On a stochastic gene expression with pre-mRNA, mRNA and protein contribution

How (maybe) very trivial changes lead to (maybe) nontrivial effects

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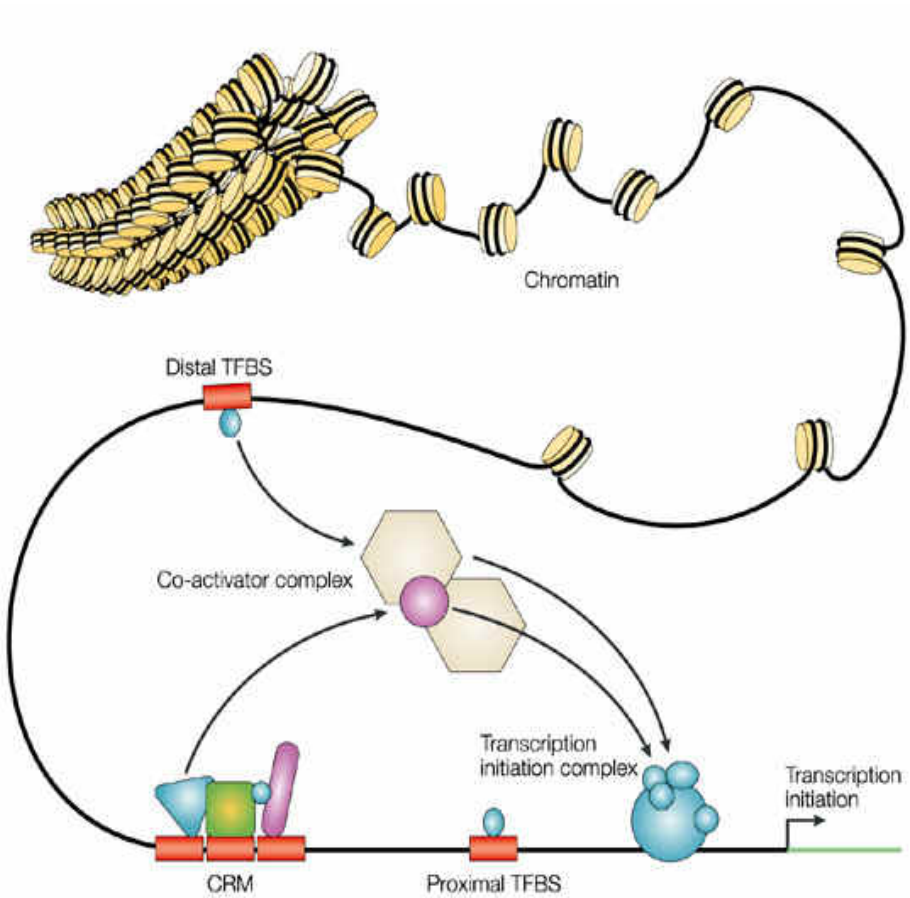
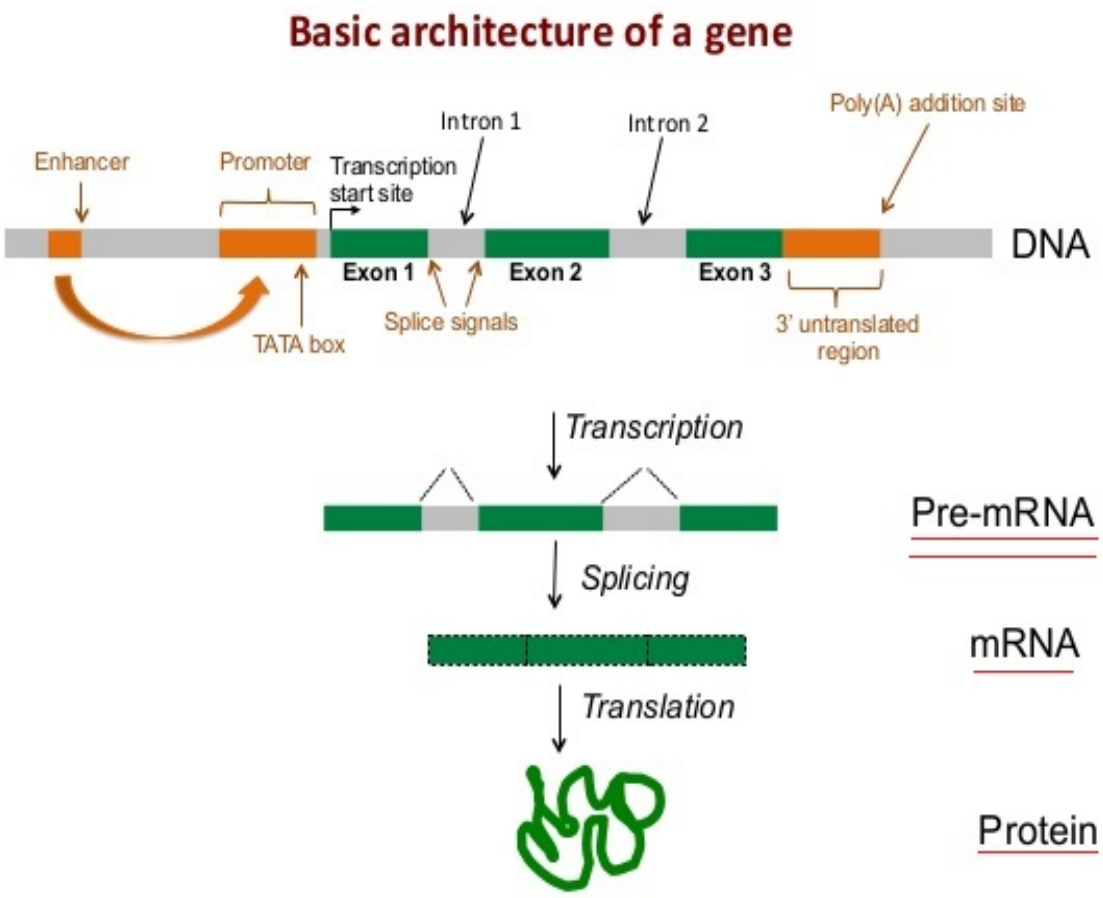
Papers

1. Bobrowski A., Lipniacki T., Pichór K., Rudnicki R., *Asymptotic behavior of distributions of mRNA and protein levels in a model of stochastic gene expression,* J. Math. Anal. Appl. 333 (2007), 753-769.
2. Jaruszewicz J., Żuk P.J., Lipniacki T.: *Type of noise defines global attractors in bistable molecular regulatory systems.* J. Theor. Biol. 317, 140-151 (2013)
3. Paździorek, P., *A Stochastic Perturbation of the Fraction of Self-renewal in the Model of Stem Cells Differentation,* preprint available at http:/mmns.mimuw.edu.pl/preprints/2013-037.pdf
4. AT, *The Dynamics of Enzyme Inhibition Controlled by Piece-wise Deterministic Markov Process* Springer Proceedings in Mathematics and Statistics: Semigroups of Operators (2014), 299-317.
5. **Rudnicki R., AT *On a stochastic gene expression with pre-mRNA, mRNA and protein contribution* J. Theor. Biol. 387 (2015), 54-67.**

Biological motivation: the complexity of gene expression process



Gene expression: three main stages



Mathematical motivation: to investigate a model which has three-dimensional phase space

- It is still much easier to interest mathematicians with three-dimensional problem, because:
- **it's geometry is usually much harder to describe**
- **some new quantitative effects are possible, which are not present in $\mathbb{R}^2$**
- **Modern programming environments (R, Mathematica, Python and "infinitely" many...) can reveal how even quite complicated three-dimensional sets look like.**
- **What with $\mathbf{R}^n$?**

Our approach

- We investigate the dependence between some types of substances (particles, molecules, etc.),
- Dynamics of these changes is described by dynamical systems, but these systems switch stochastically,
- **Intensities of the switches depend on the state of the phase space we currently are,**
- We want to know what is the behaviour of the process after sufficiently long time,
- **We can solve this problem in the language of semigroups of operators**,
- We can show that the density of this process is stabilisizing.

Explosion of models based on PDMP (M.H.A Davis, 1984)

Brief review ([1])

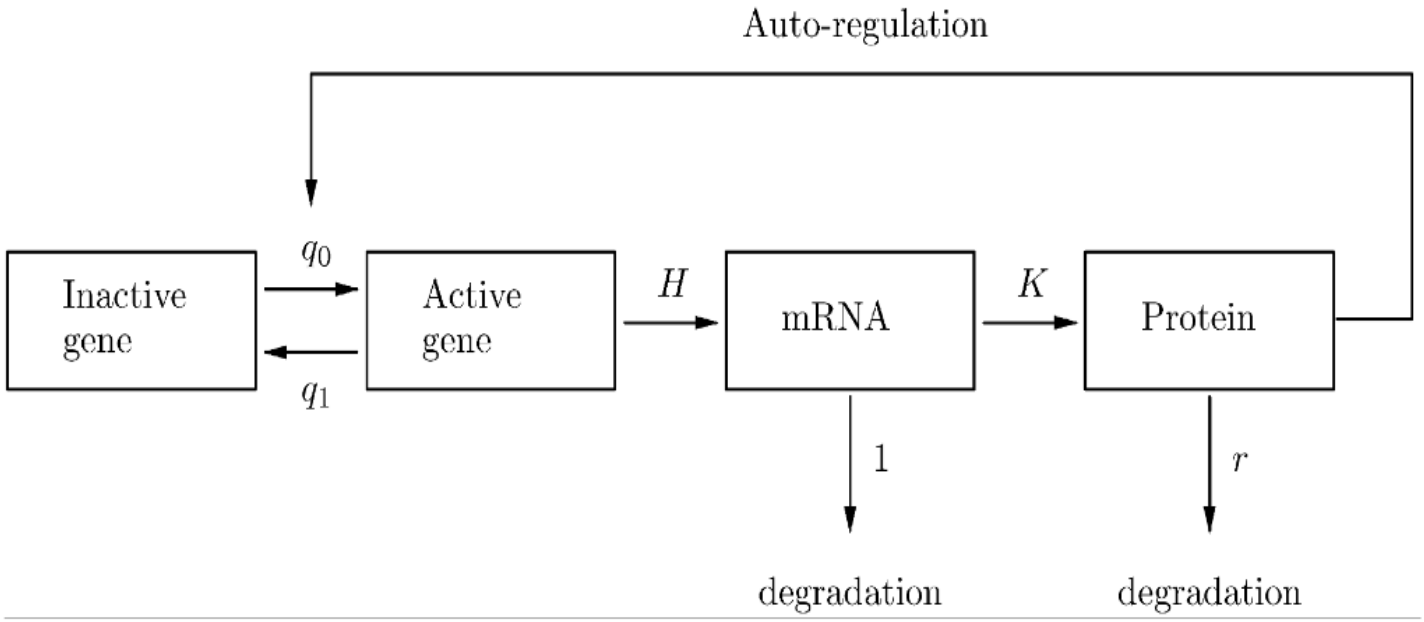


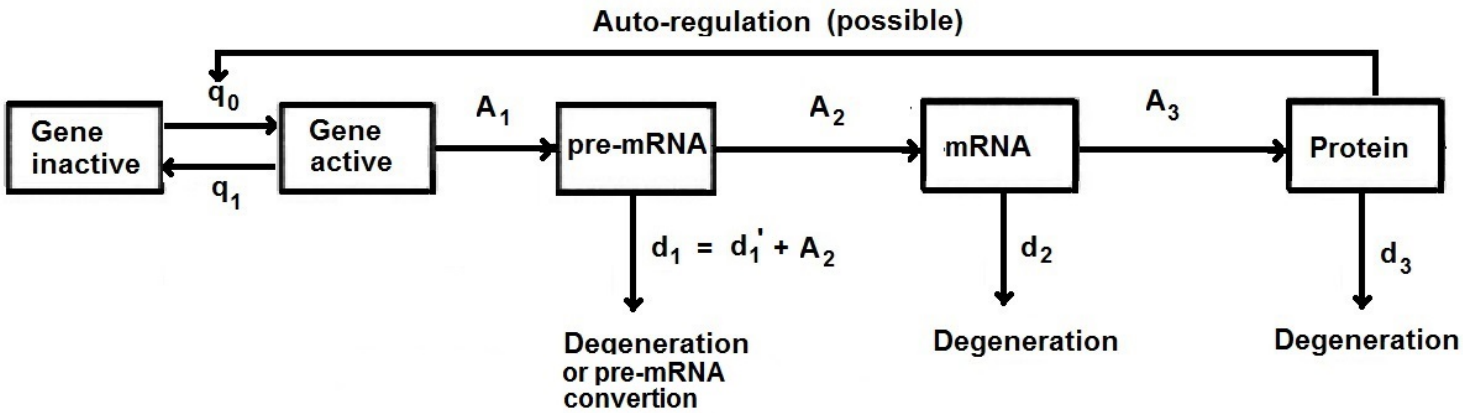
Fig. 1. Simplified diagram of auto-regulated gene expression.

$$I \xrightarrow{q_0(x_2)} A, \qquad I \xleftarrow{q_1(x_2)} A,$$

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = \gamma(t) - x_1,$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = r(x_1 - x_2).$$

Our model ([5])


Auto-regulation (possible)
Gene inactive
Gene active
q0
q1
A1
pre-mRNA
A2
mRNA
A3
Protein
d1 = d1' + A2
d2
d3
Degeneration or pre-mRNA convertion
Degeneration
Degeneration

Model with pre-mRNA contribution

We just add third equation, considering pre-mRNA production.

$$\begin{cases} 0 \xrightarrow{q_0(x_1,x_2,x_3)} 1, \ 0 \xleftarrow{q_1(x_1,x_2,x_3)} 1 \\ \dfrac{dx_1}{dt} = A_1\gamma(t) - d_1x_1 \\ \dfrac{dx_2}{dt} = A_2x_1 - d_2x_2 \\ \dfrac{dx_3}{dt} = A_3x_2 - d_3x_3, \end{cases} \tag{1}$$

gdzie $A_i > 0$ i $d_i > 0$. We can simplify this system to obtain:

$$\begin{cases} \frac{dx_1}{dt} = \gamma(t) - x_1 \\ \frac{dx_2}{dt} = a(x_1 - x_2) \\ \frac{dx_3}{dt} = b(x_2 - x_3), \end{cases} \tag{2}$$

gdzie $a, b > 0$.

What is $\gamma(t)$?

Definition

Let $i_0 \in \{0,1\}$, $T_0 = 0$, $x = (x_1, x_2)$ (or $x = (x_1, x_2, x_3)$) and then:

$$\gamma(t) = \begin{cases} i_0, & t \in [T_0, T_1) \\ 1 - i_0, & t = T_1 \end{cases}$$

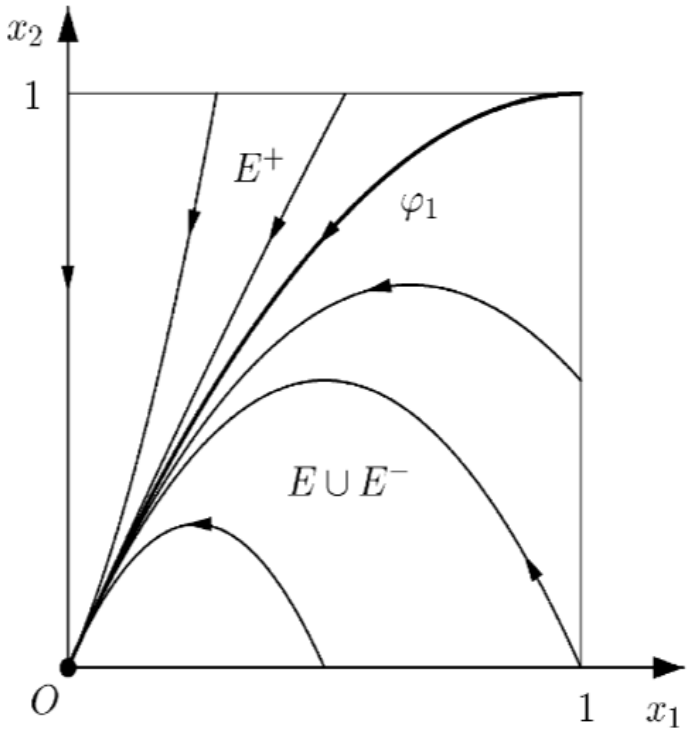
T_1 is called "time of the first jump of the process" and it is a random variable with the distribution:

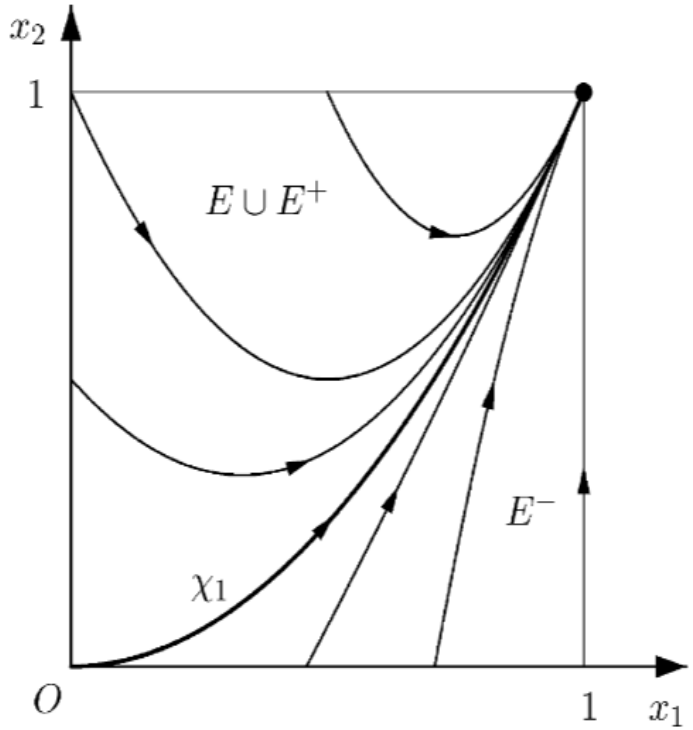
$$F_{x,i_0}(t) = Prob(T_1 \leqslant t) = 1 - exp\left(- \int_0^t q_{i_0}(\pi_{i_0}(s,x))ds \right).$$

Comment

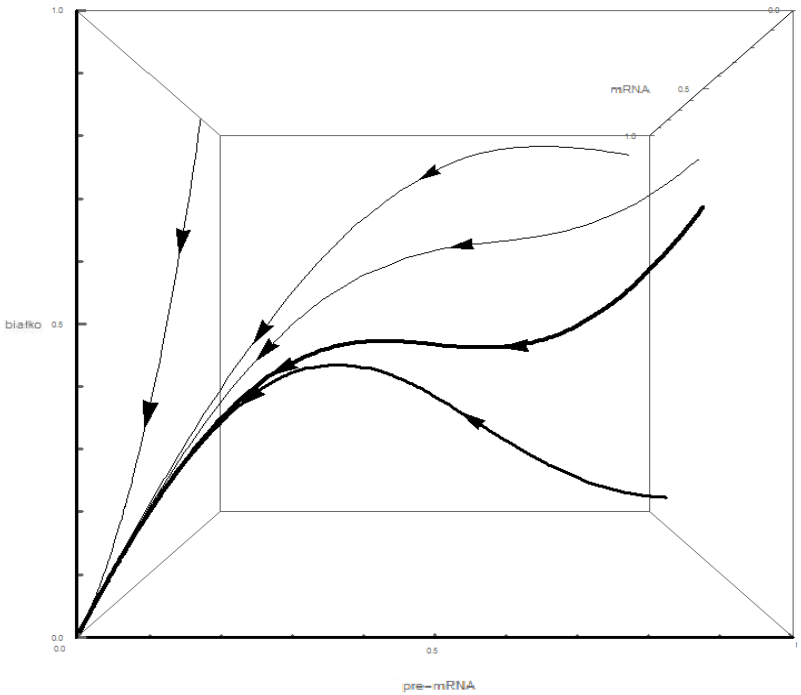
With constant value of q_{i_0} this distribution is just exponential distribution with the parameter q_{i_0}. In a similar way the following random variables: $T_i, i = 2, ...,$ are called "times of the n-th jumps of the process".

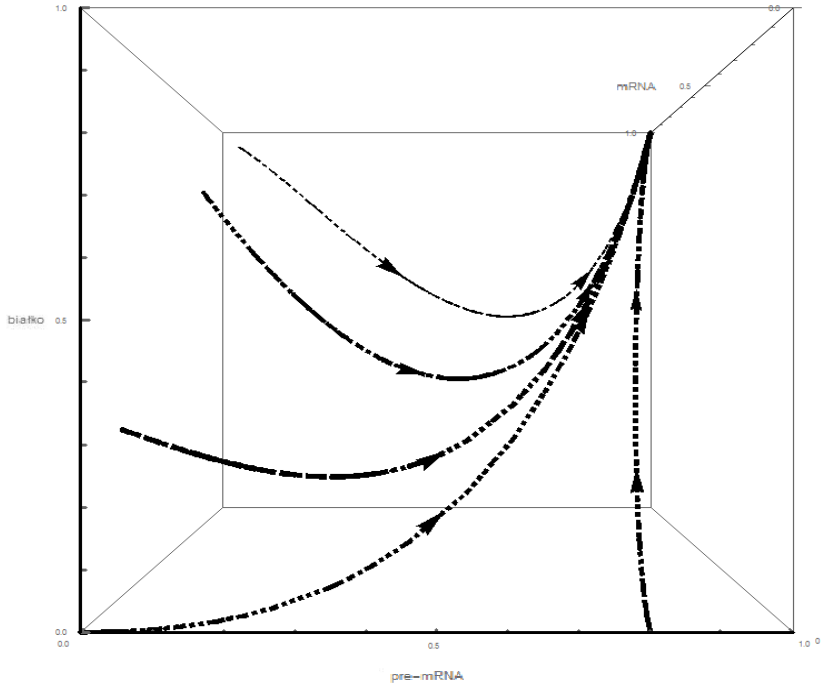
Model with mRNA and proteins - deterministic flows





Model with pre-mRNA contribution - deterministic flows





Tools: Markov semigroups induced by PDMP

Let (X, Σ, m) be a $\sigma-$finite measure space with measure m. By D we denote the subset of $L^1 := L^1(X, \Sigma, m)$ which is the set of the densities, i.e.:

$$D = \{f \in L^1 : f \geqslant 0, ||f||_{L^1} = 1\}$$

Definicja

A linear D preserving mapping $P : L^1 \to L^1$, $(P(D) \subset D)$ is called a Markov operator.

Markov semigroups

Definition

A family $\{P(t)\}_{t\geqslant 0}$ of Markov operators, which satisfies the following conditions:

- $P(0) = \mathrm{Id}$ (identity condition),
- $P(t+s) = P(t)P(s)$ for $s,\ t \geqslant 0$ (semigroup condition),
- for each $f \in L^1$ the function $t \longrightarrow P(t)f$ is continuous with respect to the L^1 norm (strong continuity),

is called a Markov semigroup.

Asymptotic stability

Asymptotic stability in the sense of Lasota

A Markov semigroup $\{P(t)\}_{t\geqslant 0}$ is *asymptotically stable* if

- there exists an *invariant density* for $\{P(t)\}_{t\geqslant 0}$, i.e. $f^* \in D$ such that $P(t)f^* = f^*$ for all $t > 0$,
- for every density $f \in D$:

$$\lim_{t\to\infty} ||P(t)f - f^*|| = 0. \tag{3}$$

Conclusion

Markov semigroup generated by PDMP is asymptotically stable $\longrightarrow$ distribution of the process converges to stationary distribution.

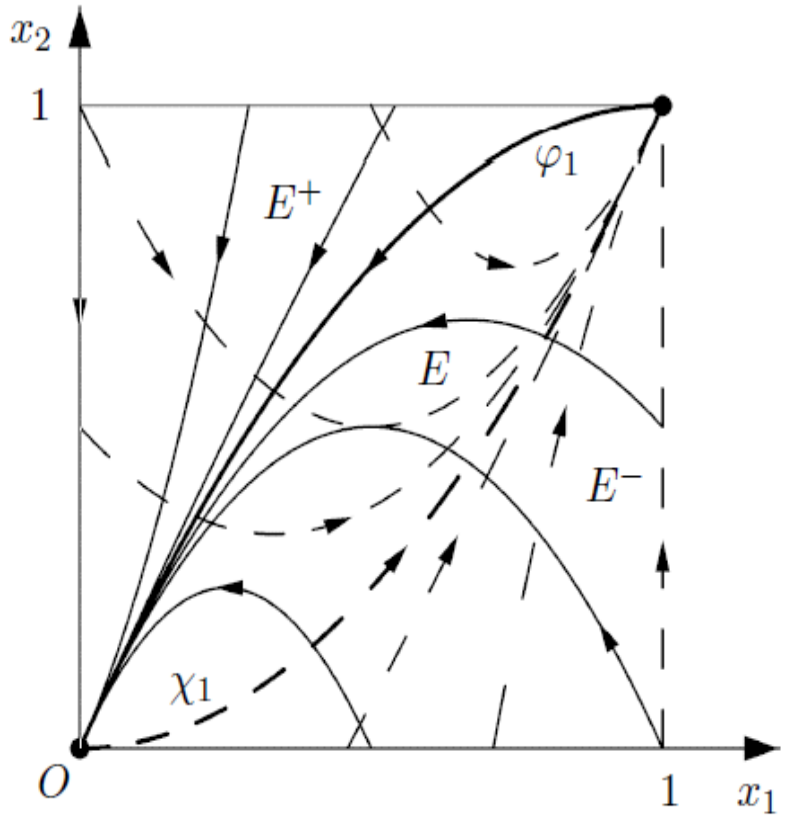
Stochastic attractor

In applications, we construct a Markov semigroup $\{P(t)\}_{t\geqslant 0}$, in the space $L^1(X \times I, \mathbb{B}(X \times I), dx \times di)$, where $I = \{0, 1\}$, and we restrict its analysis to the set called **stochastic attractor**, i.e. a measurable subset S of X, such that:

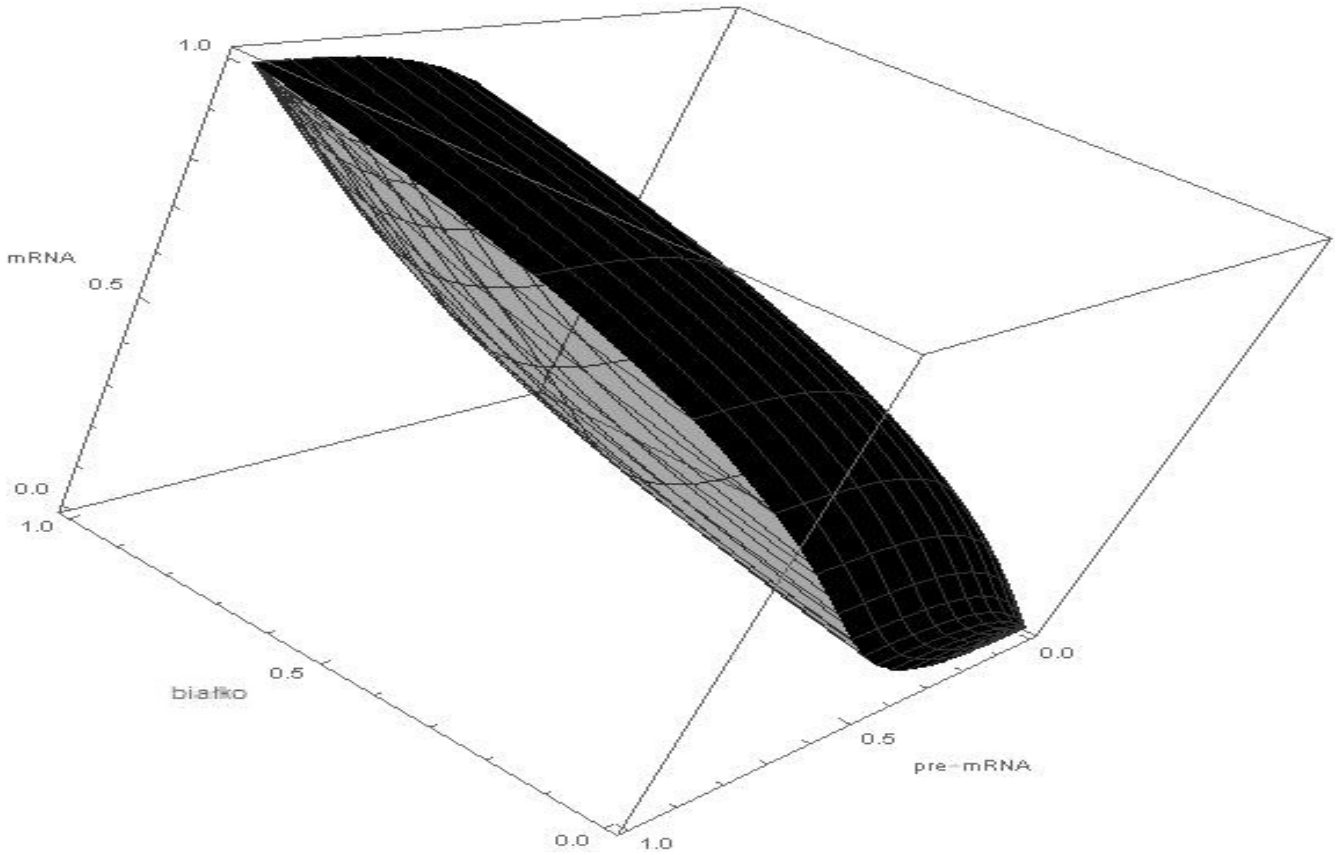
$$\lim_{t\to\infty} \int_{S\times I} P(t)f(x, i)dx\ di = 1 \tag{4}$$

for every function $f \in L^1(X \times I)$. This will let us to restrict the domain of $\{P(t)\}_{t\geqslant 0}$ only to functions $f \in L^1(S \times I)$. What is more, we want to find an attractor, which plays the role of support of the invariant density.

Model with mRNA and proteins - attractor



Model with pre-mRNA contribution: attractor

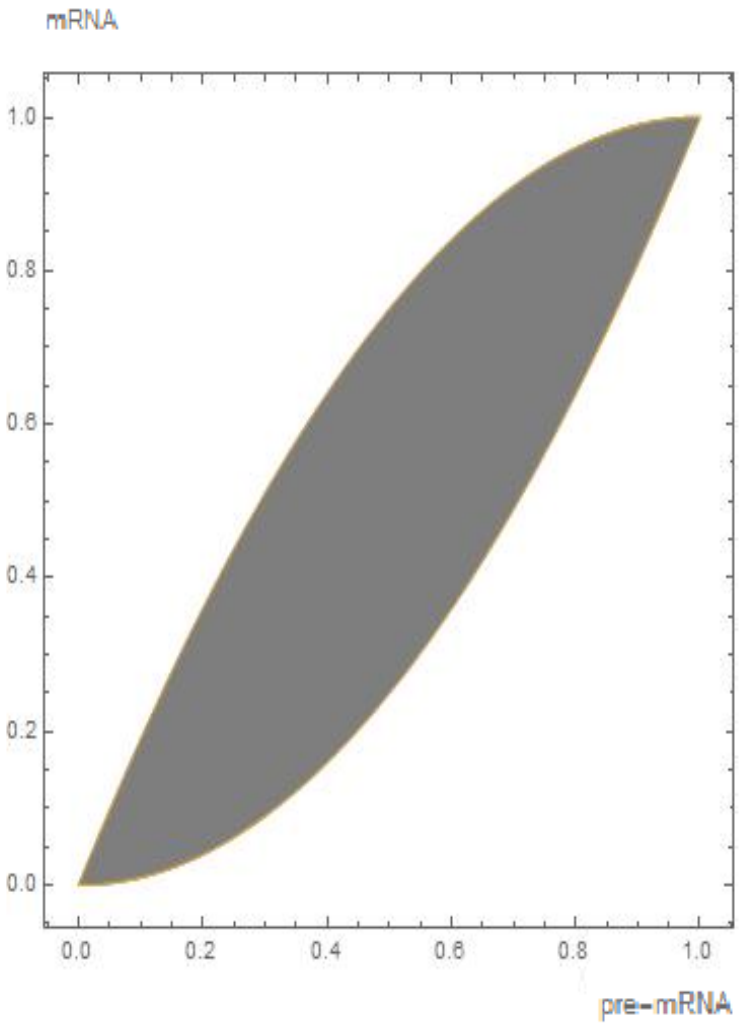


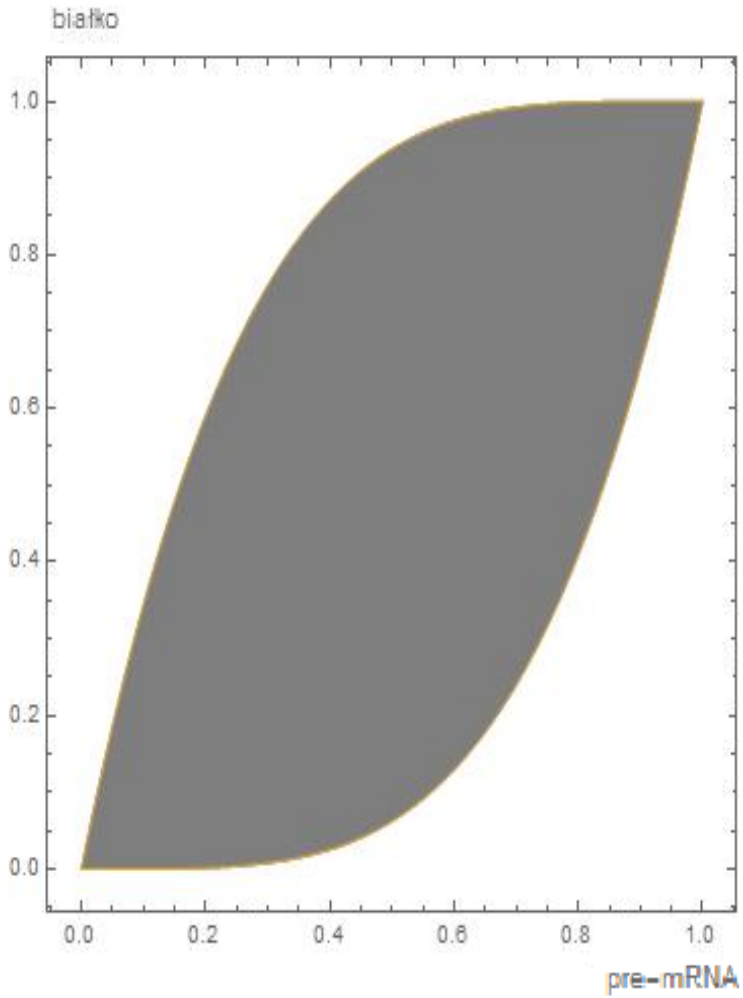
Theorem

Let $q_i(\mathbf{x}) > 0,\ i = 0, 1$ dla $\mathbf{x} \in [0,1]^3$. Then a Markov semigroup $\{P(t)\}_{t \geqslant 0}$ is asymptotically stable and the support of the invariant density is $\mathbb{A} = A \times \{0,1\}$, where A is expressed in the basis of the eigenvectors:

$$A = \{(x - y + z,\ x^a - y^a + z^a,\ x^b - y^b + z^b) : 1 \geqslant x \geqslant y \geqslant z \geqslant 0\}. \quad (5)$$

Projections on the plane



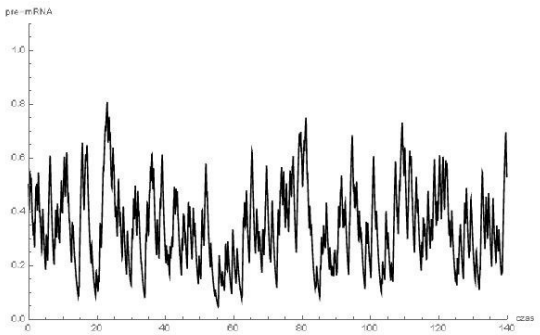


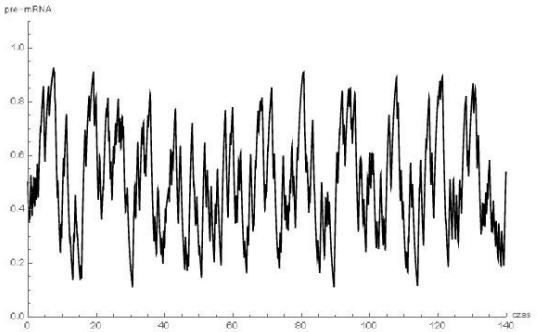
Communications between states

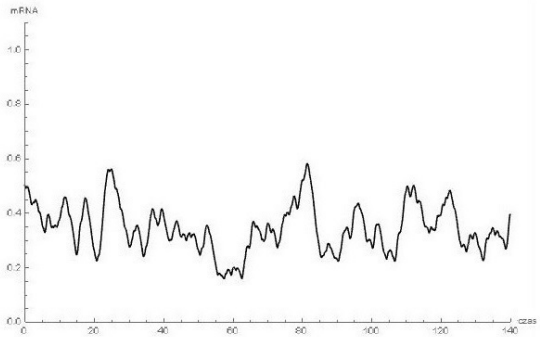
Communications between states in $\mathbb{A}$

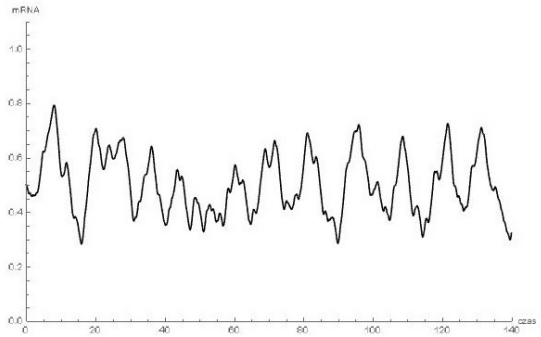
We obtain the answer for the following question which could not be solved by the standard control theory: is it possible to join any two points in the interior of A combining the trajectories of both of the flows?

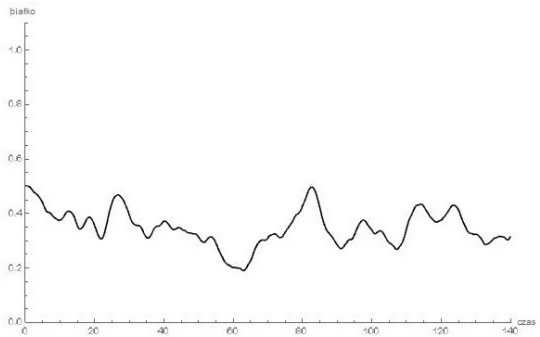
Trajectories

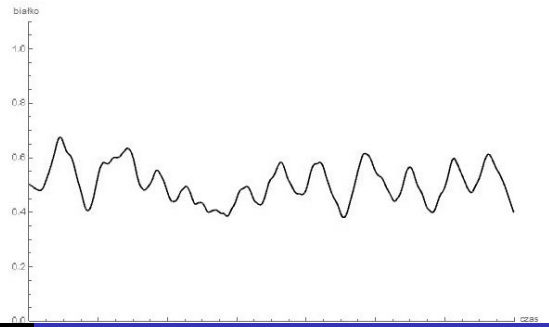




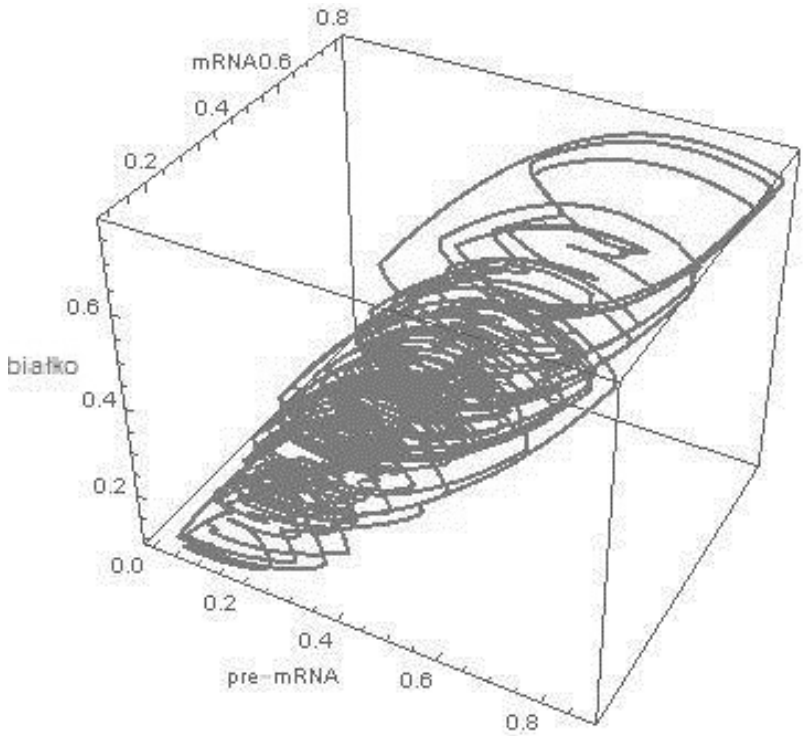


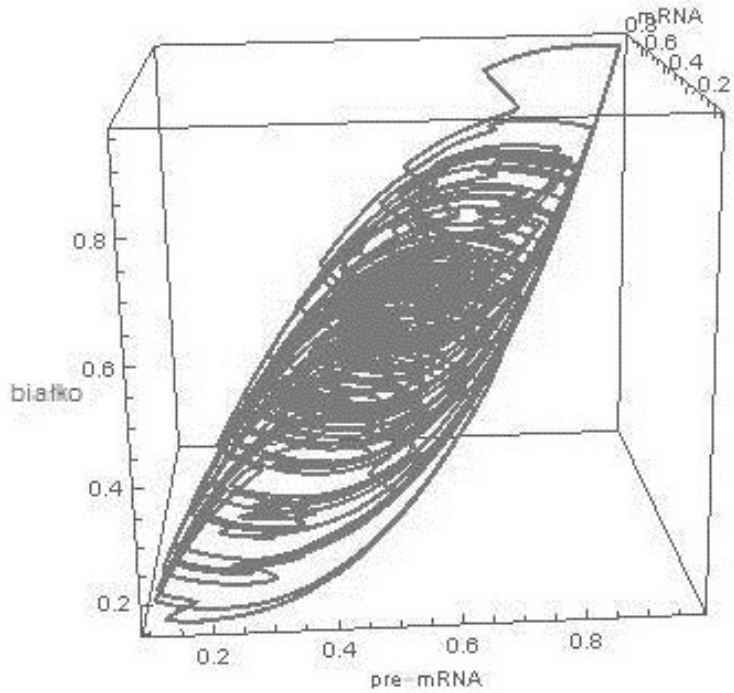




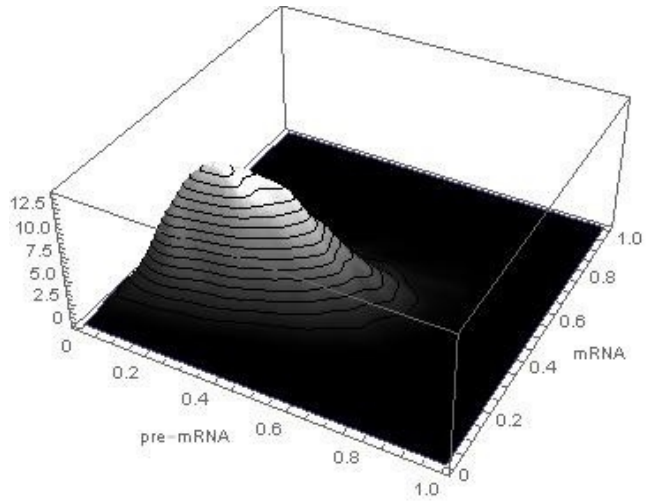


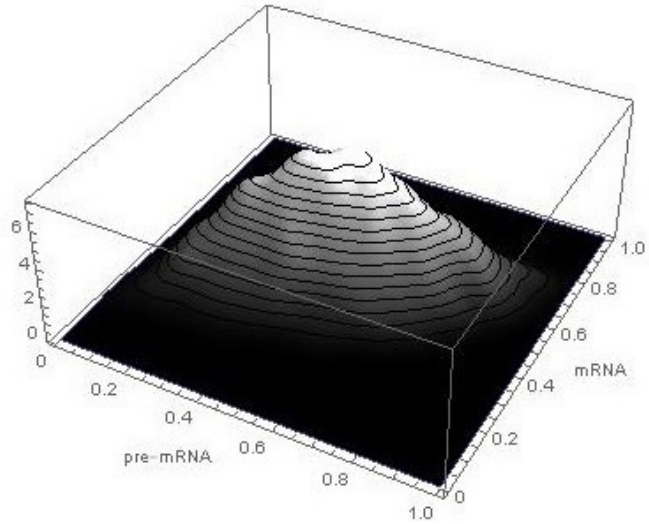
Trajectories (in $\mathbb{R}^3$)

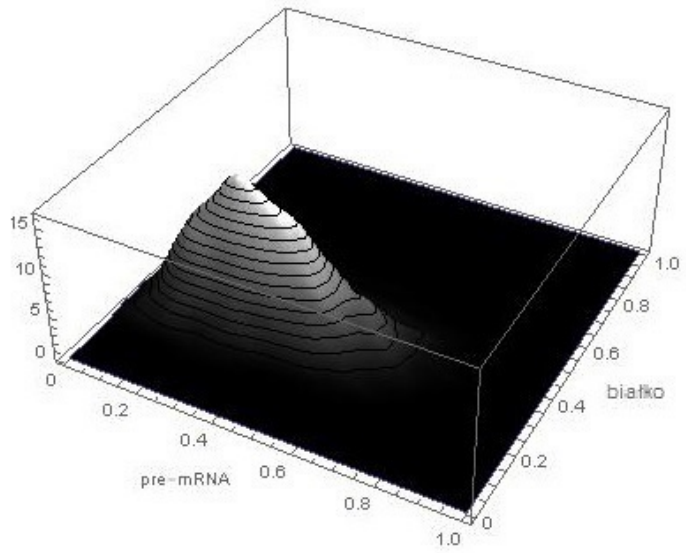


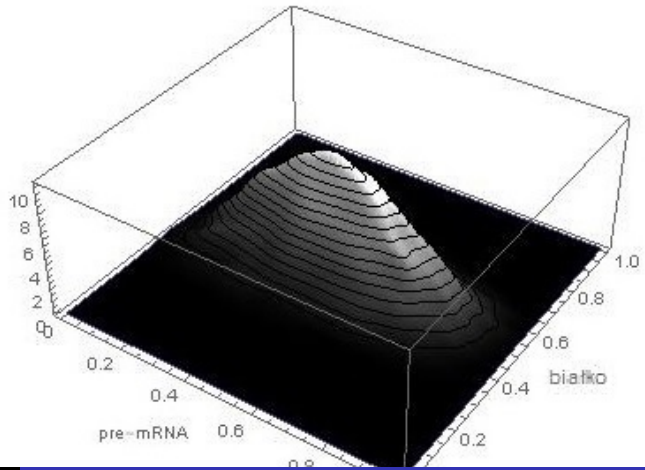


Estimation of stationary distribution







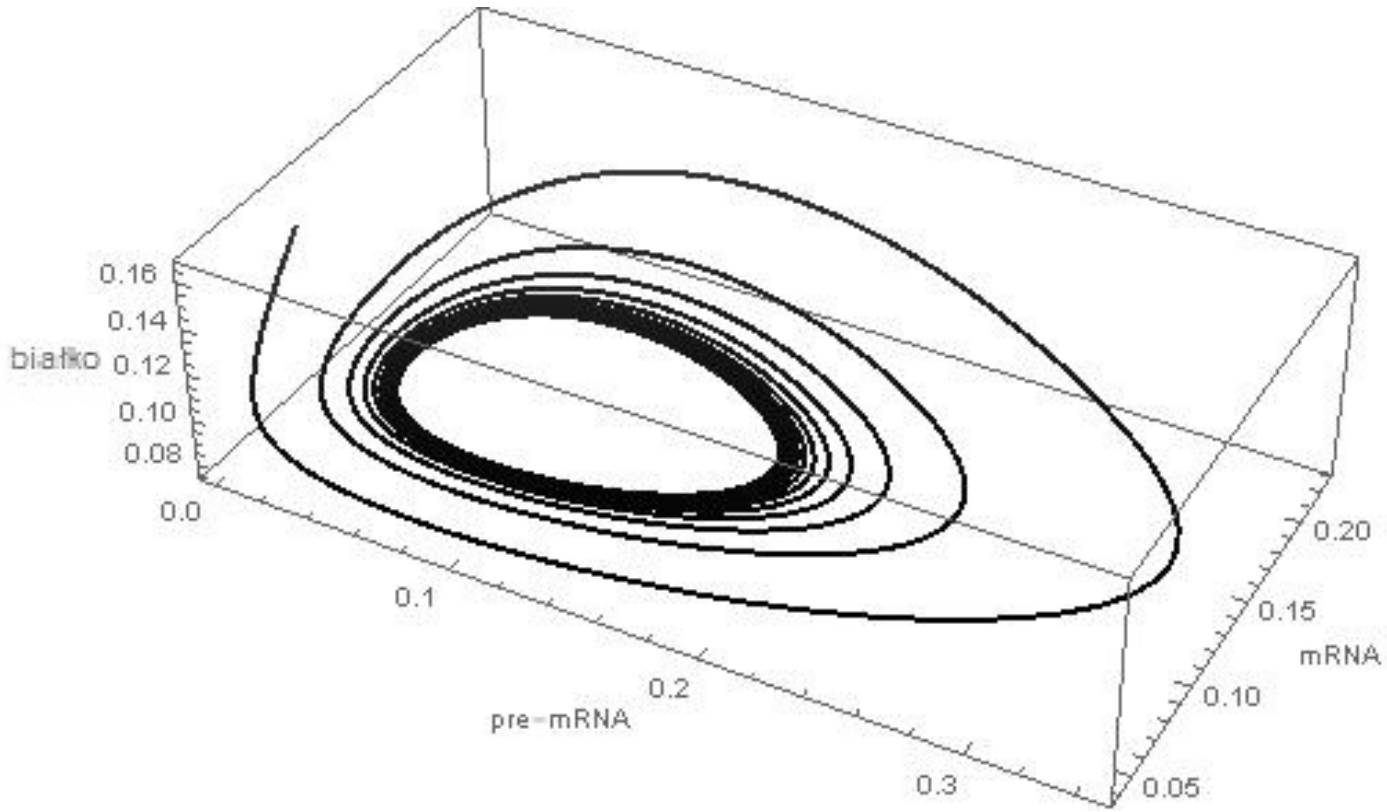


We shall consider particularly interesting behavior of our model, when both of the jump rates q_0 and q_1 tend to infinity, unlike their ratio. In this case, we can replace the stochastic process $\gamma(t)$ by its expected value $\Gamma := \mathbb{E}\gamma = \frac{q_0}{q_0+q_1}$ [**?**, **?**] to obtain a state called *deterministic* or *adiabatic* limit. Hence, the system **??** transforms to deterministic system of three ODEs:

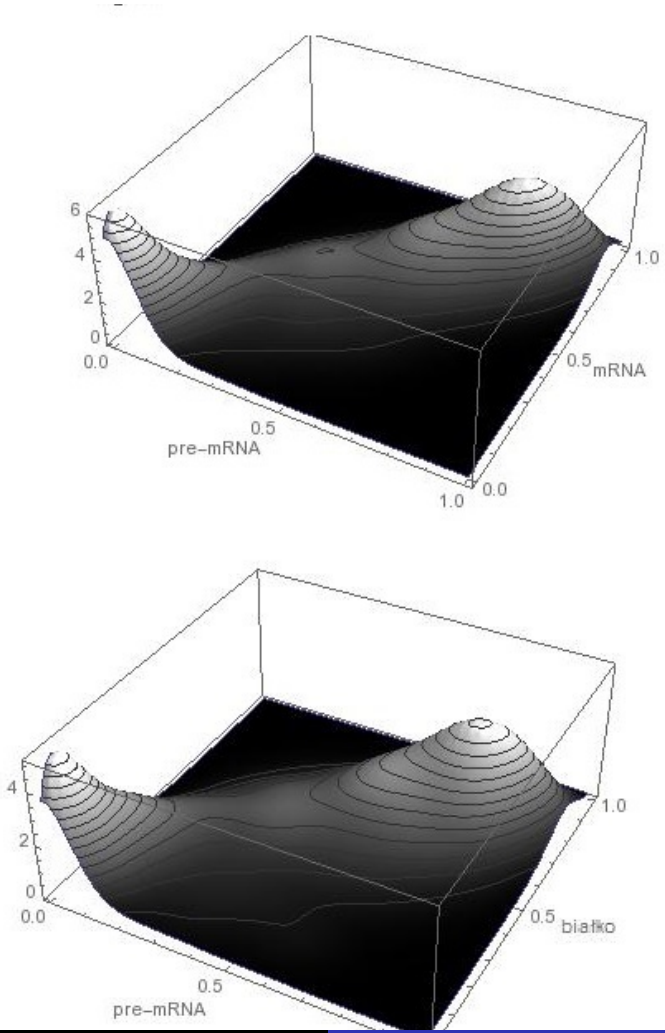
$$\begin{cases} \dfrac{dx_1}{dt} = \Gamma(x_3) - x_1 \\ \dfrac{dx_2}{dt} = a(x_1 - x_2) \\ \dfrac{dx_3}{dt} = b(x_2 - x_3). \end{cases} \tag{6}$$

Depending on the values of the parameters a i b we investigate some specific types of behavior [2]. We consider the case of the negative autoregulation, i.e. when Γ jest a decreasing function of x_3.

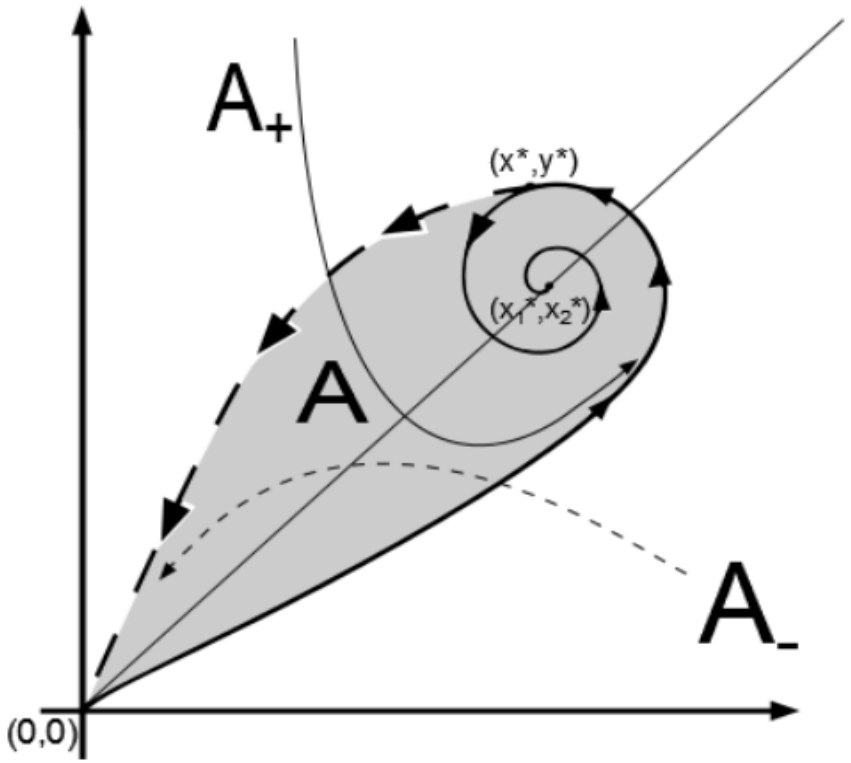
A limit cycle in the adiabatic limit and negative autoregulation (a=1, b=1)



Bistability in the adiabatic limit and positive autoregulation (a=1, b=1)



Other models, perspectives



Non-linear model of stem cells differentiation (Paździorek).

Other models, perspectives

- The systems with stable and unstable points.
- What about a general theory?
- Multi-dimensional attractors?