Project Title:

Quantum-chemical studies of base-induced DNA cleavage

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The original intention for our FY2012 RICC allocation was to support a project being carried out by Drs. Shuji Ikeda and Kazuki Tainaka in the Laboratory for Synthetic Biology, RIKEN Quantitative Biology Center. Their work involves the development of a method for the quantitative cleavage of DNA by the inclusion of modified nucleobases; the modified nucleobases specify precise cleavage sites, and cleavage is initiated by treatment with a base. They are working to optimize and characterize the mechanism of this reaction, and we had hoped to use computational modeling to yield additional insight.

Unfortunately, the computational aspect of this projected proved to be intractable and did not provide any usable insight regarding the reaction mechanism or possible routes for optimization. We optimized structures for several reactant/product pairs (using DFT) and putative transition states and attempted to simulate the entire reaction using a nudged-elastic-band calculations, but results were inconclusive and the computational portion of this project was ultimately abandoned.

Subsequently, our allocated time on RICC was used to support two other projects. In the first, we developed a kinetic model of a reaction system in which a single substrate modified by an opposing pair of enzymes was able to generate sustained oscillations. An article describing this work was recently published in Cell Reports, and a Japanese press release can be read at http://www.riken.go.jp/r-world/info/release/press/2012/121019/detail.html. RICC was used for the screening of a large number of randomly-chosen parameter sets; these calculations used software developed by Dr. Jolley specifically for usage on RICC.

In the second project, we were seeking to parameterize a model of the transcriptional/translational portion of the mammalian circadian clock. Calculations performed on RICC supported this project in two ways. The first was the execution of a parallel evolutionary algorithm to optimize the agreement of our model outputs with experimental data. The second involved Metropolis Monte Carlo calculations that explored the model's parameter space to determine the degree to which the model's parameter landscape was modified by the inclusion of different experimental constraints. Both types of calculation used parallel code developed by Dr. Jolley specifically for execution on RICC. A publication describing this work is currently in preparation and should be submitted soon.

Fiscal Year 2012 List of Publications Resulting from the Use of RICC

[Publication]

Jolley CC, Ode KL, Ueda HR. “A design principle for a posttranslational biochemical oscillator.” Cell Reports 2(4):938-50 (Oct. 25 2012)

[Oral presentation at an international symposium]

- “Modeling the mammalian circadian clock.” American Physical Society March Meeting, Boston, USA. 26 Feb – 02 March 2012.
- “The parameter landscape of a mammalian circadian clock model.” Foundations of Systems Biology in Engineering, Tsuruoka, Japan. 21-25 October 2012.
- “Exploring the parameter space of the mammalian circadian clock.” Winter q-bio Meeting, Honolulu, USA. 18-23 February 2013.