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Abstract: Ordinary differential equations (ODEs) are popular tools for modeling complicated dynamic systems in many areas. When multiple replicates of measurements are available for the dynamic process, it is of great interest to estimate mixed-effects in the ODE model for the process. We propose a semiparametric method to estimate mixed-effects ODE models. Rather than using the ODE numeric solution directly, which requires providing initial conditions, this method estimates a spline function to approximate the dynamic process using smoothing splines. A roughness penalty term is defined using the ODEs, which measures the fidelity of the spline function to the ODEs. The smoothing parameter, which controls the trade-off between fitting the data and maintaining fidelity to the ODEs, can be specified by users or selected objectively by generalized cross validation. The spline coefficients, the ODE random effects, and the ODE fixed effects are estimated in three nested levels of optimization. Two simulation studies show that the proposed method obtains good estimates for mixed-effects ODE models. The semiparametric method is demonstrated with an application of a pharmacokinetic model in a study of HIV combination therapy.

Keywords: dynamic models, nonlinear, mixed-effects models, smoothing, splines**,** differential equation, system, model, parameter estimation, pharmacokinetics