Discussion of "Parameter Estimation for Differential Equations: A Generalized Smoothing Approach"

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The authors are to be congratulated for their elegant approach to reconciling mechanistic dynamic models with time series data. Their methodology appears to be readily applicable to a range of challenging inference problems. I would like to compare and contrast the deterministic dynamic modelling approach, adopted by the authors, with a stochastic dynamic modelling approach. For the sake of discussion, ordinary differential equations (ODEs) can be compared to stochastic differential equations (SDEs), though similar considerations will apply to other models, such as Markov chains.

A drawback of the authors' method is that the fitted model is not readily apparent. One may be led to interpret the fitted model as an ODE with parameter vector $\hat{\theta}$, but of course the trajectories fitted to the data do not perfectly follow this ODE. There is allowance for some deviation, controlled by the parameter λ, and this deviation may be important for both the qualitative and quantitative behaviour of the system. The differences between stochastic dynamic models and their approximating ODEs, termed the "deterministic skeleton" of the model, have been found to be relevant in ecological systems (Coulson et al., 2004). One related issue is, how should trajectories be simulated from the fitted model? In the context of the tank reactor, for example, it would seem desirable if the variability between simulated trajectories were comparable to variability between replications of the experiment. Additionally, such simulated trajectories should be available to a researcher who is aware of only the reported values of $\hat{\theta}$ and λ.

One way around these difficulties is to consider the equivalent SDE, given by the authors in Section 5.2, as the fitted model. The authors are reluctant to do this since "lack of fit in nonlinear dynamics is due more to mis-specification of the system under consideration than to stochastic inputs." I would argue that it should be acceptable to interpret the noise as model mis-specification combined with random variation; such interpretations are certainly routine in linear regression, for example. Quite general methods exist for carrying out inference in the context of partially observed nonlinear SDE systems (Ionides et al., 2006). However, the authors' penalized spline approach has considerable computational advantages that should motivate future work into

clarifying the relationship between the penalized splines and comparable SDE models.

References

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Ionides, E. L., Bretó, C., and King, A. A. (2006). Inference for nonlinear dynamical systems. *Proceedings of the National Academy of Sciences of the USA*, 103:18438–18443.