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On the dynamics of the discrete delay models of Glucose-Insulin systems

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Abstract.

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

$$G_{n+1} = \alpha G_n - \beta G_n I_{n-m_i} + \Gamma \quad (0.1)$$

$$I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}). \quad (0.2)$$

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

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Introduction and Preliminaries

Our main motivation in studying the dynamics of the systems (0.1-0.2) is the dynamics of the differential version systems of (0.1-0.2), namely of the system

$$\dot{G}(t) = -K_{xg}G(t) - K_{xgi}G(t)I(t-\tau_i) + \frac{T_{gh}}{V_G} \quad (0.3)$$

$$\dot{I}(t) = -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g) \quad (0.4)$$

invertigated in [3].

However, it is very interesting to see the connection of (0.3-0.4) to (0.1-0.2). In practice, when formulating (0.3-0.4), we actually replace the first derivative $\dot{G}(t)$ and $\dot{I}(t)$ of G and I at t by their first right approximation

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

for $h > 0$ sufficient small. Thus, formally, system (0.3-0.4) comes from

$$\begin{aligned} \frac{\tilde{G}(t+h)-\tilde{G}(t)}{h} &= -K_{xg}G(t) - K_{xgi}G(t)I(t-\tau_i) + \frac{T_{gh}}{V_G} \\ \frac{\tilde{I}(t+h)-\tilde{I}(t)}{h} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g), \end{aligned}$$

for small h. If we set

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

then preceding system becomes

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

or

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

where

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

2. The results

We consider the following discrete system of Glucose and Insulin

$$G_{n+1} = \alpha G_n - \beta G_n I_{n-m_i} + \Gamma \quad (0.5)$$

$$I_{n+1} = \lambda I_n + \Delta f(G_{n-m_g}), \quad (0.6)$$

where

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

defined on positive reals, $\alpha, \lambda \in (0, 1)$ and $\beta, \Gamma, \lambda, \Delta$ are positive parameters. The derivative of f is

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

so f is increasing. We have

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

and

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

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

$$\sup_{G\geqslant 0} f'(G) = f'(G_0) = \frac{(\gamma+1)^2(\gamma-1)}{4\gamma G_0}, \quad \text{if } \gamma > 1, \quad \text{where } G_0 = \sqrt[\gamma]{\frac{\gamma-1}{\gamma+1}}G_*,$$

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

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

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

System (0.5-0.6) has a unique positive equilibrium $(\overline{G}, \overline{I})$, which consists of the basal levels of glucose and insulin concentrations. These levels satisfy the following system

$$\begin{aligned} \overline{G}(1-\alpha+\beta\overline{I}) &= \Gamma \\ \overline{I} &= \frac{\Delta}{1-\lambda} f(\overline{G}). \end{aligned}$$

We now let

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

Proposition. *For every persistent solution (G_n, I_n) of the system (0.5-0.6), we have*

$$\begin{aligned} I_m \leqslant \overline{I} \leqslant I_M \leqslant \frac{\Delta}{1-\lambda} \sup_{G\geqslant 0} f(G) \\ G_m \leqslant \overline{G} \leqslant G_M \leqslant \frac{\Gamma}{1-\alpha+\beta I_m}. \end{aligned}$$

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

$$\begin{aligned} &\tilde{I}_0 = I_M, \quad \tilde{I}_n \geqslant I_m, \quad G_m \leqslant \tilde{G}_n \leqslant G_M, \quad \forall n \in \mathbb{Z}, \\ &\tilde{\tilde{G}}_0 = G_m, \quad \tilde{\tilde{G}}_n \leqslant G_M, \quad I_m \leqslant \tilde{\tilde{I}}_n \leqslant I_M, \quad \forall n \in \mathbb{Z}, \\ &\tilde{\tilde{\tilde{I}}}_0 = I_m, \quad \tilde{\tilde{\tilde{I}}}_n \leqslant I_M, \quad G_m \leqslant \tilde{\tilde{\tilde{G}}}_n \leqslant G_M, \quad \forall n \in \mathbb{Z}, \\ &\tilde{\tilde{\tilde{\tilde{G}}}}_0 = G_M, \quad \tilde{\tilde{\tilde{\tilde{G}}}}_n \geqslant G_m, \quad I_m \leqslant \tilde{\tilde{\tilde{\tilde{I}}}}_n \leqslant I_M, \quad \forall n \in \mathbb{Z}. \end{aligned}$$

We have the following inequality

$$\begin{aligned} I_M = \tilde{I}_0 &= \lambda \tilde{I}_{-1} + \Delta f(\tilde{G}_{-1-m_g}) \leqslant \alpha \tilde{I}_0 + \Delta f(\tilde{G}_{-1-m_g}) \\ I_M = \tilde{I}_0 &\leqslant \frac{\Delta}{1-\lambda} f(\tilde{G}_{-1-m_g}). \end{aligned}$$

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

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

On the other hand,

$$\begin{aligned} G_m = \tilde{\tilde{G}}_0 &= \alpha \tilde{\tilde{G}}_{-1} - \beta \tilde{\tilde{G}}_{-1} \tilde{\tilde{I}}_{-1-m_i} + \Gamma \\ &\geqslant \alpha \tilde{\tilde{G}}_0 - \beta \tilde{\tilde{G}}_0 \tilde{\tilde{I}}_{-1-m_i} + \Gamma \\ &\tilde{\tilde{G}}_0 (1 - \alpha + \beta \tilde{\tilde{I}}_{-1-m_i}) \geqslant \Gamma \\ &G_m (1 - \alpha + \beta \tilde{\tilde{I}}_{-1-m_i}) \geqslant \Gamma. \end{aligned}$$

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

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

which is a contradiction. Therefore, the hypothesis that $\tilde{G}_{-1-m_g} < \overline{G}$ is false. So ve have $\tilde{G}_{-1-m_g} \geqslant \overline{G}$, and consequently, $I_M \geqslant \overline{I}$ and $G_M \geqslant \overline{G}$. 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 $I_m \leqslant \overline{I}$ and $G_m \leqslant \overline{G}$. The proof is complete.

Theorem 1. *Assume that (G_n, I_n) is a persistent solution of the system (0.5-0.6). If one of $\{G_n\}_n$ and $\{I_n\}_n$ does not oscillte around its basal level, then both of them converge to their basal levels.*

Proof. From the proof of Proposition 1 we have

$$\begin{aligned} \frac{\Delta}{1-\lambda} f(G_m) \leqslant I_m \leqslant \overline{I} \leqslant I_M \leqslant \frac{\Delta}{1-\lambda} f(G_M) \\ G_M(1 - \alpha + \beta I_m) \leqslant \Gamma \leqslant G_m(1 - \alpha + \beta I_M). \end{aligned}$$

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

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

Now, we let (G_n, I_n) be an oscillated solution of the system of equation (0.5-0.6). Here, the oscillation means the oscillation around the basal levels.

Theorem 2. *Put*

$$L_1 = \frac{\Delta}{1-\lambda} \sup_{\overline{G},\infty)} f'(G), \quad L_2 = \frac{\Delta}{1-\lambda} \sup_{G\in[0,\overline{G}]} f'(G),$$
$$L_3 = \frac{\Gamma\beta}{(1-\alpha+\beta\overline{I})(1-\alpha+\beta I_M)}, \quad L_4 = \frac{\Gamma\beta}{(1-\alpha+\beta\overline{I})(1-\alpha+\beta I_m)}.$$

If $L_1L_2L_3L_4 < 1$, then every positive solution of the (0.5-0.6) 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

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

As before, we have

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

It follows that

$$I_M - \overline{I} \leqslant \frac{\Delta}{1-\lambda}\Big(f(\tilde{G}_{-1-m_g}) - f(\overline{G})\Big) \leqslant L_1(G_M - \overline{G}),$$

and

$$\overline{I} - I_m \leqslant \frac{\Delta}{1-\lambda}\Big(f(\overline{G}) - f(G_m)\Big) \leqslant L_2(\overline{G} - G_m).$$

On the other hand,

$$\overline{G} - G_m \leqslant \frac{\Gamma}{1-\alpha+\beta\overline{I}} - \frac{\Gamma}{1-\alpha+\beta I_M} \leqslant L_3(I_M - \overline{I}),$$

and

$$G_M - \overline{G} \leqslant \frac{\Gamma}{1-\alpha+\beta I_m} - \frac{\Gamma}{1-\alpha+\beta\overline{I}} \leqslant L_4(\overline{I} - I_m).$$

Therefore, we get

$$I_M - \overline{I} \leqslant L_1 L_2 L_3 L_4 (I_M - \overline{I}),$$
$$G_M - \overline{G} \leqslant L_1 L_2 L_3 L_4 (G_M - \overline{G}),$$

so $I_M = \overline{I} = I_m$, $G_M = \overline{G} = G_m$ and this completes the proof.

Remark. Theorem 2 is still true in the case $\alpha = 1$. Indeed, in this case the system (0.5-0.6) becomes

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

and the basal levels satisfy the following system

$$\begin{aligned} \overline{G}\beta\overline{I} &= \Gamma \\ \overline{I} &= \frac{\Delta}{1-\lambda} f(\overline{G}). \end{aligned}$$

It is proved in [3] that if

$$\gamma > \frac{G_*^\gamma + (\overline{G})^\gamma}{G_*^\gamma},$$

there are m_* anM_* such that $m_* < \overline{G} < M_*$ and

$$m_* f(M_*) = M_* f(m_*) = \overline{G} f(\overline{G}).$$

Moreover, we conclude that

$$m_* \leqslant G_m \leqslant \overline{G} \leqslant G_M \leqslant M_*,$$
$$\overline{I} \cdot \overline{G} \frac{1}{M_*} \leqslant I_m \leqslant \overline{I} \leqslant I_M \leqslant \overline{I} \cdot \overline{G} \frac{1}{m_*}.$$

Since

$$\frac{G_m}{\overline{G}} \geqslant \frac{\overline{I}}{\tilde{\overline{I}}_{-1-m_i}} \geqslant \frac{\overline{I}}{I_M},$$

so

$$\overline{G} - G_m = \overline{G}\Big(1 - \frac{G_m}{\overline{G}}\Big) \leqslant \overline{G}\Big(1 - \frac{\overline{I}}{I_M}\Big) \leqslant \frac{\overline{G}}{I_M}(I_M - \overline{I}) \leqslant \frac{\overline{G}}{\overline{I}}(I_M - \overline{I}).$$

On the other hand, we have

$$G_M - \overline{G} \leqslant M_* - \overline{G} = \frac{M_*}{\overline{I}}\Big(\overline{I} - \frac{\overline{I}\cdot\overline{G}}{M_*}\Big) \leqslant \frac{M_*}{\overline{I}}(\overline{I} - I_m).$$

Therefore, if

$$\frac{\overline{G}}{\overline{I}} \cdot \frac{M_*}{\overline{I}} < 1,$$

then $G_M = \overline{G} = G_m$. So, the proof is complete.

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