

## **Award: “Analytical Electrostatics: Methods and Biological Applications”**

**Sponsor: National Institute for General Medical Science**

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### **Abstract:**

Ions play an essential role in governing the structure and function of nucleic acids, including DNA compaction in living cells or DNA packaging for therapeutics. However, visualizing the ions at atomic detail and understanding how they facilitate interactions between biological molecules is extremely challenging. Direct experimental detection of individual ions around nucleic acids remains elusive; computational approaches which properly model individual ions, are not fully developed. Most current detailed computational approaches are prohibitively expensive (e.g., explicit solvent simulations) for large scale or systematic studies. On the other hand, the corresponding implicit solvent models reduce computational effort at the expense of simplifying assumptions that preclude their application to biologically relevant highly charged systems: for example, these approaches miss ion-induced attractive forces that lead to DNA compaction. The absence of accurate and facile computational models in this field hinders progress in many areas fundamental to biomedical science. **Through this supplement we propose to combine the efforts of three research groups to pioneer a new approach, bridging theory and experiment to visualize ions around DNA and understand their interactions with the polymer.** This approach uses the fast analytical salvation tools created by the Onufriev group together with the electrostatic and grand canonical Monte Carlo algorithms and software developed by N. Baker’s group. Unlike previous simulations of this type which have typically used highly simplified models of the mobile ions, the grand canonical Monte Carlo simulations we propose will include detailed treatments of ions that include key physical effects such as solvation and desolvation upon ion pairing or ion-nucleic acid binding. This new approach will be tested and fine-tuned through collaboration with L. Pollack’s research group, using small angle X-ray scattering to probe the changing distribution of trivalent ions around DNA. In addition to testing of the new computational methodology, the combined computational and experimental study will provide molecular-scale insight into the very diverse roles of ionic species in regulating DNA structure and assembly. At the end of the proposed research period, we plan to have sufficient preliminary results to support an independent collaborative research project to further expand our approach, improve existing software (ISIM and APBS) to incorporate the more sophisticated ion models, adopt the new models for molecular dynamics (NAB package), and finally apply these tools to investigate fundamental problems of nucleic acid structure and thermodynamics.