

POPULATION DYNAMICS

MATHEMATICAL MODELS AND METHODS

RYSZARD RUDNICKI

Schedule:

Discrete structured models:

- discrete time models,
- continuous time models,
- finite examples and their asymptotics,
- the evolution of paralog families in genomes,
- nonlinear discrete models.

Influence of delay:

- models with delay,
- stability,
- periodicity.

Continuous structured models:

- cell cycle model,
- age structured McKendrick's model,
- erythrocytes dynamics,
- size structured model,
- general approach,
- other examples and remarks.

Discrete structured models

1. GENERATION (DISCRETE TIME) MODELS

1. Population is divided into n subpopulations ($1 \leq n \leq \infty$).
2. We consider disjoint generations of individuals.
3. An individual from j -th subpopulation "produces" with probability p_{ij} a new individual in i -th subpopulation.

x_i^k - the number of individuals in the subpopulation i in the generation k .

$$P = [p_{ij}], \mathbf{x}^k = [x_1^k, \dots, x_n^k]^T.$$

$$\mathbf{x}^{k+1} = P\mathbf{x}^k.$$

Asynchronous exponential growth

Theorem 1 (Perron). *Let $n < \infty$, the matrix P has non-negative entries and for some positive integer r the matrix P^r has all positive entries. Then there exist a constant $\lambda > 0$ and the sequences $\mathbf{x}^* = (x_1^*, \dots, x_n^*)$ and $\mathbf{y}^* = (y_1^*, \dots, y_n^*)$ with positive terms such that for each $\mathbf{x} \in \mathbb{R}^n$ we have*

$$\lim_{k \rightarrow \infty} \lambda^{-k} P^k \mathbf{x} = \mathbf{x}^* \langle \mathbf{y}^*, \mathbf{x} \rangle,$$

where $\langle \cdot, \cdot \rangle$ is the scalar product in \mathbb{R}^n .

$$\mathbf{x}^k \approx C \lambda^k \mathbf{x}^*$$

$$p_i^k = \frac{(P^k \mathbf{x})_i}{\sum_{j=1}^n (P^k \mathbf{x})_j}$$

The vector $\mathbf{p}^k = (p_1^k, \dots, p_n^k)$ describes the probability distribution of subpopulations in the k -th generation.

$$p_i^* = \frac{x_i^*}{\sum_{j=1}^n x_j^*}.$$

Perron theorem \implies

$$\lim_{k \rightarrow \infty} \mathbf{p}^k = \mathbf{p}^*.$$

Thus, independently on the initial state the probability distribution of the population into subpopulations converges to \mathbf{p}^* and the size of the population grows exponentially as $k \rightarrow \infty$.

Asynchronous exponential growth.

If the matrix P has non-negative entries then the matrix P^r has all positive entries \iff for each i, j there is a sequence i_0, i_1, \dots, i_r such that $i_0 = j$, $i_r = i$ and

$$p_{i_r i_{r-1}} \cdots p_{i_2 i_1} p_{i_1 i_0} > 0. \quad (1)$$

Consider a directed graph G in which the vertices are subpopulations. We have the directed edge (a, b) in G iff $p_{ba} > 0$, i.e. an individual in the subpopulation a can be a parent of a child in the subpopulation b . Condition (1) means that there is a directed path of the length r which joins the vertex j with the vertex i .

2. CONTINUOUS TIME MODELS

In time interval from t to $t + \Delta t$ an individual from the subpopulation j can:

- (a) "move" with probability $p_{ij}\Delta t + o(\Delta t)$ to the subpopulation i ,
- (b) "produce" with probability $b_{ij}\Delta t + o(\Delta t)$ a new individual in the subpopulation i ,
- (c) die with probability $d_j\Delta t + o(\Delta t)$.

$x_i(t)$ - the number of individuals in the subpopulation i at time t .

$$x'_i(t) = \sum_{j=1}^n q_{ij}x_j(t), \quad \text{for } i = 1, \dots, n.$$

where $q_{ij} = b_{ij} + p_{ij}$ for $i \neq j$ and

$$q_{ii} = b_{ii} - d_i - \sum_{\substack{j=1 \\ j \neq i}}^n p_{ji}.$$

(K) For $i \neq j$ we have $q_{ij} \geq 0$ and there exists a sequence (i_1, i_2, \dots, i_m) such that $i_1 = i$, $i_m = j$ and $q_{i_{r+1}, i_r} > 0$ for $r = 1, \dots, m - 1$.

Theorem 2. *If $n < \infty$, then there exist a constant λ and sequences $\mathbf{x}^* = (x_1^*, \dots, x_n^*)$, $\mathbf{y}^* = (y_1^*, \dots, y_n^*)$ with positive terms such that for each solution $\mathbf{x}(t)$ we have*

$$\lim_{t \rightarrow \infty} e^{-\lambda t} \mathbf{x}(t) = \mathbf{x}^* \langle \mathbf{y}^*, \mathbf{x}(0) \rangle .$$

$$\mathbf{x}(t) \approx C e^{\lambda t} \mathbf{x}^* .$$

3. FINITE EXAMPLES AND THEIR ASYMPTOTICS

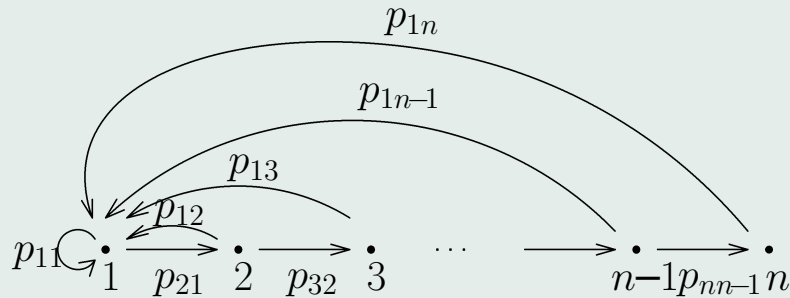
Example 1. Discrete age structured population model.

a generation - the set of individuals at a given time t (e.g. a year)

subpopulation i - individuals with age $i \leq a < i + 1$,

$p_{j+1,j} = 1 - \mu_j$, μ_j - the death rate at age j

$p_{1,j} = b_j$, b_j - the birth rate at age j



The diagram of connections in the age structured model.

Here $p_{j+1,j} = 1 - \mu_j$ and $p_{1,j} = b_j$, where μ_j is the death rate and b_j is the birth rate at age j .

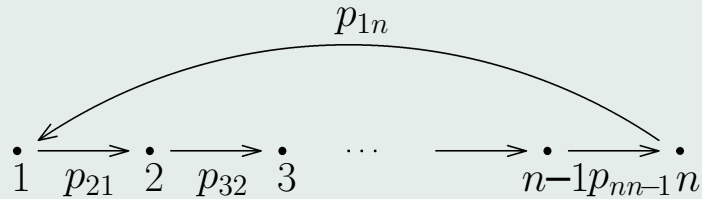
$$P = \begin{bmatrix} b_1 & b_2 & \cdots & \cdots & b_n \\ 1 - \mu_1 & 0 & \cdots & \cdots & 0 \\ 0 & 1 - \mu_2 & \ddots & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 - \mu_{n-1} & 0 \end{bmatrix}. \quad (2)$$

1. If n_1 and n_2 are minimal and maximal reproduction ages, then $b_j = 0$ for $j < n_1$ and $j > n_2$. The assumptions of the Perron theorem are fulfilled. $\iff n_1 < n_2 = n$. If $n_1 < n_2 < n$ then we have the same asymptotic behaviour but the vector y^* is not positive.

2. Baby boom and baby bust.

3. Magicicada - 13- and sometimes 17-year life cycles.





The diagram of connections in the age structured model in the situation when only individuals in the age n can have descendants.

$$P = \begin{bmatrix} 0 & 0 & \dots & 0 & b \\ 1 - \mu_1 & 0 & \dots & \dots & 0 \\ 0 & 1 - \mu_2 & \ddots & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 1 - \mu_{n-1} & 0 \end{bmatrix},$$

Example 2. Space structured model.

a generation - the set of individuals at a given time t (e.g. a year)

a subpopulation - individuals living in a given region

$$p_{ij} > 0,$$

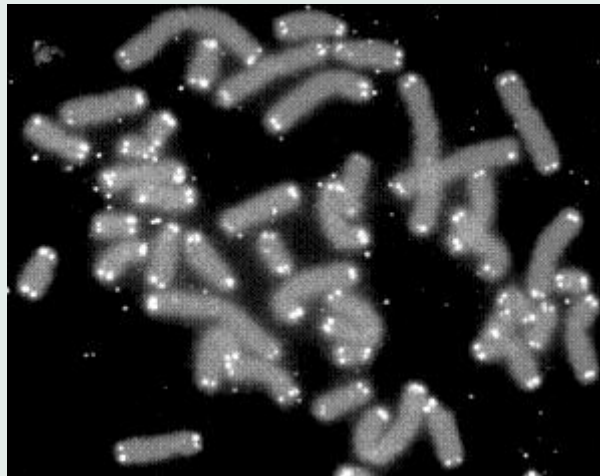
The assumptions of the Perron theorem are fulfilled.

Example 3. Space and age structured model.

Example 4. Maturity structured model.

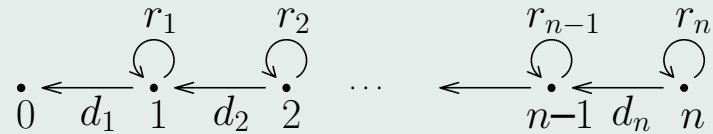
Example 5. Telomere shortening.

A telomere is a region of repetitive DNA at the end of a chromosome, which protects the end of the chromosome from deterioration.



DNA sequences would be lost in every replicative phase until they reached a critical level, at which point cell division would stop. The telomere shortening mechanism normally limits cells to a fixed number of divisions.

A cell from the i -th subpopulation can die with probability μ_i or divide and its daughter cell can have the telomere with the length i with probability a_i or $i - 1$ with probability $1 - a_i$. The cells which belong to 0-th subpopulation cannot divide and they finally die. Let $r_i = 2a_i(1 - \mu_i)$ and $d_i = 2(1 - a_i)(1 - \mu_i)$. The mean number of descendants of a cell from the i -th subpopulation in the same subpopulation is r_i and in the $(i - 1)$ -th subpopulation is d_i .



The diagram of connections in the telomere shortening. In this case $p_{i,i} = r_i$ and $p_{i-1,i} = d_i$.

$$P = \begin{bmatrix} 0 & d_1 & 0 & \cdots & 0 \\ 0 & r_1 & d_2 & \ddots & 0 \\ 0 & 0 & r_2 & \ddots & \ddots \\ \vdots & \ddots & \ddots & \ddots & d_n \\ 0 & 0 & \cdots & 0 & r_n \end{bmatrix}.$$

The assumptions of the Perron theorem are not fulfilled.

Asynchronous exponential-polynomial growth:

There exists a constant λ and for each \mathbf{x} there are constants $c_i(\mathbf{x})$ such that

$$x_i^k \approx k^{n-i} \lambda^k c_i(\mathbf{x}) \quad (3)$$

for large k .

Example 6. (birth and death process).

1. Subpopulation i consists of cells which contain i copies of a given gen.
2. The length of life of a cell of type i has exponential distribution with expected value $1/\lambda_i$.
3. Cells of type i can die in time interval $(t, t + \Delta t)$ with probability $\mu_i \Delta t + o(\Delta t)$.
4. Cells of type i can mutate in time interval $(t, t + \Delta t)$ to type $i + 1$ with probability $b_i \Delta t + o(\Delta t)$ and to type $i - 1$ with probability $d_i \Delta t + o(\Delta t)$.

$$x'_i(t) = -a_i x_i(t) + b_{i-1} x_{i-1}(t) + d_{i+1} x_{i+1}(t), \quad i \in \mathbb{N}_0,$$

where $a_i = -\lambda_i + \mu_i + b_i + d_i$ and $b_{-1} = 0$.



The diagram of connections in the general birth-death process. Here $a_{ii} = -a_i$, $a_{i+1,i} = b_i$, $a_{i-1,i} = d_i$.

If $b_i > 0$, $d_i > 0$, and $n < \infty$, then we have asynchronous exponential growth.

Stochastic version of the birth-death process

A stochastic process describing the size of one population.

Assume that if at time t the number of individuals is i , then in the time interval Δt with probability $b_i\Delta t + o(\Delta t)$ appears a new individual and with probability $d_i\Delta t + o(\Delta t)$ dies one individual.

Let $x_i(t)$ denotes the probability that the size of the population is i .

Then the sequence $(x_i(t))_{i \geq 0}$ satisfies the system with $a_i = b_i + d_i$ for $i \geq 0$.

For example: $b_i = bi$ and $d_i = di$

$d_i = 0$ for $i \geq 0$ - the pure birth process,

$b_i = 0$ for $i \geq 0$ - the pure death process,

$d_i = 0, b_i = b$ for $i \geq 0$ - Poisson process with the parameter b .

4. THE EVOLUTION OF PARALOG FAMILIES IN GENOMES

R. Rudnicki, J. Tiuryn, D. Wójtowicz, J. Math. Biology 2006.



We divide genes into classes. Class i contains genes, which appear i - times in a genome.

- 1 – yellow, purple, brown, black – 4 types
- 2 – orange, orange, pink, pink, white, white – 3 types
- 3 – light green, light green, light green – 1 type
- 4 – red, red, red, red, purple, purple, purple, purple, green, green, green, green – 3 types
- 5 – cyan, cyan, cyan, cyan, cyan, orange, orange, orange, orange, orange – 2 types
- 6 – 0 types
- 7 – blue, blue, blue, blue, blue, blue, blue – 1 type

Distribution $(\frac{4}{14}, \frac{3}{14}, \frac{1}{14}, \frac{3}{14}, \frac{2}{14}, 0, \frac{1}{14}, 0, 0, \dots)$

P.P. Słonimski (+10), *Microbial genomics II*, 1998. The first law of Genomics

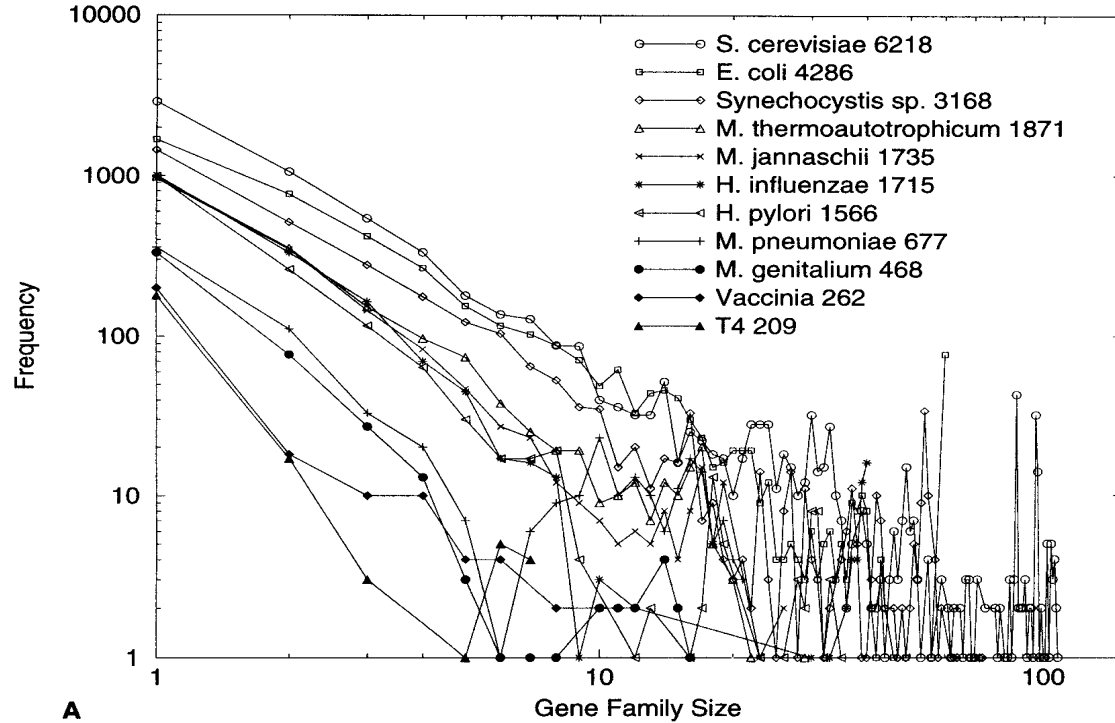
Let x_n be a number of types of genes in class n

$$x_n \sim \frac{1}{2^n n}, \quad n = 2, 3, \dots$$

M.A. Huynen, E. van Nimwegen, *Mol. Biol. Evol.*, **15** (1998), 583–589.

$$x_n \sim n^{-\alpha}, \quad n = 1, 2, 3, \dots$$

α decreases if the total number of genes increases, $\alpha \in (2, 3)$



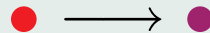
	<i>R</i>	<i>S</i>	$\alpha = 2.81$
$x_1 =$	1894	(1168)	2048
$x_2 =$	292	292	292
$x_3 =$	83	94	93
$x_4 =$	29	36	43

	<i>R</i>	<i>S</i>	$\alpha = 2.45$
$x_1 =$	3769	(3368)	4601
$x_2 =$	842	842	842
$x_3 =$	233	281	311
$x_4 =$	83	105	154

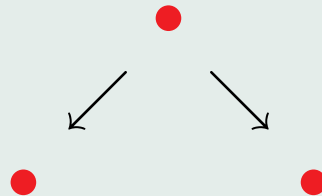
Operations on genes



$d\Delta t$ - prob. of gene removal in time interval Δt



$m\Delta t$ - prob. of gene mutation in time Δt



$r\Delta t$ - prob. of gene duplication in time Δt

If a gene \bullet belongs to class n , then we have n -copies of it: $\bullet\bullet\bullet\bullet\bullet\bullet$ ($n = 6$)

Let consider only mutation $\bullet \longrightarrow \bullet$.

Prob. of mutation of "red" genes in time Δt is $\approx n \cdot m\Delta t$

$$\begin{array}{ccc} \bullet\bullet\bullet\bullet\bullet\bullet & \longrightarrow & \bullet\bullet\bullet\bullet\bullet\bullet \\ \approx n \cdot m\Delta t & & \approx 1 - n \cdot m\Delta t \end{array}, \quad \begin{array}{ccc} \bullet\bullet\bullet\bullet\bullet\bullet & \longrightarrow & \bullet\bullet\bullet\bullet\bullet\bullet \\ \approx 1 - n \cdot m\Delta t & & \approx n \cdot m\Delta t \end{array}$$

Let $x_n(t)$ be a number of types of genes in the class n at time t . As a result of mutation

$$\approx x_n(t) \cdot n \cdot m\Delta t$$

types of these genes go to classes $n - 1, 1$.

$$\begin{aligned}
 x_1(t + \Delta t) - x_1(t) = & -dx_1\Delta t - rx_1\Delta t + 2dx_2\Delta t \\
 & + 2mx_2\Delta t + \sum_{n=2}^{\infty} mn x_n \Delta t + o(\Delta t),
 \end{aligned}$$

$$\begin{aligned}
 x_n(t + \Delta t) - x_n(t) = & -dnx_n\Delta t - rnx_n\Delta t - mn x_n \Delta t \\
 & + r(n-1)x_{n-1}\Delta t + d(n+1)x_{n+1}\Delta t \\
 & + m(n+1)x_{n+1}\Delta t + o(\Delta t)
 \end{aligned}$$

for $n \geq 2$.

removal, duplication, mutation.

$$x'_1 = -(d+r)x_1 + 2(m+d)x_2 + \sum_{n=2}^{\infty} mnx_n$$

$$x'_n = -(d+r+m)nx_n + r(n-1)x_{n-1} + (d+m)(n+1)x_{n+1}, \quad n \geq 2$$

Conservation law:

Let $\varphi(t) = \sum_{n=1}^{\infty} nx_n(t)$. Then

$$\varphi(t) = e^{(r-d)t}\varphi(0).$$

The total number of genes grows exponentially and $\lambda = r - d$ is the growth rate.

Naïve proof:

$$\varphi'(t) = \sum_{n=1}^{\infty} nx'_n(t) = (r-d) \sum_{n=1}^{\infty} nx_n(t) = (r-d)\varphi(t)$$

Let

$$y_n(t) = e^{-\lambda t} n x_n(t)$$

for $n \in N$ and $y(t) = (y_n(t))_{n \in N}$. Then

$$y_1' = -2ry_1 + (2m + d)y_2 + \sum_{n=3}^{\infty} my_n,$$

$$y_n' = -(d + r + m + \frac{r-d}{n})ny_n + rny_{n-1} + (d + m)ny_{n+1}$$

for $n \geq 2$.

$$y'(t) = Qy(t), \tag{4}$$

where Q is an infinite dimensional matrix.

Properties: if $y(0) \geq 0$, then $y(t) \geq 0$ for $t > 0$ and

$$\sum_{n=1}^{\infty} y_n(t) \equiv \text{const.}$$

Let consider a space of absolutely summable sequences l^1 with the norm $\|y\| = \sum_{n=1}^{\infty} |y_n|$.

$$D = \{y \in l^1 : y \geq 0, \|y\| = 1\}$$

$y \in D$ is called **distribution** or **density**.

Let $P(t)y = y(t)$, where $y(t)$ is a solution of (4) with the initial condition $y(0) = y$. If $y \in D$, then $y(t) \in D$.

The family $\{P(t)\}_{t \geq 0}$ is a **Markov semigroup** on l^1 , i.e.

(a) for $t > 0$ the operator $P(t) : l^1 \rightarrow l^1$ is linear and $P(t)D \subset D$.

(b) $P(0) = Id$, $P(t + s) = P(t)P(s)$, $s, t \geq 0$,

(c) for each $y \in l^1$, the function $t \mapsto P(t)y$ is continuous.

Asymptotic stability

$y^* \in D$ is called **invariant density** if $P(t)y^* = y^*$ for $t \geq 0$.

$\{P(t)\}$ – is **asymptotically stable**, if there exists an invariant density y^* such that

$$\lim_{t \rightarrow \infty} \|P(t)y - y^*\| = 0 \quad \text{for } y \in D.$$

Theorem 3. *If $m > 0$, then the semigroup $\{P(t)\}$ is asymptotically stable.*

Corollary 1. **Distribution** of sizes of classes stabilizes as $t \rightarrow \infty$, i.e. for each k we have

$$\lim_{t \rightarrow \infty} \frac{x_k(t)}{\sum_{i=1}^{\infty} x_i(t)} = \frac{cy_k^*}{k}.$$

Theorem 4 (Lasota-Yorke). *If there exists $h \geq 0$ such that for each density y we have*

$$P(t)y \geq h + \varepsilon_t(y) \quad \text{and} \quad \|\varepsilon_t(y)\| \rightarrow 0,$$

then the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable.

Proof of Theorem 3. Let $y(0) \in D$. Since

$$y_1'(t) \geq -(2r + m)y_1(t) + m,$$

we have

$$\liminf_{t \rightarrow \infty} y_1(t) \geq \frac{m}{2r+m}.$$

$$h = \left(\frac{m}{2r+m}, 0, 0, \dots\right). \quad \square$$

Stationary solutions

$y^* \in D$ is an invariant density $\Leftrightarrow Qy^* = 0$.

General case:

$$0 = -(2r + m)y_1^* + (m + d)y_2^* + \sum_{n=1}^{\infty} my_n^*,$$

$$0 = -(d + r + m + \frac{r-d}{n})ny_n^* + rny_{n-1}^* + (d + m)ny_{n+1}^*; \quad n \geq 2.$$

$$\sum_{n=1}^{\infty} y_n^* = 1.$$

Fix y_1^* . Find $y_2^* = f_1(y_1^*)$, $y_{n+1}^* = f_n(y_n^*, y_{n-1}^*)$ for $n \geq 2$.

Let assume that growth rate $\lambda = 0$, i.e. $r = d$.

Then $y_n^* = C\beta^n$, where $\beta = \frac{r}{r+m}$.

Corollary 2. $\lim_{t \rightarrow \infty} x_n(t) = C \frac{\beta^n}{n}$.

Słonimski's Conjecture $\iff r = d = m$.

Paralogous families in genomes (bacteria and yeasts) and the parameter of the best-fit model.

Species	#(Families)	β	m/r
<i>B. mallei</i>	703	0.732	0.366
<i>G. sulfurreducens</i>	581	0.702	0.38
<i>P. putida</i>	745	0.764	0.309
<i>B. anthracis Ames</i>	815	0.673	0.486
<i>S. oneidensis</i>	586	0.687	0.456
<i>S. cerevisiae</i>	732	0.501	0.996
<i>C. glabrata</i>	576	0.475	1.105
<i>K. lactis</i>	465	0.527	0.898
<i>D. hansenii</i>	755	0.564	0.773
<i>Y. lipolytica</i>	632	0.545	0.835

About the naïve proof and the generation of the semigroup.

$Q = (q_{ij})_{i,j \geq 1}$ is called a **Kolmogorov matrix** if

1) $q_{ij} \geq 0$ for $i \neq j$,

2) $\sum_{i=1}^{\infty} q_{ij} = 0$ for $j \geq 1$.

Theorem 5. *Let Q be a Kolmogorov matrix. The matrix Q generates a Markov semigroup on $l^1 \iff$ there exists a $\theta > 0$ such that the equation $Q^*x = \theta x$ has no non-zero solutions $x \in l^\infty$.*

5. NONLINEAR DISCRETE MODELS

Example. (Age structured model with limited resources)

$x(a, t)$ – the number of individuals with age a at time t

$$N(t) = \sum_{a=1}^{\infty} x(a, t)$$

$$\mu = \mu(a, N(t)), 0 \leq \mu \leq 1.$$

$b = b(a, N(t))$ – the mean number of children at time t of an individual with age a .

Example.

$$\mu(a, N(t)) = \mu(a) \text{ or } \mu = N(t)/N_{\max}$$

$$b = (1 - N(t)/N_{\max})p(a),$$

where N_{\max} is the maximum size of the population and $p(a)$ is the mean number of children in the best conditions.

$$N(t) = \sum_{a=1}^{\infty} x(t, a),$$
$$x(t+1, a+1) = (1 - \mu(a, N(t)))x(t, a), \quad \text{for } a \geq 1,$$
$$x(t+1, 1) = \sum_{a=1}^{\infty} b(a, N(t))x(t, a).$$

If we assume that the maximum age is a_{\max} , then the infinity in this system should be replaced by a_{\max} and we should also assume that

$$\mu(a_{\max}, N) = 1.$$

Example. (Penna model)

m – maximum life span.

$$N(t) = \sum_{m=1}^{\infty} \sum_{a=1}^m x(t, a, m),$$

$$x(t+1, a+1, m) = (1 - \mu(a, m, N(t)))x(t, a, m), \quad \text{for } a < m,$$

$$x(t+1, a+1, m) = 0, \quad \text{for } a \geq m,$$

$$x(t+1, 1, m) = \sum_{m=1}^{\infty} \sum_{a=1}^{m'} b(a, m, m', N(t))x(t, a, m').$$

$$\mu = N(t)/N_{\max}$$

$$b = (1 - N(t)/N_{\max})p(m, m'),$$

where N_{\max} is the maximum size of the population and $p(m, m')$ is the birth matrix $p(m, m')$, i.e. $p(m, m')$ is the probability that a parent with maximum life span m' gives birth to a child with maximum life span m .

6. MODELS WITH DELAY

Verhulst with delay:

$$N'(t) = \sigma \left(1 - \frac{N(t-h)}{K} \right) N(t). \quad (5)$$

Models with a delayed feedback:

$$N'(t) = -\mu N(t) + f(N(t-h)), \quad (6)$$

Examples. Linear

$$N'(t) = -\mu N(t) + aN(t-h), \quad (7)$$

dynamic of red blood cells:

$$N'(t) = -\mu N(t) + \lambda e^{-N(t-h)}, \quad (8)$$

Others:

1. The distributed delay:

$$N'(t) = -dN(t) + \int_0^a f(N(t-h))g(dh).$$

2. The delay depending on the size of the population.

3. Systems of equations with delay.

4. Partial differential equations with delay.

How to solve them? - method of steps

$$x'(t) = f(x(t), x(t - h)), \quad h > 0. \quad (9)$$

$$x(t) = \varphi(t), \quad t \in [-h, 0].$$

$$x'(t) = f(x(t), \varphi(t - h)), \quad t \in [0, h], \quad (10)$$

If the solution is defined in the whole interval $[0, h]$, then next we consider the interval $t \in [h, 2h]$. Since the values of the function $x(t - h)$ are known for $t \in [h, 2h]$, we again solve an ordinary differential equation for $t \in [h, 2h]$. In this way we solve (9) in consecutive intervals $[nh, (n + 1)h]$.

7. STABILITY

A solution $x_0(t)$ is called *stable*, if for each $\varepsilon > 0$, there is $\delta > 0$ such that

$$|x(\theta) - x_0(\theta)| < \delta \quad \text{for } \theta \in [-h, 0]$$

⇓

$$|x(t) - x_0(t)| < \varepsilon \quad \text{for } t \geq 0.$$

A solution $x_0(t)$ is called *asymptotically stable*, if it is stable and

$$\lim_{t \rightarrow \infty} |x(t) - x_0(t)| = 0. \tag{11}$$

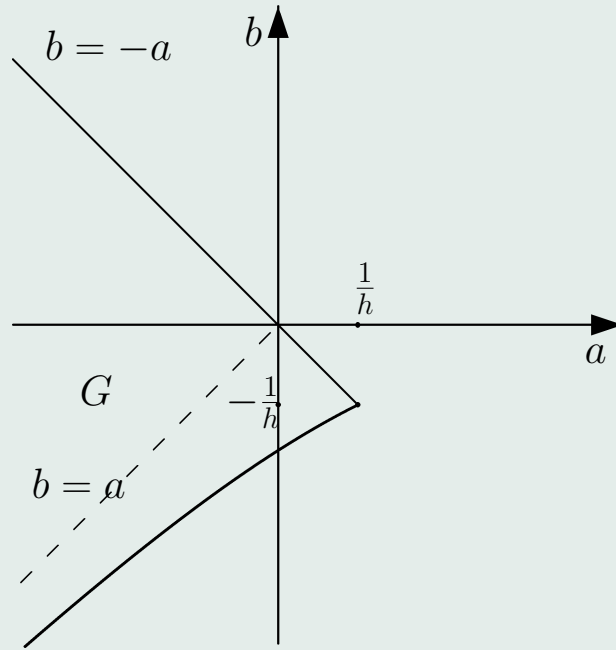
$$f(N_0, N_0) = 0, a = \frac{\partial f}{\partial x}(N_0, N_0), b = \frac{\partial f}{\partial y}(N_0, N_0).$$

The linearization in the neighbourhood of a stationary point:

$$x'(t) = ax(t) + bx(t - h). \quad (12)$$

Theorem. If all roots of the function $p(z) = z - a - be^{-zh}$ have negative real parts then the solution $x \equiv N_0$ is asymptotically stable.

Intuition: if z is a root of the function $p(z)$, then e^{zt} is a solution of (12).



G – the domain of coefficients a, b , in which the stationary solution of (12) is asymptotically stable.

$$a = \frac{y \cos(hy)}{\sin(hy)}, \quad b = -\frac{y}{\sin(hy)}, \quad 0 \leq y < \frac{\pi}{h},$$

Global stability

$x(t)$ a solution of (9) with the initial condition $x(\theta) = \varphi(\theta)$ for $\theta \in [-h, 0]$.

Let $x_t(\theta) := x(t + \theta)$ for $\theta \in [-h, 0]$.

$V : C[-h, 0] \rightarrow \mathbb{R}$

$$\dot{V}(\varphi) = \lim_{t \rightarrow 0^+} \frac{1}{t} [V(x_t) - V(\varphi)]. \quad (13)$$

Example. Let

$$V(\varphi) = g(\varphi(0)) + \int_{-h}^0 \Psi(\varphi(\theta)) d\theta,$$

$$\dot{V}(\varphi) = g'(\varphi(0))f(\varphi(0), \varphi(-h)) + \Psi(\varphi(0)) - \Psi(\varphi(-h)).$$

$$V(\varphi) = g(\varphi(0)) + \int_{-h}^0 \Psi(\varphi(\theta)) d\theta,$$

$$\begin{aligned} \dot{V}(\varphi) &= \lim_{t \rightarrow 0^+} \frac{1}{t} \left[g(x_t(0)) + \int_{-h}^0 \Psi(x_t(\theta)) d\theta - g(\varphi(0)) - \int_{-h}^0 \Psi(\varphi(\theta)) d\theta \right] \\ &= \lim_{t \rightarrow 0^+} \frac{1}{t} \left[g(x(t)) - g(x(0)) + \int_{-h}^0 \Psi(x(\theta + t)) d\theta - \int_{-h}^0 \Psi(x(\theta)) d\theta \right] \\ &= g'(x(0))x'(0) + \lim_{t \rightarrow 0^+} \frac{1}{t} \left[\int_{t-h}^t \Psi(x(\theta)) d\theta - \int_{-h}^0 \Psi(x(\theta)) d\theta \right] \\ &= g'(x(0))f(x(0), x(-h)) + \lim_{t \rightarrow 0^+} \frac{1}{t} \left[\int_0^t \Psi(x(\theta)) d\theta - \int_{-h}^{t-h} \Psi(x(\theta)) d\theta \right] \\ &= g'(\varphi(0))f(\varphi(0), \varphi(-h)) + \Psi(\varphi(0)) - \Psi(\varphi(-h)). \end{aligned}$$

A functional $V : C[-h, 0] \rightarrow \mathbb{R}$ is called a *Lapunov functional* for equation (9) on an invariant set X , if $\dot{V} \leq 0$ on X .

Theorem. Let $\{\varphi \in \bar{X} : \dot{V}(\varphi) = 0\} = \{N_0\}$. If $x(t)$ is a bounded solution with the initial function $\varphi \in X$, then $x(t) \rightarrow N_0$, as $t \rightarrow \infty$.

(S) for each $L > 0$ there is $K > 0$ such that

$$V(\varphi) \leq L \Rightarrow |\varphi(0)| \leq K,$$

(S) \implies boundedness of solutions.

Example. $f(x)x > 0$ for $x \neq 0$ and $\liminf_{|x| \rightarrow \infty} |f(x)| > 0$ and $|c| < 1$, then a zero-solution of the equation

$$x'(t) = -f(x(t)) + cf(x(t-h))$$

is globally asymptotically stable.

Let $F(x) = \int_0^x f(r) dr$ and

$$V(\varphi) = F(\varphi(0)) + \frac{1}{2} \int_{-h}^0 f^2(\varphi(r)) dr, \quad (14)$$

where $F(x) = \int_0^x f(r) dr$ Then $V \geq 0$ and

$$\begin{aligned} \dot{V}(\varphi) &= F'(\varphi(0))\varphi'(0) + \frac{1}{2}f^2(\varphi(0)) - \frac{1}{2}f^2(\varphi(-h)) \\ &= f(\varphi(0))(-f(\varphi(0)) + cf(\varphi(-h))) + \frac{1}{2}f^2(\varphi(0)) - \frac{1}{2}f^2(\varphi(-h)) \\ &\leq -\frac{1}{2}(1 - c^2)f^2(\varphi(0)). \end{aligned}$$

Condition (S) follows from the fact that $\lim_{|x| \rightarrow \infty} F(x) = \infty$.

8. THE EXISTENCE OF PERIODIC SOLUTIONS

The appearance of periodic solutions with the growth of delay.

1. The method of the Hopf bifurcation.

$$x'(t) = f(x(t), x(t - h)) \quad (15)$$

and we change h .

$f(0, 0) = 0$, thus $x \equiv 0$ is a solution.

We assume that for $h = 0$ a zero-solution of (15) is asymptotically stable.

Is a critical value $h_* > 0$ such that $x \equiv 0$ is stable for $h < h_*$ and unstable for $h > h_*$ and there exists a periodic solution for $h > h_*$? Is this periodic solution orbitally stable?

We substitute $y(t) = x(ht)$ to (15) and obtain

$$y'(t) = hx'(ht) = hf(y(t), y(t-1)). \quad (16)$$

$$y'(t) = f(y(t), y(t-\tau), \mu), \quad (17)$$

where τ is a positive constant and μ is a bifurcation parameter.

We assume that the function $x \equiv 0$ is a solution of (17), i.e. $f(0, 0, \mu) = 0$. Let

$$y'(t) = a(\mu)y(t) + b(\mu)y(t-\tau) \quad (18)$$

be the linearization of (17) in zero for a given μ , i.e. $a(\mu) = \frac{\partial f}{\partial y_1}(0, 0, \mu)$ and

$$b(\mu) = \frac{\partial f}{\partial y_2}(0, 0, \mu).$$

We assume that the quasi-characteristic equation

$$a(\mu) + b(\mu)e^{-\tau\lambda} = \lambda \quad (19)$$

has a solution $\lambda(\mu)$, which is a differentiable function of μ in the neighbourhood of zero and have the following properties

$$\operatorname{Re} \lambda(0) = 0, \quad \operatorname{Im} \lambda(0) > 0, \quad \operatorname{Re} \lambda'(0) \neq 0. \quad (20)$$

Then there exists $\mu_0 > 0$ and $a_0 > 0$ such that for each $a \in (0, a_0)$ there exists $\mu \in (-\mu_0, \mu_0)$ and a periodic solution $y_\mu(t)$ of (17) with the parameter μ which has the amplitude a .

Moreover the period of the solution y_μ tends to $\frac{2\pi}{\operatorname{Im} \lambda(0)}$ as $\mu \rightarrow 0$.

Example.

$$x'(t) = -\sigma x(t-h)(1+x(t)), \quad \lambda > 0, \quad (21)$$

which can be obtained if we substitute $x(t) = -1 + N(t)/K$ in (5). Let $h_* = \pi/(2\sigma)$, $y(t) = x(ht)$, $\mu := \sigma h - \sigma h_*$. Then

$$y'(t) = -\left(\mu + \frac{\pi}{2}\right)y(t-1)(1+y(t)). \quad (22)$$

The linear part is of the form

$$y'(t) = -\left(\mu + \frac{\pi}{2}\right)y(t-1).$$

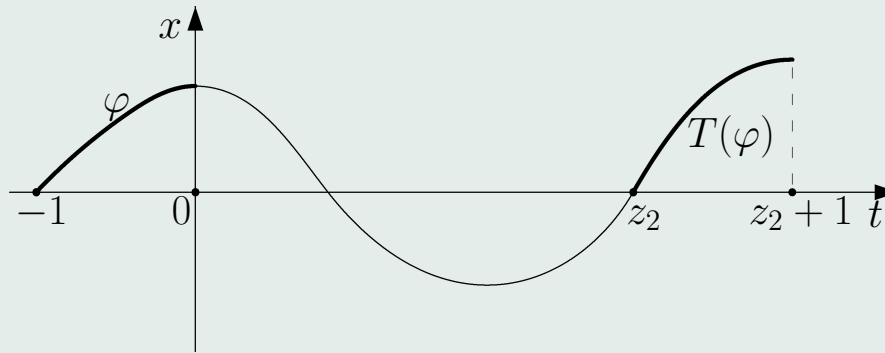
The characteristic equation:

$$-\left(\mu + \frac{\pi}{2}\right)e^{-\lambda} = \lambda.$$

In this case $\lambda(0) = \frac{\pi i}{2}$ and $\operatorname{Re} \lambda'(0) \neq 0$.

After passing h through the point h_* a periodic solution appears and this solution is asymptotically stable.

2. Application of the [Browder theorem](#) on the ejective fixed point in the space of slowly-oscillating functions.

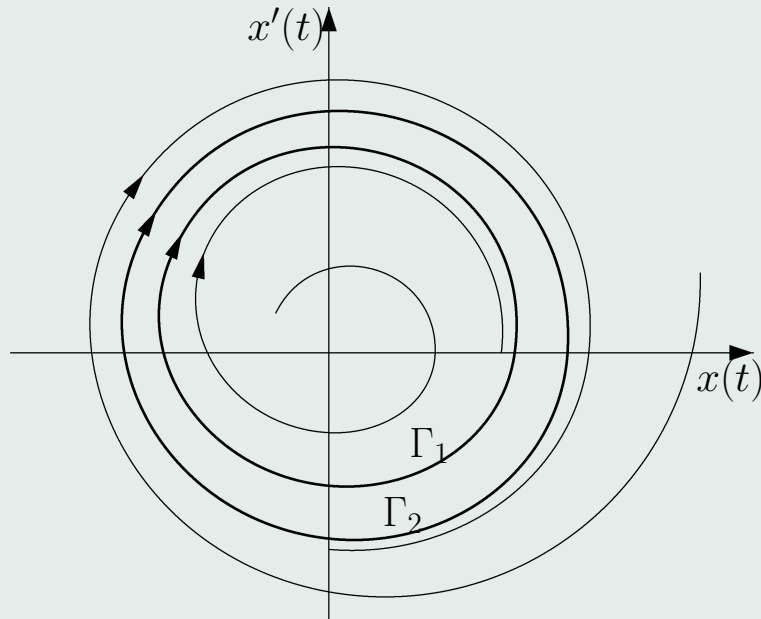


$T : K \rightarrow K$, K - non-decreasing functions φ , $\varphi(-1) = 0$.

A fixed point $x_0 \in K$ of the transformation T is called *ejective*, if there is a neighbourhood U of x_0 such that for every $x \in U \setminus \{x_0\}$ there is a positive integer $n = n(x)$ such that $T^n(x) \in K \setminus U$.

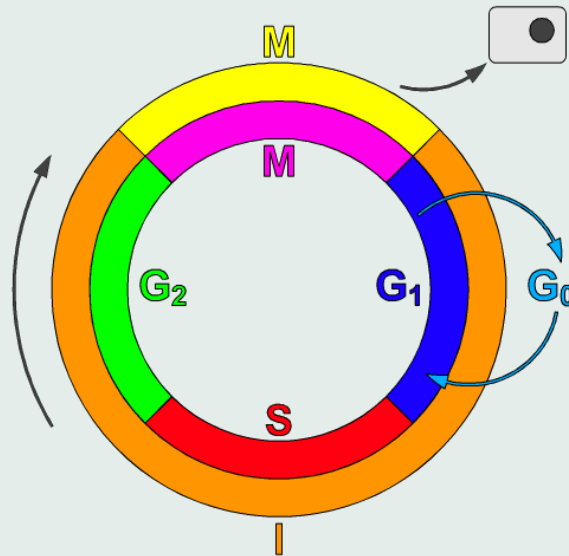
Browder theorem. Let K be an infinite dimensional closed and convex subset of a Banach space X and let $T : K \rightarrow K$ be a continuous function and $T(K)$ be relatively compact. Then T has at least one fixed point which is not ejective.

3. Poincaré-Bendixon method in the phase space (x, x') .



Continuous structured models

9. CELL CYCLE MODEL



G_1 - growth, S - DNA synthesis, G_2 - protein synthesis, M - mitosis.

Duration t_A of $A = G_1$ is highly variable

duration t_B of $B = S + G_2 + M$ is almost constant.

Lasota-Mackey (1984), Tyson-Hannsgen (1986),
Tyrcha (1988) (two-phase models)

The length t_A of phase A is random:

$$\text{Prob}(t \leq t_A \leq t + \Delta t \mid t_A \geq t) \cong \varphi(x(t))\Delta t,$$

where $x(t)$ is size or maturity (amount of "mitogen").

Size growth:

$$\frac{dx}{dt} = g(x),$$

$\pi(t, x_0)$ - size of a cell at time t with initial size x_0 .

$$F(t) := \text{Prob}(t_A \geq t)$$

$$\frac{F(t) - F(t + \Delta t)}{F(t)} \cong \varphi(\pi(t, x_0))\Delta t,$$

$$F'(t) = -F(t)\varphi(\pi(t, x_0)),$$

$$(\ln F(t))' = -\varphi(\pi(t, x_0)),$$

$$\ln F(t) = \ln F(0) - \int_0^t \varphi(\pi(s, x_0)) ds,$$

$$F(t) = \exp \left\{ - \int_0^t \varphi(\pi(s, x_0)) ds \right\}.$$

For $y \geq x_0$ we define $t(x_0, y)$ as a t such that $\pi(t, x_0) = y$.

$$\frac{\partial t}{\partial y} \cdot g(\pi(t, x_0)) = 1 \implies \frac{\partial t}{\partial y} = \frac{1}{g(y)}.$$

Y - size of the cell at time t_A .

$$\text{Prob}(Y \geq y) = \text{Prob}(\pi(t, x_0) \geq y) = \exp \left\{ - \int_0^{t(x_0, y)} \varphi(\pi(s, x_0)) ds \right\}.$$

$$\frac{\partial}{\partial y} \left(\int_0^{t(x_0, y)} \varphi(\pi(s, x_0)) ds \right) = \frac{\varphi(y)}{g(y)}$$

$$\text{Prob}(Y \geq y) = \exp \left(- \int_{x_0}^y \frac{\varphi(r)}{g(r)} dr \right).$$

Let

$$Q(y) = \int_0^y \frac{\varphi(r)}{g(r)} dr.$$

$$\text{Prob}(Y \geq y) = \exp(Q(x_0) - Q(y)).$$

Let ξ be a random variable with exponential distribution:

$$\text{Prob}(\xi \geq x) = H(x) = e^{-x}.$$

$$\begin{aligned} \text{Prob} \left(Q^{-1}(Q(x_0) + \xi) \geq y \right) &= \text{Prob} (Q(x_0) + \xi \geq Q(y)) \\ &= \text{Prob} (\xi \geq Q(y) - Q(x_0)) \\ &= \exp(Q(x_0) - Q(y)) = \text{Prob}(Y \geq y). \end{aligned}$$

$$Y = Q^{-1}(Q(x_0) + \xi)$$

and the initial size of a daughter cell is

$$\gamma\left(Q^{-1}(Q(x_0) + \xi)\right),$$

where $\gamma(y) = \frac{1}{2}\pi(t_B, y)$.

X_n the initial size of cell in the n -th generation:

$$X_{n+1} = \gamma\left(Q^{-1}(Q(X_n) + \xi_n)\right),$$

where (ξ_n) is a sequence of independent random variables with exponential distribution.

Relation between the distribution of the size of cells in two successive generations is given by

$$X_{n+1} = S(X_n, \xi_n)$$

If the distribution μ_y of the random variable $S(y, \xi_n)$ is absolutely continuous with respect to m . Then

$$Pf(x) = \int k(x, y)f(y) dy,$$

where $k(x, y)$ is the density of μ_y

$$Pf(x) = - \int_0^{\lambda(x)} \frac{\partial}{\partial x} \left\{ H(Q(\lambda(x)) - Q(y)) \right\} f(y) dy,$$

$$\lambda = \gamma^{-1}.$$

Results:

$$\alpha(x) = Q(\lambda(x)) - Q(x).$$

1. If $\alpha(x) > 1$ for sufficiently large x , then P is *asymptotically stable*, i.e.

$$\lim_{n \rightarrow \infty} \|P^n f - f_*\| = 0 \quad \text{for } f \in D.$$

2. If $\alpha(x) \leq 1$ for sufficiently large x , then P is *sweeping*, i.e.

$$\lim_{n \rightarrow \infty} \int_0^c P^n f(x) dx = 0 \quad \text{for } f \in D \text{ and } c > 0.$$

3. If $\alpha(x) \geq c$ for all $x \geq 0$ and some $c \in \mathbb{R}$, then

$$\lim_{n \rightarrow \infty} \|P^n f - P^n g\| = 0 \quad \text{for } f, g \in D.$$

10. AGE STRUCTURED MCKENDRICK'S MODEL

General remarks on structured models:

1. An individual is described by a parameter $x \in \mathbb{R}^n$ (age, size etc.).
2. $u(t, x)$ describes the distribution of x at time t .

$\int_A u(t, x) dx$ – number of individual (biomass) in set A .

Age structured (demographic) model

McKendrick (1926), VonFoester (1959).

A parameter is the age of an individual $a \in [0, c)$.

We assume that in a time interval $[t, t + \Delta t]$ an individual with age a can

(a) with probability $b(t, a)\Delta t + o(\Delta t)$ "produce" a new individual:

$$u(t, 0) = \int_0^c b(t, a)u(t, a) da$$

(b) with probability $\mu(t, a)\Delta t + o(\Delta t)$ die.

$$u(t + \Delta t, a + \Delta t) - u(t, a) = -\mu(t, a)u(t, a)\Delta t + o(\Delta t).$$

↓

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} = -\mu(t, a)u,$$

$$u(t, 0) = \int_0^c b(t, a)u(t, a) da$$

$$u(0, a) = u_0(a)$$

$N(t) = \int_0^c u(t, a) da$ – total number of individuals at time t ,

$p(t, a) = \frac{u(t, a)}{N(t)}$ – age profile.

Theorem 6 (Ergodicity Norton(1928)). *Let u, \bar{u} be solutions with initial conditions $u(0, a), \bar{u}(0, a)$ which are chosen such that not everybody is beyond child-bearing age. Then*

$$\lim_{t \rightarrow \infty} \frac{\bar{p}(t, a)}{p(t, a)} = 1.$$

Corollary 1 Asynchronous growth. If b and d are independent on t , then there exist a constant $\lambda \in \mathbb{R}$ and a function $p_*(a)$ such that for each solution u there exists a constant C which satisfy

$$\lim_{t \rightarrow \infty} e^{-\lambda t} N(t) = C \quad \text{oraz} \quad \lim_{t \rightarrow \infty} p(t, a) = p^*(a).$$

Corollary 2 Periodic case. If b and d are periodic function with period T , then there exist a constant $\lambda \in \mathbb{R}$ and a function $p_*(t, a)$ periodic with respect to t with period T such that for each solution u there exists a constant C which satisfy

$$\lim_{t \rightarrow \infty} \frac{u(t, a)}{e^{\lambda t} p^*(t, a)} = C.$$

Stationary distribution

$$\mu(t, a) = \mu(a), \quad b(t, a) = b(a), \quad u(t, a) = e^{\lambda t} p(a).$$

$$\begin{aligned} \lambda p(a) + p'(a) &= -\mu(a)p(a), \\ p(0) &= \int_0^c b(a)p(a) da \end{aligned}$$

$$\begin{aligned} p(a) &= p(0) \exp \left\{ - \int_0^a (\lambda + \mu(s)) ds \right\}, \\ 1 &= \int_0^c b(a) \exp \left\{ - \int_0^a (\lambda + \mu(s)) ds \right\} da \end{aligned}$$

$$\varphi(\lambda) = \int_0^c e^{-\lambda a} b(a) e^{-\int_0^a \mu(s) ds} da.$$

$\varphi'(\lambda) < 0$, $\varphi(-\infty) = +\infty$, $\varphi(+\infty) = 0 \implies \varphi(\lambda_0) = 1$ for a unique $\lambda_0 \in \mathbb{R}$.

$$p(0) \cdot \int_0^c e^{-\lambda_0 a - \int_0^a \mu(s) ds} da = 1.$$

$$p(a) = p(0) e^{-\lambda_0 a - \int_0^a \mu(s) ds}.$$

T - the length of life, $F(a) = P(T \geq a)$ - *survival function*

$F(a)$ - the probability of being still alive at age a

$$P(T \in [a, a + \Delta a] | T \geq a) = \mu(a) \Delta a + o(\Delta a)$$

$$\frac{F(a) - F(a + \Delta a)}{F(a)} = \mu(a) \Delta a + o(\Delta a)$$

$$\frac{F'(a)}{F(a)} = -\mu(a).$$

$$F(a) = e^{-\int_0^a \mu(s) ds}. \quad p(a) = p(0) e^{-\lambda_0 a} F(a).$$

Question: How to find Ulpian's table if we read only obituary?

$$\varphi_a(x) = P(T \geq a + x | T \geq a) = \frac{P(T \geq a + x)}{P(T \geq a)} = \frac{F(a + x)}{F(a)}$$

$\varphi_a(x)$ - probability that *remaining life* at age a is at least x .

$$D(a) = - \int_0^{\infty} x \varphi'_a(x) dx = \int_0^{\infty} \varphi_a(x) dx = \int_0^{\infty} \frac{F(a + x)}{F(a)} dx.$$

expected remaining life at age a (Ulpian's table).

11. ERYTHROCYTES DYNAMICS

M. Ważewska–Czyżewska i A. Lasota, *Matematyczne problemy dynamiki układu krwinek czerwonych*, Roczniki PTM, *Matematyka Stosowana* **6** (1976), 23–40.

$n(t, a)$ - age distribution of red cells at time t ,

$N(t) = \int_0^\infty n(t, a) da$ number of red cells at time t

$n(t, 0) = p(t)$ - production of new cells in unit time,

$S(t) = \frac{p'(t)}{p(t)}$ – degree of arousal of the system.

The change of the number of red cells in blood circulation causes arousal of the system,

h time for the production of a mature erythrocyte.

Assumption: $S(t) = -\frac{d}{dt}\gamma N(t - h)$

h -delay in the action of the system

γ - arousal of the system

$$\frac{n'(t, 0)}{n(t, 0)} = -\frac{d}{dt}\gamma N(t - h) \implies n(t, 0) = \rho e^{-\gamma N(t-h)}$$

ρ - demand of the organism for oxygen.

$d(t, a)$ - death rate

$$n(t + \Delta t, a + \Delta t) - n(t, a) = -d(t, a)n(t, a)\Delta t + o(\Delta t).$$

↓

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -d(t, a)n,$$
$$n(t, 0) = \rho e^{-\gamma N(t-h)}$$

Simplified model

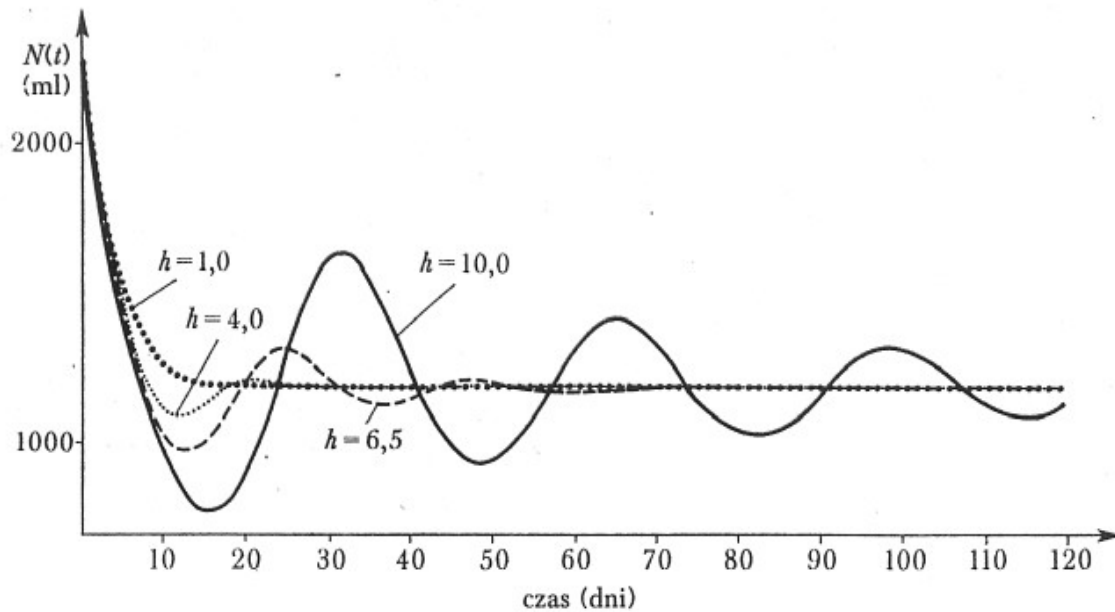
$$\mu = \frac{1}{N(t)} \int_0^{\infty} d(t, a)n(t, a) da$$

coefficient of destruction

$$\int_0^{\infty} \left\{ \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} \right\} da = - \int_0^{\infty} d(t, a)n da$$

$$N'(t) + n(t, \infty) - n(t, 0) = -\mu N(t)$$

$$N'(t) = -\mu N(t) + \rho e^{-\gamma N(t-h)}$$



Rys. 4. Rozwiązania równania (19) odpowiadające kryzie hemolitycznej

Results in the paper

1. Properties of the stationary solutions of the partial differential equation.
2. Fitting of the functions in the model to medical data.
3. Conclusions concerning the course of the diseases under different parameters.
4. Stability of the stationary solution of the equation with delay.

Inspiration to further studies:

Medical treatment:

M. Ważewska-Czyżewska, A. Lasota, M. C. Mackey, Minimizing therapeutically induced anemia, J. Math. Biol., 13 (1981) 149–158.

M. Ważewska-Czyżewska (1984), Erythrokinetics.

Periodic diseases:

M.C.Mackey and L.Glass, Science (1977)

L.Glass and M.C. Mackey (1988), From Clocks to Chaos, The Rhythms of Life.

Dynamics of differentiation of blood cells in the bone marrow

Mathematics:

existence of periodic solutions and limit cycle

stability and chaos of first order PDE

12. SIZE STRUCTURED MODEL

Continuity equation

Consider a cell model without mortality and proliferation

$x \in G \subset \mathbb{R}^n$ - a parameter describing a cell

$$x'(t) = g(t, x(t)) \quad (23)$$

x - age $\implies g \equiv 1$,

x mass (volume) of a cell $\implies g(t, x) = \lambda x$ or $g(t, x) = \lambda x^{2/3}$.

$u(t, x)$ - distribution of x

$$\frac{\partial u(t, x)}{\partial t} + \operatorname{div}(g(t, x)u(t, x)) = 0,$$

where

$$\operatorname{div}(g(t, x)u(t, x)) = \sum_{i=1}^n \frac{\partial}{\partial x_i}(g(t, x)u(t, x)).$$

Proof. Given a domain $D \subset G$ with the smooth boundary S

$$I(\Delta t) = \int_D u(t + \Delta t, x) dx - \int_D u(t, x) dx. \quad (24)$$

$$I(\Delta t) = -\Delta t \int_S (n(x) \cdot g(t, x)u(t, x)) d\sigma(x) + o(\Delta t), \quad (25)$$

Gauss-Ostrogradski theorem

$$\int_S (n(x) \cdot g(t, x)u(t, x)) d\sigma(x) = \int_D \operatorname{div}(g(t, x)u(t, x)) dx. \quad (26)$$

Size structure

x - **size**, $0 < a \leq x \leq 1$,

$$x' = g(x)$$

$d(x)$, $b(x)$ - **death** and **division rates**

$$\int_a^1 b(x) dx = \infty, \quad x \mapsto (a, x - a), \quad x \geq 2a.$$

$\Delta t \int_0^m (d(x) + b(x))u(t, x) dx$ - **lost of cells with size** $\leq m$

$\Delta t \int_0^{2m} 2b(r)u(t, r) dr$ - **new cells with size** $\leq m$

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

where $\mu(x) = d(x) + b(x)$.

Theorem. If $g(2x) \neq 2g(x)$ at least for one $x \in [a, 1]$, then there exist $\lambda \in \mathbf{R}$ and positive functions f_* and w such that

$$e^{-\lambda t} u(t, \cdot) \rightarrow f_* \int_a^1 u(x, 0) w(x) dx \quad \text{in } L^1(a, 1).$$

Sketch of the proof

0. $u'(t) = Au$.

1. There exist $\lambda \in \mathbf{R}$ and positive functions v, w such that $Av = \lambda v$ and $A^*w = \lambda w$.

2. $P(t) = e^{-\lambda t} T(t)$ is a Markov semigroups on $L^1(X, \Sigma, m)$, where $m(B) = \int_B w(x) dx$.

3. $\{P(t)\}$ has a positive invariant density \Rightarrow asymptotic stability of $\{P(t)\}$

4. The Lebesgue measure and the measure m are equivalent $\Rightarrow e^{-\lambda t} u(t, \cdot)$ converges to Cf_* in $L^1(a, 1)$.

$\{P(t)\}$ – **partially integral** if there exist $t > 0$, $q(x, y) \geq 0$

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

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

Theorem 7. Let $\{P(t)\}_{t \geq 0}$ be a partially integral Markov semigroup. Assume that the semigroup $\{P(t)\}_{t \geq 0}$ **has** only one invariant density f_* . If $f_* > 0$ then the semigroup $\{P(t)\}_{t \geq 0}$ is asymptotically stable.

13. GENERAL APPROACH

General reproduction operator:

Individual with x has k descendants, then $\mathcal{P}_k(x, A)$ is the probability that any its descendant has the parameter in the set $A \subset G$ at the birth.

x - age $\implies \mathcal{P}_k(x, A) = 1_A(0)$.

x - size \implies

$$\mathcal{P}_2(x, A) = \begin{cases} 1, & \text{if } x/2 \in A, \\ 0, & \text{if } x/2 \notin A. \end{cases}$$

$b_k(x)\Delta t$ - probability that an individual with parameter x has k descendants in time $[t, t + \Delta t]$,

$$\mathcal{P}(x, A) = \sum_{k=1}^{\infty} kb_k(x)\mathcal{P}_k(x, A).$$

$\mathcal{P}(x, A)\Delta t$ - probability that an individual with parameter x has a descendant in the set A .

Kolmogorov's backward equation

$m_{t,x}$ - distribution of the parameter at time t if at time 0 we have one individual with parameter x

$$u(t, x) = \int_G f(y) m_{t,x}(dy).$$

Then

$$\frac{\partial u}{\partial t} = \underbrace{-\mu u + \sum_{i=1}^n g_i \frac{\partial u}{\partial x_i} + \int_G u(t, y) \mathcal{P}(x, dy)}_{\mathcal{A}^* u}.$$

$$Sf(x) = \int_G f(y) \mathcal{P}(x, dy)$$

Kolmogorov's forward (Fokker-Planck) equation for the distribution of densities:

$$\frac{\partial u}{\partial t} = \mathcal{A}u,$$

Example 1: If there exists a linear bounded operator $P : L^1(G) \rightarrow L^1(G)$ such that $P^* = S$ then F-P equation has the form

$$\frac{\partial u(t, x)}{\partial t} + \operatorname{div}(g(x)u(t, x)) = -\mu(x)u(t, x) + Pu(t, x).$$

Example 2: McKendrick's model

$$\mathcal{A}f(a) = -\mu(a)f(a) - f'(a),$$

$$D(\mathcal{A}) = \{f \in L^1 : f' \in L^1, f(0) = \int_0^c 2b(a)f(a) da\}$$

$$\mathcal{A}^*f(a) = -\mu(a)f(a) + f'(a) + 2b(a)f(0).$$

Kolmogorov's backward equation:

$$\frac{\partial}{\partial t}u(t, a) = -\mu(a)u(t, a) + \frac{\partial}{\partial a}u(t, a) + 2b(a)u(t, 0).$$

14. OTHER EXAMPLES

Example 1. Simple Cell Cycle Structured Cell Population Model.

$0 \leq x \leq 1$ - the position in the cell cycle, $x' = g(x)$

division at maturity 1,

new cells - maturity 0

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} (g(x)u(t, x)) = -\mu(x)u(t, x),$$

$$u(0, x) = u_0(x).$$

Example 1. Simple Cell Cycle Structured Cell Population Model.

$0 \leq x \leq 1$ - the position in the cell cycle, $x' = g(x)$

division at maturity 1,

new cells - maturity 0

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} (g(x)u(t, x)) = -\mu(x)u(t, x),$$

$$u(t, 0) = 2u(t, 1),$$

$$u(0, x) = u_0(x).$$

Example 1. Simple Cell Cycle Structured Cell Population Model.

$0 \leq x \leq 1$ - the position in the cell cycle, $x' = g(x)$

division at maturity 1,

new cells - maturity 0

$$\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} (g(x)u(t, x)) = -\mu(x)u(t, x),$$

$$g(0)u(t, 0) = 2g(1)u(t, 1),$$

$$u(0, x) = u_0(x).$$

Example 2. The Age Structured Cell Population Model with Telomere loss.

Ends of chromosomes, called telomeres, shorten each time a cell divides. When a critical number is reached no further divisions occur.

$$\begin{aligned}\frac{\partial}{\partial t}u_j(t, a) + \frac{\partial}{\partial a}u_j(t, a) &= -b_j(a)u_j(t, a), \quad j = 0, \dots, N, \\ u_j(t, 0) &= 2 \sum_{k=j}^N p_{jk} \int_0^{\infty} b_k(a)u(t, a) da \\ u_j(0, a) &= \varphi_j(a).\end{aligned}$$

Example 3. Two-phase model of cell cycle

Parameter: **maturation (or biological age)**: size, concentration of a special substance

First phase (resting phase) - random duration,

Second phase (proliferating phase) - duration constant τ

$p(t, m, a)$ – proliferating cells, $n(t, m, a)$ – resting cells

$$a' = 1, m' = V(m)$$

$\gamma(m), \delta(m)$ – death rates

$$N(t, m) = \int n(t, m, a) da, \quad \bar{N}(t) = \int N(t, m) dm$$

$\beta = \beta(\bar{N}, m)$ – rate of entering prolif. phase

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial(Vp)}{\partial m} = -\gamma p \quad (27)$$

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \frac{\partial(Vn)}{\partial m} = -(\delta + \beta)n \quad (28)$$

$$p(t, m, 0) = \beta(\bar{N}(t), m)N(t, m) \quad (29)$$

$$n(t, m, 0) = 2p(t, h(m), \tau)h'(m) \quad (30)$$

δ, γ and β do not depend on m

$$\frac{\partial N}{\partial t} + \frac{\partial(VN)}{\partial m} = -(\delta + \beta(\bar{N}))N + 2e^{-\gamma\tau}\beta(\bar{N}(t - \tau))k'(m)N(t - \tau, k(m)),$$

where $k(m) = g(h(m))$, $g(m) = \pi(-\tau, m)$,

$$\bar{N}'(t) = -(\delta + \beta(\bar{N}))\bar{N} + 2e^{-\gamma\tau}\beta(\bar{N}(t - \tau))\bar{N}(t - \tau)$$

Theorem 8. *Assume that the delay equation has a constant solution $\bar{N}_0 \neq 0$ and \bar{N}_0 is globally asymptotically stable. If*

$$(\delta + \beta(\bar{N}_0)) \log k'(0) < V'(0) \quad (31)$$

then there exists a stationary solution $N_0(m)$ of our equation and for every solution $N(t, m)$ of it we have

$$\lim_{t \rightarrow \infty} \int |N(t, m) - N_0(m)| dm = 0. \quad (32)$$

Advanced structured models:

1. With time delay.
2. With nonlinear term connected with limited resources.
3. With the second order terms connected with stochastic noise.

Ad1. e.g. delay connected cell cycle,

Ad2. e.g. probability of division depends on total numbers of cells (nonlocal and nonlinear term in the equation).

Ad3. e.g. if parameter is some phenotype property and evolution is influenced by mutation.