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Stability analysis of a glucose insulin dynamic system using matrix Lambert W function

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Abstract

In this paper we investigate the stability of the glucose-insulin dynamical system. We find an explicit expression for the eigenvalues of the dynamical system with single delay. Using matrix function definitions, we use the Lambert W matrix function from which we form the expression.

Keywords: Delay; Stability; Glucose-Insulin dynamics; Lambert W function.
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1 Introduction

For ordinary dynamic systems (i.e., non-delayed), various methods are available in literature such as linear least-squares, Lambert method, gradient-weighted least-squares, Kalman filtering and other robust techniques [Ljung (1999); Panich (2010); Massimailiano et al., (2014); Corless et al., (1996)]. They have been widely used in signal processing, neural system, robotics, civil engineering and biology. On the other hand, stability of systems with unknown time-delay is still a challenging problem that has attracted continuous attention during the last four decades [Ren (2005)]. Even though considerable efforts have been made on parameter estimation, there are still many open problems in time-delay identification due to difficulty in formulation [Richard (2003); Belkoura et al., (2008); El-Fallah and El-Sallam (2011); Khan and Khan (2010); Khan (2011)]. Obviously, one can expect that the more accurate the knowledge on the delay is, the higher the achievable control performances will be [Richard (2003)]. If the time-delay is known, then, many powerful control techniques (e.g.,

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Smith predictor, Finite Spectrum Assignments (FSA)) can be applied.

One of the best algebraic method to solve system of ordinary differential equation with time delay is Lambert method. Here, we presented a method that makes use of the Lambert W function and analytical solutions of first-order Delay Differential Equations (DDEs). The Lambert W function has been known to be useful in solving DDEs. From the solutions in terms of the Lambert W function, the dominant characteristic roots can be obtained and used to estimate time-delays. The function is already embedded in various software packages (e.g., MATLAB) and thus, the presented method can be readily used for time-delay systems. The presented method and the provided application in glucose insulin dynamical system show ease of formulation and accuracy of time-delay estimation. Also, Galidakis (2007) defined an extension of the Lambert function into a new class called Generalized Hyper Lambert Functions, Nastou et al., (2013) used these functions in order to derive closed-form solutions to a class of first order differential equations using this new class of Lambert functions. Further, the applicability of the Lambert function in applications are clearly explained in Galidakis (2007); Nastou et al., (2013).

Over the last four decades, mathematical models have been developed to describe glucose-insulin dynamics [Li et al., (2006)]. Some of these mathematical models are interested in analysing the glucose disappearance and insulin sensitivity during an intravenous glucose tolerance test [Dalla Man et al., (2002)] and the capture of plasma glucose and insulin dynamics during, as well as after, periods of mild-to-moderate exercise [Yang et al., (1996)]. Others focus on overestimation of glucose effectiveness and the underestimation of insulin sensitivity [Bergman et al., (1979)], capture absorption, distribution and disposal dynamics [Mukhopadhyay et al., (2004)]. Recently, mathematical models have been developed to capture the integral impact of physical activity to glucose and insulin [Li et al., (2006); Pedersen et al., (2013)].

The estimation of time delay for this dynamical system is presented by Li et al., [Li et al., (2001)] while analysis study of mathematical models of the dynamic of glucose and insulin with delays has been presented [De Gaetano and Arino (2000); Edelstein-Keshet (1988); Gatewood et al., (1968)]. The main idea of the methodology is to express the solution of a DDE as the sum of a series of infinitely many exponential functions. The basic foundation of the methodology, i.e., the assumption that the principal branch of the Lambert W function defines the stability of the system, is well established for first order systems. Furthermore, the discretization method for delay systems has been presented [Gatewood et al., (1968)]. In this work, we focus on the mathematical model presented in [Li et al., (2006)] and we are interested in the expression of the eigenvalues and stability of the glucose-insulin dynamical system.

2 Model description

The minimal model, which is the model currently mostly used in physiological research on the metabolism of glucose, was proposed in the early nineteen-eighties for the interpretation of the glucose and insulin plasma concentrations subsequent by IVGTT. Consider the following general and more realistic model [Jansson et al., (1980)] for the interaction of glucose and insulin, the special case of "dynamic model". Thus, the differential equations corresponding to the glucose model are:

$$\begin{aligned} \frac{dG(t)}{dt} &= -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7, \\ \frac{dI(t)}{dt} &= -b_2 I(t) + b_6 G(t-\tau), \end{aligned} \tag{2.1}$$

with the initial conditions $G(t) \equiv G(0)$, for all t and $I(t) \equiv I(0)$, for all $t \in [-\tau, 0]$, where τ $[min]$ denotes a delay before the pancreas can respond to changes in blood glucose. As in the minimal

model, $G(t)$ $[mg/dl]$, $I(t)$ $[\mu UI/ml]$ is the plasma glucose, insulin concentration at time t $[min]$, respectively. The parameters are described in Table-I. Also, the parameter α in the response function $\frac{G(t)}{\alpha G(t)+1}$ is non-negative and $\frac{1}{\alpha}$ is the half-saturation constant. The reason for this is simply due to the limit of time and the capacity of insulins ability of digesting glucose.

Table I: Parameters description for the Dynamic model

Parameters & Units	Description
b_0 $[mg/dl]$	Theoretical glycemia at time 0 after the instantaneous glucose bolus intake
b_1 $[min^{-1}]$	Insulin-independent constant of tissue glucose uptake rate
b_2 $[min^{-1}]$	Constant rate describing the spontaneous decrease of tissue glucose uptake ability
b_3 $[pM/(mg/dl)]$	Insulin-dependent increase in tissue glucose uptake ability
b_4 $[min^{-1}\ pM^{-1}]$	Constant amount of the insulin-dependent glucose disappearance rate constant per pM of plasma insulin concentration
$\tau(=b_5)$ $[min]$	Target glycemia
b_6 $[min^{-1}\ pM/(mg/dl)]$	Constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration throughout the previous τ minutes
b_7 $[(mg/dl)min^{-1}]$	Constant increase in plasma glucose concentration due to constant baseline liver glucose release

Consider the linearized system around the interior equilibrium (G^*, I^*) by substituting, $u_1(t) = G(t) - G^*, u_2(t) = I(t) - I^*$ in (2.1), we obtain,

$$\begin{aligned} \frac{du_1}{dt} &= -\left(b_1 + \frac{b_4 I^*}{(\alpha G^*+1)^2}\right)u_1(t) - \frac{b_4 G^*}{(\alpha G^*+1)}u_2(t), \\ \frac{du_2}{dt} &= -b_2 u_2(t) + b_6 u_1(t-\tau). \end{aligned} \tag{2.2}$$

Definition 2.1. The linear time-delay system (2.2) is stable (or precisely asymptotically stable) if all the solutions of the system (2.2) lie in the complex open left half-plane $\mathbb{C}^-$. Furthermore, the real part of the rightmost solution is called stability exponent, that represents the effect of the most dominant characteristic root on the system behavior.

3 Stability analysis of dynamical system

The linearized glucose-insulin dynamical system (2.2) can be expressed in state space as,

$$\dot{y}(t) = Ay(t) + By(t-\tau), \tag{3.1}$$

where,

$$A = -\begin{bmatrix} b_1 + \dfrac{b_4 I^*}{(\alpha G^* + 1)^2} & \dfrac{b_4 G^*}{(\alpha G^* + 1)} \\ 0 & b_2 \end{bmatrix}, B = \begin{bmatrix} 0 & 0 \\ b_6 & 0 \end{bmatrix}.$$

Defining $y = \{G, I\}^T$, where ^{T} indicates transpose. A and B are the linearized coefficient matrix of the glucose-insulin model and are functions of parameters. Also, in this case the rank of B is one. If an initial state (or value) $y(0)$ is given to the system (3.1), there exists a unique solution with respect to the state variables. On the other hand, for the existence of a unique solution in the system (3.1), an initial function, not a value, must be given in the interval from τ past to the initial time 0:

$$y(t) = g(t), \quad t \in [-\tau,\ 0]. \tag{3.2}$$

In order to solve the differential equation (3.1), let us bring it to the frequency domain by the Laplace transform. Letting $L[\cdot]$ be the Laplace transform, the system (3.1) can be described in the frequency domain as

$$sy(s) - g(0) = Ay(s) + B\left(e^{-s\tau}y(s) + \int_0^\tau e^{-s\gamma}g(\gamma - \tau)d\gamma\right), \tag{3.3}$$

where $y(s) = L[y(t)]$. Further modify (3.3) to

$$\begin{aligned} (sI - A - Be^{-s\tau})y(s) &= g(0) + B\int_0^\tau e^{-s\gamma}g(\gamma - \tau)d\gamma \\ \Leftrightarrow y(s) &= (sI - A - Be^{-s\tau})^{-1}\left(g(0) + B\int_0^\tau e^{-s\gamma}g(\gamma - \tau)d\gamma\right). \end{aligned} \tag{3.4}$$

We assume the solution for (3.1) is of the form as,

$$y(t) = e^{st}C \tag{3.5}$$

where s is 2×2 matrix and C is constant 2×1 vector. Typically, the characteristic equation for (3.1) is obtained by assuming a nontrivial solution of the form $e^{st}C$ where s is a scalar variable and C is constant 2×1 vector [Hale (1997)]. Alternatively, one can assume the form of (3.5) to derive the solution to systems of DDEs in (3.1) using the matrix Lambert W function.

Accordingly, the solutions can be obtained by operating the inverse Laplace transform to $y(s)$ in (3.4). For this, the characteristic equation

$$\det[s - A - Be^{-s\tau}] = 0. \tag{3.6}$$

Equation (3.6) must be solved to find the poles for applying the residue theorem. It is well known that the equation (3.6) has infinitely many solutions due to the presence of the exponential term, $e^{-s\tau}$, induced by the time delay term $y(t - \tau)$ and cannot be solved algebraically. Therefore, one has to rely on numerical methods, but the solutions are never exhibited in the complete forms in the practical sense. The Lambert W function is defined as [Sun Yi et al., (2007)]:

$$W(H)e^{W(H)} = H. \tag{3.7}$$

For detailed explanations on definition and properties of the function, refer to [Sun Yi et al., (2007); Sun Yi and Ulsoy (2006)]. Based on the Lambert W function, a new approach has been developed for systematic analysis and control of systems with time-delays [Sun Yi (2009)]. The function allows

handling of the exponential term in the characteristic equation thanks to its definition in equation (3.7) which is not unique since the solution of (3.7) is not always the Lambert W function of H [Corless et al., (2007)]. Then, using the Lambert W function, the characteristic root is obtained from equation (3.6) as:

$$s = \frac{1}{\tau} W(B\tau e^{-A\tau}) + A. \tag{3.8}$$

It should be stressed that (3.8) is an explicit expression of the characteristic roots of the system (3.1). The expression (3.8) is favorable for exploring qualitative features of them and the branches of W enable us to identify the positions of all of them in the complex plane at a glance and compute them readily with the help of Mathematica, Maple or Matlab. The explicit expression (3.8) immediately offers the following stability condition which is fundamental in this paper.
The matrix Lambert W function, $W(H)$, is complex valued, with a complex argument H, and has an infinite number of branches $W_k(H_k)$, where $k = -\infty, \cdots, -1, 0, 1, \cdots, \infty$ [Asl and Ulsoy (2003)]. Corresponding to each branch, k, of the Lambert W function, W_k, there is a solution Q_k from (3.8), and for $H_k = B\tau Q_k$, the Jordan canonical form J_k is computed from $H_k = Z_k J_k Z_k^{-1} J_k = diag(J_{k1}(\lambda_1), J_{k2}(\lambda_2), \cdots, J_{kp}(\lambda_p))$, where $J_{ki}(\lambda_i)$ is 2×2 Jordan block and m is multiplicity of the eigenvalue λ_i. Then, the matrix Lambert W function can be computed as

$$W_k(H_k) = Z_k\{diag(W_k(J_{k1}(\lambda_1)), \cdots, W_k(J_{kp}(\lambda_p)))\}Z_k^{-1} \tag{3.9}$$

where

$$W_k(J_{ki}(\lambda_i)) = \begin{bmatrix} W_k(\lambda_i) & W'(\lambda_i) \\ 0 & W_k(\lambda_i) \end{bmatrix} \tag{3.10}$$

With the matrix Lambert W function, W_k, given in (3.9), s_k is computed from (3.8). The principal $(k = 0)$ and other $(k \neq 0)$ branches of the Lambert W function can be calculated from a series definition [Corless et al., (1996)] or using commands already embedded in various commercial software packages, such as Matlab, Maple, and Mathematica. With W_k, equation (3.7) becomes

$$W_k(H_k)e^{W_k(H_k)} = H_k, \tag{3.11}$$

finallay, the Q_k is obtained from

$$W_k(B\tau Q_k)e^{W_k(B\tau Q_k)+A\tau} = B\tau, \tag{3.12}$$

and then from (3.5), s_k becomes,

$$s_k = \frac{1}{\tau} W_k(B\tau Q_k) + A. \tag{3.13}$$

Now substitute (3.13) into (3.5), then we obtain the free solution to (3.1) as:

$$y(t) = \sum_{k=-\infty}^{\infty} C_k e^{s_k \tau}, \tag{3.14}$$

where C_k is the coefficient matrix computed from a given preshape function $y(t) = g(t)$, which is initial state of DDEs (3.1), for $t \in [-\tau, 0]$ [Sun Yi and Ulsoy (2006)]. Each branch of the Lambert W function can be computed analytically in terms of the parameters of the DDE in equation (3.1) as shown in [Corless et al., (1996)] (see Fig. 1). One can explicitly determine how the parameters are involved in the solution and, furthermore, how each parameter affects each characteristic root. Each eigenvalue is distinguished by k, which indicates the branch of the Lambert W function as seen in equation (3.14). The function is already embedded in various software packages, such as Matlab.

For system (3.1) to be stable, all characteristic roots must have negative real parts. Calculating the solution for all the branches is not possible. To work around this difficulty, the proposers of this methodology assume that for any branch k of the matrix Lambert W function, there is a unique solution Q_k to (3.13) and a corresponding s_k matrix. This assumption, based on observations from many examples, leads to a stronger conjecture: when the rank of B in (3.1) is at least 1, i.e., B does not have a repeated zero eigenvalue, the characteristic roots with largest real part correspond to the s_0 matrix, found using the principal branch of the matrix Lambert W function. This conjecture is formally stated in [Sun Yi (2009)] and it is the basis for several derivative works [Wei et al., (2014); Sun Yi (2009); Sun Yi et al., (2012, 2010, 2012)].

By setting $k = 0$ and varying only k from $-\infty$ to ∞, we can solve (3.12) to get Q_k; then using (3.13), we determine the transition matrices of the system (3.1). Using the various commercial software packages, such as Maple, Matlab, Mathematica, we can plot the characteristic values which is obtained by the principal branch that are closest to the imaginary axes and determine the stability of the system.

Therefore, $\Re\{$ characteristic values for $k\} \geq \Re\{$ all other characteristic values $\}$.

The characteristic roots of the system are found analytically in terms of the Lambert W function. While the problem remains infinite dimensional, a one-to-one correspondence between the characteristic roots of the system and the branches of this multi-valued function is assumed. The stability question is then solved by earmarking the dominant characteristic roots of the system with the branches of the Lambert W function corresponding to $k = 0, \pm 1, \cdots \pm m$, where m is the nullity of the matrix B in (3.1). Therefore, only a few branches have to be considered to determine whether a solution is stable or not. Furthermore, the existence of an explicit solution expressed in terms of a power series, allows analyzing the stability of the system of DDE (2.2).

For linearized DDE case, it has been proven that the root obtained using the principal branch always determines stability [Shin and Mori (2006)], and such a proof can readily be extended to systems of DDEs where A and B commute. That is, the eigenvalues of A, obtained using the principal branch for each of $k = 0$, and $k = -1$ (shown in Fig. 1) are closest to the imaginary axis, and their real parts are negative. Furthermore, using additional branches to calculate the characteristic values always yields characteristic values whose real parts are further to the left in the plane. Thus, we conclude that the glucose insulin dynamical system is stable.

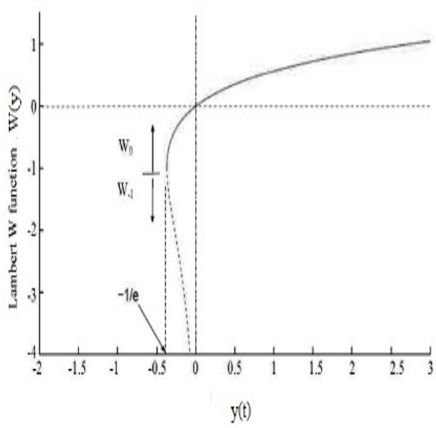

Fig. 1: Two real branches of the Lambert W function: the principal branch, $k = 0$ and $k = -1$. Those two branches are used to identify the dominant characteristic roots of DDEs (Corless et al.,

(1996)).

4 CONCLUSIONS

(a). In the section 2, we proposed a glucose insulin dynamical system which can be expressed as systems of linear DDEs.

(b). In the section 3, analytical solutions to systems of DDEs are derived. Based on the solutions, method for analysis and stability for systems with time-delays were developed and applied to systems of glucose insulin dynamical system.

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