Optimal Experimental Design for Biological Systems

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***Short Abstract* — How often, when and where should a phenomenon of interest be observed to receive reliable results? Generally, experimentalists face the dilemma between accuracy and costs of an experiment. Each experiment has its own specific challenges. However, optimization methods form the basic computational tool to address eminent questions of optimal experimental design. We will present a general optimization framework for dynamical systems and will illustrate its performance on some key biological models and discuss its relevance to a glucose model for diabetes treatment.**

***Keywords* — Optimal experimental design, optimization, dynamical systems, glucose metabolism.**

I. Background

OPTIMAL experimental design is a growing topic that spans books [1,2] and review papers [3,4]. In particular, optimal experimental designs for biological and medical experiments have grown in importance [5,6,7]. The major idea behind experimental design is to minimize a utility function that reduces the errors or uncertainty in the recovered model parameters. For example, in the A-optimal design the mean square error is minimized, while in the D-design the ellipsoid of uncertainty is reduced. Although adequate for linear problems, these designs based on Fisher information can be grossly inaccurate for nonlinear problems [1,2].

II. New Optimal Experimental Design Framework

Most biological models are based on nonlinear systems of ordinary differential equations. Due to this end, we rather than basing the design criteria on linearization, tackle the full nonlinear problem head-on. The optimal design problem naturally lead to bi-level optimization problems where the nonlinear parameter estimation serves as the inner optimization problem, i.e.,

$$\min_{w} \mathbf{E}_{p_\mathrm{t}} \|p_\mathrm{opt}(w) - p_\mathrm{t}\|$$

$$\text{subject to}$$

$$w \geq 0 \quad \text{and}$$

$$p_\mathrm{opt}(w) = \arg\min_p \|m(y(p)) - d\| \ \text{ s.t. } y' = f(t, y, p).$$

Here, $\mathbf{E}$ is the expected value over the true parameter p_t, p_opt is the recovered parameter given design w, where d are observations and m the projection of the state solution y of the differential equation onto the obervations d, see [7]. We developed method to solve this challenging bi-level optimization efficiently.

III. Results

We will illustrate our optimal experimental design framework on basic biological systems such as logistic growth and Lotka-Volterra systems. Moreover, we present new optimal experimental designs for the intravenous glucose tolerance based on the Minimal Model. Our theoretical investigations also provided surprising results: For some experiments it can be advantageous to rather measure twice at the same time than at different time points.

IV. Conclusion

We developed a robust experimental design framework for problems that evolve from biological applications. The design problem lead to a bi-level stochastic optimization problem where the underlying problem is the nonlinear regression model used to evaluate the parameters. The flexibility of our framework to various types of biological models and design objectives makes it a powerful tool for designing biological experiments.

Acknowledgements: This work is supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R21GM107683.

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