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Time Delays in Drug Administration: Effect, Transit, Tricks and Oscillations ⋆

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Abstract: Time delays naturally occur in the administration of drugs, either to mimic normal physiological processes, like the pulsatile release of hormones, or to properly take into account physiological mechanisms (such as distribution to target tissue) which do not occur on a time scale short enough to be considered instantaneous. A number of avenues have been taken to represent these lags mathematically, some more direct than others. We present different approaches employed in pharmacokinetic-pharmacodynamic (PKPD) modeling, in a simple model for the regulation of the glucose-insulin system, and also in the design of pulsatile release mechanism where oscillations are driven by the finite relaxation of a hydrogel membrane. We also illustrate the explicit use of delay-differential equations in a PKPD model for a chemotherapeutic intervention.

Keywords: Nonlinear Dynamics, Lag time, Pharmacometrics, Distribution of delays

1. INTRODUCTION

The monitoring of drug concentration in plasma and its relation with clinical symptoms has a long history, going back at least to the middle of the nineteenth century (Buchanan (1847), Wagner (1981)). The discipline of *pharmacokinetics* ("what the body does to the drug"), developed in the middle of the twentieth century, and the parallel discipline of *pharmacodynamics* ("what the drug does to the body") progressively appeared as more precise descriptions of mechanisms of drug action at the receptor and molecular levels became possible.

With advances in computing power, and improved sophistication of statistical techniques, the subspeciality of population pharmacometrics evolved, and an amalgamation of it with pharmodynamics lead to the emergence of *pharmacometrics*," the science of interpreting and describing pharmacology in a quantitative fashion" (Ette (2007)), so that *quantitative pharmacology* and *pharmacometrics* are employed somewhat interchangeably.

A need to mathematically integrate the modeling at the interface of pharmacokinetics and pharmacodynamics occurs when "[c]ertain pharmacologic effects lag behind plasma drug concentrations...Equilibration delays between plasma and the site of drug action can lead to a lag between pharmacologic response and plasma drug concentrations" (Lalonde (2006), page 68). Such a delayed action occurs during surgery (Sheiner *et al.* (1979)), for example, when the effect of the anesthetic, namely the QT interval duration, cannot be instantaneously correlated to the plasma concentration of the drug, but only appear affected after a certain time lag.

A clever mathematical representation for this lagged effect is the introduction of an additional compartment in the classical compartmental pharmacokinetic framework, the "effect" compartment, the dynamics of which are adjusted to reflect the temporal dynamics of the drug effect" (Sheiner *et al.* (1979), page 359) (see Fig. 1). This compartment is considered to be linked to the plasma (central) compartment by a first-order process with rate constant k_{1e}, and have drug dissipating from it also by a first-order process, with rate constant k_{eo}. The first of these rate constants is assumed to be small with respect to all other rate constants so that the transfer of mass to the effect compartment is negligible.

If A_1 represents the amount of drug in the central compartment, labeled 1 in Fig. 1, and A_e is the hypothetical amount of drug in the effect compartment, then

$$\frac{dA_e}{dt} = k_{1e}A_1 - k_{eo}A_e \tag{1}$$

This amounts to introducing a one-link chain and using the linear chain trick (Smith (2011)) to represent the delay between the central and effect compartments.

This same trick appears in numerous disguises in the modeling of pharmaceutical interventions, either directly with explicit administration apparatus, or more generally to decribe physiological series of events. It is interesting to compare and contrast the use of this technique with a more explicit incorporation of the time delay, this incorporation being, hopefully, a little closer to the physiology (Holford (1991)).

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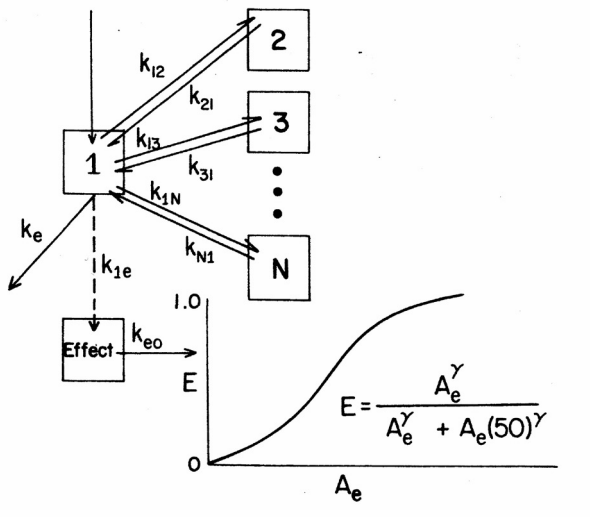

Fig. 1. Combined pharmacokinetic and pharmacodynamic model with an effect compartment described by (1). Reproduced from Sheiner *et al.* (1979).

We recall here two such examples, the first one from a model of insulin regulation and interaction with glucose, the second dealing with oscillatory release of drugs. In the last section, we re-interpret a model of myelosuppression following a chemotherapeutic intervention.

2. GLUCOSE-INSULIN REGULATION

The concentration of glucose in the blood is controlled mainly by insulin secreted from the pancreas, a common dysregulation of this mechanism leading to a diabetic condition. A full description of the glucose-insulin regulatory pathways would involve a number of additional components, such as glucagon, but here we only consider a modification (detailed in Engelborghs *et al.* (2001)) of a relatively simple model for internal glucose regulation (Sturis *et al.* (1991)]): this model was originally designed to provide evidence that a pancreatic pacemaker is not necessary to explain the existence of oscillations in the glucose concentration observed in healthy subjects. In particular, we restructure the model to study the interactions between the internal regulation of glucose of a patient, and an external system of insulin administration. This approach mimics the representation of hormonal replacement intervention having the structure of two parallel delayed feedback loops (Milton *et al.* (1995)).

The original modeling equations are

$$\begin{aligned}
\frac{dx}{dt} &= f_1(z) - E(x/V_1 - y/V_2) - x/t_1 \\
\frac{dy}{dt} &= E(x/V_1 - y/V_2) - y/t_2 \\
\frac{dz}{dt} &= f_5(h_3) + I - f_2(z) - f_3(z)f_4(y) \\
\frac{dh_1}{dt} &= 3(x - h_1)/t_3 \\
\frac{dh_2}{dt} &= 3(h_1 - h_2)/t_3 \\
\frac{dh_3}{dt} &= 3(h_2 - h_3)/t_3
\end{aligned}$$

in which x denotes the plasma insulin, y is the insulin in the interstitial fluid, z is the glucose in the glucose space and I denotes the insulin input. The auxiliary variables h_i represent a three-step process between insulin and glucose production, the choice of a three-step process determined by data-based adjustment of a step increase in insulin level. The functions f_i describe respectively the effect of glucose on insulin secretion (f_1), the effect of glucose on glucose utilization(f_2, f_3), the effect of insulin on glucose utilization (f_4) and the effect of insulin on glucose production (f_5); the first four functions are monotone increasing while the later is monotone decreasing.

The modified version of the model consists of two compartments represent plasmatic insulin and plasmatic glucose. Its mathematical expression simply represents fluid exchanges between the compartments and the external medium. These changes decrease the number of physiological compartments (one insulin compartment instead of two) and lead to the incorporation of a discrete time delay to account for the delayed production of glucose by the liver stimulated by the presence of insulin, thus replacing the three auxiliary variables.

In this modified system, we let I represent insulin and G glucose; we introduce a function $f_1(G)$ representing the pancreatic insulin supply, the ratio I/t_1 as the degradation rate of the insulin by the body, and a constant Eg representing the quantity of glucose supplied by the external medium through injection at a constant rate (corresponding to food intake). An additional function $f_5(I)$ represents the production of hepatic glucose (the liver has a non negligible reaction time, which we represent as a discrete delay τ_2), whereas the functional expression $f_2(G) + f_3(G)f_4(I)$ represents the utilization of glucose by certain tissues, and, finally, a discrete time delay τ_1 stands for the reaction time of the external system. Diabetes implies a decrease in the internal insulin production in the pancreas, hence this process is well described by the term $\alpha f_1(G)$, where α is a real number in the interval $[0, 1]$. In otherwords, α represents the affection degree of the patient: the smaller α is, the more affected the patient is. We can thus write

$$\begin{aligned}
\frac{dI}{dt} &= \alpha f_1(G(t)) - I/t_1 + (1-\alpha)f_1(G(t-\tau_1)) \qquad (2) \\
\frac{dG}{dt} &= Eg + f_5(I(t-\tau_2)) - (f_2(G(t)) + f_3(G(t))f_4(I(t))
\end{aligned}$$

A stationary solution can be shown to exist for (2), and a stability analysis of this equilibrium has been performed: the characteristic equation takes the unequivocally unpleasant form