Analysis of simple tumour-growth models

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Outline

- Introduction
- Simple models
  - exponential growth
  - logistic growth
  - Gompertz growth
  - Minimal mitotic oscillator cascade model
- Attractors
- Bifurcation theory
- Computer exercises (octave)

Logistic growth population model

Density-dependent growth

$$\frac{dN}{dt} = f(N) = rN\Big(1 - \frac{N}{K}\Big)$$

$N(t) \geq 0$: tumour size

$r > 0$: intrinsic growth rate
$K > 0$: carrying capacity

Solution of initial value problem:

$$N(t) = \frac{N(0)e^{rt}}{1 + (e^{rt} - 1)N(0)/K}$$

$K = \infty$: then exponential growth

Equilibria

$N = 0 \quad$ and $\quad N = K$

Stability analysis of $R = 0$
consider linearized equation where $x = N$

$$\frac{dx}{dt} = rx \text{ solution } x(t) = x(0)e^{rt}$$

since $r > 0$ perturbations lead to divergence

Conclusion: unstable

Stability analysis of $N = K$
consider linearized equation where $x = N - K$

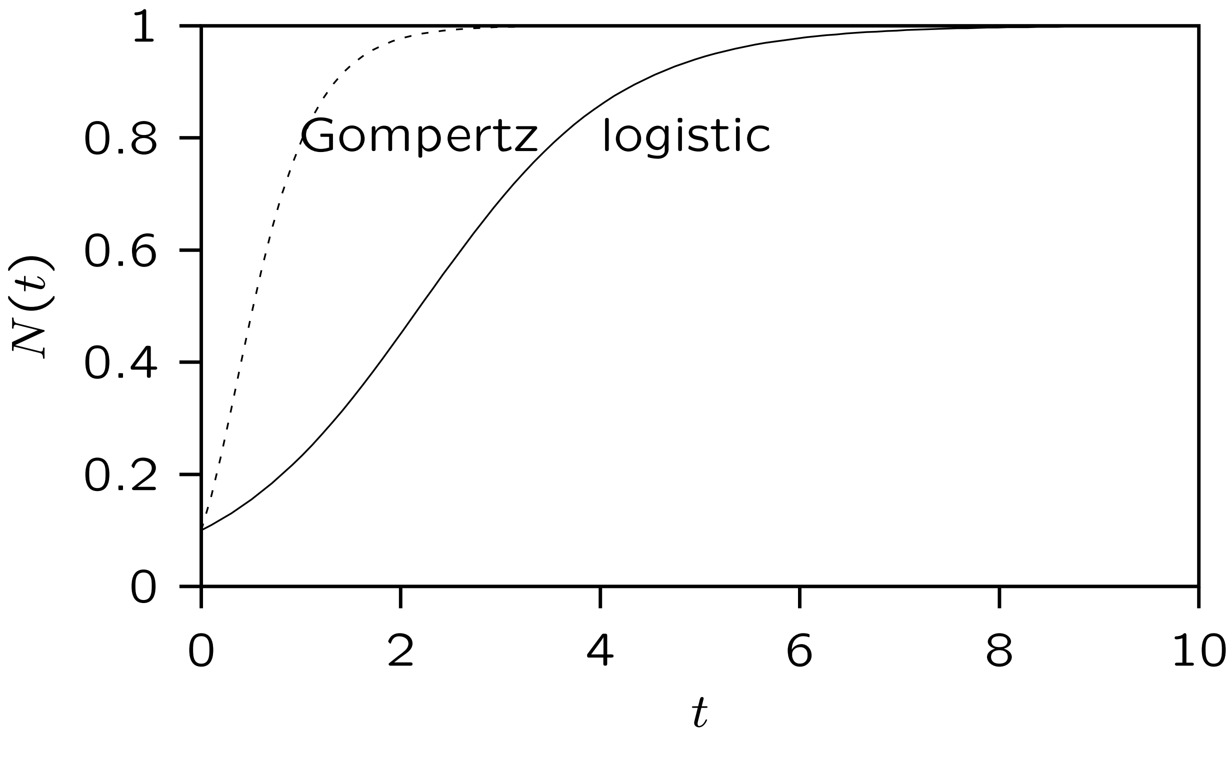
$$\frac{dx}{dt} = \left(\frac{df}{dN}\right)_K x = -rx \text{ solution } x(t) = x(0)e^{-rt}$$

since $r > 0$ perturbations lead to convergence

Conclusion: stable

Logistic growth and Gompertz:

$r = 1$ en $K = 1$



Gompertz growth population model

Non-autonomous growth equation

$$\frac{dN}{dt} = f(t, N) = r_0 e^{-\alpha t} N$$

$N(t) \geq 0$: tumour size

$r_0 > 0$: initial intrinsic growth rate
$\alpha > 0$: exponential decay rate of growth

Solution of initial value problem:

$$N(t) = K(\frac{N_0}{K})^{e^{-\alpha t}}$$

where

$$K = N_0 e^{r_0/\alpha}\,, \quad \text{that is} \quad \alpha = \frac{r_0}{\ln(\frac{K}{N_0})}$$

Another formulation

$$\frac{dN}{dt} = -\alpha \ln(N/K)\, N$$

Logistic growth with predation

$$\frac{dN}{dt} = rN\Big(1 - \frac{N}{K}\Big) - p$$

$N(t):$ tumour size

$r > 0:$ intrinsic growth rate

$K > 0:$ carrying capacity

$p:$ constant loss rate (due to treatment?)

Equilibria

$$N^* = K\Big(\frac{1}{2} \pm \sqrt{\frac{1}{4} - \frac{p}{rK}}\Big)$$

$0 \leq p < rK/4:$ two positive equilibria
$p = p_T = rK/4:$ one equilibrium $N^* = 1/2K$
$p > rK/4:$ no solution!

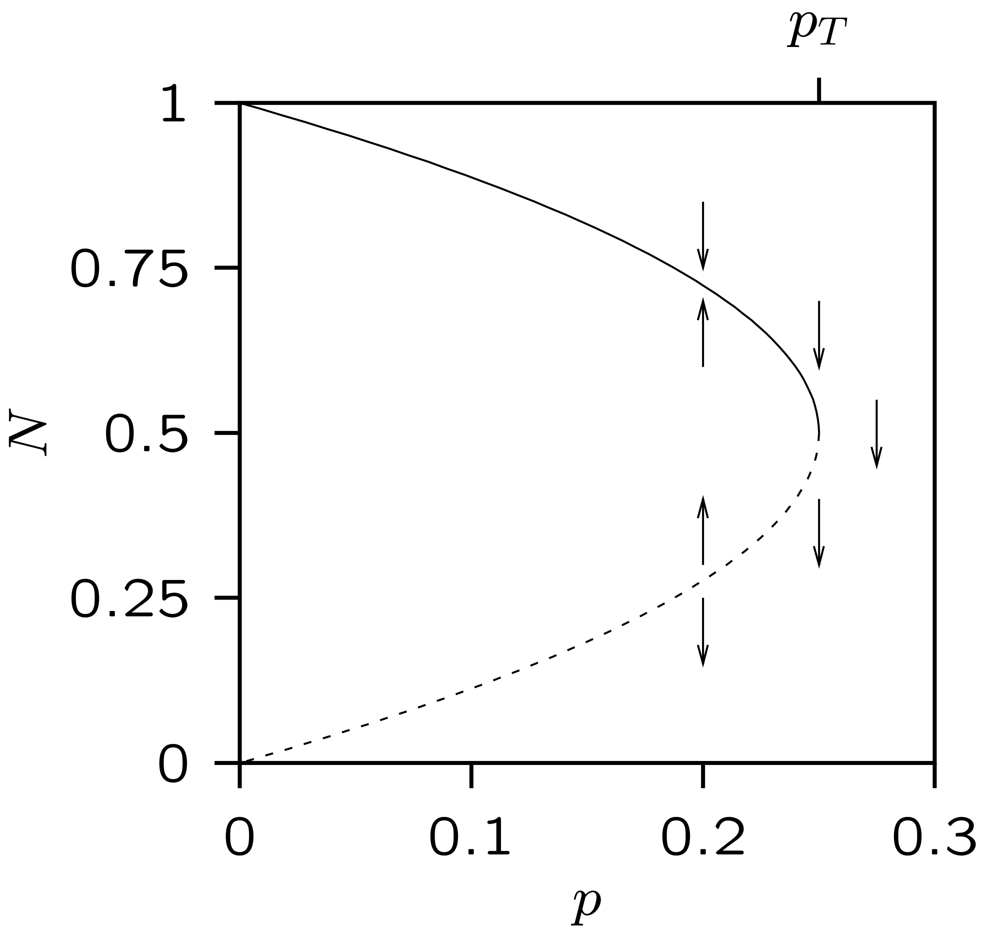
Stability

$0 \le p \le rK/4$

$$\frac{dx}{dt} = \mp r\Big(\sqrt{1 - \frac{4p}{rK}}\Big)x$$

$p < p_T$ then:
$\text{Stable}: \; N^* = K(1/2 + \sqrt{(}1/4 - p/rK))$
$\text{Unstable}: \; N^* = K(1/2 - \sqrt{(}1/4 - p/rK))$
$R(0) > K(1/2 - \sqrt{(}1/4 - p/rK))$:
convergence to stable equilibrium
$R(0) < K(1/2 - \sqrt{(}1/4 - p/rK))$:
solution becomes negative

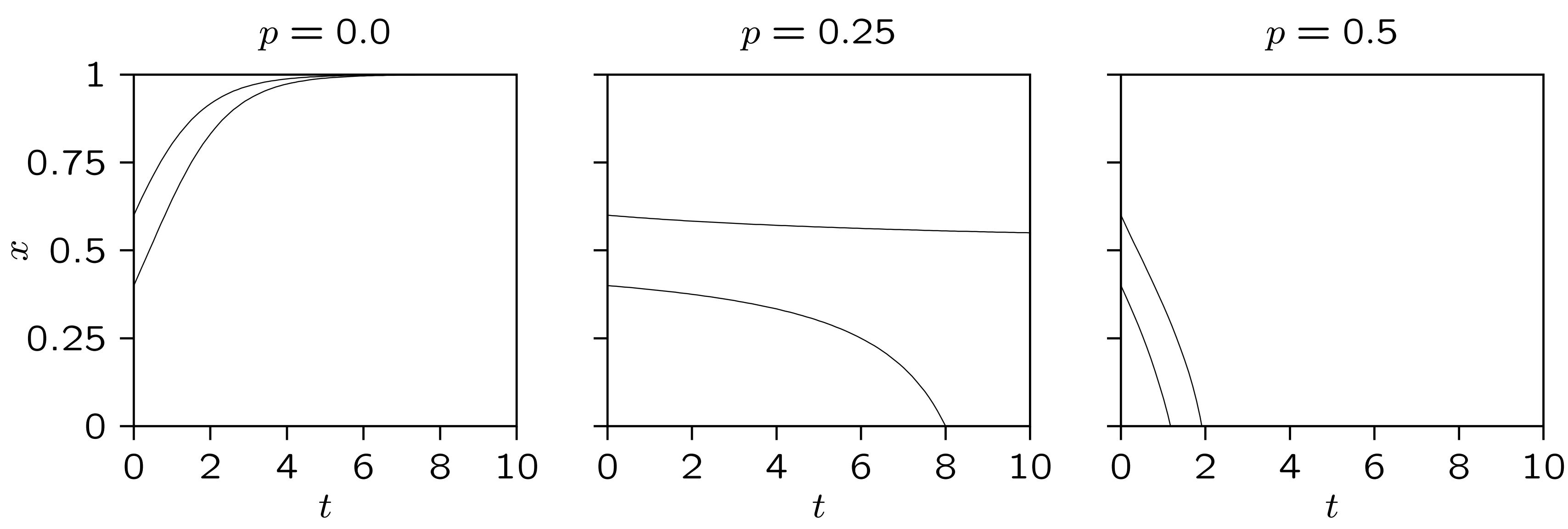
Logistic growth with predation where:
$r = 1$ en $K = 1$



Bifurcation at $p = p_T$
solid line : stable equilibrium
dashed line : unstable equilibrium

Logistic growth with predation

where $r = 1$ en $K = 1$



Stability of Gompertz model

We formulate the model as an equivalent autonomous system:

$$\frac{dN}{dt} = f(N, r) = rN$$
$$\frac{dr}{dt} = g(N, r) = -\alpha r$$

$N(t)$: tumour size

$r(t)$: actual growth rate

and initial conditions:

$N(0) = N_0$ and $r(0) = r_0$

Equilibria

Trivial solution

$$\begin{aligned} N &= 0 \\ r &= 0 \end{aligned}$$

and positive (tumour size) solution

$$\begin{aligned} N &= K \\ r &= 0 \end{aligned}$$

Stability analysis is much more difficult!
Now two state-variables

Linearization: Jacobian matrix J

$$\begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \end{pmatrix} = \mathbf{J} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} \mathbf{J}_{11} & \mathbf{J}_{12} \\ \mathbf{J}_{21} & \mathbf{J}_{22} \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

$$\begin{pmatrix} \frac{dx}{dt} \\ \\ \frac{dy}{dt} \end{pmatrix} = \begin{pmatrix} \frac{\partial f}{\partial N} & \frac{\partial f}{\partial r} \\ \\ \frac{\partial g}{\partial N} & \frac{\partial g}{\partial r} \end{pmatrix}_{N^*,r^*} \begin{pmatrix} x \\ \\ y \end{pmatrix}$$

where $x(t) = N(t) - N^*$ and $y(t) = r(t) - r^*$

characteristic equation

When characteristic equation is satisfied

$$\lambda^2 + (\mathbf{J}_{11} + \mathbf{J}_{22})\lambda + \mathbf{J}_{11}\mathbf{J}_{22} - \mathbf{J}_{12}\mathbf{J}_{21} = 0$$

There are two solutions:

$$\lambda_{1,2} = 0.5(\mathbf{J}_{11} + \mathbf{J}_{22})$$
$$\pm\sqrt{(0.5(\mathbf{J}_{11} + \mathbf{J}_{22}))^2 - (\mathbf{J}_{11}\mathbf{J}_{22} - \mathbf{J}_{12}\mathbf{J}_{21})}$$

$\lambda_{1,2}$ are called *eigenvalues*

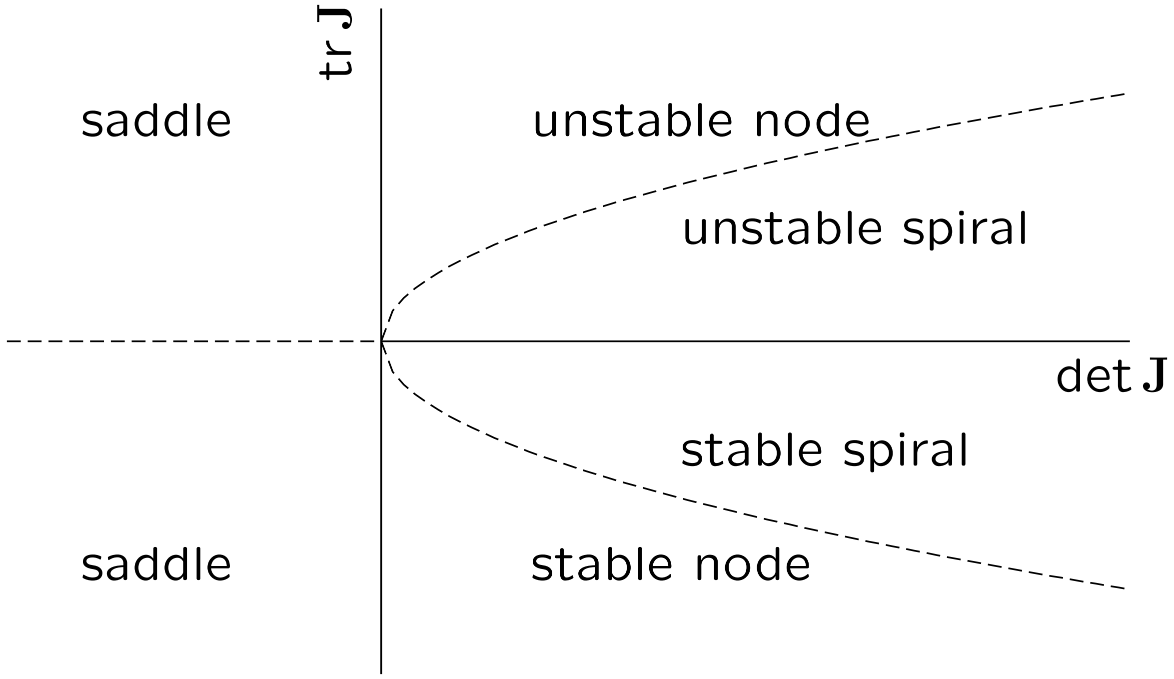
General solution

$$\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = c_1 e^{\lambda_1 t}\mathbf{v}_1 + c_2 e^{\lambda_2 t}\mathbf{v}_2$$

λ_1 and λ_2 are eigenvalues; $\mathbf{v}_1$ and $\mathbf{v}_2$ eigenvectors of the Jacobian $\mathbf{J}$ calculated in equilibrium.

Constants c_1 and c_2 are fixed by the initial conditions $x(0)$ en $y(0)$

Classification of equilibrium points



$$\mathrm{tr}\,\mathbf{J} = \mathbf{J}_{11} + \mathbf{J}_{22} = \mathrm{Re}\,\lambda_1 + \mathrm{Re}\,\lambda_2$$
$$\det\mathbf{J} = \mathbf{J}_{11}\mathbf{J}_{22} - \mathbf{J}_{12}\mathbf{J}_{21} = \lambda_1\lambda_2$$
$$\mathrm{disc}\,\mathbf{J} = 0.25\,(\mathrm{tr}\,\mathbf{J})^2 - \det\mathbf{J}$$

where $\lambda_{1,2} = 0.5(\mathrm{tr}\,\mathbf{J} \pm \sqrt{\mathrm{disc}\,\mathbf{J}})$

Equilibrium is stable when: $\mathrm{Re}\,\lambda_1 < 0$ and $\mathrm{Re}\,\lambda_2 < 0$

Stability of Gompertz model

non-zero solution $N^* = K$

$$\begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \end{pmatrix} = \begin{pmatrix} r & N^* \\ & \\ 0 & -\alpha \end{pmatrix}_{\substack{N^* = K \\ r^* = 0}} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 & K \\ 0 & -\alpha \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

$\mathrm{tr}\,\mathbf{J} = -\alpha$ and $\det\mathbf{J} = 0$

eigenvalues $\lambda_1 = 0$ and $\lambda_2 = -\alpha$
eigenvectors

$$\mathbf{v}_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathbf{v}_2 = \begin{pmatrix} -K/\alpha \\ 1 \end{pmatrix}$$

- α primary parameter
  K depends on initial value N_0 and therefore no stability

- K primary parameter
  α depends on N_0
  Because one zero eigenvalue no stability
  If $r_0 > 0$ then: $N_0 < K$ then $\alpha > 0 \Rightarrow \lambda_2 < 0$ and locally convergence to K while $N_0 > K$ implies $\alpha < 0$ and convergence to K is impossible

  It can be shown that globally with $r_0 > 0$

  - $0 < N(0) \leq K$: solution converges to K for $t \to \infty$

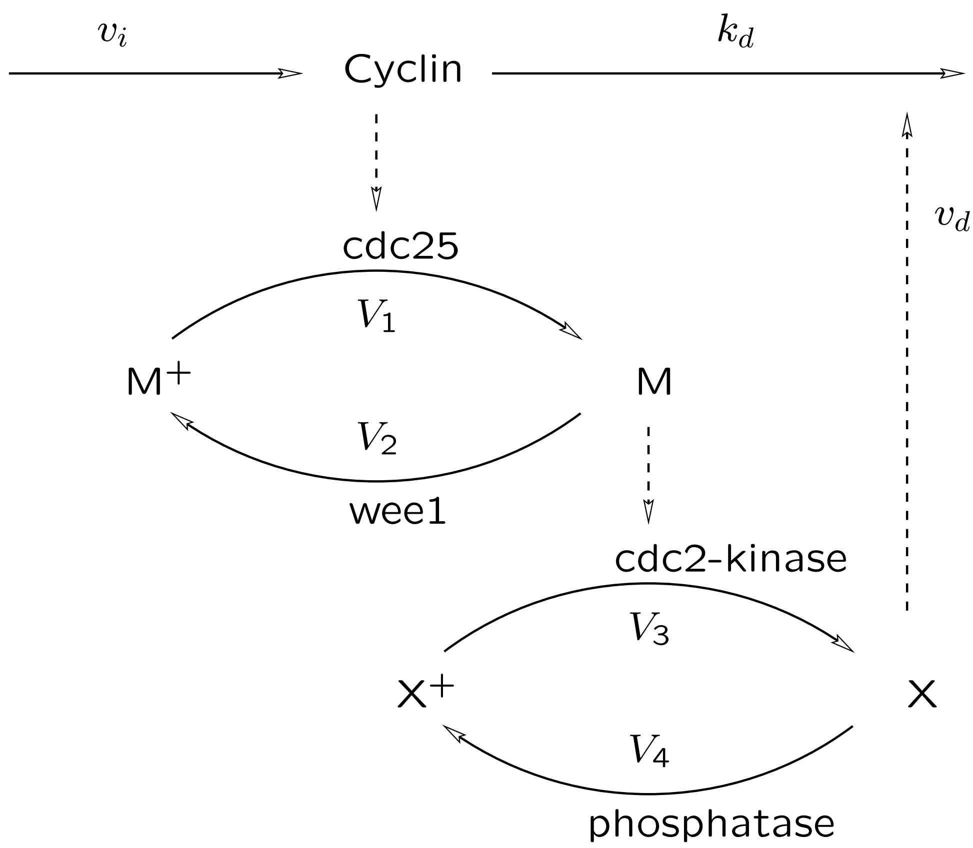
  - $N(0) > K$: solution grows unbounded for $t \to \infty$

  - $N(0) = K$: $\alpha = 0$ and therefore $N(t) = N_0 = K$

Bifurcation theory

- Find equilibrium
- Stability analysis
- Continuation by varying one free parameter
- Find bifurcation point
- Continuation by varying another free parameter

minimal cascade model of Goldbeter (1997)



mitotic oscillator

The Goldbeter model for mitotic oscillator:

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C \ ,$$
$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M}$$
$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

where

$$V_1 = V_{M1} \frac{C}{K_c + C} \quad , \quad V_3 = V_{M3} M$$

$C(t)$: concentration cyclin

$M(t)$: fraction active cdc2-kinase

$X(t)$: fraction active cyclin protease

parameter values

The name cyclin reflects its periodic variation during cell cycle

Only interphase and mitosis in the dividion cycle are distinguished

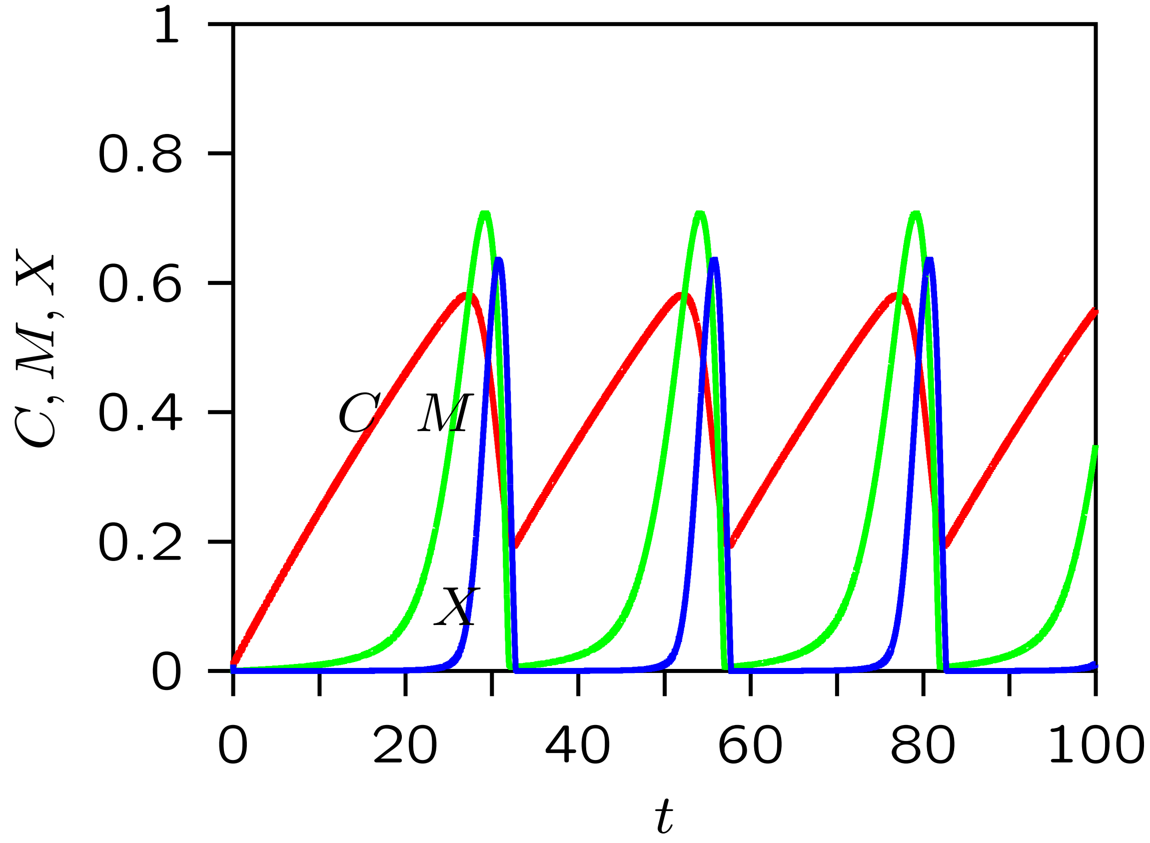
Model parameter are realistic for rapidly dividing amphibian embryonic cells

Period of the mitotic oscillator is of the order of 30 min

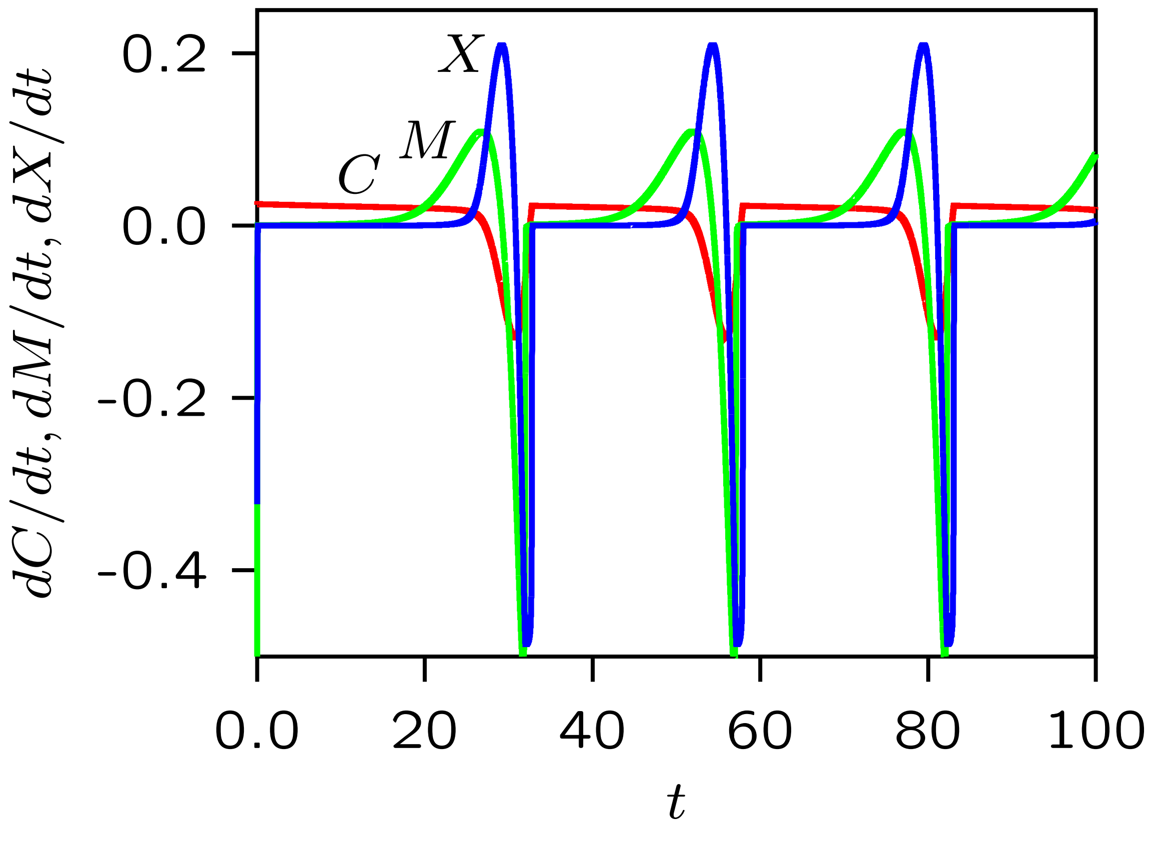
Parameters: $K_1 = K_2 = K_3 = K_4 = 0.005$, $v_i = 0.025$ μM/min, $v_d = 0.25$ μM/min, $K_d = 0.02$ μM, $k_d = 0.01$ min^{-1}, $V_{M1} = 3$, $V_2 = 1.5$, $V_{M3} = 1$ and $V_4 = 0.5$, $K_c = 0.5$ μM

Initial conditions:
$C(0) = 0.01$ μM, $M(0) = X(0) = 0.01$

oscillations

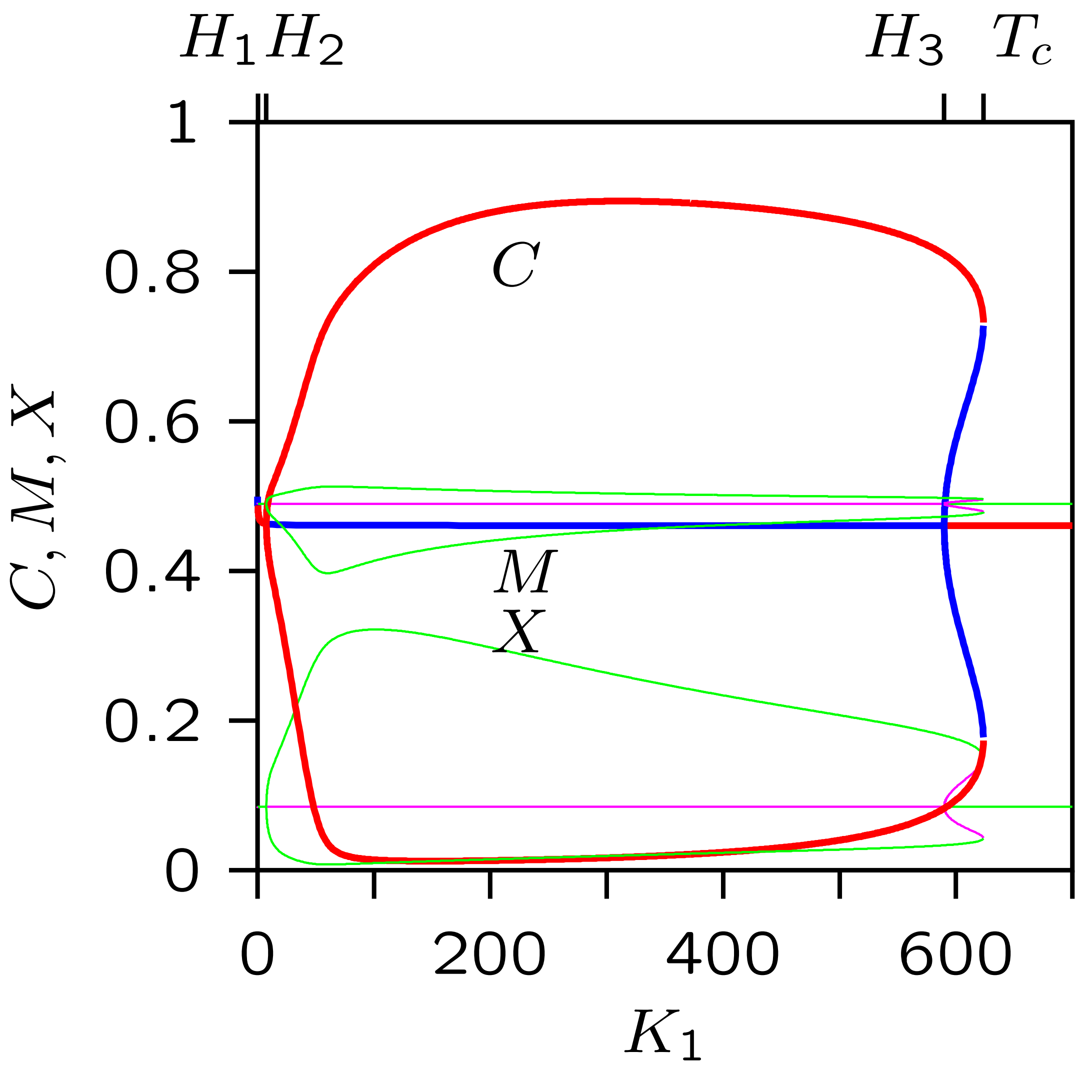


oscillations



One-parameter diagram

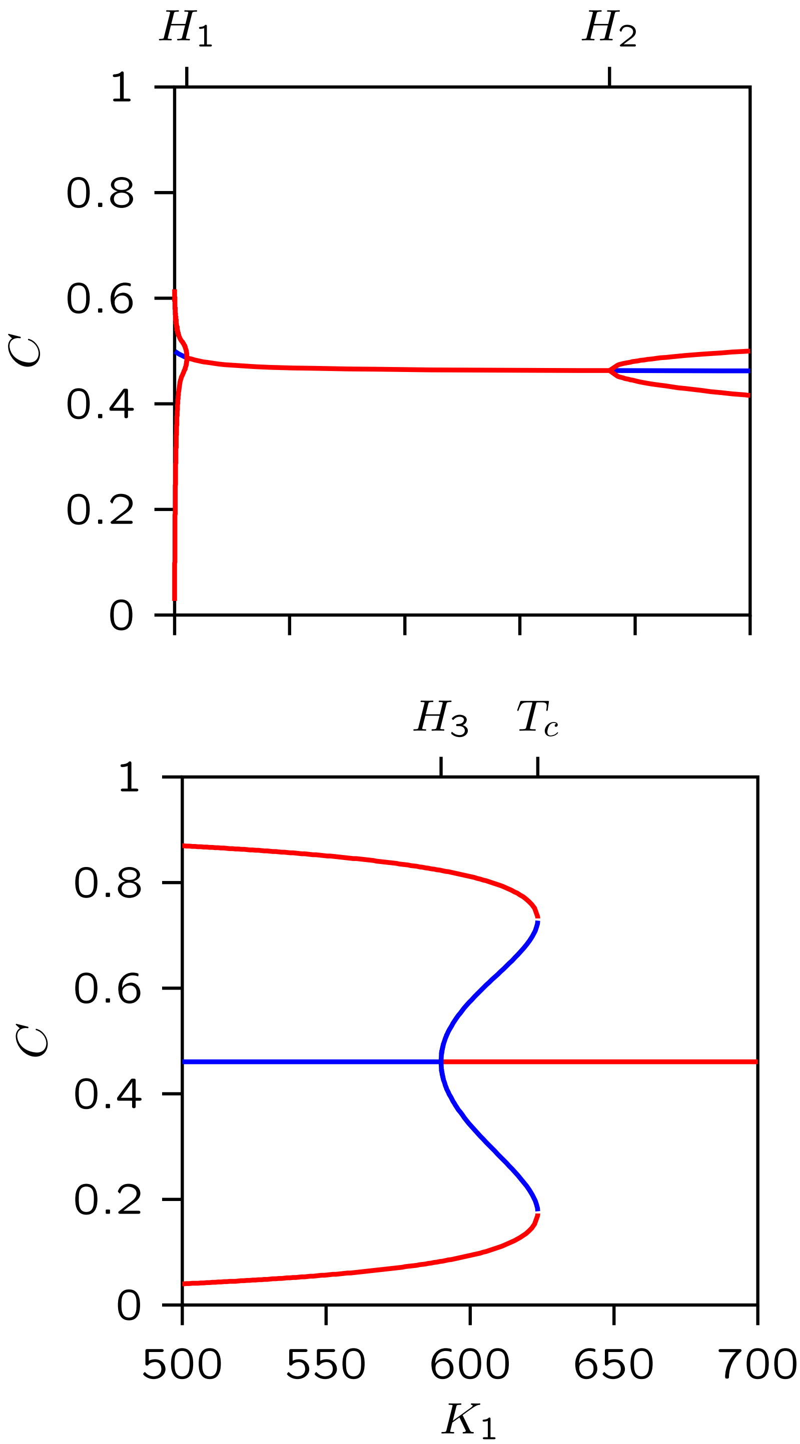
$K_3 = K_4 = 0.002$

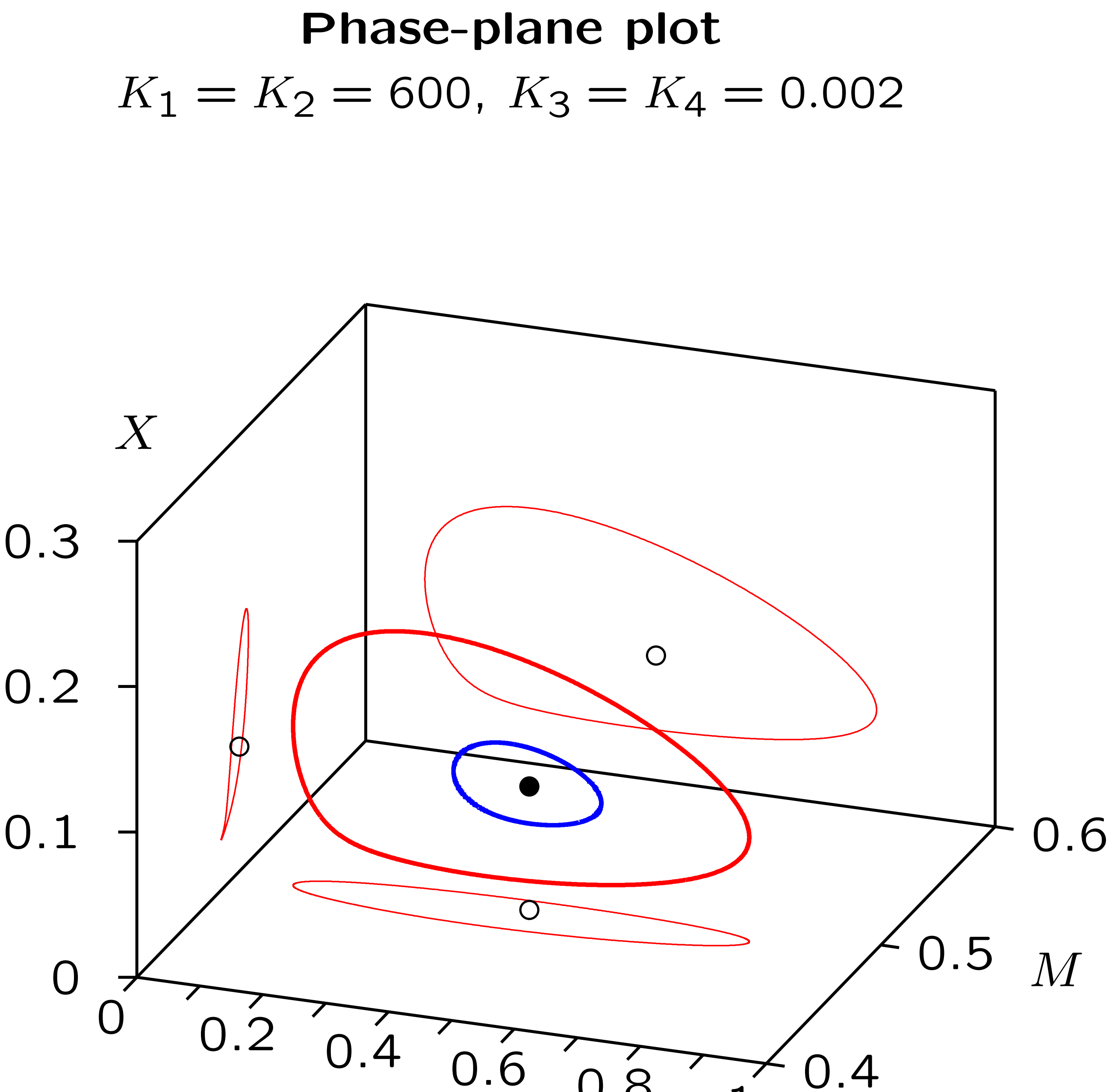


H Hopf bifurcation point

T_c Tangent bifurcation point for cycle

One-parameter diagram(details)




Phase-plane plot
$K_1 = K_2 = 600,\ K_3 = K_4 = 0.002$
X
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
C
0.4
0.5
0.6
M