BIOFIZMAT 5

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2018 - Mathematical Biology Year

7-th Forum of Polish Mathematicians
with the Participation of Ukrainian Mathematicians
12 -17 September, Olsztyn

Session: Mathematical models of gene regulation and signaling pathways

Exact results in self-regulating genes

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Protein production directly out of gene

$$\text{DNA} \xrightarrow{k} \text{protein} \xrightarrow{\gamma} \varnothing$$

birth and death process - Markov jump process

We assume that if at time t there was n protein molecules, then

- probability of production (birth) of one protein molecule at the time interval $(t, t+h)$ is equal to $kh + o(h)$
- probability of degradation (death) of one protein molecule at the time interval $(t, t+h)$ is equal to $\gamma nh + o(h)$
- probability of more than one reaction to take place at the time interval $(t, t+h)$ is equal to $o(h)$.

f(n,t) - probability that there are n protein molecules in the cell at time t

We can write an expression for the total probability:

$$\begin{cases} f(n,t+h) = khf(n-1,t) + (n+1)\gamma hf(n+1,t) + (1-kh-n\gamma h)f(n,t) + o(h), \\ f(0,t+h) = \gamma hf(1,t) + (1-kh)f(0,t) + o(h). \end{cases}$$

Master equation

$$\begin{cases} \frac{df(n,t)}{dt} = kf(n-1,t) + (n+1)\gamma f(n+1,t) - (k+n\gamma)f(n,t), \ n \geq 1, \\ \frac{df(0,t)}{dt} = \gamma f(1,t) - kf(0,t) \end{cases}$$

stationary probability distribution

$$\begin{cases} kf(n-1) + (n+1)\gamma f(n+1) - (k+n\gamma)f(n) = 0, \ n \geq 1, \\ \gamma f(1) - kf(0) = 0 \end{cases}$$

$$\begin{cases} kf(n-1) + (n+1)\gamma f(n+1) - (k+n\gamma)f(n) = 0, \ n \geq 1, \\ \gamma f(1) - kf(0) = 0 \end{cases}$$

from the equation for n=0 we get $kf(0) = \gamma f(1)$

from the equation for n=1 we get $kf(1) = 2\gamma f(2)$

for an arbitrary n we have $kf(n) = (n+1)\gamma f(n+1)$

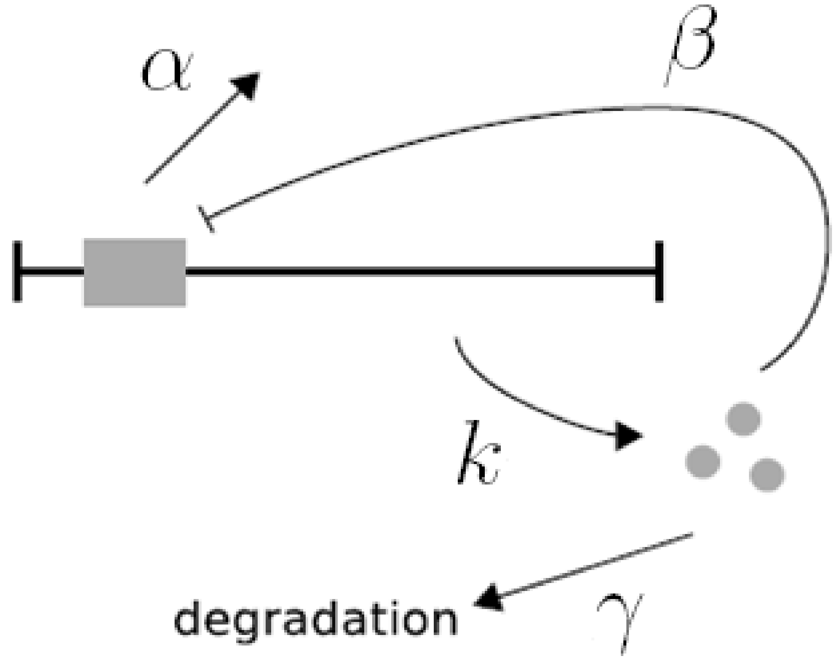
we say that the dynamics satisfies detailed balance conditions

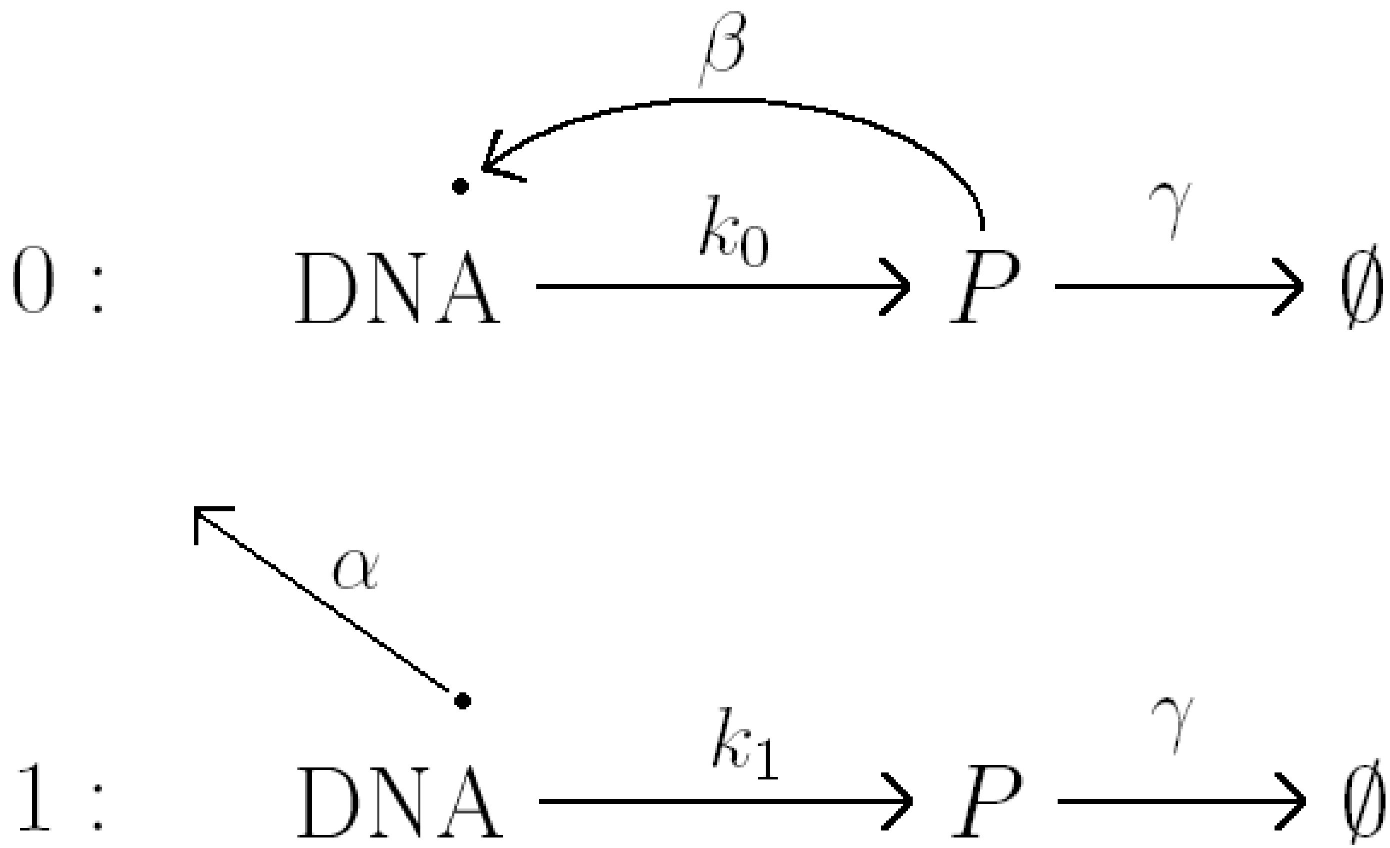
we get $f(n) = f(0)(k/\gamma)^n/n!$

and finally we get the stationary probability distribution

$$f(n) = \frac{(\frac{k}{\gamma})^k}{n!} e^{-\frac{k}{\gamma}}$$

Self-repressing gen





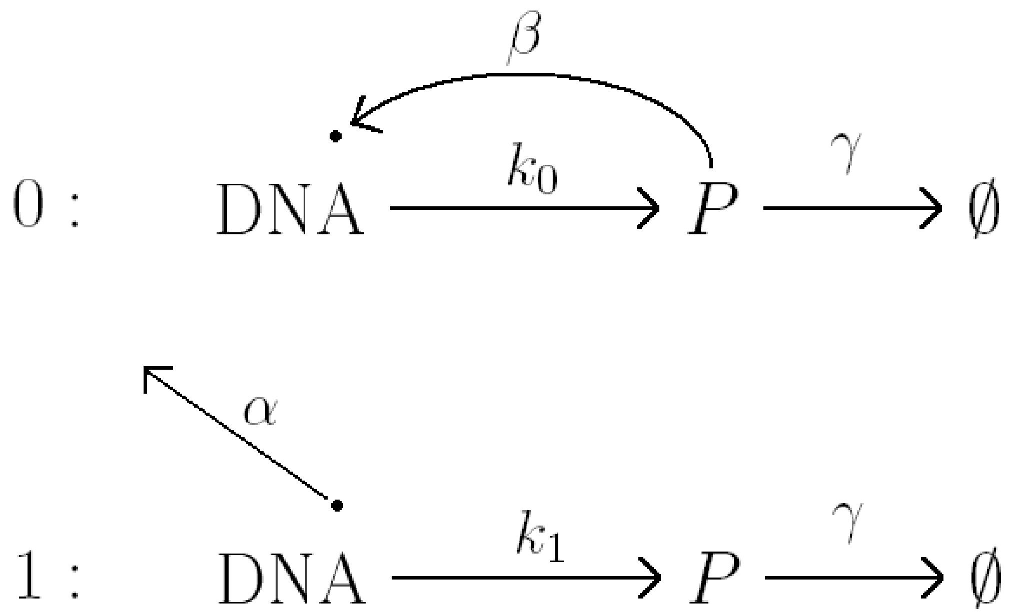
0 :
DNA
β
k_0
P
γ
$\emptyset$
1 :
DNA
α
k_1
P
γ
$\emptyset$

Master equation

$f_0(n,t), f_1(n,t)$ probability that there are n protein molecules in the cell and gen is respectively at state 0 or 1 at time t

$$\frac{df_0(n,t)}{dt} = k_0[f_0(n-1) - f_0(n)] + \gamma[(n+1)f_0(n+1) - nf_0(n)] - \beta \cdot nf_0(n) + \alpha f_1(n)$$

$$\frac{df_1(n,t)}{dt} = k_1[f_1(n-1) - f_1(n)] + \gamma[nf_1(n+1) - (n-1)f_1(n)] + \beta \cdot nf_0(n) - \alpha f_1(n)$$



$$\frac{df_0(n,t)}{dt} = k_0[f_0(n-1) - f_0(n)] + \gamma[(n+1)f_0(n+1) - nf_0(n)] - \beta \cdot nf_0(n) + \alpha f_1(n)$$

$$\frac{df_1(n,t)}{dt} = k_1[f_1(n-1) - f_1(n)] + \gamma[nf_1(n+1) - (n-1)f_1(n)] + \beta \cdot nf_0(n) - \alpha f_1(n)$$

$$A_i = \sum_{n=0}^{+\infty} f_i(n),\ i = 0, 1 \qquad \langle n \rangle_i = \sum_{n=0}^{+\infty} n f_i(n)$$

$$F_0(z,t) = \sum_{n=0}^{+\infty} z^n f_0(n,t) \quad \text{and} \quad F_1(z,t) = \sum_{n=0}^{+\infty} z^n f_1(n,t)$$

$$F_i(z=1,t) = A_i(t), \quad i = 0, 1$$

$$\frac{\partial}{\partial z}\frac{\partial F_i}{\partial t}_{|z=1} = \frac{d < n >_i}{dt}$$

$$\frac{\partial F_i}{\partial z}(z,t)_{|z=1} = < n >_i (t)$$

$$\frac{\partial^2 F_i}{\partial z^2}(z,t)_{|z=1} = < n(n-1) >_i (t)$$

In the stationary state we obtain a system of algebraic equations for moments

$$A_0 + A_1 = 1$$
$$\beta \langle n \rangle_0 - \alpha A_1 = 0$$
$$k_0 A_0 - \gamma \langle n \rangle_0 - \beta \langle n^2 \rangle_0 + \alpha \langle n \rangle_1 = 0$$
$$k_1 A_1 - \gamma \langle n \rangle_1 + \gamma A_1 + \beta \langle n^2 \rangle_0 - \alpha \langle n \rangle_1 = 0$$

The above system is not closed, equations for lower moments involve higher moments

How to close it ?

Self-consistent mean-field approximation

$$\frac{df_0(n,t)}{dt} = k_0[f_0(n-1) - f_0(n)] + \gamma[(n+1)f_0(n+1) - nf_0(n)] - \beta\, n f_0(n) + \alpha f_1(n)$$

$$\frac{df_0(n)}{dt} = k_0[f_0(n-1) - f_0(n)] + \gamma[(n+1)f_0(n+1) - nf_0(n)] - \beta \frac{< n >_0}{A_0} f_0(n) + \alpha f_1(n)$$

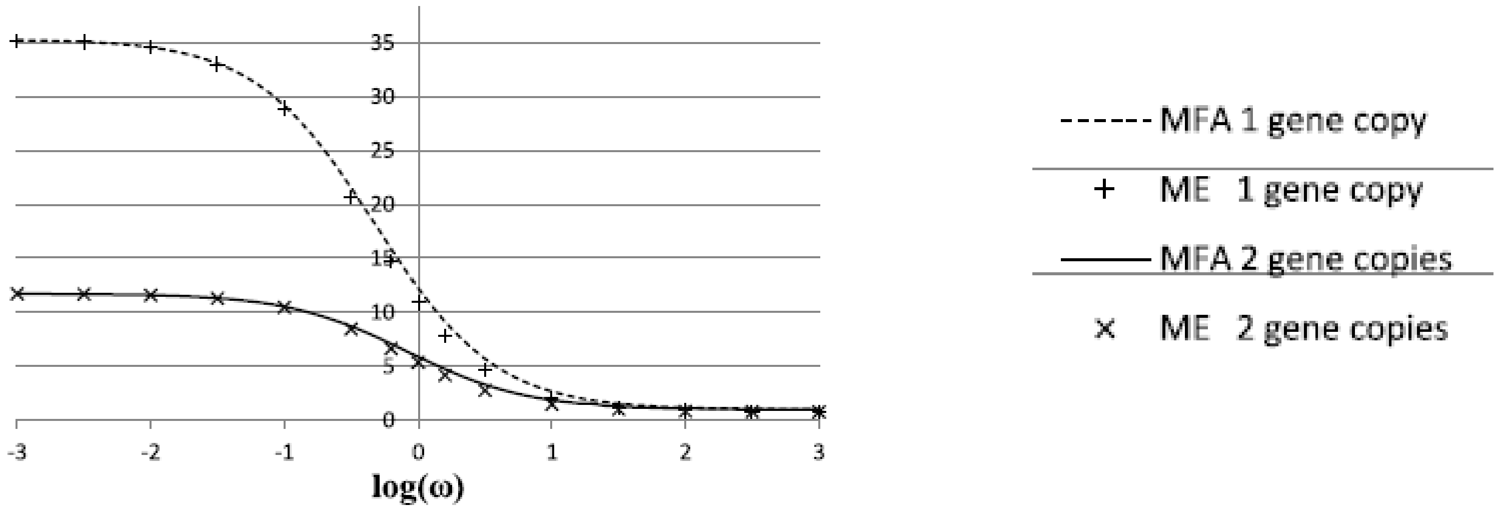
We use generating function approach and obtain a closed system of equations

$$\begin{aligned}
&A_0 + A_1 = 1 \\
&\beta \langle n \rangle_0 - \alpha A_1 = 0 \\
&k_0 A_0 - \gamma \langle n \rangle_0 - \beta \tfrac{\langle n \rangle_0}{A_0} \langle n \rangle_0 + \alpha \langle n \rangle_1 = 0 \\
&k_1 A_1 - \gamma \langle n \rangle_1 + \gamma A_1 + \beta \tfrac{\langle n \rangle_0}{A_0} \langle n \rangle_0 - \alpha \langle n \rangle_1 = 0
\end{aligned}$$

We obtained formulas

for expected values and variance of n

Bulletin of Mathematical Biology 2013, JM and Paulina Szymańska



Fano Factor = variance/expected value as a function of $\omega = \frac{\alpha}{\gamma}$

Fast switching gene
adiabatic limit

$$\omega = \frac{\alpha}{\gamma} = \infty$$

$$A_0 + A_1 = 1$$
$$\beta\langle n\rangle_0 - \alpha A_1 = 0$$
$$k_0 A_0 - \gamma\langle n\rangle_0 - \beta\langle n^2\rangle_0 + \alpha\langle n\rangle_1 = 0$$
$$k_1 A_1 - \gamma\langle n\rangle_1 + \gamma A_1 + \beta\langle n^2\rangle_0 - \alpha\langle n\rangle_1 = 0$$

We assume

$$< n >_0 = \ A_0 < n >$$

$$< n >_1 = \ A_1 < n >$$

and we solve the system of equations

Alternatively

In the adiabatic limit, for every given number of molecules n, the gene is in the equilibrium and we may write

$$A_0(t) \ = \ \frac{\alpha}{\alpha + \beta n(t)} \qquad A_1(t) \ = \ \frac{\beta n(t)}{\alpha + \beta n(t)}$$

We construct the following birth and death process

- probability of production (birth) of one protein molecule at the time interval $(t, t+h)$ is equal to $(k_0 A_0 + k_1 A_1)h + o(h)$
- probability of degradation (death) of one protein molecule at the time interval $(t, t+h)$ is equal to $\gamma n h + o(h)$

We recovered detailed balance and so we can write a formula for stationary state

Singular perturbations

$$\frac{df_0(n,t)}{dt} = k_0[f_0(n-1) - f_0(n)] + \gamma[(n+1)f_0(n+1) - nf_0(n)] - \beta \cdot nf_0(n) + \alpha f_1(n)$$

$$\frac{df_1(n,t)}{dt} = k_1[f_1(n-1) - f_1(n)] + \gamma[nf_1(n+1) - (n-1)f_1(n)] + \beta \cdot nf_0(n) - \alpha f_1(n)$$

$$f(n,\sigma),\ \ \sigma = +,- \qquad\qquad \alpha = \frac{a}{\varepsilon},\ \ \beta = \frac{b}{\varepsilon}$$

$$\frac{df(n,\sigma)}{dt} = L_\varepsilon f(n,\sigma) = \frac{1}{\varepsilon}L_0 f(n,\sigma) + L_1 f(n,\sigma)$$

$$f = f_0 + \varepsilon f_1 + \varepsilon^2 f_2 + \ldots$$

$$Goal: \quad \varepsilon \to 0 \qquad \frac{d\tilde{f}(n)}{dt} = \tilde{L}\tilde{f}(n)$$

$$\frac{1}{\varepsilon} \qquad L_0 f_0 = 0 \qquad a f_0(n,-) = bn f_0(n,+)$$

1 $$\frac{d f_0(n,\sigma)}{dt} = L_0 f_1(n,\sigma) + L_1 f_0(n,\sigma)$$

$$\frac{d f_0(n,\sigma)}{dt} - L_1 f_0(n,\sigma) \in Ran L_0 = (Ker L_0^*)^{\perp}$$

$$Ker(L_0^*)^{\perp} \sim (x,-x)$$

$$\tilde{f}_0(n) = f_0(n,+) + f_0(n,-)$$

$$\frac{d\tilde{f}(n)}{dt} = (k_0 A_0(n-1) + k_1 A_1(n-1))\tilde{f}(n-1) - (k_0 A_0(n) + k_1 A_1(n))\tilde{f}(n) + degradation \ \ terms$$

In general, we consider a Markov jump process
with intensities of jumps k(x,y) for any two discrete states $x \neq y$

We start with a process which satisfies detailed balance conditions

For example, if $$k_0(x,y) = e^{-\beta(U(y)-U(x))}$$

then the stationary state is given by $$\rho_0 = \frac{e^{-U}}{Z}$$

Then we add an extra flux f(x,y) = - f(y,x) of energy in the transition x → y
which cannot be written as the difference V(x) – V(y) for some potential V

We set $$k_\epsilon(x,y) = k_0(x,y)e^{\frac{\beta\epsilon}{2}f(x,y)}$$

The goal is to construct an ε expansion
for the non-equilibrium stationary state ρ_ε

Time delays in production

Differential equation in adiabatic limit

$$\frac{dx}{dt} = \frac{k}{1 + \frac{\beta x(t-\tau)}{\alpha}} - \gamma x$$

Stochastic model

$$F_{0,0}(u,t;t-\tau) = \sum_{n=0}^{\infty} u^n f_{0,0}(n,t;t-\tau),$$

$$F_{1,0}(u,t;t-\tau) = \sum_{n=0}^{\infty} u^n f_{1,0}(n,t;t-\tau)$$

$$F_{0,0}(1,t) = \sum_{n=0}^{\infty} f_{0,0}(n,t;t-\tau) \equiv A_{0,0},$$

$$F_{1,0}(1,t) = \sum_{n=0}^{\infty} f_{1,0}(n,t;t-\tau) \equiv A_{1,0}$$

$$A_0 + A_1 = 1$$
$$\beta < n >_0 - \alpha A_1 = 0$$
$$k_0 A_{0,0} - \gamma < n >_0 - \beta \frac{< n >_0}{A_0} < n >_0 + \alpha < n >_1 = 0$$
$$k_0 A_{1,0} - \gamma < n >_1 + \gamma A_1 + \beta \frac{< n >_0}{A_0} < n >_0 - \alpha < n >_1 = 0$$

small time delays

$$A_{0,0} = A_0 - \beta\tau < n >_0$$

$$A_{1,0} = \beta\tau < n >_0$$

Expected value increases with time delay
Variance decreases with time delay

thank you for attention

more on

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