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JOBIM 2012

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BioSpring: an interactive and multi-resolution software for flexible docking and for mechanical exploration of large biomolecular assemblies

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1 Introduction

Recent advances in experimental techniques allow us to solve larger and larger biomolecular 3D structures. However, even if structure is known to be strongly linked to biological function, static states often lack in providing dynamical information that are crucial for the understanding of the subtle mechanisms occurring at the molecular level. Thus, molecular simulations are nowadays used to complete experimental biostructural studies, especially to better understand the dynamic behaviour and the fundamental mechanisms involved in a biomolecular complex. In spite of the increasing computational resources, classical modeling methods are still not well adapted to quickly characterize biomechanics of biomolecular assemblies, mainly because of the limited timescale accessible to all-atom simulations. For these reasons, it's necessary to develop new simulation approaches especially designed to study very large biological structures formation and stability. We present **BioSpring**, an unconventional and innovative software, implementing a method based on a **spring network model** adding **non-bonded interactions**, guided by an **electrostatic map**, and using **advanced human interaction techniques** dedicated to **interactive molecular modeling**. The interactive simulation tool BioSpring allows a user to quickly study the biomechanical properties, by interactively highlighting rigidity, flexibility, and allosteric effects, in order to provide new hypotheses about a biomolecular system. Finally, our approach is also designed to help a user in the complex task of modeling large biomolecular complexes before using more time-consuming and costly classical simulation tools.

2 Method

2.1 Spring Network Simulation Model

$$\vec{F}_{spring}(p) = \sum_{p' \in Springs(p)} k_{stiffness} \vec{u}_{pp'} (d_{pp'} - e_{pp'})$$

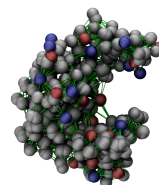
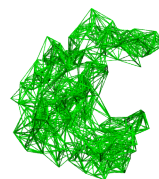
2.2 User-defined non bonded interaction

$$s_{pp'} = (r_p + r_{p'}) - d_{pp'}$$

$$\vec{F}_{linearsteric}(p) = \begin{cases} \vec{0} & \text{if } s_{pp'} \leq 0 \\ \sum_{p' \neq p} -k_{steric} \vec{u}_{pp'} s_{pp'} & \text{else} \end{cases}$$

$$\vec{F}_{coulomb}(p) = \sum_{p' \neq p} -\vec{u}_{pp'} \frac{q_p q_{p'}}{4\pi\epsilon_0 d_{pp'}^2}$$

$$\vec{F}_{lennardjonessteric}(p) = \sum_{p' \neq p} \vec{u}_{pp'} 4\epsilon_{pp'} \left[\left(\frac{\sigma_{pp'}}{9d_{pp'}} \right)^9 + \left(\frac{\sigma_{pp'}}{7d_{pp'}} \right)^7 \right]$$

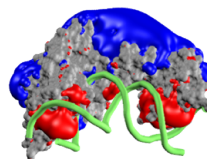


2.3 Interaction of the flexible structure and a potential map

$$\vec{F}_{map}(p \in V_{i,j,k}) \simeq \begin{bmatrix} E_{i+1,j,k} - E_{i-1,j,k} \\ E_{i,j+1,k} - E_{i,j-1,k} \\ E_{i,j,k+1} - E_{i,j,k-1} \end{bmatrix}$$

2.4 human/molecule interaction model

$$\vec{F}_{control}(p \in Selection) = -k_{control} [\vec{P}(tool) - \frac{1}{|Selection|} \sum_{p' \in Selection} \vec{P}(p')] \\ \vec{F}_{feedback}(tool) = -k_{feedback} [\vec{P}(tool) - \frac{1}{|Selection|} \sum_{p' \in Selection} \vec{P}(p')]$$



3 Applications

3.1 Modeling DNA sequence recognition within RecA nucleoprotein filaments [2]

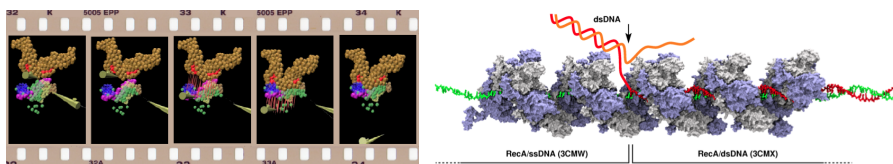


Figure 1. Bimanual haptic interactive modelling (left), and description of RecA-induced DNA strand exchange (right)

3.2 Adenylate Kinase (AK) interactive closure

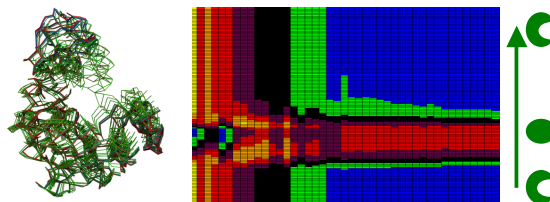


Figure 2. Bimanual haptic interactive study of AK closure (left) and RMSD results (right)

4 Conclusion

BioSpring was especially designed for molecular sketching and modeling. The main goals of *BioSpring* is to provide a tool to get interactively a quick overview of biomechanical properties, to help user in the complex task of modeling large biomolecular complexes, in order to perform an interactive flexible docking, and also to Providing/Exploring/Testing new hypothesis prior to more complex investigations. This software can be plugged with *VMD* using the *MDDriver* [1] library, with or without force feedback using a haptic device. *BioSpring* should be used to quickly explore biomechanical properties of biomolecules, for interactive molecular modeling and docking, prior to further investigation using classical simulation tools.

References

- [1] Delalande, Férey, Grasseau, Baaden. Complex Molecular Assemblies at Hand via Interactive Molecular Simulation. *J. Comput. Chem.*, 30(15), 2375-87, 2009
- [2] Saladin, Amourda, Poulain, Férey, Baaden, Zacharias, Delalande, & Prévost, Modeling the early stage of DNA sequence recognition within RecA nucleoprotein filaments, *Nucleic Acids Res.*, 38, 6313-23, 2010