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BISTABILITY AND SELF-OSCILLATIONS IN CELL CYCLE CONTROL

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A qualitative model of cell cycle control is presented and its transition from bistability to limit cycle oscillations and vice versa is discussed. The origin of this model is the two-dimensional system of kinetic equations introduced by Novak–Tyson which is illustrated computationally and analytically. For this purpose a qualitative model is numerically reconstructed from the steady state behavior of the dynamical variables including the bifurcation parameter. Then, the reconstructed cubic polynomial model is generalized to an appropriate canonical form and is analyzed in terms of Lyapunov values. On this basis, the relationship between bistability and self-oscillatory behavior of mitotic cell cycle is approached qualitatively.

Keywords: Stability analysis; Lyapunov values; cell cycle.

1. Introduction

As a survey paper on the cell cycle we can refer to [Murray & Kirschner, 1991]. The cell cycle consists of two controlled growth processes: The chromosomal cycle, in which the genetic material is duplicated and the cytoplasmic cycle where the two nuclei are formed. Robustness is essential for these processes, since each daughter nucleus must receive the exact replica of each chromosome. The cytoplasmic cycle is less tightly controlled and lasts significantly longer than the chromosomal. During this cycle, the cytoplasmic material duplicates including all cell structures — organelles, mitochondria etc. The growth is predominantly continuous during the G1, S and G2 — phases, pausing briefly only during mitosis [Tyson *et al.*, 2001, 2002, 2003]. Since these cycles operate controlled in mature organisms, the ratio between cell mass and nuclear mass remains approximately constant [Novak *et al.*, 2001]. In case of embryonic organisms it is in addition possible that these processes are acting in an uncoupled manner. Such a behavior has been observed for example during embryo-genesis of a frog, the egg undergoes twelve rapid synchronous mitotic divisions to form a ball called blastula, consisting of 4096 cells. Recently, many effective mathematical approaches have been developed to study the mitotic (M-phase) control mechanisms. Several biochemically sound cell cycle models have been constructed but these are too complicated to understand by informal verbal reasoning. After studying the models in mathematical terms, the obtained results have been compared in quantitative details with experimental observations. On this basis, experimental and theoretical investigations of cell cycle control have revealed nonlinear phenomena such as self-oscillations and bistability

[Tyson *et al.*, 2001, 2002, 2003, Novak *et al.*, 2001; Li *et al.*, 2004; Petrov & Timmer, 2004; Petrov *et al.*, 2004]. The close relationship between some kind of self-oscillatory and bistable dynamics of cell cycle have been pointed out in [Petrov & Timmer, 2004; Qu *et al.*, 2003a, 2003b]. The purpose of this paper is to clarify a principal relationship between these two types of cell cycle dynamics by giving a simple mathematical model which is analyzed regarding its bifurcation behavior.

2. Reconstruction Analysis and Suggesting Considerations

We consider the Novak–Tyson model of cell cycle control derived for budding yeast and demonstrate bistable behavior [Novak *et al.*, 2001]. The model has the form of the following pair of nonlinear differential equations:

$$\begin{aligned} \frac{dx}{dt} &= k_1' - (k_2' + k_2'' y)x \\ \frac{dy}{dt} &= (k_3' + k_3'' A)\frac{1-y}{j_3+1-y} - k_4 \frac{mxy}{j_4+y} \end{aligned} \tag{1}$$

Here, x and y are concentrations of cyclin/Cdk dimers and active Cdh1/APC complexes, respectively. The cell mass is denoted by m. The parameter A represents the concentration of protein phosphatase that removes from Cdh1 the inhibitory phosphate groups placed there by cyclin/Cdk. In this way A plays the role of activator of Cdh1. The k's are rate constants, and the j's are Michaelis-Menten constants. Nullclines of Eq. (1) are

$$x\text{-nullcline:}\quad x = \frac{b}{j_2+y},$$

$$y\text{-nullcline:}\quad x = (1-y)\frac{j_4+y}{j_3+1-y}\,\frac{z}{y}.$$

Here, $b = k_1/k_2'' = 0.04$, $j_2 = k_2'/k_2'' = 0.04$, $j_3 = j_4 = 0.04$ and $z = k_3' + k_3'' A/k_4 m$ taken from [Novak *et al.*, 2001] is called "reciprocal" mass. The x-nullcline is a hyperbola and the y-nullcline is a z-shaped curve intersecting the x-nullcline in three points, two stable ones and one unstable, for $j_3 = j_4 \ll 1$. For other values of the parameters, the number and type, stable or unstable, of the intersection points may vary. The bifurcation diagram for dynamical system Eq. (1) is illustrated in Fig. 1. It presents the steady state concentration of x (cyclin/Cdk) plotted as a function of the bifurcation parameter z. Saddle-node bifurcations occur at $z = 0.05418$ and $z = 0.2604$.

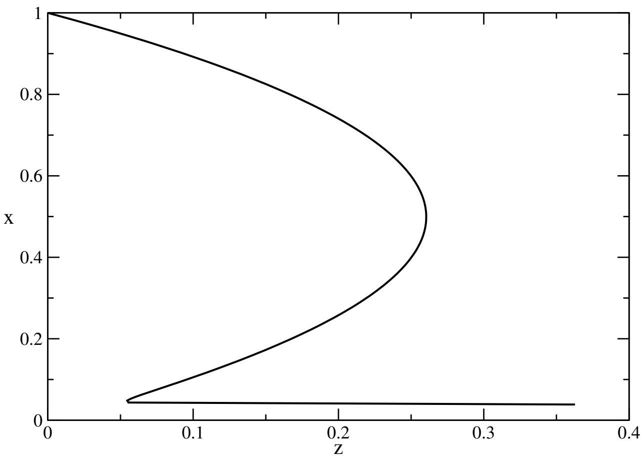

Fig. 1. Z-shaped bifurcation diagram of the Novak–Tyson model for the budding yeast cell cycle bistable.

For a further mathematical analysis, the bifurcation diagram is approximated by a polynomial of third order which conserves the Z-shaped form, as illustrated in Fig. 2. In the following section the effect of conserving the bifurcation behavior will be evaluated analytically by using Lyapunov values. But first, two-dimensional dynamical system is reconstructed such that the right-hand side of the differential equation contains only polynomials up to third order. Additionally, the Z-shaped bifurcation diagram is sufficiently near to those presented in Fig. 2. For this purpose the method of reconstruction described in [Petrov *et al.*, 2002a, 2002b, 2003] and, developed in [Georgiev, 2003a] is used which is based on a theorem given in [Georgiev, 2003b].

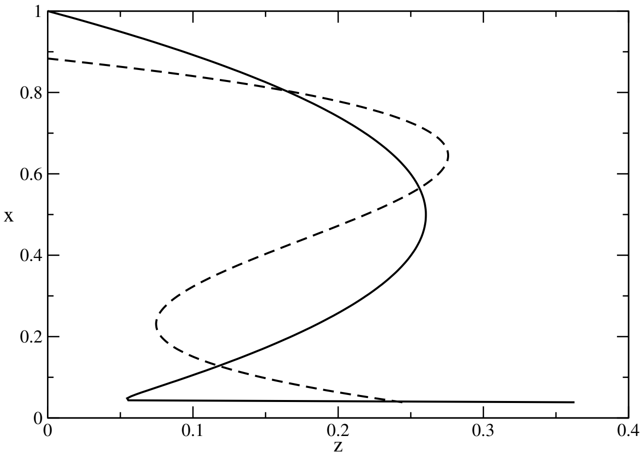

Fig. 2. Z-shaped bifurcation diagrams of the Novak–Tyson model (solid line) and the reconstructed one (dashed line).

For two-dimensions this theorem claims:

Theorem 1. *Let $x(t)$ and $z(t)$ be a real-valued and analytic functions defined on interval (a, b), such that for $\forall\, t \in (a, b)$, the curve $\vec{c}(t) \equiv \{x(t), z(t)\}$ is simple and regular. Then there exists real-valued analytic functions $F_1(x, z)$ and $F_2(x, z)$, defined on the curve $\vec{c}(t)$ and such that $x(t)$and $z(t)$ present a solution to*

$$\frac{dx}{dt} = F_1(x, z), \quad \frac{dz}{dt} = F_2(x, z). \tag{2}$$

In our case, $x(t)$ and $z(t)$ are implicitly given by functions parameterizing the bifurcation diagram

$$0 = a_3x^3 + a_2x^2 + a_1x + a_0 - kz. \tag{3}$$

We assume the requirements of Theorem 1 are valid by supposing that the simplicity and regularity of the curve $\mathbf{c}(t)$ holds. For almost-periodic analytic functions, this condition is satisfied by truncating the curve $\mathbf{c}(t)$ and regarding its remainder near the limit cycle [Georgiev, 2003a]. Thus, we can accept the existence of dynamical system of type (2) having an equilibrium point in the form of (3). Then we can construct a new system in the following more specific form by considering x as a cyclin/Cdk concentration and new dynamical variable z as a "reciprocal" cell mass:

$$\begin{aligned} \frac{dx}{dt} &= a_3x^3 + a_2x^2 + a_1 + a_0 - kz, \\ \frac{dz}{dt} &= b_1x + b_2z + b_0. \end{aligned} \tag{4}$$

Here we treat the parameter $z_0 = a_0 > 0$ as a relatively constant part of the reciprocal mass varying independently (or very slowly) on the key-regulator which is the concentration x by subtracting the second part of reciprocal cell mass $r_m = z_0 - kz$ from z_0. In this way the system of equations (3) presents a model of a negative feedback dynamics for the key-regulator x and dynamical variable z. Qualitatively and quantitatively the dynamics of Eq. (3) is near to that generated by the system (1). As a result of the numerical approximation we obtain the following values for the polynomial coefficients

$$a_0 = 74.7817 \quad a_1 = -91.2115$$
$$a_2 = 12.3726 \quad a_3 = -1.5696$$
$$b_0 = 3.9790 \quad b_1 = 0.0375$$
$$b_2 = -16 \quad k = 1.6667.$$

By replacing these values in Eq. (4), we obtain the solution shown in Fig. 3. In the following Fig. 4, a disposition of the corresponding limit cycle with respect to the polynomial approximation of the Novak–Tyson bifurcation diagram for budding yeast is given in the phase plane formed by the cyclin/Cdk — dimer and the reciprocal cell mass.

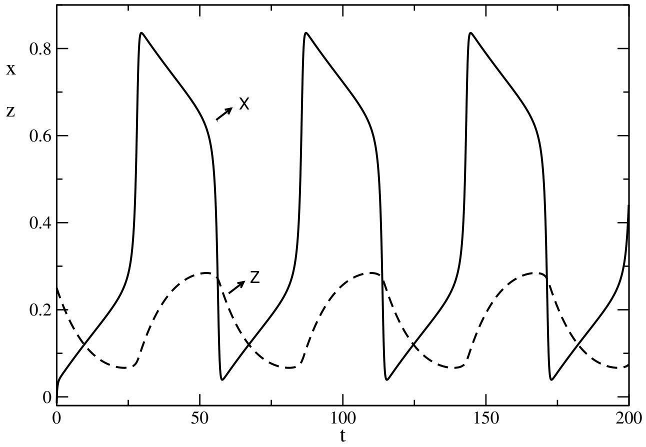

Fig. 3. Oscillations of cyclin/Cdk — dimer as solutions of Eq. (4).

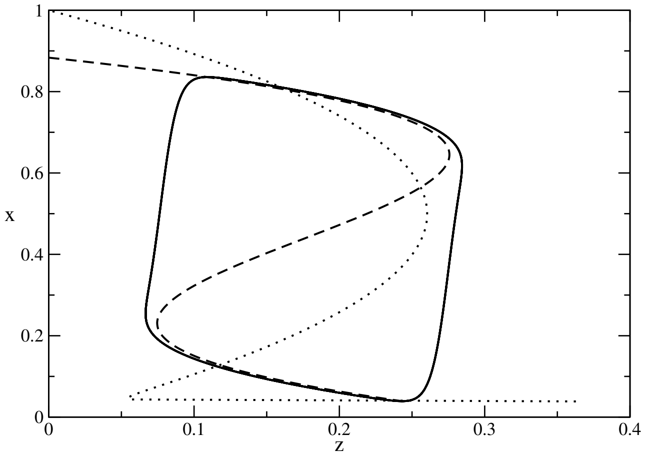

Fig. 4. Limit cycle disposition with respect to the polynomial approximation of the Novak–Tyson bifurcation diagram.

It is displayed that the limit cycle of the reconstructed dynamical system occupies the same region of the phase plane, where the forced oscillations of the Novak–Tyson model take place. Thus we should accept that the reconstructed polynomial model (4) simulates approximately the bistable behavior of the Novak–Tyson model but as self-oscillatory instead of forced oscillations. On the other hand, some part of the cell mass now depends on the key-regulator (cyclin/Cdk). Thus, the reciprocal cell mass z is considered as a dynamical variable.

3. Determining Lyapunov Value Formulas of the Generalized Model

Theorem 1 does not only play the role of suggesting the existence of an approximative model, it also shows that if we have a sufficiently exact approximation of the original bifurcation diagram, the quantitative and qualitative behavior will be close to that of Novak and Tyson. In order to analyze the bifurcation behavior, Eq. (4) is transformed to the coordinates (u, v) by applying

$$\begin{aligned} x &= x_0 + u, \\ z &= z_0 + v, \end{aligned} \tag{5}$$

where (x_0, z_0) is the steady state. Then, the transformed system is expanded up to third order such that the system can be represented by the canonical form

$$\begin{aligned} \frac{du}{dt} &= au + bv + a_{20}u^2 + a_{30}u^3, \\ \frac{dv}{dt} &= cu + dv. \end{aligned} \tag{6}$$

It is shown in the following that the bifurcation behavior is completely determined by Eq. (6), such that it is not necessary to regard the full model for any further analysis. Let us therefore consider (6). The characteristic equation of the linearized system has the form

$$\chi^2 + R\chi + r = 0, \tag{7}$$

where $R = -(a + d)$ is the trace and $r = ad - bc$ the determinant of the linearized flux. Furthermore, we apply the theory of Lyapunov values to bifurcation analysis at the following boundaries:

(i) $R = -(a + d) = 0$ under condition $r = ad - bc > 0$
(ii) $r = ad - bc = 0$ under condition $R = -(a + d) > 0$.

Case (i) is considered in [Petrov *et al.*, 2004], in which the corresponding formula of Bautin [1984] for the first Lyapunov value is presented and derived. The dynamical interpretation of this value is explained in [Petrov *et al.*, 2004] and [Nikolov & Petrov, 2004]. Moreover a detailed presentation of the theory of Lyapunov values is presented in [Andronov *et al.*, 1966] and more recently in [Neimark & Landa, 1992]. For case (i), the Lyapunov value is determined by

$$L_1(R = 0) = \frac{\pi}{4r\sqrt{r}}\left[2a\, a_{20}^2 - a_{30}(a^2 + bc)\right]. \tag{8}$$

Only the coefficients up to third order contribute to the determination of the first Lyapunov value. If L_1 has nonzeroth value, then it determines the whole bifurcation behavior of the system at the boundary (i). This fact is due to the following general proposition proven by Andronov [Andronov *et al.*, 1966]:

Theorem 2. *At transition through the point of boundary* $R = 0$ (*as* R *decreases for example*), *a stable periodic solution, for* $L_1(0) < 0$, *is generated by stability loss of the steady state solution of the full system; for* $L_1(0) > 0$, *the steady state stability is lost by merging the state with the unstable periodic solution of Eq.* (*6*).

For $L_1(0) < 0$, a reversible process is possible as R increases. Then a stable periodic solution vanishes and the steady state solution restores its stability by merging the limit cycle. That is why this type of transition through the bifurcation boundary of type (i) is sometime called "soft loss of stability". In the literature the name Hopf bifurcation is often used. For $L_1(0) > 0$ the type of bifurcation is called "hard loss of stability". The conditions for this type of bifurcation are not explicitly treated in the context of the well-known Hopf theorem. Whereas in the framework of the theory of Lyapunov values (Theorem 2) they are considered.

Let us now consider the boundary case (ii). Following Bautin [1984] for the first Lyapunov value, we obtain

$$l_1(r = 0) = ab^2\frac{ca_{20}}{(a^2 + bc)^2}. \tag{9}$$

Evidently, in this case the bifurcation behavior is determined only by the coefficients of the quadratic approximation. It is therefore sufficient only to consider Eq. (6).

4. On the Equivalence Between a Simple Qualitative Model and Cubic Truncation of the Generalized Model

In order to study the transition from bistability to self-oscillatory behavior, it is useful to regard an even simpler model. Let us now consider the system given by the dynamical equation

$$\frac{dx}{dt} = -(x^3 - mx + l)$$

For $m > 0$, it has two stable stationary states and one unstable. The transitions between the stable states have been extensively studied by Nitzan *et al.* [1974]. As in Sec. 2, for our purposes, we can treat the parameter l as a constant part of the cell mass varying independently or very slowly on the key-regulator concentration x. By adding to l a second part of cell mass kz depending on the variable z, we obtain the whole mass $M = l + kz$ as a sum of parameter l and dynamical term kz. Moreover, we introduce for the dynamical variables x and z multiplicative and additive scaling parameters n, s, p and q respectively, in order to simulate quantitatively the key-regulator oscillations. Then the following negative feedback dynamics for the key-regulator x and dynamical mass z can be defined:

$$\begin{aligned} \frac{dx}{dt} &= -n^2(x+p)^3 + m(x+p) \\ &\quad - \frac{l}{n} - \frac{ks(z+q)}{n}, \\ \frac{dz}{dt} &= \frac{n(x+p) - s(z+q)}{Ts}, \end{aligned} \tag{10}$$

with parameter values:

$$\begin{gathered} k = 1 \quad l = 0.1 \\ m = 0.5 \quad n = 2 \\ p = -0.45 \quad q = -0.21 \\ s = 1.8 \quad T = 40. \end{gathered} \tag{11}$$

In addition, system (10) is qualitatively identical to the FitzHugh–Nagumo model (FNm) [Fitzhugh, 1960, 1961; Nagumo *et al.*, 1962] and therefore similar to the Hindmarsh–Rose model [Hindmarsh & Rose, 1984]. Similar dynamical behavior of (10) with respect to the FNm is therefore expected, such as saddle-node and Hopf bifurcations found in the FNm, see e.g. [Murray, 1990; Keener & Sneyd, 1998; Fall *et al.*, 2002]. However, these results and analysis methods are not sufficient for our purposes because of the necessity to analyze the transition between different types of bifurcations — from bistability loss bifurcation to Hopf bifurcation and vice versa. That is why we apply the specific bifurcation analysis method of Andronov's to describe the transitions through all bifurcational boundaries in the parametric space of model (10). Consequently, the obtained qualitative results are also valid for FNm.

The solution of system (10) is shown in Fig. 5 and the phase plot of the limit cycle is presented in Fig. 6, where the Z-shaped stationary curve of (10) and the bifurcation diagram of the Novak–Tyson model are still present. In addition, the limit cycle occupies the same region as for forced oscillations in the case of bistability described by the Novak–Tyson model. Thus, approximately, we consider Eq. (10) as an alternative self-oscillatory model of the mitotic cell cycle of budding yeast.

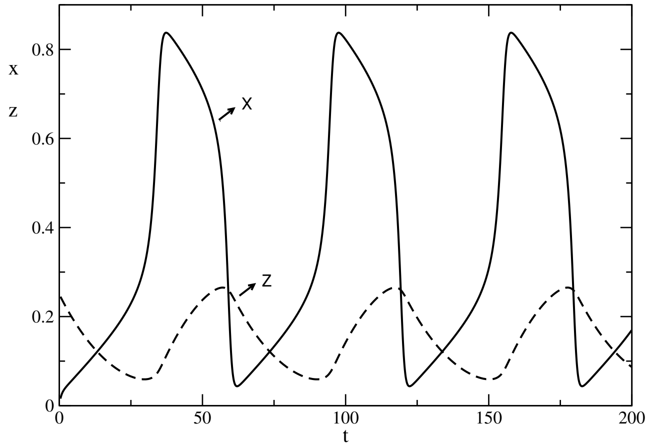

Fig. 5. Solutions of the simple qualitative model Eq. (10).

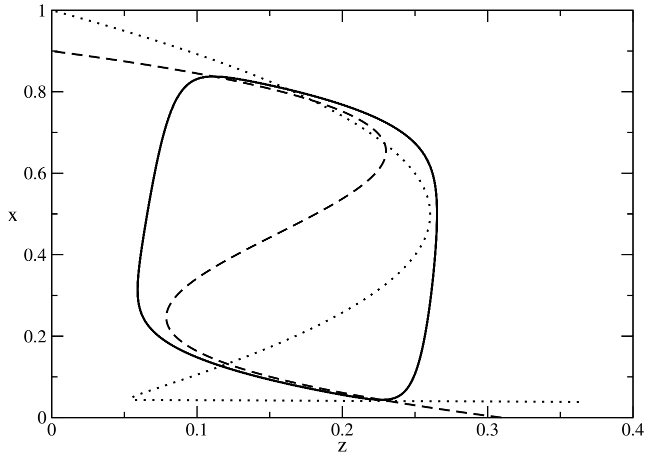

Fig. 6. Z-shaped bifurcation diagrams and limit cycle of Eq. (10).

The model (10) is remarkable with the following valuable properties:

(1) The cubic truncation of the generalized Z-shaped model of type (3.1-2) is reducible to (4.1-2) after canonization (3.3-4).
(2) The transition of model (4.1-2) from bistability to limit cycle behavior can be demonstrated analytically and numerically with mathematical accuracy.

On the other hand, we have shown in the previous section that the bifurcation behavior of the generalized Z-shaped model is fully determined by the coefficients of the cubic truncation. Thus the property (1) solves the problem of transition behavior by reducing it to (2). To prove the assertion (1), we firstly substitute Eq. (5) in Eq. (10). As a result we obtain the system

$$\begin{aligned} \frac{du}{dt} &= au + bv + a_{20}u^2 + a_{30}u^3, \\ \frac{dv}{dt} &= cu + dv, \end{aligned} \tag{12}$$

which is the same as the cubic truncation (6) with the additional condition that the coefficients have the form

$$\begin{gathered} a = m - 3n^2(x_0 + p)^2 \quad b = -\frac{ks}{n} \\ c = \frac{1}{T} \quad d = -c \\ a_{30} = -n^2 \quad a_{20} = -3n^2(x_0 + p). \end{gathered} \tag{13}$$

This is a system of five independent equations for five unknown parameters k, m, n, T and $x_0 + p$, having single-valued solution if the coefficients $a, b, c, d, a_{20}, a_{30}$ are known. The inequalities $d < 0$, $a_{03} < 0$ must be fulfilled in order to assure the Z-shaped character of the corresponding stationary curves. In this way the assertion (1) is proven.

The systems (10) and (12) are equivalent under condition that the relations (13) hold. Thus defining the bifurcation behavior of the simple model (10) or (12) we simultaneously solve the problem for determining a transition from bistable to self-oscillatory behavior of the generalized Z-shaped model of Novak–Tyson.

5. Structural Stability Analysis of the Simple Qualitative Model

As done before, we apply the theory of Lyapunov values to bifurcation analysis at the following boundaries:

(i) $R = -(a + d) = 0$ under condition $r = ad - bc > 0$
(ii) $r = ad - bc = 0$ under condition $R = -(a + d) > 0$.

For the simple qualitative model (10) the equations of boundaries (i) and (ii) are

$$\begin{gathered} R = \frac{3n^2(x_0 + p)^2 - m + 1}{T} = 0, \quad r > 0 \\ r = 3n^2(x_0 + p)^2 - m + k = 0 \quad R > 0. \end{gathered} \tag{14}$$

Apart from (14) we have the steady state equations of (10) in the form

$$\begin{gathered} l = n(m - k)(x_0 + p) - n^3(x_0 + p)^3, \\ z_0 = \frac{n}{s}(x_0 + p) - q. \end{gathered} \tag{15}$$

By replacing $x_0 + p$ from Eq. (14) to Eq. (15), the following bifurcation curves in the parametric plane (k, l) can be obtained:

$$\begin{gathered} l_R = \frac{1}{3^{3/2}}\left(\frac{m-1}{T}\right)^{1/2}\left(\frac{3k - 2m - 1}{T}\right), \\ l_r = 2\left[\frac{m-k}{3}\right]^{3/2}. \end{gathered} \tag{16}$$

Supported by the numerical analysis, see below, the negative sign of the square root of $(x_0 + p)^2$ has to be taken for deriving l_R. It is convenient to rewrite the formulas (8) and (9) for the Lyapunov values at boundaries (14) respectively

$$\begin{gathered} L_1(R = 0) = \frac{\pi}{4r\sqrt{r}}[2a\, a_{20}^2 - a_{30}(a^2 + bc)], \\ l_1(r = 0) = ab^2\frac{ca_{20}}{(a^2 + bc)^2}. \end{gathered} \tag{17}$$

By replacing the numerical values (except l) from (11) to (13), we obtain bifurcation points (values of bifurcation parameter l) on the bifurcation curves (i) or (ii). Then by changing the other bifurcation parameter k in Eq. (16), we obtain the bifurcation curves $l_R(k)$ and $l_r(k)$ in the parametric plane (l, k).

Let us first consider the case for the bifurcation value on (i) obtained by taking l from Eq. (16) at values (11). In this case the Lyapunov value is equal to the positive number $L_1 = 94.5665$. Due to Andronov's Theorem 2, the equilibrium state of the system (10) is unstable at the bifurcation point ($l = 0.2620$, $k = 1$) in the parametric plane (l, k). For this case Fig. 7 shows oscillations with constant amplitude of the key regulator x and reciprocal cell mass z.

A small decrease of the bifurcation parameter l is chosen ($l = 0.2600$) in Fig. 8. It is seen that after a small displacement from the bifurcation point, an unstable (with increasing amplitude) self-oscillation emerges first, therefore a hard loss of stability of the steady state takes place. However, after some time, a finite jump of oscillation amplitude occurs suddenly. This shows that the transition is a typical "hard self-excitation" (not only "hard loss of stability"), which type of behavior continues to be in computational agreement with the corresponding

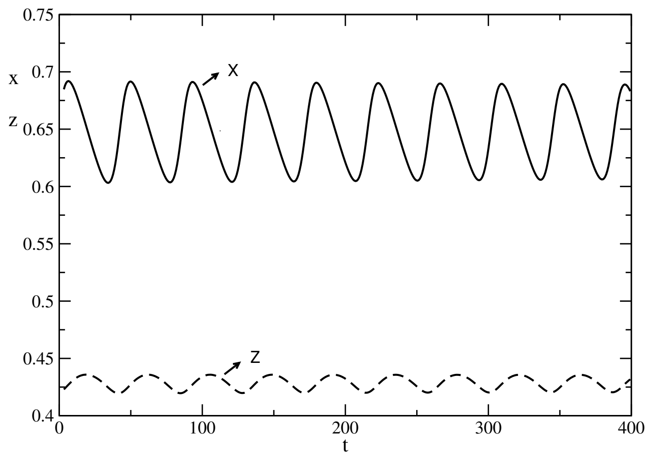

Fig. 7. Oscillations of the simple qualitative model at the bifurcation point ($l = 0.2620, k = 1$).

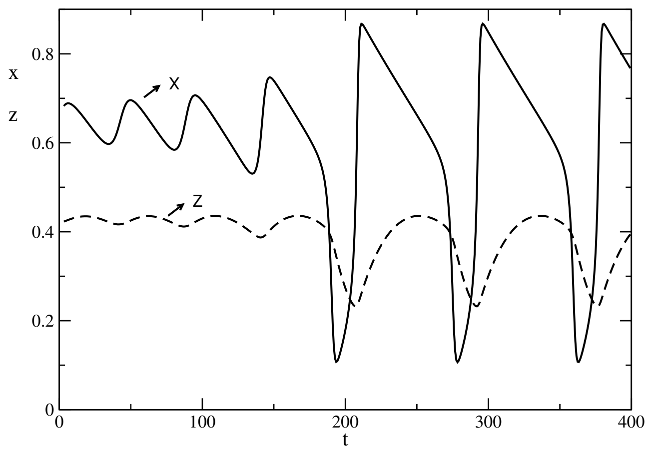

Fig. 8. Response of the simple qualitative model to small displacement of l at the bifurcation point.

assertion in the second part of Andronov's Theorem 2. In our case, the knowledge of positive sign of the Lyapunov value plays the role of a suggested consideration to obtain the computational results presented in Figs. 7 and 8.

Some additional explanations seem to be necessary in the case presented in Fig. 8. The notion "hard loss of stability" is more general than "hard self-excitation of oscillations". In many cases [Bautin, 1984; Nikolov & Petrov, 2004; Andronov *et al.*, 1966], a hard loss of stability is followed only by destabilization of the steady state and the vanishing of the unstable small cycle, without being surrounded in the phase plane, by a finite stable limit cycle. This is not the case here. In our considerations we have a finite stable limit cycle (self-oscillation), that occurs firstly in the neighborhood of a small unstable limit cycle and is surrounding a stable equilibrium point. Then the small limit cycle and steady state merge at the unstable equilibrium point surrounded by the stable finite cycle. This type of occurrence of a self-excited finite oscillation is called "hard self-excitation". Evidently, it is a specific type of "hard loss of stability", which is the more general term.

However, as we have shown here, the theory of Lyapunov values can be used as an analytical basis and suggested consideration to find a computational illustration of this nonlinear effect. In Fig. 9, the bifurcation line $l_R(k)$ is plotted together with the bifurcation curve $l_r(k)$. It is easy to show that if the inequality $r = ad - bc > 0$ holds, there are no self-oscillations of the system (10) above $l_R(k)$, and below, the self-oscillations exist at every point of this region. This means we exclude the small part of $l_R(k)$ below the point of self-intersection between $l_R(k)$ and $l_r(k)$.

As for the bifurcation curve $l_r(k)$, the following consideration could be made: On considering the well-known Cardano's formulas for the roots of the cubic equation (15), the equation of steady states of our model (10), we obtain that the semi-inequality

$$l_r \leq 2\left[\frac{m-k}{3}\right]^{3/2} \tag{18}$$

is a necessary and sufficient condition for existence of three real roots of Eq. (15). Moreover, the opposite inequality

$$l_r > 2\left[\frac{m-k}{3}\right]^{3/2} \tag{19}$$

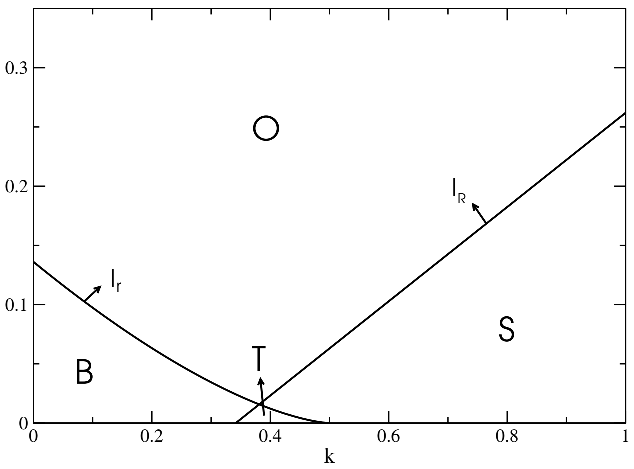

Fig. 9. Two bifurcation curves of the simple qualitative model.

presents a necessary and sufficient condition for the existence of only one real root. Similar mathematical assertions can be found in the above mentioned paper of Nitzan *et al.* [1974]. It follows that below the bifurcation curve $l_r(k)$ (see Fig. 9), the system (10) has three steady states, and above $l_r(k)$, it has only one equilibrium state under the assumption that $R = -(a + d) > 0$.

The above assertions follow from the numerical results of the Lyapunov values. As mentioned before, on the bifurcation curve (i) we have $L_1 = 94.5665 > 0$. Now we can indicate that on the bifurcation curve (ii) the corresponding Lyapunov value is $l_1 = -2.6552$, which is important since this value is different from zero. In accordance with the theory of Lyapunov values [Georgiev, 2003b], l_1 does not vanish at the bifurcation curve $l_r(k)$ and shows that the corresponding steady state is unstable. Moreover, it follows that hard transition from three to one steady states takes place at these region.

Figure 9 is one of the final results in this paper. It is shown that for practical computations there are three main regions in the parameter plane (l, k), where the considered qualitative model (10) shows essentially different dynamical behavior. Three steady states (one unstable and two stable) exist in the area B, which is the region of bistability, where only forced oscillations of the system (10) are possible. In this case, we have indeed the behavior considered from Novak and Tyson for budding yeast [Novak *et al.*, 2001]. By increasing the parameter k, the region O can be entered, where only one stable steady state exists. The vanishing of the other two steady states is of hard loss type. If the system is in region O, then further increase of k leads to transition from region O to S, where finite self-oscillations occur. This type of transition is called "hard self-excitation" and belongs to the type of bifurcation of hard stability loss. Thus both transitions from B to O and O to B are of this type.

As for the triangle T, we should note that its two smaller sides cannot be considered as bifurcation boundaries of types (i) and (ii), because the corresponding inequalities are not satisfied there. That is why the Lyapunov values theory cannot be applied to distinguish soft and hard loss of stability at these sides of T. Nevertheless, according to the general theorems of the nonlinear differential equation theory [Neimark & Landa 1992], we can assert that in the triangle T, the system has three unsteady states, all surrounded by one limit cycle.

6. Further Results from the Computation of Lyapunov Values

It will be shown however, that not the whole curve $l_r(k)$ is a bifurcation boundary of hard loss of stability. For values larger than $k = 1.0833$ a type of soft self-excitation takes place.

For values smaller than $k = 1.0833$, the Lyapunov value becomes negative and in accordance with Theorem 2, we obtain soft loss of stability. In Fig. 10 the graphical dependence of the Lyapunov value on the system parameter k is shown. We call it Lyapunov values curve. The horizontal line presents the two curves $l_r(k)$ and $l_R(k)$ which look like a straight line because of the large vertical scale (too large Lyapunov absolute values). If we reduce the vertical scale, the graphical presentation of Lyapunov values curve and bifurcation curve is shown in Fig. 11.

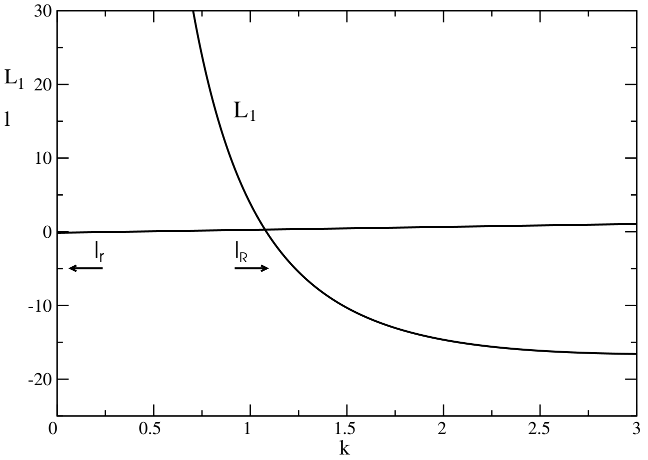

Fig. 10. Dependence of the Lyapunov value L_1 on the parameter k.

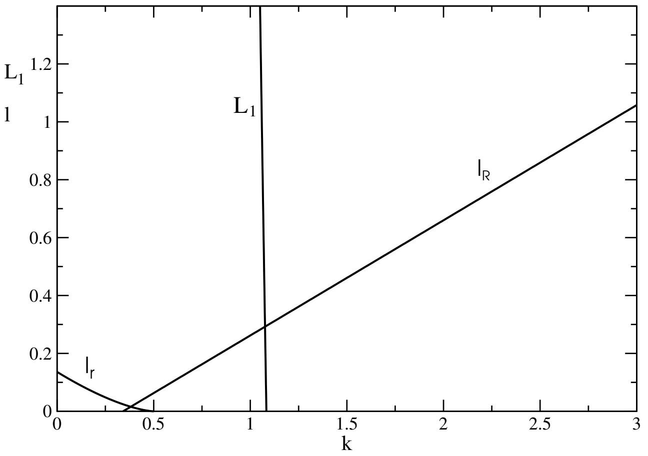

Fig. 11. Bifurcation boundaries and the Lyapunov value L_1.

Now, the two bifurcation curves look like those presented in Fig. 9, but the Lyapunov values curve is presented by an almost straight vertical line because of the very small vertical scale. In view of these results we can assert that the loss of stability at transition through the bifurcation boundary $l_R(k)$ can both be hard and soft.

In detail, the formula (17) for the Lyapunov value can be transformed in an expression of the system parameters including k

$$L_1 = \frac{3\pi n^2\left(2m - \frac{ks}{n} - \frac{1}{T}\right)}{4\left(\frac{ks}{n} - \frac{1}{T}\right)\sqrt{\frac{\left(\frac{ks-1}{T}\right)}{T}}}, \tag{20}$$

which represents the Lyapunov value in function of the parameter k, as shown in Figs. 10 and 11. From the condition for vanishing right-hand side of Eq. (20) we obtain a formula for critical value of the parameter k

$$k = \frac{n(2mT-1)}{sT}, \tag{21}$$

at which the Lyapunov value changes its sign. By replacing the parameter values (11) in Eq. (21), we obtain the above-mentioned numerical value $k = 1.0833$, which separates the bifurcation curve in two parts: hard self-excitation and soft self-excitation.

It is of importance to note here the critical role of the parameter k which determines the transition from forced oscillatory (bistability) to self-oscillatory (limit cycle) behavior of the cell cycle dynamics. From one side k is a coefficient of proportionality in the dynamical part of reciprocal cell mass z, on the other side it is a bifurcation parameter leading the system from regions B to S and vice versa. Thus, the larger k is the influence on the reciprocal mass increases and the system goes to the self-oscillatory region S. Vice versa, for smaller k the dynamical part of reciprocal mass is smaller and system moves to the region of forced oscillations B, at which the well-known check points take place [Novak *et al.*, 2001].

7. Concluding Remarks

In the literature, the question for soft or hard loss of stability of dynamical models of cell cycle control has not been considered with a necessary profundity. By now, the analysts and modelers establish only the existence of bistability and self-oscillations [Petrov & Timmer, 2004; Petrov *et al.*, 2004; Qu *et al.*, 2003a, 2003b] without treating the question of bifurcation character, despite the fact that it concerns essentially the debate point for norm and pathology in the cell cycle control [Tyson *et al.*, 2001, 2002, 2003; Novak *et al.*, 2001; Li *et al.*, 2004; Petrov & Timmer, 2004]. This paper presents an initial attempt to apply the theory of Lyapunov values to analyzing the bifurcation behavior of Novak–Tyson type at transition from bistability to limit cycle dynamics and vice versa.

Frog eggs and budding yeast are widespread subjects of experimental and theoretical investigations of cell cycle kinetics. Previously, it has been shown that the appearance and disappearance of a limit cycle in the cell cycle control model of frog eggs are always due to a soft loss of stability type [Petrov *et al.*, 2004]. In this paper we demonstrate analytically that the cell cycle of budding yeast can be modeled on the basis of Novak–Tyson Z-shaped diagram as a self-oscillation obtained by hard-excitation of one stable dynamics, which has also been obtained after bifurcation from bistable behavior of the cell kinetics. Thus, the transition from bistability to limit cycle dynamics and vice versa takes place in the cell cycle of budding yeast. Contrary to the frog eggs cell cycle, the appearance and disappearance of a limit cycle in the cell cycle dynamics of budding yeast are both of hard and soft loss of stability.

As mentioned in Sec. 4, the above conclusions are also valid for Fitzhugh–Nagumo model, if the term "cell cycle" is exchanged by "cell cycle" and the expression "budding yeast cell cycle" should be replaced by "single action potential". In this way, the interpretation of the "all or nothing"-scenario of nerve excitation [Fitzhugh, 1960, 1961] can be explained in terms of bistability behavior in the considered model. On the other hand, the "frog eggs cell cycle" should be substituted by the expression "repetitive action potential" and can be interpreted in the sense of limit cycle behavior. It is possible that the dynamical mechanism of cell cycle and nerve excitation is very similar, but that means that the Fitzhugh–Nagumo model and Novak–Tyson bifurcation diagram might have some paradigmatic importance, which merits to be analyzed in more detail in the future.

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