Some aspects of mathematical modelling of cell cycle

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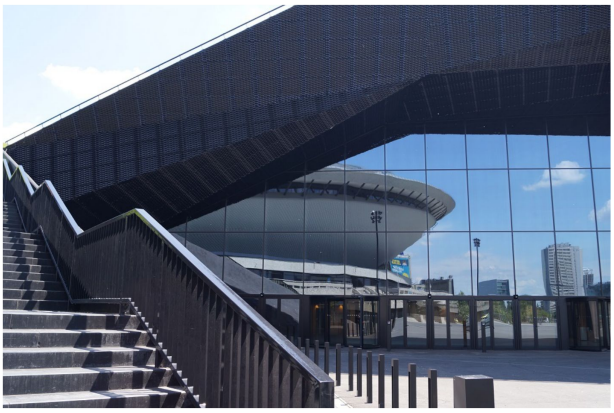
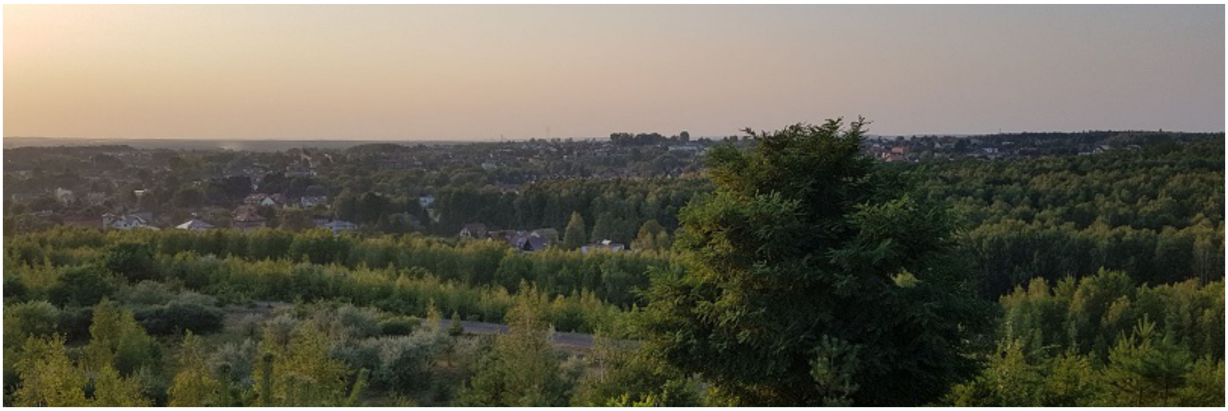
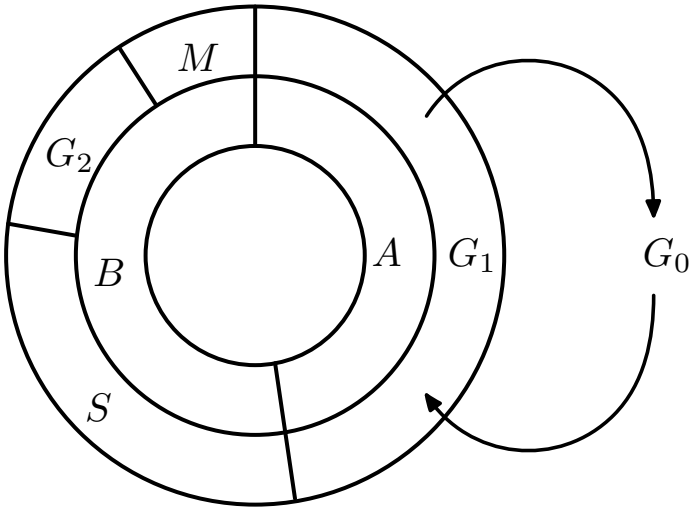




The cell cycle is a series of events that take place in a cell leading to its replication. It is regulated by a complex network of protein interactions.



Schematic model of the cell cycle

G_1 - growth, S - DNA synthesis, G_2 - protein synthesis, M -mitosis; G_0 quiescence phase
$A = G_1 -$ growth phase (variable duration)
$B = S + G_2 + M -$ proliferating phase (constant duration)

$$\frac{\mathrm{d}[\mathrm{ERG}]}{\mathrm{d}t} = \varepsilon \frac{k_{15}}{1 + ([\mathrm{DRG}]/J_{15})^2} - k_{16}[\mathrm{ERG}] \tag{1}$$

$$\frac{\mathrm{d}[\mathrm{DRG}]}{\mathrm{d}t} = \varepsilon \left(k'_{17}[\mathrm{ERG}] + \frac{k_{17}([\mathrm{DRG}]/J_{17})^2}{1 + ([\mathrm{DRG}]/J_{17})^2} \right) - k_{18}[\mathrm{DRG}] \tag{2}$$

$$\frac{\mathrm{d}[\mathrm{cycD}]}{\mathrm{d}t} = \varepsilon k_9[\mathrm{DRG}] + V_6[\mathrm{CycD : Kip1}] + k_{24\mathrm{r}}[\mathrm{CycD : Kip1}] - k_{24}[\mathrm{CycD}][\mathrm{Kip1}] - k_{10}[\mathrm{CycD}] \tag{3}$$

$$\frac{\mathrm{d}[\mathrm{cycD : Kip1}]}{\mathrm{d}t} = k_{24}[\mathrm{CycD}][\mathrm{Kip1}] - k_{24\mathrm{r}}[\mathrm{CycD : Kip1}] - V_6[\mathrm{CycD : Kip1}] - k_{10}[\mathrm{CycD : Kip1}] \tag{4}$$

$$\frac{\mathrm{d}[\mathrm{cycE}]}{\mathrm{d}t} = \varepsilon(k'_7 + k_7[\mathrm{E2F}_A]) - V_8[\mathrm{cycE}] - k_{25}[\mathrm{CycE}][\mathrm{Kip1}] + k_{25\mathrm{r}}[\mathrm{CycE : Kip1}] + V_6[\mathrm{CycE : Kip1}] \tag{5}$$

$$\frac{\mathrm{d}[\mathrm{cycE : Kip1}]}{\mathrm{d}t} = k_{25}[\mathrm{CycE}][\mathrm{Kip1}] - k_{25r}[\mathrm{CycE : Kip1}] - V_6[\mathrm{CycE : Kip1}] - V_8[\mathrm{CycE : Kip1}] \tag{6}$$

$$\frac{\mathrm{d}[\mathrm{cycA}]}{\mathrm{d}t} = \varepsilon k_{29}[\mathrm{E2FA}][\mathrm{mass}] - k_{30}[\mathrm{Cdc20}][\mathrm{cycA}] - k_{25}[\mathrm{CycA}][\mathrm{Kip1}] + k_{25r}[\mathrm{CycA : Kip1}] + V_6[\mathrm{CycA : Kip1}] \tag{7}$$

$$\frac{\mathrm{d}[\mathrm{cycA : Kip1}]}{\mathrm{d}t} = k_{25}[\mathrm{CycA}][\mathrm{Kip1}] - k_{25r}[\mathrm{CycA : Kip1}] - V_6[\mathrm{CycA : Kip1}] - k_{30}[\mathrm{Cdc20}][\mathrm{CycA : Kip1}] \tag{8}$$

$$\begin{aligned}\frac{\mathrm{d}[\mathrm{Kip1}]}{\mathrm{d}t} = {} & \varepsilon k_5 - V_6[\mathrm{Kip1}] - k_{24}[\mathrm{CycD}][\mathrm{Kip1}] + k_{24r}[\mathrm{CycD : Kip1}] + k_{10}[\mathrm{CycD : Kip1}] - k_{25}[\mathrm{Kip1}]([\mathrm{CycE}] + [\mathrm{CycA}]) \\ & + k_{25r}([\mathrm{CycE : Kip1}] + [\mathrm{CycA : Kip1}]) + V_8[\mathrm{CycE : Kip1}] + k_{30}[\mathrm{Cdc20}][\mathrm{CycA : Kip1}]\end{aligned} \tag{9}$$

$$\frac{\mathrm{d}[\mathrm{E2F}]}{\mathrm{d}t} = k_{22}([\mathrm{E2FT}] - [\mathrm{E2F}]) - (k'_{23} + k_{23}([\mathrm{CycA}] + [\mathrm{CycB}]))[\mathrm{E2F}] \tag{10}$$

$$\frac{\mathrm{d}[\mathrm{cycB}]}{\mathrm{d}t} = \varepsilon \left(k'_1 + \frac{k_1([\mathrm{CycB}]/J_1)^2}{1 + ([\mathrm{CycB}]/J_1)^2} \right) - V_2[\mathrm{CycB}] \tag{11}$$

$$\frac{\mathrm{d}[\mathrm{Cdh1}]}{\mathrm{d}t} = (k'_3 + k_3[\mathrm{Cdh20}]) \frac{1 - [\mathrm{Cdh1}]}{J_3 + 1 - [\mathrm{Cdh1}]} - V_4 \frac{[\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]} \tag{12}$$

$$\frac{\mathrm{d}[\mathrm{Cdc20}_T]}{\mathrm{d}t} = \varepsilon(k'_{11} + k_{11}[\mathrm{CycB}]) - k_{12}[\mathrm{Cdc20}_T] \tag{13}$$

$$\frac{\mathrm{d}[\mathrm{Cdc20}]}{\mathrm{d}t} = k_{13}[\mathrm{IEP}] \frac{[\mathrm{Cdc20}_T] - [\mathrm{Cdc20}]}{J_{13} + [\mathrm{Cdc20}_T] - [\mathrm{Cdc20}]} - k_{14} \frac{[\mathrm{Cdc20}]}{J_4 + [\mathrm{Cdc20}]} - k_{12}[\mathrm{Cdc20}] \tag{14}$$

$$\frac{\mathrm{d}[\mathrm{PPX}]}{\mathrm{d}t} = \varepsilon k_{33} - k_{34}[\mathrm{PPX}] \tag{15}$$

$$\frac{\mathrm{d}[\mathrm{IEP}]}{\mathrm{d}t} = k_{31}[\mathrm{CycB}] \frac{1 - [\mathrm{IEP}]}{J_{31} + 1 - [\mathrm{IEP}]} - k_{32}[\mathrm{PPX}] \frac{[\mathrm{IEP}]}{J_{32} + [\mathrm{IEP}]} \tag{16}$$

$$\frac{\mathrm{d}[\mathrm{GM}]}{\mathrm{d}t} = k_{27}[\mathrm{mass}]\mathrm{H}\left(\frac{[\mathrm{Rb}_{hypo}]}{[\mathrm{Rb}_T]} \right) - k_{28}[\mathrm{GM}] \tag{17}$$

$$\frac{\mathrm{d}[\mathrm{mass}]}{\mathrm{d}t} = \varepsilon \mu[\mathrm{GM}] \tag{18}$$

$$\frac{d[ERG]}{dt} = \frac{k_{15}}{[DRG]/J_{15})^2} - k_{16}[ERG] \tag{1}$$

$$\frac{d[DRG]}{dt} = \varepsilon\left(G]+\frac{k_{17}([DRG]/J_{17})^2}{1+([DRG]/J_{17})^2}\right) - k_{18}[DRG] \tag{2}$$

$$\frac{d[cycD]}{dt} = \varepsilon k_9[DRG]+ cD : Kip1]+k_{24r}[CycD : Kip1] - k_{24}[CycD][Kip1] - k_{10}[CycD] \tag{3}$$

$$\frac{d[cycD : Kip1]}{dt} = k_{24}[CycD][k_{24r}[CycD : Kip1] - V_6[CycD : Kip1] - k_{10}[CycD : Kip \tag{4}$$

$$\frac{d[cycE]}{dt} = \varepsilon(k_7' + k_7[E2F_A]) - V_8[cycE [CycE][Kip1]+k_{25r}[CycE : Kip1]+V_6[C ip1] \tag{5}$$

$$\frac{d[cycE : Kip1]}{dt} = k_{25}[CycE][Kip1] - k_{25r}[Cyc ip1] - V_6[CycE : Kip1] - k : Kip1] \tag{6}$$

$$\frac{d[cycA]}{dt} = \varepsilon k_{29}[E2FA][mass] - k_{30}[Cdc20][cycA] - ycA][Kip1]+k_2 A : Kip1]+V_6[CycA : Kip1] \tag{7}$$

$$\frac{d[cycA : Kip1]}{dt} = k_{25}[CycA][Kip1] - k_{25r}[CycA : Kip1] - CycA ip1] - k_{30}[Cdc20][CycA : Kip1] \tag{8}$$

$$\begin{aligned}\frac{d[Kip1]}{dt} =& \varepsilon k_5 - V_6[Kip1] - k_{24}[CycD][Kip1]+k_{24r}[CycD : K k_{10}[CycD : Kip1] - k_{25}[Kip1]([CycE]+[CycA]) \\ &+ k_{25r}([CycE : Kip1]+[CycA : Kip1])+V_8[Cy k_{30}[Cdc20][CycA : Kip1]\end{aligned} \tag{9}$$

$$\frac{d[E2F]}{dt} = k_{22}([E2FT] - [E2F]) - (k_{23}' + k_{23}([CycA]+ B]))[E2F] \tag{10}$$

$$\frac{d[cycB]}{dt} = \varepsilon\left(k_1' + \frac{k_1([CycB]/J_1)^2}{1+([CycB]/J_1)^2}\right) - V_2[CycB \tag{11}$$

$$\frac{d[Cdh1]}{dt} = (k_3' + k_3[Cdh20])\frac{1-[Cdh1]}{J_3+1-[Cd [Cdh1]}{J_4+[Cdh1]} \tag{12}$$

$$\frac{d[Cdc20_T]}{dt} = \varepsilon(k_{11}' + k_{11}[CycB]) dc20_T] \tag{13}$$

$$\frac{d[Cdc20]}{dt} = k_{13}[IEP] [Cdc20] ac20_T] - [Cdc20]} - k_{14}\frac{[Cdc20]}{J_4+[Cdc20]} - k_{12}[Cdc20] \tag{14}$$

$$\frac{d[PPX]}{d k_{34}[PPX] \tag{15}$$

$$\frac{]}{dt} = k_{31}[CycB]\frac{1-[IEP]}{J_{31}+1-[IEP]} - k_{32}[PPX]\frac{[IEP]}{J_{32}+[IEP]} \tag{16}$$

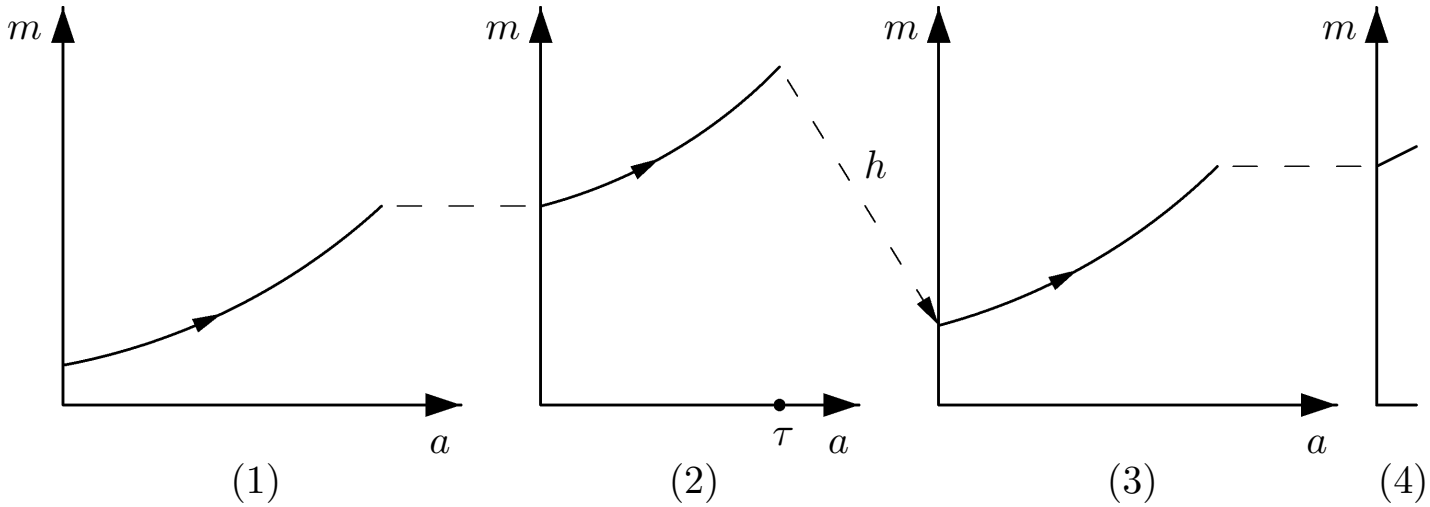
$$\frac{d[GM]}{dt} = k_{27}[mass]H\left(\frac{[Rb_{hypo}]}{[Rb_T]}\right) - k_{28}[GM] \tag{17}$$

$$\frac{d[mass]}{dt} = \varepsilon\mu[GM] \tag{18}$$

a –age, x –size, m –maturity,
maturity m describes the position of a cell in the cell cycle.

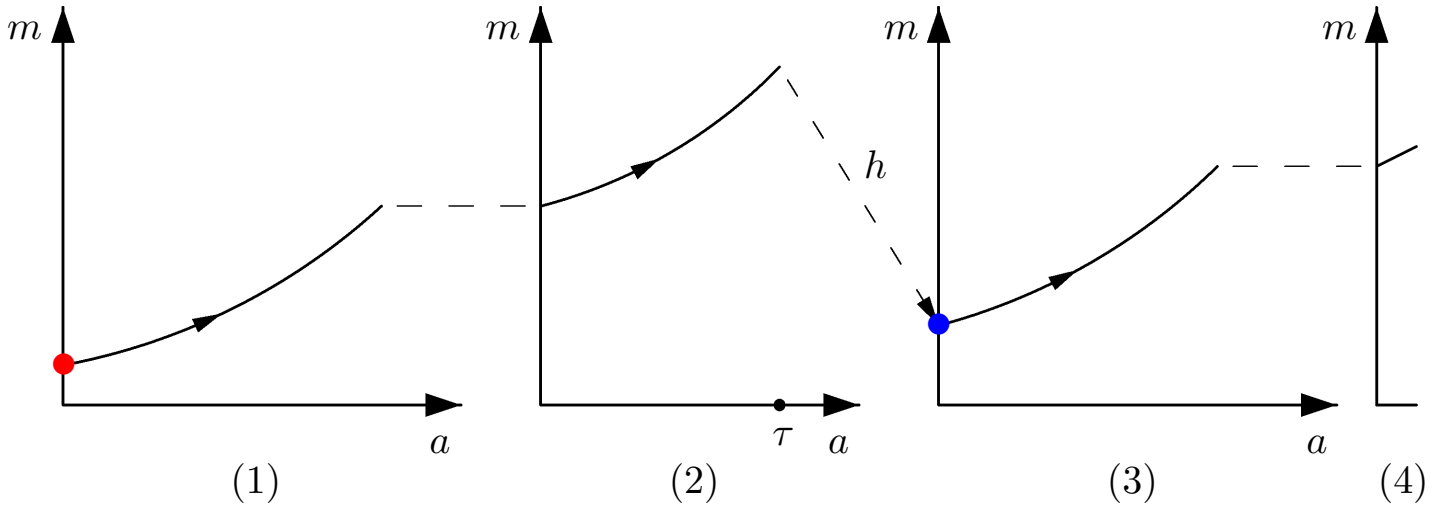
Types of models: maturity or size models;
one or two (four) phases models;
continuous or discrete time models.

Continuous time model:



Evolution of maturity:
a mother cell: (1) – resting phase, (2) – proliferating phase
a daughter cell: (3) – resting phase, (4) – proliferating phase.

Discrete time (generational) model:



describe the relation between the initial maturity of mother● and daughter cells●

Find an operator P s.t. if f is a density of distribution of maturity in mother cells.then Pf is ... daughter cells.

Lasota, Mackey (1984), Tyson, Hannsgen (1986), Tyrcha (1988)

1. Rubinow (1968):

$m \in [0,1]$, a new born cell has maturity 0, a cell splits at maturity 1, $v = g(m)$ – maturation velocity:

$$m'(t) = g(m)$$

All cells have identical cell cycles.

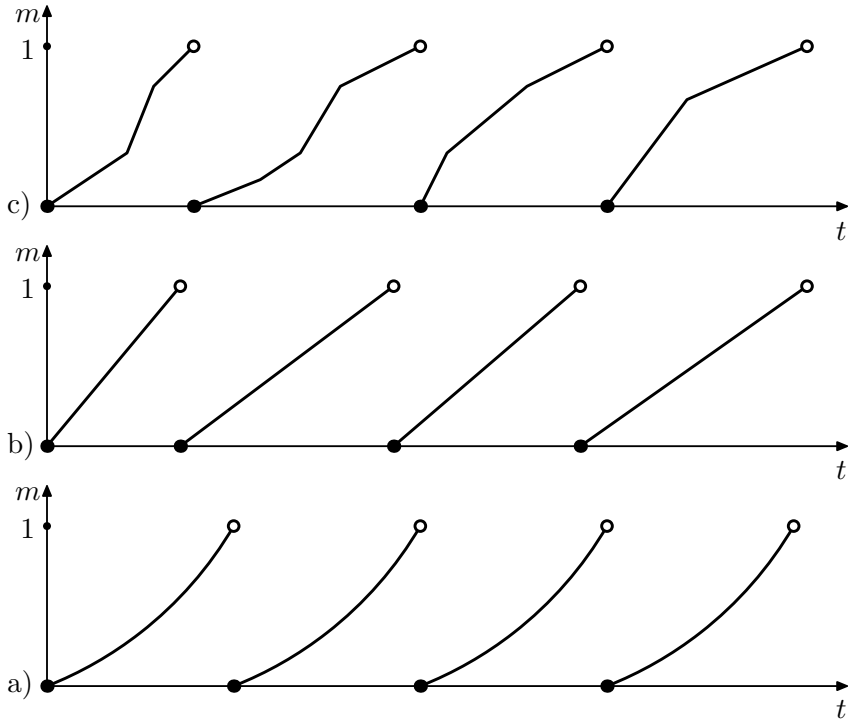
2. Lebowitz and Rubinow (1974):

maturation velocity v is fixed at the birth and is constant during the cell cycle

maturation velocity of the daughter cells is chosen with some distribution depending on m.v. of the mother cell.

3. Rotenberg (1983):

During the cell cycle, a cell can change its maturation velocity.



Sample graphs of maturity in the models: a) Rubinow, b) Lebowitz-Rubinow, c) Rotenberg.

4. Bell-Anderson (1967).

The cell maturity grows with rate $g(m)$, i.e. $m' = g(m)$, $m(0) = m_0$, $\pi_t m_0 = m(t)$,
it splits with intensity $p(m)$ into two daughter cells with maturity $h(m)$
$u(t, m)$ - density of cells with maturity m

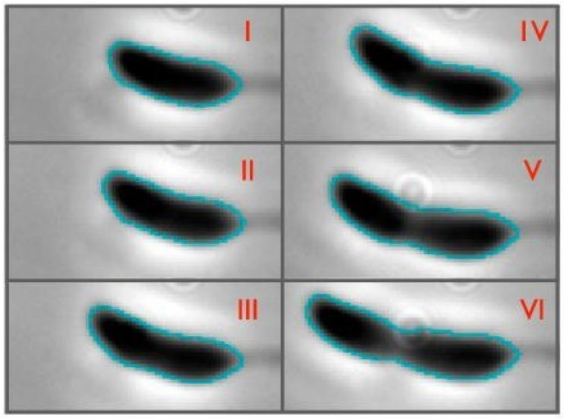
$$\frac{\partial u}{\partial t} + \frac{\partial (gu)}{\partial m} = -p(m)u(t,m) + 2p(k(m))k'(m)u(t,k(m)), \quad k = h^{-1}$$

5. Two-phase model, M.C. Mackey, R.R. (1994).

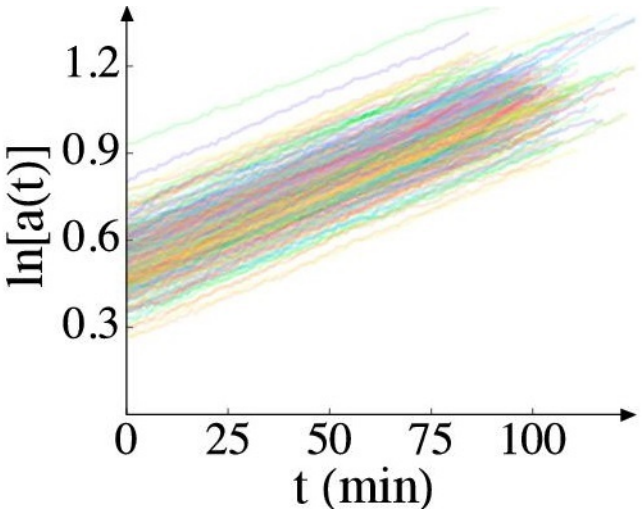
$$\frac{\partial u}{\partial t} + \frac{\partial (gu)}{\partial m} = -p(m)u(t,m) + 2p(k(m))k'(m)u(t-\tau,k(m)),$$

$k(m) = \pi_{-\tau}(h^{-1}(m))$.

5b. K. Pichór, R.R. (2019) - a system of two PDEs with two boundary conditions.



From: Iyer-Biswas et al. PNAS 2014,111(45),15913



We are able to measure: **the length of the cell cycle** and the size x of cells, but not maturity m and intensity of splitting $p(m)$.

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RESEARCH ARTICLE

WILEY

Cell cycle length and long-time behavior of an age-size model

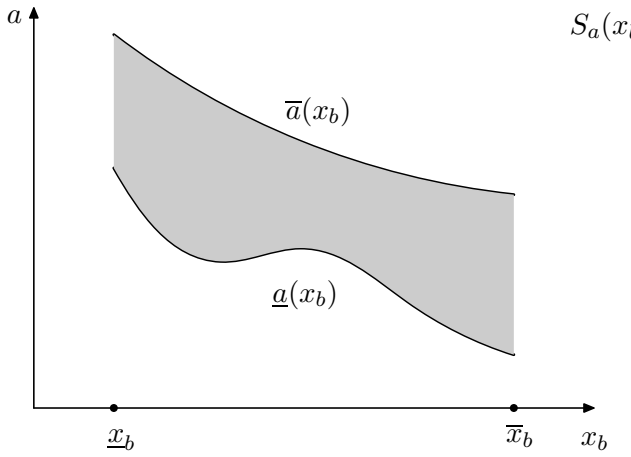
Katarzyna Pichór[1] | Ryszard Rudnicki[2]

a -age, x_b -initial size, x -size, $h(x) = x/2$.

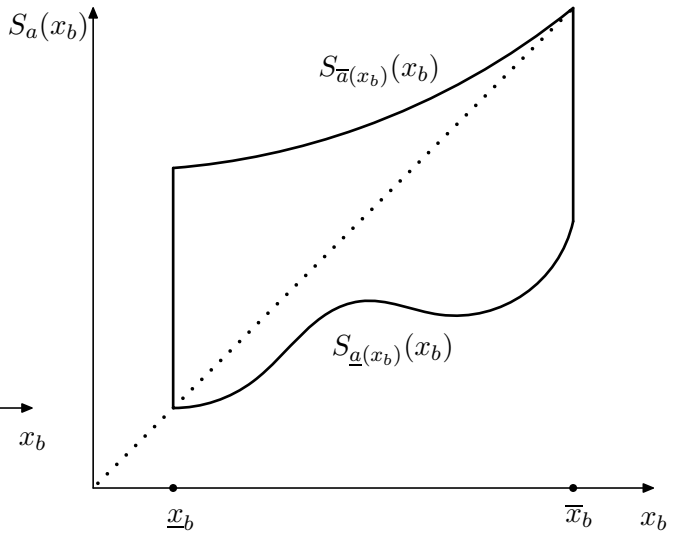
$q(x_b, a)$ -density distribution of the cycle length l,

$\Phi(x_b, a) = \mathsf{Prob}(l \geq A) = \int_A^\infty q(x_b, r)\, dr$ -*survival function*,

$S_a x_b = \frac{1}{2}\pi_a x_b$ -the initial size of a daughter cell



The area where q is positive



The relation between the initial sizes of mother and daughter cells

1

Let f be the density of initial sizes of mother cells. If they split at age a, then

$$P_a f(x_b) = \frac{2g(\pi_{-a}(2x_b))}{g(2x_b)} f(\pi_{-a}(2x_b))$$

is the density of initial sizes of daughter cells.

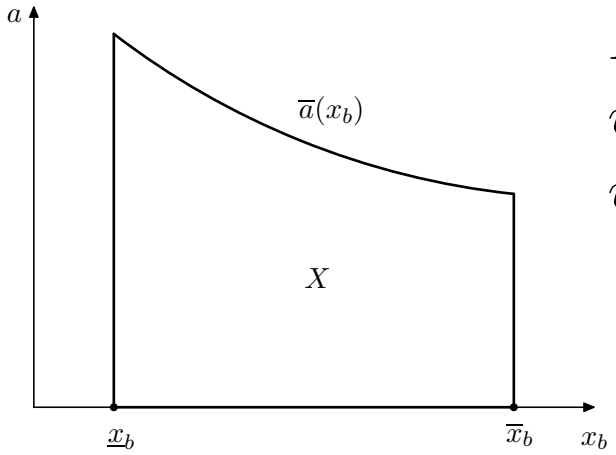
$$P_a^* f(x_b) = f(S_a(x_b)).$$

$p(x_b, a) = q/\Phi$ - intensity of splitting
$u(t, x_b, a)$ -the number of cells having initial size x_b and age a at time t,

$$2\int_0^\infty \Big(P_a\big(p(\cdot, a)u(t, \cdot, a)\big)\Big)(x_b)\, da$$

-the number of new born cells per unit time.

$$\begin{aligned}
&\frac{\partial u}{\partial t}(t, x_b, a) + \frac{\partial u}{\partial a}(t, x_b, a) = -p(x_b, a)u(t, x_b, a),\\
&u(t, x_b, 0) = 2\int_0^\infty \Big(P_a\big(p(\cdot, a)u(t, \cdot, a)\big)\Big)(x_b)\, da,\\
&u(0, x_b, a) = u_0(x_b, a).
\end{aligned}$$



$$E = L^1(X),$$
$$u(t)(x_b, a) = u(t, x_b, a),$$
$$u(t) \colon E \to E.$$

asynchronous exponential growth (AEG):

if $g(2x) \neq 2g(x)$ for some x, then

$$\lim_{t\to\infty} e^{-\lambda t} u(t) = \alpha(u_0)v,$$

$\alpha \in L(E, \mathbb{R})$, $v \in E$, $\lambda \in \mathbb{R}$.

λ - Malthusian parameter,
v - stable distribution of initial size and age.
The real process should be close to a stationary state v, so it is easy to estimate biological parameters.

Sketch of the proof:

$z(t, x_b, a) = u(t, x_b, a)/\Phi(x_b, a)$,
$z(t)(x_b, a) = z(t, x_b, a)$:

$$z'(t) = \mathcal{A}z(t),$$

$$\mathcal{A}f(x_b, a) = -\frac{\partial f}{\partial a}(x_b, a)$$

$$\mathcal{D}(\mathcal{A}) = \left\{ f \in W_1(X) : \quad \mathcal{T}f(x_b) = \mathcal{P}f(x_b) \right\}.$$

$\mathcal{P}f(x_b) = 2\int_0^\infty \Big(P_a(q(\cdot, a)f(\cdot, a))\Big)(x_b)\, da$

$\mathcal{T}f(x_b) = f(x_b, 0)$, $W_1(X) = \left\{ f \in E : \frac{\partial f}{\partial a} \in E \right\}$,

$\|f\|_{W_1(X)} = \|f\|_E + \left\| \frac{\partial f}{\partial a} \right\|_E$.

C_0-semigroup $\{S(t)\}_{t\geq 0}$:
B - a Banach space, $S(t)\colon B \to B$, $t \geq 0$, linear and bounded operators,
$S(0) = Id$, $S(t+s) = S(t)S(s)$, $s, t \geq 0$,
(c) for each $x \in B$, the function $t \mapsto S(t)x$ is continuous.

The infinitesimal generator A of C_0-semigroup $\{S(t)\}_{t\geq 0}$ is defined by

$$Ax = \lim_{t\downarrow 0} \frac{1}{t}(S(t)x - x)$$

whenever the limit exists. The domain $D(A)$ of A, is the set of $x \in B$ for which this limit does exist.
We often used the notation $S(t)x = e^{At}x$.

Proposition 1 *The operator $\mathcal{A}$ generates a positive C_0-semigroup $\{T(t)\}_{t\geq 0}$ on E.*

The proof is based on a perturbation method related to operators with boundary conditions and unbounded perturbations in L^1 space [Gwiżdż and Tyran-Kamińska, Positivity. 2019].

Proposition 2 *The operator $\mathcal{A}^*$ has an eigenvalue $\lambda > 0$ and a corresponding eigenfunction v such that*

$$c_1\Phi(x_b, a) \leq v(x_b, a) \leq c_2\Phi(x_b, a) \qquad (1)$$

for some positive constants c_1 and c_2 independent of x_b and a.

Steps: 1. Identifying the domain of $\mathcal{A}^*$

2. Checking that $\mathcal{A}^*$ has a positive eigenfunction corresponding to the eigenvalue λ if some integral operator K_λ on $C[\underline{x}_b, \overline{x}_b]$ has a positive fixed point.

3. The existence of positive eigenvectors of K_λ.

4. Checking that for some λ the eigenvector of K_λ is a fixed point of K_λ.

Proposition 3 *There exists a unique, up to a multiplicative constant, eigenfunction f_i of $\mathcal{A}$ corresponding to the eigenvalue λ.*

Next we introduce the semigroup $\{P(t)\}_{t\geq 0}$ given by $P(t)f = e^{-\lambda t}T(t)f$ defined on the space $E_1 = L^1(X, \mathcal{B}(X), \mu)$ with the measure μ given by $d\mu = v\, d\ell$.
$\{P(t)\}_{t\geq 0}$ is a stochastic semigroup,
f_i is an invariant density f_i of $\{P(t)\}_{t\geq 0}$ and $\lim_{t\to\infty} P(t)f = f_i$ for each density f.
Finally, we translate this result in terms of the semigroup $\{T(t)\}_{t\geq 0}$ and obtain AEG.

(X, Σ, m) — σ-finite measure space.
$D = \{f \in L^1 : \ f \geq 0, \ \|f\| = 1\}$ – densities.

Stochastic operator: $P : L^1 \to L^1$ linear, $P(D) \subset D$.
Stochastic semigroup: C_0-semigroup of stochastic operators.

$f_* \in D$ -invariant if $P(t)f_* = f_*$ for $t \geq 0$.
$\{P(t)\}$ -asymptotically stable if there is a density f_* s.t.

$$\lim_{t\to\infty} \|P(t)f - f_*\| = 0 \quad \text{for} \quad f \in D.$$

$\{P(t)\}$ -partially integral if there exist $t > 0$, $k(t, x, y) \geq 0$

$$\int_X \int_X k(t, x, y)\, m(dx) m(dy) > 0$$

$$P(t)f(x) \geq \int k(t, x, y) f(y)\, m(dy) \quad \text{for} \quad f \in D.$$

Theorem 1 *If a partially integral stochastic semigroup* $\{P(t)\}_{t\geq 0}$ *has a unique invariant density* f_* *and* $f_* > 0$*, then it is asymptotically stable.*

Proposition 4 *The semigroup* $\{P(t)\}_{t\geq 0}$ *is partially integral.*

The proof by using Dyson-Phillips expansion theorem: (how to write $e^{(A+B)t}$ using e^{At} and B).

The key role play condition $g(2x) \neq 2g(x)$ for some $x \in (\underline{x}_b, \overline{x}_b)$.

It is enough to check that $\{T^*(t)\}_{t\geq 0}$ is partially integral ($P(t)f = e^{-\lambda t}T(t)f$ and symmetry in the definition partially integral semigroup).

Corollaries and remarks

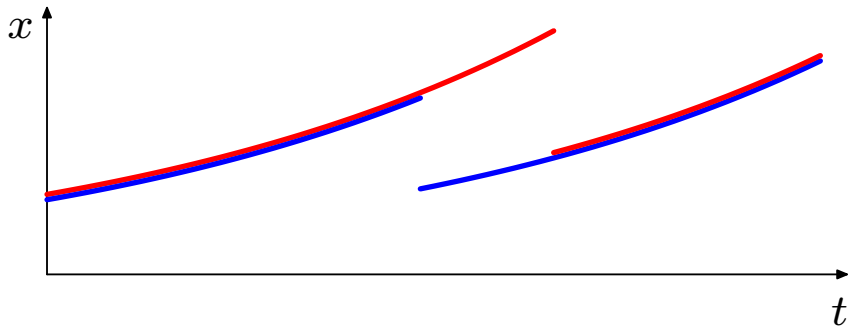
1. Chemostat. The AEG law holds for microorganisms cultured in a chemostat. In order to grow cells under constant environmental conditions, culture liquid should be removed from the system with rate $D = \lambda$.

2. Age-size structured model: Let $w(t, x, a)$ be the number of cells having size x and age a at time t.
The function w satisfies the following problem:

$$\frac{\partial w}{\partial t}(t,x,a) + \frac{\partial w}{\partial a}(t,x,a) + \frac{\partial (gw)}{\partial x}(t,x,a) = -\bar{p}(x,a)w(t,x,a),$$
$$w(t,x,0) = 4\int_0^\infty \bar{p}(2x,a)w(t,2x,a)\,da,$$
$$w(0,x,a) = w_0(x,a).$$

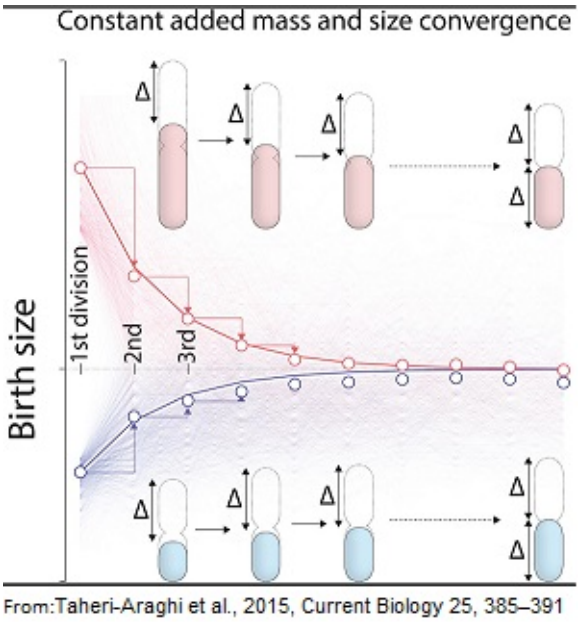
Corollary 1 *$w(t, x, a)$ satisfies AEG condition.*

3. Case $g(2x) = 2g(x)$, for example $g(x) = cx$:
AEG does not hold.
$\{T(t)\}_{t\geq 0}$ irreducible: $\int_0^\infty T(t)f\,dt > 0$ for $f \geq 0$, $f \neq 0$,
but there are two functions $f_1, f_2 \geq 0$, $f_1, f_2 \neq 0$ s.t.
$T(t)f_1 \cdot T(t)f_2 \equiv 0$ for all $t \geq 0$.



Growth of mother and daughter cells in the case $g(x) = cx$.

Rod-shaped bacteria, e.g. *E. coli*, *C. crescentus* and *B. subtilis* change only their length.
Variety of distinct models of cell cycle and cell division. Most of models with the assumption $g(x) = \kappa x$ but with various descriptions of the cell cycle length.



Additive model (or a constant Δ model):
the difference $\Delta(x_b) = x_d - x_b$ between the size at division x_d and the initial size x_b of a cell is a random variable independent of x_b.If $h(x)$ is the density distribution of Δ, then

$$q(x_b, a) = \kappa x_b e^{\kappa a} h\left(x_b e^{\kappa a} - x_b\right)$$

The coefficient of variation $c_v = \sigma/\mu$ of Δ for *E. coli* $c_v \in (0.17, 0.28)$. σ -standard deviation, μ -the mean.

Target size model: a cell with initial size x_b attempts to divide at a target size $x_d = f(x_b)$.

The expected length of the cell cycle is

$$\tau_0(x_b) = \kappa^{-1} \ln(f(x_b)/x_b),$$

but $\tau_0(x_b)$ is additively perturbed by a symmetric random variable ξ, and finally $\tau(x_b) = \tau_0(x_b) + \xi$ is the length of the cell cycle.

If $h(a)$ is the density distribution of ξ, then $q(x_b, a) = h(a - \tau_0(x_b))$ is the density of $\tau(x_b)$.

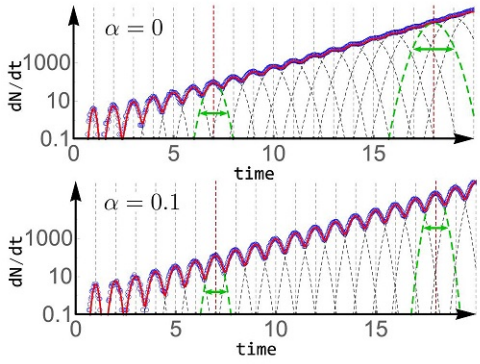
h has a truncated normal distribution located in some interval $[-\varepsilon, \varepsilon]$ seems to be more suitable. $f(x_b) = 2x_b^{1-\alpha} x_0^{\alpha}$, $\alpha \in [0, 1]$ and $x_0 > 0$.

Paradoxes of exponential growth $g(x) = \kappa x$

If the population starts with a single cell of size x, cells from nth generation have size $x_n(t) = 2^{-n}e^{\kappa t}x$ at time t. Since $\underline{x}_b \leq x_n(t) \leq \overline{x}_b$, population consists of a few generations at each time and all cells in each generation have the same size.

if $\overline{x}_b/\underline{x}_b < 2$, then there exist a sequence $\alpha_n \to \infty$ and $c > 0$ s.t. if $t \in [\alpha_n, \alpha_n + c]$, then the population consists only of cells from the nth generation, thus all cells have the same size and they cannot split in this time interval. Consequently the size of **the population never reaches an exponential growth**.

For *E. coli* $x_b = 2.32 \pm 0.38\ \mu m$ (mean $\pm$ SD).



From: F. Jafarpour, Phys Rev Lett. 2019

It takes the population a longer time to reach its balanced growth for greater α because

$$\overline{x}_b/\underline{x}_b = e^{2\kappa\varepsilon/\alpha}$$

How to correct exponential growth of size, to obtain AEG ?

Maybe assume that κ depends on x_b ?

Individual cells can have different growth rates, **but** the average growth rate does not depend on the initial size of cells!

There should be another factor which decides about the growth rate of an individual cell! Maturity?... or stochastic fluctuations of κ during the cell cycle?

The methodology developed here can be applied to models: with asymmetric divisions; with different velocities of proliferation; with stochastic growth of individuals...

2. Stochastic growth of x:
a cell having initial size x_b grows according to Itô stochastic differential equation

$$d\xi_t^{x_b} = g(\xi_t^{x_b})\,dt + \sigma(\xi_t^{x_b})\,dW_t, \tag{2}$$

where W_t, $t \geq 0$, is a Wiener process.
We obtain a C_0-semigroup for the evolution of densities of distribution of (x_b, a) and can prove **AEG**. It means that we can also show AEG for densities of (x, a), but these densities do not define a semigroups of operators!

Chaos

(Ω, ρ) - metric space, $\pi\colon [0,\infty) \times \Omega \to \Omega$.
π is a semiflow on Ω if π is a continuous function, $\pi_0\omega = \omega$, $\pi_{t+s}\omega = \pi_t(\pi_s\omega)$ for $t, s \geq 0$, $\omega \in \Omega$.

μ - probability measure on the σ-algebra $\mathcal{B}(\Omega)$ of Borel subsets of Ω.
μ is invariant w.r. π if $\mu(\pi_t^{-1}(A)) = \mu(A)$ for $A \in \mathcal{B}(\Omega)$, $t \geq 0$.

μ is supported on Ω if $\mu(U) > 0$ for each nonempty open subset U of Ω.

Invariant measure μ is exact if $\lim_{t\to\infty} \mu(\pi_t(A)) = 1$ if $\mu(A) > 0$. Exactness implies ergodicity and mixing.

System $(\Omega, \mathcal{B}(\Omega), \mu, \pi)$ with invariant and exact measure μ supported on Ω is called stochastically chaotic.

Stochastic chaos implies many other chaotic behaviours, for example:

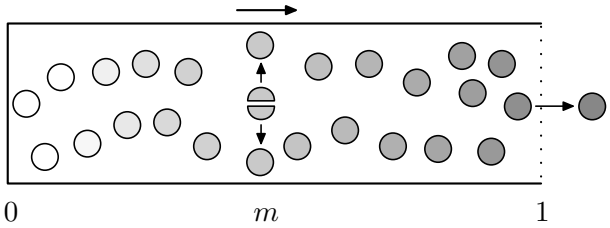
Chaos in the sense of Auslander-Yorke: each trajectory is unstable, there exists a dense trajectory.

existence turbulent trajectory in the sense of Bass: trajectory $t \to \pi_t \omega$ and its translation $t \to \pi_{t+\tau} \omega$ are almost uncorrelated for large τ (the lack of memory).

Chaos in precursors of blood cells

Maturity is the morphological state of a cell.
Processes of maturation and division: a newly born cell has the same maturity m as its mother at division.

Uncontrolled process:



Each cell can split with the same probability.
When one cell reaches the maturity 1 it leaves the bone marrow and one of cells from the bone marrow splits.

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial m}(g(m)m) = g(1)u(t,1)u(t,m)$$

If $u(0,m) = u_0(m)$, then $\pi_t u_0(m) = u(t,m)$.

R.R., Chaos **19** (2009).

The semiflow π is stochastically chaotic.

Bell and Anderson size model with $g(x) = x$:

$$\frac{\partial u}{\partial t} + x\frac{\partial u}{\partial x} = -(d+b)u(t,x) + 4bu(t,2x),$$

If $u(0,m) = u_0(m)$, then $\pi_t u_0(m) = u(t,m)$.

R.R., J. Math. Anal. Appl. **393** (2012).
If we choose the space Ω in a "proper way", then the semiflow π is stochastically chaotic.


Thank You!