20, no. 12, pp. 1398–1405, 2001.
[46] M. D. Altman, J. P. Bardhan, J. K. White, and B. Tidor, "An efficient and accurate surface formulation for biomolecule electrostatics in non-ionic solution," in *Engineering in Medicine and Biology Conference (EMBC)*, 2005.
[47] S. S. Kuo, M. D. Altman, J. P. Bardhan, B. Tidor, and J. K. White, "Fast methods for simulation of biomolecule electrostatics," in *International Conference on Computer Aided Design (ICCAD)*, 2002.
[48] Y. Saad and M. Schultz, "GMRES: A generalized minimal residual algorithm for solving nonsymmetric linear systems," *SIAM Journal of Scientific and Statistical Computing*, vol. 7, pp. 856–869, 1986.
[49] L. Greengard and V. Rokhlin, "A fast algorithm for particle simulations," *Journal of Computational Physics*, vol. 73, pp. 325–348, 1987.
[50] K. Nabors and J. White, "FASTCAP: A multipole accelerated 3-D capacitance extraction program," *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, vol. 10, no. 10, pp. 1447–1459, 1991.
[51] J. R. Phillips and J. K. White, "A precorrected-FFT method for electrostatic analysis of complicated 3-D structures," *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, vol. 16, no. 10, pp. 1059–1072, 1997.
[52] M. D. Altman, J. P. Bardhan, B. Tidor, and J. K. White, "FFTSVD: A fast multiscale boundary-element method solver suitable for BioMEMS and biomolecule simulation," *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, vol. 25, no. 2, pp. 274–284, 2006.
[53] K. Nabors, F. T. Korsmeyer, F. T. Leighton, and J. White, "Preconditioned, adaptive, multipole-accelerated iterative methods for three-dimensional first-kind integral equations of potential theory," *SIAM Journal on Scientific Computing*, vol. 15, no. 3, pp. 713–735, 1994.
[54] D. P. Bertsekas, *Nonlinear Programming*, 2nd ed. Athena Scientific, 1999.
[55] S. J. Wright, *Primal-Dual Interior Point Methods*. SIAM, 1997.
[56] J. P. Bardhan, M. D. Altman, B. Tidor, and J. K. White, *manuscript in preparation*.
[57] J. P. Bardhan, J. H. Lee, M. D. Altman, S. Benson, S. Leyffer, B. Tidor, and J. K. White, "Biomolecule electrostatic optimization with an implicit Hessian," in *Modeling and Simulation of Microsystems (Nanotech)*, 2004.
[58] G. Biros and O. Ghattas, "Parallel Lagrange–Newton–Krylov–Schur methods for PDE-constrained optimization. Part II: the Lagrange–Newton solver and its application to optimal control of steady viscous flows," *SIAM Journal of Scientific Computing*, vol. 27, no. 2, pp. 714–739, 2005.
[59] E. Haber and U. M. Ascher, "Preconditioned all-at-once methods for large, sparse parameter estimation problems," *Inverse Problems*, vol. 17, pp. 1847–1864, 2001.
[60] J. P. Bardhan, J. H. Lee, S. S. Kuo, M. D. Altman, B. Tidor, and J. K. White, "Fast methods for biomolecule charge optimization," in *Modeling and Simulation of Microsystems (Nanotech)*, 2003.
[61] J. P. Bardhan, M. D. Altman, D. J. Willis, S. M. Lippow, J. K. White, and B. Tidor, *submitted to the Journal of Chemical Physics*.
[62] Z. Zhu, "Efficient techniques for wideband impedance extraction of complex 3-dimensional geometries," Master's thesis, Massachusetts Institute of Technology, 2002.
[63] S. Balay, K. Buschelman, W. D. Gropp, D. Kaushik, M. Knepley, L. C. McInnes, B. F. Smith, and H. Zhang, "PETSc home page," 2001, http://www.mcs.anl.gov/petsc.
[64] P. G. Martinsson and V. Rokhlin, "A fast direct solver for boundary integral equations in two dimensions," *Journal of Computational Physics*, vol. 205, pp. 1–23, 2005.
[65] L. Greengard, personal communication.
[66] P. E. Gill, W. Murray, M. A. Saunders, and M. H. Wright, "Inertia-controlling methods for general quadratic programming," *SIAM Review*, vol. 33, no. 1, pp. 1–36, 1991.