Sparse-grid-based Experimental Design Method to Reduce System Dynamics Uncertainty in Nonlinear Biological Models

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Abstract — A sparse-grid-based experimental design algorithm is created that discriminate between potential model hypothesis with experimental distinguishable differences in the model output dynamics. The algorithm determines how to perturb the system in order to reduce the uncertainty in the model dynamics.

I. PURPOSE

Model-based design of experiment methods use mathematical models of biological systems to inform experimental processes so that maximally informative data is collected from the system. Most commonly, these methods utilize the Fisher information matrix (FIM) to optimize the experiment to reduce the uncertainty in the parameter values [1-3]. An alternative approach [4] recently developed determines what to measure and when to measure it to reduce output dynamics uncertainty. The algorithm has been extended in [5] to support parallel experiment design. This work is an extension of the work done in both [4] and [5] to explore how to stimulate or perturb the experimental system in addition to determining what to measure and when to measure it. This enhances the ability of the global model-based experiment design method to resolve uncertainties in the dynamics by eliciting different dynamical behaviors due to the nonlinearity of the biological systems.

The algorithm sequentially specifies an experiment design point that defines the experimental conditions (inputs), model outputs, and sampling times for those outputs that will resolve the dynamics of the biological system within experimental limits. Due to considerable uncertainty in model parameter values, models encoding a biological system may exhibit a number of different system dynamics. The experiment design point is chosen to maximize a distinguishability criterion that quantifies the ability of the experimental setup to resolve between these potential dynamics. The objective of experimental design focuses on reducing dynamical output uncertainty rather than identifying system parameter values [6]. The algorithm herein and in [4] and [5] rely extensively on sparse grid screening of the uncertain parameter space to locate the acceptable parameter region(s) where the model output matches the experimental data within the expected uncertainty of the measurement. The algorithm is terminated if all of the parameters from the acceptable region generate similar output dynamics that cannot be differentiated by current experimental techniques.

These sparse-grid-based design of experiment method are particularly appropriate when the initially available experimental data is limited. These approaches differ from other model-based experimental design methods in that it simultaneously reduces uncertainty in both parameter and dynamics without many requirements on the a priori information. The approach is also global since it examines the entire space with system dynamics compatible with the available data. The software has been built and evaluated via simulation. Experiments in the lab are planned to directly compare the sparse-grid-based methods to more traditional FIM-based experiment designs. The algorithm is hypothesized to be more efficient than the FIM-based experimental design in terms of number of experiments it takes to resolve the dynamics of the system.

II. CONCLUSION

Sparse grid-based experimental design algorithm selects design points that discriminate between competing hypotheses with experimentally distinguishable differences in the predicted system output dynamics. The algorithm determines how to perturb the system to resolve uncertainties in the dynamics. The design of experiment method simultaneously reduces uncertainty in both parameter and dynamics by reducing dynamical output uncertainty rather than identifying system parameter values. It also has few requirements on a priori information, and is a global experiment design method.

References

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