7TH FORUM OF POLISH MATHEMATICIANS

Dynamics of a bistable genetic switch

Marta Tyran-Kamińska (Katowice)

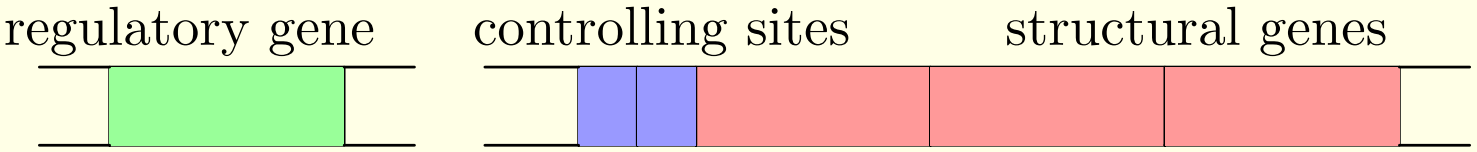
Michael C. Mackey (Montreal)

16 September 2016

Outline

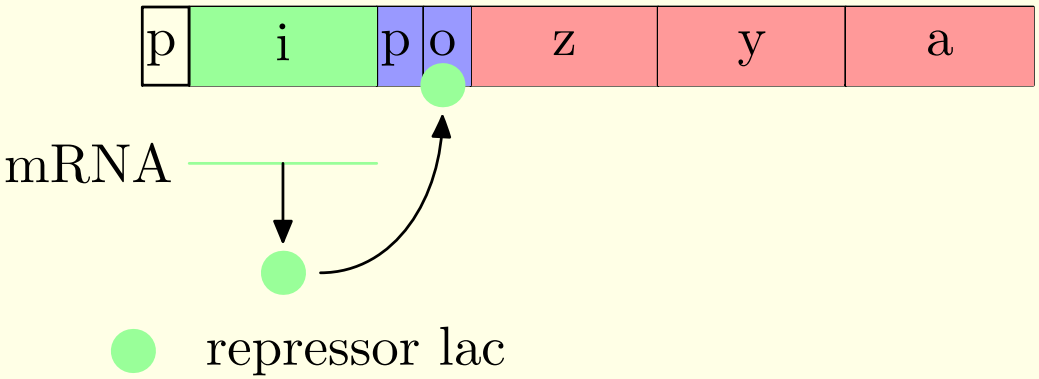
- ◇ The operon concept
- ◇ Transcriptional regulation
- ◇ Simple model of a repressible operon
- ◇ Transcriptional bursting
- ◇ A genetic switch

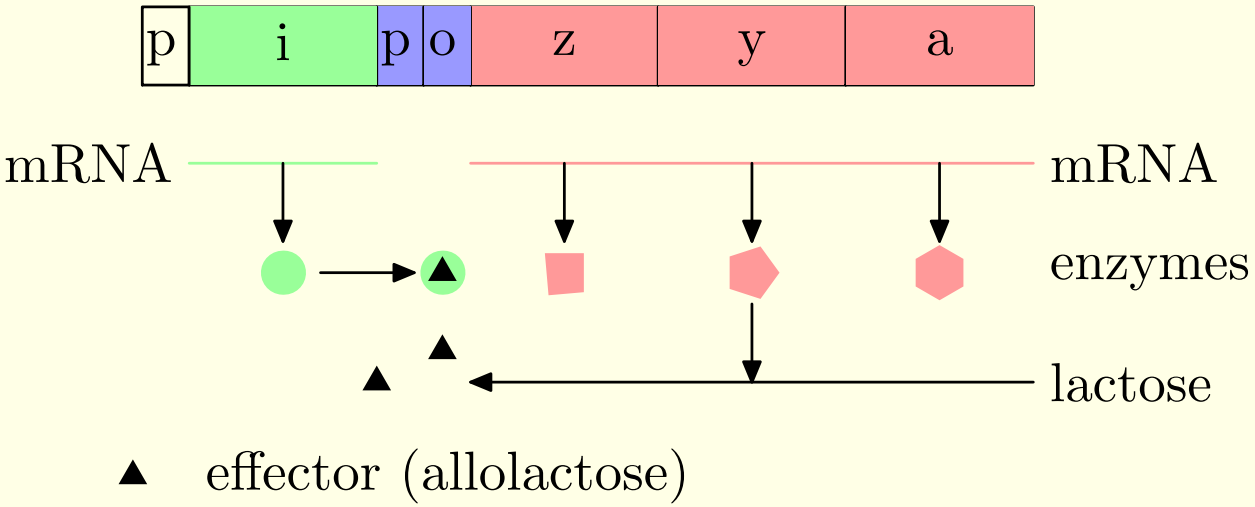
Operon: Jacob & Monod (1960)



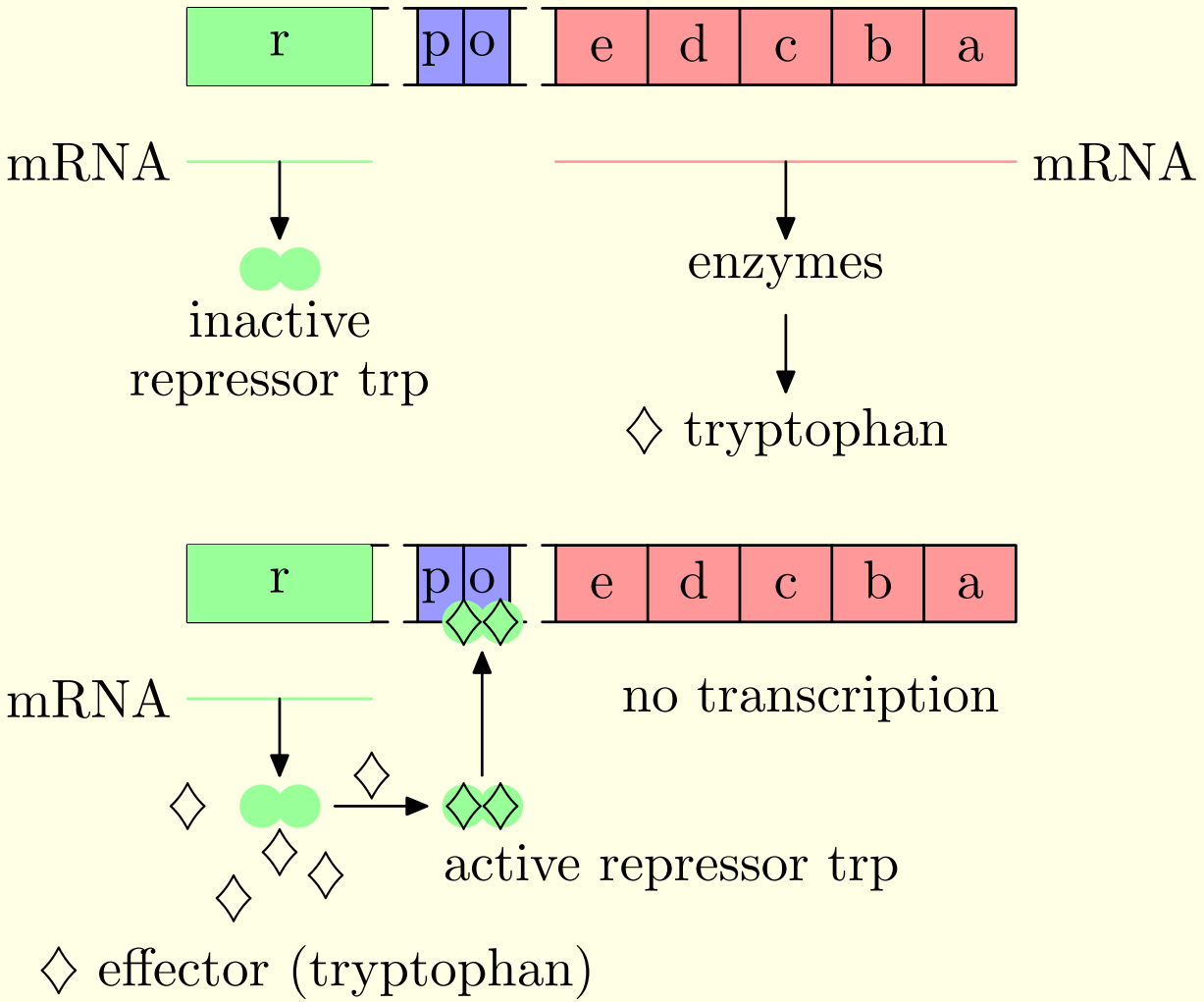
- ◇ *structural genes* - nucleotide sequences of DNA encoding proteins
- ◇ *regulatory proteins* (encoded by *regulatory genes*) - proteins that affect the expression of structural genes; *activators* stimulate gene transcription and *repressors* inhibit the initiation of transcription
- ◇ *controlling sites* - binding sites for RNA polymerase (*promoters*) and for repressors (*operators*)

The lactose (*lac*) operon





The tryptophan (*trp*) operon



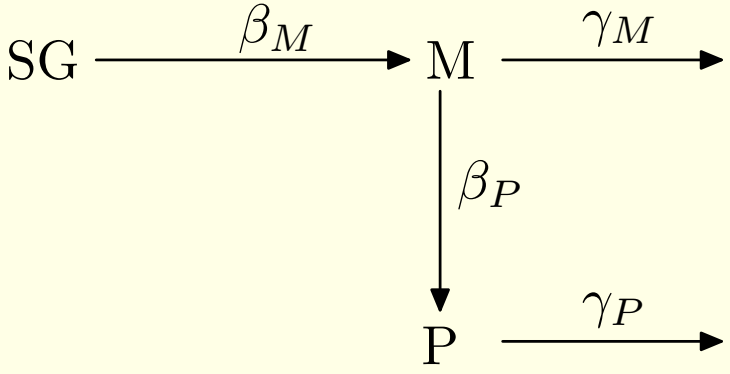
Transcriptional regulation

- ◇ *negative control* - a regulatory protein acts as a repressor, binding to DNA and inhibiting transcription;
- ◇ *positive control* - a regulatory protein acts as an activator, stimulating transcription;
- ◇ *inducible operon* - transcription is normally off and must be turn on;
- ◇ *repressible operon* - transcription is normally on and must be turn off.

The *lac* operon is a negative inducible operon. The *trp* operon is a negative repressible operon.

No control

The simplest operon consists of one structural gene and one promoter. The gene is constitutive, meaning that it is expressed continuously by a cell



$$\frac{dM}{dt} = \beta_M SG - \gamma_M M,$$
$$\frac{dP}{dt} = \beta_P M - \gamma_P P,$$

where M and P denote mRNA and protein molecules. Eventually fixed stationary levels are reached

$$M^* = \frac{\beta_M}{\gamma_M} SG, \quad P^* = \frac{\beta_P}{\gamma_P} M^*.$$

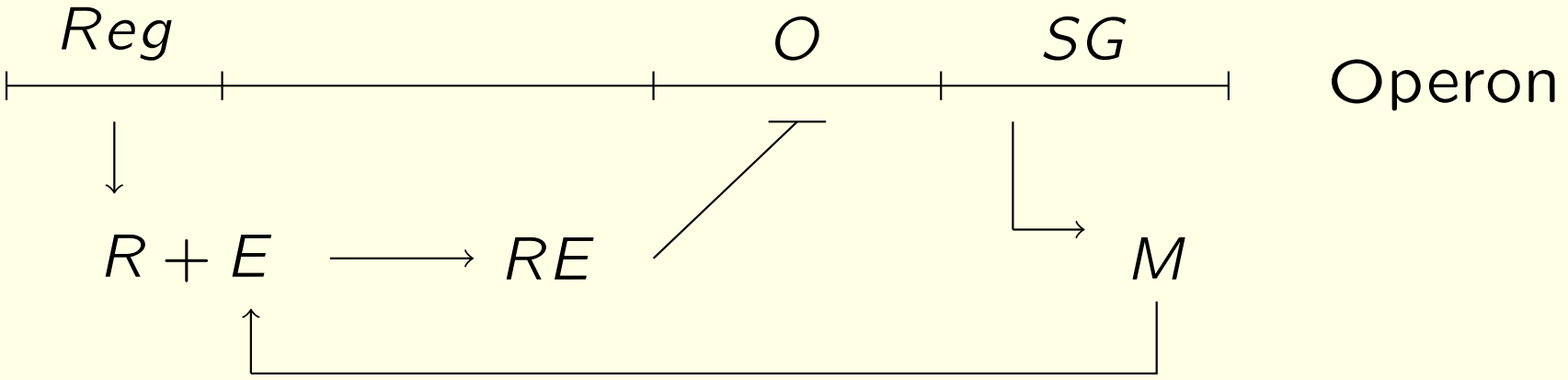
Deterministic rate equation

- ◇ Goodwin: (1965) Adv. Enz. Regul. 3, 425
- ◇ Griffith: (1968) J Theor. Biol. 20, 202
- ◇ Tyson & Othmer: (1978) Prog. Biophy. 5, 1

$$\frac{dM}{dt} = b_{\max}\varphi(E) - \gamma_M M,$$
$$\frac{dE}{dt} = \beta_E M - \gamma_E E,$$

$b_{\max}$ - maximum level of transcription, $\varphi(E)$ - variation of the DNA transcription rate with effector level E

Negative repressible operon



R - repressor, O - operator, E - effector, M - mRNA

$$\varphi(E) = \bar{\varphi}_m \frac{1 + K_1 E^n}{1 + K E^n}, \quad R + nE \overset{K_1}{\rightleftharpoons} RE_n, \quad O + RE_n \overset{K_2}{\rightleftharpoons} ORE_n$$

n - number of effector molecules, $K = K_1(1 + K_2 R_{tot})$,

$R_{tot} = R + K_1 R \cdot E^n + K_2 O \cdot RE_n \approx R(1 + K_1 E^n)$,

$\bar{\varphi}_m$ - maximal DNA transcription rate

The equations

We scale variables (M, E) to (x_1, x_2) satisfying

$$\frac{dx_1}{dt} = \gamma_{x_1}\left(\kappa_d f(x_2) - x_1\right),$$
$$\frac{dx_2}{dt} = \gamma_{x_2}(x_1 - x_2),$$

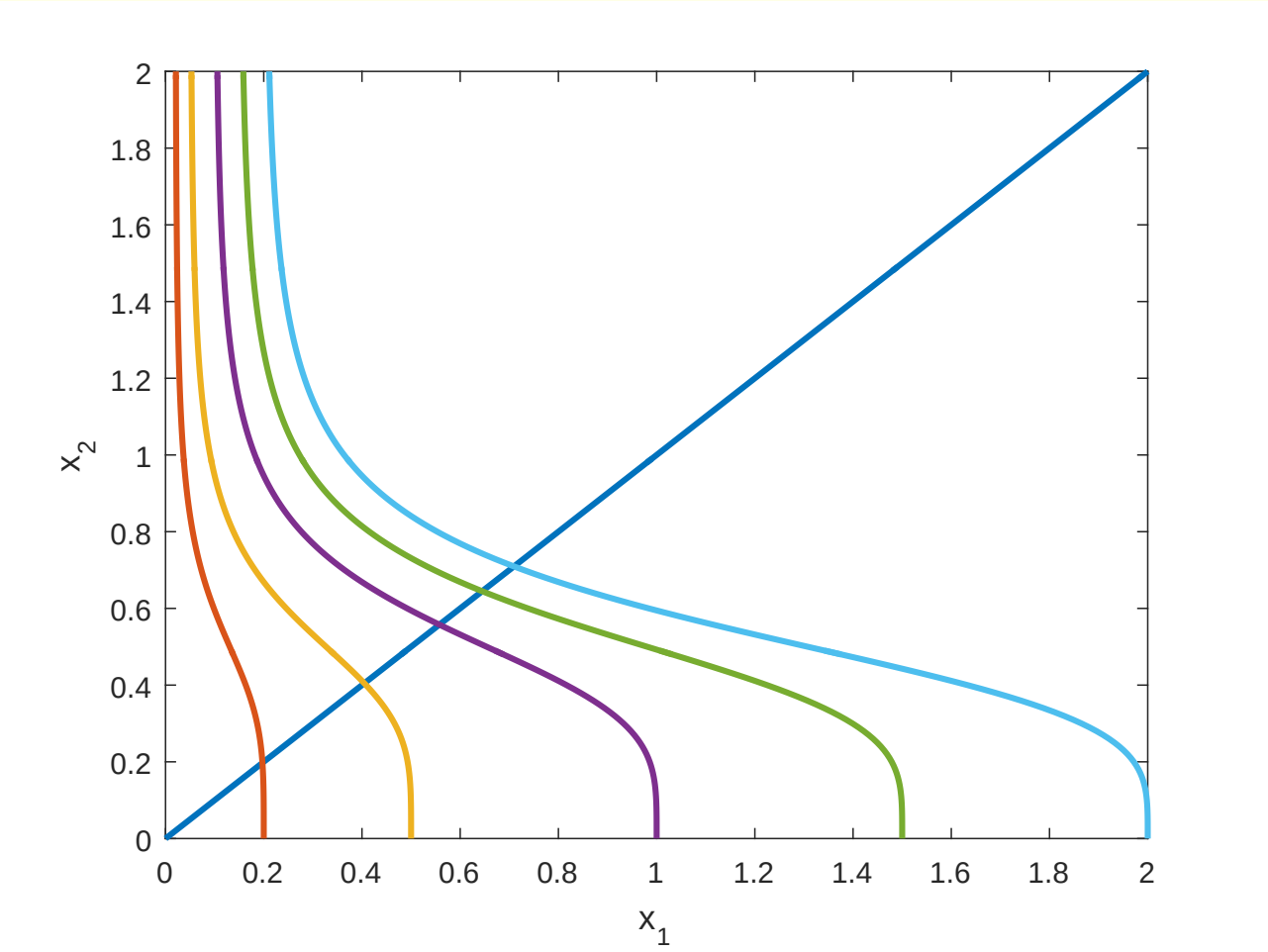
where $\gamma_{x_1}, \gamma_{x_2}, \kappa_d > 0$ and

$$f(x) = \frac{1 + x^n}{1 + \Delta x^n}, \quad \Delta \geq 1.$$

There is only one steady state, it is globally stable and it is the positive solution of

$$x_2 = x_1, \quad x_1 = \kappa_d f(x_2).$$

Graphical investigation of the steady states



graphs of $x_1 = \kappa_d f(x_2)$ with increasing κ_d

Transcriptional/translational bursting

Experimentally observed that

- ◇ some organisms transcribe DNA/mRNA discontinuously, Golding, Paulsson, Zawilski, Cox: (2005) Cell; Cai, Friedman, Xie: (2006) Nature;
- ◇ the *amplitude* of molecules production through bursting is exponentially distributed with density

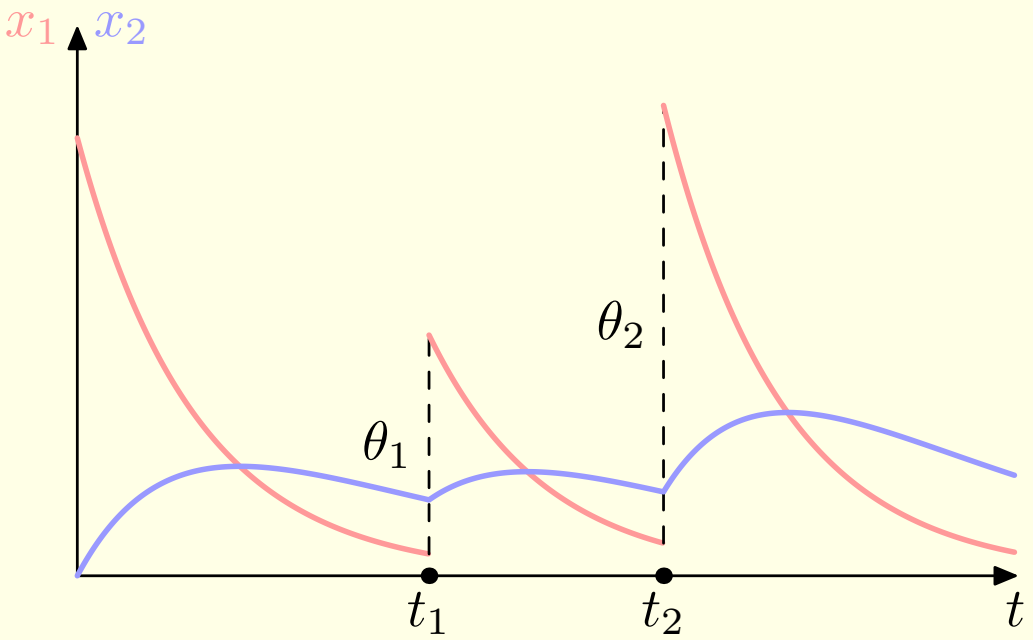
$$h(y) = \frac{1}{b} e^{-y/b},$$

  where b is the average burst size;
- ◇ the *frequency* of bursting φ is dependent on the level of the molecules.

Dynamics with bursting

Transcription occurs at random times $0 < t_1 < t_2 < \ldots$, in between, the process evolves according to

$$\frac{dx_1}{dt} = -\gamma_{x_1} x_1, \qquad \frac{dx_2}{dt} = \gamma_{x_2}(x_1 - x_2).$$



$$\Pr(\theta_1 > x) = e^{-x/b}$$

$$\Pr(t_1 > t) = e^{-\int_0^t \varphi(x_2(s))ds}$$

Dynamics with bursting

- When bursting is present, replace the deterministic dynamics

$$\frac{dx_1}{dt} = \gamma_{x_1}\left(\kappa_d f(x_2) - x_1\right), \qquad \frac{dx_2}{dt} = \gamma_{x_2}(x_1 - x_2),$$

  with stochastic dynamics

$$\frac{dx_1}{dt} = -\gamma_{x_1} x_1 + \Xi(h, \varphi(x_2)), \qquad \frac{dx_2}{dt} = \gamma_{x_2}(x_1 - x_2),$$

- $\Xi(h, \varphi)$ is a jump Markov process occurring at rate $\varphi = \gamma_{x_1}\kappa_b f$ with amplitude distributed with density h.

- There is a unique stationary distribution of (x_1, x_2) but we are unable to find its formula.

Reduced model

Typically the degradation rate of mRNA is much greater than that of the effector so $x_1 \approx \kappa_d f(x_2)$ and the two equations reduce to a single equation

$$\frac{dx}{dt} = \gamma(\kappa_d f(x) - x), \quad f(x) = \frac{1 + x^n}{1 + \Delta x^n}.$$

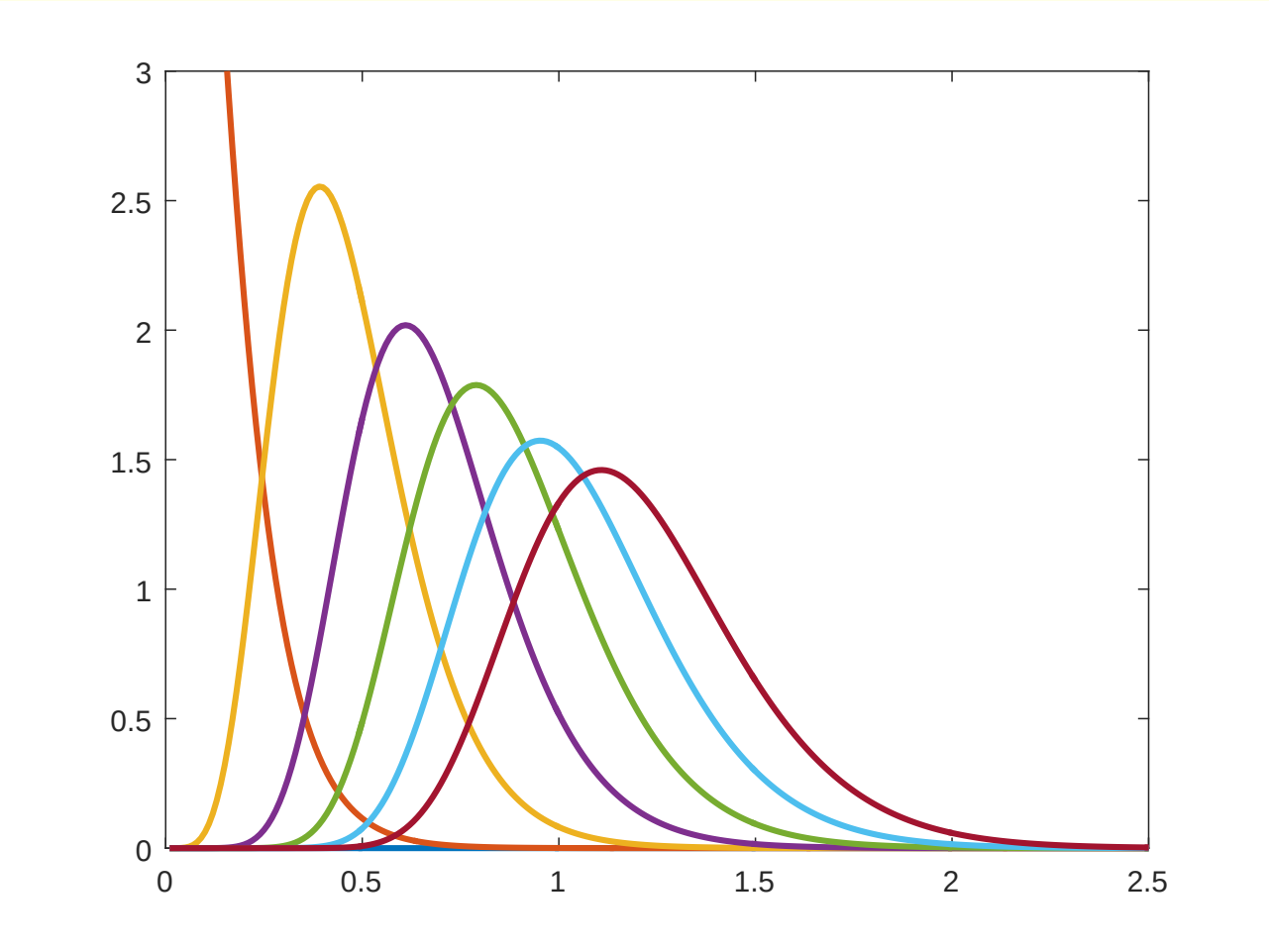
When bursting is present we obtain

$$\frac{dx}{dt} = -\gamma x + \Xi(h, \varphi(x)), \quad \varphi(x) = \gamma \kappa_b f(x).$$

The stationary distribution has a density of the form

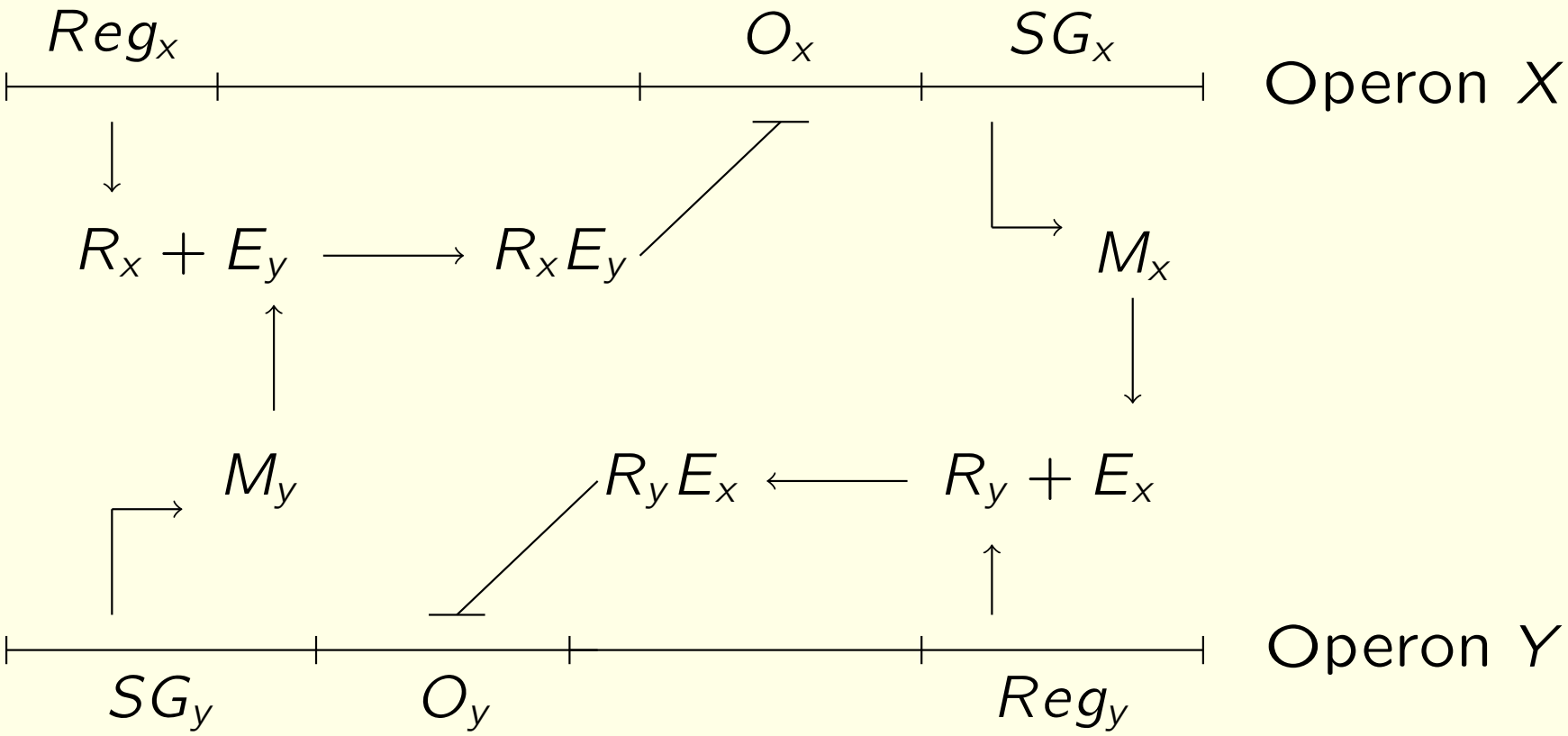
$$u_*(x) = \mathcal{C} e^{-x/b} x^{\kappa_b - 1} (1 + \Delta x^n)^\theta, \quad \theta = \frac{\kappa_b}{n\Delta}(1 - \Delta) < 0.$$

Stationary distribution



$n = 2, \Delta = 3, b = 0.1, \kappa_b$ increases from left to right

Model development of a genetic switch



Equations for the switch

We introduce dimensionless variables (x_1, x_2, y_1, y_2) to obtain

$$\frac{dx_1}{dt} = \gamma_{x_1}[\kappa_{d,x} f_x(y_2) - x_1], \tag{1}$$

$$\frac{dx_2}{dt} = \gamma_{x_2}(x_1 - x_2), \tag{2}$$

$$\frac{dy_1}{dt} = \gamma_{y_1}[\kappa_{d,y} f_y(x_2) - y_1], \tag{3}$$

$$\frac{dy_2}{dt} = \gamma_{y_2}(y_1 - y_2), \tag{4}$$

$$f_x(y_2) = \frac{1 + y_2^{n_x}}{1 + \Delta_x y_2^{n_x}} \quad \text{and} \quad f_y(x_2) = \frac{1 + x_2^{n_y}}{1 + \Delta_y x_2^{n_y}}. \tag{5}$$

Steady states

The steady states of the system (1)-(4) are given by $x_1^* = x_2^* = x^*, y_1^* = y_2^* = y^*$ where (x^*, y^*) is the solution of

$$x_2 = \kappa_{d,x} f_x(y_2) \tag{6}$$

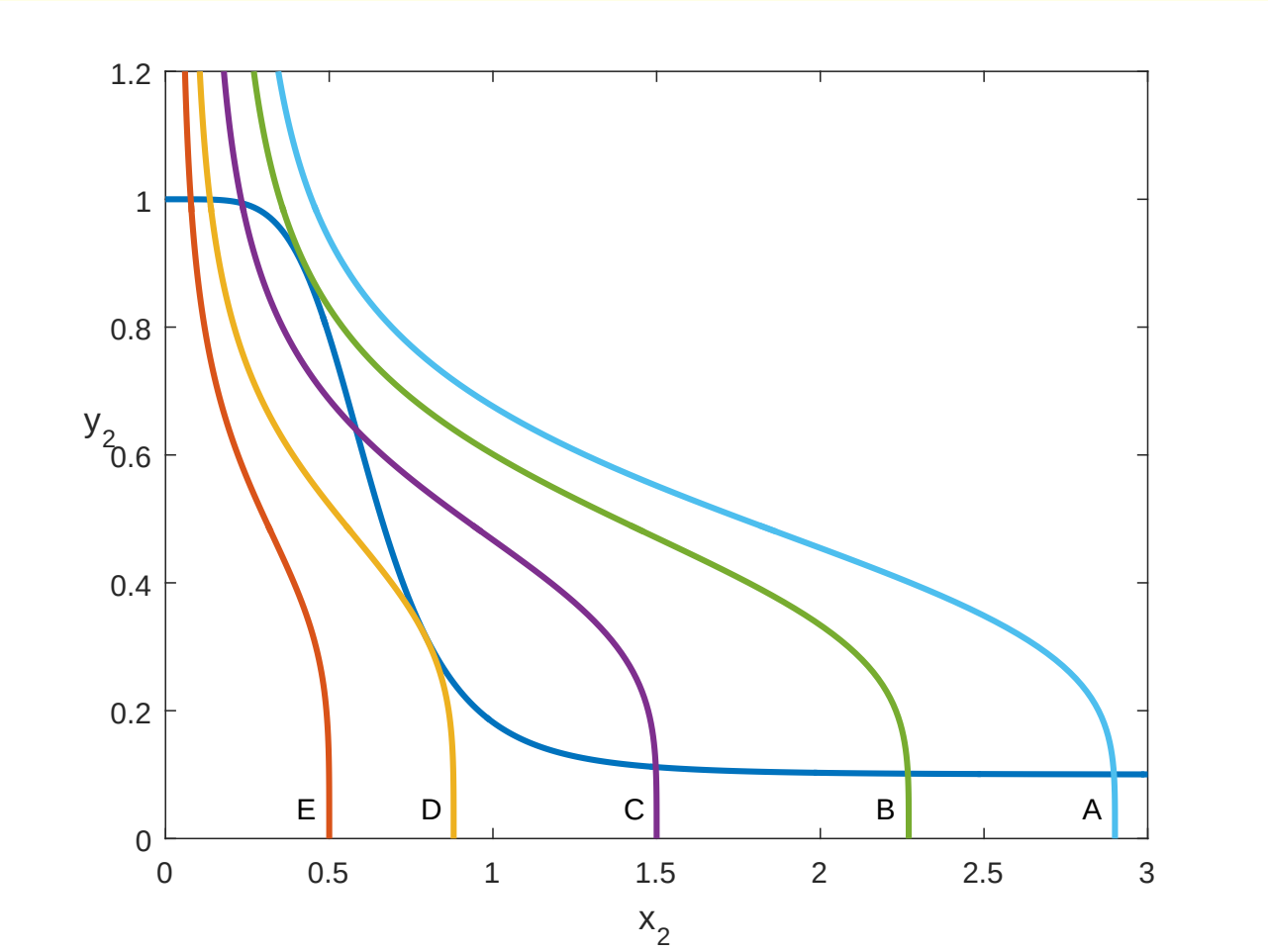
$$y_2 = \kappa_{d,y} f_y(x_2). \tag{7}$$

For each solution (x^*, y^*) of (6)-(7) there is a steady state W^* of the model, and the parameters

$$(\kappa_{d,x}, \kappa_{d,y}, \Delta_x, \Delta_y, n_x, n_y)$$

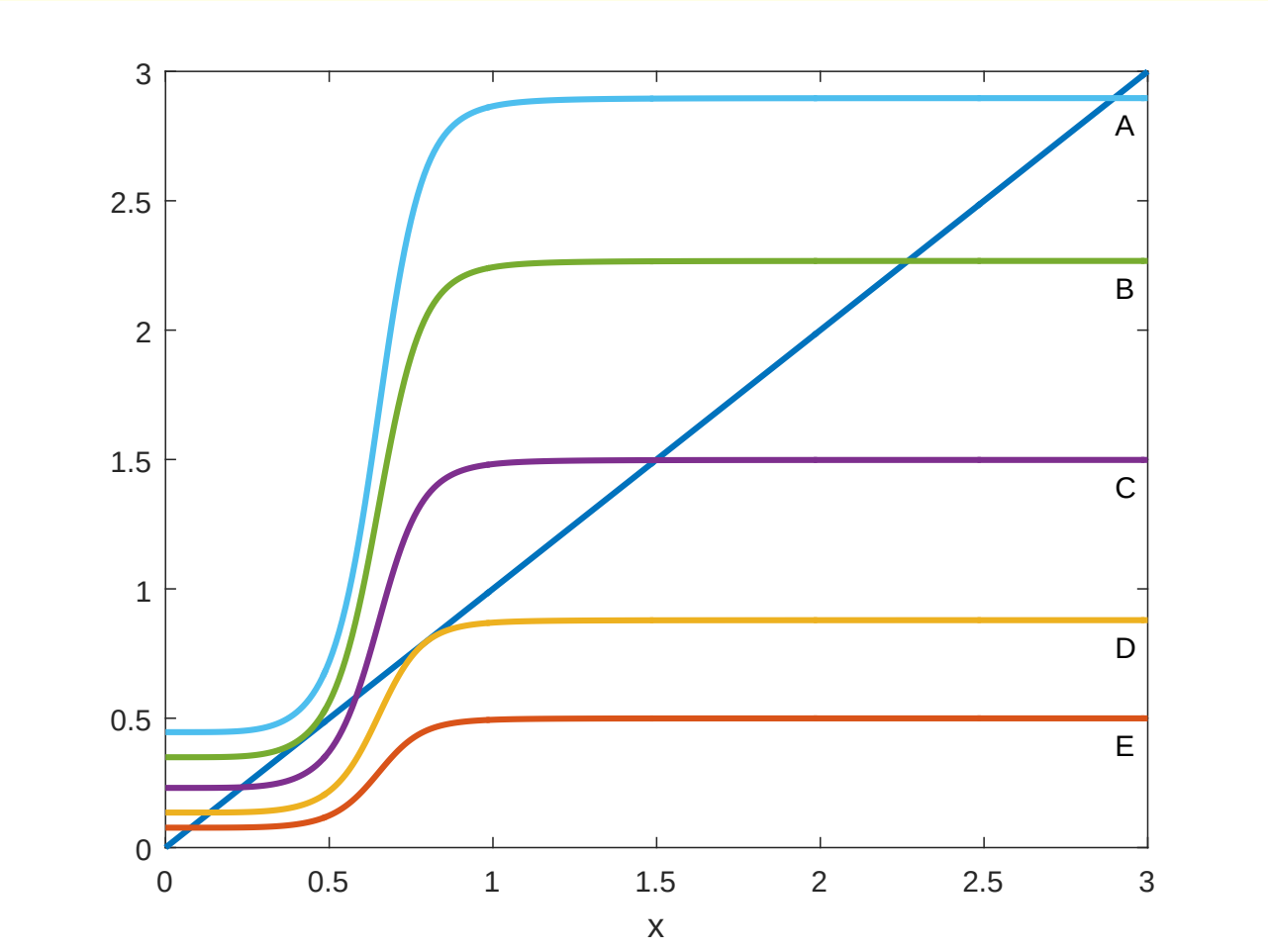
will determine whether W^* is unique or has multiple values.

Graphical investigation of the steady states



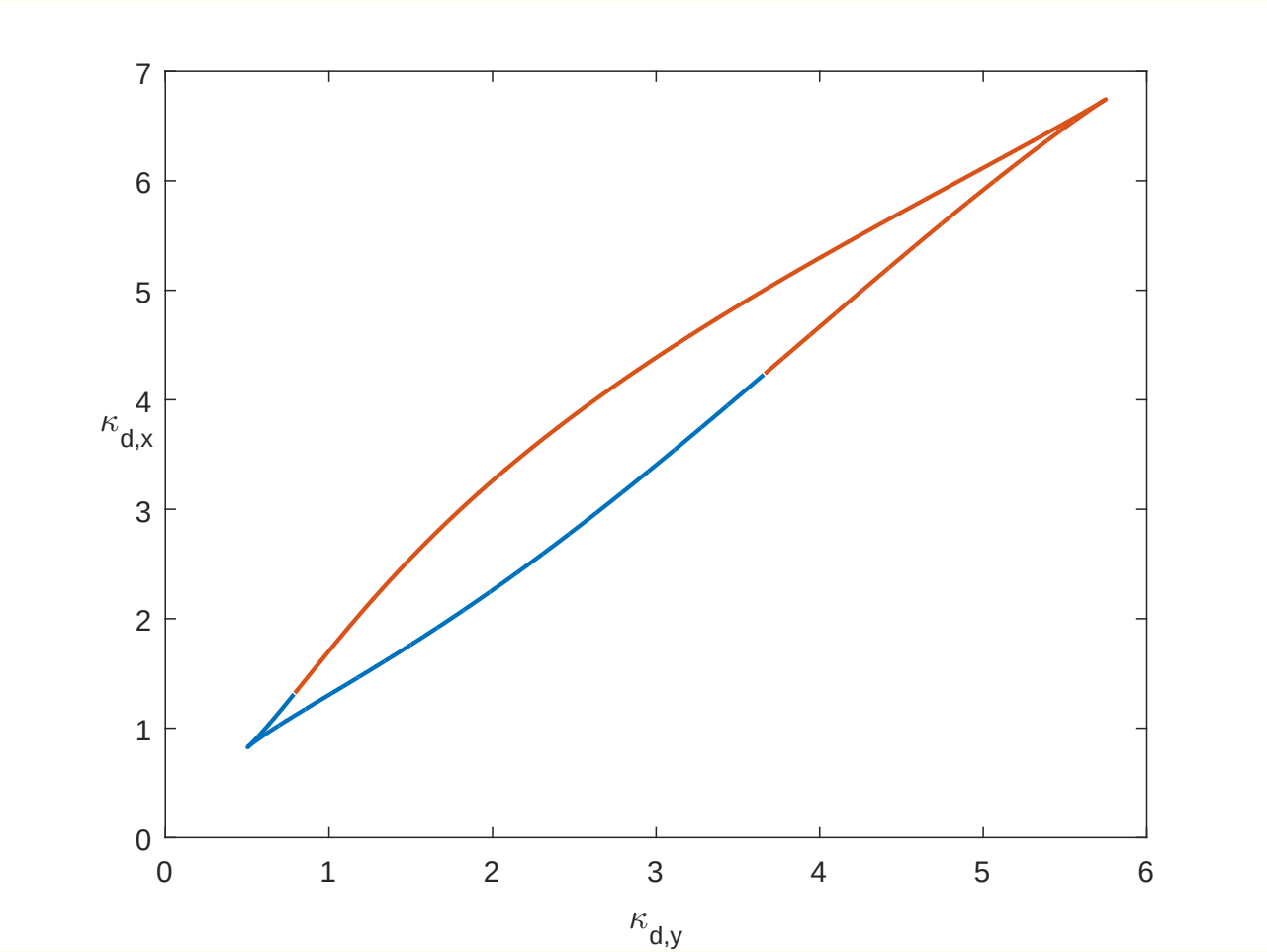
graphs of $y_2 = \kappa_{d,y} f_y(x_2)$ and $x_2 = \kappa_{d,x} f_x(y_2)$ with decreasing $\kappa_{d,x}$

Graphical investigation of the steady states



possible steady state solutions of $x = \kappa_{d,x} f_x(\kappa_{d,y} f_y(x))$

Graphical investigation of the steady states



region of bistability for $n_x = 2,\ n_y = 3,\ \Delta_x = 12,\ \Delta_y = 10$

Reduced model with bursting

Two slow variables, one in each gene

The four equations reduce to

$$\frac{dx}{dt} = \gamma_x[\kappa_{d,x} f_x(y) - x],$$
$$\frac{dy}{dt} = \gamma_y[\kappa_{d,y} f_y(x) - y].$$

The stochastic analogs are

$$\frac{dx}{dt} = -\gamma_x x + \Xi(h_1, \varphi_1(y)) \quad \text{with} \quad \varphi_1(y) = \gamma_x \kappa_{b,x} f_x(y),$$
$$\frac{dy}{dt} = -\gamma_y y + \Xi(h_2, \varphi_2(x)) \quad \text{with} \quad \varphi_2(x) = \gamma_y \kappa_{b,y} f_y(x).$$

One slow variable

If there is a single dominant slow variable (assume it is in the gene X) relative to all of the other three the full switch reduces to a single equation

$$\frac{dx}{dt} = \gamma[\kappa_{d,x} f_x(\kappa_{d,y} f_y(x)) - x],$$

where γ is the dominant (smallest) degradation rate. The stochastic analog is

$$\frac{dx}{dt} = -\gamma x + \Xi(h, \varphi(x)) \quad \text{with} \quad \varphi(x) = \gamma \kappa_{b,x} \mathcal{F}(x),$$

$$\mathcal{F}(x) = f_x(\kappa_{b,y} f_y(x)) = \frac{1 + (\kappa_{b,y} f_y(x))^{n_x}}{1 + \Delta_x (\kappa_{b,y} f_y(x))^{n_x}}$$

Monomeric repression of one of the genes

For $n_x = 1$, $\mathcal{F}$ takes the simpler form

$$\mathcal{F}(x) = \frac{(1+\kappa_{b,y}) + (\Delta_y + \kappa_{b,y})x^{n_y}}{\Lambda + \Gamma x^{n_y}},$$

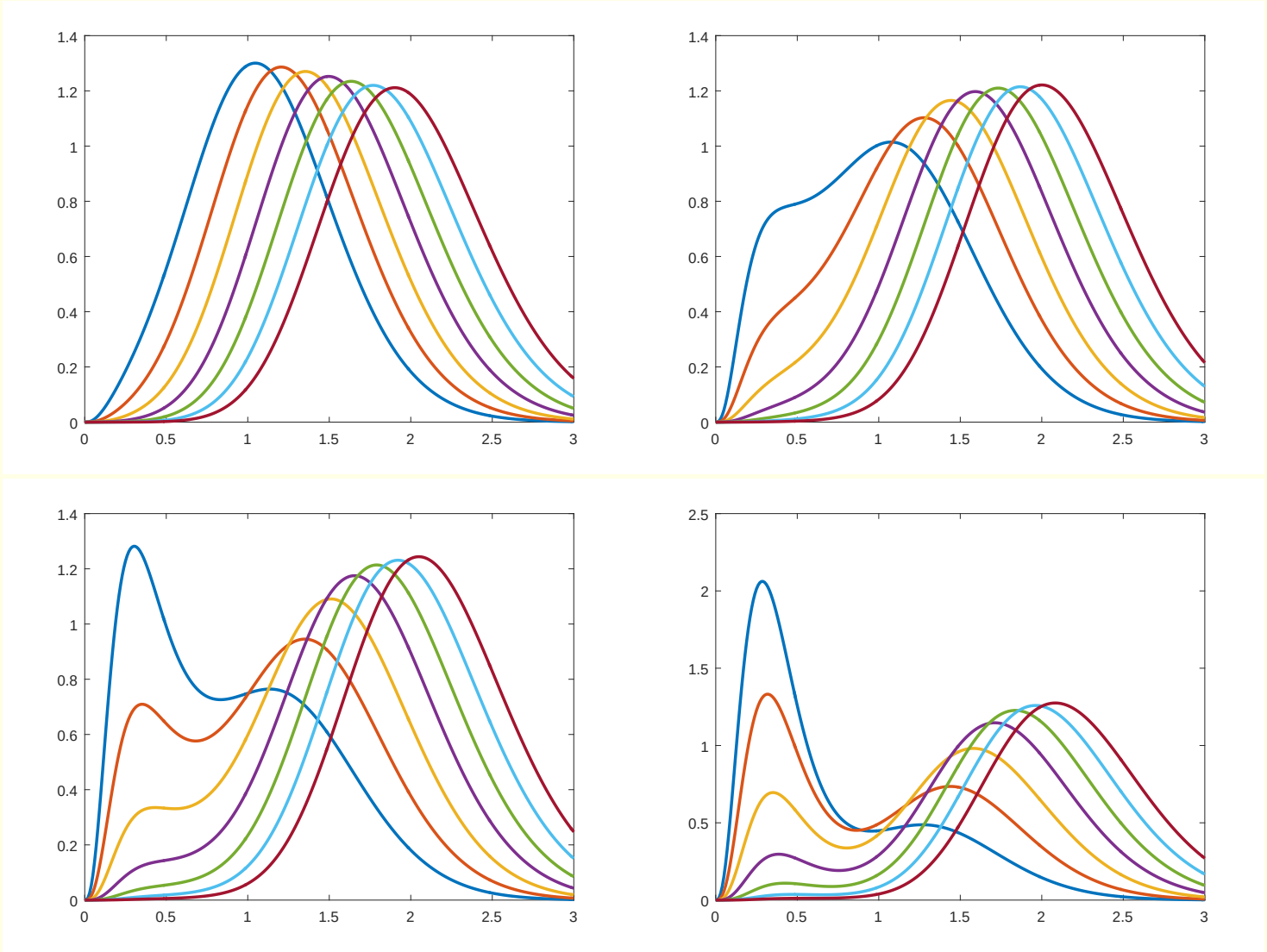
where $\Lambda = 1+\Delta_x\kappa_{b,y} > 0, \quad \Gamma = \Delta_y+\Delta_x\kappa_{b,y} > 0.$

We have the explicit representation

$$u_*(x) = \mathcal{C}e^{-x/b}x^{A-1}[\Lambda + \Gamma x^{n_y}]^\theta$$

with

$$A = \frac{\kappa_{b,x}(1+\kappa_{b,y})}{\Lambda} > 0, \quad \theta = \frac{\kappa_{b,x}\kappa_{b,y}(\Delta_x - 1)(\Delta_y - 1)}{n_y\Lambda\Gamma} > 0.$$



$$\kappa_{b,y} = 1,\ \Delta_x = 12,\ \Delta_y = 10,\ \kappa_{b,x} \in [25, 37],\ n_y = 2, 3, 4, 6$$

Conclusions and further questions

- ◇ Analytic results are available for the stationary density of molecular species only in one dimensional situations
- ◇ The presence of noise may induce bistability in gene regulatory models
- ◇ Stochastic models are in terms of Markov processes. How to approach if there is noise and memory?
- ◇ Transcriptional and translational time delays are expected to have a significant impact on the dynamics of gene expression. The delays might be state dependent

References

[1] M.C. Mackey, M. Tyran-Kamińska, *The limiting dynamics of a bistable molecular switch with and without noise*, J. Math. Biol. (2016) 73:367–395.

[2] M.C.Mackey, M. Santilan, M. Tyran-Kamińska, E. Zeron, *Simple mathematical models of gene regulatory dynamics*, Lecture Notes on Mathematical Modelling in the Life Sciences, Springer, in press.

[3] W. Biedrzycka, M. Tyran-Kamińska, *Existence of invariant densities for semiflows with jumps*, J. Math. Anal. Appl. (2016) 435:61–84.

This work was supported by the Natural Sciences and Engineering Research Council (NSERC, Canada) and the Polish NCN grant 2014/13/B/ST1/00224

Thank you for your attention!