Project Name:
Application of Optimal Experimental Design Techniques in the Context of Systems Biology

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Project Overview:
This project involves the development and application of computational modeling technologies for experimental design. Systems biology will only be successful if as a community we are successful in constructing truly accurate and predictive models of complex biological phenomena. Iterative rounds of experimental measurement and computational analysis are essential for model building, but progress can be made most efficiently by devising new experiments that explore new behaviors and modalities not covered by previous experiments. We are engaged in using a variety of control and optimization techniques to construct a toolbox for solving these problems and ultimately applying them to *E. coli* biochemical networks.

Faculty Involved:
Bruce Tidor (MIT)
Eugénio Ferreira (U Minho)
Isabel Rocha (U Minho)
Miguel Rocha (U Minho)
Ana C. Veloso (U Minho)
PhD Students Involved:
Joshua Apgar (MIT)
Anya Castillo (MIT)
Jared Toettcher (MIT)
Bracken King (MIT)
Aurore Zyto (MIT)
Rafael Costa (U Minho)

Expected Deliverables:
• MATLAB, SMBL, S-systems, and KroneckerBio initial models of a collection of biological pathways and E. coli biochemical networks.
• MATLAB, SMBL, S-systems, and KroneckerBio refined models of a collection of biological pathways and E. coli biochemical networks.
• Metrics for the information content of various alternative experiments based on Shannon entropy and the Fischer information matrix.
• Controller-based optimization methodology to develop manipulated input trajectories for model parameter estimation, together with associated sensitivity analysis and controllability information.
• Results of optimization methodology to biochemical pathways and E. coli biochemical networks.
• Proposed re-engineering plans for E. coli with improved bioproduction

capabilities.

Results:
• MATLAB and KroneckerBio initial models have been produced for DNA damage pathways, oscillating reactions, and EGFR signaling pathways.
• An initial version of KroneckerBio has been produced with fundamental sensitivity analysis, parameter estimation, and optimization capabilities.
• Shannon entropy information metrics have developed and applied to a variety of different systems to demonstrate the usefulness of the measure and to develop estimates with good convergence properties.
• Early version of controller-based optimization methodology has been developed and applied to test systems.

Timeline (through August 2008):
• Develop additional models and modeling capabilities, particularly into the KroneckerBio framework, including feature fitting.
• Begin model refinement based on additional experimental results and biochemical knowledge.
• Rafael Costa will visit MIT to learn the techniques being used and to begin construction of the E. coli models.