Study of the stability for Drug Delivery Models

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Abstract. In this work, mathematical models of drug delivery are presented. We are particularly interested in studying the stability of these models to release the drug in a polymer matrix and detect its transfer to the overall biological tissue. These results are illustrated on two models. In order to gain protocol treatment, instead of using the optimal control theory, Lyapunov’s stability theorem is used to study the stability of the first nonlinear system. For the second, we proceed by establishing the properties of the equilibrium point (which is strongly related to the stability of the nonlinear system) by modifying the system into a canonical equation and studying the spectrum of its Jacobian matrix to show that the system is stable.

1. Introduction

Researchers in biological and drug delivery systems are relying on process dynamics to deepen their understanding of cell behavior and develop treatments, controlled-release devices, and drug administration protocols to manage the disease, which are more effective. Recently, a mathematical model that elucidates the integrated process of drug release from a polymeric matrix and consequent transport of drug particles into the biological tissue was presented in [4]. The proposed model includes the degradation of the polymer, the dynamics of solubilization, the kinetics of diffusion as well as the phenomenon of recrystallization which takes an active part in the release of the drug from the polymer matrix. In addition, this model also incorporates tissue diffusion phenomena, binding/unbinding, advection and internalization into the biological tissue.

The model is presented as a system of nonlinear partial differential equations which has been solved numerically with a relevant set of given data (initial and boundary conditions).

A quantitative analysis was carried out, thanks to a numerical computation based on the values of the parameters of the model. However, one of the important goals for a mathematical model which is to find a desirable treatment protocol for patients was not considered. The control of the process of administering a pharmaceutical compound to achieve a therapeutic effect (Drug delivery) is essential to the health of millions of people around the world. One can use optimal control theory to design treatment protocol, as in [7, 8, 14, 15, 16]. But regarding to parameters of system which are different from one patient to another, solution for optimal control problem should be carried out for each patient separately. In this work and in order to gain protocol treatment, instead of using the optimal control theory, We study the stability of the system, we show that Lyapunov’s theory of stability does not allow us to establish the properties of the equilibrium point to conclude. In fact the point of equilibrium in this case is a critical point, neither the function of Lyapunov [10, 11, 13] nor the theory of Routh-Herwitz [6, 11]...
allows the treatment of this case. To remedy this lack, by modifying the system into a canonical
equation and studying the spectrum of its Jacobian matrix to establish that the equilibrium
point is stable.

2. The mathematical models
The proposed mathematical model is a two-phase system. The first one consists of the drug
release process from a polymer matrix, considered a reservoir, where the drug is incorporated
at the onset. This phase considers polymer degradation and drug release with the processes of
diffusion, dissolution, and association/recrystallization from a local drug delivery device, as well
as its further transport to biological tissue.

This phase is followed by a second phase which is the subsequent transport of the drug
particles into the biological tissue which is the site of delivery. The model for this phase takes
into account the phenomena of specific or non-specific binding, dissociation and internalization
in biological tissues.

The two systems are coupled only through interface conditions. This is why we undertake a
stability study for each system separately.

Firstly we do the stability for polymeric matrix modes from [4]

2.1. Drug Dynamics in the Polymeric Matrix
The manifestation of the dynamics of drug release in the polymer matrix is governed by two
equations, the first is an ordinary differential equation and the second is a partial differential
equation. They are given by:

\[
\begin{align*}
\frac{\partial C_1}{\partial t} &= -kC_1^2(C_l - C_0) - \beta_0 C_1 + \delta_0 C_0, \\
\frac{\partial C_0}{\partial t} &= D_0 \frac{\partial^2 C_0}{\partial x^2} + kC_1^2(C_l - C_0) + \beta_0 C_1 - \delta_0 C_0,
\end{align*}
\]

These equations are set for \( x \in (0, l_0) \) where \( l_0 \) represents the length of the polymer matrix.
The variable \( C_1 \) is the available molar concentration of solid drug, \( C_0 \) represents the available
molar concentration of free drug, the rate of dissolution is denoted by \( k \), the constant \( C_l \)
represents the solubilization limit drug, the constant \( \beta_0 \) denotes the dissociation rate, the
association rate is represented by the constant \( \delta_0 \), the effective diffusion coefficient of the free
drug in the matrix is denoted by \( D_0 \). This coefficient is defined according to the diffusivity in
the polymer phase, the diffusivity in liquid-filled pores, the porosity, and the drug partitioning
between the liquid-filled pores and solid phase. For more details and in particular for the
formulas giving these parameters, the reader may consult [17].

Since only longitudinal diffusion is taken into account, this model is considered to be one-
dimensional.

2.1.1. Lyapunov Stability
The theory of stability is of great importance in the analysis of dynamic systems, where different
problems such as stability at points of equilibrium (fixed points) or stability of input-output are
analyzed. The characterization of stability at equilibrium points of the dynamic system is usually
done using the stability theory of Lyapunov [1, 10, 11, 12]. Lyapunov direct method [10, 5]
provides a way to analyze the stability of dynamical systems without solving the differential
equations. It is especially advantageous when the solution is difficult or even impossible to find
with classical methods.

A point of equilibrium is said to be stable if system solutions that start close to that point
remain close to it and are said to be asymptotically stable if, in addition, all solutions converge
at that equilibrium point. Otherwise the point will be unstable. Mathematically, it is presented as follows:

Let the dynamic $n \times n$ system be described by its state equations

$$\dot{x}(t) = f(x(t))$$  \hspace{1cm} (2)

where the function $f : D \rightarrow \mathbb{R}^n$, defined on the domain $D \subset \mathbb{R}^n$ and taking values in $\mathbb{R}^n$, is considered to be a locally Lipschitz map.

Now consider the equilibrium point $x^* \in D$, i.e. assume that $f(x^*) = 0$ then the stability of the equilibrium point can be determined by Lyapunov’s theorem\[1, 10, 11\], which states that $V : D \rightarrow \mathbb{R}$ is a continuously differentiable function in the domain $D \subset \mathbb{R}^n$ that contains the origin, the derivative of of the functional $V$ along the trajectories is expressed as:

$$\dot{V} = \sum_{i=1}^{n} \frac{\partial V(x)}{\partial x_i} \dot{x}_i = \sum_{i=1}^{n} \frac{\partial V(x)}{\partial x_i} f_i(x)$$  \hspace{1cm} (3)

**Theorem 2.1.** Let $x^* = 0$ be a point of equilibrium in the domain $D \subset \mathbb{R}^n$. Let $V : D \rightarrow \mathbb{R}$ be completely differentiable such that

(i) $V(x) > 0$ for all $x \in D - \{x^*\}$ and $V(x^*) = 0$.

(ii) $\dot{V} \leq 0$ for all $x \in D$,

then the point of equilibrium $x^*$ is a stable point. If in addition $\dot{V} < 0$ in $D - \{x^*\}$, then stability is asymptotic.

The main idea of Lyapunov’s theory [1, 11] is that, since $V(x) \geq 0$ and $\dot{V} \leq 0$, the Lyapunov function tends to zero along the solutions of $\dot{x}(t) = f(x(t))$, i.e. if the Lyapunov function $V(x)$ is negative along the trajectories of the system, $V(x)$ will decrease as times goes forward. Note that the Lyapunov direct method is a sufficient condition to show the stability of systems, which means the system may still be stable even one cannot find a Lyapunov function candidate to conclude the system stability property. However, if a function $V$ satisfying these conditions can be found, then the stability is assured everywhere in state space.

Now, to determine the function of Lyapunov $V(x)$ one way is to assume the quadratic form:

$$V(x_1, x_2) = \lambda_1 x_1^2 + \lambda_2 x_2^2$$

and notice that $V(x_1, x_2) = \text{constant}$, gives circles in the phase plane, that is closed curves. For simplicity, we suppose in the following $\lambda_1 = \lambda_2 = 1$, then Differentiating $V$ with respect to $t$ along the trajectories of the system (1) lead to

$$\dot{V} = \frac{d}{dt} V(C_1, C_0) = \frac{\partial V(C_1, C_0)}{\partial C_1} \dot{C}_1 + \frac{\partial V(C_1, C_0)}{\partial C_0} \dot{C}_0$$

which, in view of Eq. 1 immediately reduces to

$$\dot{V}(C_1, C_0) = -2[k(C_1 - C_0)(C_1^2 - C_0^2) + (C_1 - C_0)(\beta_0 C_1 - \delta_0 C_0 - D_0 C_0 \frac{\partial^2 C_0}{\partial x^2})]$$

$$= -2[\beta_0 C_1^2 + \delta_0 C_0^2 + g(C_1, C_0)]$$  \hspace{1cm} (4)
Where

\[ g(C_1, C_0) = C_1^2 [k(C_1 - C_0)(C_1 - C_0)] - C_1 C_0 (\beta_0 + \delta_0) - D_0 C_0 \frac{\partial^2 C_0}{\partial x^2}. \]

A sufficient condition for the derivative of \( V(C_1, C_0) \) to be negative, is that the following inequation holds

\[ g(C_1, C_0) \geq \beta_0 C_1^2 + \delta_0 C_0^2 \]  \hspace{1cm} (5)

We conclude that when this partial differential inequality is satisfied then the origin is locally asymptotically stable.

It should be noted that, as the necessary and sufficient conditions allowing the asymptotic stability of the trivial equilibrium point of this system are not expressed explicitly, one cannot express an opinion concerning the sharpness of the condition Eq. 5. Also, since inequality 5 is only sufficient for asymptotic stability, it is difficult, to give a physical interpretation of the resulting inequalities.

2.2. Drug Dynamics in the Biological Tissue

As a consequence of the solubilization phenomenon, the free drug diffuses into the biological tissue through the polymer matrix as a result of the mass flow through the interface. This results in a model demonstrating the dynamics of a drug in an homogeneous single-layered biological tissue exhibiting isotropic diffusion characteristics, described by the following equations [4].

\[
\begin{align*}
\frac{\partial X_1}{\partial t} &= D_1 \frac{\partial^2 X_1}{\partial x^2} - \gamma_1 \frac{\partial X_1}{\partial x} - c_1^f X_1 X_2 + c_1^i X_3 + c_1^s X_4 + c_1^2 X_5, \\
\frac{\partial X_2}{\partial t} &= -c_1^f X_1 X_2 + c_1^i X_3 + c_{i1} X_3, \\
\frac{\partial X_3}{\partial t} &= c_2^f X_1 X_2 - c_2^i X_3 - c_{i1} X_3, \\
\frac{\partial X_4}{\partial t} &= -c_2^f X_1 X_4 + c_2^i b_2 + c_{i2} X_5, \\
\frac{\partial X_5}{\partial t} &= c_2^f X_1 X_4 - c_2^i X_5 - c_{i2} X_5, \\
\frac{\partial X_6}{\partial t} &= c_{i1} X_3 + c_{i2} X_5 - kid X_6, \\
\end{align*}
\]

(6)

These equations are set for \( x \in (l_0, l_1) \), with \( l_1 - l_0 \) being the length of the tissue. The molar available concentration of free drug in the tissue is denoted by \( X_1 \) and the effective diffusion coefficient of free drug in the porous biological tissue is denoted by \( D_1 \). The advection is represented by its magnitude \( \gamma_1 \). Note that \( D_1 \) is formulated according to the free diffusivity of the biological tissue, its porosity and the tortuosity of its pore path [4].

The variable \( X_2 \) denotes the molar concentration of available binding sites on ECM (extracellular matrix), where the velocity of second-order interaction between ECM sites and free drug in the tissue is denoted by the association rate constant \( c_1^f \).

The molar concentration of drug bound to nonspecific ECM binding sites is depicted by \( X_3 \) and the first-order breakdown velocity of ECM sites-free drug complex is denoted by the dissociation rate coefficient \( c_1^i \), while the internalization rate of drug bound to non-specific ECM binding sites is denoted by the coefficient \( c_{i1} \).

\( X_4 \) is The molar concentration of available SR (specific binding receptors) and the velocity of second-order interaction between free drug in the biological tissue and the specific binding receptors is depicted by the association rate constant \( c_2^f \).
To study the stability of models (6) consider the following Lyapunov function

$$V(X_1, X_2, X_3, X_4, X_5, X_6) = \lambda_1 X_1^2 + \lambda_2 X_2^2 + \lambda_3 X_3^2 + \lambda_4 X_4^2 + \lambda_5 X_5^2 + \lambda_6 X_6^2$$

Notice that $V(X_1, X_2, X_3, X_4, X_5, X_6) = \text{constant}$, gives circles in the phase plane, that is closed curves. This is a consequence of the property positive definite that the function $V(X_1, X_2, X_3, X_4, X_5, X_6)$. For simplicity, suppose $\lambda_i = 1$ for $i = 1, 2, \ldots, 6$, then differentiating $V$ with respect to $t$ along the trajectories of the system (6) leads to

$$\dot{V}(X_1, X_2, X_3, X_4, X_5, X_6) = 2 \left[ X_1 \dot{X}_1 + X_2 \dot{X}_2 + X_3 \dot{X}_3 + X_4 \dot{X}_4 + X_5 \dot{X}_5 + X_6 \dot{X}_6 \right]$$

which can be written as

$$\dot{V}(X_1, X_2, X_3, X_4, X_5, X_6) = 2 \left[ G(X_1, X_2, X_3, X_4, X_5, X_6) - F(X_1, X_2, X_3, X_4, X_5, X_6) \right]$$

where

$$G(X_1, X_2, X_3, X_4, X_5, X_6) = X_1 (D_1 \frac{\partial^2 X_1}{\partial x^2} + c'_1 X_3 + c'_2 X_5) + X_2 (c'_1 X_3 + c_1 X_3)$$

$$+ X_3 c'_1 X_1 X_2 + X_4 (c'_2 X_5 + c_2 X_5) + X_5 c'_2 X_1 X_4$$

$$+ X_6 (c_1 X_3 + c_2 X_5 - c_{id} X_6)$$

and

$$F(X_1, X_2, X_3, X_4, X_5, X_6) = X_1 \gamma_1 \frac{\partial X_1}{\partial x} + c'_1 X_1^2 X_2 + c'_2 X_1 X_4^2 + c'_2 X_1 X_2^2$$

$$+ c'_1 X_3^2 + c_1 X_3^2 + X_2 c'_2 X_1 X_4 + c'_2 X_3^2 - c_2 X_5^2 + c_{id} X_6^2$$

The sufficient condition of the derivative of $V(X_1, X_2, X_3, X_4, X_5, X_6)$ is guaranteed to be negative whenever

$$G(X_1, X_2, X_3, X_4, X_5, X_6) - F(X_1, X_2, X_3, X_4, X_5, X_6) \leq 0$$
The Lyapunov Direct method gives conditionally stability for the model (6) because the conditions for stability hold where the differential in equation (8) is solved. Once again, since inequality 8 is only sufficient for asymptotic stability in some space, it is difficult, to give a physical interpretation of the resulting inequalities. In the following we will show that Lyapunov Indirect Method (Routh-Hurwitz Stability [1, 6, 11]) also do not permits the conclude for the local stability.

2.2.2. Local stability

We begin this study by recalling the following results

**Definition 2.1. Routh-Hurwitz Stability [6]** A matrix $A \in \mathbb{R}^{n \times n}$ is called Hurwitz or asymptotically stable if and only if

$$Re(\lambda_i) < 0, \forall i = 1, 2, \ldots, n$$

where $\lambda_i$ are the eigenvalues of the matrix $A$.

Lyapunov asserts that the problem of the stability of a solution of an original system of ordinary differential equations is reduced to the problem of the stability of the zero equilibrium position for another system [11].

**Théorème 1. (Indirect Method Theorem)** Let $E_0$ be an singular point for $x = f(x)$ where $f$ is a continuously differentiable function from $D$, a neighborhood of $E_0$, into $\mathbb{R}^n$. Let

$$J(f)(E_0) = \left( \frac{\partial f_i}{\partial x_j} \right)_{E_0}$$

be the jacobian matrix at $E_0$. Then

(i) The equilibrium $E_0$ is asymptotically stable if $J(f)(E_0)$ is a hurwitz matrix.

(ii) The equilibrium $E_0$ is unstable if $Re(\lambda) > 0$ for one or more of the eigenvalues of $A$.

In order to study the local stability of system (6), the corresponding linearized system at the equilibrium point $E = (0, 0, 0, 0, 0, 0)$ is considered

$$\begin{align*}
\frac{\partial X_1}{\partial t} &= c_1^r X_3 + c_5^r X_5, \\
\frac{\partial X_2}{\partial t} &= (c_1^r + c_1)X_3, \\
\frac{\partial X_3}{\partial t} &= (-c_1^r - c_1)X_3, \\
\frac{\partial X_4}{\partial t} &= (c_2^r + c_2)X_5, \\
\frac{\partial X_5}{\partial t} &= (-c_2^r - c_2)X_5, \\
\frac{\partial X_6}{\partial t} &= c_4X_3 + c_6X_5 - kidX_6,
\end{align*}$$

(9)
which can be written as:
\[
\begin{pmatrix}
\dot{X}_1 \\
\dot{X}_2 \\
\dot{X}_3 \\
\dot{X}_4 \\
\dot{X}_5 \\
\dot{X}_6
\end{pmatrix} =
\begin{pmatrix}
0 & 0 & c_1^r & 0 & c_5^r & 0 \\
0 & 0 & (c_1^r + c_{i1}) & 0 & 0 & 0 \\
0 & 0 & (-c_1^r - c_{i1}) & 0 & 0 & 0 \\
0 & 0 & 0 & (c_2^r + c_{i2}) & 0 & 0 \\
0 & 0 & 0 & (-c_2^r - c_{i2}) & 0 & 0 \\
0 & 0 & c_{i1} & 0 & c_{i2} & -kid
\end{pmatrix}
\begin{pmatrix}
X_1 \\
X_2 \\
X_3 \\
X_4 \\
X_5 \\
X_6
\end{pmatrix}
\]

The matrix of this linear system is the Jacobian matrix \( J(f)(E_0) \) of system (6) at the equilibrium point \( E_0 = (0, 0, 0, 0, 0) \).

The characteristic polynomial of this Jacobian matrix \( J(f)(E_0) \) of system (6) is given by:
\[
P(\lambda) = \det (J(f)(E_0) - \lambda I_6)
\]

where \( \lambda \) denotes the eigenvalue and \( I_6 \) is the identity matrix of order 6.

The structure of the sparse matrix \( J(f)(E_0) \) allows us an easy computation of \( P(\lambda) \), we find
\[
P(\lambda) = \lambda^3 \times (\lambda + c_1^r + c_{i1}) \times (\lambda + c_2^r + c_{i2}) \times (\lambda + c_{id})
\]

the classical characteristic equation is defined by equating the characteristic polynomial to zero. Therefore, eigenvalues of \( J(f)(E_0) \) are: \( \lambda_1 = 0 \) with multiplicity 3, \( \lambda_2 = -(c_1^r + c_{i1}) \), \( \lambda_3 = -(c_2^r + c_{i2}) \) and \( \lambda_4 = -c_{id} \).

All parameters are positives, so the three eigenvalues \( \lambda_2, \lambda_3 \) and \( \lambda_4 \) are negatives. Since \( \lambda_1 = 0 \), the equilibrium \( E_0 \) is a critical point and one cannot conclude using the indirect Lyaponov theorem 1.

To investigate the asymptotic behavior of systems (6) and (10), recall the following fundamental facts, which can be obtained from the theory of differential equations (see e.g. [9]):

- The oscillatory and stability properties of difference system (10) completely characterize the same properties of differential system (6)
- If linear system (10) is locally (globally) asymptotically stable, then (6) is also locally (globally) asymptotically stable
- If the the Jacobian matrix \( J(f)(E_0) \) is non defective [2], then the equilibrium point of system (10) is locally stable.

Thus, to conclude we need to show that the matrix \( J(f)(E_0) \) is non defective [2].

Note that \( \lambda_2, \lambda_3 \) and \( \lambda_4 \) are simple eigenvalues and thus they are non defective eigenvalues. It remains to study the properties of \( \lambda_1 \) and to show eventually that it is a non defective eigenvalue. For this we wo solve \( J(f)(E_0)X = 0 \).

We have
\[
\begin{align*}
c_1^rx_3 + c_2x_5 &= 0 \\
(c_1^r + c_{i1})x_3 &= 0, \\
(-c_1^r - c_{i1})x_3 &= 0, \\
(c_2^r + c_{i2})x_5 &= 0, \\
(-c_2^r - c_{i2})x_5 &= 0, \\
c_{i1}x_3 + c_{i2}x_5 - kidx_6 &= 0,
\end{align*}
\]
It is easy to see that the set of solutions of (12) is given by

\[ S = \{ X \in \mathbb{R}^6, x_3 = x_5 = x_6 = 0 \} \]

and thus

\[ \ker(J(f)(E_0)) = \text{span}\{e_1, e_2, e_4\}, \]

where \( e_i \) is the the \( i \)th vector of the canonical basis of \( \mathbb{R}^6 \).

This imply that \( \dim (\ker(J(f)(E_0))) = 3 \).

Since the algebraic multiplicity of \( \lambda_1 \) is 3 and the dimension of the linear space \( \ker(J(f)(E_0)) \) is 3, we conclude that \( \lambda_1 \) is a non defective eigenvalue. This ends the proof that \( J(f)(E_0) \) is non defective. Which imply \( E_0 \) is a stable equilibrium point and thus system (6) is stable at the origin.

So we arrive to the following result:

**Theoreme 2.** The system (6), describing drug dynamics in the biological tissue, is stable at the equilibrium point \( E_0 = (0, 0, 0, 0, 0, 0) \).

This means that the free drugs, small changes in medication dose or receptors concentration do not destabilize the system.

3. Conclusion

The present study deals with the establishment of the stability of a mathematical prognostic model for drug release from a polymeric matrix and subsequent intracellular drug transport. We have shown that the system is stable at the equilibrium point. This means that a little variation in drug dose or small physiological changes (receptors concentration) do not lead to an unstable system. This conclusion is obtained without computing the solutions of the system neither analytically nor numerically. Thus, the theoretical stability analysis done in the present work contributes to a better understanding of the underlying biochemical processes that govern the drug transport to the biological cells.

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