Structure, Vol. 12, 1–2, January, 2004, ©2004 Elsevier Science Ltd. All rights reserved

Previews

Spanning the Length Scales of Biomolecular Simulation

The first model of the cooperative DNA binding of two important regulatory proteins, CAP and lac repressor, seamlessly unites atomistic and continuum descriptions of biomolecules and suggests variable DNA loop winding in response to protein binding.

In this issue of ***Structure*** (Schulten et al., 2004), three theoretical physicists present a novel study on the cooperative DNA binding of two important regulatory proteins. Schulten, Balaeff, and Mahadevan are well known for their well-informed interpretations of biological structure/function relationships based on thorough theoretical treatment of the underlying physical processes, and this investigation of a textbook example of a genetic control system is no exception. The major innovation presented in the paper is a coupling of atomic and continuum-elastic representations of biomolecular structures across the different physical lengths. The work is based on recent developments in theoretical physics, but here the results have been made accessible to a biological audience by virtue of modeling CAP and lac repressor binding to DNA.

There is much interest in the development of multiscale techniques that maintain continuity between the parameters used to compute physical properties for each scale (Abraham et al., 1998). A good example of such a bridge is the well-established connection between quantum-mechanical treatment of small molecules, and molecular mechanics treatment of macromolecules (VandeVondele and Rothlisberger, 2000). How to combine quantum and atomistic descriptions of matter both in material science and in biology is straightforward and well characterized. Coupling atomic with continuum elastic models (Abraham et al., 1998), however, is difficult to achieve in biology due to the inherent complexity of molecular polymorphism (Gerstein and Krebs, 1998).

Large-scale biomolecular assemblies have often been termed molecular machines (Alberts, 1998) because, in general, they undergo functionally relevant conformational changes while transducing chemical energy into mechanical energy. A casual glance into recent issues of ***Structure*** reveals that concurrent structural biology is, to large extent, concerned with the quest to characterize the moving parts of a biomolecular machine—its springs, shafts, levers, and axles. A reduction in complexity is an important prerequisite for the simulation of large (mega-Dalton) molecular machines. In the last decade significant progress has been made toward such a reduction, in particular for DNA models like those that are of interest here. It is possible to obtain useful information on the dynamics, long-range coupling, and elastic properties of polynucleotides without assuming atomic detail (Westcott et al., 1995). Consequently, Schulten et al. refined the parameters of an *elastic rod* model of DNA against the measured curvature and twist of the CAP binding site, and elastic rod structures were successfully used as scaffolds for idealized all-atom models of the DNA loop and of complexes with bound protein.

The successful handshaking between multiple length scales of modeling encourages the development elastomechanic models for large biomolecular assemblies to go beyond an atomic level of detail. Normal (or vibrational) modes are a tool to study the motion of large assemblies based on a deformable elastic model, and recently these modes were successfully adapted to low-resolution protein structures (Chacón et al., 2003). The basic assumption (and limitation) of physics-based deformable models is that the potential energy of the system varies quadratically about a given minimum energy conformation. This idea is rooted in the observation that biomolecules behave, more than expected, as if the energy surface were parabolic, even though the potential contains many local minima (Horiuchi and Go, 1991).

What are the advantages and limitations of physics-based deformable models? In Figure 1 we compare the use of a traditional atomic molecular dynamics refinement protocol with an elastic model. The task at hand is to fit the crystal structure of RNA polymerase in the closed state (Figure 1A) into an electron microscopy map of the open state using 15 displacement vectors as constraints (Wriggers and Chacón, 2001), giving rise of a conformational change of $\sim$7 Å rms deviation. Both atomic simulation and elastic deformation equally increase the cross-correlation of the atomic model with the target density from 86% (Figure 1A) to 89% (Figures 1B and 1C). The elastic warping (Figure 1C) is effective, but the stereochemistry of the atomic model (Figure 1B) is maintained better due to the local rearrangement of atoms in response to the forced global change, which gives rise to a 3 Å rms deviation between the two flexed conformations (Figures 1B and 1C).

The example in Figure 1 demonstrates that physics-based deformable models may be very useful also in the modeling of proteins, but harmonic models are limited to relatively small deviations from a known structure and only cover a subset of the possible conformational search space. In the present state these models are best used as dimensionality reduction and refinement tools. To fully extend the success of elastic DNA modeling to proteins, and to understand the biochemistry of structural plasticity, we recognize the need for an inharmonic modeling technique. The challenge is to derive plausible deformation pathways when the deviations from an initial structure become large, or when the crossing of a barrier between conformational states becomes an issue. Many investigators have already identified this challenge and in the near future further significant discoveries can be expected that are based on a hybrid modeling of biomolecular machines across multiple length scales.

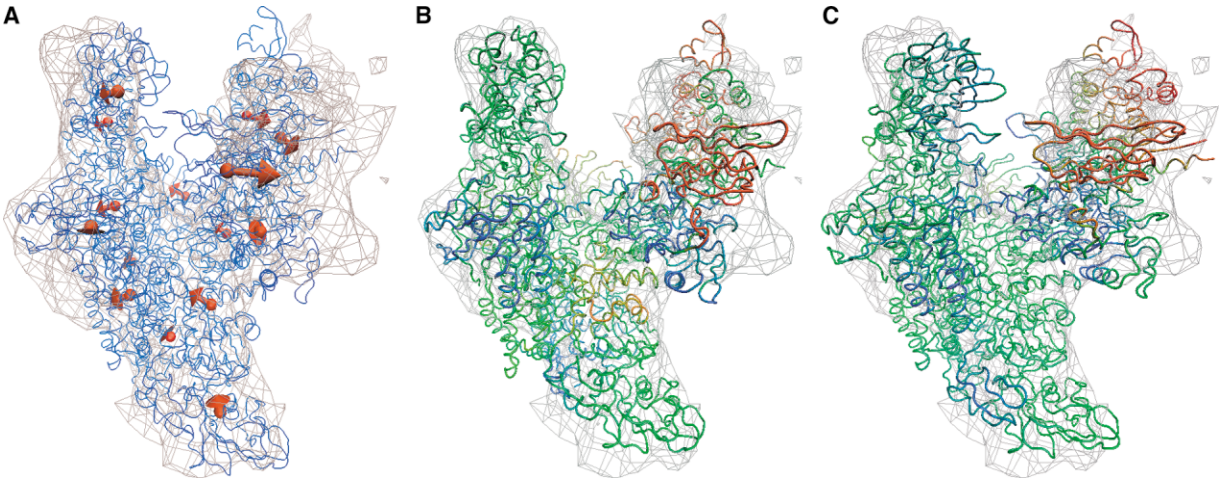

Figure 1. Comparison of Atomic and Continuum Elastic Flexible Fitting of RNA Polymerase

(A) Fifteen displacement vectors (red), computed as described in (Wriggers and Chacón, 2001), predict the motion of the crystal structure (blue tube) toward the electron microscopy map (gray wireframe).

(B) The displacements were applied in a molecular dynamics simulation (Wriggers and Chacón, 2001) to bring the domains of the atomic model into register with the map. Warmer colors indicate larger deformations relative to the crystal structure in (A).

(C) The sparsely sampled displacements in (A) were extended to the atom positions of the crystal structure using the 3D Bookstein *thin plate splines* method (Bookstein, 1991). Compelled by the displacements, the Bookstein method warps the embedding space while minimizing the deformation energy of the continuum.

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