

# A Transient-State Analysis of Tyson's Model for the Cell Division Cycle by Means of KCC-Theory

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**Abstract.** The transient-state stability analysis for the trajectories of Tyson's equations for the cell-division cycle is given by the so-called KCC-Theory. This is the differential geometric theory of the variational equations for deviation of whole trajectories to nearby ones. The relationship between Lyapunov stability of steady-states and limit cycles is thoroughly examined. We show that the region of stability (where, in engineering parlance, the system is “hunting”) encloses the Tyson limit cycle, while outside this region the trajectories exhibit aperiodic behaviour.

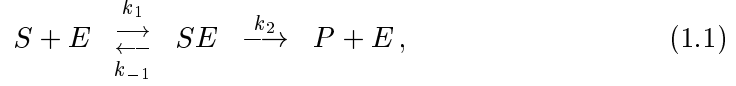
## 1. Some Biology

Living biological systems are very complex but, at the same time, they are highly ordered in a remarkably efficient way. Such systems store the information and the means necessary for cellular reproduction, organization, control, etc. in each generation. This information is stored for any particular species in the genome, which is the total collection of genetic material in the chromosomes of an organism. This genetic information is encoded in molecules of DNA, which is a double helix molecule containing the four bases: adenine (A), guanine (G), cytosine (C) and thymine (T). It is known that a large number of cell types are capable of protein production and its self-regulation and control. The regulatory mechanism in cellular physiology starts with the synthesis of mRNA copied from a gene. This process is called *transcription*.

Next, a protein (an enzyme) is generated according to the genetic code carried by mRNA. This second step is called *translation*. The enzymes act on definite compounds called substrates. There are several biochemical reactions in which the enzymes are involved, but we mention here only *association* (two proteins

combine together to form a complex) and *disassociation* (a substrate splits in two reaction products: an enzyme and a product).

For example, consider the simple reaction



where  $k_1, k_{-1}, k_2$  are constant rate parameters. The double arrow symbol  $\rightleftharpoons$  indicates that the reaction is reversible, while the single arrow  $\rightarrow$  indicates that the reaction can go only one way. The overall mechanism is the conversion of the substrate  $S$ , via the enzyme catalyst  $E$ , into a product  $P$ . One molecule of  $S$  combines with one molecule of  $E$  to form one of the complex  $SE$ , which eventually produces one molecule of  $P$  and one molecule of  $E$ , again.

The *Law of mass action* states that the rate of a reaction is proportional to the product of the concentrations of the reactants. If we denote by  $s, e, c, p$  the concentrations of the reactants  $S, E, SE, P$ , then (1.1) leads to the following system of differential equations:

$$\begin{aligned} \frac{ds}{dt} &= -k_1 es + k_{-1} c, & \frac{de}{dt} &= -k_1 es + (k_{-1} + k_2) c, \\ \frac{dc}{dt} &= k_1 es - (k_{-1} + k_2) c, & \frac{dp}{dt} &= k_2 c. \end{aligned} \quad (1.2)$$

The method of describing biochemical reactions of type (1.1) by means of systems of differential equations of type (1.2) is called the Michaelis-Menten kinetics. Tyson used a set of six equations similar to (1.2), but more complex, to model the cell-cycle [10].

## 2. Tyson's Model for the Cell Division Cycle

Somatic cells reproduce by duplicating their contents and then dividing in two. This cell-division cycle is the fundamental means by which all somatic cell types are duplicated in an individual. The cell cycle has four phases: interphase, mitosis, synthesis and some gap phases.

$$\underbrace{|\xrightarrow{G_1}| |\xrightarrow{S}| |\xrightarrow{G_2}|}_{\text{interphase}} \underbrace{|\xrightarrow{M}|}_{\text{division}}. \quad (2.1)$$

During interphase the cell grows continuously; during mitosis (M) it divides (mitosis is the process of nuclear division). DNA replication takes place in the part of interphase known as synthesis (S). The  $G_1$  phase is the gap between the completion of mitosis (M) and the beginning of DNA synthesis. The  $G_2$  phase is the interval between the end of DNA synthesis and the beginning of mitosis. The standard cell cycle (for adult somatic cells) is generally quite long in mammals, its length depending on the type of cell (for brain cells a very long period, and for the liver a shorter period). Cells in  $G_1$ , if they have not yet committed themselves

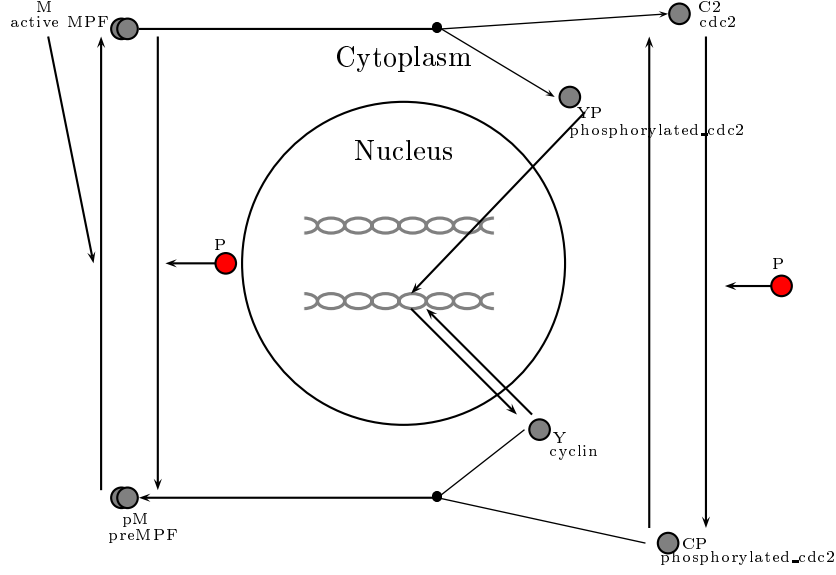


Fig. 1: The cell cycle regulatory pathway.

to DNA replication, can pause in their progress through the cell cycle and enter a specialized resting state, often called  $G_0$ , where they can remain for days, weeks or even years before resuming proliferation [1]. This is a very important state because if the  $G_1$  phase is too short, or  $G_0$  is missing, the cell continues to divide endlessly. This abnormal behaviour of the cell is usually called *cancer*.

The shortest (eucaryotic) division cycle is the *early embryonic cell cycle* that occurs in many embryos immediately after fertilization, serving to subdivide a large egg cell into many small cells as quickly as possible. In these cycles no growth occurs and the  $G_1, G_2$  phases are drastically curtailed [1].

$$| \xrightarrow{S} | \xrightarrow{M} | \xrightarrow{S} | \xrightarrow{M} | \longrightarrow \dots \quad (2.2)$$

The mitotic cycles in both embryonic and somatic cells appear to be controlled by the action of an enzyme, the maturation promoting factor (MPF), that peaks abruptly at metaphase (M). The enzyme MPF is a heterodimer composed of two other proteins: *cyclin* and a protein kinase (*cdc2*). The interplay between *cyclin* and *cdc2* in generating MPF is understood in detail.

Based on the Michaelis-Menten theory, and after considerable simplification of the chemistry, the cell cycle regulatory pathway can be expressed by the following system of differential equations of Tyson:

$$\begin{aligned} \frac{du}{dt} &= (v - u)(k + k_4 u^2) - k_6 u, \\ \frac{dv}{dt} &= k_1 - k_6 u, \end{aligned} \quad (2.3)$$

where  $u$  and  $v$  are the relative concentration of active MPF and total cyclin minus degraded cyclin relative to total  $cdc2$ , respectively [10]. The parameter ranges are as follows:

- $k = 0.018 \text{ min}^{-1}$  is the rate constant for the dephosphorylation of  $cdc2$ ,
- $k_1 = 0.015 \text{ min}^{-1}$  is the rate constant of *cyclin* synthesis,
- $k_4 = 10 - 1000 \text{ min}^{-1}$  (*adjustable*) is the rate constant describing the autocatalytic activation of MPF by the dephosphorylation of  $cdc2$ ,
- $k_6 = 0.1 - 10 \text{ min}^{-1}$  (*adjustable*) is the rate constant describing breakdown of the active  $cdc2$ –*cyclin* complex.

Tyson [10] has shown that, depending on the values of  $k_4$  and  $k_6$ , the cell cycle regulatory system exhibits three different *modes of control*. For small values of  $k_6$ , the system displays a steady state of high MPF activity, which can be associated with the metaphase arrest of unfertilized eggs (A). For moderate values of  $k_6$ , the system executes autonomous oscillations modelling rapid cell cycling in early embryos (B). For large values of  $k_6$ , the system is attracted to an excitable steady state of low MPF activity, which corresponds to interphase arrest of resting somatic cells or to growth-controlled bursts of MPF activity in proliferating somatic cells (C).

In the following, we are going to use the KCC-theory in order to gain information on the Jacobi stability of the total cyclin trajectory, denoted by  $v(t)$  in the differential system (2.3). It is known that the level of MPF is the parameter that leads the cell through the cell cycle. We now briefly remark here on the role of cyclin.

It is known that the cyclin accumulation and destruction control the activation and inactivation of MPF. In other words, the cyclin has to build up to a threshold concentration to activate MPF, and the destruction of cyclin is coupled to inactivation of MPF and exit from mitosis. This is relevant for the cell cycle because if the destruction of cyclin is delayed, or the level of cyclin does not decrease below threshold value, the cell stays in mitosis, i.e. divides continuously. This is a model of cancer dynamics.

### 3. The KCC Theory

We now study the Tyson model given by the system (2.3) by means of KCC theory in the formalism of P.L. Antonelli [2, 3].

Let us recall first some basics. Let  $(x^1, \dots, x^n) = (x)$ ,

$$\left( \frac{dx^1}{dt}, \frac{dx^2}{dt}, \dots, \frac{dx^n}{dt} \right) = \left( \frac{dx}{dt} \right) = \dot{x}$$

and  $t$  be  $2n+1$  coordinates of an open connected subset  $\Omega$  of the Euclidean  $(2n+1)$ -dimensional space  $\mathbb{R}^n \times \mathbb{R}^n \times bBR^1$ . And let us consider a second order differential

equation (SODE) of the form

$$\frac{d^2 x^i}{dt^2} + g^i(x, \dot{x}, t) = 0, \quad i \in \{1, 2, \dots, n\}, \quad (3.1)$$

where each function  $g^i(x, \dot{x}, t)$  is  $C^\infty$  in a neighbourhood of some initial conditions  $((x)_0, (\dot{x})_0, t_0)$  in  $\Omega$ .

In order to find the basic differential invariants of the system (3.1) under the non-singular coordinate transformations

$$\begin{aligned} \bar{x}^i &= f^i(x^1, \dots, x^n), & i \in \{1, 2, \dots, n\}, \\ \bar{t} &= t, \end{aligned} \quad (3.2)$$

we define the KCC-covariant differential of a contravariant vector field  $\xi^i(x)$  on the open subset  $\Omega$  by

$$\frac{D\xi^i}{dt} = \frac{d\xi^i}{dt} + \frac{1}{2} g_{;r}^i \xi^r, \quad (3.3)$$

where the semicolon ; indicates partial differentiation with respect to  $\dot{x}$ . The idea of this approach belongs to Kosambi [6] and to E. Cartan [4] (who corrected his work) and S. S. Chern (for the most general version) [5]. The Einstein's summation convention is used throughout.

Using (3.3), the system (3.1) becomes

$$\frac{D\dot{x}^i}{dt} = \frac{1}{2} g_{;r}^i \dot{x}^r - g^i = \varepsilon^i, \quad (3.4)$$

where  $\varepsilon^i$  defined here is a contravariant vector field on  $\Omega$  and is called the *first KCC-invariant*. It is interpreted as external force [2].

If the trajectories  $x^i(t)$  of (3.1) are varied into nearby ones according to

$$\bar{x}^i(t) = x^i(t) + \xi^i(t) \eta, \quad (3.5)$$

where  $\eta$  denotes a parameter with  $|\eta|$  small and where  $\xi^i(t)$  are the components of some contravariant vector field defined along  $x^i$ . Substituting in (3.1) and taking the limit  $\eta \rightarrow 0$  one obtains the variational equations

$$\frac{d^2 \xi^i}{dt^2} + g^i_{;r} \frac{d\xi^r}{dt} + g^i_{,r} \xi^r = 0, \quad (3.6)$$

where the comma , indicates partial differentiation with respect to  $x^r$ .

Using now the KCC-covariant differential (3.3), one obtains (3.6) in the covariant form

$$\frac{D^2 \xi^i}{dt^2} = P_r^i \xi^r, \quad (3.7)$$

where

$$P_j^i = -g^i_{,j} - \frac{1}{2} g^r g^i_{;r;j} + \frac{1}{2} \dot{x}^r g^i_{,r;j} + \frac{1}{4} g^i_{;r} g^r_{,j} + \frac{1}{2} \frac{\partial g^i_{;j}}{\partial t} \quad (3.8)$$

is called the *second KCC-invariant* of the system (3.1), or *deviation curvature tensor*. Its eigenstructure is an alternative to the classical Floquet theory, with the eigenvalues of  $P_j^i$  replacing the Floquet exponents [8]. Thus, the eigenvalues of  $P_j^i$  have negative real parts if and only if the Floquet exponents have negative real part. Note that (3.7) is the *Jacobi field equation* when the starting system (3.1) are geodesic equations in either Finsler or Riemannian geometry. This justifies our usage of the term *Jacobi stability* for KCC-Theory.

The third, fourth and fifth invariants are:

$$\begin{aligned} R_{jk}^i &= \frac{1}{3} (P_{j;k} - P_{k;j}), \\ B_j^i{}_{k\ell} &= R_{jk;\ell}, \\ D_j^i{}_{k\ell} &= g_{;j;k;\ell}^i. \end{aligned} \tag{3.9}$$

A basic result of the KCC-theory is the following

**THEOREM A** *Two SODE's of form (3.1) on  $\Omega$  can be locally transformed, relative to (3.2), one into other, if and only if their five KCC-invariants  $\varepsilon$ ,  $P_j^i$ ,  $R_{jk}$ ,  $B_j^i{}_{k\ell}$ ,  $D_j^i{}_{k\ell}$  are equivalent tensors. In particular, there are local coordinates  $(\bar{x})$  for which  $g^i(\bar{x}, \dot{\bar{x}}, t) = 0$  if and only if all five KCC-tensors vanish.*

In order to clarify, within Lyapunov theory, the distinction between the stability of a steady-state, as given in the linear analysis, and Jacobi stability of whole trajectories or transient-states, as considered in KCC-analysis, let us consider the one-dimensional case

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= -g(x, y), \end{aligned} \tag{3.10}$$

with a steady-state given by  $(x_0, y_0)$ . The variational equation (3.6) in this case takes the form

$$\ddot{\xi} + (g_{;1}^1)_0 \dot{\xi} + (g_{;1}^1)_0 \xi = 0, \tag{3.11}$$

where the coefficients are evaluated at some *fixed reference trajectory*  $(x_0(t), y_0(t))$  and are functions of the parameter along this curve,  $t$ . In case they are evaluated for the steady-state  $(x_0, 0)$ , and are therefore constants, we get the *linear stability analysis* equation, which results from expanding  $g(x, y)$  in first order around the steady-state. As KCC-analysis starts with a *reference trajectory*, i.e., a fixed solution of (3.1), which is not a steady-state, it is concerned with Lyapunov stability of *whole* trajectories, while *linear* stability analysis is based on deviation with respect to a *point*, namely, the steady-state [8].

Note that, if we evaluate  $P_1^1$  at the steady-state  $(x_0, 0)$ , then we will have simply  $P_1^1 = -g_{;1}^1 + (g_{;1}^1)^2/4$ , and, from the linear analysis of (3.11), the roots of the characteristic polynomial are  $r = -(g_{;1}^1)/2 \pm \sqrt{P_1^1}$ . Thus, *the sign of the damping coefficient  $(g_{;1}^1)_0$  determines the stability of the steady-state, but has no influence on the curvature  $P_1^1$* . It is also true that replacing  $t$  by  $-t$  changes the sign of

the damping coefficient and that, generally, the equation (3.7) is invariant under time-reversal as long as  $g^i$  is independent of  $t$ . Therefore, there is a Lyapunov stability analysis for steady-states (so called linear analysis) and there is a Lyapunov stability analysis for whole trajectories (also known as KCC- or Jacobi stability analysis), and these are complementary but *distinct* from one another.

#### 4. KCC Theory for Tyson Model

In order to study Tyson's model of the cell cycle by means of the KCC theory presented above, we first eliminate the variable  $u$ . The Tyson model (2.3) can be written as a SODE:

$$\ddot{x} + g(x, y, t) = 0, \quad (4.1)$$

where we have put  $x = v$ , and  $y = dx/dt$  and

$$g = A y^3 + (B x + C) y^2 + (D x + E) y + F x + G. \quad (4.2)$$

The constants  $A, B, C, D, E, F, G$  can be expressed by means of the parameters  $k_1, k_4, \dots$  from (2.3). Applying KCC theory, we investigate the stability of production of the total cyclin (relative to the total *cdc2*).

The SODE (3.1), for  $n = 1$ , has deviation curvature

$$P_1^1 = -g_{,1}^1 - \frac{1}{2} g^1 g_{;1;1}^1 + \frac{1}{2} y g_{,1;1}^1 + \frac{1}{4} g_{;1}^1 g_{;1}^1 \quad (4.3)$$

or, taking  $g^1 = g$ , as in (4.2),

$$\begin{aligned} P_1^1 = & -\frac{3}{4} A^2 y^4 + (-ABx - AC) y^3 + \left( -\frac{3}{2} EA - \frac{3}{2} DAx \right) y^2 \\ & + \left( -\frac{1}{2} D - 3FAx - 3GA \right) y + \left( \frac{1}{4} D^2 - FB \right) x^2 \\ & + \left( -GB + \frac{1}{2} DE - FC \right) x - F - GC + \frac{1}{4} E^2 \end{aligned} \quad (4.4)$$

obtained by means of the computer algebra package FINSLER [9], based on MAPLE [7].

We consider an one-dimensional SODE of form (4.1) where the function  $g(x, y, t)$  is  $C^\infty$  in a neighbourhood of some initial condition  $(x_0, y_0, t_0) \in \Omega \subset \mathbb{R}^3$ . In one-dimensional case, the Jacobi field equation, or variational equation in covariant form (3.7),  $D^2 \xi^1 / dt^2 = P_1^1 \xi^1$ , indicates that the deviation will be *periodic*, as for the *simple harmonic oscillator*, if  $P_1^1 < 0$ , and *aperiodic* otherwise, as for the *wave-guide equation* (similar to an harmonic oscillator with reverse sign), where the trajectories diverge. We may therefore state [2]

##### PROPOSITION 4.1

a. *The trajectories of (4.1) are Jacobi stable in  $\Omega$  if and only if  $P_1^1 < 0$  everywhere in  $\Omega$ . This is equivalent to periodic deviation for (3.7).*

b. *The trajectories of (4.1) are Jacobi unstable in  $\Omega$  if and only if  $P_1^1 \geq 0$  everywhere in  $\Omega$ . This is equivalent to aperiodic deviation for (3.7).*

Let us begin our calculations. Using the above notations, from (2.3) we get

$$g^1 = \frac{k_4 y^3}{k_6^2} + \frac{(x k_6 k_4 - 3 k_1 k_4) y^2}{k_6^2} + \frac{(k_6^3 - 2 x k_6 k_4 k_1 + k k_6^2 + 3 k_4 k_1^2) y}{k_6^2} \quad (4.5)$$

$$+ \frac{x k_6^3 k + x k_6 k_4 k_1^2 - k_1 k_6^3 - k_1 k k_6^2 - k_4 k_1^3}{k_6^2}, \quad (4.6)$$

and therefore we have  $A = k_4/k_6^2$ ,  $B = k_4/k_6$ ,  $C = -3k_1 k_4/k_6^2$ ,  $D = -2k_4 k_1/k_6$ ,  $E = (k_6^3 + k k_6^2 + 3k_4 k_1^2)/k_6^2$ ,  $F = k_6 k + (k_4 k_1^2)/k_6$ ,  $G = (-k_1 k_6^3 - k_1 k k_6^2 - k_4 k_1^3)/k_6^2$ . The final expression for  $P_1^1$  thus becomes

$$\begin{aligned} P_1^1 = & -\frac{3}{4} \frac{k_4^2 y^4}{k_6^4} + \left( -\frac{k_4^2 x}{k_6^3} + 3 \frac{k_4^2 k_1}{k_6^4} \right) y^3 \\ & + \left( 3 \frac{k_4^2 k_1 x}{k_6^3} - \frac{1}{4} \frac{6 k_4 k_6^3 + 6 k_4 k k_6^2 + 18 k_4^2 k_1^2}{k_6^4} \right) y^2 \\ & + \left( -\frac{1}{4} \frac{(12 k_6 k_4^2 k_1^2 + 12 k_4 k_6^3 k) x}{k_6^4} \right. \\ & \left. - \frac{1}{4} \frac{-16 k_4 k_1 k_6^3 - 12 k_4^2 k_1^3 - 12 k_4 k_1 k k_6^2}{k_6^4} \right) y - k_4 k x^2 \\ & - \frac{1}{4} \frac{(-4 k_6 k_4^2 k_1^3 - 12 k_4 k_6^3 k_1 k) x}{k_6^4} \\ & - \frac{1}{4} \frac{2 k_6^5 k + 3 k_4^2 k_1^4 + 10 k_6^3 k_4 k_1^2 - k^2 k_6^4 + 6 k_4 k_1^2 k k_6^2 - k_6^6}{k_6^4}. \end{aligned}$$

Let us remark that the curvature tensor  $P_1^1$  is a fourth order polynomial in  $y$  whose coefficients are functions of  $x$ , the parameters  $k_4$  and  $k_6$ , as well as the other  $k$ 's.

Let us consider the steady states, say  $(u_0, v_0)$  of the system (2.3). This are the solutions of the system

$$\begin{aligned} (v - u)(k - k_4 u^2) - k_6 u &= 0, \\ k_1 - k_6 u &= 0. \end{aligned}$$

In our notation, by eliminating the variable  $u$ , we obtain as steady state the point  $(x_0, y_0) \equiv (v_0, (dv/dt)_0) \in TM$ , where

$$\begin{aligned} x_0 &= \frac{k_1(k_6^3 + k k_6^2 + k_4 k_1^2)}{(k k_6^2 + k_4 k_1^2) k_6} \\ y_0 &= 0. \end{aligned} \quad (4.7)$$



In Tyson's work the parameters  $k$  and  $k_1$  are constant, while  $k_4$  and  $k_6$  vary within a range, describing *three distinct modes* of the cell developmental cycle. Here, we will keep  $k_4$  also constant, as it suffices to vary  $k_6$  to span all the modes. So, we will take

$$k = 0.018, \quad k_1 = 0.015, \quad k_4 = 180, \quad (4.8)$$

leading to specific boundary  $k_6$  values for regions A, B, C, namely

$$\begin{aligned} \text{mode A: } & [0.1, 0.2), \\ \text{mode B: } & [0.2, 1.5), \\ \text{mode C: } & [1.5, 10]. \end{aligned}$$

With these values, the steady state (4.6) becomes  $x_0 = x_0(k_6)$ ,  $y_0 = 0$ . We wish now to determine  $P_1^1$  in the neighbourhood of  $(x_0, y_0)$ . By continuity of  $P_1^1$ , it will suffice to compute the curvature coefficients  $P_1^1(x_0, y_0)$ . The equation  $P_1^1(x_0, y_0) = 0$  has two real solutions:

$$k_6^{(1)} = 0.1924781307, \quad k_6^{(2)} = 1.900932822,$$

and the graph of the function  $P_1^1(x_0, y_0)$  against  $k_6$ , divided into the three distinct regions A, B, C, are as follows.

Next, we will allow the value of the parameter  $k_4$  to vary along its range, plotting  $P_1^1(x_0, y_0)$  against the two control parameters  $k_4$  and  $k_6$ . The results of Jacobi stability analysis are compatible with the classical phase plane analysis (see last paragraphs in section 3 for detail).

Next, it follows graphs of  $P_1^1(x, y)$  for *transient states* in the regions A, B and C. We have chosen values of  $k_6$  within each region such that, for the particular point  $(x_0, y_0)$ , the steady-state within the  $(x, y)$ -range considered,  $P_1^1(x_0, y_0)$  assumes a special value. In the graphs, we have  $(v, vt) \equiv (x, y)$  as variables.

For mode A, we took  $k_6$  such that  $P_1^1(x_0, y_0) = 0$ , the steady-state around which trajectories start to converge, as they do all along region B. This point may be interpreted as the response of the (unfertilized) egg to a chemical change that will lead to rapid growth in the following stage, such as fertilization.

For mode B, we have two graphs, one for each local minima within this region of negativity for  $P_1^1(x_0, y_0)$ . The first, or deepest, can be associated with Tyson's limit cycle, and the second with Tyson's excitable switch.

For mode C, we again took  $k_6$  such that  $P_1^1(x_0, y_0) = 0$ , marking the limit of the (small)  $k_6$ -range within this region where  $P_1^1(x_0, y_0)$  is negative. This point indicates the limit in  $k_6$ -values for which the cell "switch back" into region B, typical of the excitable state described in Tyson's work.

We can see with the last four graphs above that none of the characteristics chosen for  $P_1^1(x_0, y_0)$  (namely,  $P_1^1(x_0, y_0) = 0$  for graphs 7 and 10, and  $P_1^1(x_0, y_0)$  a local minima for graphs 8 and 9) are preserved as we move away from the steady-states into transient ones,  $(x, y)$ . Those characteristics, linked to known results from Tyson's model, occur at the steady-states, the dynamics changing when the

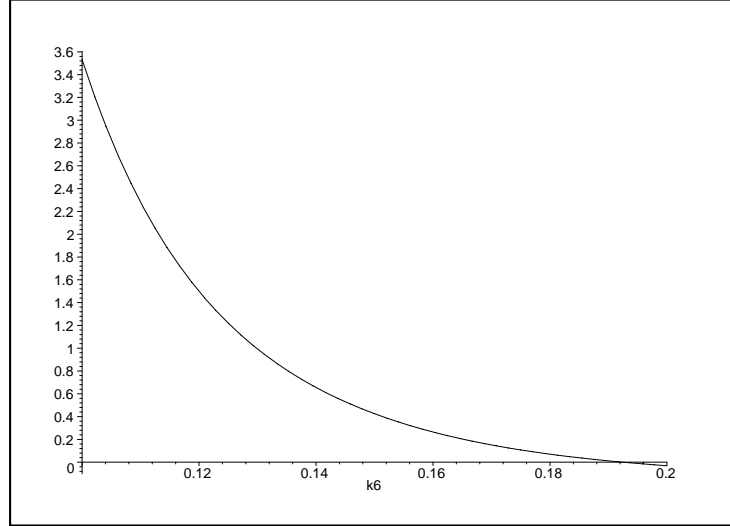


Fig. 2: This graph shows  $P_1^1(x_0, y_0)$  at the steady-states for  $k_6$  varying within region A. The deviation vector is aperiodic for most of the range. Note that it becomes periodic for  $k_6$  values close to the B range.

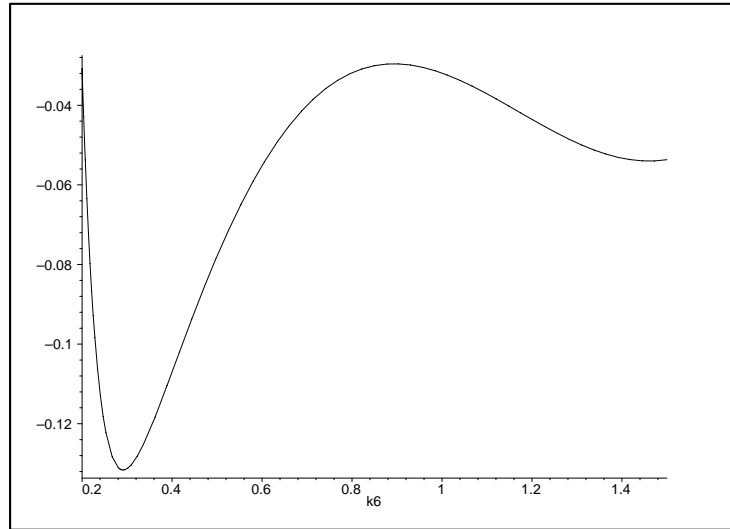


Fig. 3: This graph shows  $P_1^1(x_0, y_0)$  at the steady-states for  $k_6$  varying within region B. The deviation vector is periodic for all of the range.

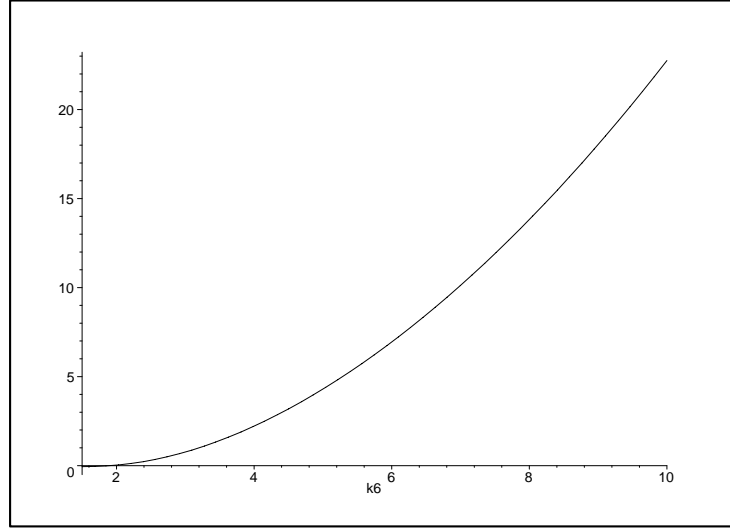


Fig. 4: This graph shows  $P_1^1(x_0, y_0)$  at the steady-states for  $k_6$  varying within region C. The deviation vector is aperiodic for most of the range.

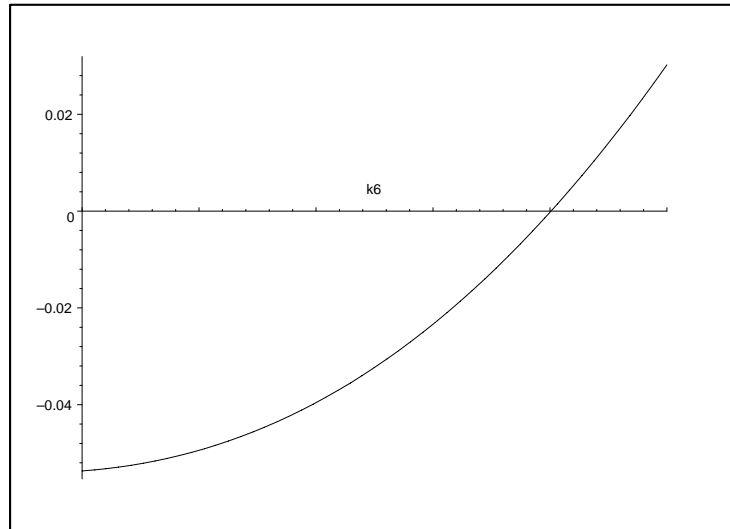


Fig. 5: This graph shows  $P_1^1(x_0, y_0)$  at the steady-states for  $k_6$  varying within the beginning of region C. The deviation vector is still periodic for  $k_6$  values close to the B range.

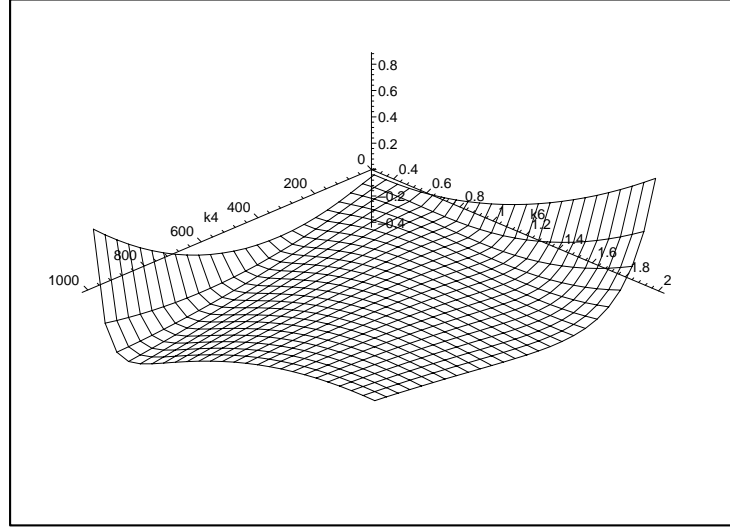


Fig. 6: This graph shows  $P_1^1(x_0, y_0)$  at the steady-states against  $k_4$  and  $k_6$ , for the whole range of  $k_4$  and the range of  $k_6$  for which negative values of  $P_1^1(x_0, y_0)$  occur, describing essentially mode B in the model. We can see that, for every value of  $k_4$  there are two points of minimum  $P_1^1(x_0, y_0)$ , corresponding to two values of  $k_6$  (associated respectively to the limit cycle and excitable switch in the model), the first always being deepest. These valleys increase in depth with increasing  $k_4$  and  $k_6$ .

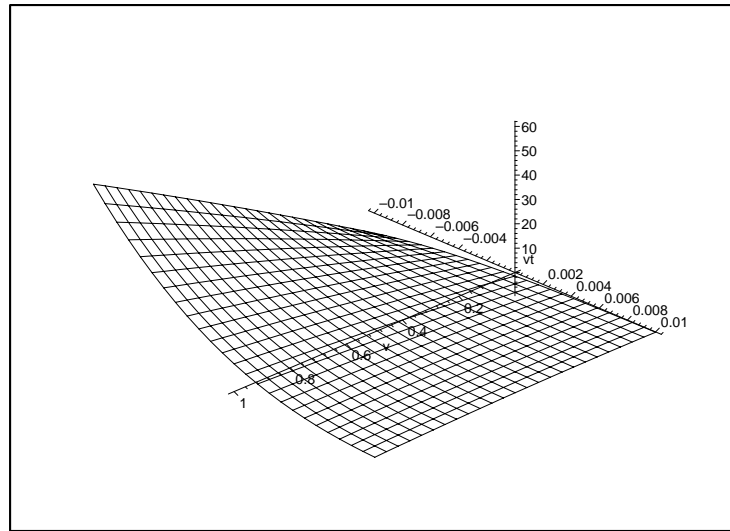


Fig. 7: This graph shows  $P_1^1$  against  $x$  ( $v$  in the graph) and  $y$  ( $vt$  in the graph) for  $k_4=180$  and  $k_6=0.1924781307$ , the unique  $k_6$ -value within region A such that  $P_1^1(x_0, y_0) = 0$  at the steady-state ( $x = 0.09143007729$ ,  $y = 0$ ).

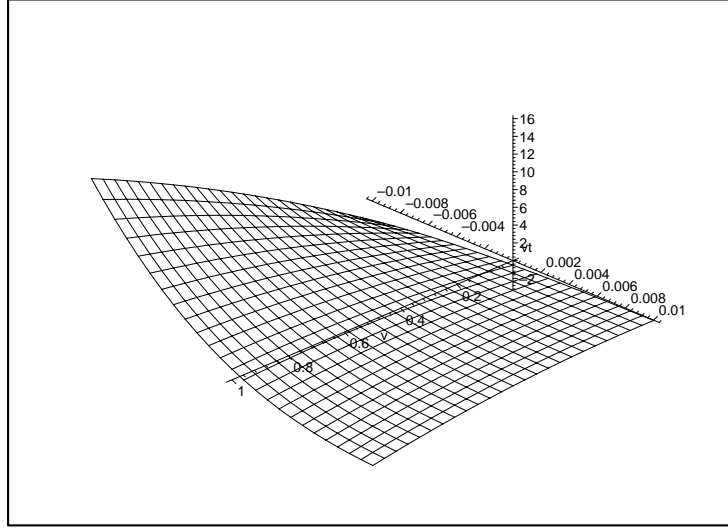


Fig. 8: This graph shows  $P_1^1$  against  $x$  ( $v$  in the graph) and  $y$  ( $vt$  in the graph) for  $k_4=180$  and  $k_6=0.2911043274$ , for which  $P_1^1(x_0, y_0)$  (Fig. 3) is most negative (associated with the limit cycle in the model), corresponding to the point ( $v = x_0 = 0.08177456483$ ,  $vt = y_0 = 0$ ,  $P_1^1 = -0.1316018785$ ) in this graph.

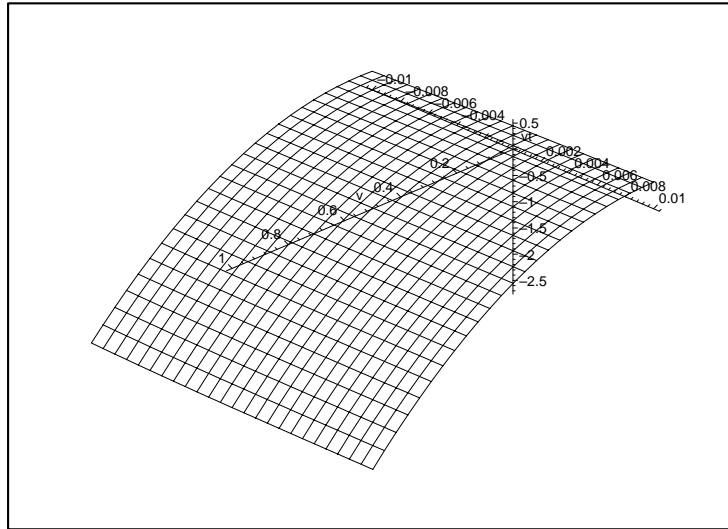


Fig. 9: This graph shows  $P_1^1$  against  $x$  ( $v$  in the graph) and  $y$  ( $vt$  in the graph) for  $k_4=180$  and  $k_6 = 1.460381230$ , for which  $P_1^1(x_0, y_0)$  (Fig. 3) has its second minimum point (associated with the excitable switch in the model), corresponding to the point ( $v = x_0 = 0.4157874576$ ,  $vt = y_0 = 0$ ,  $P_1^1 = -0.0540182526$ ) in this graph.

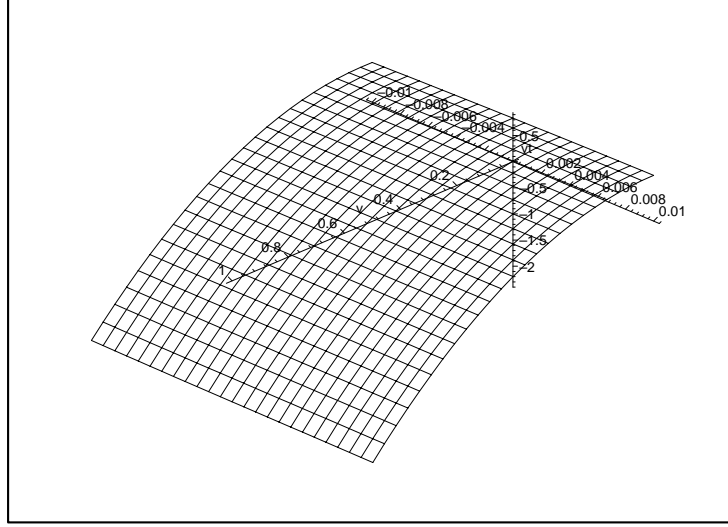


Fig. 10: This graph shows  $P_1^1$  against  $x$  ( $v$  in the graph) and  $y$  ( $vt$  in the graph) for  $k_4=180$  and  $k_6=1.900932822$ , the unique  $k_6$ -value within region C such that  $P_1^1(x_0, y_0) = 0$  at the steady-state ( $x = 0.5214518040$ ,  $y = 0$ ).

system enters transient states. The perturbations around steady-states must be rather small in order to preserve expected behaviour from the system.

On the other hand, the transient analysis shows that, for values of  $k_6$  up to middle range within region B, the system goes unstable ( $P_1^1$  positive) when  $v$  (the total cyclin) is large and decreases ( $vt \equiv dv/dt < 0$ ). The larger  $v$  and  $|vt|$  are, the more unstable the dynamics. Some stability ( $P_1^1$  negative) is observed when  $v$  is small and decreases ( $vt \equiv dv/dt < 0$ ). As for increasing  $v$  ( $vt \equiv dv/dt > 0$ ), the stability is unaffected, regardless the amount of  $v$  (Figs.7 and 8).

From middle range  $k_6$  values within region B onwards, the dynamics changes and becomes stable ( $P_1^1$  negative) for small values of  $v$  and unstable ( $P_1^1$  positive) for large ones, unresponsive of  $vt \equiv dv/dt$  (Fig. 9 and 10).

## 5. Conclusion

Evaluating the deviation curvature tensor  $P_1^1$ , associated with the second-order ODE obtained from the original equations, at the steady-states of the system give us information about the behaviour of trajectories, or transient (non-steady) states, in an open region, or neighbourhood, of these steady-states. In region A, the unfertilized egg stage, the deviation vector is aperiodic for most of the  $k_6$ -range, becoming periodic (Jacobi stable) close to region B. In the B stage, rapid cell cycling in the early embryo, the deviation vector is periodic for the whole  $k_6$ -range, with two distinct local minima, the deepest being associated with the

Tyson limit cycle and the other, being close to the boundary with region C, is associated with Tyson's excitable switch. Region C, near the boundary with B, has  $P_1^1(x_0, y_0)$  still negative, but as  $k_6$  increases this becomes positive and ever more so. Thus, in most of region C, the deviation vector is aperiodic and the process is Jacobi unstable. But, close to the B-boundary, the cell exhibits bursts of growth-controlled  $(k_4, k_6)$  MPF-activity. Allowing  $k_4, k_6$  to change (the above has  $k_4 = 180$ ) we still have the two minima in the negative  $P_1^1(x_0, y_0)$  region for most of the  $k_4$ -range (see Fig. 6).

Comparing the two analytical methods, we have that, in the work of Tyson, several steady-states are investigated using the standard linear analysis, determining the three distinct regions along the range of the parameter  $k_6$  (we have kept  $k_4$  constant, which suffices to span all cases). This analysis involves linearizations via the Jacobian of the non-linear system, which is two dimensional for his model. If the steady-state is a stable one, then small perturbations away from this point will be damped out, provided they are small enough so as not to escape from the basin of attraction, which is not specified from the linear analysis. On the other hand, KCC analysis is one based on the study of Lyapunov stability of whole trajectories in a region, therefore, in this case, the perturbations represent close-by trajectories to the reference trajectory. The results of such method, even when derived at a particular point, yields information about the behaviour of trajectories (solutions to the non-linear system) in a neighbourhood, or open region surrounding that point.

If we suppose that the value of  $P_1^1$  at the steady-state is non-zero, it will consequently be non-zero in an open region around the steady-state. For the Tyson model, the steady-states in Regions A and C are stable in the linear sense. This means that the eigenvalues of the Jacobian are both negative if real or have negative real parts if complex. But calculation of  $P_1^1(x_0, y_0)$  at the steady-states, with values of  $k_6$  in the ranges corresponding to those regions, shows positivity for almost all the ranges, away of their boundaries with region B, which implies KCC instability in an open region around these points. In fact,  $P_1^1(x_0, y_0)$  is strictly negative within a  $k_6$ -range strictly containing region B. This implies is that, selecting a non-steady-state solution as a reference trajectory in the region around the steady-state, then near-by trajectories, i.e., the perturbed trajectories, diverge. Furthermore, for the Tyson model,  $P_1^1$  is negative in the vicinity of a steady-state if and only if the eigenvalues of the Jacobian are complex at that point, which does not imply negativity or positivity of their real parts. Likewise, we must have real eigenvalues for  $P_1^1$  to be positive, which does not imply their positivity or negativity. Therefore the open region surrounding a steady-state, either linearly stable or unstable, may be KCC-unstable or -stable, these being independent stability concepts and analyses.

We may interpret the positivity of  $P_1^1(x_0, y_0)$  for most (linearly stable) steady-states in region A, apart from those where  $k_6$  values are close to the region B range, as telling us that when the unfertilized egg is disturbed enough to leave the basin of attraction the trajectory moves away from the steady-state. In other words, the egg stops developing as usual and possibly dies away due to the value of  $k_6$  being too far

away from what it should be for proper development. This picture is suggested by the divergence between trajectories in the region. Likewise, for most of mode C, for values of  $k_6$  away from the region B range, the positivity of  $P_1^1(x_0, y_0)$  for linearly stable steady-states may indicate the same kind of instability as in region A, so that if the cell is perturbed out the basin of attraction, diverging from the normal path of development due to, say, abnormal chemical levels, then it dies away. On the other hand, the negativity of  $P_1^1(x_0, y_0)$  in a region strictly containing mode B, where we have linearly unstable steady-states, indicates simply the convergence of trajectories in the region, or the existence of the (already known) cycle, with its typical annular region around each linearly unstable steady-state point. This picture could not be obtained from classical linear analysis.

## 6. Acknowledgements

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