CELLULAR GROWTH AND BERWALD CURVATURES

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1. Introductory biological background

Genome= the total collection of genetic material in the chromosomes of an organism.

DNA= a double stranded molecule made out of two complementary strands of equal length containing four bases: adenine (A), guanine (G), cytosine (C) and thynine (T), held together (quite strongly) by hydrogen bands.

mRNA= the twin sister of a single stranded *DNA*: it keeps the same A, C, G bases while T (thynine) is replaced by U (uracil).

Protein= a sequence of amino acids (20 types).

1
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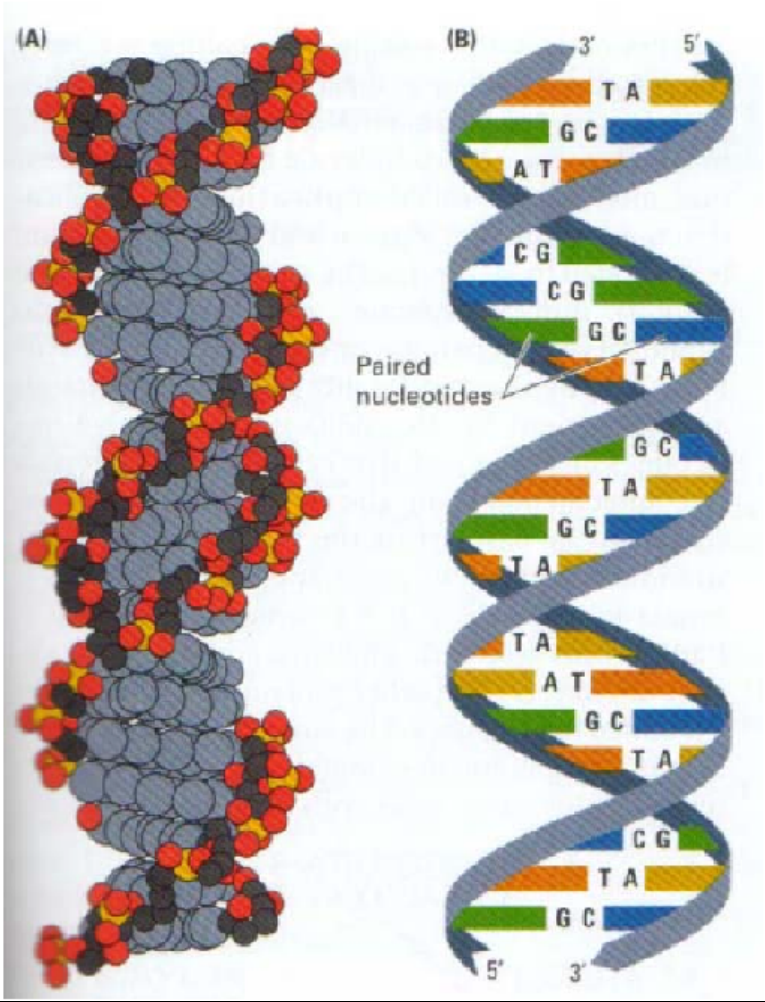
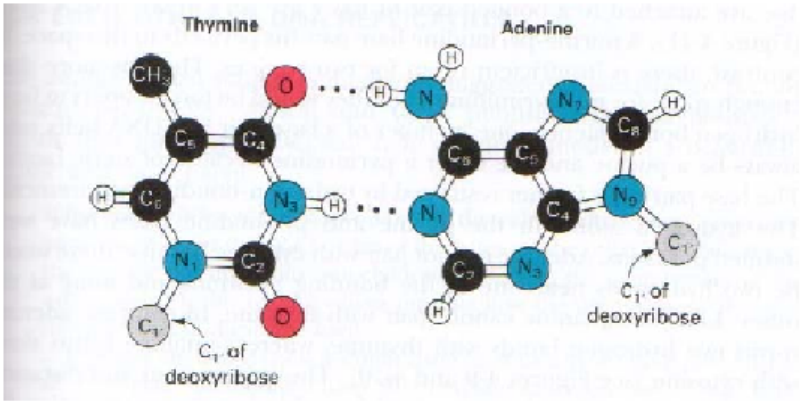
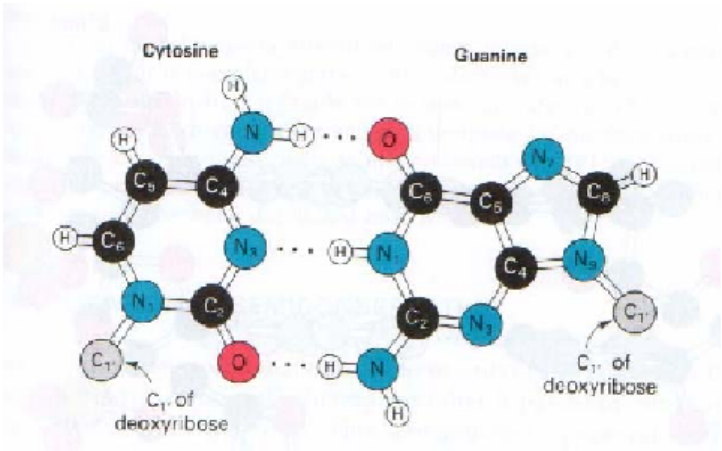
19
20
21
22
X
Y

DNA Structure







2. Central Dogma of Molecular Biology

What is a gene?

The unit of hereditary information that occupies a fixed position (locus) on chromosomes (*Encyclopedia Britannica*).

A gene is a segment of DNA together with a transformation to a segment (s) of mRNA (*A. Carbone and M. Gromov, [CG]*).

-**alternative splicing** in eukariotic cells, i.e. the same segment of **DNA** may lead to the production of different **mRNA**s

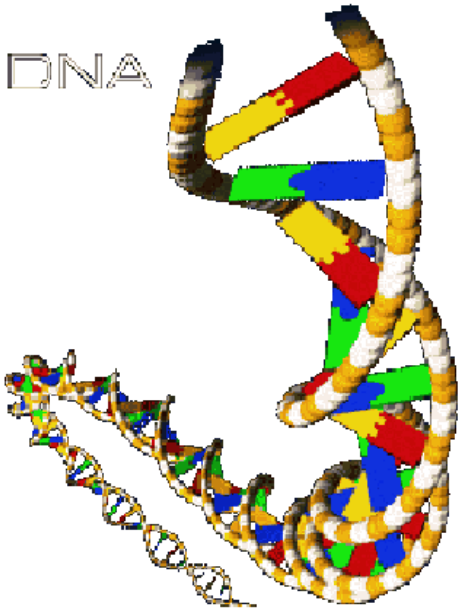
-**overlapping genes**, i.e. different segments of **mRNA** are produced from overlapping segments of **DNA**.

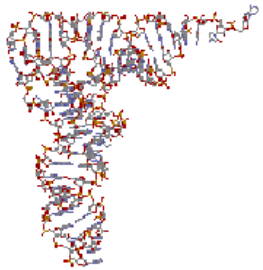
$$DNA \xrightarrow{F} mRNA \xrightarrow{G} \text{protein}$$

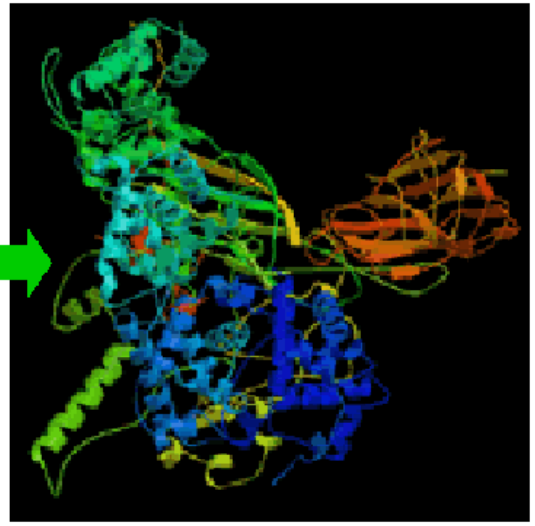
$$\boxed{\text{gene} = (G \circ F)^{-1}(\text{protein})}$$

Central Dogma

transcription translation

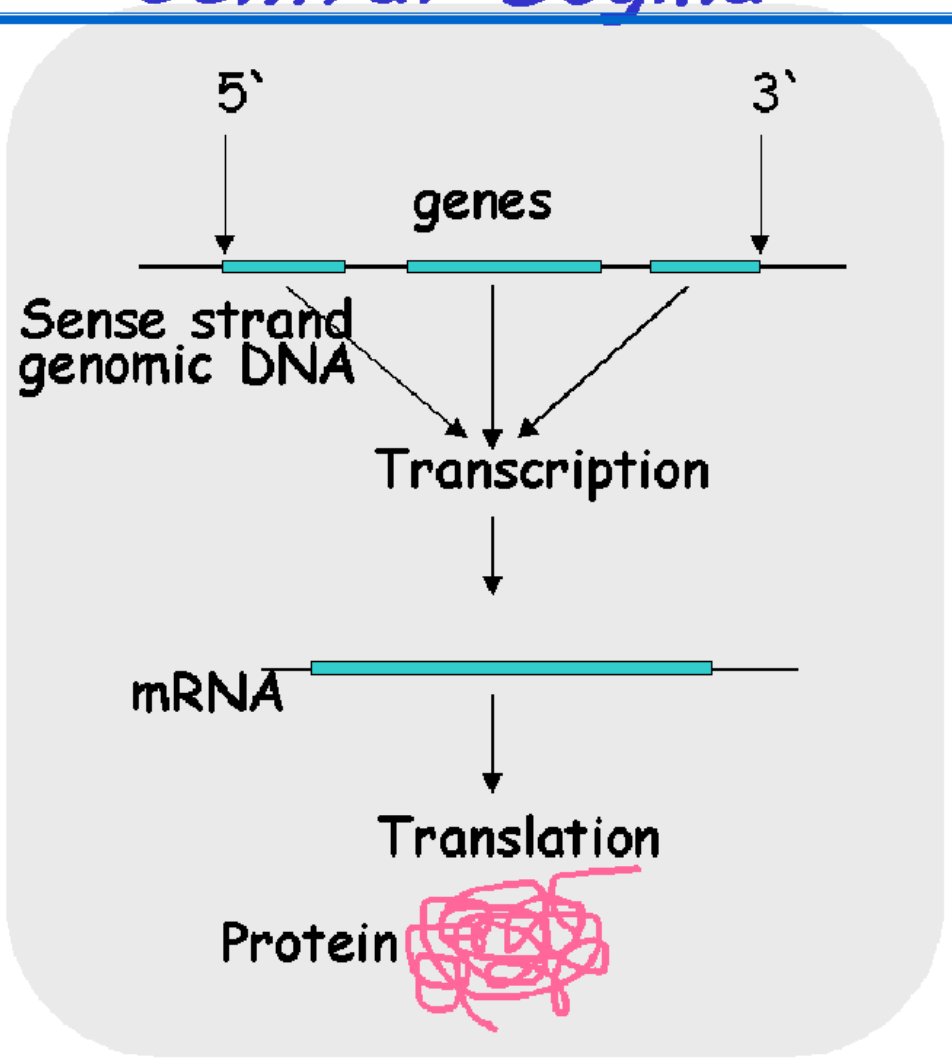




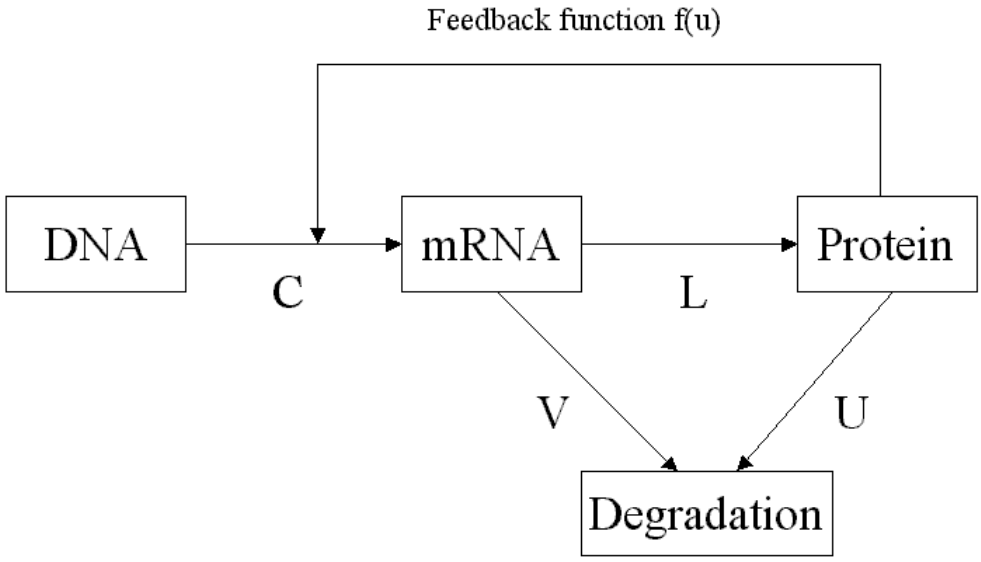


DNA mRNA Protein

Central Dogma



3. Differential equations



$$\frac{dr}{dt} = f(p) - V \cdot r \qquad \frac{dp}{dt} = L \cdot r - U \cdot p,$$

where the variables $r = r(t)$, $p = p(t)$ are functions of time, and:

n	The number of genes in the genome.
r	$mRNA$ concentrations, n-dimensional vector-valued functions of t.
p	Protein concentrations, n-dimensional vector-valued functions of t.
$f(p)$	Transcription functions, n-dimensional vector polynomials on p.
L	Translations constants, $n \times n$ nondegenerate diagonal matrix.
V	Degradations rates of $mRNA$'s, $n \times n$ nondegenerate diagonal matrix.
U	Degradations rates of Proteins, $n \times n$ nondegenerate diagonal matrix.

- $mRNA$ production: $\dfrac{d^2r}{dt^2} + 2G(r, \dot{r}) = 0,$
- *Protein* production: $\dfrac{d^2p}{dt^2} + 2H(p, \dot{p}) = 0.$

Finslerian example: $F^2 = \frac{1}{2}e^{2(\alpha x^1 + \beta x^2)}\left[\left(\dfrac{dx^1}{dt}\right)^2 + \left(\dfrac{dx^2}{dt}\right)^2\right]$ (Volterra-Hamilton system).

4. Michaelis-Menten kinetics

- *Enzyme*
- *Substrate*
- *Biochemical reactions*

  association : two proteins combine together to form a complex

  disassociation : a substrate splits in two reaction products: an enzyme and a product.

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} SE \xrightarrow{k_2} P + E,$$

S : substrate; E : enzyme (catalyst); P: product,
k_1, k_{-1}, k_2 constant rate parameters.

- *Law of mass action*

$$\frac{ds}{dt} = -k_1 es + k_{-1} c, \qquad \frac{de}{dt} = -k_1 es + (k_{-1} + k_2) c,$$
$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2) c, \qquad \frac{dp}{dt} = k_2 c.$$

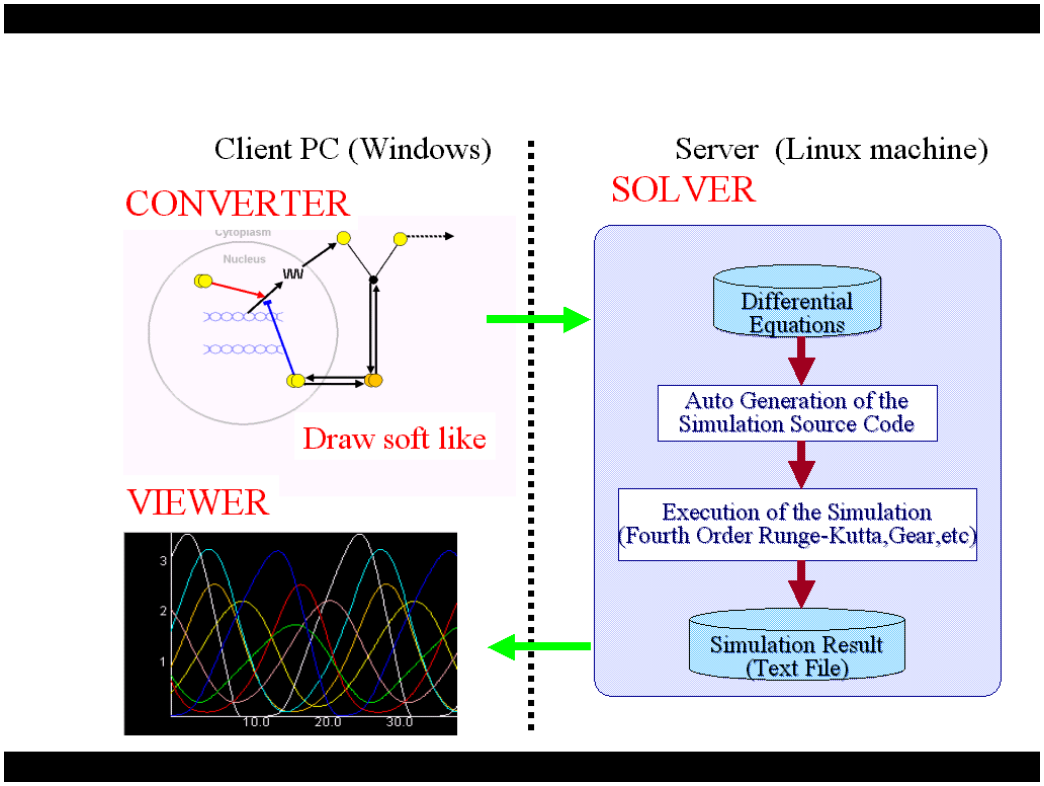
s, e, c, p : concentrations of the reactants S, E, SE, P.

- **Phase plane analysis.**
- **Hopf bifurcation and limit cycles.**

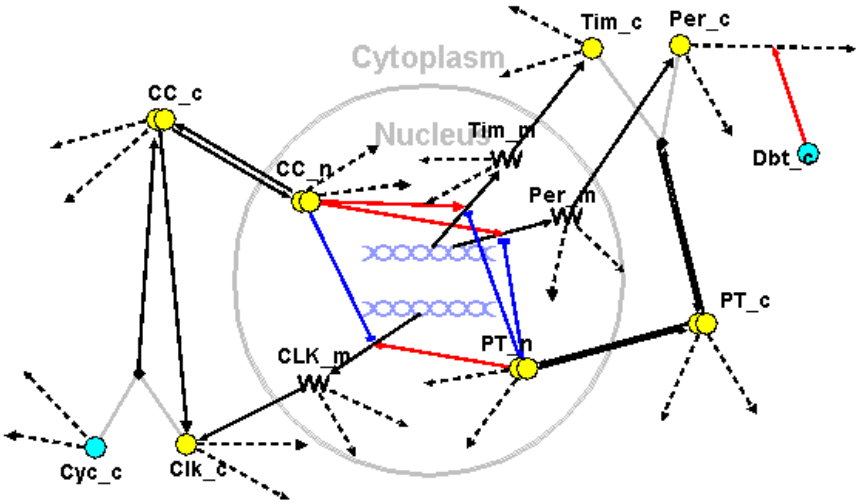
5. SIBIL: a software for simulations of biological systems

The Holy Grail of Molecular Biology: construct faithful mathematical model of living cell (genes, proteins, protein complexes, mRNA, etc.).

- **System architecture.**



- **Circadian rhythm in Drosophila.**



6. Differential system in Drosophila

$$\frac{dPer_m}{dt} = S_1 \cdot \frac{\left(\frac{CC_p}{P_1}\right)^p}{1 + \left(\frac{PT_n}{M_1}\right)^m + \left(\frac{CC_n}{P_1}\right)^p} - D_1 \cdot \frac{Per_m}{L_1 + Per_n} - d \cdot Per_m$$

$$\frac{dPer_c}{dt} = S_2 \cdot Per_m - A_1 \cdot Per_c \cdot Tim_c + A_2 \cdot PT_c - D_2 \cdot Dbt_c \cdot \frac{Per_c}{L_2 + Per_c} - d \cdot Per_c$$

$$\frac{dTim_m}{dt} = S_3 \cdot \frac{\left(\frac{CC_n}{Q_1}\right)^q}{1 + \left(\frac{PT_n}{N_1}\right)^n + \left(\frac{CC_n}{Q_1}\right)^q} - D_3 \cdot \frac{Tim_m}{L_3 + Tim_m} - d \cdot Tim_m$$

$$\frac{dTim_c}{dt} = S_4 \cdot Tim_m - A_1 \cdot Per_c \cdot Tim_c + A_2 \cdot PT_c - D_4 \cdot \frac{Tim_c}{L_4 + Tim_c} - d \cdot Tim_c$$

$$\frac{dPT_c}{dt} = A_1 \cdot Per_c \cdot Tim_c - A_2 \cdot PT_c - V_1 \frac{PT_c}{K_1 + PT_c} + V_2 \frac{PT_n}{K_2 + PT_n} - D_5 \frac{PT_c}{L_5 + PT_c} - d \cdot PT_c$$

$$\frac{dPT_n}{dt} = V_1 \frac{PT_c}{K_1 + PT_c} - V_2 \frac{PT_n}{K_2 + PT_n} - D_6 \frac{PT_n}{L_6 + PT_n} - d \cdot PT_n$$

$$\frac{dClk_n}{dt} = S_5 \cdot \frac{\left(\frac{PT_n}{R_1}\right)^r}{1 + \left(\frac{CC_c}{O_1}\right)^o + \left(\frac{PT_n}{R_1}\right)^r} - D_7 \cdot \frac{Clk_n}{L_7 + Clk_n} - d \cdot Clk_n$$

$$\frac{dCC_c}{dt} = A_3 \cdot Clk_c \cdot Cyc_c - A_4 \cdot CC_c - V_3 \frac{CC_c}{K_3 + CC_c} + V_4 \frac{CC_n}{K_4 + CC_n} - D_9 \frac{CC_c}{L_9 + CC_c} - d \cdot CC_c$$

$$\frac{dCC_n}{dt} = V_3 \frac{CC_c}{K_3 + CC_c} - V_4 \frac{CC_n}{K_4 + CC_n} - D_{10} \frac{CC_n}{L_{10} + CC_n} - d \cdot CC_n$$

$$\frac{dClk_c}{dt} = S_6 \cdot Clk_m - A_3 \cdot Clk_c \cdot Cyc_c + A_4 \cdot CC_c - D_8 \cdot \frac{Clk_c}{L_8 + Clk_c} - d \cdot Clk_c,$$

where we have 10 variables of time

$Tim_m, Per_m, Clk_m,$	mRNAs
$Tim_c, Per_c, Clk_c,$	proteins translated from mRNAs
$PT_c, PT_n, CC_c, CC_n,$	protein complexes
$Dbt_c, Cyc_c,$	catalysts, (i.e. constants)

and 56 constant parameters $S_1, ..., S_6; D_1, ..., D_{10}; A_1, ..., A_4; B_1, B_2, B_3; C_1, C_2, C_3; M_1, N_1, O_1, P_1, Q_1, R_1, K_1, ..., K_4; L_1, ..., L_{10}; V_1, ..., V_4; o, p, q, r, m, n, d.$

7. A simple example: Tyson's Model for the Cell Division Cycle

- *Cell cycle*

$$\underbrace{| \overset{G_1}{\rightarrow} | \overset{S}{\rightarrow} | \overset{G_2}{\rightarrow}}_{interphase} \underbrace{| \overset{M}{\rightarrow} |}_{division} .$$

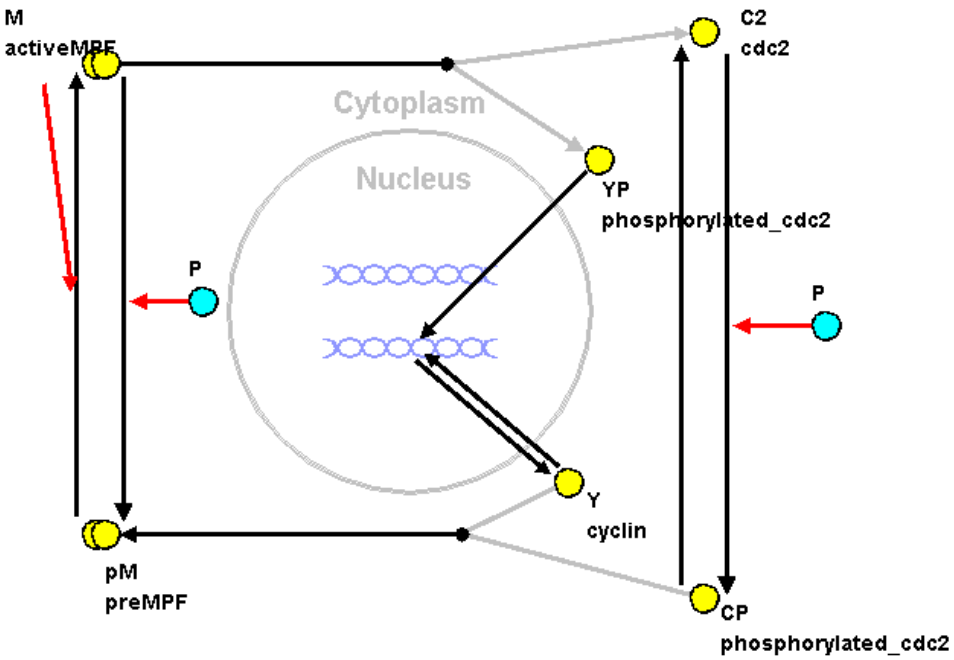
- *Early embryonic cell cycle*

$$| \overset{S}{\rightarrow} | \overset{M}{\rightarrow} | \overset{S}{\rightarrow} | \overset{M}{\rightarrow} | \rightarrow \ldots$$

- *Maturation promoting factor (MPF)* peaks abruptly at metaphase (M).

$$cyclin + cdc \rightarrow MPF.$$

- *The cell cycle regulatory pathway.*



- **Differential system of cell cycle regulatory pathway.**

$$\begin{aligned}
\frac{dC_2}{dt} &= k_6 \cdot M - k_8 \cdot P \cdot C_2 + k_9 \cdot CP \\
\frac{dCP}{dt} &= -k_3 \cdot CP \cdot Y + k_8 \cdot P \cdot C_2 - k_9 \cdot CP \\
\frac{dpM}{dt} &= k_3 \cdot CP \cdot Y - pM \cdot F(M) + k_5 \cdot P \cdot M \\
\frac{dM}{dt} &= pM \cdot F(M) - k_5 \cdot P \cdot M - k_6 \cdot M \\
\frac{dY}{dt} &= k_1 \cdot aa - k_2 \cdot Y - k_3 \cdot CP \cdot Y \\
\frac{dYP}{dt} &= k_6 \cdot M - k_7 \cdot YP,
\end{aligned}$$

where $F(M) = k + k_4 \dfrac{M}{CT^2}$.

- **Tyson model.**

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

u and v are the relative concentration of active MPF and total cyclin minus degraded cyclin relative to total *cdc*2, respectively.

Parameter ranges:

k:= 0.018 min^{-1} rate constant for the dephosphorylation of *cdc*2,

k_1:= 0.015 min^{-1} rate constant of *cyclin* synthesis,

k_4: = 10 - 1000 min^{-1} (adjustable) constant describing the auto catalytic activation of MPF by the dephosphorylation of *cdc*2,

k_6:= 0.1 - 10 min^{-1} (adjustable) constant describing breakdown of the active *cdc*2-*cyclin* complex.

8. The KCC Theory

Find the basic invariants of the SODE

$$\frac{d^2x^i}{dt^2} + g^i(x, \dot{x}, t) = 0,\ i \in \{1, 2, \ldots, n\},$$
$$x(t_0) = x_0, \dot{x}(t_0) = \dot{x}_0,\ (x, \dot{x}, t) \in \Omega \subset \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^1$$

under the nonsingular coordinate transformation

$$\bar{x}^i = f^i(x^1, \ldots, x^n),\ i \in \{1, 2, \ldots, n\},$$
$$\bar{t} = t.$$

- **KCC-covariant differential**

$$\frac{D\xi^i}{dt} = \frac{d\xi^i}{dt} + \frac{1}{2}\, g^i_{;r}\xi^r,$$

";" partial differentiation with respect to $\dot{x}$.

- **First KCC- invariant**

$$\frac{D\dot{x}^i}{dt} = \frac{1}{2}\, g^i_{;r}\dot{x}^r - g^i = \varepsilon^i$$

Lemma. *The functions $g^i = g^i(x, \dot{x}, t)$ are 2 homogeneous in $\dot{x}$ if and only if $\varepsilon^i = 0$.*

Variation of the trajectories into nearby one

$$\bar{x}^i(t) = x^i(t) + \xi^i(t)\eta.$$

The *variational equations*

$$\frac{d^2\xi^i}{dt^2} + g^i{}_{;r}\, \frac{d\xi^r}{dt} + g^i{}_{,r}\xi^r = 0,$$

"," indicates partial differentiation with respect to x^r.

$$\frac{D^2\xi^i}{dt^2} = P^i_r\xi^r,$$

where

$$P^i_j = -g^i{}_{,j} - \frac{1}{2}\, g^r g^i{}_{;r;j} + \frac{1}{2}\, \dot{x}^r g^i{}_{,r;j} + \frac{1}{4}\, g^i{}_{;r} g^r{}_{;j} + \frac{1}{2}\frac{\partial g^i{}_{;j}}{\partial t}$$

The Second KCC-invariant of the system or *deviation curvature tensor.*

The **third, fourth and fifth invariants** are:

$$R^i_{jk} = \frac{1}{3}\,(P^i_{j;k} - P^i_{k;j}),$$
$$B_j{}^i{}_{k\ell} = R^i_{jk;\ell},$$
$$D_j{}^i{}_{k\ell} = g^i_{;j;k;\ell}.$$

A basic result of the KCC-theory is the following

Theorem A. *Two* SODE's *on Ω can be locally transformed, one into the other, if and only if their five* KCC*-invariants ε^i, P^i_j, R^i_{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.*

9. Stability of trajectories

• **Linear stability**: the Liapunov stability of the steady states.

Theorem B. *If a first order system has steady state (x_0, y_0), it is stable iff the real part of the eigen values of its Jacobian at (x_0, y_0) are strict negative. If the eigen values have only imaginary part, then (x_0, y_0) is neutrally stable, otherwise it is unstable.*

• **Jacobi stability**: the Liapunov stability of the whole trajectories, or transient states.

Theorem C. *The trajectories of the SODE are JACOBI STABLE iff the real parts of the eigenvalues of the deviation curvature tensor (P^i_j) are strict negative everywhere in Ω, otherwise it is JACOBI UNSTABLE.*

The eigenstructure of the deviation curvature tensor P^j_i is an alternative to the classical Floquet theory, with the eigenvalues of P^j_i replacing the Floquet exponents.

10. The one dimensional case

Let us consider the FODE

$$\dot{x}^1 = F(x^1, x^2),\ \dot{x}^2 = G(x^1, x^2)$$

and let us assume that we can eliminate one variable so that we obtain the SODE

$$\dot{x} = y,\ \dot{y} = -g^1(x, y),$$

with a steady-state given by $(x_0,\ 0)$.

The variational equation

$$\ddot{\xi} + (g^1_{;1})_0\ \dot{\xi} + (g^1_{,1})_0\ \xi = 0,$$

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.

- **Second invariant**: $P^1_1 = -g^1_{,1} - \frac{1}{2}\, g^1 g^1_{;1;1} + \frac{1}{2}\, y g^1_{,1;1} + \frac{1}{4}\, g^1_{;1} g^1_{;1}$.

Consequence.

a. *The trajectories of SODE are Jacobi stable in Ω if and only if $P^1_1 < 0$ everywhere in Ω. This is equivalent to periodic deviation for the FODE.*
b. *The trajectories are Jacobi unstable in Ω if and only if $P^1_1 \geq 0$ everywhere in Ω. This is equivalent to aperiodic deviation for the FODE.*

- **Linear stability analysis** of the steady states.
- **Jacobi stability analysis** of the whole trajectories.

11. Jacobi stability for cell cycle

- **Tyson model (FODE)**

$$\frac{du}{dt} = (v-u)(k+k_4u^2) - k_6u$$
$$\frac{dv}{dt} = k_1 - k_6u,$$

u and v are the relative concentration of active MPF and total cyclin minus degraded cyclin relative to total $cdc2$.

- **The associated SODE**

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

where $x = v$, $y = dx/dt$ and

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

The constants A, B, C, D, E, F, G can be expressed by means of the parameters $k_1, k_4, \ldots$.

> The embrionic cell development can be described by the Jacobi stability analysis of production of the total cyclin (relative to the total $cdc2$).

The second invariant for the Tyson model:

$$P_1^1 = -\frac{3}{4}A^2\,y^4 + (-A\,B\,x - A\,C)\,y^3 + (-\frac{3}{2}E\,A - \frac{3}{2}D\,A\,x)\,y^2$$
$$+ (-\frac{1}{2}D - 3\,F\,A\,x - 3\,G\,A)\,y + (\frac{1}{4}D^2 - F\,B)\,x^2$$
$$+ (-G\,B + \frac{1}{2}D\,E - F\,C)\,x - F - G\,C + \frac{1}{4}E^2$$

Remark.

The variational equation, $D^2\xi^1/dt^2 = P_1^1\,\xi^1$, 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.

- **The final expression for P_1^1**

$$P_1^1 = -\frac{3}{4}\frac{{k_4}^2\,y^4}{{k_6}^4} + (-\frac{{k_4}^2\,x}{{k_6}^3} + 3\,\frac{k4^2\,k_1}{{k_6}^4})\,y^3$$
$$+ (3\,\frac{{k_4}^2\,k_1\,x}{{k_6}^3} - \frac{1}{4}\,\frac{6\,k_4\,{k_6}^3 + 6\,k_4\,k\,{k_6}^2 + 18\,{k_4}^2\,{k_1}^2}{{k_6}^4})\,y^2$$
$$+ (-\frac{1}{4}\,\frac{(12\,k_6\,k4^2\,{k_1}^2 + 12\,k_4\,{k_6}^3\,k)\,x}{{k_6}^4}$$
$$- \frac{1}{4}\,\frac{-16\,k_4\,k_1\,{k_6}^3 - 12\,{k_4}^2\,{k_1}^3 - 12\,k_4\,k_1\,k\,{k_6}^2}{{k_6}^4})y - k_4\,k\,x^2$$
$$- \frac{1}{4}\,\frac{(-4\,k_6\,{k_4}^2\,{k_1}^3 - 12\,k_4\,{k_6}^3\,k_1\,k)\,x}{{k_6}^4}$$
$$- \frac{1}{4}\frac{2\,{k_6}^5\,k + 3\,{k_4}^2\,{k_1}^4 + 10\,{k_6}^3\,k_4\,{k_1}^2 - k^2\,{k_6}^4 + 6\,k_4\,{k_1}^2\,k\,{k_6}^2 - {k_6}^6}{{k_6}^4}$$

Numerical results I.

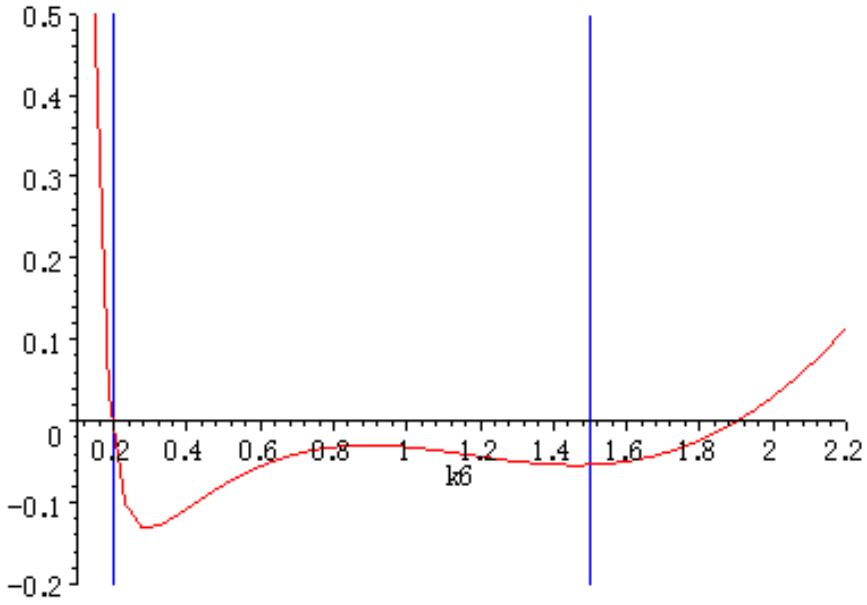


Figure 2. This graph shows $P_1^1(x_0,\ y_0)$ at the steady-states for $k_6 \in [0.1, 10]$.

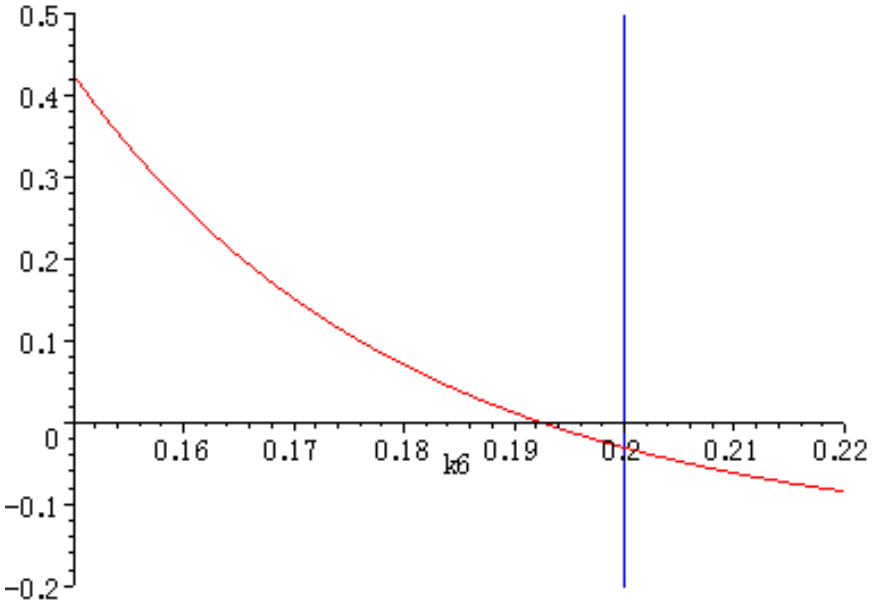


Figure 3. This graph shows $P_1^1(x_0,\ y_0)$ at the steady-states for k_6 varying within region A. The deviation vector is aperiodic for most of the range. Note that it becomes periodic for k_6 values close to the B range.

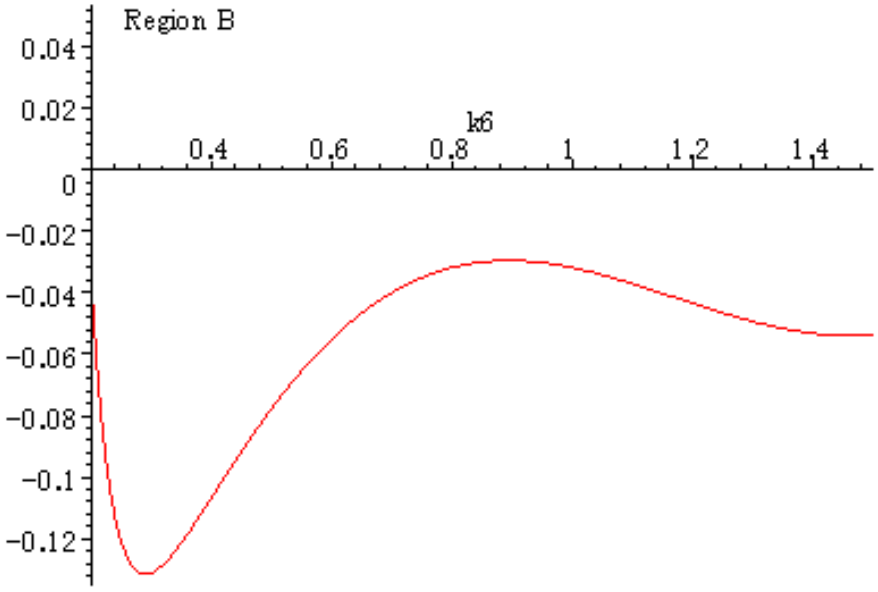


Figure 4. This graph shows $P_1^1(x_0,\ y_0)$ at the steady-states for k_6 varying within region B. The deviation vector is periodic for all of the range.

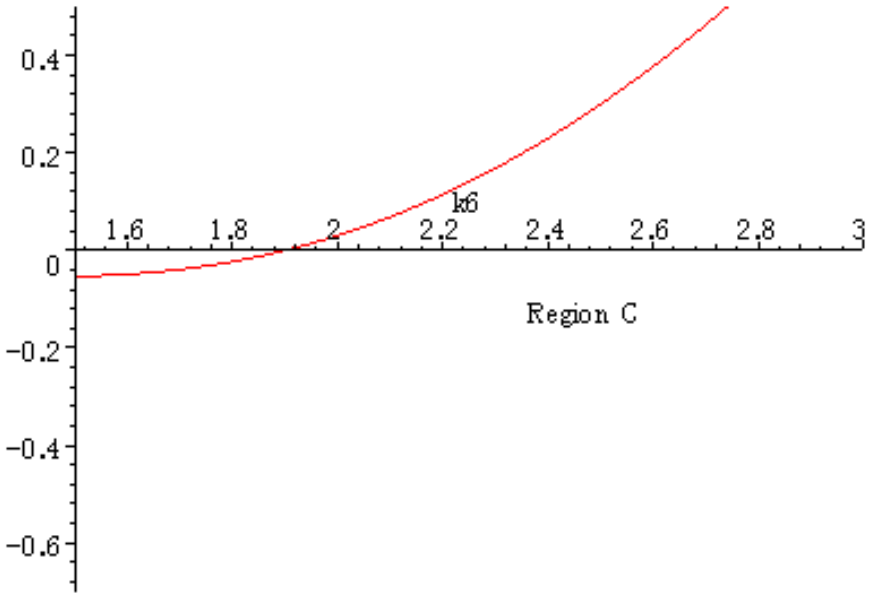


Figure 5. This graph shows $P_1^1(x_0,\ y_0)$ at the steady-states for k_6 varying within region C. The deviation vector is aperiodic for most of the range.

Numerical results II.

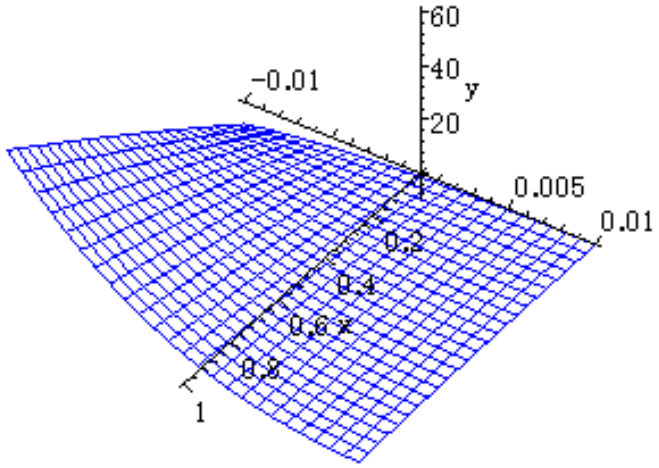


Figure 7. This graph shows P_1^1 against x and y for k_4=180 and k_6=0.1924781307, the unique k_6-value within region A such that $P_1^1(x_0,\ y_0) = 0$ at the steady-state ($x = 0.09143007729,\ y = 0$).

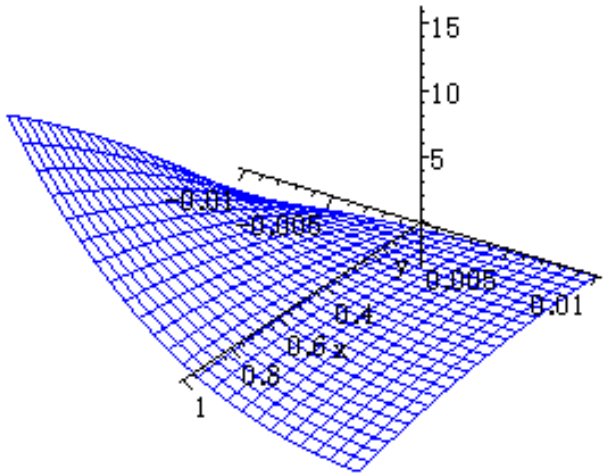


Figure 8. This graph shows P_1^1 against x and y for k_4=180 and k_6=0.2911043274, for which $P_1^1(x_0,\ y_0)$ (Figure 3) is most negative (associated with the limit cycle in the model), corresponding to the point ($x_0 = 0.08177456483,\ y_0 = 0,\ P_1^1 = -0.1316018785$) in this graph.

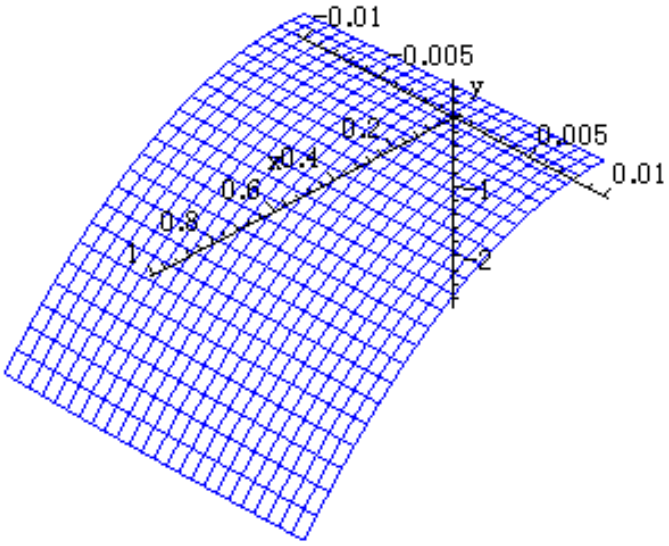


Figure 9. This graph shows P_1^1 against x and y for k_4=180 and k_6=1.460381230, for which $P_1^1(x_0,\ y_0)$ (Figure 3) has its second minimum point (associated with the excitable switch in the model), corresponding to the point ($x_0 = 0.4157874576,\ y_0 = 0,\ P_1^1 = -0.0540182526$) in this graph.

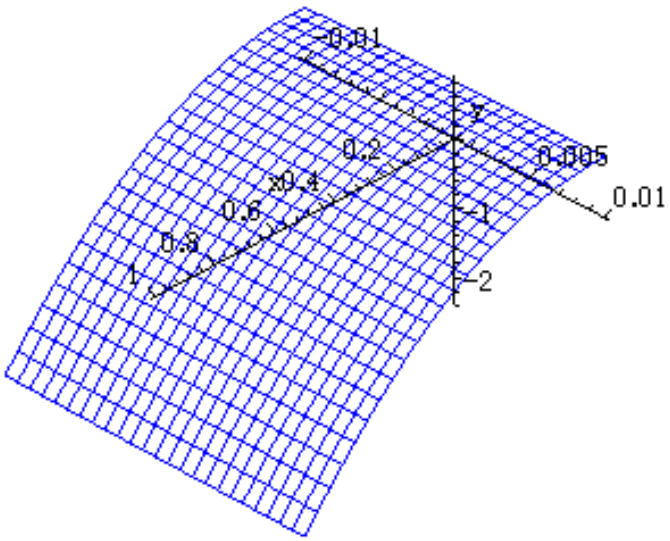


Figure 10. This graph shows P_1^1 against x and y for k_4=180 and k_6=1.900932822, the unique k_6-value within region C such that $P_1^1(x_0,\ y_0) = 0$ at the steady-state ($x = 0.5214518040,\ y = 0$).

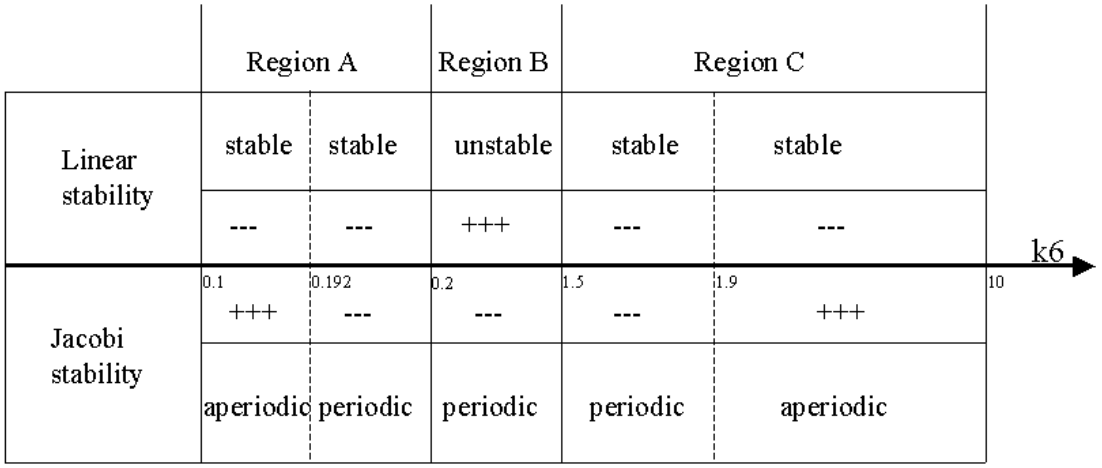
12. Conclusion

- **Linear stability analysis.**

• *Mode A-Linear Stability*: steady state of high MPF activity that corresponds to the metaphase arrest of unfertilized eggs.

• *Mode B-Linear Unstability*: autonomous oscillations (limit cycle) that corresponds to rapid cyclin gin early embrios.

• *Mode C-Linear Stability*: excitable steady state with low MPF activity that corresponds to the interphase arrest of resting cells.



- **Jacobi stability analysis.**

• *Mode A*: Jacobi stability for almost all values of k_6, but become instable near the boundary with mode B.

The egg stops developing as usual and dies away.

• *Mode B*: Jacobi unstability with two distinct local minima, one corresponding to the limit cycle of the system (the deepest one) and the other corresponding to the cell excitable switch. The instability region is larger than initialy estimated by linear stability analysis.

• *Mode C*: Jacobi stability for almost all values of k_6, but become instable near the boundary with mode B.

The cell is perturbed out the basin of attraction and it dies away or it divides endlessly.

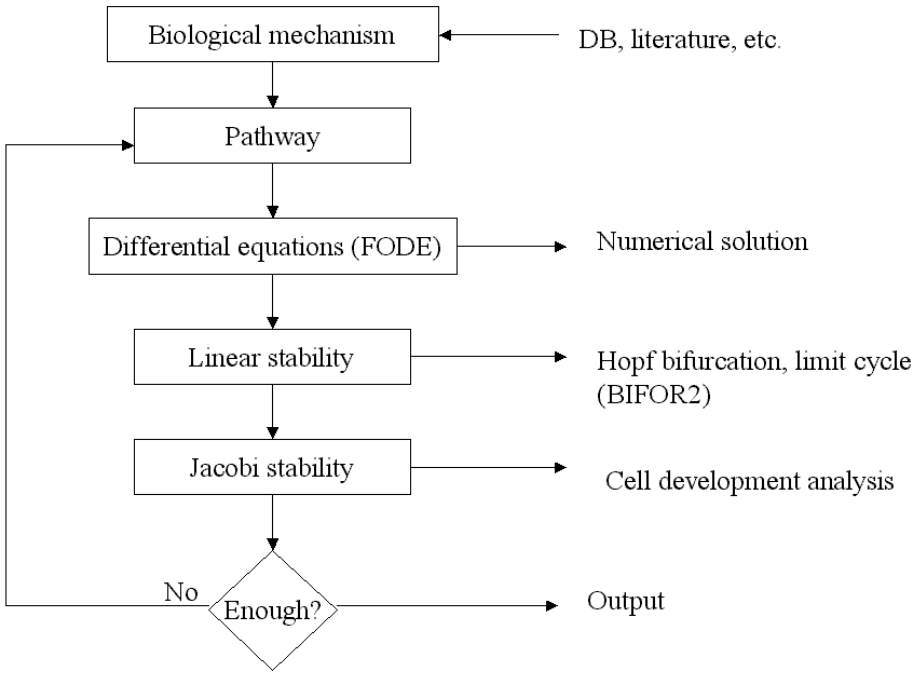
Remarks.

• Estimation of the eigenvalues of P_i^j at a certain point gives the behavior of the trajectories in a neighbourhood of that point.

• Jacobi stability analysis gives a more accurate picture of cell growth than the linear stability analysis alone.

Future work.

The process of cell development investigation and drug design.



Open problems.

1. Biological meaning of the geometry associated to a SODE (in the sense of Bryant or Foulon)?

2. What kind of mathematics do we need to get a fightfull picture of the cell that can be implemented as a software?

References

[Al] Alberts, B., Bray, D., Lewis, J., Rolf, M., Roberts, K., Watson, J.D., *Molecular Biology of the Cell, Third Edition,*, Garland Publ. Inc. (1994).

[AB] Antonelli, P., L., Bradbury, R.H., *Volterra-Hamilton models in the Ecology and Evolution of Colonial organisms*, World Scientific (1996).

[AIM] Antonelli, P., L., Ingarden, R., Matsumoto, M., *The theory of sprays and Finsler spaces with applications in physics and biology*, Kluwer Acad. Publ., FTPH **58** (1993).

[Ant1] Antonelli, P.L., *Equivalence problem for Systems of second-order ordinary differential equations*, Encyclopedia of Mathematics, Kluwer Acad. Publ. (2000).

[Ant1] Antonelli, P.L., *Mathematical ecology*, Encyclopedia of Mathematics, Kluwer Acad. Publ. (2000).

[CG] Carbone, A., Gromov, M., *Mathematical slices of Molecular Biology*, Gazette des Mathématiciens, Numérce spécial, Société Mathématique de France **88,** (Avril 2001), 11–80.

[Car] Cartan, E., *Observations sur le mémoir précédent*, Math. Zeitschrift **37,** (1933), 619–622.

[Ch] Chern, S. S., *Sur la géometrie d'un système d'equations differentialles du second ordre*, Bull. Sci. Math. **63,** (1939), 206–212.

[CHC] Chern, T., He, H., Church, G., *Modeling gene expression with differential equations*, 1999 Pacific Symposium on Bioinformatics, World Scientific (1999), 29–40.

[Ko] Kosambi, D. D., *Parallelism and path-space*, Math. Zeitschrift **37,** (1933), 608–618.

[Maple] http://maplesoft.com..

[Mirs] Minorsky, N., *Nonlinear Oscillations*, D. Van Nostrand Company, Inc., Princeton, New Jersey, (1962).

[SHNI] Sabau, V.S., Hashimoto, S., Nemoto, Y., Ihara, S., *Cell simulation for circadian rhythm based on Michaelis-Menten model*, to appear in Journal of Biological Physics, Kluwer Acad. Publ. (2002).

[Ty] Tyson, J., *Modeling the cell division cycle: cdc2 and cyclin interactions*, Proc. Natl. Acad. Sci. USA, Cell Biology **88,** (August 1991), 7328–7332.