

## **Biophysical Simulations Enabled by Ultrasimulation Facility**

### **I. Preamble:**

An important consequence of the ongoing tremendous progress in molecular biology, is that many living processes are understood at a level that atomistic simulations can be used to elucidate fundamental biological mechanisms and engineer biological solutions to national problems. The challenges involved in predictive modeling of biological processes arise from the large size and long timescales of biochemical phenomena, combined with the need for extreme accuracy. Nevertheless, the computational tools for applying such simulations to a wide range of important biochemical problems are well developed and to a large degree limited by available computer speeds. The proposed Ultrasimulation Facilities allow predictive biological simulations on a much wider range of biological problems than is currently feasible and will lead to breakthroughs with profound impacts on human health, energy production, environmental protection, and national security.

### **II Overview of biophysical simulation methods**

A wide variety of chemical simulation methods are available that vary in accuracy, scalability, and computational cost. At one extreme are quantum mechanical methods that can in principle predict any biochemical property to high accuracy but are in practice computationally limited to relatively small molecular systems. At the other extreme is classical molecular mechanics (MD) that simulates the motions of atoms using simplified ball and spring” force fields that have limited accuracy. These different methods are complementary—for example classical molecular dynamics can provide information on large-scale conformational changes in enzymes, while quantum mechanical simulations can determine the effect of these changes on the catalytic activity of the enzymes. Both of these methods are extremely computationally costly when applied to biological problems, and the 10 to 100-fold increase in computational capability proposed in the Ultrasimulation Facility would dramatically broaden the range of bioscience problems that could be addressed by simulation.

The current state-of-the-art in biophysical modeling are the so-called First Principles Molecular Dynamics (FPMD) methods that simulate the motions of atoms in biochemical systems using a quantum mechanical description of the atomic interactions. The FPMD applications have been highly optimized for DOE’s current teraFLOP-speed computers on which they are capable of simulating up to a few hundred atoms for a few picoseconds. However, these methods also constitute a nearly exact simulation of nature, and even within these computational limitations, it is becoming an important tool for studying fundamental biochemical processes. The results for small biochemical systems currently being simulated on teraFLOP scale computers provide tantalizing glimpses of the value of longer time and larger system size simulations that will be made possible with faster computers.

### **III. Improvements in biophysical simulations enabled by Ultrasimulation Facility**

Using Earth Simulator (ES)-class computers, we expect major progress in the predictive power of classical MD and FPMD techniques for simulations of biological systems. We also expect major progress in the development and use of coupled techniques linking

various quantum mechanical approaches, such as FPMD and Quantum Monte Carlo methods, and linking quantum mechanical and classical atomistic approaches. These coupled techniques will provide codes that both experimentalists and theorists can use to guide, interpret and predict new phenomena and future experiments. We estimate that access to ES-class computers will enable FPMD simulations of systems comprising 3000-4000 atoms for several picoseconds, as well as of systems comprising 200-300 atoms in the nanosecond range. Within the biology arena, the use of ES-computers will enable microscopic modeling of DNA repair mechanisms and drug/DNA interactions, effectively bringing quantum simulations into the realm of biology.

**Examples of specific science that could be enabled by Ultrasimulation Facility:**

- *Fundamental bioscience:* Hybrid Classical MD/FPMD simulations of ion motions in transmembrane channels
- *Energy production:* Simulations to assist in metabolic engineering of microbes to produce fuels.
- *Health effects of radiation exposure:* FPMD simulations to elucidate mechanisms of DNA repair enzymes
- *Pharmaceutical design:* FPMD simulations of anticancer drug interactions with DNA
- *Environmental restoration:* FPMD simulations to re-engineer cytochrome P450 enzymes to oxidize chemical contaminants