

“Quantitative Experiment Design for Highly Uncertain Biological Systems”

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Abstract: Many biological systems are highly uncertain thus their descriptive mathematical models have structures that are not fully defined by underlying physical and chemical principles and have parameters that are not well constrained by existing data. Experiments to resolve the biological system behaviors and their associated mathematical model are expensive, so it is vital to design experiments that will be nearly optimal among available experiments in terms of constraining the model structure and parameters the most. Our sequential experiment design approach addresses these issues by using sparse grid interpolation to identify multiple areas of parameter space that are consistent with available data and clustering these identified parameters based on simulated model response and the limits of experimental measurement. By analyzing the expected experimental variance and the variance due to different model responses, we choose a measurement to provide maximal discrimination among currently acceptable solutions. This experiment design criterion is similar to the Hunter-Reiner criterion since it looks for the largest difference in predicted dynamics, but it also avoids design points with large expected measurement error as recommended by Buzzi-Ferraris & Forzatti. This approach further differs from other experiment design methods in that it simultaneously addresses both parameter- and structural- based uncertainty, is applicable to some ill-posed problems where the number of uncertain parameters exceeds the amount of data, places very few requirements on the model type, available data, and *a priori* parameter estimates, and is performed over the global uncertain parameter space. We illustrate this approach on models of the mitogen-activated protein kinase cascade, one with 3 uncertain parameters and one with 18 uncertain parameters. The results show that system dynamics are highly uncertain with an initial set of limited experimental data. Nevertheless, the algorithm requires only three additional experimental data points to simultaneously discriminate between possible model structures and acceptable parameter values. This sparse grid-based experiment design process provides a systematic and computationally efficient exploration over the entire uncertain parameter space of potential model structures to resolve the uncertainty in the nonlinear systems biology model dynamics.

Bio: Ann Rundell is an assistant professor in the Weldon School of Biomedical Engineering at Purdue University. She received her BS in Electrical Engineering from the University of Pennsylvania. Prior to graduate school, Ann worked for three years at Artel, Inc. in Windham, Maine as an engineer designing small portable photometric instrumentation systems for the clinical and environmental marketplaces. Eventually Ann returned to school to earn her MS and PhD degrees from the School of Electrical and Computer Engineering at Purdue University. Her graduate research was on modeling and control of the immune system. Upon completion of her PhD she worked at MIT Lincoln Laboratory as a member of the Technical Staff for three years prior to joining academia as a faculty member. Her research interests apply systems and control theory to control cellular and physiological processes for developing and designing diagnostics and therapeutics. She has co-authored more than 20 peer reviewed articles, is a senior member in IEEE, serves as a Section Editor for the Encyclopedia of Systems Biology, and recently received the NSF CAREER award.