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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.

Keywords: Optimization problems, Biomedical control, Biomedical systems, Control applications, Control algorithms

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.

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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 is used directly to consider effectiveness of the drug dose. In this case it is the full time series profile of TPT-L bound to DNA that is 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* $\varphi : W \longrightarrow W$ *is a mapping between Banach spaces that satisfies*

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

(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:

$$\begin{aligned} \dot{z}(t) &= f(z(t)), \qquad z(0) = z_0 + Bd & (1) \\ y(t) &= Cz(t) & (2) \end{aligned}$$

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

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

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 Equation (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:

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

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:

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

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:

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

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

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

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. $N : [0,T] \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ *is Lipschitz on the ball* $B(\overline{a})$ *of radius* $\overline{a}$ *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 $z_i \in B(\overline{a})$ *and* $h : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ *is continuous, symmetric and* $h(0,0) = 0$*;*
3. *Let* $a \leq \overline{a}$ *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* $\tilde{T} = T^{\left(1 + \frac{1}{r} - \frac{1}{s}\right)}$.

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 Equation* (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 Equation (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.

3. Reference time-series

Now consider the problem, for (1)–(2), of choosing a dose, or sequence of doses, such that particular points on the times series curve for y are achieved. Therefore, let $Y_{\mathrm{d}} = \begin{pmatrix} y_{\mathrm{r}}(t_1) & y_{\mathrm{r}}(t_2) & \dots & y_{\mathrm{r}}(t_m) \end{pmatrix}^T$ denote a vector of points on a desired time-series curve y_{r}. The control problem is to achieve these points for a suitable dose d, or doses d_i.

Consider the problem with l doses at regular intervals of T starting at $t = 0$:

$$\begin{aligned} \dot{z}_i(t) &= f(z_i(t)), \quad z_i(0) = z_{i-1}(T) + Bd_i && (6) \\ y_i(t) &= Cz_i(t) && (7) \\ Y_i &= \begin{pmatrix} y_i(t_{1_i}) & \dots & y_i(t_{m_i}) \end{pmatrix}^T && (8) \end{aligned}$$

where $z_1(0) = z_0 + Bd_1$ and $i = 1, \dots, l$.

Proceeding in a similar manner as in the previous section, let $\hat{d}_i$ denote initial guesses for the doses, which give rise to output time series of the form:

$$\hat{y}_i(t) = C\hat{z}_i(t) \qquad \text{and} \qquad \hat{Y}_i = \begin{pmatrix} \hat{y}_i(t_{1_i}) & \hat{y}_i(t_{2_i}) & \dots & \hat{y}_i(t_{m_i}) \end{pmatrix}^T$$

where $\hat{z}_i(t)$ is the solution of the initial value problem given by (6)–(7) with $\hat{d}_i$ replacing d_i. Again, let $x_i(t) = z_i(t) - \hat{z}_i(t)$ and $u_i = d_i - \hat{d}_i$ in (6)–(8) to yield the following:

$$\dot{x}_i(t) = A_i(t)x_i(t) + N_i(t, x_i(t)), \qquad x_i(0) = x_{i-1}(T) + Bu_i$$

where $A_i(t)$ is the Jacobian matrix of f evaluated at $\hat{z}_i(t)$ and $x_0(T) = 0$. With respect to this perturbed system the output becomes

$$y_i(t) = Cx_i(t) + \hat{y}_i(t)$$

and so the aim is to choose the u_i such that

$$Cx_i(t_{k_i}) = y_{\mathrm{r}}(\tau_i + t_{k_i}) - \hat{y}_i(t_{k_i}) \quad k_i = 1_i, \dots, m_i$$

for $i = 1, \ldots, l$ where $\tau_i = (i-1)T$. Neglecting (for now) the nonlinearities, this corresponds to choosing $u = (u_1, \ldots, u_l)^T$ such that:

$$Mu = \begin{pmatrix} M_{11} & 0 & \ldots & 0 \\ M_{21} & M_{22} & \ldots & 0 \\ \vdots & \vdots & & \vdots \\ M_{l1} & M_{l2} & \ldots & M_{ll} \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ \ldots \\ u_l \end{pmatrix} = Y_{\mathrm{d}} - \hat{Y}$$

where

$$M_{ij} = \begin{pmatrix} C\phi_i(t_{1_i}, 0)\phi_{i-1}(T, 0) \ldots \phi_j(T, 0)B \\ \vdots \\ C\phi_i(t_{m_i}, 0)\phi_{i-1}(T, 0) \ldots \phi_j(T, 0)B \end{pmatrix}$$

since (in the linear case)

$$Cx_i(t_{k_i}) = C\phi_i(t_{k_i}, 0)\left(x_{i-1}(T) + Bu_i\right).$$

The matrix $M \in \mathbb{R}^{m \times l}$ is unlikely to be invertible and so the least squares solution is chosen:

$$u_* = M^\dagger \left(Y_{\mathrm{d}} - \hat{Y}\right),$$

where $M^\dagger$ is the pseudo-inverse of M. Now considering the full nonlinear system, let

$$\begin{aligned} \mathcal{N}_i x(t_{k_i}) = C \int_0^{t_{k_i}} & \phi_i(t_{k_i}, s) N_i(s, x_i(s))\, \mathrm{d}s \\ & + C\phi_i(t_{k_i}, 0) \int_0^T \phi_{i-1}(T, s) N_{i-1}(s, x_{i-1}(s))\, \mathrm{d}s + \cdots \\ & + C\phi_i(t_{k_i}, 0) \ldots \phi_2(T, 0) \int_0^T \phi_1(T, s) N_1(s, x_1(s)) \mathrm{d}s \end{aligned}$$

and

$$\mathcal{N}x = (\mathcal{N}_1 x(t_{1_1}), \ldots, \mathcal{N}_1 x(t_{N_1}), \quad \ldots \quad, \mathcal{N}_l x(t_{1_l}), \ldots, \mathcal{N}_l x(t_{N_l}))^T.$$

Then the linear approach suggests choosing u such that:

$$u_* = M^\dagger \left(Y_{\mathrm{d}} - \hat{Y} - \mathcal{N}(x)\right),$$

but, as in the last section this leads to an implicit equation for x (the solution on $[0,\tau]$, $\tau = l \times T$, obtained by piecing together the x_i). Again, to overcome this a fixed-point is sought of the following operator, Ψ:

$$(\Psi x)(\tau_i + t) = \phi_i(t,0)\left[x_{i-1}(T) + BM_i^\dagger\left[Y_\mathrm{d} - \hat{Y} - \mathcal{N}x\right]\right] + \int_0^t \phi_i(t,s)N(s,x_i(s))\,\mathrm{d}s \quad (9)$$

where $M_i^\dagger$ is the i^{th} row of $M^\dagger$.

If a fixed-point of Ψ exists then the output corresponding to the fixed point is given by:

$$\begin{aligned} Y &= MM^\dagger\left(Y_\mathrm{d} - \hat{Y} - \mathcal{N}(x)\right) + \mathcal{N}(x) + \hat{Y} \\ &= MM^\dagger Y_\mathrm{d} + \left(I - MM^\dagger\right)\left(\hat{Y} + \mathcal{N}(x)\right). \end{aligned}$$

Hence the difference between the achieved profile and the target profile is given by:

$$Y - Y_\mathrm{d} = \left(I - MM^\dagger\right)\left(\hat{Y} - Y_\mathrm{d} + \mathcal{N}(x)\right),$$

where the right-hand side is the orthogonal projection onto $(\operatorname{ran} M)^\perp$. Thus it is seen that the reference profile is matched on the range of M.

To illustrate the application of the fixed point theorem to the problem of obtaining given points on a reference time-series, the single-dose case is considered first by the following theorem:

Theorem 3. *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. $N : [0,T] \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ *is Lipschitz on the ball* $B(\overline{a})$ *of radius* $\overline{a}$ *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 $z_i \in B(\overline{a})$ *and* $h : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ *is continuous, symmetric and* $h(0,0) = 0$*;*

3. *Let $a \leq \overline{a}$ be such that*

$$\left[\sqrt{m}\,\|M^\dagger\|\,\|\phi_1\|\,\|B\|\,\|C\| + 1\right]\|\phi_1\|\tilde{T}K = \tilde{K} < 1$$

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

If the target profile, $Y_{\rm d}$, is close to that corresponding to the initial dose, $\hat{Y}$, in the sense that

$$\|Y_{\rm d} - \hat{Y}\| \leq \frac{a\left(1-\tilde{K}\right)}{T^{1/r}\|\phi_1\|\,\|B\|\,\|M^\dagger\|} \tag{10}$$

then the operator Ψ in (9) (single-dose case) has a unique fixed point.

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

$$\begin{aligned}\|\Psi w - \Psi v\|_r &\leq \tilde{T}\|\phi_1\|K\|w-v\|_r \\ &+ \sqrt{m}\,\tilde{T}\|M^\dagger\|\|\phi_1\|^2\|B\|\,\|C\|K\|w-v\|_r \\ &= \left(\sqrt{m}\,\|M^\dagger\|\,\|\phi_1\|\,\|B\|\,\|C\|\right. \\ &\qquad\qquad \left.+\,1\right)\|\phi_1\|\tilde{T}K\|w-v\|_r\end{aligned}$$

Let $x_0 = 0$, $x_1 = \Psi x_0 = \phi_1(\cdot,0)BM^\dagger\left[Y_{\rm d} - \hat{Y}_T\right]$ 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

$$\left[1 + \frac{\tilde{K}}{1-\tilde{K}}\right]\|\phi_1(\cdot,0)BM^\dagger\left[Y_{\rm d} - \hat{Y}_T\right]\|_r \leq a$$

which is guaranteed by (10). Applying Theorem 1 proves the required result. □

For the full multiple-dosing case the following result is obtained:

Theorem 4. *Suppose that the following are satisfied:*

1. *$N(\cdot,x(\cdot)) \in L^s(0,\tau;\mathbb{R}^n)$ whenever $x(\cdot) \in L^r(0,\tau;\mathbb{R}^n)$, $r,s \geq 1$ are real numbers;*

2. *$N : [0, \tau] \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ is Lipschitz on the ball $B(\overline{a})$ of radius $\overline{a}$ about the origin in $L^r(0, \tau; \mathbb{R}^n)$:*

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

for $z_i \in B_{\overline{a}}$ and $h : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ is continuous, symmetric and $h(0, 0) = 0$.

There exists an $a \leq \overline{a}$ and a $\tilde{K}$ such that if the target profile, Y_{d}, is close to that corresponding to the initial dose, $\hat{Y}$, in the sense that

$$\|Y_{\mathrm{d}} - \hat{Y}\| \leq \frac{a\left(1 - \tilde{K}\right)}{\tau^{1/r}\|\phi\|\,\|B\|\,\|M^{\dagger}\|} \tag{11}$$

then the operator Ψ in (9) has a unique fixed point.

PROOF. First note that on the ball $B(a)$:

$$\|\Psi w - \Psi v\|_r \leq (k_1 + k_2 K)\,\|w - v\|_r$$

for suitable constants k_1 and k_2, where $K = \sup_{0 \leq w, v \leq a} h(w, v)$. Therefore, choosing $a \leq \overline{a}$ such that

$$k_1 + k_2 K = \tilde{K} < 1$$

it is seen that Ψ is a contraction on $B(a)$.

Let $w = 0$, $v = \Psi w$ so that

$$v(\tau_i + t) = \phi_i(t, 0) B M_i^{\dagger}\left[Y_{\mathrm{d}} - \hat{Y}\right]$$

and S be the ball

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

S is contained within the ball $B(a)$ provided (11) is satisfied. Applying Theorem 1 proves the required result. □

4. Example

To illustrate the theory of the previous two sections the results are applied to a model for the *in vitro* kinetics of the anti-cancer agent topotecan [1]. The model describes the distribution and activity of the drug when added to a medium containing human cancer cells (data from the MCF-7 breast cancer cell line was used by Evans et al. [1] in estimating the model parameters). The concentration of pharmacologically active drug is denoted by L while the corresponding concentration for the inactive form is denoted by H. A schematic of the model is shown in Figure 1.

To allow for mixing in the physical medium (as seen in the experimental data) it is divided into two pools: the medium pool (denoted by a subscript m), which represents the majority of the physical medium and is the pool into which the drug is added; and an extracellular pool (denoted by a subscript e), which represents the part of the physical medium in which the cells are located. Therefore active drug enters the system via the medium pool (where reversible hydrolysis to the inactive form takes place) and can then mix with the extracellular pool (with reversible first order rate processes). Reversible hydrolysis also occurs in the extracellular pool.

From the extracellular pool active drug diffuses across the cell membrane into the cytoplasm (denoted by a subscript c) and this process is first order in both directions. Reversible hydrolysis of the active form of the drug also occurs in the cytoplasm. Only active drug in the cytoplasm is assumed to enter the nucleus (denoted by a subscript n), where it binds to the target. The concentration of active drug bound to DNA, represented in the model by L_n, can therefore be related to the effect of the drug. Evans et al. [1] used the AUC for L_n over the first hour following administration as a surrogate for drug effect. More recently, Chappell et al. [5] directly coupled the kinetic model, using L_n, to a cell cycle model in order to model the effect of a dose on the cell cycle.

The model equations are as follows:

$$\begin{aligned}
\dot{L}_m &= -(k_{om} + k_{mi})L_m + k_{cm}H_m + k_{mo}v_0 L_e \\
\dot{H}_m &= k_{om}L_m - (k_{cm} + k_{mi})H_m + k_{mo}v_0 H_e \\
\dot{L}_e &= \frac{k_{mi}}{v_0}L_m - (k_{mo} + k_{om} + k_i)L_e + k_{cm}H_e + \frac{k_e}{v_1}L_c \\
\dot{H}_e &= \frac{k_{mi}}{v_0}H_m + k_{om}L_e - (k_{cm} + k_{mo})H_e \\
\dot{L}_c &= k_i v_1 L_e - (k_e + k_{oc})L_c + k_{cc}H_c + k_{dl}v_2 L_n - k_b(B_T - L_n)L_c \\
\dot{H}_c &= k_{oc}L_c - k_{cc}H_c + k_{dh}v_2 L_n \\
\dot{L}_n &= \frac{k_b}{v_2}(B_T - L_n)L_c - (k_{dl} + k_{dh})L_n
\end{aligned}$$

where $v_0 = V_e/V_m$ is the ratio of the volumes of the extracellular pool (V_e) and medium pool (V_m), $v_1 = V_e/V_c$ is the ratio of the volumes of the extracellular pool and cytoplasm (V_c), and $v_2 = V_n/V_c$ is the ratio of the volumes of the nucleus (V_n) and cytoplasm. The corresponding initial conditions for the model are:

$$L_m(0) = (1 + v_0)d,\ H_m(0) = L_e(0) = H_e(0) = L_c(0) = H_c(0) = L_n(0) = 0.$$

The problem is to choose the dose d.

4.1. AUC: Single dose

The first problem considered is to achieve an AUC for L_n, over a one hour exposure, of 43.2 mol·s/m^3 (12 μM·h), which is expected to require a dose greater than 10 mmol/m^3 (μM) [1]. Using the approach of Section 2 the known initial condition z_0 in (1) is the zero vector, since no drug is present prior to the start of the experiment; the matrix defining the structure of the input dose, B, is given by

$$B = \begin{pmatrix} (v_0 + 1) & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}^T.$$

Once an initial estimate, $\hat{d}$, is made for the dose and the perturbed system about the resulting trajectory, $\hat{z}(\cdot)$, obtained, the proof of Theorem 2 provides a constructive means for determining the fixed-point of Ψ defined in (4). Once this fixed-point has been determined then (3) is used to determine u_* and the required dose is $\hat{d} + u_*$.

For initial estimates for the dose, $\hat{d}$, up to 40 mmol/m^3 (μM) the required dose can be found, using this approach, to be 10.53 mmol/m^3 (μM), which gives a peak concentration of bound drug (L_n) of 13.55 mmol/m^3 (μM). A plot of the resulting nuclear bound drug is shown in Figure 2. For initial estimates less than that required for the prescribed AUC, the approach results in the required dose. As the initial estimate for the dose exceeds that required convergence becomes an issue since the value of m_T decays exponentially with the estimate used. In particular, the weighted error for the initial estimate, $\|y_\mathrm{d} - \hat{y}_T\|/m_T$, grows in a parabolic fashion ensuring that (5) no longer holds (see Figure 3).

4.2. AUC: Multiple doses

Suppose that it is necessary, in the previous problem, to limit the peak concentration of bound drug (L_n) or to limit the administered dose d at any instant. A straightforward way to do this is to split the dose into N multiple doses, d_i, given at equal time points, $t_i = (i-1)T/N$, throughout the full dosing period T (where $T = 1$ h in this example). The approach taken in the previous section can then be applied on each of the dosing intervals ($[t_i, t_{i+1})$ for $i = 1, \ldots, N$) as a single dose AUC problem. The problem of determining doses to give a certain AUC across the whole of the time interval $[0, T]$ then becomes N separate single-dose problems such that the total sum is the required AUC.

For $N = 2$ two doses are applied, one at $t = 0$ and the other at $t = 30$ minutes, and the problem is split into two single-dose AUC problems corresponding to these doses. The second single-dose AUC problem, on the last 30 minutes of exposure, uses the final state of the first problem (i.e., at 30 minutes) as the known initial condition. It therefore only remains to split the target AUC into the sum of two values that are to be achieved on the two dosing intervals. The limiting factor in dividing the AUC is the value for the first interval, since prior to the first dose no drug is present in the system and so the target concentration, L_n, has to build up. However, if the value chosen is too small the dose required for the second interval might be too high. If the aim of the dosing strategy is to achieve a total AUC of 43.2 mol·s/m^3 (12 μM·h), but limit L_n to less than 13 mmol/m^3 (μM) then the AUC can be split into 20.34 mol·s/m^3 (5.65μM·h) and 22.86 mol·s/m^3 (6.35μM·h). The first of these values is chosen to be the maximum possible while limiting the peak bound concentration to less than 13 mmol/m^3 (μM). The necessary doses for these two single-dose AUC problems are 9.95 mmol/m^3 (μM)

and 1.17 mmol/m^3 (μM), respectively. On the two time intervals the peak concentrations of bound drug are 12.91 mmol/m^3 (μM) and 13.01 mmol/m^3 (μM), respectively. A plot of the resulting nuclear bound drug is shown in Figure 2 where the profile is seen to give a lower peak than the single dose case and maintains a more constant level.

Extending to four doses given at 0, 15, 30, and 45 minutes, the AUC can be split into 8.46, 11.52, 11.52, and 11.7 mol·s/m^3 (2.35, 3.2, 3.2, and 3.25 μM·h). With more doses there is greater flexibility in splitting the required AUC, though the value than can be achieved on the first interval is limited since no drug is present before administration. The values that the target AUC are divided into are chosen to flatten the time-series plot of bound nuclear (target) drug. The corresponding doses are 9.29, 1.05, 0.55, and 0.79 mmol/m^3 (μM), and the peak concentrations of bound drug are 12.17, 12.98, 12.91, and 13.11 mmol/m^3 (μM). A plot of the resulting nuclear bound drug is shown in Figure 2 where the profile is seen to maintain a much more constant level than the single or double dose cases.

It should be noted that this method does not exploit the fact that at the end of any given dosing period there is drug stored within the compartments and that the amount of drug present is dependent on all of the previous doses. Although an approach based on that taken with the time-series problem in Section 3 would exploit this dependence, it would not utilise the fact that on any given dosing period there exists a dose that gives the required AUC exactly.

From Figure 2 it is seen that a potentially limiting factor is the initial rise in drug bound to the target. This initial rise is dependent on the size of the first dose, which then affects subsequent doses. For example, notice that in the case of four equally spaced doses the bound concentration does not approach the constant level until the second dose, whereas for the single and double dose cases this happens for the first dose, though there is corresponding over-shoot of the average level. The effect of these issues is that the first dose might be constrained by a maximum target level (in this example bound active drug), which then limits the initial slope and hence the AUC that can be achieved on the first dosing interval. Subsequent dosing intervals are then limited in turn as a result. To overcome these points the AUC problem can be reformulated in terms of achieving a particular time-series, such as a constant level, that has the required AUC.

4.3. Time-series: Reconstruction of dose

To illustrate the theory of Section 3 a theoretical example is considered first in which a time-series corresponding to a particular dosing regime is used to try to find the original dosing schedule. More precisely, the following sequence of doses is applied every 15 minutes for a total duration of one hour: 2, 5, 2, and 1 mmol/m^3 (μM). The time series is sampled at times 5, 10, 15, 20, 25, 30, 40, and 50 minutes after the first dose.

Starting with an initial guess of 1, 0, 0, and 0 mmol/m^3 (μM) the method finds the original dosing scheme. Similarly, if the scheme were grossly overestimated, say with an initial guess of 10, 10, 10, and 10 mmol/m^3 (μM), the method finds the original dosing scheme. The desired sample points are plotted in Figure 4 together with the time series for the nuclear bound drug, L_n. Unsurprisingly, there is good correspondence between the time-series profile and the target one.

4.4. Time-series: Modifying existing series

The target profile from the previous section is modified by reducing all points to 10% of their previous values and the method run again. This scenario represents the case where the profile of an existing dosing scheme needs to be reduced. The dosing scheme in this case is given by 0.20, 0.45, 0.16, and 0.08 mmol/m^3 (μM). The resulting profile for bound active drug is plotted in Figure 5, together with the target points. There is good correspondence between the time series for the dosing scheme and the target.

Conversely, the target profile from the previous section is doubled and the method run again. In this case the dosing scheme returned is given by 4.09, 11.50, 5.30, and 2.55 mmol/m^3 (μM). The resulting profile for bound active drug is plotted in Figure 6, together with the target points. Again, there is good correspondence between the time series for the dosing scheme and the target.

It was seen in Section 3 that the method for finding the required dose is guaranteed to achieve the required profile on the range of the matrix M, provided the profile corresponding to the initial estimate for the dose is close enough to the target. The aim in modifying the series arising from a given dose is to minimise the orthogonal projection of the target profile onto $(\operatorname{ran} M)^{\perp}$ and therefore enabling a good correspondence between actual and target series to be achieved.

4.5. Time-series: Constant profile

While considering the problem of obtaining a given AUC from multiple doses it was found that the problem could be reformulated in terms of reproducing a constant, or piecewise constant, time-series. First the problem of achieving a target dose consisting of a constant 10 mmol/m^3 (μM) with four doses 15 minutes apart is considered. The dosing scheme obtained is 7.67, 0.08, 0.54, and 0.33 mmol/m^3 (μM) and the resulting time series for bound nuclear active drug is shown in Figure 7. As was noted for the multiple-dose AUC problem the initial slope of the bound drug curve is determined by the initial dose, which is influenced for the time-series problem by the first target point, $y_{\mathrm{r}}(t_1)$. This example highlights a limitation of the method for finding the doses in that the doses should be constrained to be non-negative. If the first time point is too close to zero the resulting first dose results in large over-shoot before the second dose is delivered and so a negative value is obtained for the second dose. By choosing a sampling of every 10 minutes up to 30 minutes, and then every 5 minutes avoids this problem, but this is not ideal. From Figure 7 it is seen that there is good correspondence between the achieved profile and the target one.

Considering the graph of the bound drug time series in Figure 7 the approximate AUC for the last 50 minutes is 30 mol·s/m^3 (8.33 μM·h). The AUC for the first 10 minutes is between 3 mol·s/m^3 (0.83 μM·h) and 6 mol·s/m^3 (1.67 μM·h), giving a total AUC of between 33 mol·s/m^3 (9.17 μM·h) and 36 mol·s/m^3 (10 μM·h). Modifying the target dose to a constant 12.5 mmol/m^3 (μM) (with four doses 15 minutes apart is considered) yields a dosing scheme of 9.87, 0.13, 0.70, and 0.42 mmol/m^3 (μM) and the resulting time series for bound nuclear active drug is shown in Figure 8. For this dosing scheme the approximate AUC is between 41.25 mol·s/m^3 (11.5 μM·h) and 45 mol·s/m^3 (12.5 μM·h). The concentration of bound active drug is limited to a maximum value of 12.85 mmol/m^3 (μM). Compared with the dosing schedule to achieve an AUC of 43.2 mol·s/m^3 (12 μM·h) it is seen that the dose has been successfully limited to below 13 mmol/m^3 (μM) and yet the target AUC has been approximately achieved; the actual AUC for this example is 42.77 mol·s/m^3 (11.88 μM·h).

5. Conclusions

A fixed point approach has been employed to determine dosing schemes that determine arbitrary area-under-curve for desired model species, or to

determine schemes that give rise to particular time series points for the desired model species. The approach is a model based one and so applicability is dependent on the validation of the proposed model.

Applying the approach for arbitrarily setting the area-under-curve multiple times can give greater flexibility in avoiding large peak values or prohibitively large doses. However, a draw-back of this computationally easier approach is that dependence between doses in a scheme is ignored.

The approach to reproduce time series data works well in the case of reconstructing an unknown dose, or modifying an existing profile. For an arbitrary profile the approach does not guarantee to determine a dose that produces it. Indeed, such a profile may be outside the range of feasible profiles.

[1] N. D. Evans, R. J. Errington, M. J. Chapman, P. J. Smith, M. J. Chappell, K. R. Godfrey, Compartmental modelling of the uptake kinetics of the anti-cancer agent topotecan in human breast cancer cells, International Journal of Adaptive Control and Signal Processing 19 (2005) 395–417.

[2] J. O'Leary, F. M. Muggia, Camptothecins: a review of their development and schedules of administration, European Journal of Cancer 34 (1998) 1500–1508.

[3] Y. H. Hsiang, L. F. Lui, Identification of mammalian DNA topoisomerase-I as an intracellular target of the anticancer drug camptothecin, Cancer Research 48 (1988) 1722–1726.

[4] C. Bailly, Topoisomerase I poisons and suppressors as anticancer drugs, Current Medicinal Chemistry 7 (2000) 39–58.

[5] M. J. Chappell, N. D. Evans, R. J. Errington, I. A. Khan, L. Campbell, R. Ali, K. R. Godfrey, P. J. Smith, A coupled drug kinetics-cell cycle model to analyse the response of human cells to intervention by topotecan, Computer Methods and Programs in Biomedicine 89 (2008) 169–178.

[6] N. D. Evans, A. J. Pritchard, A control theoretic approach to containing the spread of rabies, IMA Journal of Mathematics Applied in Medicine and Biology 18 (2001) 1–23.

[7] H. Hermes, Controllability and the singular problem, Journal of the Society for Industrial and Applied Mathematics, Series A: Control 2 (1964) 241–260.

[8] E. J. Davison, E. C. Kunze, Some sufficient conditions for the global and local controllability of nonlinear time varying systems, SIAM Journal on Control 8 (1970) 489–497.

[9] K. Magnusson, A. J. Pritchard, Local exact controllability of nonlinear evolution equations, in: R. Conti (Ed.), Recent advances in differential equations, Academic Press, London, 271–280, 1981.

[10] N. Carmichael, M. D. Quinn, Fixed-point methods in nonlinear control, IMA Journal of Mathematical Control and Information 5 (1988) 41–67.

[11] L. Collatz, Functional analysis and numerical mathematics, Academic Press, New York, 1966.

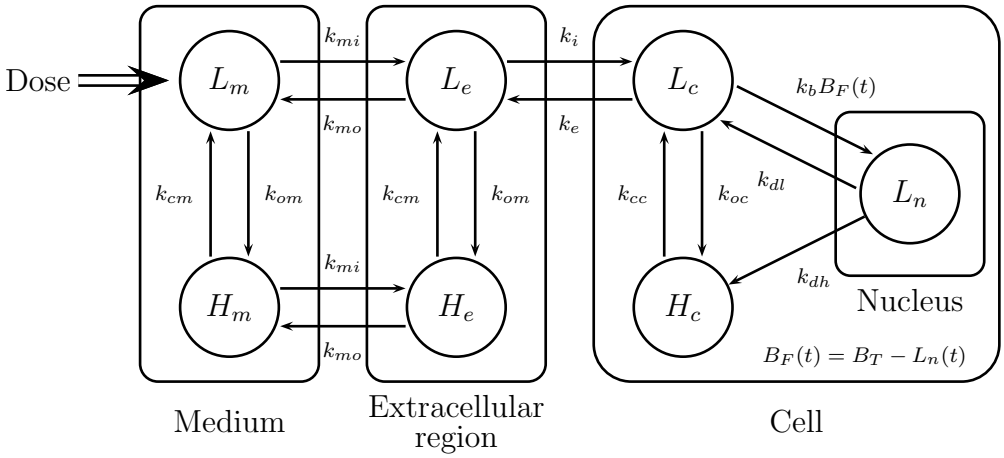

Figure 1: Schematic of the mathematical model developed by Evans et al. [1] to investigate the uptake kinetics of TPT in a culture medium containing human breast cells (MCF-7 cell line) in suspension.

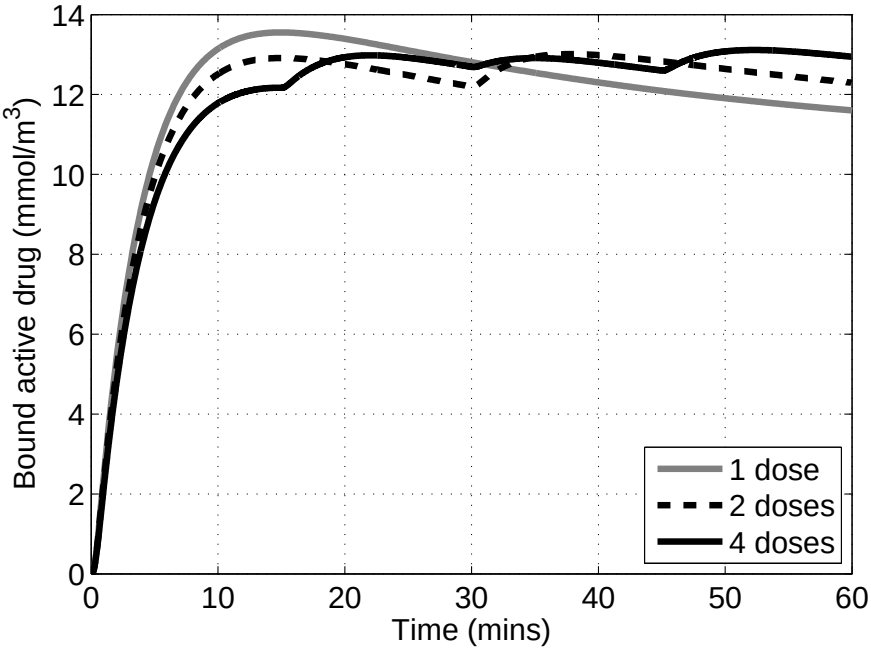

Figure 2: Plots of bound active drug, $L_n(t)$, against time with total area-under-curve of 43.2 mol·s/m^3 (12 μM·h). Plots correspond to single, double and quadruple doses.

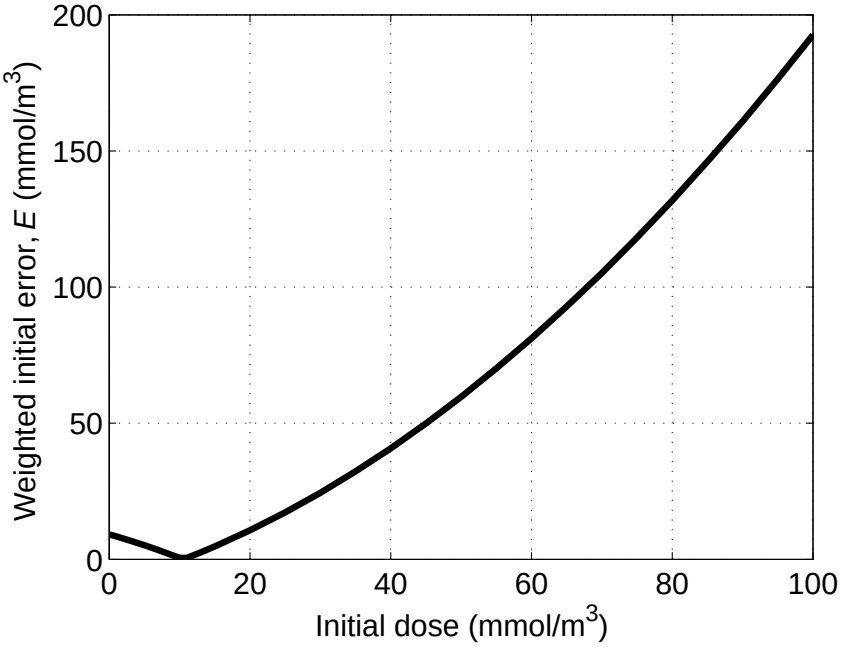

Figure 3: Plot of weighted initial error, $E = \|y_{\mathrm{d}} - \hat{y}_T\|/m_T$, against initial dose estimate, $\hat{d}$, for the single-dose AUC problem.

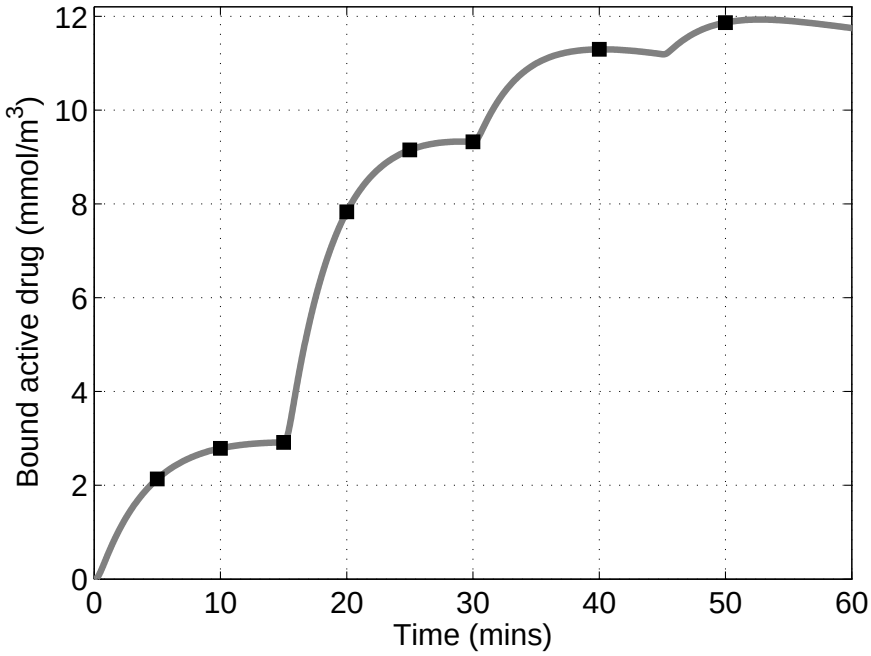

Figure 4: Plot of bound active drug, $L_n(t)$, against time with target time series points (square boxes) when reconstructing an unknown dosing scheme.

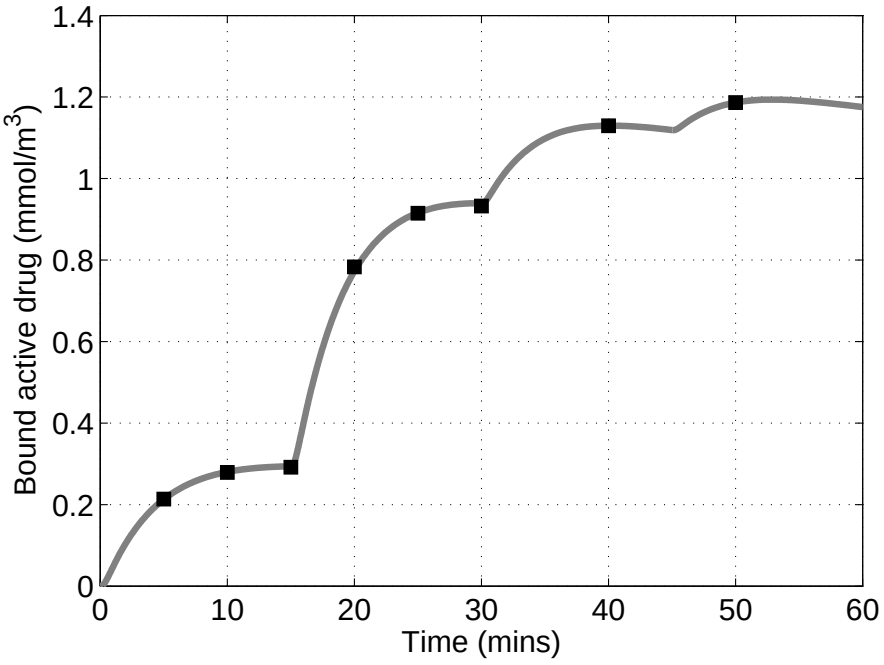

Figure 5: Plot of bound active drug, $L_n(t)$, against time with target time series points (square boxes) when previous target is reduced to 10% of its original value.

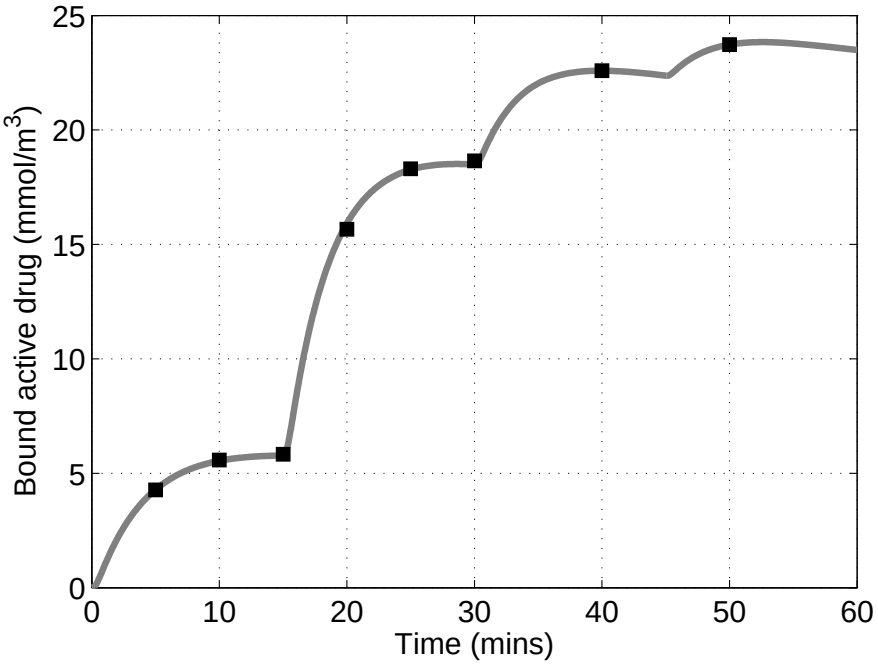

Figure 6: Plot of bound active drug, $L_n(t)$, against time with target time series points (square boxes) when target from Figure 4 is double its original level.

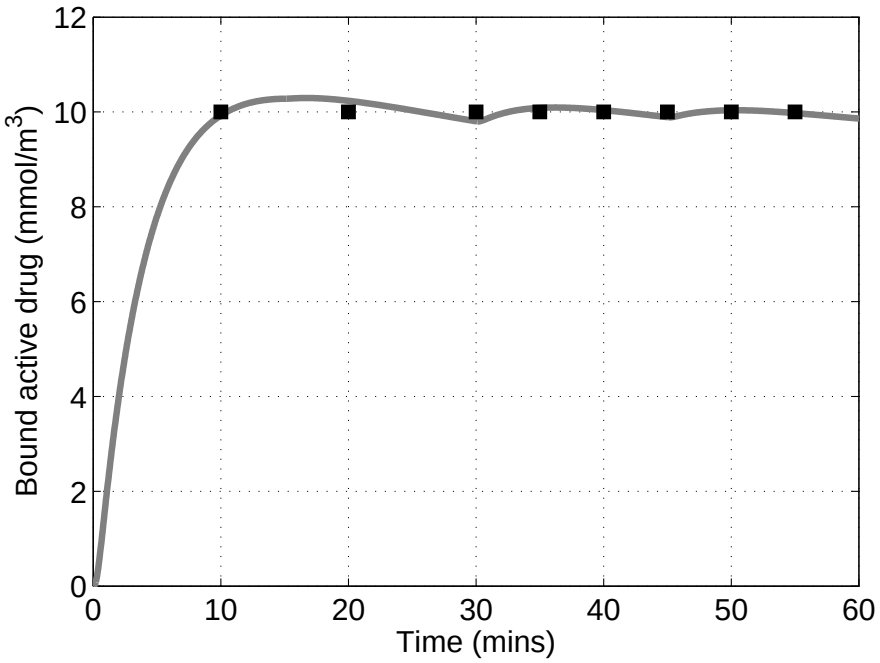

Figure 7: Plot of bound active drug, $L_n(t)$, against time with a constant (10 μM) target time series points (square boxes).

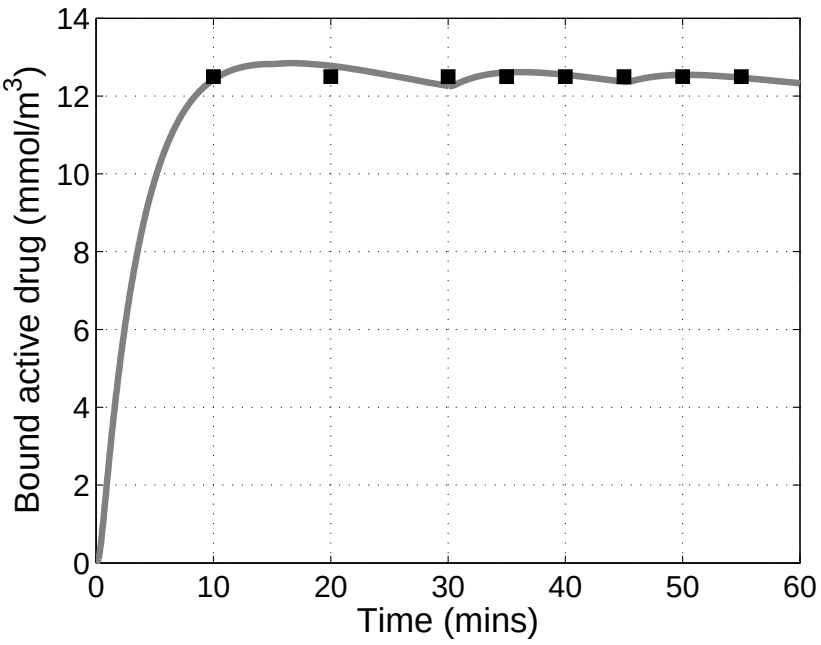

Figure 8: Plot of bound active drug, $L_n(t)$, against time with a constant target (12.5 μM) time series points (square boxes).