Origin and breakdown of synchrony of the cell cycles in early development

E. Presnov & Z. Agur

Department of Applied Mathematics and Computer Science

The Weizmann Institute of Science, Rehovot 76100, Israel

E-mail: presnov@wisdom.weizmann.ac.il & maagur@weizmann.weizmann.ac.il

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Abstract

The regulation of the mitotic clock was examined using a theoretical model for the embryonic cell-cycle (Norel & Agur, 1991). Now the model is extended to account for the temporal regulation of early embryonic events. We show that a slow increase in the transcription ratio of *cdc*25 and *wee*1 suffices for explaining the observed synchrony and constant duration of divisions in the first 11 cleavage cycles in *Xenopus*, followed by a progressive increase in cell-cycle length and break of synchrony in further divisions. A new additional feedback for the autocatalysis generates stable chaotic oscillations in the system. This stabilizing feedback involves a change in the sign of the autocatalysis. It may be interpreted as a periodic change a ratio of *cdc*25/*wee*1 activity.

Key words: bifurcation delay, biochemical oscillations, *cdc*25/*wee*1 activity ratio, cyclin, cell cycle, early development, fast-slow dynamics, Hopf bifurcation, limit cycle, MPF, relaxation oscillations, strange attractor.

Contents

1 Introduction

The cell cycle can be viewed as the overt expression of a cellular oscillator. Equally it can be thought of as a complex developmental process that takes place within a single cell (Kirschner, 1992)

Evidence that, at least in certain kinds of eggs, the cell cycle is regulated by autonomous oscillator can be provided by a series of self-perpetuating chemical reactions in the cytoplasm. The system for the initiation and completion of mitosis in cells involves several genes. The key element is a protein kinase $p34^{cdc2}$ encoded by the gene *cdc*2. The amount of the *cdc*2 gene product does not vary during cell division but its kinase activity is positively regulated by other gene products that appear and disappear during specific stages of the cell cycle.

Recently, it has been shown that $p34^{cdc2}$ and cyclin combine to form a heterodimer, MPF, which when activated, triggers all the major events of mitosis and cell division. A striking feature of MPF is its ability to auto-activate, so that injection of a small portion of an egg with high MPF activity into a second egg with low activity stimulates an increase in MPF activity in the second.

In a previous work (Norel & Agur, 1991) a mathematical model of cell cycle progression is presented, integrating recent biochemical information about the interaction of $p34^{cdc2}$ kinase and cyclin. Underlying this model is the principle of parsimony: by elucidating the minimal assumptions needed to retrieve the observed dynamics, it is

determined whether putative thresholds and time-delays, thought to be missing in the biochemical model (Murray & Kirschner, 1989a) are indeed essential.

It is shown that the interplay of two biochemicals — cyclin and maturation promotion factor (MPF) — is sufficient to explain the embryonic cell's oscillatory behavior. The model can also account for a progressive increase in cell cycle length and for a finite, roughly constant, number of cell-divisions, characterizing senescent cell lineages. To show this it is noticed that the changes in active MPF and cyclin concentrations are accelerated by the activity of the gene *cdc25* (positive regulation - activation) and retarded by that of the gene *wee1* (negative regulation - inhibition). In fission yeast, these genes control the entry into mitosis, and it seems likely that the ratio of *cdc*25/*wee*1 activity is altered by signals that influence the entry into mitosis (Murray & Kirschner, 1989a). This control is described by a function F for the activity ratio *cdc*25/*wee*1, which changes once per cycle, and the sensitivity of the period and amplitude of the oscillations to the modulation by F is studied (Norel & Agur, 1991).

Numerical computations of the model show a gradual increase in phase, or cell cycle length. However, the pattern of change in MPF and cyclin phases and amplitude depend on the modulated reaction. When only the rate of change in MPF concentration is modulated through the function F, the amplitude of MPF oscillations progressively decreases and the amplitudes of cyclin oscillations increases, and the minimum rapidly reached a value close to zero. The latter effect may be interpreted as a cell cycle arrest.

When both processes are modulated, the amplitude does not change but the phase increases and tends to infinity, when the function F tends to zero. In both cases the number of cell divisions until a cell cycle arrest is reached depends on the step size of the function F.

Based on these results it is suggested that the modulation of the MPF and cyclin reaction rates by *cdc*25/*wee*1 activity ratio may be responsible for the roughly constant number of cell divisions observed in some cell lineages (Norel & Agur, 1991).

2 Temporal regulation in early embryo

What coordinates the temporal sequence of events in the embryo? Although the exact timing of specific events differs dramatically between species, the reproducibility within a species argues strongly for the existence of specific regulators of the temporal program (Kirschner, 1992). Based on these observations we now use the Norel & Agur model to account for the temporal regulation of early development. In particular, we wish to explain the seemingly constant length of cell cycles and their synchrony in the first 11 cleavage cycles in *Xenopus* and the increase in average cycle length and break of synchrony between the 12th and 16th cycles (Newport & Kirschner, 1982).

In Norel & Agur (1991) C and M denote the cyclin and the active MPF concentrations at any given moment, and $\dot{C}$ and $\dot{M}$ the rate of change in these concentrations. For

formally describing the MPF activation, they use the assumptions that (i) in the early embryos, cyclin synthesis suffices for the activation of MPF and for the induction of mitosis (Murray & Kirschner, 1989a), and that (ii) MPF activity is autocatalytic (Nurse, 1990; Murray & Kirschner, 1989b). These assumptions are taken account of in the first two terms in equation (1a). The third term in this equation describes the inactivation of MPF by a putative inactivase (which may be, for example, a phosphatase, Murray & Kirschner, 1989b), whose activity remains constant throughout the cell cycle (Murray & Kirschner, 1989a). In (1b) the rate of change in cyclin concentration, $\dot{C}$, is given by the difference between its constant rate of accumulation (O'Farrell et al.,1989), and its rate of degradation. Because cyclin is known to be an essential component of active MPF (North,1989), and its rapid degradation occurs immediately after the maximum in MPF activity, it is assumed that its degradation rate depends on the cellular concentration of active MPF. For simplicity, it is also assumed that no constraints exist with respect to space and nutrients. Using the above assumptions, the following dimensionless equations are obtained (Norel, 1990):

$$\begin{cases} \dot{M} = eC + fCM^2 - g\frac{M}{M+1}, & \text{(1a)} \\ \dot{C} = i - CM. & \text{(1b)} \end{cases} \tag{1}$$

To simplify the analysis, let us introduce a new scale for the variables M and C, so that the system of differential equations (1) is replaced by the following system:

$$\begin{cases} \dot{x} = ay + bx^2y - d\frac{x}{x+1}, \\ \dot{y} = 1 - xy, \end{cases} \tag{2}$$

where $x = M$, $y = C/i$, $a = ei$, $b = fi$, $d = g$. The system (2) is similar to (1) in yielding a limit cycle behavior, i.e. an oscillatory change in MPF and cyclin concentrations.

2.1 Limit cycles

A local bifurcation theory allows us to investigate the existence of limit-cycles and their stability for small perturbation of the Hamiltonian systems (see Arnold, 1983).

We consider a nondegenerate singular point (a stationary solution) of the system (2). Without loss of generality we may assume that this singular point is at the point $S1 = (1, 1)$ that is $\dot{x} = f(S1) = 0$ and $\dot{y} = g(S1) = 0$ (Figure 1). Therefore we have the condition $d = 2a + 2b$. The operator of the linear part of the field (2) at the point S1 is

$$L = \begin{pmatrix} 2b - \frac{1}{4}d & a + b \\ -1 & -1 \end{pmatrix}. \tag{3}$$

The conditions of bifurcation of the center at singularity S1 is expressed by the following relations for the operator L at the point S1:

$$\begin{cases} trace = 0, \\ discriminant < 0. \end{cases} \tag{4}$$

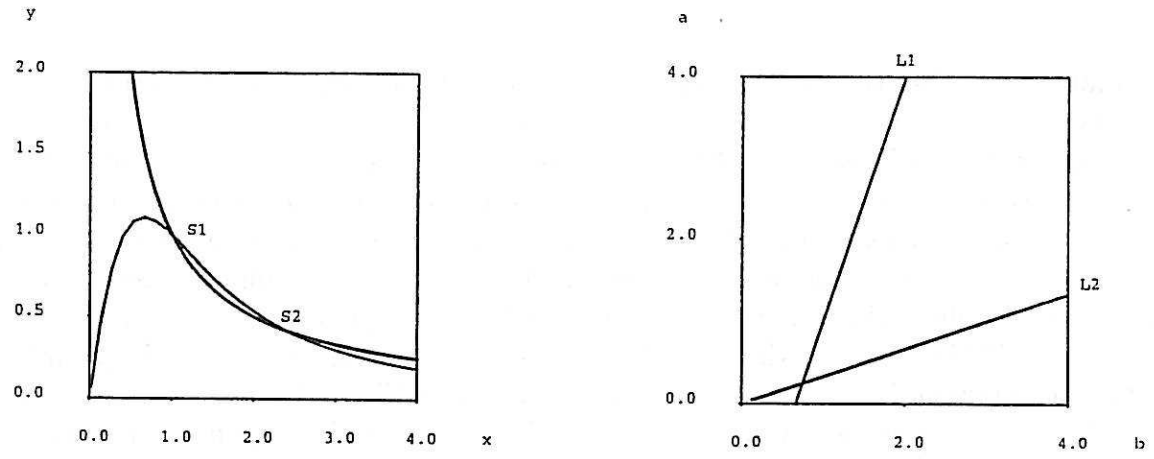

Figure 1: The autonomous system (2).
Left: Null clines ($\dot{x} = 0$ and $\dot{y} = 0$) and the singular points (crosses these isoclines: S1 $= (1, 1)$ and S2 $= (k + \sqrt{k^2 + k}; -1 + \sqrt{1 + l})$, where $k = 1/l = a/b$; see (7). Right: Projection (sharp corner) of generic cases domain (7) into the plane (b, a) is bounded by the lines of the singular cases L1: *trace* $= -a + 3b - 2 = 0$ and L2: *determinant* $= 3a - b = 0$. From the left side of line L1 the singular point S1 is stable, the singular point S2 is not stable. From the right of line $L1$ singularity S1 is unstable.

(It is clear that if *discriminant* < 0, then *determinant* > 0; see also conditions (7)). Conditions (4) means that a pair of conjugate eigenvalues of the operator L at singular point S1 must be pure imaginary. As a consequence we have the following conditions for parameters: $d = 2a + 2b; a = 3b - 2; b > 0.75$ and $d > 0$ thereafter. We choose the translation and the multipliers normalizing the expansion of coordinates and time for this significance of parameters so that it transforms the original system (2) into the system

$$\begin{cases} \dot{u} = \omega v + P(u, v), \\ \dot{v} = -\omega u + Q(u, v) \end{cases} \tag{5}$$

with a singular point S1 $= (0, 0)$ in new coordinates (u,v). P and Q contain terms of degree 2 and greater. The linear part of the system (5) is a harmonic oscillator (Hamiltonian system) with the first integral $H = \frac{1}{2}(u^2 + v^2)$. The phase trajectories of the harmonic oscillator are concentric cycles around point S1.

Let us consider a perturbation system

$$\begin{cases} \dot{u} = \omega v + \epsilon P(u, v), \\ \dot{v} = -\omega u + \epsilon Q(u, v), \end{cases} \tag{6}$$

where $\epsilon \ll 1$ is a small parameter. In other words, we have a one-parameter family of the system (6). Obviously the singularity S1 is a fixed, simple (nondegenerate) singular point of a perturbation equations too. We are interested in the metamorphosis of the configuration of phase curves in the neighborhood of the point S1 under a small change in these equations.

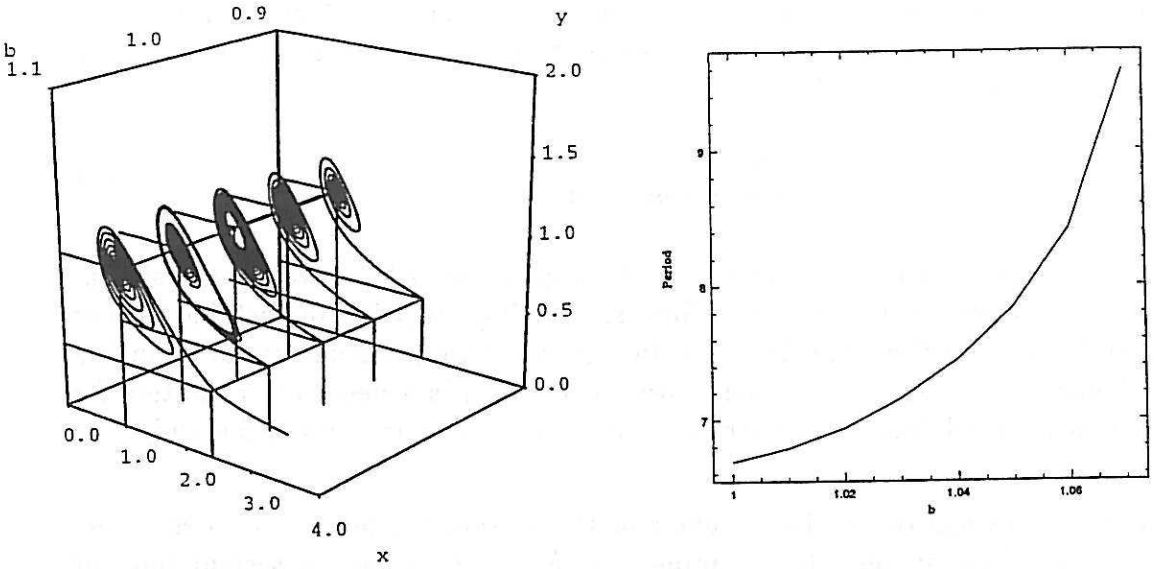

Figure 2: The autonomous system (2).
Left: Birth of a limit cycle as b passes through 1. Right: The increase of regular oscillations period for $b \in (1, 1.08)$.

Let δH be the increment of the Hamiltonian H under one revolution along the closed phase curve $H = h$. Then

$$\delta H \approx \oint \dot{H}\, dt = \oint u(\omega v + \epsilon P) + v(-\omega u + \epsilon Q)\, dt = \epsilon G(r).$$

Consequently, in the first approximation, the condition for the birth of a cycle of radius r_0 is $G(r_0) = 0$. After the detailed considerations we have

$$G(r) = -\frac{b}{2\omega^3}\pi r^4 + \frac{2b-1}{\omega}\pi r^2 + 4\pi\omega.$$

and $r_0 = 2\omega = 2\sqrt{4b-3}$. The condition of the stability of the limit cycle r_0 is: $\epsilon G'(r_0) < 0$ and in our case it is true if $\epsilon > 0$.

2.2 Hopf bifurcation

There are no analytic methods that permit us to investigate an integral behavior of nonlinear differential equations. Therefore we need heuristic arguments in order to choose the parameter values for which periodical solutions of these equations exist. The parameter values from conditions (4) allow us to locate the limit cycle of the system (2).

Without loss of generality let the point S1 $= (1, 1)$ be again a simple singular point of the system (2). There is a plane $2a + 2b - d = 0$ in the parameter space $Z = (a, b, d)$,

which corresponds to the systems with a singularity at the point S1. This plane is not a hypersurface of singular cases in the function space Z. However, this plane in our function space may intersect some of these hypersurfaces, and therefore we must consider on this plane a domain of generic cases (Figure 1):

$$\begin{cases} trace > 0, \\ determinant > 0. \end{cases} \tag{7}$$

We note here that recently C.D.Thron (1991, unpublished) has investigated similar equations. He considers a system, whose defined simple singular point, of unstable focal or unstable nodal type, satisfies conditions (7). In this way Thron was successful in finding limit cycle behavior. It should be noted, however, that (7) is a necessary condition for the existence of a closed trajectory with a single simple singular point inside only, but this condition is not sufficient.

For a closer investigation of the behavior of the system (2) let us consider a one-parameter family of the system, for example, $a = b$. In this case the second singular point S2 is fixed too. Let us investigate a neighborhood of the bifurcation value of parameters $b = 1$, that is a case where a pair of conjugate eigenvalues of the operator (3) at the equilibrium S1 crosses the imaginary axis from left to right. As b passes through 1 the focus at the point S1 loses stability. In this case the corresponding pair of conjugate eigenvalues of operator (3) is equal to $\pm i$. For $b = 1$, at the point S1 the focus is also stable, but not robust: the phase curves approach S1 nonexponentially. For $b = 1 + \epsilon$ where $\epsilon > 0$, moving from the focus to a distance proportional to $\sqrt{\epsilon}$, the phase curves wind onto a stable limit cycle. Consequently the loss of stability in the passage of b through 1 takes place with the birth of a stable cycle whose radius increases with $\sqrt{\epsilon}$ (Figure 2).

In other words, the stationary state S1 loses stability and a stable periodic regime arises, whose amplitude is proportional to the square root of the deviation of the parameter from the critical value. This form of loss of stability is called a mild loss of stability, since the oscillating behavior for small criticality differs little from the equilibrium state. It is a Hopf bifurcation or a soft generation of self-sustained oscillations.

2.3 Scenario of development 1

Based on our results we suggest that a progressive increase in zygotic transcription of *cdc*25 is responsible for the increase in cell cycle in early development. As long as the contribution of zygotic transcription to the overall concentration of *cdc*25 is very small and activation of MPF is dominated by the maternal *cdc*25 product, the cycles are similar in all cells and hence, divisions are synchronized. When the shift occurs and the control becomes dominated by the zygote, cell cycle duration is locally controlled by the nuclear product of each cell. Now the concentration of *cdc*25 is more likely to vary between

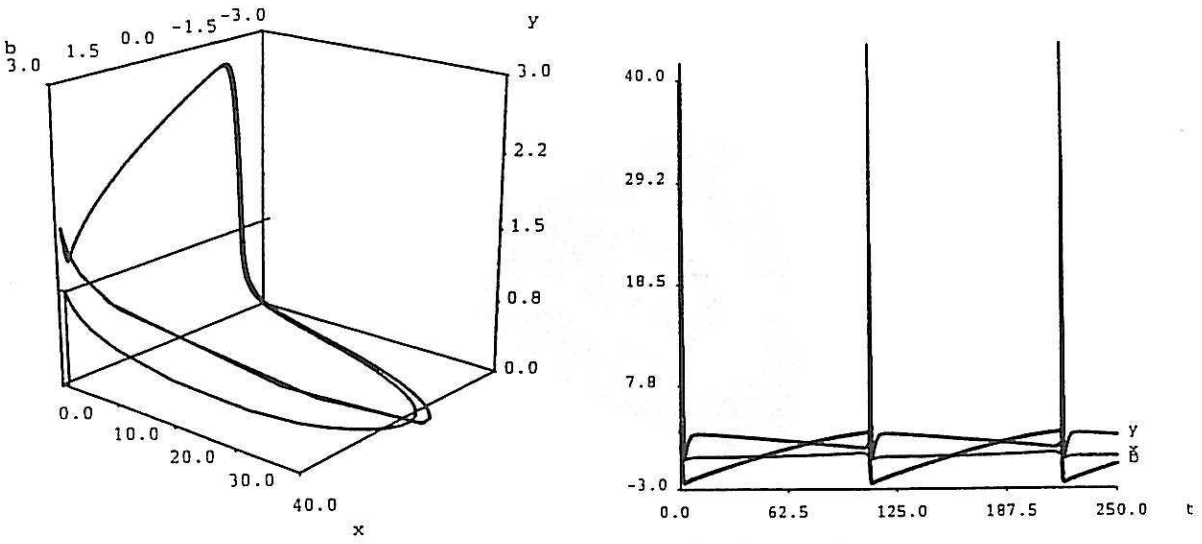

Figure 3: The relaxation oscillations.
The behavior of the fast-slow system (8) for $x_0 = 1.2$, $y_0 = 1$, $a = 1$, $b = 3$, $d = 8$, $\epsilon = 0.1$. Left: Phase trajectory in the space (x, y, b): limit cycle. Right: Time plot for the x, y, b: bursting. The variable b can be negative.

cells and we observe a transition from a single limit cycle to a family of limit cycles. It is plausible that differences in nucleocytoplasmic ratio, due to asymmetric divisions, are responsible for the small changes in b as it presumably affects the concentration of chemicals in cytoplasm and, hence, the reaction rates; lower ratio will mean less *cdc*25 and hence shorter cycles. Synchrony may be broken down due to the small differences in cycle duration between the different cell lineages.

3 Feedbacks

Modeling the dynamics (which is relatively simple) rather than the biochemistry (which is relatively complicated) might be a useful approach for biological phenomena involving a trigger mechanism (checkpoints in the cell-cycle) which leads to some specific action (Zeeman, 1977). In our case, to a first approximation the dynamics are given by the system (2). However, this approximation does not allow for variation of a, b, d with time. If a, b, d represent some biochemical controls their values may vary by many orders of magnitude, i.e., the system may possess a time hierarchy. This time hierarchy may be included in the system (2) in an implicit form and to make it explicit we have to transform the coordinate system (x, y). To keep matters as simple as possible we will suppose that we the system has only one level of time hierarchy.

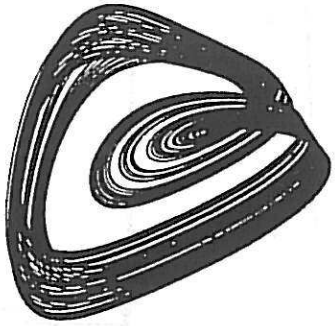

Figure 4: A strange attractor.
The behavior of the autonomous system (8) for $x_0 = 1.5$, $y_0 = 1.5$, $a = 1$, $b = 2.4$, $d = 8$, $\epsilon = 1$ in the space (x, y, b). This strange attractor has on the face of it the shape of Möbius band. But a more detailed examination shows us that this "band" is not a manifold and that it is folded like a baker transformation (see, for example, Bergé et al., 1988). This transformation allows the mixing up of trajectories. Only one trajectory is shown. Perspective changed by "XPRISM3".

3.1 Relaxation oscillations and strange attractor

Let us consider first the following system, where a, d are constant and b is the biochemical control variable.

$$\begin{cases} \dot{x} = ay + bx^2y - d\frac{x}{x+1}, \\ \dot{y} = 1 - xy, \\ \dot{b} = \epsilon(1 - x^2y). \end{cases} \quad (8)$$

The system (8) contains the fast subsystem (2) and if $\epsilon \ll 1$ it is a fast-slow system. Let one of eigenvalues for the operator (3) of this fast subsystem at the singular point S1 be equal to zero, i.e *determinant* $= 0$. In this case the fast-slow system (8) can have regular relaxation oscillations, that is the trajectories form an attracting cycle (see Figure 3).

If we assume now that in (8), $\epsilon = 1$, so that (8) is no longer a fast-slow system, we obtain a chaotic behavior. At first a doubling of the limit cycle period takes place, during the variation of the coefficient b, with an appearance of double cycle. After the loss of stability of this double cycle a new attractor in the system (8), $\epsilon = 1$, is born. This attractor has a chaotic behavior and is denoted a strange attractor (Figures 4 - 6).

$\diamond$*Remark.* An attractor is a set in a phase space, which attracts neighboring conditions (transients). Attractors that are not equilibrium states or strictly periodic oscillations have been given the name strange attractors. The transition of a system to such a behavior means that in it, complicated non-periodic oscillations are observed, the details of which are very sensitive to small changes in initial conditions. At the same time, the average characteristics of the behavior are stable and do not depend on the initial conditions (when they vary within some domain) (see Hess & Markus, 1987).

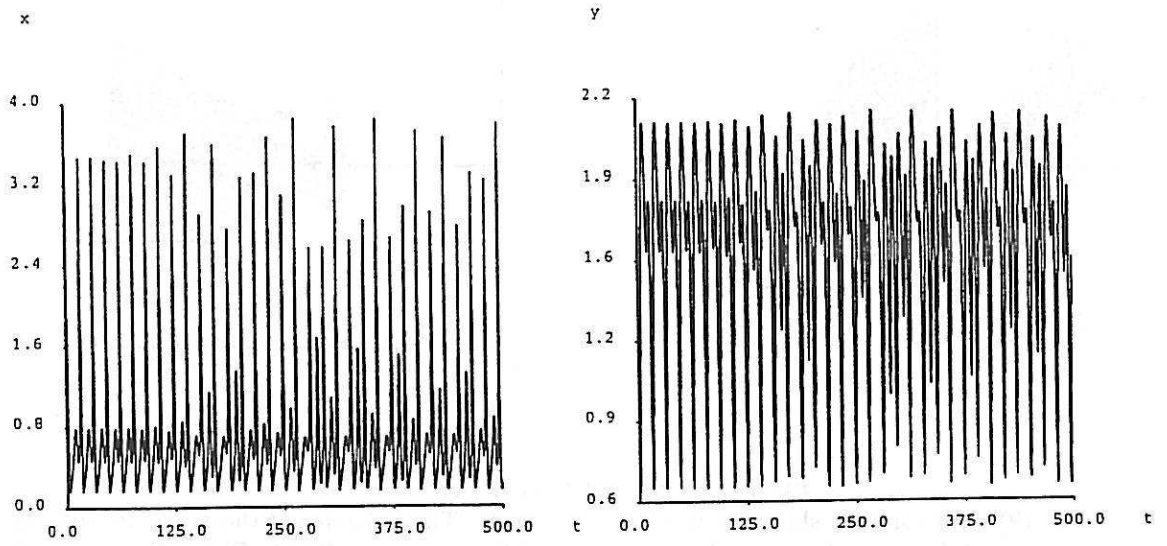

Figure 5: Breakdown of symmetry of double cycle.
Breakdown of symmetry of double cycle for (8), $\epsilon = 1$. Time plots of the strange attractor for the autonomous system (8) for $x_0 = 1.5$, $y_0 = 1.5$, $a = 1$, $b = 2.4$, $d = 8$, $\epsilon = 1$. The amplitudes and periods of oscillations for x and y are disordered behaviors. Left: Variable x. Right: Variable y.

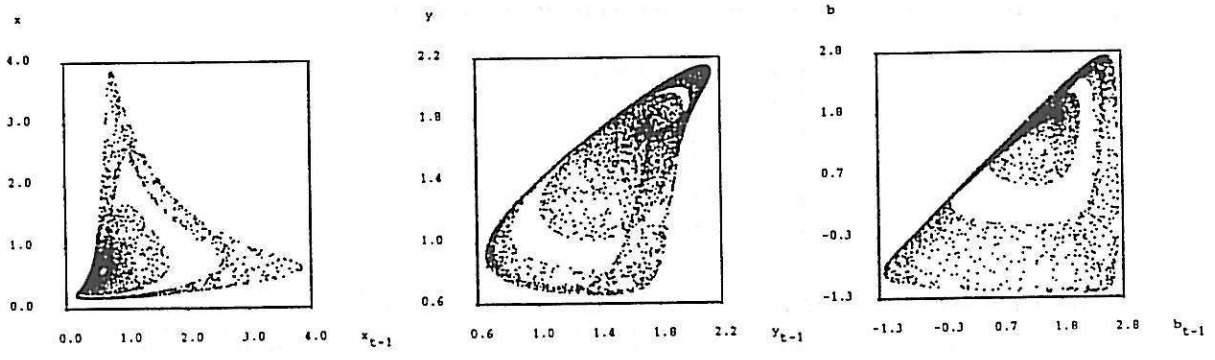

Figure 6: Chaotic characteristics of the strange attractor.
MAP plots of each variable at the time t as a function of the same variable at time $t-1$ for the autonomous system (8) for $x_0 = 1.5$, $y_0 = 1.5$, $a = 1$, $b = 2.4$, $d = 8$, $\epsilon = 1$ Left: Variable x. Center: Variable y. Right: Variable b.

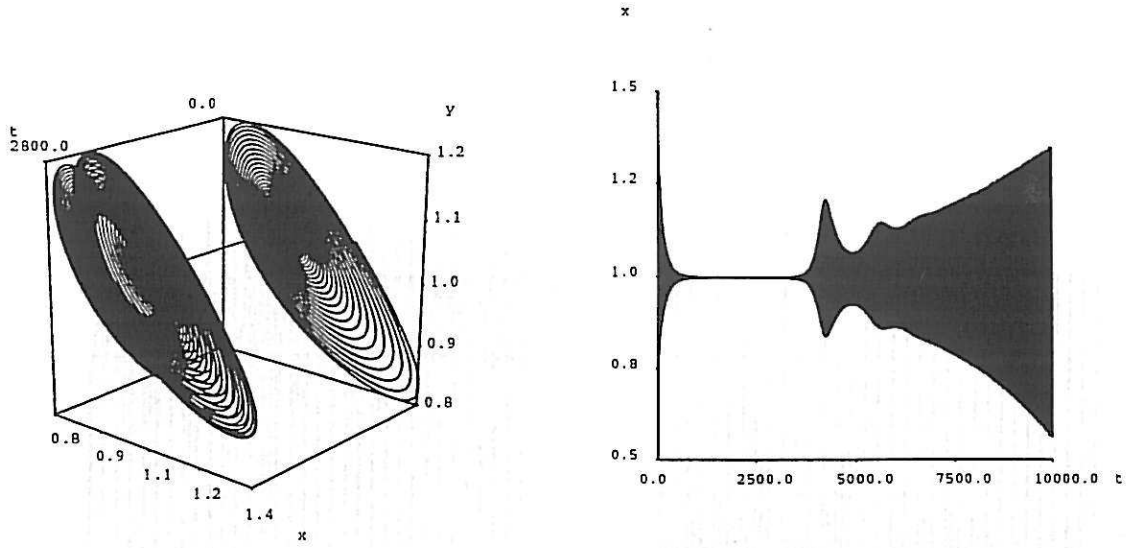

Figure 7: Bifurcation delay.
For the systems (9) with complex slow and fast dynamics. Left: The behavior of the one trajectory in the space-time (x, y, t) for $x_0 = 1.2$, $y_0 = 1$, $a = 1$, $b = 1.006$, $d = 4$, $\epsilon = 0.004$. Right: Time plot of x for $x_0 = 1.2$, $y_0 = 1, a = 1$, $b = 1$, $d = 4$, $\epsilon = 0.001$. Here, we can see the rapid onset of oscillatory behavior, first decreasing in amplitude but then increasing. The oscillatory behavior dies away to almost zero amplitude before increasing again (see also a similar result by Collier et. al., 1992 and a description of general theory in the works Shishkova, 1973; Neishtadt, 1987, 1988; Benoît, 1991; Arnold, 1992).

A more complex model assumes that the biochemical control of the system includes also the coefficients a and d. Now $\dot{a}$, $\dot{b}$, $\dot{d}$ are proportional to (in suitable units equal to) the deviation the system (2) from its equilibrium state. (Any system t ends to come back to an equilibrium state with a force which is proportional to its deviation from this equilibrium state.) The equilibrium solution of the fast system (2) is $(x(t) = 1, y(t) = 1)$, so that we obtain the following system with the time hierarchy:

$$\begin{cases} \dot{x} = ay + bx^2y - d\frac{x}{x+1}, \\ \dot{y} = 1 - xy, \\ \dot{a} = \epsilon(1 - y), \\ \dot{b} = \epsilon(1 - x^2y), \\ \dot{d} = \epsilon(0.5 - \frac{x}{x+1}). \end{cases} \tag{9}$$

Here x, y are the fast variables and a, b, d are the slow variables, if ϵ is small ($\epsilon \ll 1$). The slower response of the equations for $\dot{a}$, $\dot{b}$, $\dot{d}$ is said to give the feedbacks. The typical behavior of the system (9) is shown in Figures 7 - 9 for $\epsilon = 10^{-5}, ..., 1$. These results show that stability of the oscillations is sensitive to the rate of reactions of the control variables a, b, d. This sensitivity suggests that, in general, the system (9) is unstable. For this reason the possibility that a and d vary during the cell cycle is not very likely.

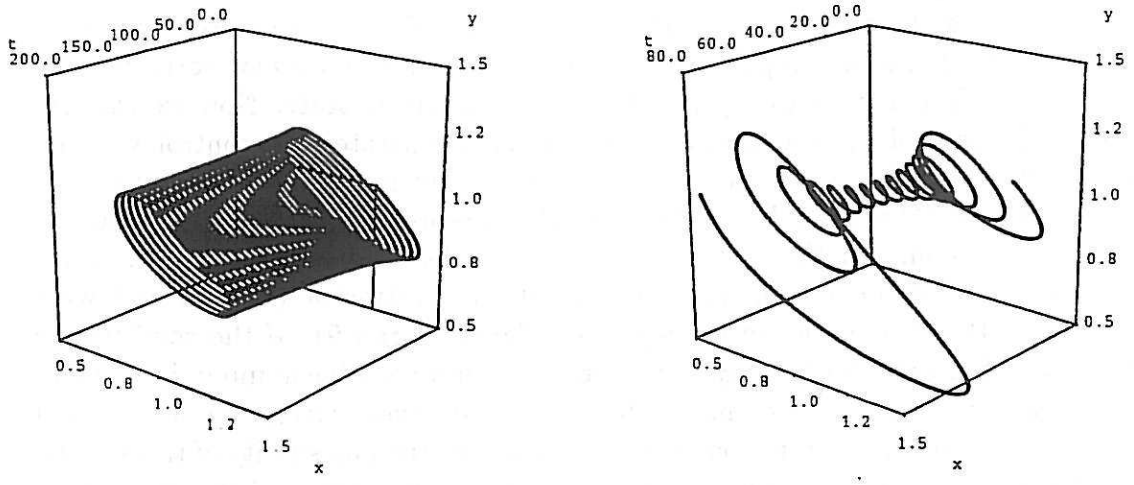

Figure 8: The behavior of trajectories of the fast-slow system (9).
Left: Limit cycle Into the space (x, y, t) for $x_0 = 1.2$, $y_0 = 1$, $a = 1$, $b = 1.006$, $d = 4$, $\epsilon = 0.00001$.
Right: Delayed bifurcation. Into the space (x, y, t) for $x_0 = 1.2$, $y_0 = 1$, $a = 1$, $b = 1.006$, $d = 4$, $\epsilon = 0.1$.
This structure is brought out even more spectacularly in Figure 7.

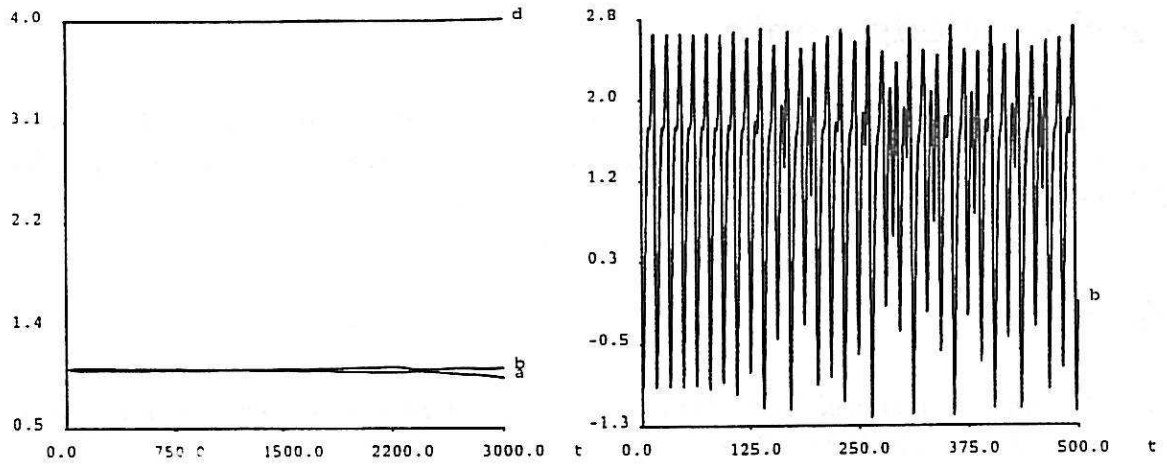

Figure 9: Dynamics of the control variables.
Left: The variables a, b, d of the fast-slow system (9) for $x_0 = 1.2$, $y_0 = 1$, $a = 1$, $b = 1.006$, $d = 4$, $\epsilon = 0.004$ (see Figure 7). Right: The variable b of the system (8), $\epsilon = 1$ with the strange attractor for $x_0 = 1.5$, $y_0 = 1.5$, $a = 1$, $b = 2.4$, $d = 8$ (see Figure 4). The amplitudes and periods of oscillations for b are disordered behaviors.

3.2 Scenario of development 2

In part 3 we replaced the assumption that the coefficient of the autocatalytic reaction gradually increases by the assumption that this coefficient is a control variable that depends on the displacement of the system from its equilibrium state. Now we can use an increase in the rate of the biochemical reaction that generates the control variable b as an explanation for the transition in early development from stable oscillations to aperiodic oscillations. The variable b in the model (8) represents a control mechanism of cell cycle progression. In the fast-slow system (9) the slow variables a, b, d are almost constant, but in the system (8) with the strange attractor ($\epsilon = 1$) and with the burst ($\epsilon \ll 1$) the variable b can be negative (Figures 3 and 9). If the coefficient b represents $\log(cdc25/wee1)$, then b may be both positive and negative number, if the ratio of $cdc25/wee1$ activity is greater or smaller than unity. By investigating the biochemical properties of the control parameter b, one can easily validate the plausibility of this model. In the model considered here, the chaotic dynamics are a consequence of the interaction of the three coupled oscillators. In the chaotic mode this gives rise to a dispersion of cell cycle times and multimodality. The existence of a cell cycle oscillator with a strange attractor has previously been considered (Engelberg, 1968; Mackey, 1985; Grasman, 1990; Lloyd et al., 1992) but here we obtained it from the suggestion about à variability of the coefficients. In general, it is of interest to establish the regulatory processes controlling the avoidance as well as the occurrence of chaos (see Hess & Markus, 1987).

4 Acknowledgments

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References

[1] V.I. Arnold. *Geometrical Methods in the Theory of Ordinary Differential Equations.* Springer, New York, 1983. 334 p.

[2] V.I. Arnold, editor. *Dynamical Systems V*, volume 5 of *Encyclopedia of Mathematical Sciences.* Springer, Berlin, 1992.

[3] E. Benoît, editor. *Dynamic Bifurcations.* Lecture Notes in Mathematics, N 1493. Springer, Berlin, 1991. 219 p.

[4] P. Bergé, Y. Pomeau, and C. Vidal. *L'ordre Dans le Chaos.* Hermann, Paris, 1988.

[5] S.M. Collier, J.H. Merkin, and S.K. Scott. Multistability, oscillations and traveling waves in a product-feedback autocatalator model. I. Thewell-stirred system. *Philosophical Transactions of the Royal Society of London, Series A*, 340:447–472, 1992.

[6] R.J. De Boer. GRIND: GReat INtegrator Differential equations. Bioinformatics Group, University of Utrecht, the Netherlands, 1983. (Version GRIND:90.8, 25 p.).

[7] J. Engelberg. On deterministic origins of mitotic variability. *Journal of Theoretical Biology*, 20:249–259, 1968.

[8] J. Grasman. A deterministic model of the cell cycle. *Bulletin of Mathematical Biology*, 52:535–547, 1990.

[9] B. Hess and M. Markus. Order and chaos in biochemistry. *Trends in Biochemical Sciences*, 12:45–48, 1987.

[10] M. Kirschner. The cell cycle then and now. *Trends in Biochemical Sciences*, 17:281–285, 1992.

[11] D. Lloyd, A.L. Lloyd, and L.F. Olsen. The cell division cycle: a physiologically plausible dynamic model can exhibit chaotic solutions. *BioSystems*, 27:17–24, 1992.

[12] M.C. Mackey. A deterministic cell cycle model with transition probability-like behaviour. In L. Rensing and N.I. Jaeger, editors, *Temporal Order*, pages 315–320. Springer, Berlin, 1985.

[13] A.W. Murray and M.W. Kirschner. Dominoes and clocks: the union of two views of the cell cycle. *Science*, 246(4930):614–621, 1989a.

[14] A.W. Murray and M.W. Kirschner. Cyclin synthesis drives the early embryonic cell cycle. *Nature*, 339(6222):275–280, 1989b.

[15] A.I. Neishtadt. Persistence of stability loss for dynamical bifurcations. I. *Differential Equations*, 23(12):1383–1391, 1987.

[16] A.I. Neishtadt. Persistence of stability loss for dynamical bifurcations. II. *Differential Equations*, 24(2):171–176, 1988.

[17] J. Newport and M. Kirschner. A major developmental transition in early *Xenopus* embryos: I. Characterization and timing of cellular changes at the midblastula stage. *Cell*, 30:675–686, 1982.

[18] R. Norel. A model for the embryonic cell-cycle and the adjustment of the mitotic clock by cyclin and MPF levels. Master's thesis, Weizmann Institute of Science, Rehovot, 1990. 32 p.

[19] R. Norel and Z. Agur. A model for the adjustment of the mitotic clock by cyclin and MPF levels. *Science*, 251:1076–1078, 1991.

[20] G. North. Regulating the cell cycle. *Nature*, 339(6219):97–98, 1989.

[21] P. Nurse. Universal control mechanism regulating onset of M-phase. *Nature*, 344(6266):503–508, 1990.

[22] P.H. O'Farrell, B.A. Edgar, D. Lakich, and C.F. Lehner. Directing all division during development. *Science*, 246(4930):635–640, 1989.

[23] M.A. Shishkova. Examination of a system of differential equations with a small parameter in the highest derivatives. *Soviet Mathematics Doklady*, 14(2):483–487, 1973.

[24] C.D. Thron. A modification of the Norel-Agur model of the cyclin-maturation promotion factor (MPF) system. (Unpublished).

[25] C.D. Thron. Mathematical analysis of a model of the mitotic clock. *Science*, 254(5028):122-123, 1991.

[26] E.C. Zeeman. *Catastrophe Theory: Selected Papers. 1972 - 1977.* Addison-Wesley, Reading (Massachusetts), 1977. 675 p.