**A General Method for Initialization of Steady-States in Complex PK/PD Systems**

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**Objective:** Steady-states for systems are typically determined by analytical solutions. However, this is not always feasible for complex systems where manual adjustment of the steady state is common. This may impact the accuracy of the results. The objective is to develop a robust method to determine the steady-state synthesis rates of endogenous species in complex systems.

**Methods:** The concept of an integral controller (Figure 1) was adapted to determine the steady-state synthesis rates of non-zero quantities for two systems. The first system, one biomarker upstream of another, was selected to allow for comparison of analytical and numerical solutions explicitly. The second system is a complex physiologically-based pharmacokinetic (PBPK) model where the synthesis rate of endogenous Immunoglobulin-G (IgG) was determined to maintain IgG homeostasis. The proposed method was evaluated during parameter estimation (at each objective function call) as well during stochastic simulations ($\tau_I$ values ranging from $5\times10^{-9}$—$5\times10^{-6}$/min). The accuracy of this method for both systems was evaluated by comparing the absolute relative error normalized to the specified physiological baseline value at $t_{ss}$ (NARE).

**Results:** The proposed method was able to bring both systems to the physiological steady-state levels. The parameter space explored for the PBPK model during an estimation exercise resulted in steady-state synthesis rates ranging from $9.7\times10^{-5}$—$9.0\times10^{-4}$ nmol/min. Further, the PBPK system was able to be stabilized within 25 days over a large range of values of $\tau_I$ (valid for $5\times10^{-8}$—$5\times10^{-6}$/min) resulting in steady-state synthesis rates of $9.5\times10^{-5}$—$8.3\times10^{-4}$ nmol/min for the parameter sets considered. The lowest value of $\tau_I$ considered ($5\times10^{-9}$/min) required a greater stabilization time. For the first system the NARE was below $10^{-6}$ for both biomarkers at $t_{ss}$. For the PBPK system, the NARE was less than $8.02\times10^{-5}$ at 25 days, both during the parameter estimation exercise and for the stochastic simulations for the valid values of $\tau_I$.

**Conclusion:** A numerical method has been adapted and tested for automating the determination of synthesis rates of endogenous species under homeostasis. This method is applicable to complex systems, such as PBPK and quantitative system pharmacological models, where analytical solutions are not practical.