MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **90** (2023) 563–580
ISSN: 0340–6253
doi: 10.46793/match.90-3.563F

Qualitative Analysis of the Minimal Higgins Model of Glycolysis

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(Received April 6, 2023)

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Abstract

Glycolysis, one of the leading metabolic pathways, involves many different periodic oscillations emerging at positive steady states of the biochemical models describing this essential process. One of the models employing the molecular diffusion of intermediates is the Higgins biochemical model to explain sustained oscillations. In this paper, we investigate the center-focus problem for the minimal Higgins model for general values of the model parameters with the help of computational algebra. We demonstrate that the model always has a stable focus point by finding a general form of the first Lyapunov number. Then, varying two of the model parameters, we obtain the first three coefficients of the period function for the stable focus point of the model and prove that the singular point is actually a bi-weak monodromic equilibrium point of type $[1,2]$. Additionally, we prove that there are two (small) intervals for a chosen parameter $a > 0$ for which one critical period bifurcates from this singular point after small perturbations.

1 Introduction

The need to understand periodic biological processes such as the circadian clock has led researchers to seek the chemical basis of oscillations in biochemical systems. One of these systems is glycolysis, which is essential for vital activities and involves the anaerobic conversion of sugar to various metabolites, including pyruvate and ATP. During glycolysis, the addition of glucose to an extract containing the primary metabolites triggers cyclic or periodic behaviors in the concentrations of these metabolites. In the context of the theory of the dynamical systems, the models based on biochemistry represent a given number of biochemical species interacting in biochemical reactions where variables of the dynamical system are concentrations and parameters are the rates of concentrations according to the model. These models commonly incorporate chemical reactions such as enzyme production of genes, RNA interference, and other vital processes occurring in living organisms evolving in time [3, 4, 8, 14, 24].

These behaviors can undergo mathematical analysis by studying their corresponding dynamical systems. A central problem in the field of dynamical systems is the center-focus problem, which was first introduced in the early 20th century by Poincaré and Andronov [18], and later studied extensively by other mathematicians and scientists [2, 5, 15, 21].

Essentially, the biochemical reaction models correspond to systems of ordinary differential equations (ODEs) with a nonlinear vector field, often described by rational functions. Note that efficient algorithms of computer algebra systems which enable a qualitative analysis of systems of ODEs are limited to polynomial systems. As a result, it is necessary to expand the corresponding vector field to the Taylor series up to some finite degree polynomials. The linear part of the polynomial vector field plays a crucial role in this analysis. If the eigenvalues of the corresponding linearized system are pure imaginary, the singular point is either a center (each orbit around the origin is an oval) or a focus (each orbit spirals away from or towards the singularity). One of the most basic indicators in distinguishing between a center and a focus are Lyapunov coefficients. If all Lyapunov coefficients are zero, the singular point is a center; otherwise, the singular point is a focus. If the first nonzero Lyapunov coefficient is negative, the singular point is a stable focus (each orbit spirals towards the singular point).

Although the problem of distinguishing between the center and the focus, the so-called center-focus problem or shortly center problem, has been considered in many studies, it is completely solved only for some low-order polynomial systems. For the quadratic systems, the solution is in [7]; for systems in the form of a linear center perturbed by homogeneous cubic terms the solution can be found in [15, 16]; for some linear centers perturbed with fifth order homogeneous polynomials see [5]. For higher-order polynomial systems, the solution was found only for some special families, mostly for Lotka-Volterra systems (e.g., [2, 26]).

The crucial information in studying the center problem can be obtained by considering the so-called return map (after choosing a ray from the singular point). Next, for both a center and a focus, isochronicity can be defined, which, roughly speaking, means that the revolution time (according to the chosen ray) is independent of the amplitude (or starting point in the case of a focus). The isochronicity can be determined by analyzing the coefficients of the so-called period function. More details about the return map and period function are given in section 2.3. The stationary points of the period function determine the so-called critical periods. In simpler cases, the period function and the critical periods can be treated by introducing the polar coordinates. Oliveria et al. presented an approach for identifying critical periods that uses the Lie bracket. They also define four categories of singular points according to the structure of the return map and the period function: (i) isochronous center, (ii) center with weakness of a finite order, (iii) isochronous weak focus of a finite order and (iv) the remaining case, when both the center and isochronicity properties are not kept at the same time. The former case is called a bi-weak monodromic equilibrium point of order $[k, l]$, where k (and l) refer to the structure of the return and period maps, respectively (see [17] for more details). The bifurcations of critical periods at the singular point for all values of the bifurcation parameter can be studied via the coefficients of the period function [21]. This problem was considered for the first time in [6]. The properties of the period function are essential for studying sub-harmonic oscillations and linearization. Chicone et al. studied multiple Hopf bifurcations in quadratic systems by using Bautin's method [1, 6] in 1989. In 1993, Rousseau et al. showed that at most three local critical periods bifurcate from a weak center in a vector field with homogeneous nonlinearity of the third degree [23]. The parameter conditions for the existence of an isochronous center or a weak center and period coefficients were obtained by Zhang et al. in 2000 using an inductive algorithm [25]. The bifurcations of the period function of a center perturbed by cubic homogeneous polynomials are studied by Romanovski et al. using computational algebra in 2003 [20]. Weak centers and local bifurcations of critical periods are investigated for a class of rational differential systems with a cubic polynomial as its numerator in 2013 [12].

The upper bounds on the number of critical periods of several families of cubic systems are obtained by moving a relevant ideal to a subalgebra generated by invariants of a group of linear transformations by Fercec et al. in 2015 [9]. For a quartic, [13] and quintic [22] polynomial system, it is shown that, at most, two critical periods can bifurcate from any nonlinear center.

Small amplitude limit cycles and the local bifurcations of critical periods for a quartic Kolmogorov system at the positive equilibrium are investigated, and the maximum number of small amplitude limit cycles bifurcating is obtained to be seven [10].

The goal of this paper is to consider the nature of the singular point and the bifurcations of critical periods in the minimal Higgins model, which is associated with glycolysis. After moving the origin of the minimal Higgins model to the singular point and expanding the corresponding vector field to the Taylor series up to the fifth-degree polynomial, the minimal Higgins model will be transformed into a system of the form

$$\begin{aligned} \frac{dx}{dt} &= \alpha x - \beta y + P(x, y) \\ \frac{dy}{dt} &= \beta x + \alpha y + Q(x, y) \end{aligned} \tag{1}$$

The rest of the paper is organized as follows. In section 2, we present the minimal Higgins model and its model components. In subsection 2.1, we give the normal form of the minimal Higgins model near the singular point. Next, we study the center-focus problem for the minimal Higgins model. In subsection 2.2, we calculate the first focus quantity. In subsection 2.3, we calculate the period constants according to two remaining parameters and give some results about the critical periods of the minimal Higgins system. In section 3, we give some conclusions.

2 The minimal Higgins model

The Higgins model, which was the first to demonstrate the general varieties of reaction pathways required for a chemical mechanism to exhibit oscillatory behavior and describe glycolytic self-oscillations, was proposed by J. Higgins in 1964 [11]. The Higgins model presents a chemical model that describes glycolysis as three essential enzymatic steps, which are the conversion of intracellular glucose to glucose 6-phosphate, the conversion of fructose 6-phosphate(F_6P) to fructose 1,6 bisphosphate(FBP), and the breakdown of fructose 1,6 bisphosphate. The Higgins model was originally proposed as the following six reactions, where E_1 and E_2 represent the enzymes and GA_3P represents glyceraldehyde 3-phosphate.

$$
\begin{aligned}
\mathrm{GLU} &\xrightarrow{\mathrm{k_1}^*} \mathrm{F_6P}\\
\mathrm{F_6P} + \mathrm{E_1}^* &\xrightarrow{\mathrm{k_2}^*} \mathrm{E_1}^* - \mathrm{F_6P}\\
\mathrm{E_1}^* - \mathrm{F_6P} &\xrightarrow{\mathrm{k_3}^*} \mathrm{E_1}^* + \mathrm{FBP}\\
\mathrm{FBP} + \mathrm{E_1}^+ &\xrightarrow{\mathrm{k\pm_4}^*} \mathrm{E_1}^*\\
\mathrm{FBP} + \mathrm{E_2} &\xrightarrow{\mathrm{k_5}^*} \mathrm{E_2} - \mathrm{FBP}\\
\mathrm{E_2} - \mathrm{FBP} &\xrightarrow{\mathrm{k_6}^*} \mathrm{E_2} + \mathrm{GA_3P}
\end{aligned}
$$

In 1996, Queeney et al. formulated these equations to derive the laws of motion for the six-reaction model and, applying steady-state approximations to the equations, obtained the following minimal two-dimensional model with suitable positive parameter changes where A is the amount of glucose, and k_1, k_2, k_3, k_4 are reaction rates [19].

$$
\begin{aligned}
\frac{dx}{dt} &= k_2xy - \frac{k_3x}{1+k_4x}\\
\frac{dy}{dt} &= k_1A - k_2xy
\end{aligned}
\tag{2}
$$

Queeney et al. performed linear stability analysis and obtained the bifurcation points by solving the characteristic equation of the minimal Higgins model. We present a detailed study of the period function and the focus quantities for system (2).

2.1 Normal form of system (2)

We compute singular point of system (2) and obtain $T(\frac{Ak_1}{B}, \frac{B}{k_2})$, where $B = k_3 - Ak_1k_4 > 0$. Then, we move the singular point T to the origin and system (2) becomes

$$
\begin{aligned}
\frac{dx}{dt} &= \frac{ABk_1k_4x}{k_3+k_4Bx} + \frac{Ak_1k_2}{B}y + k_2xy + \frac{k_4B^2x^2}{k_3+k_4Bx},\\
\frac{dy}{dt} &= -Bx - \frac{Ak_1k_2}{B}y - k_2xy.
\end{aligned}
\tag{3}
$$

Since the right-hand sides of the equations in system (3) involve rational terms, we expand system (3) in the Taylor series before computing the period constants. To this end, we obtain the following Taylor series expansions of system (3):

$$\frac{dx}{dt} = \frac{ABk_1k_4}{k_3}x + \frac{Ak_1k_2}{B}y + k_2xy + \sum_{j\geq 2} \frac{(-1)^j B^{j+1} k_4^{j-1}}{k_3^j} x^j$$
$$\frac{dy}{dt} = -Bx - \frac{Ak_1k_2}{B}y - k_2xy. \tag{4}$$

It is easy to see that the convergence radius of the power series in $\frac{dx}{dt}$ equals $k_3/(k_4B)$.

System (4) has the Jacobian matrix at the origin

$$J = \begin{bmatrix} \frac{ABk_1k_4}{k_3} & \frac{Ak_1k_2}{B} \\ -B & -\frac{Ak_1k_2}{B} \end{bmatrix} \tag{5}$$

having the trace

$$Tr(J) = \frac{Ak_1(B^2k_4 - k_2k_3)}{Bk_3},$$

and the determinant

$$Det(J) = \frac{Ak_1k_2B}{k_3}.$$

For system (4), the necessary and sufficient condition for only pure imaginary eigenvalues of J are that the determinant $Det(J) > 0$ and the trace $Tr(J) = 0$. Since $Ak_1 > 0$, $Tr(J) = 0$ if and only if

$$B^2 = \frac{k_2k_3}{k_4}.$$

To assure $Det(J) > 0$, we must choose the positive square root

$$B = \sqrt{\frac{k_2k_3}{k_4}} \tag{6}$$

and in turn, from $B = k_3 - Ak_1k_4$ we get

$$A = \frac{k_3 - B}{k_1k_4} \tag{7}$$

and as $A > 0$, we have $k_3 > B$, whence we additionally get the condition

$$k_2 < k_3 k_4. \tag{8}$$

Then, recalling that the eigenvalues must be pure imaginary, the real-Jordan canonical form of system (4) can be obtained by a standard procedure, i.e., firstly finding a complex eigenvector (the other is just a complex conjugate) and then taking the real part as the first and the imaginary part as the second column vector of the transforming matrix. Introduce the notation (for the purpose of more compact expressions)

$$a = \sqrt{\sqrt{\frac{k_3 k_4}{k_2}} - 1}. \tag{9}$$

Obviously, a is strictly positive by (8). Further, by combining (6), (7) and (9) we represent A in terms of a as

$$A = \frac{a^2(1+a^2)k_2}{k_1 k_4^2}. \tag{10}$$

The matrix

$$M = \begin{bmatrix} -a^2 & a \\ 1+a^2 & 0 \end{bmatrix}$$

enables that $M^{-1}JM$ is in the canonical form, i.e.

$$M^{-1}JM = \begin{bmatrix} 0 & -\beta \\ \beta & 0 \end{bmatrix}$$

where, by finally using (6), (9) and (10)

$$\beta = \sqrt{Det(J)} = \sqrt{\frac{ABk_1k_2}{k_3}} = \frac{ak_2}{k_4}.$$

To transform system (4) into the real canonical form, we define the following transformation.

$$M\begin{bmatrix}X\\Y\end{bmatrix}=\begin{bmatrix}-a^2X+aY\\(1+a^2)X\end{bmatrix}=\begin{bmatrix}M_X\\M_Y\end{bmatrix}$$

Substituting M_X and M_Y to x and y in system (4), replacing X, Y by x and y, respectively, multiplying by M^{-1} and dividing by β, i.e. rescaling the time, we obtain the system

$$\begin{aligned}\dot{x}&=-y+ak_4x^2-k_4xy\\ \dot{y}&=x-\frac{k_4}{1+a^2}x^2+\frac{(1-a^2)k_4}{a(1+a^2)}xy+\frac{k_4}{1+a^2}y^2\\ &+\frac{ak_4^2}{(a^2+1)^2}(ax-y)^3\frac{1}{1-ak_4(ax-y)/(a^2+1)}.\end{aligned}\qquad(11)$$

From (11) we see that the parameter variety (under condition (6)) is two-dimensional: all parameters depend only on k_4 and the a; in other words, they depend only on k_4 and the ratio k_3/k_2 since $(a^2+1)^2=k_4\frac{k_3}{k_2}$. However, to obtain system (11), we divide the vector field by $\beta=\frac{ak_2}{k_4}$, so k_2 disappeared by time rescaling.

2.2 Focus quantities of system (11)

We compute the first focus quantity of system (11). By denoting $\dot{x}=f_1(x,y)$, $\dot{y}=f_2(x,y)$ we compute the first focus quantity. Being in the canonical form, the Lyapunov function reads $\psi(x,y)=x^2+y^2+....$ From the classical identity $\frac{d\psi}{dx}f_1(x,y)+\frac{d\psi}{dy}f_2(x,y)=g_1(x^2+y^2)^2+g_2(x^2+y^2)^3+...$ and comparison of the coefficients at monomials, we obtain the first Lyapunov coefficient as

$$g_1=1/4(A_{11}A_{20}+3B_{03}-B_{02}B_{11}-2A_{20}B_{20}-B_{11}B_{20}+B_{21})$$

where $A_{ij}=\frac{\partial f_1}{i!j!\partial x^i\partial y^j}$ and $B_{ij}=\frac{\partial f_2}{i!j!\partial x^i\partial y^j}$. Inserting the actual values of A_{ij}, B_{ij} for system (11), we finally get the first focal quantity in the very closed form

$$g_1 = -\frac{a(2+a^2)k_4^2}{4(1+a^2)}.$$

The g_1 is clearly negative since $a > 0$. A parameter condition that makes the linearized eigenvalues of the system pure imaginary and, at the same time, makes the value of g_1 zero, does not exist for this system. Therefore, we conclude that the singularity point of the Minimal Higgins system is always a stable focus.

As an example, we consider the parameter values $k_4 = 2$, $a = 1$. In this case, system (11) has a stable focus at $(0, 0)$ with the eigenvalues $\pm i$ and the first Lyapunov coefficient $g_1 = -\frac{3}{2}$, as illustrated in Fig. 1.

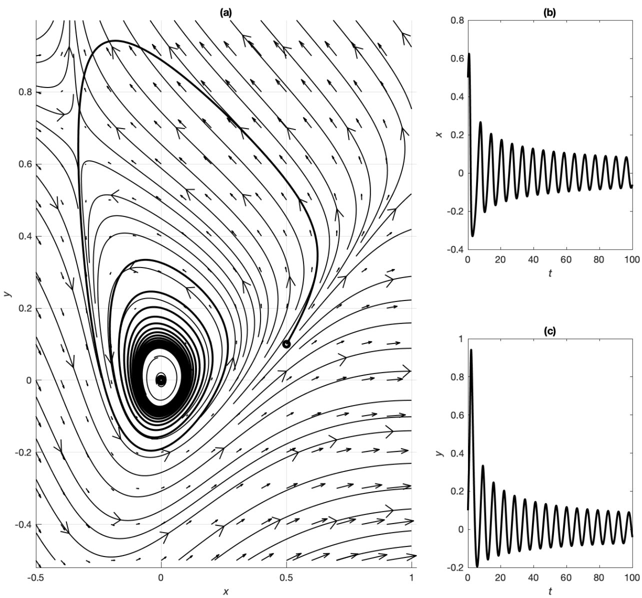

Figure 1. Spiraling trajectories towards a stable focus of system (11) with parameter values $k_4 = 2$ and $a = 1$. The two initial points are $(0.005, 0.001)$ and the origin.

2.3 Period functions of a stable focus and bifurcations of critical periods of system (11)

To study the period functions of system (11), we move to polar coordinates $x = r\cos\theta, y = r\sin\theta$ using the abbreviation $c = \cos\theta$, $s = \sin\theta$, and applying the Taylor series expansion around $r = 0$. So, the system (11) becomes

$$\begin{aligned} \frac{dr}{dt} &= r^2(\alpha_0 + \alpha_1 r + \ldots) \\ \frac{d\theta}{dt} &= 1 + \beta_1 r + \beta_2 r^2 + \beta_3 r^3 + \ldots \end{aligned} \tag{12}$$

where

$$\begin{aligned} \alpha_0 &= \frac{k_4(a^2(1+a^2)c^3 + a^3c^2s + (1-a^2)cs^2 + as^3)}{a(1+a^2)}, \\ \alpha_1 &= \frac{ak_4^2(ac-s)^3 s}{(1+a^2)^2}, \\ \beta_1 &= -\frac{2k_4}{1+a^2}c^3 + \frac{(1-2a^2-a^4)k_4}{a(1+a^2)}c^2 s - k_4 cs^2, \\ \beta_2 &= \frac{ak_4^2(ac-s)^3 c}{(1+a^2)^2}, \\ \beta_3 &= \frac{a^2k_4^3(ac-s)^4 c}{(1+a^2)^3}, \end{aligned}$$

are homogeneous trigonometric polynomials in θ. Elimination of time in system (12) yields

$$\frac{dr}{d\theta} = \sum_{k=2}^{\infty} R_k(\theta) r^k, \tag{13}$$

where $R_k(\theta)$ are such functions of θ that (the analytic solution exists by the Implicit Function Theorem)

$$r(\theta) = \rho + \sum_{j=2}^{\infty} V_j(\theta)\rho^j = \rho(1 + \sum_{j=2}^{\infty} V_j(\theta)\rho^{j-1}) =: \rho V(\theta) \tag{14}$$

is solution of (13) satisfying the initial condition $r(0) = \rho$ for some ρ close enough to zero.

For computing the coefficients of the period function, we have to integrate coefficients at powers of ρ in the series

$$\begin{aligned}\left(\frac{d\theta}{dt}\right)^{-1} &= \left(1+\beta_1 r+\beta_2 r^2+\beta_3 r^3+\ldots\right)^{-1}\\ &= (1+\beta_1\rho(1+V_2\rho+V_3\rho^2+\ldots)+\beta_2\rho^2(1+V_2\rho+V_3\rho^2)\\ &+\beta_3\rho^2(1+V_2\rho+V_3\rho^2+\ldots)^2+\ldots)^{-1}\\ &= 1-\beta_1\rho+(\beta_1^2-\beta_2-\beta_1V_2)\rho^2\\ &+(-\beta_1^3+2\beta_1\beta_2-\beta_3+2(\beta_1^2-\beta_2)V_2-\beta_1V_3)\rho^3+\ldots,\end{aligned}$$

Now, to determine at least T_2 and T_3, which are the coefficients of the period function we have to compute V_2 and V_3 as is evident from

$$\begin{aligned}T_0 &= \frac{1}{2\pi}\int_0^{2\pi} d\theta = 1\\ T_1 &= -\frac{1}{2\pi}\int_0^{2\pi} \beta_1\ d\theta\\ T_2 &= \frac{1}{2\pi}\int_0^{2\pi} \beta_1^2-\beta_2-\beta_1V_2\ d\theta\\ T_3 &= \frac{1}{2\pi}\int_0^{2\pi} -\beta_1^3+2\beta_1\beta_2-\beta_3+2(\beta_1^2-\beta_2)V_2-\beta_1V_3\ d\theta.\end{aligned} \tag{15}$$

Thus, we compute V_2 and V_3. Substituting (14) into (12) in place of r and computing

$$\begin{aligned}0=\frac{dr}{d\theta}\cdot\frac{d\theta}{dt}-\frac{dr}{dt} &= \rho^2\Big(\frac{dV_2(\theta)}{d\theta}+\frac{dV_3(\theta)}{d\theta}\rho+\ldots\Big)\\ &(1+\beta_1\rho V(\theta)+\beta_2\rho^2V(\theta)^2+\ldots)\\ &-\rho^2V(\theta)^2(\alpha_0+\alpha_1\rho V(\theta)+\alpha_2\rho^2V(\theta)^2+\ldots)\end{aligned} \tag{16}$$

dividing by ρ^2 and abbreviating $V_j := V_j(\theta)$, $j=2,3$, we obtain the identity

$$\begin{aligned}0 &= \Big(\frac{dV_2}{d\theta}+\frac{dV_3}{d\theta}\rho+\ldots\Big)(1+\beta_1\rho(1+V_2\rho+\ldots)+\beta_2\rho^2(1+V_2\rho+\ldots)^2+\ldots)\\ &-(1+V_2\rho+\ldots)^2(\alpha_0+\alpha_1\rho(1+V_2\rho+\ldots)+\alpha_2\rho^2(1+V_2\rho+\ldots)^2+\ldots)\\ &= -\alpha_0+\frac{dV_2}{d\theta}+\rho\Big(-\alpha_1-2\alpha_0V2+\beta_1\frac{dV_2}{d\theta}+\frac{dV_3}{d\theta}\Big)+\ldots\end{aligned}$$

holding true for all ρ close enough to 0. For $\rho = 0$ we get

$$\frac{dV_2}{d\theta} = \alpha_0$$

and by extracting the coefficient at ρ we see that

$$\frac{dV_3}{d\theta} = -\beta_1 \frac{dV_2}{d\theta} + 2\alpha_0 V_2 + \alpha_1 = \alpha_1 - \beta_1\alpha_0 + 2\alpha_0 V_2.$$

By initial condition in (14), we have $V_2(0) = V_3(0) = 0$, so we successively get

$$\begin{aligned} V_2 &= \int_0^\theta \alpha_0 \; d\theta \\ &= \frac{k_4}{(1+a^2)} \left(p_0 + p_1 \cos\theta + q_1 \sin\theta + p_3 \cos 3\theta + q_3 \sin 3\theta\right) \end{aligned}$$

with

$$\begin{aligned} &p_0 = (2+a^2)/3, \quad p_1 = -(3+a^2)/4, \quad p_3 = (1-a^2)/12, \\ &q_1 = \frac{1+2a^2+3a^4}{4a}, \quad q_3 = \frac{-1+2a^2+a^4}{12a} \end{aligned}$$

and

$$V_3 = \int_0^\theta \alpha_1 - \beta_1\alpha_0 + 2\alpha_0 V_2 \; d\theta. \tag{17}$$

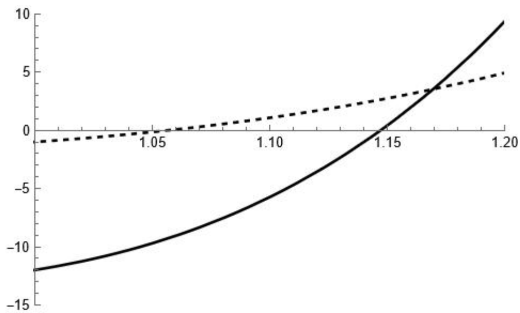

Figure 2. Graph of $T_2 \cdot \frac{24a^2(a^2+1)}{k_4^2}$ (dashed line) and $T_3 \cdot \frac{72a^2(a^2+1)^2}{k_4^3}$ (solid line) near $a^* \approx 1.0567262175781924344$.

Note that all terms that we have to integrate for V_3 are either homogeneous trigonometric polynomials or linear functions in θ so the integration is possible, however long, as well as the obtained expressions. Using Wolfram Mathematica we obtain

$$V_3 = u_0 + u_1\theta + \sum_{n=1}^{6}(v_n \cos n\theta + w_n \sin n\theta) \tag{18}$$

where

$$\begin{aligned}
&u_0 = \frac{\left(115a^8+298a^6+422a^4+257a^2-2\right)k_4^2}{288a^2\left(a^2+1\right)^2}, \quad u_1 = \frac{a^3k_4^2}{8\left(a^2+1\right)},\\
&v_1 = -\frac{\left(a^2+2\right)\left(a^2+3\right)k_4^2}{6\left(a^2+1\right)^2}, \quad w_1 = \frac{\left(a^2+2\right)\left(3a^4+2a^2+1\right)k_4^2}{6a\left(a^2+1\right)^2},\\
&v_2 = -\frac{\left(57a^8+99a^6+116a^4+3a^2+1\right)k_4^2}{192a^2\left(a^2+1\right)^2}, w_2 = -\frac{\left(11a^6+51a^4+15a^2+11\right)k_4^2}{96a\left(a^2+1\right)^2},\\
&v_3 = \frac{\left(1-a^2\right)\left(a^2+2\right)k_4^2}{18\left(a^2+1\right)^2}, \quad w_3 = \frac{\left(a^2+2\right)\left(a^4+2a^2-1\right)k_4^2}{18a\left(a^2+1\right)^2},\\
&v_4 = -\frac{\left(9a^8+26a^6-6a^4+3a^2-2\right)k_4^2}{96a^2\left(a^2+1\right)^2}, \quad w_4 = -\frac{\left(11a^6-a^4+8a^2-8\right)k_4^2}{96a\left(a^2+1\right)^2},\\
&v_5 = 0, \quad w_5 = 0,\\
&v_6 = -\frac{5\left(a^8+3a^6+4a^4-5a^2+1\right)k_4^2}{576a^2\left(a^2+1\right)^2}, \quad w_6 = -\frac{5\left(a^6+a^4-3a^2+1\right)k_4^2}{288a\left(a^2+1\right)^2}.
\end{aligned} \tag{19}$$

Finally, we compute the period constants (15) using the actual parameters of our family of systems (11) in normal form. We obtain the following (recall (9)) results:

$$\begin{aligned}
T_0 &= 1\\
T_1 &= 0\\
T_2 &= \frac{\left(4a^6+a^4-7a^2+1\right)k_4^2}{24a^2\left(a^2+1\right)}\\
T_3 &= \frac{\left(5a^8+12a^6-7a^4-26a^2+4\right)k_4^3}{72a^2\left(1+a^2\right)^2}.
\end{aligned} \tag{20}$$

As already mentioned in the introduction in [17], the authors consider four types of singular points relating to the return map and period map. From subsections 2.2 and 2.3, it is evident that the origin of system (11) is a bi-weak monodromic equilibrium point of type [1, 2]. Below is the main bifurcational result concerning this singular point of (11).

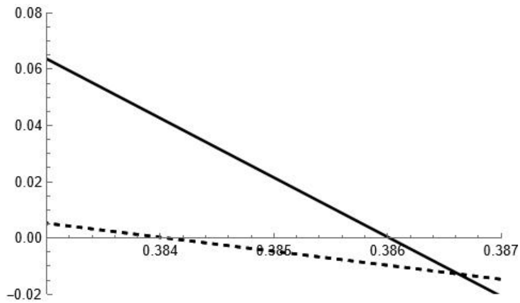

Figure 3. Graph of $T_2 \cdot \frac{24a^2(a^2+1)}{k_4^2}$ (dashed line) and $T_3 \cdot \frac{72a^2(a^2+1)^2}{k_4^3}$ (solid line) near $a_* \approx 0.38447985657140968088464$5.

Definition 1. Any value $r > 0$ ($r < r^*$) for which $T'(r) = 0$ is called a critical period.

When we consider bifurcations of critical periods, we are interested in an upper bound of the number of critical periods in a small neighborhood of the singular point. It is the so-called problem of bifurcations of critical periods considered for the first time in [6].

Theorem 1. *Let a_* be a solution of $T_2 = 0$ near point $a = 0.3845$ and let a^* be a solution of $T_2 = 0$ near $a = 1.0567$. Let $I_1 = [a^*, a^* + \epsilon)$ and $I_2 = [a_*, a_* + \epsilon)$. If in system (11) $a \in I_1 \cup I_2$, then one critical period bifurcates from the origin after small perturbations.*

Proof. From Figs. 2 and 3 one can see that a_* and a^* are (the only positive) zeroes of T_2. For system (11), the above results reveal that one critical period bifurcates from the origin after small perturbations, if $a \in [a^*, a^* + \epsilon)$ then clearly $T_2 > 0$ (and is arbitrary small) while $T_3 < 0$ (see Fig. 2). One can choose such a that $|T_2| \ll |T_3|$. This means that one critical period bifurcates from the singular point.

Similar, if $a \in [a_*, a_* + \epsilon)$ then clearly $T_2 < 0$ (and is arbitrary small) while $T_3 > 0$ (see Fig. 3). Again, one can choose such a that $|T_2| \ll |T_3|$ which means that one critical period bifurcates from the singular point. ∎

3 Conclusion

The study of the bifurcations of the critical periods of the dynamical models has been one of the central aspects in the investigation of the glycolysis process since it allows one to determine stable regimes. In this work, we examined the center-focus problem for the minimal Higgins model. We showed that the model exhibits only a stable oscillatory regime given by a stable focus point. We presented the first three period constants and the first Lyapunov coefficient for the stable focus singularity. We showed also some results for the system with fixed parameters.

***Acknowledgment*:** This work is supported by the Slovenian Research Agency (research cores no. ”P1-0306”, ”P1-0288”, project no. ”BI-TR/19-22-003”) and the Scientific and Technological Research Council of Turkey (TUBITAK) under project 119F017.

We acknowledge COST (European Cooperation in Science and Technology) actions CA15140 (Improving Applicability of Nature-Inspired Optimisation by Joining Theory and Practice (ImAppNIO)) and IC1406 (High-Performance Modelling and Simulation for Big Data Applications (cHiPSet)) and Tomas Bata University in Zlín for accessing Wolfram MATHEMATICA.

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