

# Chapter XXXIII

## The System for Population Kinetics: Open Source Software for Population Analysis

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### **ABSTRACT**

*This chapter describes the System for Population Kinetics (SPK), a novel Web service for performing population kinetic analysis. Population kinetic analysis is a widely-used tool for extracting information about the probability distributions of unknown parameters in kinetic models. The statistical population model is usually hierarchical, with a nested structure encompassing both variation between subjects and residual unexplained variation associated with the model predictions. The complexity of the analysis is largely driven by the nonlinearity of the models employed. Here, we provide a concise introduction to the topic and a historical perspective for the benefit of the reader who is new to these concepts. Next, we briefly describe the SPK open source system and its multi-tiered architecture, indicating the user goals it set to achieve and elucidating its practical usage with examples.*

### **INTRODUCTION**

Population kinetic analysis is an increasingly important tool for modeling and analyzing biomedical kinetic (time series) data affected by an unfavorable signal-to-noise ratio and relatively short duration. Population kinetics is characterized by the simultaneous modeling of population “typical values” of kinetic parameters and the variability of these kinetic parameters (between subjects) as well as the residual errors in measurement. Its historical development and use, especially in drug development, has been extensively reviewed elsewhere (Pillai et al., 2005). Since the pioneering work of Beal and Sheiner (Beal and Sheiner, 1982) and the development of the NONMEM software (Beal et al, 1989-

2006), population kinetics has been invoked as a useful, and sometimes essential, step in understanding the determinants (demographic, clinical and genetic) of biological variation among experimental subjects. This is particularly useful in presence of sparse data at the individual level. What appears at first to be random variability is gradually explained by invoking deterministic covariates in a process often described as model building (Mandema et al., 1992; Ette and Ludden, 1995). Population kinetic analysis describes the information available at the population level: both typical values and variability estimates. By providing reliable population estimates, these can also be used to inform likely kinetic profiles at the individual subject level. An application where this concept has been applied is individualized, pharmacokinetic-based dosing (Jelliffe et al., 1998; Salinger et al., 2006, among others). Indeed, it can be argued that the first step towards individualized medicine is the understanding of the magnitude of variation among subjects in drug disposition and effect, the knowledge of which then allows one to deploy statistical models that link such observed, quantified variation to other covariates more amenable to direct measurement. The next step is the individualization of models of drug disposition and effect through the availability of individual covariates, thus allowing customized prediction of the events surrounding dose administration (Sheiner and Beal, 1992). Population kinetics is complicated by the fact that the underlying models for drug disposition and effect (termed pharmacokinetics and pharmacodynamics, or PK-PD, respectively), or indeed any other biological phenomenon, are nonlinear in their parameters. That the parameters vary among subjects according to unknown probability distributions adds further layers of complexity. The nonlinear dependence on the parameters prevents the likelihood function required for model fitting from being written in closed form (Davidian and Giltinan, 1995). Thus, since its optimization requires the solution of a multidimensional integral. Indeed, even numerical evaluation of the likelihood is extremely demanding, so much so that optimization of the true likelihood function remains to a large degree impractical.

The availability of the NONMEM software (Beal and Sheiner, 1982), which implements various linearization-inspired parametric approximations to the maximum likelihood problem, as well as the appearance of other modeling software tools, has greatly contributed to the impact of population kinetics on the science and practice of drug development (Sheiner and Steimer, 2000). However, since population kinetics is, in its present realizations, tackled via numerical software predicated on a series of assumptions and approximations, there remains the need for complementary approaches that build on modern software development practices. These should supply the user with a variety of established and novel approximations or approaches to population maximum likelihood, so that the model building process can be adapted to an ever greater variety of data sets and experimental situations. The System for Population Kinetics (SPK) is being developed at the University of Washington with these issues in mind. The SPK has been developed as part of the Core Research and Service missions of the Resource Facility for Population Kinetics (RFPK), a NIH/NIBIB research resource devoted to the development and application of modeling and simulation technology to relevant biomedical problems.

This chapter describes the philosophy behind the SPK, its components and its implementation as a web service, currently available at <http://spk.rfpk.washington.edu>. The SPK is first and foremost an open source product, and as such it builds on the availability of many open source tools. Its flexible modular structure allows rapid deployment of new features and user documentation. With the open source release of the SPK, it is our hope that this software tool will become a collaborative effort spanning many user communities and developers associated with population kinetic analysis.

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