Estimating kinetic parameters from batch data: breaking correlations using mixed-effects models

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Fitting kinetic parameters often involves data that are obtained from batch or semi-batch experiments, where relevant quantities (e.g., concentration, temperature) are measured at various times through each run, resulting in a set of time series. Kinetic parameters are then fit to these data, often with the use of nonlinear least squares procedures. However, application of standard least squares methods implicitly imposes strong statistical assumptions on the data, in particular, that each individual measurement is statistically independent. In reality, batch datasets often exhibit within-run correlations that violate this assumption, resulting in biased parameter estimates and overly tight confidence intervals.

In this talk, we explore mixed-effects models,[1] which introduce hidden variables that vary from run to run, but remain constant within a run. These models, which have been used by the pharmaceutical industry for decades,[2] provide a flexible framework that can account for both run-to-run variability and within-run correlations. Additionally, mixed-effects models naturally accommodate unbalanced datasets, where some runs have considerably more time points than others, without any additional processing. Fortunately, implementations for fitting these models already exist in common software packages such as SAS and Matlab. Using these routines, we demonstrate the differences in parameter estimates and confidence intervals between the standard nonlinear least squares methods and mixed-effects models for an elementary textbook problem, highlighting how estimates for even simple systems can be improved through mixed-effects modeling.

[1] Laird, N. and Ware, *J. Biometrics* (1982) 38: 963–974.
[2] Pillai, G., Mentré, F., and Steimer, JL. *J Pharmacokinet Pharmacodyn* (2005) 32: 161–183.