General Letters in Mathematics, Vol. 4, No.3 , June 2018, pp.120 -130
Available online at http:// www.refaad.com
https://doi.org/10.31559/glm2018.4.3.5

A Model of Oral and Parenteral Drug Administration with Control

Nzerem, F.E.*, and Ugorji H.C

Department of Mathematics and Statistics, University of Port Harcourt, Nigeria
* frankjournals@yahoo.com

Abstract: Drug administration is largely a frontier in pharmacokinetics and pharmacodynamics. Kinetics and dynamics are of science in general, and therefore issues on drug administration may be of interdisciplinary interest. This paper treated pharmacokinetics from the standpoints of a subject-specific drug administration and control. A compartment-based mathematical model of drug administration was presented. Besides the endearing impacts of drug administration, the optimal control of drug regimen is a sine qua non to the therapeutic benefits derivable from a drug at the physiologic site(s). This argument motivated the control method applied hereto. The variable of interest for control is the time-dependent drug concentration in the bloodstream. It was considered essential since the concentration of a drug in the body within a finite time horizon is partly a measure of therapeutic response. To this end, the optimal controller discussed here must be, and indeed is, the one that could furnish the concentration that is both therapy-effectual and time-minimizing. It is only when these two conditions are met that a drug regimen may be seen to have achieved the desired goal.

Keywords: *Concentration, Clearance rate, delay, differential equations, optimal, Riccati differential equation.*
2010 MSC No.: *49J30, 49K15, 92C45, 93C15*

1. Introduction

The issue of drug intake and concentration at various compartments in biological tissues, especially of humans, is of great interest in pharmacokinetics. The problem of predicting a realistic outcome of regulated drug dosing (administration) requires concerted efforts. This is the basis for seeking mathematical models which will contribute to the understanding of such bio-transport phenomena. The analytic details supplied by such models are a veritable tool that could inform clinical practise. Topical, oral and parenteral routes are the mostly used mediums of drug administration. Here parenteral dosage forms shall refer to administration by injection or infusion. For effective study of the trajectory of administered drugs the body is seen as a physiologic system which is often decomposed into a group of interacting subsystems, known as *compartments [1]*.The compartment model is the standard for both pharmacokinetic and mathematical models of drug administration. When the body is considered holistically, it is just seen as a compartment. In such a case it is a kinetically homogeneous material, with a uniform behaviour, having no barriers to the movement of drug. A two or three compartment model consists of the central region and the peripheral region. Pharmacokinetic studies have been done on administered drugs or chemicals enroute various compartments of the body. The compartment model has been used for description the concentration of tracers in the arterial blood [2, 3]. In a related study, Scarlett and Katie [4] studied the dosing of nanoparticle in the stead of drug. In Koch [5] one and two compartment models were used in describing drug pharmacokinetics. The three compartment model was used by Groh et al. [6] to describe the interaction of the chemotherapeutic agent with the microenvironment of tumour cells.

An essential aspect of drug administration is the concept of optimal control. Any or all of the following three factors may call for the implementation of the said concept: the need to be abreast of

the minimal concentration of the drug that could yield the utmost benefit, the time effectiveness of the drug, and the cost effectiveness of the drug regime. Numerous models have incorporated optimal control strategies that aim at maximal benefits in the course of chemotherapy. One of such may be found in DePillis and Radunskaya [7]. Seema et al. [8] sought treatment regime that could, among other things, minimize the cancer cell count in the treatment of leukaemia. In their contribution, Sacrifice et al. [9] focussed on the optimal control of malaria. Away from the Maximum Principle employed by the later to furnish the necessary conditions for the existence of optimal control, Ghaffari and Nasserifar [10] used Lyapunov stability theorem to seek optimal treatment strategies. The ultimate goal is to seek a minimal drug regime that could achieve the utmost benefit when administered to a subject within some finite time horizon.

In the present work the drug administration was modelled. There is the need to ensure that drug concentration in any compartment (or systemic concentration) is kept at the barest minimum, especially in the event of regimentation. It is in keeping with this consideration that optimal control of drug concentration was sought in this work. This was done in a bid to accentuate the (patho-) physiologic implication(s) of drug concentration.

2. Mathematical model

Pharmacokinetics reveals what the body does to administered drugs; pharmacodynamics reveals what administered drugs do to the body. Many drugs transit from one compartment to the other at the rate described by the first order kinetics. Two of the major concerns in drug administration are the instantaneous change of the concentration and clearance of the drug. Clearance may be affected by some factors, to wit, the overall health of the individual consumer, drug interaction with another drug(s) administered concomitantly, and some patient-specific endogenous factors. In pharmacokinetics drugs are assumed to completely metabolized and eliminated from the body. Most drugs are metabolized in the liver and excreted through the kidneys. We consider two different types of drug administration and absorption: the drug is orally (p.o.) administered. In this case absorption is through the stomach or intestines, and the drug is administered by an intravenous bolus injection (i.v.) into the bloodstream.
The distribution of p.o. drugs is quite delayed. In this case of i.v. drugs there is almost immediate complete distribution.

If c (t) is the concentration of drug in the compartment at time t, then the law of mass balance suggests an equation containing c(t) in the form

$\frac{dc}{dt}$ = rate of mass of drug in (i.e. loading) – rate of mass of drug out (i.e. clearance)

A first order drug loading together with Michaelis-Menten clearance leads to an initial value problem of the form

$$\frac{dc}{dt} = r_f - U_{\max}\frac{c}{K_m + c}, \quad c(0) = c_0 \tag{2.1}$$

where r_f indicates the feeding rate, U_{max} the maximal elimination rate and K_m the concentration at which the elimination rate is $1/2U_{max}$. The rate of change of the drug concentration if no absorption is assumed is

$$\frac{dc}{dt} = -U_{\max}\frac{c}{K_m + c} \equiv -\kappa c \quad c(0) = c_0 \ . \tag{2.2}$$

The equation above depicts a decay in concentration. In oral drug absorption and distribution the gastrointestinal (GI) track and the blood are respectively involved. The GI track is the first compartment from where diffusion of drug to the blood (second compartment) occurs in an

irreversible trend. It is the traditional site for the purposes of time delayed release therapies. Suppose $c_I(t)$ is the drug concentration in the intestine and $c_b(t)$ the concentration in the blood. The rates of change in a unit dose drug administration governed by a first-order kinetics read

$$\left.\begin{aligned} \frac{dc_I}{dt} &= -\alpha c_I(t) & c_I(0) &= c_o \\ \frac{dc_b}{dt} &= \alpha c_I(t) - \beta c_b(t) & c_b(0) &= 0 \end{aligned}\right\}, \qquad (2.3a,b)$$

where $\alpha > 0$ is the inter-compartmental rate constant and $\beta > 0$ is the clearance constant, and where a and b stand for the first and second equations of (2.3) respectively. The solution set of equation (2.3) is

$$\left.\begin{aligned} c_I(t) &= c_0 e^{-\alpha t} \\ c_b(t) &= \frac{\alpha c_0}{\beta - \alpha}\left[e^{-\alpha t} - e^{-\beta t}\right] \qquad \alpha \neq \beta \end{aligned}\right\} \qquad (2.4\ a,b)$$

2.1 Intravenous drug administration

A central compartment could be associated with the blood plasma, and a peripheral compartment associated with the tissue. A drug can be injected into, as well as removed from, the central compartment. It diffuses in and out of the peripheral compartment almost instantaneously. In the two compartments under consideration the *blood* and the *tissues* are the main exchangers. The drug (or, in this case, bolus) is injected into the blood-stream and it is transmitted to the exigent tissue for therapeutic purposes.

Let $c_b(t)$ and $c_T(t)$ represent the concentration of drug in the blood and tissue respectively and let c_0 be the initial concentration of drug injected through intravenous course. The set of equations describing the drug administration is

$$\left.\begin{aligned} \frac{dc_b}{dt} &= -(\alpha_b + e)c_b + \beta_T c_T; & c_b(0) &= c_0 \\ \frac{dc_T}{dt} &= \alpha_b c_b - \beta_T c_T \end{aligned}\right\} \qquad (2.5\ a,\ b)$$

where α_b is the rate at which part of the drug is delivered to the tissue by the blood and e is the rate of clearance of the residue eliminated. The matrix method is a good method of solution to the above set of equations. The matrix equation of (2.5) takes the form

$$c(t) = \begin{pmatrix} c_b(t) \\ c_T(t) \end{pmatrix}, \qquad J = \begin{pmatrix} -(\alpha_b + e) & \beta_T \\ \alpha_b & -\beta_T \end{pmatrix}. \qquad (2.6)$$

Then write (2.5) as

$$c'(t) = Jc(t) \qquad (2.7)$$

with initial condition

$$c(0) = \begin{pmatrix} c_0 \\ 0 \end{pmatrix}. \tag{2.8}$$

Our goal is to transform the system (2.5) to an algebraic equation so that solution may be found easily. The Laplace transform technique is the right method of attack now. The Laplace transform is an integral transform in which the linear operator L{$f(t)$} transforms a function $f(t)$ with $t \in \square \geq 0$ from the time domain to a function $F(s)$ with $s \in \square$ in an image domain. Apply Laplace transform of (2.7) to get

$$\mathcal{L}\left(c'(t)\right) = \mathcal{L}\left(Jc(t)\right) \tag{2.9}$$

where $\mathcal{L}(.)$ is the Laplace transform of its argument.

We may write

$$G(s)\hat{c}(s) = c(0) \tag{2.10}$$

where

$$G(s) = \begin{pmatrix} s+\alpha_b+e & \beta_T \\ \alpha_b & s+\beta_T \end{pmatrix}, \qquad \hat{c}(s) = \begin{pmatrix} c_b'(s) \\ c_T'(s) \end{pmatrix}, \tag{2.11}$$

We assume $\det(G(s)) \neq 0$. We compute this determinant as

$$\det(G(s)) = det(sI - J) = \left| \begin{pmatrix} s & 0 \\ 0 & s \end{pmatrix} - \begin{pmatrix} -(\alpha_b+e) & \beta_T \\ \alpha_b & -\beta_T \end{pmatrix} \right| \tag{2.12}$$

where I is the identity matrix. The resulting quadratic equation is

$$s^2 + (\alpha_b + e + \beta_t)s + e\beta_t \equiv (s+\eta_1)(s+\eta_2) \tag{2.13}$$

where η_1 and η_2 are the zeros of s.

$$\eta_{1,2} = \frac{-(\alpha_b+e+\beta_t) \pm \sqrt{D}}{2}, \qquad D = (\alpha_b+e+\beta_t)^2 - 4e\beta_t \neq 0. \tag{2.14}$$

We note that $\det(J) = e\beta_T \neq 0$. Therefore, $\det(G(s)) > 0 \ \forall s \geq 0$. From the above we write the relations for $c'(s)$ as

$$\hat{c}_b(s) = \frac{c_0(s+\beta_T)}{(s+\eta_1)(s+\eta_2)} \tag{2.15}$$

and

$$\hat{c}_T(s) = \frac{-c_0\alpha_b}{(s+\eta_1)(s+\eta_2)} \tag{2.16}$$

We return from the image domain to the time domain by using the inverse Laplace transform of (2.15) and (2.16). This gives

$$c_b(t) = \frac{c_0}{\eta_2 - \eta_1}\left\{(-\eta_1 + \beta_T)e^{-\eta_1 t} - (-\eta_2 + \beta_T)e^{-\eta_2 t}\right\} \tag{2.17}$$

$$c_T(t) = \frac{c_0\alpha_b}{\eta_1 - \eta_2}\left\{e^{-\eta_1 t} - e^{-\eta_2 t}\right\} \tag{2.18}$$

Equations (2.17) and (2.18) are the drug concentrations in the blood and in the tissue respectively. Observe that both $c_b(t)$ and $c_T(t) \to 0$ as $t \to \infty$. Therefore, if the metabolic process of the body is in a physiological state the drug concentration obeys the decay process. In a similar way, one may derive a three compartment model for drug concentration and absorption (for instance, see Khanday *et al.*[21], Hill *et al.*[22]).

3. Optimal control

In this section we shall employ a control strategy to maintain the drug bloodstream concentration within a reasonable therapeutic window, and therefore analyse the effects of the strategy on effective dosing requirements. Scarlett and Katie [4] applied control strategy to the analysis of nanoparticle dosing strategies for cancer therapy. The principle of optimal control is applied largely to drug combination therapies (Ratajczyk et al. [23], Moore [24]). In the event of drug delivery, there is usually a time lag between the time of administration and time it takes the drug to reach the physiologic site of drug action. This may be seen as equilibration delays which induce a lag between pharmacologic response and plasma drug concentrations. Time delays in pharmacokinetics may be physiological or patho-physiological. In the latter case one may see Stijin et al. [11]. In the present we consider physiological/harmless delays in drug distribution. It is pertinent to note that both p.o. and parenteral strategies encounter distribution delays, albeit at varying level. We could infer, from the foregoing, that delay differential equations (DDEs) may be harnessed for the purpose of detailing the behaviour and control of pharmacokinetic drug administration (see Jacques and Andreea [12]).

Let

$$\mathbf{f} : \mathbb{R}^n \times \mathcal{U} \to \mathbb{R}^n \tag{3.1}$$

be a bounded, Lipschitz continuous function, where $\mathcal{U}$ is some compact subset of, say, $\mathbb{R}^m$.

Consider the differential equation

$$\left.\begin{aligned} \dot{\mathbf{c}}_\mathbf{b}(s) &= \mathbf{f}(\mathbf{c}_\mathbf{b}(s), \mathbf{u}(s)) \qquad (t_0 < s < t_f) \\ \mathbf{c}_\mathbf{b}(t_0) &= c_0 \end{aligned}\right\}, \tag{3.2}$$

where $t_0 \geq 0$ is some initial time, $t_f > 0$ is a fixed terminal time, c_0 is a prescribed initial point, and $\mathbf{u}(.) \in \mathcal{U}$ is the *control*. Solutions $\mathbf{c_{bi}}(.)$, (i =1, 2, 3,…,*n*) of (3.2) evolve at some subsequent times $t_i > t_0$, within the prescribed time interval. If $\mathbf{u_i}(.)$ (i =1, 2, 3,…,*n*) is a set of controls, then we may define the set of admissible controls as

$$\mathcal{U} \triangleq \{\mathbf{u} : [t_0, t_f] \to \mathcal{U} \mid \mathbf{u}(.) \text{ is measurable}\}. \tag{3.3}$$

We note that each of such admissible controls has its degree of optimality.

If for some given constant *C*

$$\left|\mathbf{f}(c_0, c)\right| \leq C, \quad \left|\mathbf{f}(c_0, c) - \mathbf{f}(c_1, c)\right| \leq \left|c_0 - c_1\right| \quad (c_0, c_1 \in \mathbb{R}^n, \mathrm{c} \in \mathcal{U}) \ , \tag{3.4}$$

then (3.2) has a unique Lipschitz continuous solution $c_b(.) = \mathbf{c_b}^{\mathbf{u}(.)}(.)$ on the time interval $[t_0 , t_f]$. We seek a control $\mathbf{u}^*(.)$, for $\mathbf{c}_\mathbf{b} \in \mathbb{R}^n$ and $t \in (t_0, t_f)$, among all other admissible controls which minimizes the *concentration* (as in our case) functional

$$G_{c_b,t}[\mathbf{u}(.)] = \int_{t_0}^{t_f} g(\mathbf{c}_\mathbf{b}(s), \mathbf{u}(s))ds + r(\mathbf{c}_\mathbf{b}(t_f)), \tag{3.5}$$

where $\mathbf{c_b}(.) = \mathbf{c_b}^{\mathbf{u}(.)}(.)$ is the solution of (3.2) and $g : \mathbb{R}^n \times \mathcal{U} \to \mathbb{R}$, $r : \mathbb{R}^n \to \mathbb{R}$

are given functions. The function g indicates some rate at which a given activity evolves. For instance, in economic expenditure-based controls, it is called the running cost per unit time and r the terminal cost. Physiologically speaking, g could be seen as the drug temporal concentration energy budget, and therefore r is the terminal concentration. Any value function V must be such that

$$V(c_0,t_0) = \inf_{u(.)\in\mathscr{U}} G_{c_b,t}[\mathbf{u}(.)] \qquad (c_0 \in \mathbb{R}^n,\ t \in [t_0, t_f]). \tag{3.6}$$

This function specifies the best possible value of the concentration functional beginning from each state and perhaps time.

3.1 Optimality criterion

First, we state, without proof, the following:

Theorem 1 (*Optimal controller* (see [15])**.** Suppose that $\mathbf{u}^*(t)$, $t \in [t_0, t_f]$ minimizes

$$G[\mathbf{u}(.), c_0, t_0] = \int_{t_0}^{t_f} g(\mathbf{c_b}(s), \mathbf{u}(s))ds + r(\mathbf{c_b}(t_f)),$$

subject to $\mathbf{c_b}^*(t_0) = c_0$ and $\mathbf{c_b}^*(t)$ is the related state trajectory. Let the (minimum) concentration attained by $\mathbf{u}^*(t)$ be:

$$G^*(c_0,t_0) = \arg \min_{u(\xi),\xi\in[t_0,t_f]} G(\mathbf{u}(.), c_b^*, t_0, t_f)\,.$$

Then, for any $t_1 \in [t_0, t_f]$, the restriction of $\mathbf{u}^*(\xi)$ optimal over the sub-interval $[t_1,t_f]$ minimizes

$$G[\mathbf{u}(.), \mathbf{c_b^*}(t_1), t_1] = \int_{t_1}^{t_f} g(\mathbf{c_b}(s), \mathbf{u}(s))ds + r(\mathbf{c_b}(t_f)),$$

subject to the initial condition $\mathbf{c_b}(t_1) = \boldsymbol{c_b}^*(t_1)$; $\mathbf{u}^*$ is optimal over $[t_1, t_f]$.
In this sub-section we investigate the *value function* $V(c_0, t_0)$ for optimality.

Theorem 2 (*Optimality* (see Lawrence [13]). For each $h > 0$ sufficiently small that $t_0 + h \le t_f$ we have

$$V(c_0,t_0) = \inf_{\mathbf{u}(.)\in\mathscr{U}} \int_{t_0}^{t_0+h} \mathrm{g}[\mathbf{c_b}(s) + \mathbf{u}(s)]ds + V(\mathbf{c_b}(t_0+h), t_0+h)]. \tag{3.7}$$

where $\mathbf{c_b}(.) = \mathbf{c_b}^{\mathbf{u}(.)}(.)$ is the solution of (3.2) for the control $\mathbf{u}(.)$.

Proof. Let $\boldsymbol{u_1}(.)$ be any chosen control. We set an ODE this chosen control, analogous to (3.2)

$$\left.\begin{aligned} \dot{\mathbf{c}}_{\mathbf{b}\,1}(s) &= \mathbf{f}(\mathbf{c_{b1}}(s), \mathbf{u_1}(s))ds \quad (t_0 < s < t_0 + h) \\ \mathbf{c}_{\mathbf{b}\,1}(t) &= c_0. \end{aligned}\right\} \tag{3.8}$$

For a fixed $\varepsilon > 0$ choose $\mathbf{u_2}(.) \in \mathscr{U}$ so that

$$V(\mathbf{c_{b_1}}(t_0+h), t_0+h) + \varepsilon \ge \int_{t_0+h}^{t_f} g(\mathbf{c_{b_2}}(s), \mathbf{u_2}(s))ds + r(\mathbf{c_{b_2}}(t_f)), \tag{3.9}$$

where

$$\left.\begin{aligned} \dot{\mathbf{c}}_{\mathbf{b_2}}(s) &= \mathbf{f}(\mathbf{c_{b_2}}(s), \mathbf{u_2}(s) \quad (t_0 + h < s < t_f) \\ \mathbf{c_{b_2}}(t_0+h) &= c_1(t_0+h). \end{aligned}\right\} \tag{3.10}$$

Define the control

$$\mathbf{u_3}(s) := \begin{cases} \mathbf{u_1}(\mathrm{s}) & \text{if } t_0 \le s < t_0 + h \\ \mathbf{u_2}(s) & \text{if } t_0 + h \le s \le t_f, \end{cases} \tag{3.11}$$

and let

$$\left.\begin{aligned}\dot{\mathbf{c}}_{\mathbf{b}_3}(s) &= \mathbf{f}(c_{b_3}(s), \mathbf{u}_3(s) \quad (t_0 < s < t_f)\\ \mathbf{c}_{\mathbf{b}_3}(t) &= c_0.\end{aligned}\right\} \tag{3.12}$$

Since the solution of the equation (3.2) is unique, we write

$$\mathbf{c}_{\mathbf{b}_3}(s) = \begin{cases}\{\mathbf{c}_{\mathbf{b}_1}(s) & \text{if } t_0 \le s \le t_0 + h\\ \mathbf{c}_{\mathbf{b}_2}(s) & \text{if } \mathrm{t}_0 + \mathrm{h} \le s \le t_f\end{cases}. \tag{3.13}$$

By definition (3.6) we have

$$\begin{aligned}V(c_b, t_0) &\le G_{c_b,t}[\mathbf{u}_3(.)]\\ &= \int_{t_0}^{t_f} g(\mathbf{c}_{\mathbf{b}_3}(s), \mathbf{u}_3(s))ds + r(\mathbf{c}_{\mathbf{b}_3}(t_f))\\ &= \int_{t_0}^{t_0+h} g(\mathbf{c}_{\mathbf{b}_1}(s), \mathbf{u}_1(s))ds + \int_{t_0+h}^{t_f} g(\mathbf{c}_{\mathbf{b}_2}(s), \mathbf{u}_2(s))ds + r(\mathbf{c}_{\mathbf{b}_2}(t_f))\\ &\le \int_{t_0}^{t_0+h} g(\mathbf{c}_{\mathbf{b}1}(s), \mathbf{u}_1(s))ds + V(\mathbf{c}_{\mathbf{b}_1}(t_0+h), t_0+h) + \varepsilon.\end{aligned}$$

The last inequality above is a consequence of (3.9). Since $\mathbf{u}_1(.) \in \mathcal{U}$ was arbitrarily chosen we conclude that

$$V(c_0, t_0) \le \inf_{u(.)\in\mathcal{U}} \left\{ \int_{t_0}^{t_0+h} g(\mathbf{c}_{\mathbf{b}}(s), \mathbf{u}(s))ds + V(\boldsymbol{c}_{\boldsymbol{b}}(t_0+h), t_0+h) \right\} + \varepsilon \tag{3.14}$$

Next, for a fixed $\varepsilon > 0$ choose $\mathbf{u}_4(.)$ such that

$$V(c_0, t_0) + \varepsilon \ge \int_{t_0}^{t_f} g(\mathbf{c}_{\mathbf{b}_4}(s), \mathbf{u}_4(s))ds + r(\mathbf{c}_{\mathbf{b}_4}(t_f)), \tag{3.15}$$

where

$$\left.\begin{aligned}\dot{\mathbf{c}}_{\mathbf{b}_4}(s) &= \mathbf{f}(\mathbf{c}_{\mathbf{b}_4}(s), \mathbf{u}_4(s) \quad (t_0 < s < t_f)\\ \mathbf{c}_{\mathbf{b}_4}(t) &= c_1.\end{aligned}\right\} \tag{3.16}$$

From (3.5) we have

$$V(\mathbf{c}_{\mathbf{b}_4}(t_0+h), t_0+h) + \le \int_{t_0+h}^{t_f} g(\mathbf{c}_{\mathbf{b}_4}(s), \mathbf{u}_4(s))ds + r(\mathbf{c}_{\mathbf{b}_4}(t_f)), \tag{3.17}$$

and thus

$$V(c_b, t) + \varepsilon \ge \inf_{\boldsymbol{u}(.)\in\mathcal{U}} \left\{ \int_{t_0}^{t_0+h} g(\boldsymbol{c}_{\boldsymbol{b}}(s), \boldsymbol{u}(s))ds + V(\mathbf{c}_{\mathbf{b}}(t_0+h), t_0+h) \right\} + \varepsilon, \tag{3.18}$$

noting that $\mathbf{c}_\mathbf{b}(.) = \mathbf{c}_\mathbf{b}^{\mathbf{u}(.)}(.)$ solves (3.2). Thus, (3.18) and (3.14) complete the proof of (3.6)

3.2 LQR control

The preceding sub-section furnished the condition for the existence of an optimal controller. Hereunder we set up a Linear Quadratic Regulator (LQR) method for achieving the therapeutic bloodstream drug concentration. In other words, we seek a minimal concentration that may well yield the desired result within the desired finite time horizon. For details on optimization by means of LQR one may be consult Murray [14] and [15].

Consider once more (2.5*a*)

$$\frac{dc_b}{dt} = -(\alpha_b + e)c_b + \beta_T c_T; \qquad c_b(0) = c_0.$$

Note that the negative sign at the right hand side indicates the transition of the drug c_b from the bloodstream to the recipient tissue c_T. At the time the drug is yet to reach the tissue, $c_T = 0$.

With this (2.5*a*) reduces to

$$\left.\begin{array}{l} \frac{dc_b}{dt} = -\xi c_b \\ c_b(0) = c_0 \end{array}\right\},$$

where $\xi = (\alpha_b + e)$.

The governing DDE that incorporates physiological time delay becomes

$$\frac{dc_b}{dt} = -\xi c_b(t-\tau) + Bu(t) \qquad (3.19)$$

subject to the history function $c_b(s) = \phi(s) \in ([t_0 - \tau, t_0]; \square^1) \quad \forall s \in [t_0 - \tau, t_0]$. In the infinite dimensional system (3.19) above: τ is the time delay; $c_b(t)$ is the system state that expresses concentration of the drug in the bloodstream; $u(t)$ is the control variable; B is a real-valued constant control input multiplier. In application, the time delay τ relates to the extent of time over which a bolus is administered, and the piecewise continuous function ϕ (s) is a history function that describes the injection pr
ofile which suggests the rate at which the drugs are administered at the commencement of treatment. Let us put (3.19) in a form amenable to LQR strategy. To do this we set

$$\left.\begin{array}{l} \dot{c}_b = A(t-\tau)c_b + Bu(t) \\ c_b(t_0) = c_0 \end{array}\right\} \qquad (3.20)$$

where $c_b \in \square^n, u \in \square^m$ are the state and the input of the system respectively; A and B are constant matrices over $\square$ of appropriate dimensions, and ξ is absorbed in A.

We seek a control $u(t)$ over $t_0 \le t \le t_f$ which for any $c_0 \in \square^n$ minimizes the concentration functional (3.5)

$$G_{c_b,t}[\mathbf{u}(.)] = \int_{t_0}^{t_f} g(\mathbf{c_b}(s), \mathbf{u}(s))ds + r(\mathbf{c_b}(t_f)),$$

which we write, in the LQR model, as

$$G(u, c_0, t_0, t_f) = \int_{t_0}^{t_f} [c_b^T(s)Q(s)c_b(s) + u^T(s)R(s)u(s)]ds + c_b(t_f)^T Sc_b(t_f). \qquad (3.21)$$

where $Q(t)$ and S are symmetric positive semi-definite $n \times n$ matrices, $R(t)$ is a symmetric positive definite weighting $m \times m$ matrix, and c_0, t_0, and t_f are fixed and given data. The matrix R is exerted on the control input in order to keep the control efforts bounded over a specified period of time. The control objective is to keep $c_b(t)$ close to 0, especially, at the final time t_f, using minimal control effort u. By the details of the previous sub-section, u(.) is an admissible control, and therefore it is measurable. The penalty functions in (3.21) are: $c_b^{\mathrm{T}}(s)Q(s)c_b(s)$ in which the transient state abnormality is penalized, $c_b^{\mathrm{T}}(t_f)Sc_b(t_f)$ in which the finite state is penalized and $u^{\mathrm{T}}(s)R(s)u(s)$ in which control defect is penalized.

It seems customary to apply the Pontryagin's *maximum principle* (see Pontryagin *et al*. [16], Kalman *et al* [17]) to find the optimal control. Therefore, we write the Hamiltonian H of the system as

$$H = c_b^T Qc_b + u^T Ru + \lambda^T(Ac_b + Bu). \qquad (3.22)$$

The necessary conditions for the existence of an optimal control are furnished by the equations:

$$\left.\begin{array}{ll} \dot{c}_b = \left(\frac{\partial H}{\partial \lambda}\right)^T = Ac_b + Bu & c_b(t_0) = c_0 \\ -\dot{\lambda} = \left(\frac{\partial H}{\partial c_b}\right)^T = Qc_b + A^T\lambda & \lambda(t_f) = Sc_b(t_f) \\ 0 = \frac{\partial H}{\partial u} = Ru + B^T\lambda & \end{array}\right\} \qquad (3.23)$$

When the last condition of (3.22) is solved for $u(.)$ we get the optimal controller

$$u^*(t) = -R^{-1}(t)\ B^T P(t)c_b(t)\ , \qquad (3.24)$$

with $\lambda = P(t)c_b(t)$, and where $P(t) \in \mathbb{R}^{n\times n}$ is the unique stabilizing matrix solution of the Riccati differential equation

$$-\dot{P}(t) = A^T(t)P(t) + P(t)A(t) - P(t)B(t)R^{-1}B^T(t)P(t) + Q(t); \quad P(t_f) = S\ . \tag{3.25}$$

We assumed that there exists a unique positive-definite solution P to the Riccati equation. Thus, here we must have $Q > 0$ and $R > 0$. In addition, the pair [A, B] is assumed *stabilizable* [18] and [A, $Q^{1/2}$] is *observable* (see [19]). The choice of specific values for the weight functions Q and R demands knowledge of the system to be controlled.

3.3 Controllability and reachability

Definition 3.1 The state equation (3.20) (or the pair [A,B]) is said to be *controllable* if for any initial state $c_b(t_0)$ and any final state $c_b(t_f)$, there exists an input sequence u_n, which transfers $c_b(t_0)$ to $c_b(t_f)$ for some finite time, t_f. Otherwise the state equation (3.20) is uncontrollable.

The set of states *controllable* to state c_1 at time t_1 from time instant t_0 is given by

$$\mathfrak{S}^*(t_0, t_1, c_1) = \{c_0 : c_1 = \varphi(t_1, t_0, c_0, u(.)), \quad u(.) \in \mathcal{U}\}\ . \tag{3.26}$$

Definition 3.2. A linear system (3.20) is *reachable* if for any c_o, $c_f \in \mathbb{R}^n$ there exists a $t_f > t_0$ and u: $[t_0, t_f] \rightarrow \mathbb{R}$ such that the corresponding solution satisfies $c_b(t_0) = c_0$ and $c_b(t_f) = c_f$.

The set of states *reachable* at time t_1 starting from state c_0 at time instant t_0 is given by

$$\mathfrak{S}(t_0, t_1, c_0) = \{c_1 : c_1 = \varphi(t_1, t_0, c_0, u(.)), \quad u(.) \in \mathcal{U}\}\ . \tag{3.27}$$

The state $c_b(t_f)$ which results from an initial state $c_b(t_0)$ and input $u(t)$ is given by [20]

$$c_b(t_f) = e^{At_f}c_b(t_0) + \int_{t_0}^{t_f} e^{A(t_f-\tau)}Bu(\tau)d\tau. \tag{3.28}$$

The annihilation of the state $c_b(t_f)$ requires the choice of the input $u(t)$ such that

$$e^{At_f}c_b(t_0) = -\int_{t_0}^{t_f} e^{A(t_f-\tau)}\,\mathrm{B}u(\tau)d\tau. \tag{3.29}$$

From (3.29) we have the constraint

$$c_b(t_0) = -\int_{t_0}^{t_f} e^{-A\tau}Bu(\tau)d\tau. \tag{3.30}$$

Towards satisfying (3.30) for any $c_b(t_0)$ Frederick [20] specified the choice of the input in the form

$$u(t) = -B^T e^{-A^T t}Z^{-1}c_b(t_0) \tag{3.31}$$

where

$$Z = \int_{t_0}^{t_f} e^{-A\tau}BB^{-1}e^{-A^T\tau}d\tau\ . \tag{3.32}$$

If an input function $u(.)$ exists such that

$$c_b(t) = \int_{t_0}^{t_f} e^{A(t-\tau)}Bu(\tau)\,\mathrm{d}\tau\ , \tag{3.33}$$

then, the state $c_b(t)$ is *reachable* at time instant t. Solution to the problem (3.20) exists if

$$c_b(t) - e^{At}c_b(t_0) \in \mathfrak{S}\ . \tag{3.34}$$

The input function can be calculated by solving the equation

$$c_b(t) - e^{At}c_b(t_0) = \int_{t_0}^{t_f} e^{A(t-\tau)}Bu(\tau)d\tau\ . \tag{3.35}$$

4. Summary and discussions

Drug administration and control are like Siamese twins. The consequential issue in drug administration is the propensity of the drug to perfuse the physiologic site for a therapeutic goal. Much as essential drugs could serve their purposes, we must be wary of their deleterious

consequences both in time and space. This underpins the need for control. In section 2 drug administration was modelled. It comprised the drug consumption and clearance in and out of a compartment. Our treatment was from the standpoint of drug temporal concentration. Our interest was the means of achieving the utmost therapeutic success derivable from relatively least drug concentration. The pharmacokinetic treatment here was the first-order kinetics which supposes that elimination is dependent on the maximum blood/plasma concentration and not on time. Moreover, the first-order kinetic elimination is clinically beneficial in achieving a therapeutic level of medication and the prognosis resulting from toxicity levels. This is the basis of control efforts that could ensure sustainable concentration within a conceivable time horizon.

Controllability is the summit of drug administration. The question here is: What is controllability in drug administration? The answer, in a lay language, is: if an initial drug concentration c_b at time t_0 say, could be effectively regulated for the purpose of therapeutic benefits up to some final time t_f at which the adverse effect, if any, of the final concentration $c_b(t_f)$ will be ineffectual, then the administration is controllable. Optimal controller seeks achieving the utmost therapeutic success derivable from the relatively least drug concentration within a finite time horizon.

If the control input can be chosen to drive any initial state to any desired final state at some final time then the system is reachable. In drug administration therefore reachability is the basis of (re)evaluating the efficacy of treatment since it is the moderator of control strategy. In a lay sense, it could be a measure of a patient-specific convalescence in the presence of drug dosing. In the aspect of specific drug administration, reachability mediates the concentration that may inputted for optimal control. Additional control inputs will be required in order to induce reachability where it is lacking. In sub-section 3.1 the optimality criterion was shown. The drug concentration was carefully adjusted by using the controller u(.) until the optimal value function $V(c_0, t_0)$ is obtained. Where reachability is nowhere near, prognosis sequel to drug toxicity may be evident. It could warn on the pathological consequences of engaging on further drug administration.

In fine, controllability and reachability may determine, in part, the propensity of any drug regimen to deliver its therapeutic task, and therefore could be the twin concepts of interest in pharmacokinetics and medicine.

References

[1] L.G. Depillis & A. Radunskaya, The Dynamics of an Optimally Controlled Tumor Model: A Case Study, Mathematical and Computer Modelling 37(11)(2003), 1221-1244, https://doi.org/10.1016/s0895-7177(03)00133-x

[2] F.W. Fairman, Linear Control Theory: the state space approach, John Wiley,(1998).

[3] A. Ghaffari & N. Nasserifar, Mathematical Modeling and Lyapunov- Based Drug Administration in Cancer Chemotherapy, Iranian Journal of Electrical & Electronic Engineering,5(3)(2009),151-158

[4] C.M. Groh, M.E Hubbard, P.F. Jones, P.M. Loadman, N. Periasamy, B.D. Sleeman, S.W. Smye, C.J. Twelves &Phillips R.M., Mathematical and computational models of drug transportintumours,J.R.So,11(49)(2014),20131173- 20131173, http://dx.doi.org/10.1098/rsif.2013.1173

[5] E.B. Hauser**,** Laplace transform in tracer kinetic modelling, International Nuclear Atlantic Conference - INAC 2013

[6] Moore. Helen, How to mathematically optimize drug regimens using optimal control, J Pharmacokinet Pharmacodyn, 45(1)(2018),127–137, https://doi.org/10.1007/s10928-018-9568-y

[7] L. Hill, A.J. MARK, C.R.WOLF &Y.K. Yukh, The Usage of a Three Compartment Model to Investigate the Metabolic Differences between Hepatic Reductase Null and Wild Type Mice, Mathematical Medicine and Biology,1-13, https://doi.org/10.1093/imammb/dqv029

[8] Introduction to Compartment Models, http://www.pmod.com/files/download/v31/doc/pkin/4614.html

[9] B. Jacques & R. Andreea, Time Delays in Drug Administration: Effect, Transit, Tricks and Oscillations, IFAC-PapersOnLine, 48(12)(2015), 111–116, https://doi.org/10.1016/j.ifacol.2015.09.362

[10] R. E. Kalman, P. L. Falb & M. A. Arbib Topics in Mathematical System Theory. McGraw-Hill, New York,(1969).

[11] M.A. Khanday , A. Rafiq &K. Nazir, Mathematical models for drug diffusion through the compartments of blood and tissue medium, Alexandria Journal of Medicine,53(3)(2017), 245–249, https://doi.org/10.1016/j.ajme.2016.03.005

[12] G.A. Koch-Noble, Drugs in the Classroom: Using Pharmacokinetics to Introduce Bio mathematical Modeling, Mathematical Modelling of Natural Phenomena.,6(6)(2011),227-244, https://doi.org/10.1051/mmnp/20116612

[13] V.Kučera, A Review of the Matrix Riccati Equation, Kybernetika, 9(1)(1973),42-61

[14] C.E. Lawrence(1997), Partial Differential Equations, https://klevas.mif.vu.lt/~algirdas/Evans.pdf

[15] Linear Quadratic Optimal Control, Lecture Notes in Control and Information Sciences,60- 83, https://doi.org/10.1007/bfb0004374

[16] R.M. Murray, Optimization-based control, (2009)

[17] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze & E.F. Mishchenko. The Mathematical Theory of Optimal Processes, (1962)**,** https://doi.org/10.1201/9780203749319

[18] E. Ratajczyk, L. Urszula & S. Heinz, Optimal Control for a Mathematical Model of Glioma Treatment with Oncolytic Therapy and TNF-α Inhibitors, Journal of Optimization Theory and Applications, 176(2)(2018), 456- 477, https://doi.org/10.1007/s10957-018-1218-4

[19] N-K. Sacrifice, H.D. Richmond, A.B. Francis, K.O. James, M. Seth &T.B. Desmond, Optimal Control Model of Malaria Disease with Standard Incidence Rate**,** Journal of Advances in Mathematics and Computer Science 23(5)(2017),1-21, https://doi.org/10.9734/jamcs/2017/35011

[20] S. Scarlett Bracey & Katie A. Evans **,** Analysis of Tracking Control Designs for a Delay Differential Equation Model Used in the Study of Nanoparticle Dosing Strategies, American Control Conference (ACC), Portland, Oregon, USA June 4-6,(2014), https://doi.org/10.1109/acc.2014.6859172

[21] K.C. Schmidt & F.E. Turkheimer, Kinetic Modeling in Positron Emission Tomography, Q J Nucl Med. 46(1)(2002),70-85.

[22] N. Seema, Helen M, &L. Suzanne, Optimal control of treatment in a mathematical model of chronic myelogenous leukemia, Mathematical Biosciences 210(1)(2007), 143–156, https://doi.org/10.1016/j.mbs.2007.05.003

[23] I. Stijn, F.Pea & J. Lipman, The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents, Advanced Drug Delivery Reviews,77(20)(2014), 3-11, https://doi.org/10.1016/j.addr.2014.07.006

[24] W. M. Wonham: On Pole Assignment in Multi-Input Controllable Linear Systems. IEEE Transactions on Automatic Control,12(6)(1967), 660-665, https://doi.org/10.1109/tac.1967.1098739