МАТЕМАТИКА

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ON THE DYNAMICS OF THE DISCRETE DELAY MODELS OF GLUCOSE-INSULIN SYSTEMS[*]

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In this paper, we study the dynamics of the discrete delay models of Glucose-Insulin systems:

$$\begin{cases} G_{n+1} = \alpha G_n - \beta G_n I_{n-m_i} + \Gamma, \\ I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}). \end{cases}$$

We are interested in providing sufficient conditions guaranteeing the fact that all positive solutions of this systems converge to the positive equilibrium.

1. Introduction

Our main motivation in studying the dynamics of the systems:

$$\begin{cases} G_{n+1} = \alpha G_n - \beta G_n I_{n-m_i} + \Gamma, \\ I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}) \end{cases} \tag{1}$$

is the dynamics of the differential version systems

$$\begin{cases} \dot{G}(t) = -K_{xg} G\ \ t\ \ - K_{xgi} G(t) I(t-\tau_i) + \dfrac{T_{gh}}{V_G}, \\ \dot{I}(t) = -K_{xi} I(t) + \dfrac{T_{iG\max}}{V_I} f\ \ G(t-\tau_g)\ \ , \end{cases} \tag{2}$$

where $\gamma, G_*, K_{xgi}, K_{xi}, T_{gh}, T_{iG\max}, V_G, V_I, \tau_g, \tau_i \in (0, \infty)$ invertigated in [3]. In [3], the author proved that (2) admits positive bounded solutions for any positive initial condition, that there is a unique positive equilibrium $(G_b, I_b),$ which consists of the basal levels of glucose and insulin concentration, and this equilibrium point is lacally asymptotically stable according to a very broad set of parameter values. That paper provides also a sufficient condition ensuring the global asymptotic stability.

However, it is very interesting to see the connection of (2) to (1). In practice, when formulating (2), we actually replace the first derivative $\dot{G}(t)$ and $\dot{I}(t)$ of *G* and *I* at *t* by their first right approximation

$$\frac{G(t+h)-G(t)}{h}, \quad \frac{\tilde{I}(t+h)-\tilde{I}(t)}{h}$$

for *h* > 0 sufficient small. Thus, formally, system (2) comes from

$$\begin{cases} \dfrac{G(t+h)-G(t)}{h} = -K_{xg} G(t) - K_{xgi} G(t) \tilde{I}(t-\tau_i) + \dfrac{T_{gh}}{V_G} \\ I_{n+1} = \dfrac{\tilde{I}(t+h)-\tilde{I}(t)}{h} = -K_{xi} \tilde{I}(t) + \dfrac{T_{iG\max}}{V_I} f\ \ G(t-\tau_g)\ \ , \end{cases}$$

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for small *h*. If we set

$$G_h(t) := G(ht), \quad I_h(t) := \tilde{I}(ht), \quad t = nh, \quad \frac{\tau_i}{h} = m_i, \quad \frac{\tau_g}{h} = m_g,$$

then preceding system becomes

$$\begin{cases} G_h(n+1) = \alpha G_h(n) - \beta G_h(n) I_h(n - m_i) + \Gamma \\ I_h(n+1) = \lambda I_h(n) + \Delta f(G_h(n - m_g)), \end{cases}$$

or

$$\begin{cases} G_{n+1} = \alpha G_n - \beta G_n I_{n-m_i} + \Gamma \\ I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}), \end{cases}$$

where

$$\alpha = 1 - hK_{xg}, \quad \beta = hK_{xgi}, \quad \Gamma = h\frac{T_{gh}}{V_G}, \quad \lambda = 1 - hK_{xi}, \quad \Delta = h\frac{T_{iG\max}}{V_I}.$$

2. The results

We consider the discrete system of Glucose and Insulin (1), where

$$f(G) = \frac{G^\gamma}{G^\gamma + C_*^\gamma}$$

defined on positive reals, m_i, m_g are two fixed positive integer, $\alpha, \lambda \in$ (0, 1) and γ, β, Γ, Δ are positive parameters. The positive initial values $G_{-m_g}, G_{-m_g+1}, \cdots, G_0; I_{-m_i}, I_{-m_i+1}, \cdots, I_0$ are given. The derivative of *f* is

$$f'(G) = \frac{\gamma G_*^\gamma G^{\gamma-1}}{(G^\gamma + G_*^\gamma)^2} > 0,$$

so *f* is increasing. After some computations, it can be seen that the system (1) admits positive bounded solutions for any positive initial conditions. We have

$$\sup_{G \ge 0} f(G) = 1$$

and

$$f''(G) = 2G_*^\gamma G^{\gamma-2} \frac{(\gamma-1)G_*^\gamma - (\gamma+1)G^\gamma}{(G^\gamma + G_*^\gamma)^2},$$

so, if $\gamma \le 1$, f' is decreasing, and if $\gamma > 1$, f' is unimodal. Thus,

$$\sup_{G \ge 0} f'(G) = f'(G_0) = \frac{(\gamma+1)^2(\gamma-1)}{4\gamma G_0}, \quad \text{if } \gamma > 1,$$

$$\text{where } G_0 = \sqrt[\gamma]{\frac{\gamma-1}{\gamma+1}} G_*,$$

$$\sup_{G \ge 0} f'(G) = f'(0) = \frac{1}{G_*}, \qquad \text{if } \gamma = 1,$$

$$\sup_{G \in [0, \bar{G}]} f'(G) = \infty, \qquad \text{if } \gamma < 1,$$

$$\sup_{G \in [\bar{G}, \infty]} f'(G) = f'(\bar{G}), \qquad \text{if } \gamma < 1.$$

Proposition 1. *System (1) has a unique positive equilibrium* $(\bar{G}, \bar{I})$, *which consists of the basal levels of glucose and insulin concentrations.*

Proof. Each equilibrium point $(\bar{G}, \bar{I})$ has to satisfy the following equations:

$$\begin{cases} \bar{G}(1-\alpha+\beta\bar{I}) = \Gamma \\ \bar{I} = \dfrac{\Delta}{1-\lambda} f(\bar{G}), \end{cases} \tag{3}$$

that is

$$\varphi(\bar{G}) = \Gamma + (\alpha-1)\bar{G} - \beta\bar{G}\cdot\bar{I} = 0, \quad \varphi(0) = \Gamma > 0.$$

We have

$$\varphi'(G) = -(1-\alpha) - \beta\frac{\Delta}{1-\lambda} f(G) - \frac{f'(G)\beta G\Delta}{1-\lambda} < 0$$

and $\lim\limits_{G\to+\infty} \varphi(G) = -\infty.$ This implies that, φ is a decreasing function for positive argument, starting from a positive value at zero, and it may hence have at most one positive root.

Remark. Recall that for any scalar difference inequality of the type:

$$x_{n+1} \le \lambda x_n + \beta, \quad \lambda,\ \beta \in \mathbb{R} \tag{4}$$

it is

$$\begin{cases} x_n \le \lambda^{n-n_0} x_0 + \beta\Sigma_{l=n_0+1}^{n}\lambda^{n-l}, \text{ if } n_0 \le n, \\ x_n \le \lambda^{-(n_0-n)} x_0 - \beta\Sigma_{l=n+1}^{n_0}\lambda^{n-l}, \text{ if } n_0 \ge n. \end{cases}$$

Similarly, by changing the inequality in (4):

$$x_{n+1} \ge \lambda x_n + \beta, \qquad \lambda,\ \beta \in \mathbb{R},$$

we have

$$\begin{cases} x_n \ge \lambda^{n-n_0} x_0 + \beta\sum_{l=n_0+1}^{n}\lambda^{n-l}, \text{ if } n_0 \le n, \\ x_n \ge \lambda^{-(n_0-n)} x_0 - \beta\sum_{l=n+1}^{n_0}\lambda^{n-l}, \text{ if } n_0 \ge n. \end{cases}$$

First, we consider the system (1) in the case $m_i = 0$:

$$\begin{cases} G_{n+1} = \alpha G_n - \beta G_n I_n + \Gamma, \\ I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}). \end{cases} \tag{5}$$

Proposition 2. *Let* (G_n, I_n) *be a positive bounded solution of the system (5). Then,* G_n *is bounded by the following sequences of upper and lower bounds:*

$$m_k \le G_n \le M_k,$$

with $M_0 = \dfrac{\Gamma}{1-\alpha}$, $\beta\Delta < \alpha(1-\lambda)$, $m_k = l(M_k)$, $M_{k+1} = l(m_k)$, and

$$l(x) = \frac{\Gamma(1-\lambda)}{(1-\alpha)(1-\lambda) + \beta\Delta f(x)}.$$

Proof. Proposition 2 is proved by induction. From the system (5) we have

$$G_{n+1} \le \alpha G_n + \Gamma.$$

Therefore, for any arbitary $n_0 \le n$, we have

$$G_n \le \alpha^{n-n_0} G_0 + \Gamma\cdot\frac{1-\alpha^{n-n_0}}{1-\alpha}.$$

Taking $n_0 \to -\infty$, it follows that

$$G_n \le \frac{\Gamma}{1-\alpha} = M_0.$$

Assume that there exists M_k such that $G_n \le M_k$. Then, from (5) we obtain

$$I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}) \le \lambda I_n + \Delta f(M_k).$$

Therefore, for any arbitary $n_0 \le n$,

$$I_n \le \lambda^{n-n_0} I_0 + \Delta f(M_k)\cdot\frac{1-\lambda^{n-n_0}}{1-\lambda}.$$

Taking $n_0 \to -\infty$, it follows that

$$I_n \le \frac{\Delta f(M_k)}{1-\lambda}$$

and from (5) we have

$$G_{n+1} = \alpha G_n - \beta G_n I_n + \Gamma \ge \left(\alpha - \frac{\beta\Delta f(M_k)}{1-\lambda}\right)G_n + \Gamma$$

and

$$G_n \ge \left(\alpha - \frac{\beta\Delta f(M_k)}{1-\lambda}\right)G_0 + \Gamma\cdot\frac{1-\left(\alpha - \frac{\beta\Delta f(M_k)}{1-\lambda}\right)^{n-n_0}}{1-\left(\alpha - \frac{\beta\Delta f(M_k)}{1-\lambda}\right)}.$$

Taking $n_0 \to -\infty$, it follows that

$$G_n \ge \frac{\Gamma}{1-\alpha+\frac{\beta\Delta f(M_k)}{1-\lambda}} = m_k = l(M_k).$$

On the orther hand, since

$$I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}) \ge \lambda I_n + \Delta f(m_k),$$

so

$$I_n \ge \lambda^{n-n_0} I_0 + \Delta f(m_k)\cdot\frac{1-\lambda^{n-n_0}}{1-\lambda}.$$

Taking $n_0 \to -\infty$, it follows that

$$I_n \ge \frac{\Delta f(m_k)}{1-\lambda},$$

which implies

$$G_{n+1} \le \left(\alpha - \frac{\beta\Delta f(m_k)}{1-\lambda}\right)G_n + \Gamma$$

and

$$G_n \le \left(\alpha - \frac{\beta\Delta f(m_k)}{1-\lambda}\right)^{n-n_0} G_0 + \Gamma\cdot\frac{1-\left(\alpha - \frac{\beta\Delta f(m_k)}{1-\lambda}\right)^{n-n_0}}{1-\left(\alpha - \frac{\beta\Delta f(m_k)}{1-\lambda}\right)}.$$

Taking $n_0 \to -\infty,$ it follows that

$$G_n \le \frac{\Gamma}{1-\alpha+\dfrac{\beta\Delta f(m_k)}{1-\lambda}} = l(m_k) = M_{k+1}.$$

The proof is complete.

Proposition 3. *Consider the sequences of bounds* $(M_k),(m_k)$ *in Proposition 2. Then:*

- (M_k) *is a bounded monotone decreasing sequence;*
- (m_k) *is a bounded monotone increasing sequence.*

Proof. We have

$$M_1 = l(m_0) = \frac{\Gamma(1-\lambda)}{(1-\alpha)(1-\lambda)+\beta\Delta f(m_0)} < \frac{\Gamma(1-\lambda)}{(1-\alpha)(1-\lambda)} = \frac{\Gamma}{1-\alpha} = M_0.$$

It is easy to see that

$$M_{k+1} = l\;\,l(M_k)\;\;,\;\; m_{k+1} = l\;\,l(m_k)\;\;.$$

Since

$$l'(x) = \frac{-\beta\Delta f'(x)}{(1-\alpha)(1-\lambda)+\beta\Delta f(x)\;^2} < 0,$$

it follows that $l(x)$ is monotonically decreasing in *x*, so that $l\;\,l(x)$ is monotonically increasing in *x*. Hence, if $M_k < M_{k-1},$ then

$$M_{k+1} = l\;\,l(M_k)\;\; \le l\;\,l(M_{k-1})\;\; = M_k$$

and

$$m_k = l(M_k) \ge l(M_{k-1}) = m_{k-1}.$$

The proof is complete.

By Proposition 2 and Proposition 3, we obtain the following theorem:

THEOREM 1. *If* $\bar{x}$ *is the only positive root of the equation* $x = l\;\,l(x)\;\;,$ *then every positive solution of the system (5) converge to the positive equilibrium* $(\bar{G},\bar{I}),$ *where* $\bar{G} = \bar{x}$ *and* $\bar{I} = \dfrac{\Delta f(\bar{x})}{1-\lambda}.$

Next, we will use ω-limit set of a persistent ([1], [2]) to study the global attraction of the basal levels of the system (1). For a persistent solution (G_n, I_n) of (1), we let $\omega(G,I) \subset \mathbb{R}_+^{m_g+m_i+2}$ be the set of all limit-points of the sequence of vectors

$$(\underline{u}_n,\underline{\vartheta}_n) = (G_{n-m_g}, G_{n-m_g+1},\cdots,G_n;\; I_{n-m_i}, I_{n-m_i+1},\cdots,I_n)\;_n\,.$$

This set is compact and invariant under the map $T:\mathbb{R}_+^{m_g+m_i+2} \to \mathbb{R}_+^{m_g+m_i+2}$ defining by $T(\underline{u}_0,\underline{\vartheta}_0) = (\underline{u}_1,\underline{\vartheta}_1).$ Here, $(\underline{u}_0,\underline{\vartheta}_0)$ is vector of initial data, which is running in the positive quarter of $\mathbb{R}_+^{m_g+m_i+2}.$ The map *T* takes the initial data to the next data. This map is well-defined. Moreover, the map *T* maps $\omega(G,I)$ *onto* (surjectively) itself.

THEOREM 2. *Let* (G_n, I_n) *be a positive bounded solution of the system (1), and denote*

$$G_m = \liminf_{n\to\infty} G_n,\quad G_M = \limsup_{n\to\infty} G_n,\quad I_m = \liminf_{n\to\infty} I_n,\quad I_M = \limsup_{x\to\infty} I_n.$$

Then

$$I_m \le \bar{I} \le I_M \le \frac{\Delta}{1-\lambda}\sup_{G\ge 0} f(G),$$

$$G_m \le \bar{G} \le G_M \le \frac{\Gamma}{1-\alpha+\beta I_m}.$$

Proof. First, we construct four full time solutions $(\tilde{G}_n,\tilde{I}_n),(\tilde{\tilde{G}}_n,\tilde{\tilde{I}}_n),(\tilde{\tilde{\tilde{G}}}_n,\tilde{\tilde{\tilde{I}}}_n),(\tilde{\tilde{\tilde{\tilde{G}}}}_n,\tilde{\tilde{\tilde{\tilde{I}}}}_n)$ such that:

$$\tilde{I}_0 = I_M, \tilde{I}_n \ge I_m, G_m \le \tilde{G}_n \le G_M, \forall n \in \mathbb{Z};$$

$$\tilde{\tilde{G}}_0 = G_m, \tilde{\tilde{G}}_n \le G_M, I_m \le \tilde{\tilde{I}}_n \le I_M, \forall n \in \mathbb{Z};$$

$$\tilde{\tilde{\tilde{I}}}_0 = I_m, \tilde{\tilde{\tilde{I}}}_n \le I_M, G_m \le \tilde{\tilde{\tilde{G}}}_n \le G_M, \forall n \in \mathbb{Z};$$

$$\tilde{\tilde{\tilde{\tilde{G}}}}_0 = G_M, \tilde{\tilde{\tilde{\tilde{G}}}}_n \ge G_m, I_m \le \tilde{\tilde{\tilde{\tilde{I}}}}_n \le I_M, \forall n \in \mathbb{Z}.$$

We have the following inequality

$$I_M = \tilde{I}_0 = \lambda \tilde{I}_{-1} + \Delta f(\tilde{G}_{-1-m_g}) \le \lambda \tilde{I}_0 + \Delta f(\tilde{G}_{-1-m_g}),$$

or

$$\tilde{I}_0 \le \frac{\Delta}{1-\lambda} f(\tilde{G}_{-1-m_g}).$$

If $\tilde{G}_{-1-m_g} < \bar{G}$, then $G_m < \bar{G}$ and

$$I_M \le \frac{\Delta}{1-\lambda} f(\tilde{G}_{-1-m_g}) < \frac{\Delta}{1-\lambda} f(\bar{G}) = \bar{I}.$$

On the other hand, we have

$$G_m = \tilde{\tilde{G}}_0 = \alpha \tilde{\tilde{G}}_{-1} - \beta \tilde{\tilde{G}}_{-1} \tilde{\tilde{I}}_{-1-m_i} + \Gamma \ge \alpha \tilde{\tilde{G}}_0 - \beta \tilde{\tilde{G}}_0 \tilde{\tilde{I}}_{-1-m_i} + \Gamma,$$

or

$$\tilde{\tilde{G}}_0 (1-\alpha+\beta \tilde{\tilde{I}}_{-1-m_i}) \ge \Gamma,$$

or

$$G_m (1-\alpha+\beta \tilde{\tilde{I}}_{-1-m_i}) \ge \Gamma.$$

But in this case $G_m < \bar{G}$ and $I_M < \bar{I}$, so

$$\Gamma \le G_m (1-\alpha+\beta \tilde{\tilde{I}}_{-1-m_i}) < \bar{G}(1-\alpha+\beta \bar{I}) = \Gamma,$$

which is a contradiction. Therefore, the hypothesis that $\tilde{G}_{-1-m_g} < \bar{G}$ is false. So we have $\tilde{G}_{-1-m_g} \ge \bar{G}$, and consequently, $I_M \ge \bar{I}$ and $G_M \ge \bar{G}$. By using two full time solutions $(\tilde{\tilde{\tilde{G}}}_n,\tilde{\tilde{\tilde{I}}}_n)$, $(\tilde{\tilde{\tilde{\tilde{G}}}}_n,\tilde{\tilde{\tilde{\tilde{I}}}}_n)$ we will get $I_m \le \bar{I}$ and $G_m \le \bar{G}$. The proof is complete.

THEOREM 3. *Assume that* (G_n, I_n) *is a persistent solution of the system (1). If one of* (G_n) *and* (I_n) *does not oscillte around its basal level, then both of them converge to their basal levels.*

Proof. From the proof of Theorem 2 we have

$$\frac{\Delta}{1-\lambda} f(G_m) \le I_m \le \bar{I} \le I_M \le \frac{\Delta}{1-\lambda} f(G_M),$$

$$G_M (1-\alpha+\beta I_m) \le \Gamma \le G_m (1-\alpha+\beta I_M).$$

From the inequality $\Gamma \le G_m(1-\alpha+\beta I_M)$, it follows that if $I_M = \bar{I}$, then $\Gamma = \bar{G}(1-\alpha+\beta \bar{I}) \le G_m(1-\alpha+\beta \bar{I})$, which implies $\bar{G} \le G_m$. Therefore $G_m = \bar{G}$. Now, the inequality $\frac{\Delta}{1-\lambda} f(G_m) \le I_m$ will give $\bar{I} \le I_m$ so that $I_m = \bar{I}$. Hence, $\lim_{n\to\infty} I_n = \bar{I}$. Again by $G_M(1-\alpha+\beta I_m) \le \Gamma$ we have $G_M = \bar{G}$, or equivalently, $\lim_{n\to\infty} G_n = \bar{G}$.

Similarly, if $I_m = \bar{I}$, then $G_M = \bar{G}$. We can conclude that both (I_n) and (G_n) converge to their basal levels. The proof is complete.

THEOREM 4. *Put*

$$L_1 = \frac{\Delta}{1-\lambda} \sup_{G\in[\bar{G},\infty} f'(G),\ L_2 = \frac{\Delta}{1-\lambda} \sup_{G\in[0,\bar{G}} f'(G),$$

$$L_3 = \frac{\Gamma\beta}{(1-\alpha+\beta\bar{I})(1-\alpha+\beta I_M)},\ L_4 = \frac{\Gamma\beta}{(1-\alpha+\beta\bar{I})(1-\alpha+\beta I_m)}.$$

If $L_1L_2L_3L_4 < 1$, *then every positive solution of the system (1) converge to the positive equilibrium, or equivalently, their basal levels are globally attractive.*

Proof. We construct two full time solutions $(\tilde{G}_n, \tilde{I}_n), (\tilde{\tilde{G}}_n, \tilde{\tilde{I}}_n)$ such that

$$\tilde{I}_0 = I_M,\ \tilde{I}_n \ge I_m,\ G_m \le \tilde{G}_n \le G_M,\ \forall n \in \mathbb{N},$$

$$\tilde{\tilde{G}}_0 = G_m,\ \tilde{\tilde{G}}_n \le G_M,\ I_m \le \tilde{\tilde{I}}_n \le I_M,\ \forall n \in \mathbb{N}.$$

As before, we have

$$I_M = \tilde{I}_0 \le \frac{\Delta}{1-\lambda} f(\tilde{G}_{-1-m_g}).$$

It follows that

$$I_M - \bar{I} \le \frac{\Delta}{1-\lambda} \ f(\tilde{G}_{-1-m_g}) - f(\bar{G}) \ \le L_1(G_M - \bar{G}), \tag{6}$$

and

$$\bar{I} - I_m \le \frac{\Delta}{1-\lambda} \ f(\bar{G}) - f(G_m) \ \le L_2(\bar{G} - G_m). \tag{7}$$

Similarly, we get

$$\bar{G} - G_m \le \frac{\Gamma}{1-\alpha+\beta\bar{I}} - \frac{\Gamma}{1-\alpha+\beta I_M} \le L_3(I_M - \bar{I}), \tag{8}$$

and

$$G_M - \bar{G} \le \frac{\Gamma}{1-\alpha+\beta I_m} - \frac{\Gamma}{1-\alpha+\beta\bar{I}} \le L_4(\bar{I} - I_m). \tag{9}$$

From (6), (7), (8) and (9), we obtain

$$I_M - \bar{I} \le L_1L_2L_3L_4(I_M - \bar{I}),$$

$$G_M - \bar{G} \le L_1L_2L_3L_4(G_M - \bar{G}),$$

which implies $I_M = \bar{I} = I_m,\ G_M = \bar{G} = G_m.$ The proof is complete.

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