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LETTERS

Comment on "Sloppy models, parameter uncertainty, and the role of experimental design"

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We explain that part of the reduction in the parameter uncertainties in the computations of Apgar *et al.* (Mol. Biosyst. 2010, 6, 1890–900) is due to a greatly increased number of effective data points.

In "Sloppy models, parameter uncertainty, and the role of experimental design", Apgar *et al.*[1] explore how experimental design can be used to constrain parameter estimation in a signaling network model of nerve growth factor in rat PC12 cells introduced in ref. 2. The main result of their work is that accurate parameter estimation in sloppy models may be feasible by a clever choice of experiments. For the model in question, the authors were able to constrain parameter uncertainties in all 48 parameters to within 10% with only 5 experiments. Previous work fitting the model[2,3] to experimental data had produced much larger errors, with the most tightly constrained parameters unknown to within a factor of 50 and some parameters being unknown to many orders of magnitude—which the previous work asserted was a sign of intrinsic 'sloppiness' in the model.

Is this model intrinsically sloppy, with some parameter combinations orders of magnitude less constrained than others? The original authors quantify sloppiness in terms of the eigenvalues of the Hessian about the best fit, which Apgar *et al.* find span approximately five orders of magnitude even for their optimal experimental design. While this is an impressive reduction from the original eigenvalue range of fifteen orders of magnitude, it still must be considered sloppy—with some parameter combinations $\sqrt{10^5} \sim 300$ times less constrained than others.

A key difference between the original work and the new contribution consists of the data being fit. The original authors[2] fit actual experimental data—68 data points with 20% errors, whereas Apgar *et al.* effectively measure all 30 species at 100 time points with 10% errors, spread between the five experiments. In the harmonic approximation that the statistical errors scale as the square of the number of experimental measurements, Apgar *et al.* had effectively 200 times as much data as the original fits. Therefore, directly comparing the resulting uncertainties for the two data sets may be misleading. If the proposed experiments were performed with a number of measurements comparable to the actual available experiments, the resulting uncertainties would be $\sqrt{200} \sim 14$ times larger, so their parameter confidence regions would be approximately a factor of 1.4, rather than $0.1 = 10\%$.

We nonetheless remain impressed and surprised by Apgar *et al.*'s result that a careful experimental design can dramatically reduce parameter uncertainties—from factors of $50–10^5$ down to a factor of 1.4, for the same amount of data. In other contexts, where massive amounts of high-quality measurements are possible, Apgar *et al.* resurrect the possibility of solving the inverse problem and extracting the parameters. Their work suggests, though, that to extract reliable parameter estimates in systems biology would demand the development of ambitious high-throughput measurements for many simultaneous components of reaction products, and likely also significant improvement of the reproducibility of biological experiments. It should be reassuring to know that optimal experimental design methods can and have been used to reduce uncertainties in predictions of direct biological interest without first determining the parameters.[4]

References

1 J. F. Apgar, D. K. Witmer, F. M. White and B. Tidor, Sloppy models, parameter uncertainty, and the role of experimental design, *Mol. BioSyst.*, 2010, **6**(10), 1890–900.
2 K. S. Brown, C. C. Hill, G. A. Calero, C. R. Myers, K. H. Lee, J. P. Sethna and R. A. Cerione, The statistical mechanics of complex signaling networks: nerve growth factor signaling, *Phys. Biol.*, 2004, **1**, 184–195.
3 R. N. Gutenkunst, J. J. Waterfall, F. P. Casey, K. S. Brown, C. R. Myers and J. P. Sethna, Universally sloppy parameter sensitivities in systems biology, *PLoS Comput. Biol.*, 2007, **3**(10), e189.
4 F. P. Casey, D. Baird, Q. Feng, R. N. Gutenkunst, J. J. Waterfall, C. R. Myers, K. S. Brown, R. A. Cerione and J. P. Sethna, Optimal experimental design in an EGFR signaling and down-regulation model, *IET Syst. Biol.*, 2007, **1**, 190–202.

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