Computational Mathematical Model Based on Lyapunov Function for the Hormonal Storage Control

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Abstract

Computational mathematical models have shown promise in the biological mechanism's reproduction. This work presents a computational mathematical model of the hormonal storage control applied to an endocrine cell. The model is based on a system of differential equations representing the internal cell dynamics and governed by the Lyapunov control function. Among the stages of these dynamics, we analyze the storage and degradation, which occur within some endocrine cells. The model's evaluation considers, as an example, the synthesis–storage-release regulation of catecholamine in the adrenal medulla. Seven experiments, varying the input parameters, were performed to validate and evaluate the model. Different behaviors could be observed according to the numerical data used for future research and scientific contributions, besides confirming that Lyapunov control function is feasible to govern the cell dynamics.

Keywords: Lyapunov function; Computational mathematical model; Hormonal storage control;

1. Introduction

The complex physiological mechanisms that keep the organism in homeostatic balance stimulate the minds of scholars to seek an understanding of this dynamic of internal control. The nervous and endocrine systems are responsible for the regulation and coordination of most of these mechanisms [9, 7]. The endocrine system, with its set of glands and cells, participates in this control through the hormones it releases. They function as chemical messengers mediating endocrine coordination. The word endocrine means secretion inward, and hormones are substances synthesized by endocrine cells and released into the blood, through which they reach the target cell or tissue [22, 24].

The functional balance of endocrine cells depends on an optimum balance between the synthesis, storage, and secretion of the hormone it produces. It involves a complex control system, from synthesis to secretion. Anomalies in this control contribute to the development of diseases. Therefore, the study and modeling of this control system are of great relevance [37].

In the study of the endocrine cells has been advances. Researches in animals using cell cultures developed to mimic events occurring in their dynamics have help to understand some mechanisms [10, 30, 33, 40].

Undoubtedly, mathematical and computational modeling is a path that can help a lot in this understanding, providing answers to many questions generated by experimental research. Mathematical modeling is already an integral part of Biology and Medicine. Models and computer simulations, using real data, are capable to generate insights. They have the potential to predict normal and abnormal behaviors of a cell, organs, and other components of living systems [11, 13, 15, 39].

The work of Cortez et al. [13] used the Lotka-Volterra equations to verify the dynamics of storage-synthesis control in a cell. In this work, we proceed by associating these equations with the classical theory of enzymatic kinetics, the Lyapunov dynamics, and the Hamilton-Jacobi-Bellman optimization equations to simulate the synthesis-storage-degradation balance in the production of catecholamines in an adrenal cell [4]. The computational model was implemented in C language, to

simulate various situations and to show the existence of the storage-degradation balance, studying the influence of the parameters on this equilibrium phase.

The remainder of this paper is organized as follows. Section 2 describes the storage control model applied to an endocrine cell. Section 3 presents the algorithm structure and experimental environment. All experiments, validation, and evaluation are approached in Section 4. Finally, Section 5 shows our conclusions and directions for future works.

2. Control Model Applied to Endocrine Gland

2.1 Endocrinophysiological System

The secretory cells are, in their majority, cubic cells and with two faces: apical and basal, with different polarities of secretory flow. Substrates (S) enter through the basement membrane for the secretion product synthesis that the gland secretes. The product synthesis occurs along the path from the basement membrane to the apical membrane, where it is released into the extracellular medium, and it reaches the blood. The model uses, as an example, the endocrine cell. The adrenal or suprarenal gland cells secrete two well-known catecholamines: EP and NEP. They call adrenaline and noradrenaline, respectively [22, 24].

The suprarenal is a gland located on the kidneys. There are two glands each over a kidney. In a cut of the gland, two regions can be distinguished with the naked eye: the cortical (the cortex) and the medulla. The adrenal cortex secretes steroid-like hormones. The medulla constitutes less than 20% of the gland, and it contains the chromaffin cells, the producers of catecholamines. These cells are called chromaffin because of their high affinity for chromium dyes [28, 31].

The sympathetic nerve fibers, from the autonomic nervous system, richly innervate the adrenal medulla [28, 35]. The adrenal chromaffin cells are modified neurons derived from the sympathetic nervous system [29]. The sympathetic nerve discharges activate the EP secretion in the blood. They also stimulate the exocytosis of catecholamine granules [1].

The synthesis of catecholamines begins with the amino acid tyrosine, which is collected from the bloodstream through the basement membrane of the chromaffin cells. The sequence of reactions for EP synthesis begins with the transformation of tyrosine into dopa, mediated by the enzyme tyrosine hydroxylase. Subsequently, the dopa-decarboxylase enzyme converts dopa into dopamine, which is pick up into reservoir granules. Inside these granules are enzymes that end up converting dopamine into NEP and then into EP, but both have hormonal action. In a few chromaffin cells, the synthesis ends at NEP. But in most cells, the reaction continues with NEP being methylated and converted to EP, by the action of the enzyme N-methyltransferase phenylethanolamine [22].

Figure 1 shows the synthesis of catecholamine, with several reactions until we get the catecholamine.

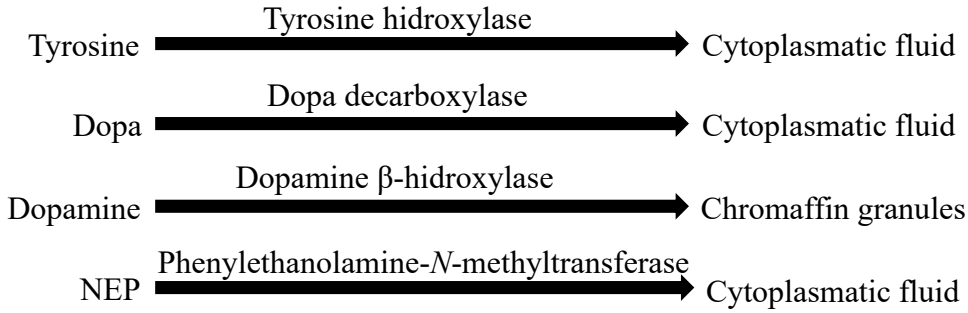

Figure 1. Enzymatic reaction sequences involved in the synthesis of catecholamine.

The regulation of adrenal catecholamine synthesis is a complex process. Nerve discharges activate the enzyme tyrosine hydroxylase and initiate synthesis [35]. However, plasma NEP inhibits this first step in synthesis through a negative feedback mechanism. When the synthesis exceeds the storage capacity, the EP is metabolized in its chromaffin cells. In the blood, catecholamines are short-lived (1-3 minutes) hormones as they are quickly removed from the plasma and metabolized [2, 42].

Catecholaminergic granules have approximately 0.3 μm of diameter. A chromaffin cell can contain approximately 30,000 granules [32]. In addition to EP and NEP, the chromaffin granules contain ATP, dopamine β-hydroxylase, lipids, β-endorphin, chromogranin and pro-opiomelanocortin peptides [32, 35].

Catecholamines are stored in large concentrations in the granules, about 0.5 μM [17]. The normal human adrenal contains 412-633μg of EP and 37-123μg of NEP [17]. EP synthesis is usually so rapid that it is only in rare circumstances that the adrenal medulla can run out of EP supply [12, 21, 8, 18]. Esler et al. [18] found that, at rest, in elderly persons, the secretion of EP is approximately 0.86 nmol/min of EP, while in young people, the secretion is around 0.17 nmol/min.

2.2 Mathematical Model

Figure 2 shows the adopted model to represent the hypothetic endocrine cell and its dynamic control of your endocrine function. The mathematical model has three distinct phases.

The first phase is the synthesis of *H*. The substrate *S* is transported from the blood to the intracellular medium with a V_T speed. The model considers continuous the plasmatic availability of *S*, being *H* produced with a V_H speed depending on the *S* concentration. The second phase is the storage of *H*. The hormone accumulates and is stored in granules at the cell through Via *S* and V_S speed. If not secreted (Via *R*), its excess goes to degradation (Via *D*). When the storage capacity exceeds the maximum limit, *H* proceeds Via *S* and V_D speed to the third phase. Degradation is activated dissociating the hormone molecule to control the hormone quantity in the cell. The recovered substrate *S* can return to the new synthesis phase.

We always consider a small amount of hormone secreted (H_R) by the cell into the plasma with a V_R speed, regardless of any massive discharge that may occur in response to some major organic need.

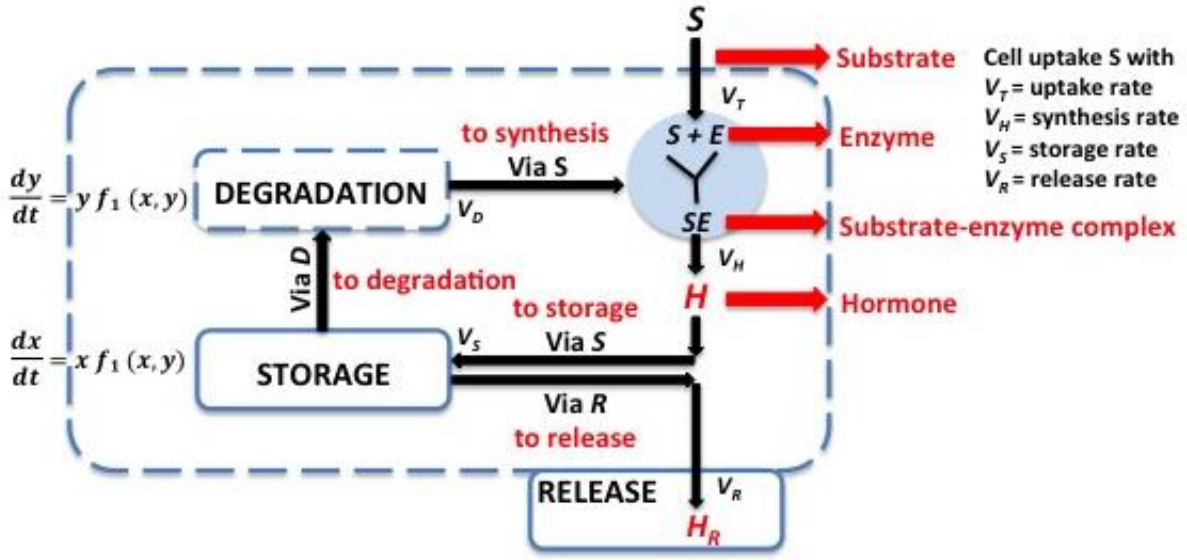

Figure 2. Model adopted for the dynamic control for the synthesis, storage, and release of hormone. *S* = substrate, *E* = enzyme, *SE* = substrate-enzyme complex, V_T = uptake rate from blood, *H* = hormone, V_H = synthesis rate. Via *S* = storage pathway, Via *D* = degradation pathway and Via *R* = release pathway from the storage, H_R = released hormone.

The hormone synthesis (*H*) is described by the following sequence of reactions:

$$\underbrace{E + S}_{1^a\ step} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underbrace{ES}_{2^a\ step} \xrightarrow{k} \underbrace{E + H}_{3^a\ step} \xrightarrow{k} \underbrace{E + H} \qquad (1)$$

where *S* is the substrate, *E* the enzyme, whose concentrations in the cell are [*S*] and [*E*], respectively. The *H* synthesis process consists of three distinct stages:

(1st) formation of a substrate-*ES* enzyme complex, by the interaction of *S* and *E*, described by the equation: $[ES] = k_1\,[E]\,[S]$;

(2nd) reverse dissociation of *ES* in *E* and *S*, in which $[ES] = k_{-1}\,[E]\,[S]$;

(3rd) dissociation of *ES* giving formation to *H*, according to $[H] = k\,[ES]$. The speed of each step depends on the constants k_1, k_{-1}, and *k*.

Usually $k > k_{-1}$ [6]. At equilibrium, the rate of hormone formation (V_H) is given by the equation $V_H = k[ES] = k/k_m[E][S]$, where the Michaellis constant is k_m, which is related to the maximum speed V_{max} of the enzymatic reaction, $k_m = 1/V_{max}$, and is given by the equation $k_m = \frac{k+k_{-1}}{k_1} \approx \frac{[E][S]}{ES}$.

Through this method, we arrive at a linearization and consequently a first-degree function of the type $y = ab + b$, where a is the angular coefficient and b is the linear coefficient. In this case, $a = -1/k_m$ and $b = 1/V_{max}$. So $y = -1/k_m\,x + 1/V_{max}$ [38].

The specificity constant limit *k* is given by the frequency at which the substrate and enzyme find each other in the solution. This limit can reach $10^{10} M^{-1}s^{-1}$ [36].

$$k \leq 10^{10} M^{-1}s^{-1} \qquad (2)$$

We call this rate limit, regardless of the substrate or the enzyme dimension [14].

The ratio between the specificity constants for two substrates is a quantitative comparison of the

enzyme's efficiency in converting the substrates.

2.2.1 Storage-Degradation Model

The storage time (t_s) is the interval in which H remains stored, Q_E is the amount of hormone in the storage, and V_S (mol/min) is the speed with which H enters into storage. The Q_E quantity depends on V_S and t_s, being limited by an internal control system. The t_s period depends on the activation of the specific mechanism. The mechanism triggers the transport of H across the cell membrane, for its release into the bloodstream.

The mechanism that controls the quantity of storage (Q_E) is the degradation. Considering the synthesis continuous, between one and other hormonal discharge into the blood, occurs degradation. The excess of H is degraded, so the released substrate becomes available for new synthesis or returns to the plasma. Thus, the control system includes variables involved in the storage and the degradation system.

We represent the activation dynamics of the storage (X) and the degradation (Y) through a system with two interrelated differential equations. The first one relates to the storage process and involves the function $f_1(x, y)$. The second one refers to the degradation using $f_2(x, y)$. According to [5, 26], we have the following equations $dx/dt = xf_1(x, y)$ e $dy/dt = yf_2(x, y)$. In these equations, the x and y variables represent, respectively, the amount of stored hormone and the amount of degradation enzyme.

In our model, the storage-degradation dynamics follow the Lotka-Volterra model [16, 20, 23]:

$$\frac{dx}{dt} = x(a - ry - px), \tag{3}$$

$$\frac{dy}{dt} = y(-b + gx + C), \tag{4}$$

where a, b, r e s are positive constants, the term ax defines the rate of the stored hormone, $-by$ refers to degradation rate, $-rxy$ and gxy relate to the interdependence between storage (X) and degradation (Y), the first favoring the storage and the second one favoring the degradation.

The term C (Eq. (4)) ensures the maintenance of optimal control, and characterizes the number of antagonistic conditions present in the cell at time t, being described by the relationship:

$$C = \xi y + U, \tag{5}$$

being ξy represents any compensatory process that at any stage of the system conducts the system to the optimal equilibrium point, and U is the stability term.

2.2.2 Lyapunov Criteria to Define the Balance

We assume that the synthesis is continuous, so the balance is dependent on the degradation process, which has the function of preventing excess storage. We consider three possible hypotheses: (1) the endocrine cell is normofunctional and the three phases (synthesis, storage, and degradation) are balanced; (2) the cell is hypofunctional, the degradation being more intense than the synthesis; and (3) the cell is hyper-functioning because the degradation process is slow comparing to synthesis and storage.

We need a U control function (Eq. (5)) that stabilizes the system and to be a Lyapunov function. This

function must be positive and guarantee asymptotic stability, in other words $dU/dt < 0$ [25, 27, 41, 43].

Boundary conditions should be considered and are the following: (1) there is a value Y_D so that $Y_{min} \leq Y_D \leq Y_{max}$, for which the gland is normofunctional; (2) for balance to exist, the term C in equations 4 and 5 must be positive, $C > 0$, and when $t \to \infty$, $U \to 0$, and $C = \xi y$; (3) U is a positive function; (4) we have $dU/dt < 0$ for points out of balance and $dU/dt = 0$.

Suppose the existence of optimal equilibrium point (x*, y*) for storage-degradation dynamics, such as $df(x^*, y^*)/dt = 0$. In other words, at this point, Eq. (3) and Eq. (4) cancel each other. Thus, from Eq. (3) we can rewrite:

$$a - ry^* - px^* = 0, \tag{6}$$

$$y^* = \frac{a - p\,x^*}{r}, \tag{7}$$

Thus, $a - px^* > 0$. Using Eq. (4) and considering boundary condition 1 we obtain that:

$$-b + gx^* + \xi y_o = 0, \tag{8}$$

$$\xi = \frac{b - gx^*}{y}, \tag{9}$$

For boundary condition (1) to be fulfilled, $\xi > 0$ and x_0 must be such that $x < b/g$, so b/g is the balance-imbalance limit. For the optimal deterministic control over a period $(0, T)$, the control function can be determined from

$$U(y(0),0) = min_V \left\{ \int_0^T C(y(t), U(t))\, dt + D(y(T)) \right\}, \tag{10}$$

where $D(y(T))$ is the function that defines the system performance. For linear stochastic dynamics and a described performance by a quadratic function, the optimal control problem can be reduced to the Hamilton-Jacobi-Bellman partial differential equation [3, 27, 43]

$$min_V \left\{ \frac{dU\,(y(t),t)}{dt} + \omega \right\} = 0, \tag{11}$$

and ω function, by definition, is:

$$\omega = m_1\,(x - x^*) + m_2\,(y - y^*) + U^2 \tag{12}$$

and U function is by definition:

$$U(y(t), t) = min_V \left\{ \int_0^T [m_1(x - x^*)^2 + m_1(y - y^*)^2 + U^2]\, dt \right\} \tag{13}$$

being m_1 and m_2 positive constants.

The solution of Eq. (11) should be investigated among the Lyapunov functions, according to the Lotka-Volterra type models. For the nonlinear stochastic dynamics, to determine the solution U (x, t) in Eq. (12), we used the Lyapunov function in the following way [25, 34, 41, 43]

$$U\,(x, y) = v_1 \left(x - x^* - x^* ln\left(\frac{x}{x^*}\right) \right) + \left(y - x^* - y^* ln\left(\frac{x}{x^*}\right) \right) \tag{14}$$

where v_1 and v_2 are positive constants to be determined, whose values can be defined by the Hamilton-Jacobi-Bellman equation [3]. The derivative of Eq. (14), considering Eq. (3) and Eq. (4), gives:

$$\frac{dU(x,y)}{dt} = v_1(x - x^*)(a - px - ry) + v_2(y - y^*)(-b + gx + \xi y + U). \quad (15)$$

Using Eqs. (12), (14), (8) and Eq. (10) in Hamilton-Jacobi-Bellman, we obtain:

$$min_V\{v_1(x - x^*)(a - px - ry) + v_2(y - y^*)(-b + gx + \xi y + U) + m_1(x - x^*)^2 + m_2(y - y^*)^2 + U^2\} = 0 \quad (16)$$

The function $U(t)$ is not limited and can be found by $\partial / \partial U$ considering Eq. (15), being $U^* = \frac{-v_2}{2}(y - y^*)$, where U^* is the optimal value for control function. The value U^*y represents the ideal enzymatic activity of the system in each instant t. Replacing $U = U^*$ in Eq. (3) and assuming that $v_1 = m_1/p$ and $v_1 = -sv_2/r$, and for $v_2 > 0$, $v_2 = 2\left(\delta + \sqrt{\delta^2 + m_2}\right)$, finally, we have that:

$$\frac{dU}{dt} = -m_1(x - x^*)^2 - \left(\sqrt{\delta^2 + m_2}\right)(y - y^*)^2 < 0 \quad (17)$$

3. Algorithm and Experimental Environment

Based on the described formulae we develop an algorithm to reproduce the functioning of an endocrine cell considering the Lyapunov function to control the storage and degradation processes. Figure 3 shows the algorithm's simple structure.

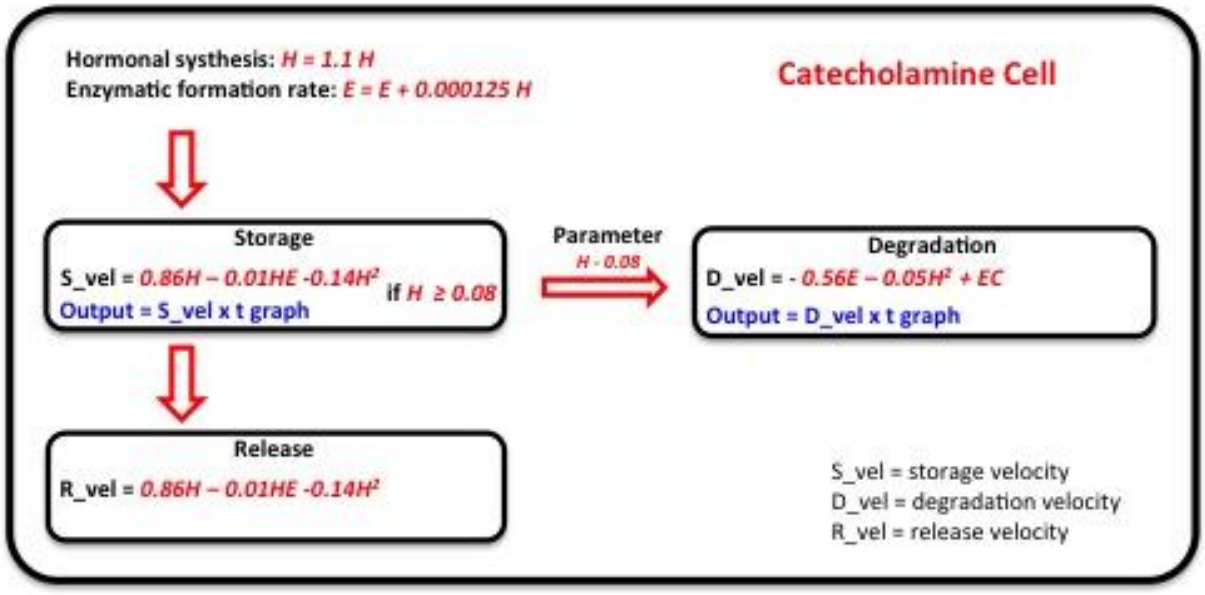

Figure 3. Algorithm's simple structure.

The algorithm simulates how the system works inside a cell using equations to represent the chemical reactions.

The algorithm has three main modules: storage, degradation, and release (Figure 4). The input parameters

are the hormone concentration (H) and enzyme concentration (E). The outputs are graphs related to the storage and degradation process speed as a function of time.

The parameters used in each formula are a the rate that enters the storage by time; r the rate that goes to degradation by time; p the rate that is secreted by time; b the rate of degradation by time, and s the rate of degradation possible by time.

Some parameters of the computational mathematical model's equations were obtained in the literature (a and p [2]). However, not all of them were found. We focused specifically on these parameters in the simulations, trying to know how they could influence the behavior of the adopted model. In this way, we test the model's ability to simulate the process control dynamics.

There are two main functions involved: storage and degradation. We analyzed the following functions used inside each one. Enzyme factor growth control E ($E = EH - H/100000$); Controlling the growth of the hormonal amount in the system H ($H = 1.1H$); Storage speed in function of time ($\frac{dx}{dt} = x(a - ry - px)$); Degradation speed as a function of time ($\frac{dy}{dt} = y(-b + gx + C)$); Balance between storage and degradation ($C = \xi y + U$) where $\xi = \frac{-bgx}{y}$.

The algorithm was executed in a computer with an Intel Core i5 of 1.70GHz with 2 cores, 6GB of RAM, and 8MB of cache memory, running the Windows 10 Pro operating system. It was implemented using Code::Blocks IDE, version 17.12, in C Language and compiled with GCC version 4.9.2.

4. Model Evaluating

We used the production of catecholamines, epinephrine (EPI) and norepinephrine (NEPI), as an example, to evaluate the proposed model. This is an endocrine gland consisting of a cortex (superficial layer) and a medulla (inner layer). In adrenal medulla, chromaffin cells store and secrete catecholamines [2]. Each cell has approximately 30,000 secretory granules [32] with about 0.3μm diameter containing about 0.5μM of catecholamines [17]. The EPI and NEPI concentrations in the normal human adrenal are 412□g to 633□g and 37μg to 123μg, respectively [17]. From all the NEPI formed, 15% remain in the granules, and 85% pass into the cytoplasm [32]. NEPI is methylated forming EPI, which is captured and stored in the granules of chromaffin cells [2, 28]. EPI is normally produced very fast so that the depletion of its EPI supply occurs only in unusual circumstances [12, 19].

The proposed model is composed of equations that have many parameters. Thus, it is necessary to know how each of them influences the model's behavior. Seven different experiments were carried out, varying the parameters, and observing the enzymatic activity in the storage and degradation processes.

Figures 4 (a) and 4 (b) show a first approximation to the storage and degradation velocities as a function of time, according to the model, for the following parametric values a = 0.86; r = 0.001; b = 0.56; s = 0.05; p = 0.14; E = 0.09; m_1 = 0.03; e H = 1.0, 2.0, 3.2, 3,9, 5.0, 5.7, 6.1 μM.

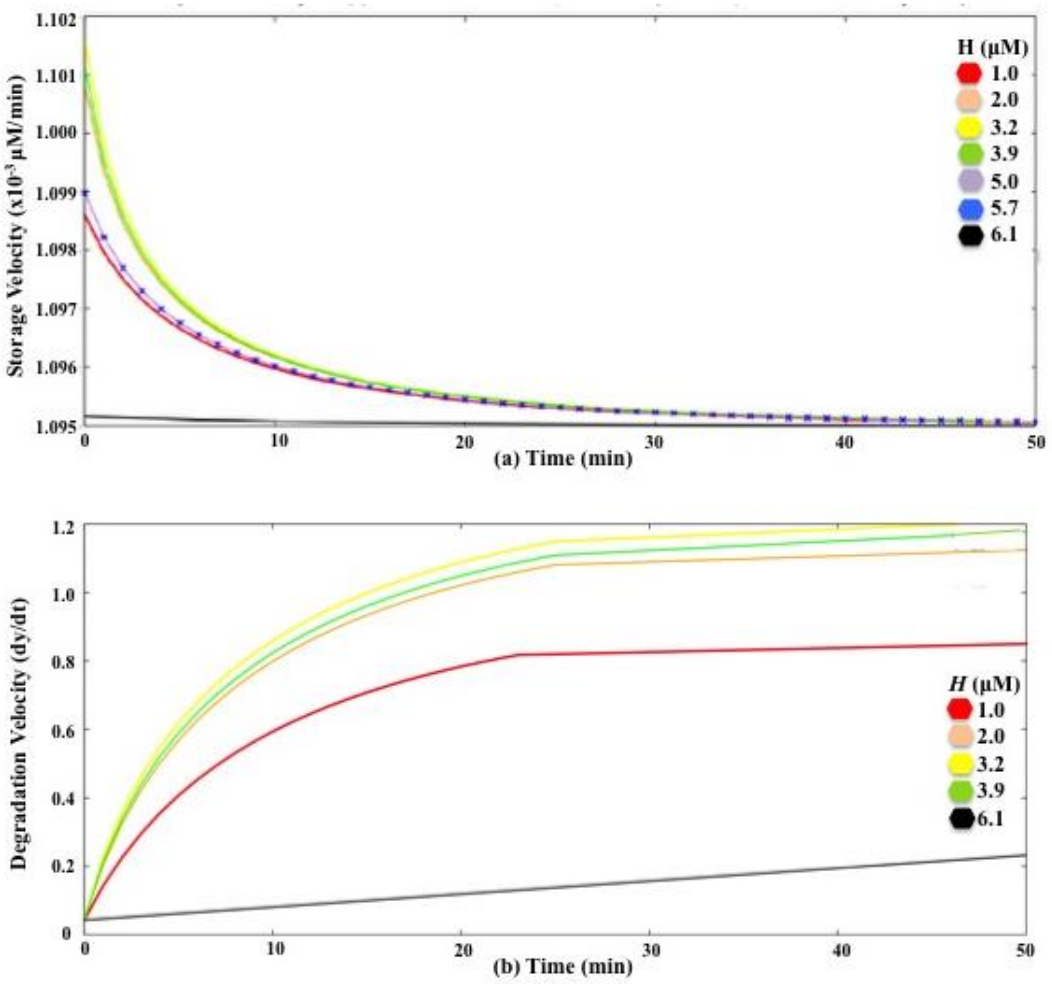

Figure 4. Storage (a) and Degradation (b) velocities as a function of time.

In Figure 4 (a), we observed that at this rate it decreases with time, for all tested hormone concentrations (from H = 1.0 to 6.1 µM), and tends to zero for t > 50 min. Figure 4 (b) shows that, unlike storage, the rate of degradation increases with time, from H = 1.0 to 3.9 µM), and reaches a plateau to t > 10 min. This plateau corresponds to the maximum degradation phase. But, while still growing, the chart for H = 6.1 µM is linear, showing that in this case the equilibrium would occur for a very long-time interval.

It is important to mention that a random variation of the input parameters (a, b, r, s, p, m_1, H, and E) did not produce valid results. It was not possible to find in the literature the variation of the enzymatic action over time. In this way, we looked for, through simulations, which function could represent the rate of growth of the enzymatic action that led us to a more realistic result. Thus, we adopted a linear function with a low angular index. In contrast, the behavior of the storage rate plot as a function of time did not increase and stabilize after a certain time. We looked for other functions that could represent enzymatic variation, such as exponential, quadratic, or logarithmic. But these were not adequate. At the end, we adopted the function

$$E = EH - 100000 \text{ or } y = xy - x/100000 \qquad (13)$$

with which we could observe the behavior of the storage speed as a function of time.

Figures 5 (a) and 5 (b) present the storage and degradation variations in time for the following parametric values a = 0.86; r = 0.001; b = 0.56; s = 0.05; p = 0.14; E = 0.09; m_1 = 0.03; e H = 1.0, 2.0, 3.2, 3,9, 5.0,

5.7, 6.1 µM, considering the equation of the variation of E (Eq.13).

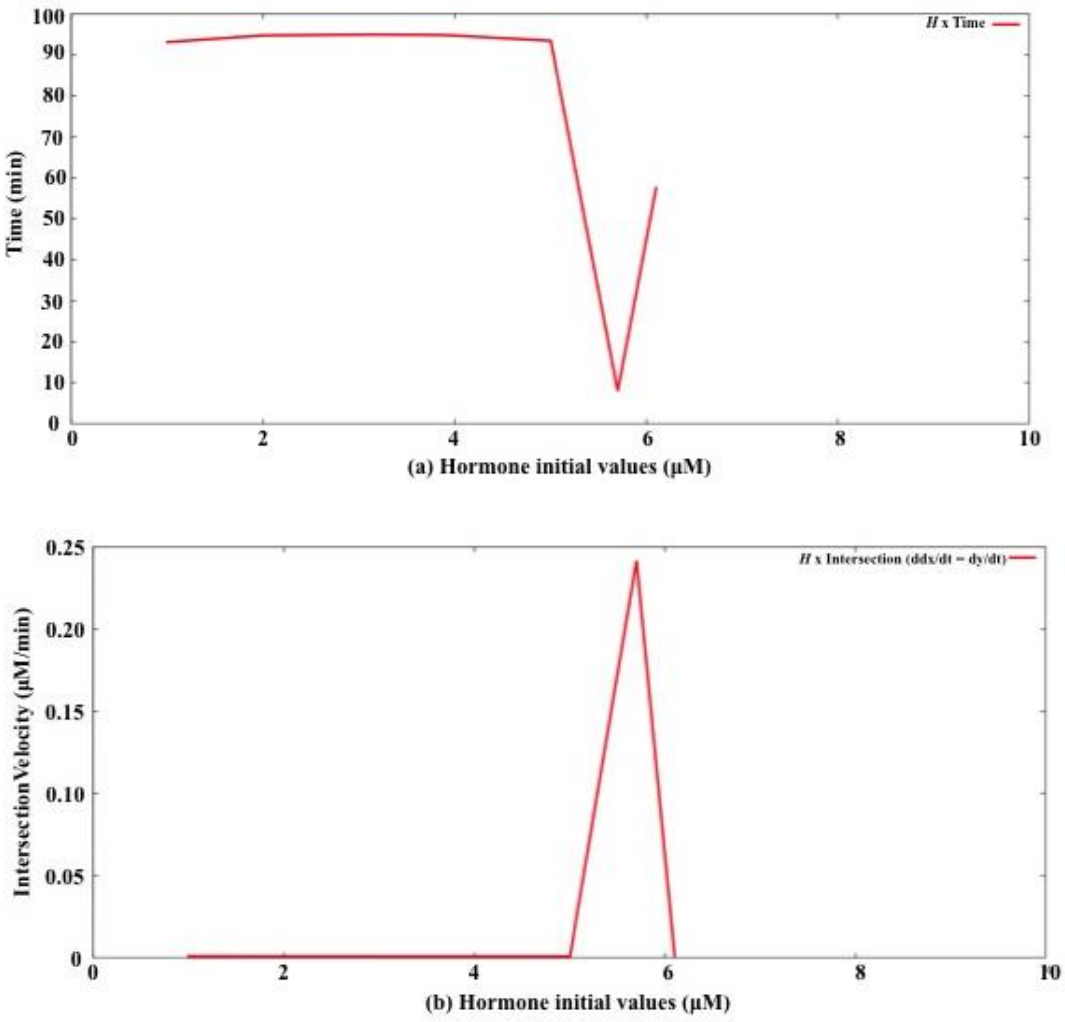

Figure 5. (a) Time versus values of the initial hormonal quantity at the intersection between storage and degradation speeds. (b) Relationship of the intersection between storage and degradation speeds with the initial hormonal amount.

In Figure 5 (a) we observe that about 9 minutes after the start of storage there is a condition of balance between this function and degradation, where H = 5,7 µM and the speed is equal to 0.24 µM/min. As one grows, the other decreases. These functions have a complementary character. They reflect each other, despite being in different sizes. These experiments were important to note that with the growth rate linear enzyme, even if the differential equations balance the system because we observed that the speed of degradation as a function of time behaves as expected, in the storage speed as a function of time there is no growth. That means that enzymatic growth using this type of function was not enough for the system to reach equilibrium within the time interval that was simulated. Following the validation of the model, we investigate the possible factors that would influence the model behavior.

Looking for more accurate results we vary the r parameter. Figures 6 (a) and 6(b) show the results for the variation of storage and time degradation for the following parametric values a = 0.86, r = 1.1, b = 4.56, s = 0.05, p = 0.14, E = 0.03, m_1 = 0.09 and H = 0.4, 0.5, 0.6, 1.5 µM. Both considering equation (13) of

the variation of E.

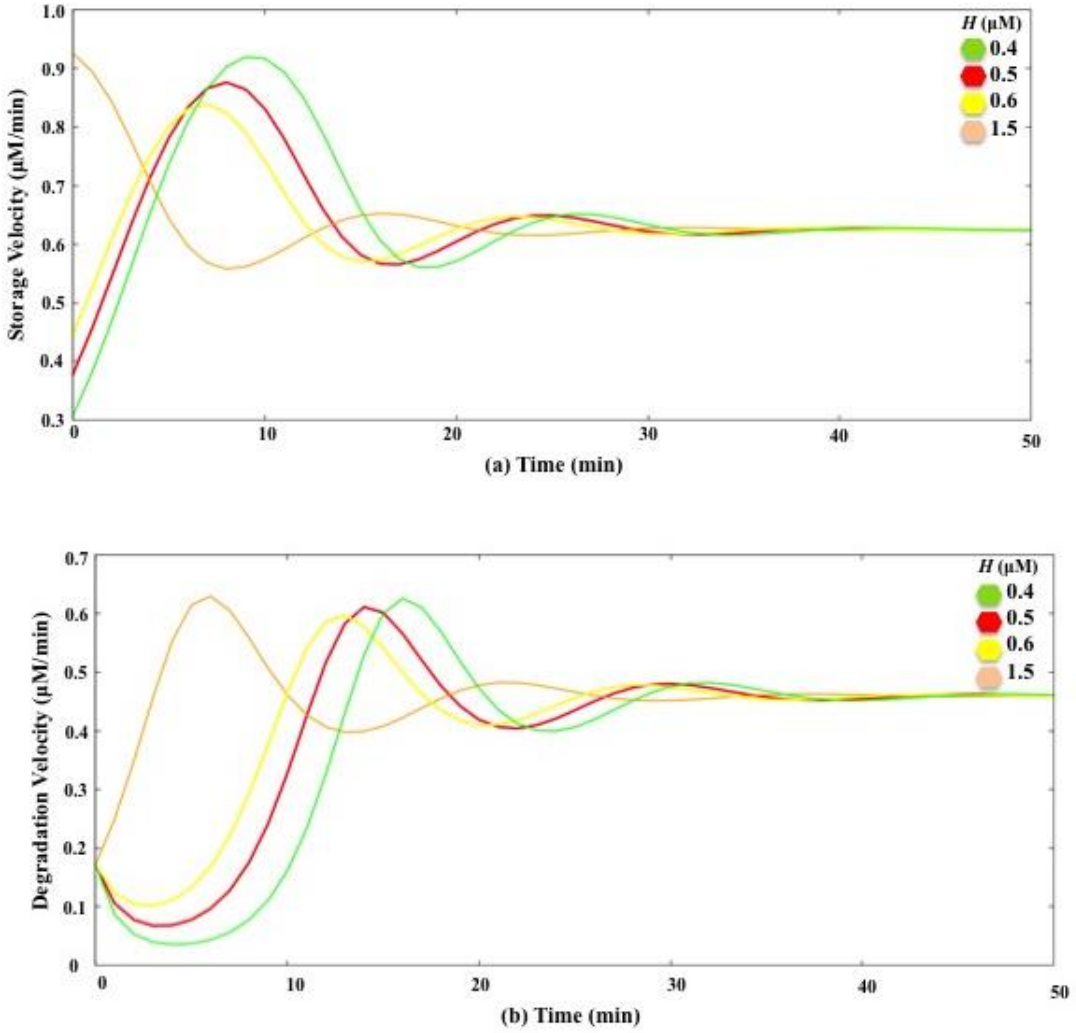

Figure 6. Storage (a) and Degradation (b) variations in time.

Cortez et al. [13] observed, using a simple mathematical model based on the classical Lotka-Volterra equations, the degradation process starting about 20 minutes after storage reaches its maximal capacity, and the degradation activity increased until $y = 0.103$ mg at $t = 35$ min, and then stabilized at $y = 0.0873$ mg. The storage and degradation velocities came into equilibrium for $V_S = V_D \approx 1.53$ µg/min (about 0.008 µmoles/min). This value is in the same magnitude order of that found in experimental studies [12].

Subsequently, we consider the intersection points between the storage and degradation speeds and the time when these intersections occur. We related these values to the initial hormonal amount. Figure 7 (a) shows the relationship between the initial hormonal amount and time. Figure 7 (b) presents the initial hormonal amount and the intersection points between the storage and degradation speeds.

Figure 7 shows more than peaks and valleys comparing to the first simulation, where we use the growth of a linear function for the enzyme rate in the system. Note that one is complement of the other, while one grows the other decreases and vice versa. We can consider that one is the reflection of the other, despite being in different scales. In Figure 7 (a) has a global maximum occurring at 18 minutes for an initial concentration of $H = 0.4$ µM. This time is spent to complete the capacity of storage. For the highest possible concentration ($H = 1.5$ µM) it is necessary a shorter time of about 8 minutes to reach this

capacity. These results have a biological sense, since the concentration is greater than the capacity, consequently this difference goes to the degradation faster. Considering that the values found in the storage speed are the same as the degradation, we noticed, in Figure 7 (b), that the highest speed occurs at highest concentration possible (H = 1.5 µM and 0.62 µM/min). The lowest speed occurs at the lowest initial hormone concentration (H = 0.4 µM and 0.56 µM/min). Therefore, the initial hormone concentration is directly proportional to the encounter speed of storage and degradation processes in the system.

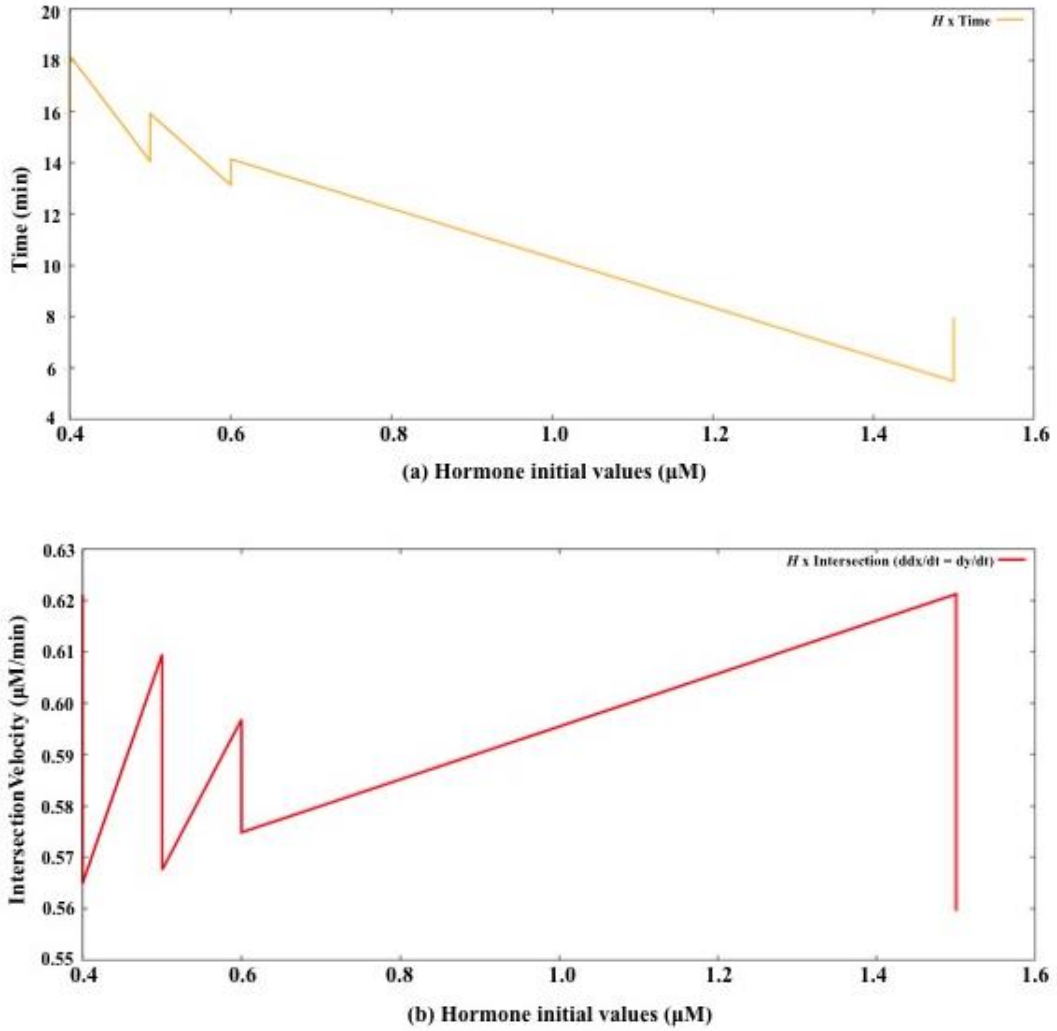

Figure 7. (a) Time versus values of the initial hormonal quantity at the intersection between storage and degradation speeds. (b) Relationship of the intersection between storage and degradation speeds at the initial hormonal amount.

In the subsequent experiments, we analyzed the variation of parameters m_1, r, s and b keeping the other parameters fixed. For all experiments we assume a = 0.86, p = 0.14, E = 0.03, H = 0.5µM.

With the parameters r = 1.1, b = 4.56, s = 0.05 fixed, we observed that the variation of m_1 (m_1 = 0.09, 0.5, 0.6, 0.7, 0.8, 0.9) does not influence the hormonal storage speed as a function of time. However, r greatly influences the rate of degradation as a function of time.

The variation of r (r = 0.95, 1.5, 2.1, 2.2) influences both the storage and degradation speeds, considering

b = 4.56, s = 0.05, m_1 = 0.09 fixed.

The variation of the parameter s behaved similarly to the variation m_1 within the tested values range (s = 0.05, 0.051, 0.052, 0.053). It does not influence the rate of hormonal storage as a function of time, but it does influence the rate of degradation. The other parameters were b = 4.56, r = 2.1, m_1 = 0.09.

Parameter b does not influence the behavior of the studied dynamics, within the range in which it was tested (b = 0.0001, 0.009, 0.9, 9.0, 99.0, 9999.0). The storage and degradation speed remained the same considering as fixed input parameters r = 2.1, s = 0.05, m_1 = 0.09.

Table 1 summarizes the intervals of the results obtained, allowing us to get a better sense of them. In this table we can observe that the intervals do not vary much. The range with the biggest difference is the one where the model was still being adjusted, using a linear function to represent growth in the enzymatic activity. The storage speed as a function of time varies in range from 0.35 μM/min to 0.85 μM/min ($0.35\ \mu M/min \leq dx/dt \leq 0.85\ \mu M/min$). For the speed of degradation as a function of time we notice a variation from 0.1 μM/min to 0.7 μM/min ($0.1\,\mu M/min \leq dy/dt \leq 0.7\,\mu M/min$). The time to reach equilibrium in the system is in the range between 30 minutes and 35 minutes ($30\,min \leq t \leq 35\,min$). The intersection speeds between storage and degradation vary between 0.57 μM/min and 0.61 μM/min ($0.57\,\mu M/min \leq dx/dt = dy/dt \leq 0.61\,\mu M/min$). The time it takes for the storage and degradation speeds are the same occurs between 13 and 16 minutes.

Table 1. Obtained results.

Test	**1°**	**2°**	**3°**	**4°**	**5°**	**6°**	**7°**
Constant	***H***	***H***	***E***	m_1	***r***	***s***	***b***
Interval (μM)	**[1, 6.1]**	**[0.5, 1.5]**	**[0.0009, 0.1]**	**[0.09, 0.9]**	**[0.95, 2.2]**	**[0.05, 0.053]**	**[0.0001, 9999]**
$\frac{dx}{dt}$ **(μM/min)**	**[1, 1.4]**	**[0.3, 1]**	**[0.3, 1.1]**	**[0.35, 0.9]**	**[0.3, 0.9]**	**[0.35, 0.85]**	**[0.35, 0.85]**
$\frac{dy}{dt}$ **(μM/min)**	**[0.00109,0.0110]**	**[0, 0.7]**	**[0, 0.7]**	**[0, 7]**	**[0, 0.7]**	**[0, 0.7]**	**[0.1, 0.7]**
***t* (min)** $\frac{dx}{dt}$ $\frac{dy}{dt}$	**[0, 50]**	**[0, 50]**	**[0, 50]**	**[0, 50]**	**[0, 50]**	**[0, 50]**	**[0, 50]**
$\frac{dx}{dt} = \frac{dy}{dt}$ **(μM/min)**	**[0, 0.25]**	**[0.55, 0.63]**	**[0.35, 0.61]**	**[0.5, 0.9]**	**[0.56, 0.64]**	**[0.57, 0.63]**	**[0.57, 0.64]**
***t* (min)** $\frac{dx}{dt} = \frac{dy}{dt}$	**[10, 90]**	**[4, 20]**	**[0, 25]**	**[0, 8]**	**[13, 16.5]**	**[13, 16.5]**	**[13, 16.5]**

5. Conclusion

In this work, we propose a computational mathematical model for the synthesis-storage-degradation control in an endocrine gland. We used catecholamine synthesis in the adrenal medulla to validate and

evaluate the model.

Several simulations were carried out to study the model's behavior, verify the parameter influence involved in the equations, and adapt the construction of the algorithm.

The study of the input parameter variations allowed us to realize the importance of the enzymatic activity variation in the behavior of the storage and degradation processes. Initially, when we used a very high input value for the hormone concentration, the storage speed as a function of time assumed a behavior consistent with the expected, but no hormone was degraded. Then, we performed experiments varying the hormone concentration, the enzyme concentration, and the degradation rates.

The results obtained are favorable to the proposal that the model associating the Lyapunov equations to those of Lokta-Volterra can be used to represent the control dynamics of the synthesis-storage and degradation of the catecholamines in the medulla of the adrenal gland. The parametric values pointed to the equilibrium condition of the equation system of the computational mathematical model are in the magnitude order of values found in the literature, and the simulations used realistic values [2] for (a = 0.86) and p (p = 0.14), which were obtained in the literature, resulting from experimental measurements. For future works, we intend to refine the model by implementing the enzyme synthesis procedure that directly influences the storage-degradation-synthesis processes of the endocrine gland, and to focus on the release function to make the model more accurate.

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