

Proximate Parameter Tuning: a novel strategy for system identification

¹Stephen J. Wilkinson, ²Neil Benson & ^{1,*}Douglas B. Kell

¹School of Chemistry and MCISB, Manchester Interdisciplinary Biocentre, University of Manchester, Manchester M1 7DN, UK. dbk@manchester.ac.uk www.mcisb.org
www.dbkgroup.org

²Pfizer Central Research, Ramsgate Road, Sandwich, Kent, CT13 9NJ

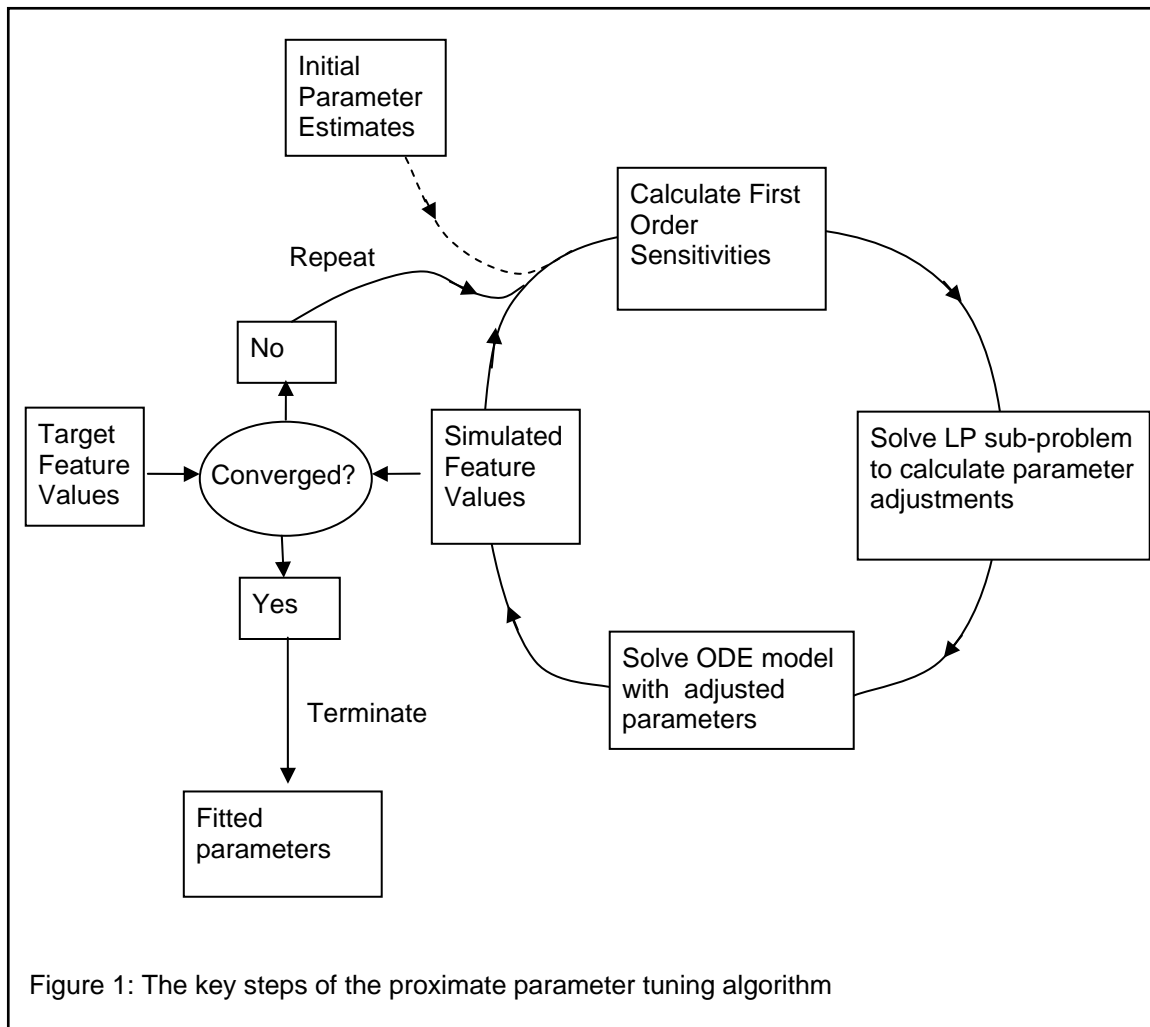
We often have knowledge of the qualitative ‘structure’ of a model and some measurements of the time series of the variables of interest (concentrations and fluxes), but little or no knowledge of the model’s parameters. This is then a system identification problem [1-5], that is commonly addressed by running a model with estimated parameters and assessing how far the model’s behaviour is from the ‘target’ behaviour of the variables, and adjusting parameters iteratively until a good fit is achieved. However, most of these problems are grossly underdetermined, such that many combinations of parameters fit a given set of variables.

We introduce the constraint that the estimated parameters should be within given bounds and as close as possible to stated nominal values.

In general, a model run using the nominal parameter values will give off-target output features since the parameters have been estimated without regard either to their measured values or to those of the output measurements. We therefore need to adjust these values so that the simulated output feature values of the model are closer to the measured (target) values. We have devised an iterative scheme in which the local sensitivity of the required model outputs with respect to all the parameters is evaluated at each iteration. This information is then used to formulate a linear programming sub-problem that predicts the smallest step to take in the parameter space in order to minimize the error between the model outputs and their target values. The parameters are then updated to these new predicted best values and the ODE model re-run to determine the actual simulated values of the output features. This iterative loop is then repeated until the error between the simulated values and the target values is reduced to a specified tolerance as illustrated in Figure 1.

This deterministic ‘proximate parameter tuning’ (PPT) algorithm turns out to be exceptionally effective and performs well compared to other gradient-based and sampling algorithms, e.g. Hooke and Jeeves, Levenberg-Marquardt, a Genetic Algorithm and an Evolutionary Programming strategy as encoded in COPASI [6]. When applied to parameter estimation in a well-established model of yeast glycolysis [7; 8], the PPT performed best 40% of the time, and 70% of the time when only gradient-based algorithms were considered [9], as well as in 3 other models tested (including the p38 signalling pathway and chemical kinetic models).

Overall, this ability of the PPT algorithm to make use of *a priori* knowledge to inform the fitting process is crucial when the measured data are scarce.



The proximate tuning algorithm presented here is a novel and efficient approach with the ability to transform the vast array of dormant biochemical knowledge using time series of variables into initial dynamic models and thus kick start the cycle of model prediction, testing and refinement that will deliver the true potential of systems biology. It also lends itself naturally to the convenient incorporation of any constraint.

- [1] Mendes, P. & Kell, D. B. (1998). Non-linear optimization of biochemical pathways: applications to metabolic engineering and parameter estimation. *Bioinformatics* **14**, 869-883.
- [2] Moles, C. G., Mendes, P. & Banga, J. R. (2003). Parameter estimation in biochemical pathways: a comparison of global optimization methods. *Genome Res* **13**, 2467-74.
- [3] Crampin, E. J., Schnell, S. & McSharry, P. E. (2004). Mathematical and computational techniques to deduce complex biochemical reaction mechanisms. *Prog Biophys Mol Biol* **86**, 77-112.
- [4] Doyle, F. J., 3rd & Stelling, J. (2006). Systems interface biology. *J R Soc Interface* **3**, 603-16.

- [5] Rodriguez-Fernandez, M., Mendes, P. & Banga, J. R. (2006). A hybrid approach for efficient and robust parameter estimation in biochemical pathways. *Biosystems* **83**, 248-65.
- [6] Hoops, S., Sahle, S., Gauges, R., Lee, C., Pahle, J., Simus, N., Singhal, M., Xu, L., Mendes, P. & Kummer, U. (2006). COPASI: a COMplex PATHway SIMulator. *Bioinformatics* **22**, 3067-74.
- [7] Teusink, B., Passarge, J., Reijenga, C. A., Esgalhado, E., van der Weijden, C. C., Schepper, M., Walsh, M. C., Bakker, B. M., van Dam, K., Westerhoff, H. V. & Snoep, J. L. (2000). Can yeast glycolysis be understood in terms of in vitro kinetics of the constituent enzymes? Testing biochemistry. *Eur J Biochem* **267**, 5313-29.
- [8] Pritchard, L. & Kell, D. B. (2002). Schemes of flux control in a model of *Saccharomyces cerevisiae* glycolysis. *Eur. J. Biochem.* **269**, 3894-3904.
- [9] Wilkinson, S. J., Benson, N. & Kell, D. B. (2007). Proximate parameter tuning for biochemical networks with uncertain kinetic parameters. *Mol Biosyst*, in press.