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Global Bifurcations of Limit Cycles in an Endocrine System Model

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Abstract

In this paper, we consider an endocrine system model carrying out a global qualitative analysis of a reduced planar quartic Topp system which models the dynamics of diabetes. In particular, studying global bifurcations and applying the Wintner–Perko termination principle, we prove that such a system can have at most two limit cycles.

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1 Introduction

In this paper, we consider an endocrine system model carrying carry out a global qualitative analysis of a reduced planar quartic Topp system which models the dynamics of diabetes [12, 17].

Diabetes mellitus is a disease of the glucose regulatory system characterized by fasting or postprandial hyperglycemia. There are two major classifications of diabetes based on the etiology of the hyperglycemia. Type 1 diabetes (also referred to as juvenile onset or insulin-dependent diabetes) is due to an autoimmune attack on the insulin secreting β cells. Type 2 diabetes (also referred to as adult onset or non-insulin-dependent diabetes) is associated with a deficit in the mass of β cells, reduced insulin secretion, and resistance to the action of insulin; see [17] and the references therein.

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Blood glucose levels are regulated by two negative feedback loops. In the short term, hyperglycemia stimulates a rapid increase in insulin release from the pancreatic β cells. The associated increase in blood insulin levels causes increased glucose uptake and decreased glucose production leading to a reduction in blood glucose. On the long term, high glucose levels lead to increase in the number of β-cells. An increased β-cell mass represents an increased capacity for insulin secretion which, in turn, leads to a decrease in blood glucose. Type 2 diabetes has been associated with defects in components of both the short-term and long-term negative feedback loops [17].

Mathematical modeling in diabetes research has focused predominately on the dynamics of a single variable, usually blood glucose or insulin level, on a time-scale measured in minutes [17]. Generally, these models are used as tools for measuring either rates (such as glucose production and uptake rates or insulin secretion and clearance rates) or sensitivities (such as insulin sensitivity, glucose effectiveness, or the sensitivity of insulin secretion rates to glucose). Two model-based studies have examined coupled glucose and insulin dynamics [17]. In each of these studies, multiple parameter changes, representing multiple physiological defects, were required to simulate glucose and insulin dynamics observed in humans with diabetes. In doing so, three distinct pathways were found to the diabetic state: regulated hyperglycemia, bifurcation and dynamical hyperglycemia [17].

In our study, we reduce the $3D$ Topp diabetes dynamics model [12, 17], to a planar quartic dynamical system and study global bifurcations of limit cycles that could occur in this system, applying the new bifurcation methods and geometric approaches developed in [3–11]. In Section 2, we consider the Topp model of diabetes dynamics. In Section 3, we give some basic facts on singular points and limit cycles of planar dynamical systems. In Section 4, we carry out the global qualitative analysis of the reduced Topp system.

2 The Topp Model of Diabetes Dynamics

In [17], a novel model of coupled β-cell mass, insulin, and glucose dynamics was presented, which is used to investigate the normal behavior of the glucose regulatory system and pathways into diabetes. The behavior of the model is consistent with the observed behavior of the glucose regulatory system in response to changes in blood glucose levels, insulin sensitivity, and β-cell insulin secretion rates.

In the post-absorptive state, glucose is released into the blood by the liver and kidneys, removed from the interstitial fluid by all the cells of the body, and distributed into many physiological compartments, e. g., arterial blood, venous blood, cerebral spinal fluid, interstitial fluid [17].

Since we are primarily concerned with the evolution of fasting blood glucose levels over a time-scale of days to years, glucose dynamics are modeled with a single-compartment mass balance equation

$$\dot{G} = a - (b + cI)G. \tag{2.1}$$

Insulin is secreted by pancreatic β-cells, cleared by the liver, kidneys, and insulin receptors, and distributed into several compartments, e. g., portal vein, peripheral blood, and interstitial fluid. The main concern is the long-time evolution of fasting insulin levels in peripheral blood. Since the dynamics of fasting insulin levels on this time-scale are slow, we use a single-compartment equation given by

$$\dot{I} = \frac{\beta G^2}{1 + G^2} - \alpha I. \tag{2.2}$$

Despite a complex distribution of pancreatic β cells throughout the pancreas, β-cell mass dynamics have been successfully quantified with a single-compartment model

$$\dot{\beta} = (-l + mG - nG^2)\beta. \tag{2.3}$$

Finally, the Topp model is

$$\begin{aligned} \dot{G} &= a - (b + cI)G, \\ \dot{I} &= \frac{\beta G^2}{1 + G^2} - \alpha I, \\ \dot{\beta} &= (-l + mG - nG^2)\beta \end{aligned} \tag{2.4}$$

with parameters as in [17].

On the short timescale, β is approximately constant and, relabelling the variables, the fast dynamics is a planar system

$$\begin{aligned} \dot{x} &= a - (b + c\,y)x, \\ \dot{y} &= \frac{\beta x^2}{1 + x^2} - \alpha\, y \end{aligned} \tag{2.5}$$

By rescaling time, this can be written in the form of a quartic dynamical system:

$$\begin{aligned} \dot{x} &= (1 + x^2)(a - (b + c\,y)x) \equiv P, \\ \dot{y} &= \beta x^2 - \alpha\, y(1 + x^2) \equiv Q. \end{aligned} \tag{2.6}$$

Together with (2.6), we will also consider an auxiliary system (see [1, 4, 16])

$$\dot{x} = P - \gamma Q, \qquad \dot{y} = Q + \gamma P, \tag{2.7}$$

applying to these systems new bifurcation methods and geometric approaches developed in [3–11] and carrying out the qualitative analysis of (2.6).

3 Singular Points and Limit Cycles

The study of singular points of system (2.6) will use two index theorems by H. Poincaré; see [1]. Let us define a singular point and its Poincaré index [1].

Definition 3.1. A singular point of the dynamical system

$$\dot{x} = P(x, y), \quad \dot{y} = Q(x, y), \tag{3.1}$$

where $P(x, y)$ and $Q(x, y)$ are continuous functions (for example, polynomials), is a point at which the right-hand sides of (3.1) simultaneously vanish.

Definition 3.2. Let S be a simple closed curve in the phase plane not passing through a singular point of system (3.1) and M be some point on S. If the point M goes around the curve S once in the positive direction (counterclockwise) then the vector coinciding with the direction of a tangent to the trajectory passing through the point M is rotated through an angle $2\pi j$ $(j = 0, \pm 1, \pm 2, \ldots)$. The integer j is called the *Poincaré index* of the closed curve S relative to the vector field of system (3.1) and has the expression

$$j = \frac{1}{2\pi} \oint_S \frac{P\,dQ - Q\,dP}{P^2 + Q^2}.$$

A singular point is *simple* if the derivative of the vector field is invertible there. Simple singular points can be classified into nodes, foci, centers and saddles. According to this definition, the index of a node, focus or center is equal to $+1$, and the index of a saddle is -1.

A polynomial vector field on the plane can be compactified to an associated vector field on the projective plane, with a circle representing the slopes of directions to infinity (Poincaré compactification). Thus we can also talk about singular points at infinity, and their indices using a local chart.

Theorem 3.3. *The indices of singular points in the plane and at infinity sum to* $+1$.

Theorem 3.4. *If all singular points are simple, then along an isocline without multiple points lying in a Poincaré hemisphere which is obtained by a stereographic projection of the phase plane (or double cover of the projective plane), the singular points are distributed so that a saddle is followed by a node or a focus, or a center and vice versa. If two points are separated by the equator of the Poincaré sphere, then a saddle will be followed by a saddle again and a node or a focus, or a center will be followed by a node or a focus, or a center.*

Consider polynomial system (3.1) in the vector form

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}, \boldsymbol{\mu}), \tag{3.2}$$

where $\boldsymbol{x} \in \mathbf{R}^2$; $\boldsymbol{\mu} \in \mathbf{R}^n$; $\boldsymbol{f} \in \mathbf{R}^2$ ($\boldsymbol{f}$ is a polynomial vector function).

Let us state two fundamental theorems from the theory of analytic functions [4].

Theorem 3.5. *Let $F(w,z)$ be an analytic function in the neighborhood of the point $(0,0)$ satisfying the following conditions*

$$F(0,0)=\frac{\partial F(0,0)}{\partial w}=\ldots=\frac{\partial^{k-1}F(0,0)}{\partial^{k-1}w}=0; \quad \frac{\partial^{k}F(0,0)}{\partial^{k}w}\neq 0.$$

Then in some neighborhood $|w|<\varepsilon$, $|z|<\delta$ of the point $(0,0)$, the function $F(w,z)$ can be represented as

$$F(w,z)=(w^k+A_1(z)w^{k-1}+\ldots+A_{k-1}(z)w+A_k(z))\Phi(w,z),$$

where $\Phi(w,z)$ is an analytic function not equal to zero in the chosen neighborhood and $A_1(z),\ldots,A_k(z)$ are analytic functions for $|z|<\delta$.

From this theorem it follows that the equation $F(w,z)=0$ in a sufficiently small neighborhood of the point $(0,0)$ is equivalent to the equation

$$w^k+A_1(z)w^{k-1}+\ldots+A_{k-1}(z)w+A_k(z)=0,$$

whose left-hand side is a polynomial with respect to w. Thus, the Weierstrass preparation theorem reduces the local study of the general case of an implicit function $w(z)$, defined by the equation $F(w,z)=0$, to the case of implicit function defined by an algebraic equation with respect to w.

Theorem 3.6. *Let $F(w,z)$ be an analytic function in the neighborhood of the point $(0,0)$ and $F(0,0)=0$, $F'_w(0,0)\neq 0$.*

Then there exist $\delta>0$ and $\varepsilon>0$ such that for any z satisfying the condition $|z|<\delta$ the equation $F(w,z)=0$ has the only solution $w=f(z)$ satisfying the condition $|f(z)|<\varepsilon$. The function $f(z)$ is expanded into the series on positive integer powers of z which converges for $|z|<\delta$, i. e., it is a single-valued analytic function of z which vanishes at $z=0$.

Let us recall some basic facts concerning limit cycles of (3.2). Assume that system (3.2) has a limit cycle

$$L_0 : \boldsymbol{x}=\boldsymbol{\varphi}_0(t)$$

of minimal period T_0 at some parameter value $\boldsymbol{\mu}=\boldsymbol{\mu}_0\in\mathbf{R}^n$.

Let l be the straight line normal to L_0 at the point $\boldsymbol{p}_0=\boldsymbol{\varphi}_0(0)$ and s be the coordinate along l with s positive exterior to L_0. It then follows from the implicit function theorem that there is a $\delta>0$ such that the Poincaré map $h(s,\boldsymbol{\mu})$ is defined and analytic for $|s|<\delta$ and $\|\boldsymbol{\mu}-\boldsymbol{\mu}_0\|<\delta$. The displacement function for system (3.2) along the normal line l to L_0 is defined as the function

$$d(s,\boldsymbol{\mu})=h(s,\boldsymbol{\mu})-s.$$

We denote derivatives of d with respect to s or components of μ by subscripts, and the m-th derivative of d with respect to s by $d_s^{(m)}$. In terms of the displacement function, a multiple limit cycle can be defined as follows [4].

Definition 3.7. A limit cycle L_0 of (3.2) is a *multiple limit cycle* iff

$$d(0, \boldsymbol{\mu}_0) = d_s(0, \boldsymbol{\mu}_0) = 0.$$

It is a *simple limit cycle* (or hyperbolic limit cycle) if it is not a multiple limit cycle; furthermore, L_0 is a limit cycle of multiplicity m iff

$$d(0, \boldsymbol{\mu}_0) = d_s(0, \boldsymbol{\mu}_0) = \ldots = d_s^{(m-1)}(0, \boldsymbol{\mu}_0) = 0,$$

$$d_s^{(m)}(0, \boldsymbol{\mu}_0) \neq 0.$$

Note that the multiplicity of L_0 is independent of the point $\boldsymbol{p}_0 \in L_0$ through which we take the normal line l.

Let us write down also the following formulae which have already become classical ones and determine the derivatives of the displacement function in terms of integrals of the vector field $\boldsymbol{f}$ along the periodic orbit $\boldsymbol{\varphi}_0(t)$ [4]:

$$d_s(0, \boldsymbol{\mu}_0) \;=\; \exp \int_0^{T_0} \boldsymbol{\nabla} \cdot \boldsymbol{f}(\boldsymbol{\varphi}_0(t), \boldsymbol{\mu}_0)\, \mathrm{d}t - 1$$

and

$$d_{\mu_j}(0, \boldsymbol{\mu}_0) = \frac{-\omega_0}{\|\boldsymbol{f}(\boldsymbol{\varphi}_0(0), \boldsymbol{\mu}_0)\|} \times$$

$$\int_0^{T_0} \exp\left(-\int_0^t \boldsymbol{\nabla} \cdot \boldsymbol{f}(\boldsymbol{\varphi}_0(\tau), \boldsymbol{\mu}_0)\, \mathrm{d}\tau\right) \times \boldsymbol{f} \wedge \boldsymbol{f}_{\mu_j}(\boldsymbol{\varphi}_0(t), \boldsymbol{\mu}_0)\, \mathrm{d}t$$

for $j = 1, \ldots, n$, where $\omega_0 = \pm 1$ according to whether L_0 is positively or negatively oriented, respectively, and where the wedge product of two vectors $\boldsymbol{x} = (x_1, x_2)$ and $\boldsymbol{y} = (y_1, y_2)$ in $\mathbf{R}^2$ is defined as

$$\boldsymbol{x} \wedge \boldsymbol{y} = x_1\, y_2 - x_2\, y_1.$$

Similar formulae for $d_{ss}(0, \boldsymbol{\mu}_0)$ and $d_{s\mu_j}(0, \boldsymbol{\mu}_0)$ can be derived in terms of integrals of the vector field $\boldsymbol{f}$ and its first and second partial derivatives along $\boldsymbol{\varphi}_0(t)$.

Now we can formulate the Wintner–Perko termination principle [16] for polynomial system (3.2).

Theorem 3.8. *Any one-parameter family of multiplicity-m limit cycles of relatively prime polynomial system* (3.2) *can be extended in a unique way to a maximal one-parameter family of multiplicity-m limit cycles of* (3.2) *which is either open or cyclic.*

If it is open, then it terminates either as the parameter or the limit cycles become unbounded; or, the family terminates either at a singular point of (3.2), *which is typically a fine focus of multiplicity* m, *or on a (compound) separatrix cycle of* (3.2) *which is also typically of multiplicity* m.

The proof of this principle for general polynomial system (3.2) with a vector parameter $\boldsymbol{\mu} \in \mathbf{R}^n$ parallels the proof of the planar termination principle for the system

$$\dot{x} = P(x, y, \lambda), \quad \dot{y} = Q(x, y, \lambda) \tag{3.3}$$

with a single parameter $\lambda \in \mathbf{R}$ (see [4], [16]), since there is no loss of generality in assuming that system (3.2) is parameterized by a single parameter λ; i. e., we can assume that there exists an analytic mapping $\boldsymbol{\mu}(\lambda)$ of $\mathbf{R}$ into $\mathbf{R}^n$ such that (3.2) can be written as (3.3) and then we can repeat everything that had been done for system (3.3) in [16]. In particular, λ is said to be a *field-rotation parameter* if it rotates the vectors of the field in one direction [1, 4, 16], e. g., γ in (2.7). If λ is a field rotation parameter of (3.3), the following theorem of Perko on monotonic families of limit cycles is valid; see [16].

Theorem 3.9. *If L_0 is a nonsingular multiple limit cycle of* (3.3) *for $\lambda = \lambda_0$, then L_0 belongs to a one-parameter family of limit cycles of* (3.3); *furthermore*:

1) if the multiplicity of L_0 is odd, then the family either expands or contracts monotonically as λ increases through λ_0;

2) if the multiplicity of L_0 is even, then L_0 bifurcates into a stable and an unstable limit cycle as λ varies from λ_0 in one sense and L_0 disappears as λ varies from λ_0 in the opposite sense; i. e., there is a fold bifurcation at λ_0.

4 Global Bifurcation Analysis

Consider system (2.6). Its finite singularities are determined by the algebraic system

$$\begin{aligned} &(1 + x^2)(a - (b + c\,y)x) = 0, \\ &\beta x^2 - \alpha\, y(1 + x^2) = 0 \end{aligned} \tag{4.1}$$

which can give us at most three singular points in the first quadrant: a saddle S and two antisaddles (non-saddles), A_1 and A_2, according to the second Poincaré index theorem (Theorem 3.4). Suppose that with respect to the x-axis they have the following sequence: A_1, S, A_2. System (2.6) can also have one singular point (an antisaddle) or two singular points (an antisaddle and a saddle-node) in the first quadrant.

To study singular points of (2.6) at infinity, consider the corresponding differential equation

$$\frac{dy}{dx} = \frac{\beta x^2 - \alpha\, y(1 + x^2)}{(1 + x^2)(a - (b + c\,y)x)}. \tag{4.2}$$

Dividing the numerator and denominator of the right-hand side of (4.2) by $x^4 (x \neq 0)$ and denoting y/x by u (as well as dy/dx), we will get the equation

$$u^2 = 0, \quad \text{where} \quad u = y/x, \tag{4.3}$$

for all infinite singularities of (4.2) except when $x = 0$ (the "ends" of the y-axis); see [1, 4]. For this special case we can divide the numerator and denominator of the right-hand side of (4.2) by y^4 $(y \neq 0)$ denoting x/y by v (as well as dx/dy) and consider the equation

$$v^2 = 0, \quad \text{where} \quad v = x/y. \tag{4.4}$$

According to the Poincaré index theorems (Theorem 3.3 and Theorem 3.4), the equations (4.3) and (4.4) give us two double singular points (saddle-nodes) at infinity for (4.2): on the "ends" of the x and y axes.

Using the obtained information on singular points and applying geometric methods developed in [3–11], we can study now the limit cycle bifurcations of system (2.6).

Applying the definition of a field rotation parameter [1, 4, 16], to system (2.6), let us calculate the corresponding determinants for the parameters a, b, c, α, and β, respectively:

$$\Delta_a = PQ'_a - QP'_a = -(1+x^2)(\beta x^2 - \alpha\, y(1+x^2)), \tag{4.5}$$

$$\Delta_b = PQ'_b - QP'_b = x(1+x^2)(\beta x^2 - \alpha\, y(1+x^2)), \tag{4.6}$$

$$\Delta_c = PQ'_c - QP'_c = xy(1+x^2)(\beta x^2 - \alpha\, y(1+x^2)), \tag{4.7}$$

$$\Delta_\alpha = PQ'_\alpha - QP'_\alpha = -y(1+x^2)^2(a - (b + c\, y)x), \tag{4.8}$$

$$\Delta_\beta = PQ'_\beta - QP'_\beta = x^2(1+x^2)(a - (b + c\, y)x). \tag{4.9}$$

It follows from (4.5)–(4.7) that in the first quadrant the signs of Δ_a, Δ_b, Δ_c depend on the sign of $\beta x^2 - \alpha\, y(1+x^2)$ and from (4.8) and (4.9) that the signs of Δ_α and Δ_β depend on the sign of $a - (b + c\, y)x$ on increasing (or decreasing) the parameters a, b, c, α, and β, respectively.

Therefore, to study limit cycle bifurcations of system (2.6), it makes sense together with (2.6) to consider also the auxiliary system (2.7) with field-rotation parameter γ:

$$\Delta_\gamma = P^2 + Q^2 \geq 0. \tag{4.10}$$

Using system (2.7) and applying Perko's results, we prove the following theorem.

Theorem 4.1. *The reduced Topp system* (2.6) *can have at most two limit cycles.*

Proof. In [2, 3, 15, 18], where a similar quartic system was studied, it was proved that the cyclicity of singular points in such a system is equal to two and that the system can have at least two limit cycles; see also [9, 11, 13, 14] with similar results.

Consider systems (2.6)–(2.7) supposing that the cyclicity of singular points in these systems is equal to two and that the systems can have at least two limit cycles. Let us prove now that these systems have at most two limit cycles. The proof is carried out by contradiction applying Catastrophe Theory; see [4, 16].

We will study more general system (2.7) with three parameters: α, β, and γ (the parameters a, b, and c can be fixed, since they do not generate limit cycles). Suppose that (2.7) has three limit cycles surrounding the singular point A_1, in the first quadrant. Then we get into some domain of the parameters α, β, and γ being restricted by definite conditions on three other parameters, a, b, and c. This domain is bounded by two fold bifurcation surfaces forming a cusp bifurcation surface of multiplicity-three limit cycles in the space of the parameters α, β, and γ.

The corresponding maximal one-parameter family of multiplicity-three limit cycles cannot be cyclic, otherwise there will be at least one point corresponding to the limit cycle of multiplicity four (or even higher) in the parameter space.

Extending the bifurcation curve of multiplicity-four limit cycles through this point and parameterizing the corresponding maximal one-parameter family of multiplicity-four limit cycles by the field rotation parameter, γ, according to Theorem 3.9, we will obtain two monotonic curves of multiplicity-three and one, respectively, which, by the Wintner–Perko termination principle (Theorem 3.8), terminate either at the point A_1 or on a separatrix cycle surrounding this point. Since on our assumption the cyclicity of the singular point is equal to two, we have obtained a contradiction with the termination principle stating that the multiplicity of limit cycles cannot be higher than the multiplicity (cyclicity) of the singular point in which they terminate.

If the maximal one-parameter family of multiplicity-three limit cycles is not cyclic, using the same principle (Theorem 3.8), this again contradicts the cyclicity of A_1 not admitting the multiplicity of limit cycles to be higher than two. This contradiction completes the proof in the case of one singular point in the first quadrant.

Suppose that system (2.7) with three finite singularities, A_1, S, and A_2, has two small limit cycles around, for example, the point A_1 (the case when limit cycles surround the point A_2 is considered in a similar way). Then we get into some domain in the space of the parameters α, β, and γ which is bounded by a fold bifurcation surface of multiplicity-two limit cycles.

The corresponding maximal one-parameter family of multiplicity-two limit cycles cannot be cyclic, otherwise there will be at least one point corresponding to the limit cycle of multiplicity three (or even higher) in the parameter space. Extending the bifurcation curve of multiplicity-three limit cycles through this point and parameterizing the corresponding maximal one-parameter family of multiplicity-three limit cycles by the field rotation parameter, γ, according to Theorem 3.9, we will obtain a monotonic curve which, by the Wintner–Perko termination principle (Theorem 3.8), terminates either at the point A_1 or on some separatrix cycle surrounding this point. Since we know at least the cyclicity of the singular point which on our assumption is equal to one in this case, we have obtained a contradiction with the termination principle.

If the maximal one-parameter family of multiplicity-two limit cycles is not cyclic, using the same principle (Theorem 3.5), this again contradicts the cyclicity of A_1 not admitting the multiplicity of limit cycles higher than one. Moreover, it also follows from the termination principle that either an ordinary (small) separatrix loop or a big loop, or an eight-loop cannot have the multiplicity (cyclicity) higher than one in this case. Therefore, according to the same principle, there are no more than one limit cycle in the exterior domain surrounding all three finite singularities, A_1, S, and A_2.

Thus, taking into account all other possibilities for limit cycle bifurcations (see [2, 3, 15, 18]), we conclude that system (2.7) (and (2.6) as well) cannot have either a multiplicity-three limit cycle or more than two limit cycles in any configuration. The theorem is proved. $\square$

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