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Optimal oral drug dosing via application of the contraction mapping theorem

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ABSTRACT

The problem of determining an oral dose, or schedule of oral doses, that gives rise to an arbitrary area-under-curve or to points on the time-series for a variable of interest in a drug kinetics model is considered. These two measures are considered as surrogates for the particular drug response to the dose. The approach taken is to formulate the problem as a fixed point one to which a version of the contraction mapping theorem can be applied. The results, illustrated for a model for the anti-cancer agent topotecan, demonstrate the applicability of the approach.

1. Introduction

One of the benefits of a drug kinetics model is that it permits the prediction of the effect of a given dose on the kinetics of the drug, such as its absorption, distribution, metabolism and elimination. Typically one, or some combination, of the model variables corresponds to pharmacological activity and this might be linked to the drug dynamics, in terms of the effect of the drug. Perhaps the simplest kinetic model is a one-compartment (variable) model describing the plasma concentration of drug with linear elimination, which gives rise to a decaying exponential time course following a bolus injection of drug. Properties of the time course, such as half-life or area-under-curve, might be indicators or predictors of the efficacy of the drug dose.

For example, Evans et al. [1] propose a model for the *in vitro* uptake kinetics of the anti-cancer agent topotecan (TPT). TPT, a water-soluble semi-synthetic derivative of *camptothecin* [2], is a reversible poison of the nuclear enzyme topoisomerase I [3], which is an enzyme used to alleviate torsional stresses during DNA replication [4]. The drug exists in two forms, a pharmacologically active parent lactone form (TPT-L), and an inactive hydroxy acid form (TPT-H). The model proposed in [1] describes the kinetics of the two forms of TPT from input into the medium to delivery to the DNA target, which is represented by a variable in the model corresponding to TPT-L bound to nuclear DNA. The area under the concentration–time curve (AUC) for this variable is used as a surrogate for the 'hit-on-target', that is, the effectiveness of the drug dose. More recently, Chappell et al. [5] coupled the kinetic model with a cell cycle dynamics model in which the concentration–time curve was used directly to consider effectiveness of the drug dose. In this case it was the full time series profile of TPT-L bound to DNA that was important in determining the effect of the drug.

In this paper the problem of determining an optimal oral dose, or oral dosing schedule, for a drug kinetics model is considered. Optimality is regarded with respect to either hit-on-target as represented by the AUC for a particular times-series, or to achieving pre-defined points on a given time-series. The approach taken is to reformulate the problem in such a way as to make the solution the fixed point of a suitable contraction mapping. The approach taken is based on that taken by Evans and Pritchard [6] for containing the outbreak of rabies in a previously naive population.

The earliest use of fixed point methods in a control context was by Hermes [7] for finite-dimensional systems. Davison and Kunze [8] describe the application of fixed point methods to finite-dimensional time-varying systems, and this approach has been extended to infinite-dimensional systems by Magnusson and Pritchard [9]. Carmichael and Quinn [10] provide an early review of the use of fixed point methods in nonlinear control and observation.

The following version of the contraction mapping theorem from [11] is used in this paper:

Theorem 1. *Suppose that* $\varphi : W \to W$ *is a mapping between Banach spaces that satisfies*

$$||\varphi x - \varphi y|| \leq k||x - y||, \quad 0 \leq k < 1$$

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(k a constant), for $x, y \in D$, a subset of W. If both the ball

$$S = \left\{ w \in W : ||w - w_1|| \leq \frac{k}{1-k} ||w_1 - w_0|| \right\}$$

and w_0 lie in D, then the iterative process $w_{i+1} = \varphi w_i$ converges to a unique fixed-point in D.

2. Arbitrary area-under-curve

Consider the problem of choosing a drug dose d for a general drug kinetic model of the following form:

$$\dot{z}(t) = f(z(t)), \quad z(0) = z_0 + Bd \tag{1}$$

$$y(t) = Cz(t) \tag{2}$$

such that a particular area-under-curve (AUC) value is obtained for the desired time course $y(t)$. Thus the problem is to choose d such that $y_T = \int_0^T y(t)\,\mathrm{d}t = y_\mathrm{d}$, for some target value, y_d.

Suppose that an initial guess is made for the dose, $d = \hat{d}$, which gives rise to the following AUC value:

$$\hat{y}_T = \int_0^T C\hat{z}(t)\,\mathrm{d}t$$

where $\hat{z}(t)$ is the solution of the initial value problem

$$\dot{\hat{z}}(t) = f(\hat{z}(t)), \quad \hat{z}(0) = z_0 + B\hat{d}.$$

Since this is unlikely to yield the desired value consider perturbations from this solution; that is, set $x(t) = z(t) - \hat{z}(t)$ and $u = d - \hat{d}$ in Eq. (1) to yield the following:

$$\dot{x}(t) = f(x(t) + \hat{z}(t)) - f(\hat{z}(t)) = A(t)x(t) + N(t, x(t)), \quad x(0) = Bu$$

where $A(t)$ is the Jacobian matrix of f (with respect to z) evaluated at $\hat{z}(t)$. With respect to this perturbed system the output of interest becomes:

$$y_T = C\int_0^T \left(x(t) + \hat{z}(t)\right)\mathrm{d}t = C\int_0^T x(t)\,\mathrm{d}t + \hat{y}_T.$$

Neglecting (for now) the nonlinearity, the problem corresponds to choosing u such that:

$$C\int_0^T \phi(s,0)Bu\,\mathrm{d}s = m_T u = y_\mathrm{d} - \hat{y}_T \quad \text{where } m_T = C\int_0^T \phi(s,0)B\,\mathrm{d}s$$

and $\phi(\cdot,\cdot)$ is the state-transition matrix for the time-varying linear system. Since m_T is a number then the unique solution (for the linear system) is given by:

$$u_* = \frac{(y_\mathrm{d} - \hat{y}_T)}{m_T}.$$

Now considering the full nonlinear system this suggests choosing u such that:

$$\begin{aligned} C\int_0^T x(t)\,\mathrm{d}t &= C\int_0^T \left[\phi(t,0)Bu + \int_0^t \phi(t,s)N(s,x(s))\mathrm{d}s\right]\mathrm{d}t \\ &= y_\mathrm{d} - \hat{y}_T, \end{aligned}$$

giving

$$m_T u = y_\mathrm{d} - \hat{y}_T - C\int_0^T\int_0^t \phi(t,s)N(s,x(s))\,\mathrm{d}s\,\mathrm{d}t$$

and so the choice for the dose is given by

$$u_* = \frac{1}{m_T}\left[y_\mathrm{d} - \hat{y}_T - C\int_0^T\int_0^t \phi(t,s)N(s,x(s))\,\mathrm{d}s\,\mathrm{d}t\right]. \tag{3}$$

This, however, gives an implicit relationship between u_* and the solution x (which requires u_*). To overcome this problem a fixed-point is sought of the following operator:

$$\begin{aligned} (\Psi x)(t) = &\int_0^t \phi(t,s)N(s,x(s))\,\mathrm{d}s + m_T^{-1}\phi(t,0)B \\ &\left[y_\mathrm{d} - \hat{y}_T - C\int_0^T\int_0^t \phi(t,s)N(s,x(s))\,\mathrm{d}s\,\mathrm{d}t\right]. \end{aligned} \tag{4}$$

If x is a fixed point of this operator, Ψ, then the AUC for the dose $\hat{d} + u_*$ is then given by:

$$y_T = C\int_0^T x(t)\,\mathrm{d}t + \hat{y}_T = C\int_0^T (\Psi x)(t)\,\mathrm{d}t + \hat{y}_T = y_\mathrm{d}.$$

Thus the desired AUC is achieved for the dose $\hat{d} + u_*$, provided there exists a fixed point of the operator Ψ defined in (4).

Theorem 2. *Suppose that the following are satisfied*:

1. *$N(\cdot, x(\cdot)) \in L^s(0,T;\mathbb{R}^n)$ whenever $x(\cdot) \in L^r(0,T;\mathbb{R}^n)$ where $r, s \geq 1$ are real numbers*;
2. *$N : [0,T] \times \mathbb{R}^n \to \mathbb{R}^n$ is Lipschitz on the ball $B(\bar{a})$ of radius $\bar{a}$ about the origin in $L^r(0,T;\mathbb{R}^n)$*:

$$||N(\cdot, z_1(\cdot)) - N(\cdot, z_2(\cdot))||_s \leq h(||z_1||, ||z_2||)||z_1 - z_2||_r$$

for $z_i \in B(\bar{a})$ and $h : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ is continuous, symmetric and $h(0,0) = 0$;
3. *Let $a \leq \bar{a}$ be such that*

$$||\phi||\left[\frac{T||\phi||\,||B||\,||C||}{|m_T|} + 1\right]\tilde{T}K = \tilde{K} < 1$$

where $K = \sup_{0\leq w,v\leq a} h(w,v)$ and $\tilde{T} = T^{(1+(1/r)-(1/s))}$.

If the AUC corresponding to the initial dose, $\hat{y}_T$, is close to the target value in the sense that

$$||y_\mathrm{d} - \hat{y}_T|| \leq \frac{a|m_T|\left(1-\tilde{K}\right)}{||\phi||T^{1/r}||B||} \tag{5}$$

then the operator Ψ in Eq. (4) *has a unique fixed point.*

Proof. To see that Ψ is a contraction on the ball $B(a)$ note that:

$$\begin{aligned} ||\Psi x_1 - \Psi x_2||_r &\leq \tilde{T}||\phi||K||x_1 - x_2||_r + T\tilde{T}|m_T|^{-1}||\phi||^2||B||\,||C||K||x_1 - x_2||_r \\ &= ||\phi||\left[\frac{T||\phi||\,||B||\,||C||}{|m_T|} + 1\right]\tilde{T}K||x_1 - x_2||_r. \end{aligned}$$

Let $x_0 = 0$, $x_1 = \Psi x_0 = m_T^{-1}\phi(\cdot,0)B\left[y_\mathrm{d} - \hat{y}_T\right]$ and S be the ball

$$S = \left\{ x \in L^r(0,T;\mathbb{R}^n) : ||x - x_1|| \leq \frac{\tilde{K}}{1-\tilde{K}}||x_1||_r \right\}.$$

S is contained within the ball $B(a)$ provided

$$\left[1 + \frac{\tilde{K}}{1-\tilde{K}}\right]||m_T^{-1}\phi(\cdot,0)B\left[y_\mathrm{d} - \hat{y}_T\right]||_r \leq a$$

which is guaranteed by Eq. (5). Applying Theorem 1 proves the required result. □

A natural extension to the problem considered in this section is to consider multiple doses. However, since it is possible to achieve any desired AUC for a single dose it seems natural to consider the problem of achieving different AUC values on different time intervals. This problem reduces to repeated application of the single dose problem above.