Feedback Control Indirect Response Models

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Objectives: Most physiological processes are subject to feedback regulation. We hypothesize that PK/PD models that do not appropriately incorporate known autoregulatory mechanisms are incomplete representations of the drug-response relationship, and may lead to an underestimation of a drug’s potency. In this study, a new general framework is introduced for modeling pharmacodynamic processes that are subject to autoregulation, which combines the widely used indirect response (IDR) model approach [1] with ideas from classical feedback control of engineered systems.

Methods: Proportional (P), integral (I), derivative (D) and linear combinations of these control terms are incorporated into IDR models to reflect the various feedback input signals, and the constants $G_p$, $G_i$, $G_d$ are their respective gains reflecting their contributions to the control input (see Figure).

![Figure Feedback control indirect response (FC IDR) model framework](image)

$$k_{m}(t) = k_{m0} + G_p (R_0 - R) + G_i \int_0^t (R_0 - R(\tau)) d\tau + G_d \frac{d(R_0 - R)}{dt}$$

Results: Model equations are derived and simulations are conducted to illustrate the framework of FC IDR models. It is demonstrated that ignoring the contributions of feedback control mechanisms in PD studies would lead to the underestimation of drug potency. Four examples [2-5] were selected from literature to illustrate the broad application of the FC IDR framework. The similarities and differences of this proposed framework and two less general approaches which also include feedback are further discussed.

Conclusions: The FC IDR modeling framework allows the drug’s effects to be quantified independently of the autoregulatory mechanisms that also act on the effect variables. It tackles the difficulties long-recognized by systems physiologists in understanding the mechanisms of drug action that underlie processes subject to feedback regulation, and may provide a bridge for development of more mechanistic systems pharmacology models.

References: