Dynamical models for the cell cycle

W. Govaerts   C. Sonck

Department of Applied Mathematics and Computer Science
Ghent University
Belgium

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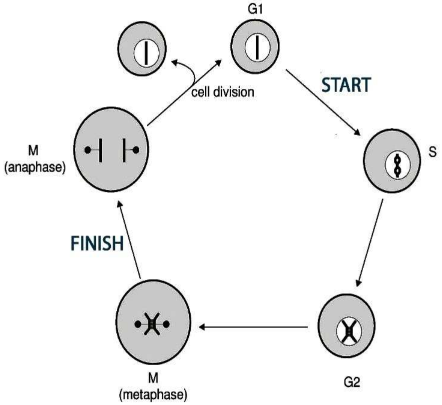
Outline

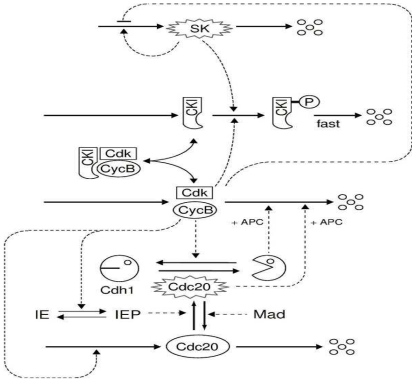
The basic mechanisms of the cell cycle

- Cell cycle: 4 phases (G1, S, G2, M)



- Irreversible transitions (Start and Finish)
- Need for tight regulation

- Antagonistic relationship between cyclin/Cdk and Cdh1/APC proteins, central components in the cell cycle.



- 2 stable steady states:
  - G1 state with high Cdh1/APC activity and low cyclin/Cdk activity
  - S-G2-M state with high cyclin/Cdk activity and low Cdh1/APC activity

Models for the cell cycle

- 2 of the models proposed by J.J. Tyson and B. Novák
  - the toy model
  - the budding yeast model
- References
  - Tyson J.J. and Novák B. (2001) Regulation of the Eukaryotic Cell Cycle: Molecular Antagonism, Hysteresis, and Irreversible Transitions. *J. theor. Biol* 210, 249-263.
  - Fall C.P., Marland E.S., Wagner J.M. and Tyson J.J., ed. (2002) *Computational Cell Biology*, Springer, Chapter 10.
- Computational results: MatCont

The toy model of Tyson and Novák

- Basic model for a fixed cell mass m:

$$\frac{dX}{dt} = k_1 - (k_2' + k_2'' Y)X,$$
$$\frac{dY}{dt} = \frac{(k_3' + k_3'' A)(1 - Y)}{J_3 + 1 - Y} - \frac{k_4 m X Y}{J_4 + Y},$$
$$\frac{dA}{dt} = k_5' + k_5'' \frac{(mX)^n}{J_5^n + (mX)^n} - k_6 A$$

with $X = [\text{cyclin/Cdk}]$, $Y = [\text{active Cdh1/APC}]$ and $A = [\text{activator of Cdh1/APC at Finish}]$

- For growing mass: equation $\dfrac{dm}{dt} = \mu m$ added
  - μ growth parameter

Equilibrium bifurcation diagram for the toy model ($k_4 = 35$)

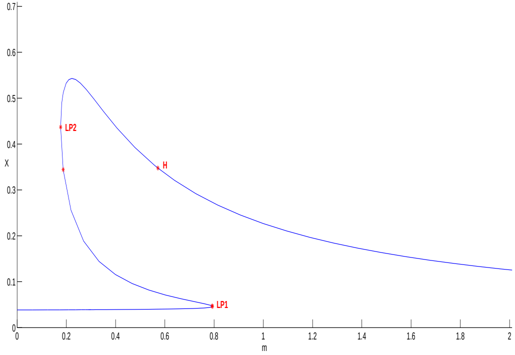


Figure: Equilibrium bifurcation diagram for the toy model (parameters $k_1 = 0.04$, $k_2' = 0.04$, $k_2'' = 1$, $k_3' = 1$, $k_3'' = 10$, $k_4 = 35$, $J_3 = 0.04$, $J_4 = 0.04$, $k_5' = 0.005$, $k_5'' = 0.2$, $k_6 = 0.1$, $J_5 = 0.3$, $n = 4$)

- 2 disjoint stable parts: before LP1, between LP2 and H
- Stable periodic orbits coming from the right and tending to a HSN orbit
- Time in S-G2-M phase tends to infinity as μ tends to 0

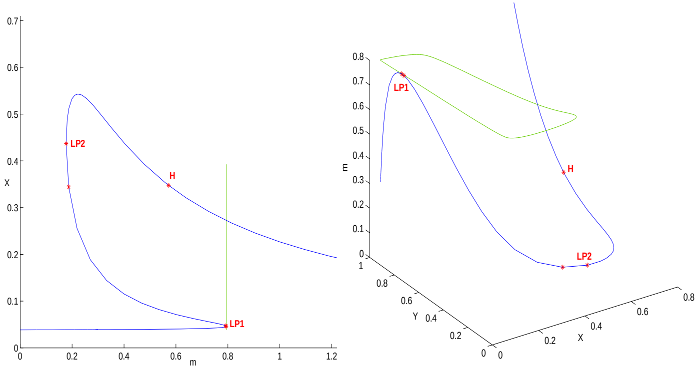


Figure: Intersection of the equilibrium bifurcation curve with the HSN orbit for the toy model in the (m, X)-plane and in the (X, Y, m)-space (for $k_4 = 35$).

Equilibrium bifurcation diagram for the toy model ($k_4 = 18$)

- In domain relevant for interpretation
  - stable equilibria before Hopf point H1
  - other parts unstable

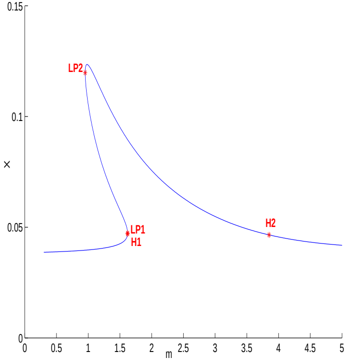


Figure: Equilibrium bifurcation diagram for the toy model (same parametervalues as before, except $k_4 = 18$)

- Stable periodic orbits coming form the right and tending to a HHS orbit
- Time in S-G2-M phase is a priori limited (independent of μ)

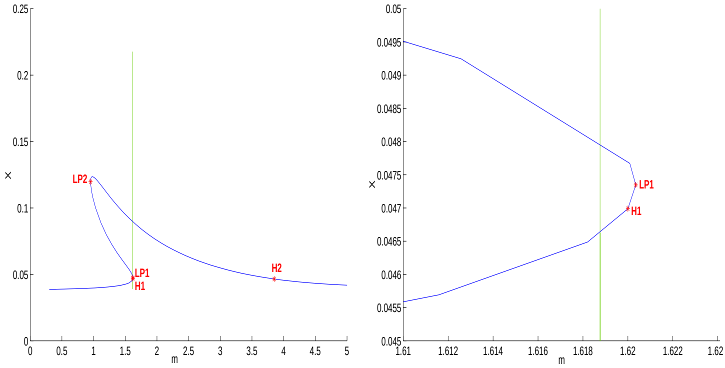


Figure: Intersection of the equilibrium bifurcation curve with the HHS orbit for the toy model in the (X, A)-plane (for $k_4 = 18$).

HSN, HHS and NCH orbits

- Large stable periodic orbits can end either in a HHS or a HSN orbit
- Transition: NCH orbit

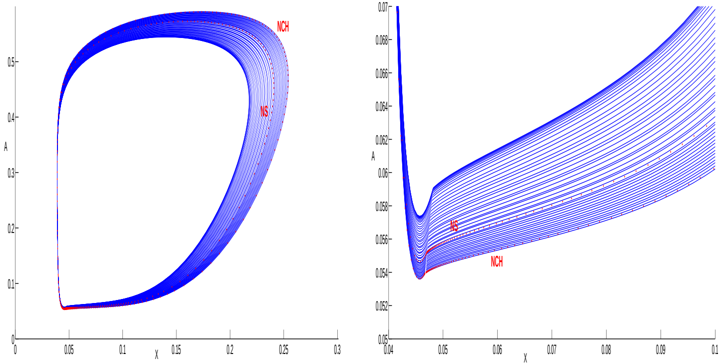
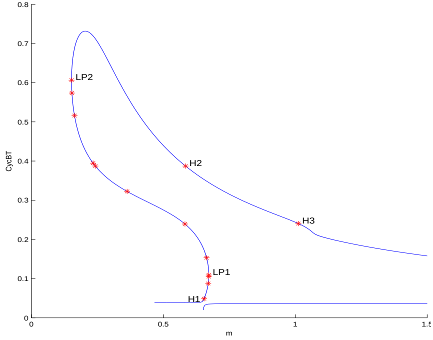


Figure: A curve of HHS orbits tending to a NCH orbit for the toy model in the (X, A)-plane.

The budding yeast model of Tyson and Novák

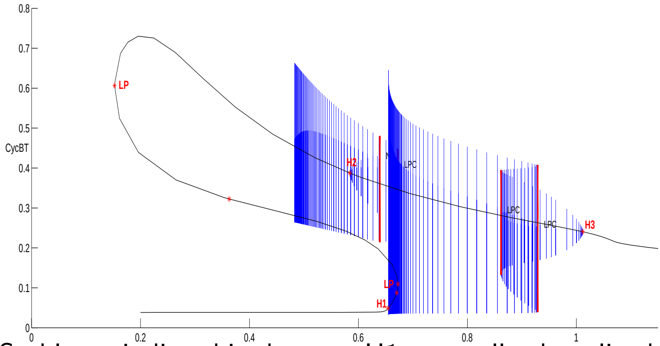
$$
\begin{aligned}
\frac{d[CycB]_T}{dt} &= k_1 - (k_2' + k_2''[Cdh1] + k_2'''[Cdc20]_A)[CycB]_T, \\
\frac{d[Cdh1]}{dt} &= \frac{(k_3' + k_3''[Cdc20]_A)(1-[Cdh1])}{J_3 + 1 - [Cdh1]} - \frac{(k_4 m[CycB] + k_4'[SK])[Cdh1]}{J_4 + [Cdh1]}, \\
\frac{d[Cdc20]_T}{dt} &= k_5' + k_5'' \frac{(m[CycB])^n}{J_5^n + (m[CycB])^n} - k_6[Cdc20]_T, \\
\frac{d[Cdc20]_A}{dt} &= \frac{k_7[IEP]([Cdc20]_T - [Cdc20]_A)}{J_7 + [Cdc20]_T - [Cdc20]_A} - \frac{k_8[Mad][Cdc20]_A}{J_8 + [Cdc20]_A} - k_6[Cdc20]_A, \\
\frac{d[IEP]}{dt} &= k_9 m[CycB](1-[IEP]) - k_{10}[IEP], \\
\frac{d[CKI]_T}{dt} &= k_{11} - (k_{12}' + k_{12}''[SK] + k_{12}''' m[CycB])[CKI]_T, \\
\frac{d[SK]}{dt} &= k_{13}' + k_{13}''[TF] - k_{14}[SK], \\
\frac{d[TF]}{dt} &= \frac{(k_{15}' m + k_{15}''[SK])(1-[TF])}{J_{15} + 1 - [TF]} - \frac{(k_{16}' + k_{16}'' m[CycB])[TF]}{J_{16} + [TF]}, \\
[CycB] &= [CycB]_T - [Trimer], \\
[Trimer] &= \frac{2[CycB]_T[CKI]_T}{\Sigma + \sqrt{\Sigma^2 - 4[CycB]_T[CKI]_T}}, \\
\Sigma &= K_{eq}^{-1} + [CycB]_T + [CKI]_T.
\end{aligned}
$$

Equilibrium bifurcation diagram



- supercritical Hopf points H1, H2 and H3
- 3 disjoint stable parts: before H1, between LP2 and H2, beyond H3

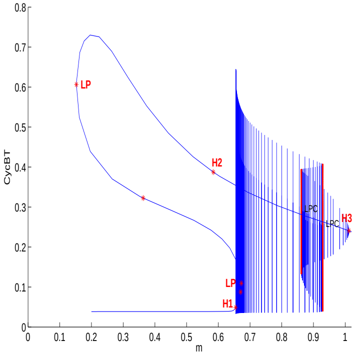
Periodic orbit bifurcation diagram

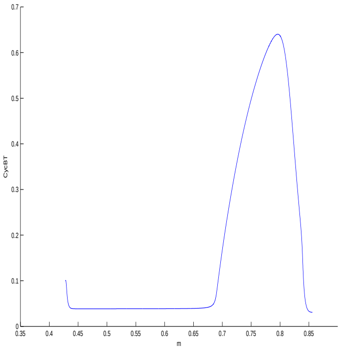


- Stable periodic orbits born at H1 are really short-lived and die at HHS orbit
- Stable periodic orbits born at H2 lose stability at LPC and return as unstable periodic orbits
- Stable periodic orbits born at H3
  - turn and become unstable at LPC1
  - turn again and become stable again at LPC2
  - die eventually at HHS orbit

The dynamic mass cell model

- Equation $\frac{dm}{dt} = \mu m$ added to the budding yeast model
- With growing mass, different stages:
  - lower left branch of stable equilibria (growth in G1 phase)
  - loses stability at H1 for $m = m_{REP} = 0.6546307$ (start of DNA replication)
  - attracted by stable periodic orbits born at H3





HSN, HHS and NCH orbits

- The large limit cycles (born at H3) can end either in a HHS or a HSN orbit dependent on parameter values
  - analogue to the case of the toy model
- Time in S-G2-M phase
  - either limited independently of growth rate μ
  - either arbitrary large for μ sufficiently small

The slow-fast system

- For a large range of initial values of m and the concentration variables: same behaviour of the initial segment of the orbit

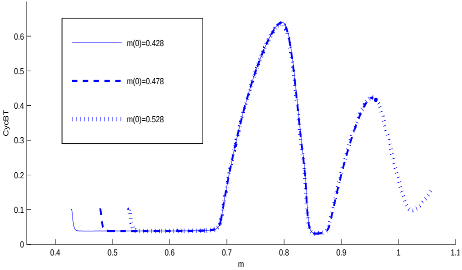


Figure: Orbits starting from $m = 0.428$, 0.478 and 0.528.

- Slow-fast system with m as slow variable and concentration variables as fast ones
- Computation of the cell cycle as a fixed point of a map possible

Growth rate versus mass increase in S-G2-M phase

- Effect of change of growth rate μ on orbits

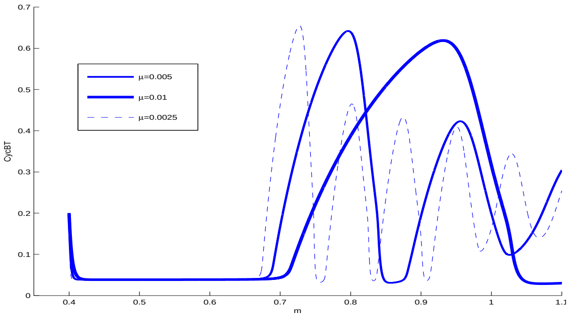


Figure: Growth of a cell for three different values of μ.

- all orbits first converge to quasi-steady state solutions
- when $m > m_{REP}$: system starts oscillating with a damped amplitude

Growth rate versus mass increase in S-G2-M phase

- m_{NEW}: mass of a newborn cell.
- m_{REP}: mass at onset of DNA replication.
- m_{DIV} = value of m at which $[CycB]_T$ reaches its first minimum value after m_{REP}.

μ	m_{REP}	m_{DIV}	$\frac{m_{DIV}-m_{REP}}{\mu}$
0.02	0.6546307	1.5933184	46.9344
0.01	0.6546307	1.0724438	41.7813
0.005	0.6546307	0.8564426	40.3624
0.0025	0.6546307	0.7557679	40.4549
0.00125	0.6546307	0.7053451	40.5715
0.000625	0.6546307	0.6797931	40.2599
0.0003125	0.6546307	0.6674274	40.9497
0.00015625	0.6546307	0.6644945	63.1282

Table: Values of the growth rate μ with corresponding values m_{REP} and m_{DIV}, and ratio $\frac{m_{DIV}-m_{REP}}{\mu}$.

- For values of μ between 0.0003125 and 0.01
  - ratio $\frac{m_{DIV} - m_{REP}}{\mu}$ nearly constant $\approx C = 40.73$.

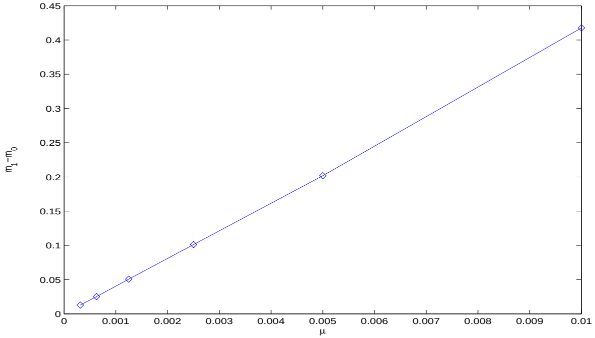


Figure: Graphical interpretation of Table 1.

Interpretation for $m_{DIV} - m_{REP} \approx C\,\mu$ [1]

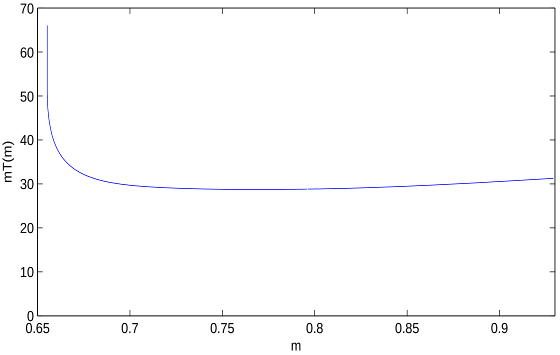


Figure: Representation of $mT(m)$ versus m for the large stable orbits born at H3.

- m in the range of the stable periodic orbits born at H3
- $T(m)$ is the period of the large stable periodic orbit at m

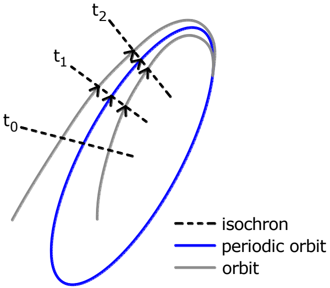
Interpretation for $m_{DIV} - m_{REP} \approx C\,\mu$ [2]

- $mT(m) \approx C_1 \approx 30$ in this range of m except for m very close to the homoclinic orbit

Put

- $\Delta t =$ time between birth of cell and cell division
- $\Delta t = \Delta_1 t + \Delta_2 t$, with
  - $\Delta_1 t =$ time between birth of cell and onset of DNA-replication (time in G1 phase)
  - $\Delta_2 t =$ time between onset of DNA-replication and cell division (time in S-G2-M phase)

Let the periodic orbits in the fast manifold during the S-G2-M phase be parameterized by a phase variable $\phi \in [0, 1]$. Orbits in the neighborhood can be parameterized accordingly by identifying points on an isochron.



During a time dt a fraction $\frac{dt}{T(m(t))}$ is traversed by the isochron that contains the fast state variable. Let ρ be the total fraction of a periodic orbit traversed during S-G2-M phase.

Interpretation for $m_{DIV} - m_{REP} \approx C\,\mu$ [3]

We then have

$$\int_0^{\Delta_2 t} \frac{dt}{T(m(t))} = \rho$$

$$\int_0^{\Delta_2 t} m(t) \frac{dt}{m(t)\,T(m(t))} = \rho$$

Taking into account that $m(t)\,T(m(t)) \approx C_1$, we conclude

$$\int_0^{\Delta_2 t} m_{REP}\, e^{\mu t} dt \approx C_1 \rho$$

$$\frac{1}{\mu} m_{REP}(e^{\mu \Delta_2 t} - 1) \approx C_1 \rho$$

$$\frac{m_{DIV} - m_{REP}}{\mu} \approx C_1 \rho$$

Interpretation for $m_{DIV} - m_{REP} \approx C\,\mu$ [4]

- $C \approx C_1 \rho$
- Total fraction of a periodic orbit traversed during S-G2-M phase: $\rho \approx \frac{C}{C_1} \approx 1.33$ is constant, i.e. independent of μ.
- Argument fails if
  - μ is very small: important part of the orbit in region close to homoclinic orbit, where $mT(m)$ is large
  - μ is large: important part of the orbit in region where no periodic orbits exists

Duration of the phases of the cell cycle

Put

- $m_{NEW} = m_{DIV}/\nu$
- $m_{DIV} = m_{NEW} e^{\mu \Delta t} = \nu m_{NEW}$
  - $e^{\mu \Delta t} = \nu$ or $\Delta t = \dfrac{\ln \nu}{\mu}$
- $m_{DIV} = m_{REP} e^{\mu \Delta_2 t} \approx m_{REP} + C\mu$
  - $\Delta_2 t \approx \dfrac{1}{\mu} \ln \left(1 + \dfrac{C\mu}{m_{REP}} \right)$
  - $\Delta_1 t \approx \dfrac{\ln \nu}{\mu} - \dfrac{1}{\mu} \ln \left(1 + \dfrac{C\mu}{m_{REP}} \right)$

Robustness of the model

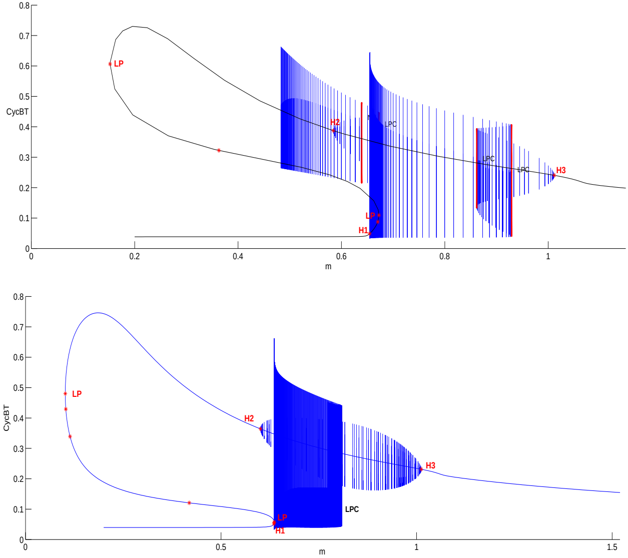


Figure: Bifurcation diagram for resp. $k'_{13} = 0$ (as before) and $k'_{13} = 0.2$.

- Different behaviour for change of parameter values
- 2-parameter study of the Hopf points and the LPCs

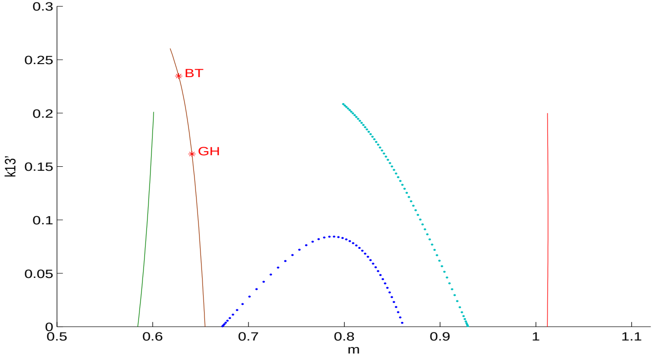
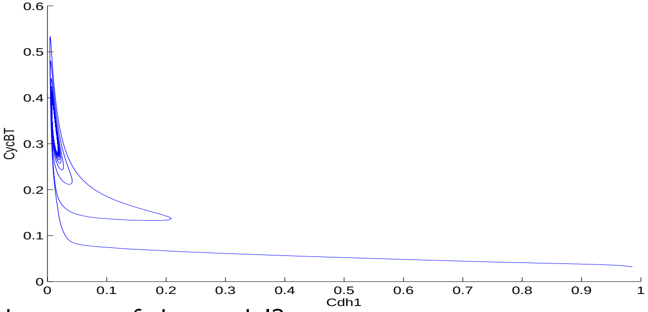


Figure: Continuation of resp. H2 (green curve), H1 (brown curve), LPC corresponding to H2 and first LPC corresponding to H3 (blue dotted line), second LPC corresponding to H3 (light blue dotted line) and H3 (red curve) in (m, k'_{13})-space.

- H1 (brown curve): loss of stability of G1 phase

- For rising value of k'_{13}: domain of bistability of periodic orbits becomes bigger
  - For example for $k'_{13} = 0.2$: "small" stable periodic orbits between green and red curve and "large" stable periodic orbits to the left of dotted light blue curve
  - Example of orbit that is attracted to "small" stable periodic orbit for $k'_{13} = 0.2$ and $m = 0.65$ (value slightly larger than that of H1)



- Robustness of the model?