Stochastic self-regulated gene expression model

Romain Yvinec [a] Michael C. Mackey [b] and Changjing Zhuge [c]

a) Institut Camille Jordan, Universite de Lyon 1, France

&

b) McGill University Montreal, QC CANADA

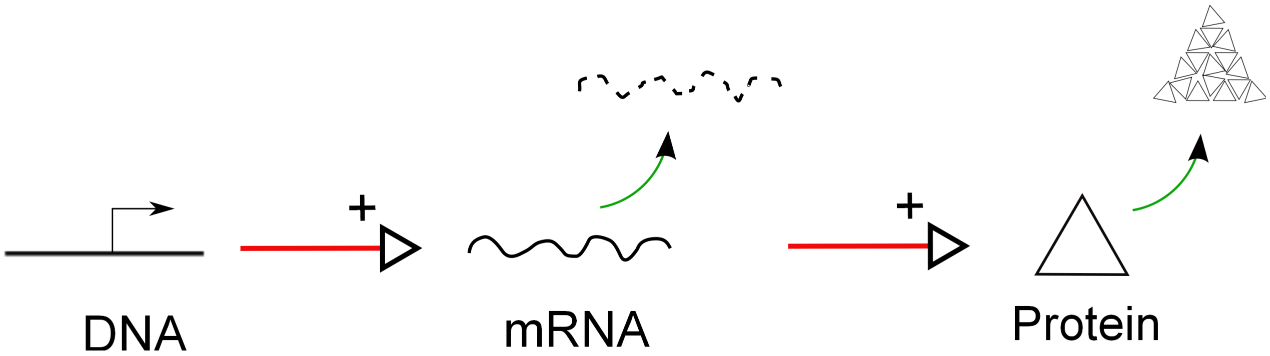
&

c) Zhou Pei-Yuan Center for Applied Mathematics, Tsinghua University, Beijing, China

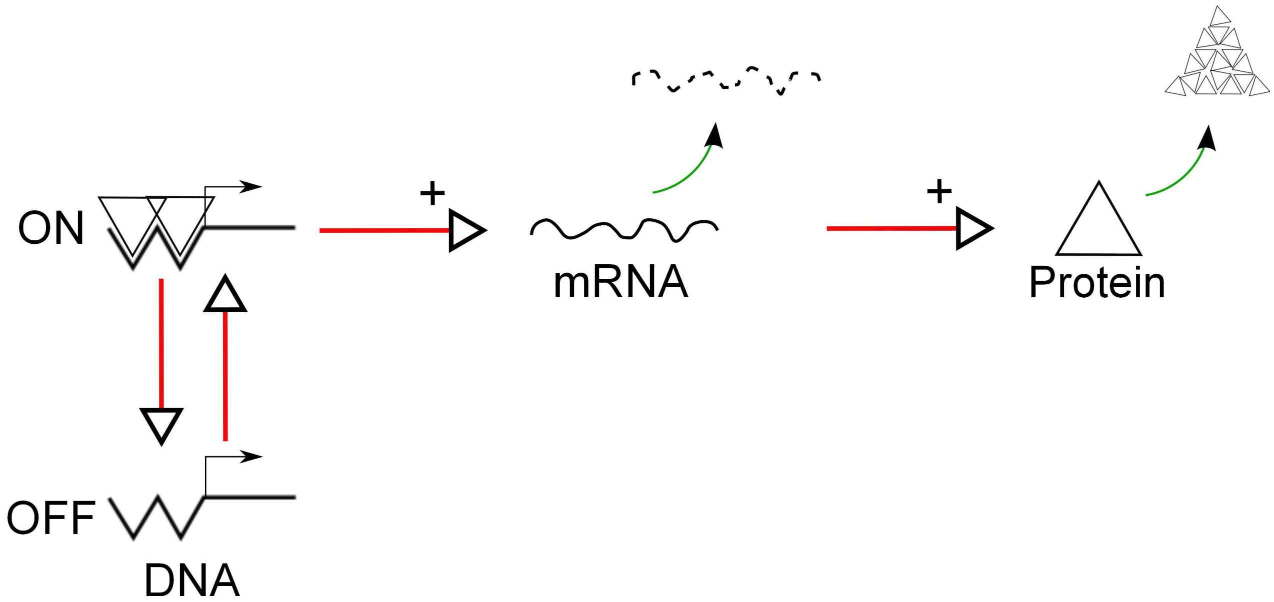
Outline

- Quick review of the standard stochastic models of gene expression
- Can we explain the **Bursting phenomena** through an adiabatic reduction of the standard model?

Central dogma

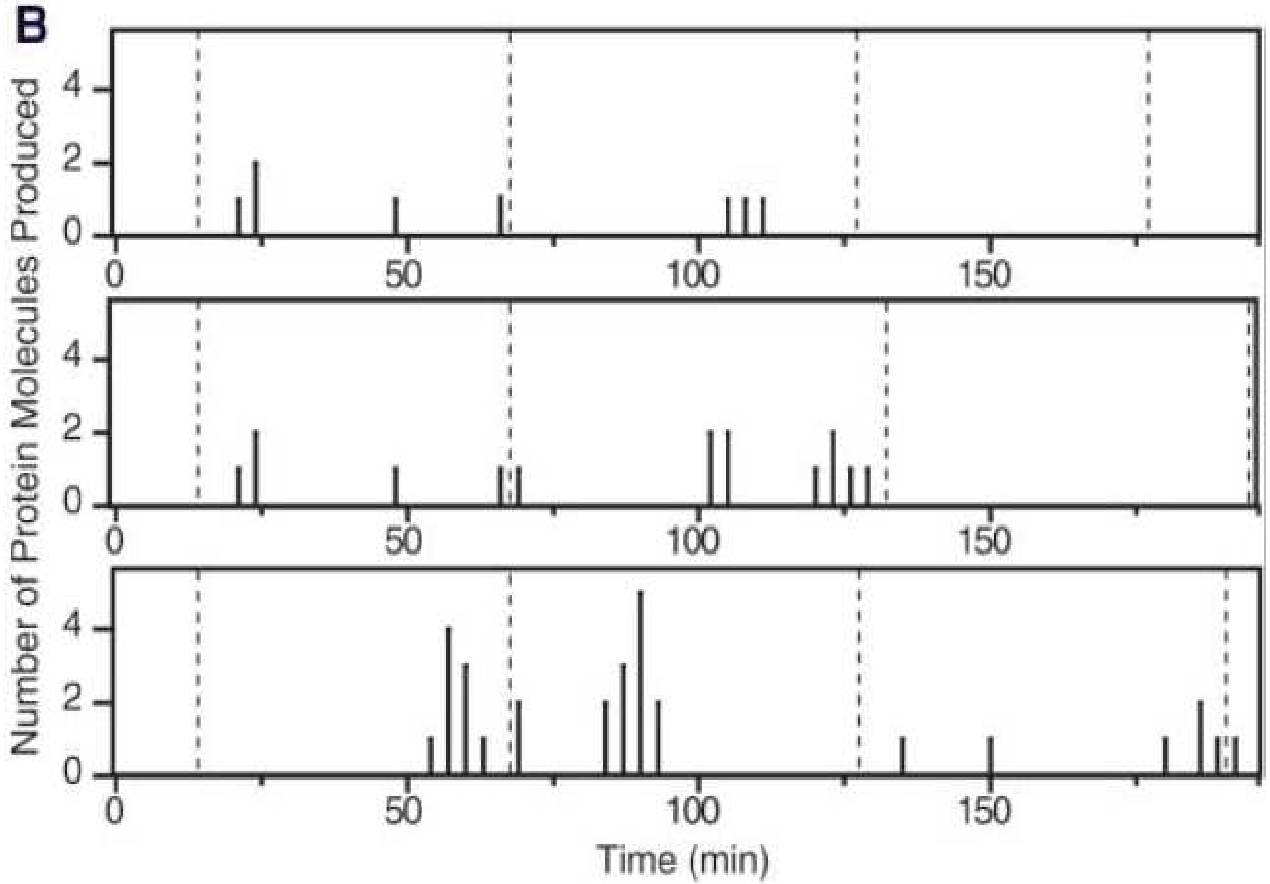


Central dogma



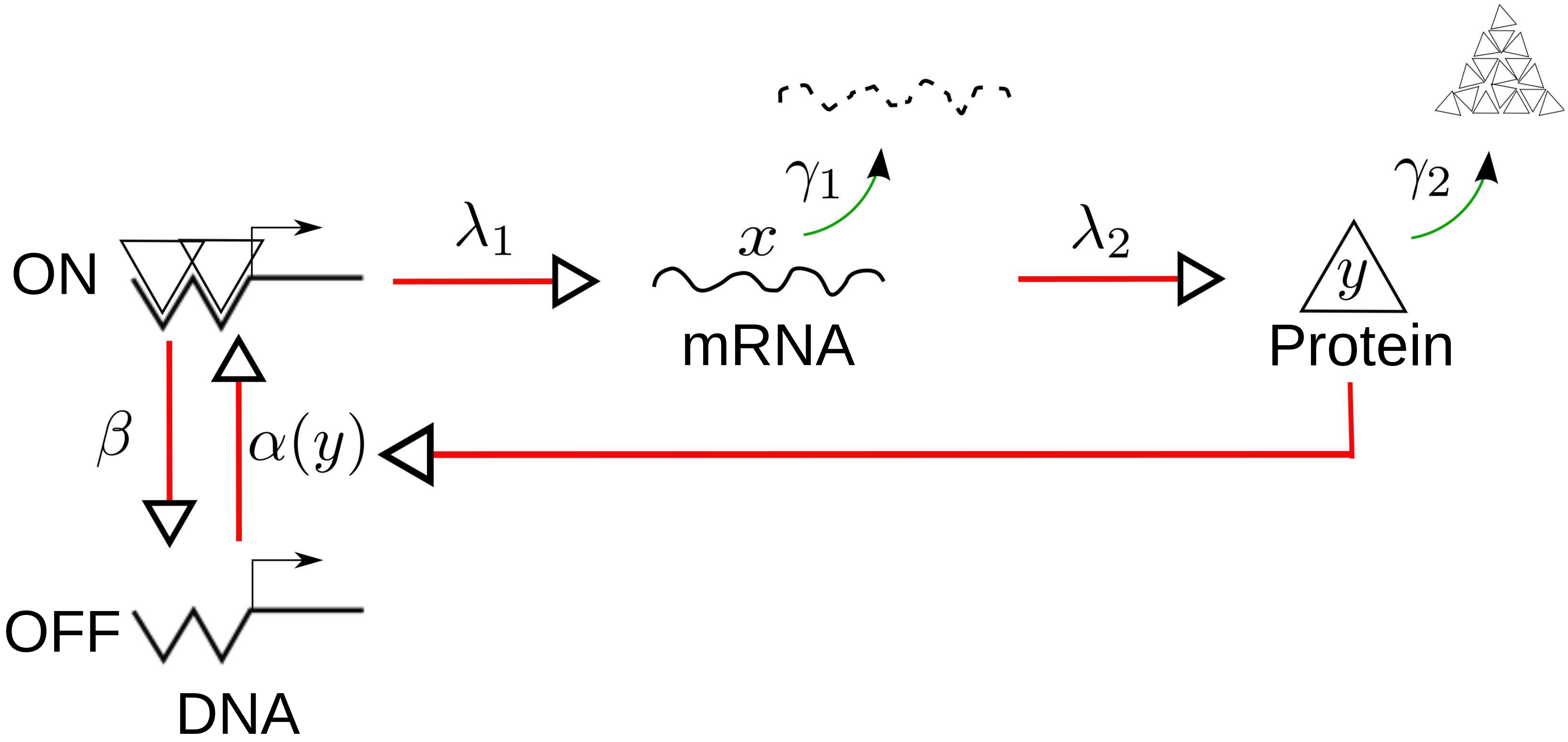
Studied either in a discrete state-space (Swain and Shahrezaei 08, Innocentini and Hornos 06) or in a continuous state-space (Lipniacki and Paszek 06, Mackey and Tyran and Y 2010)

The bursting phenomena

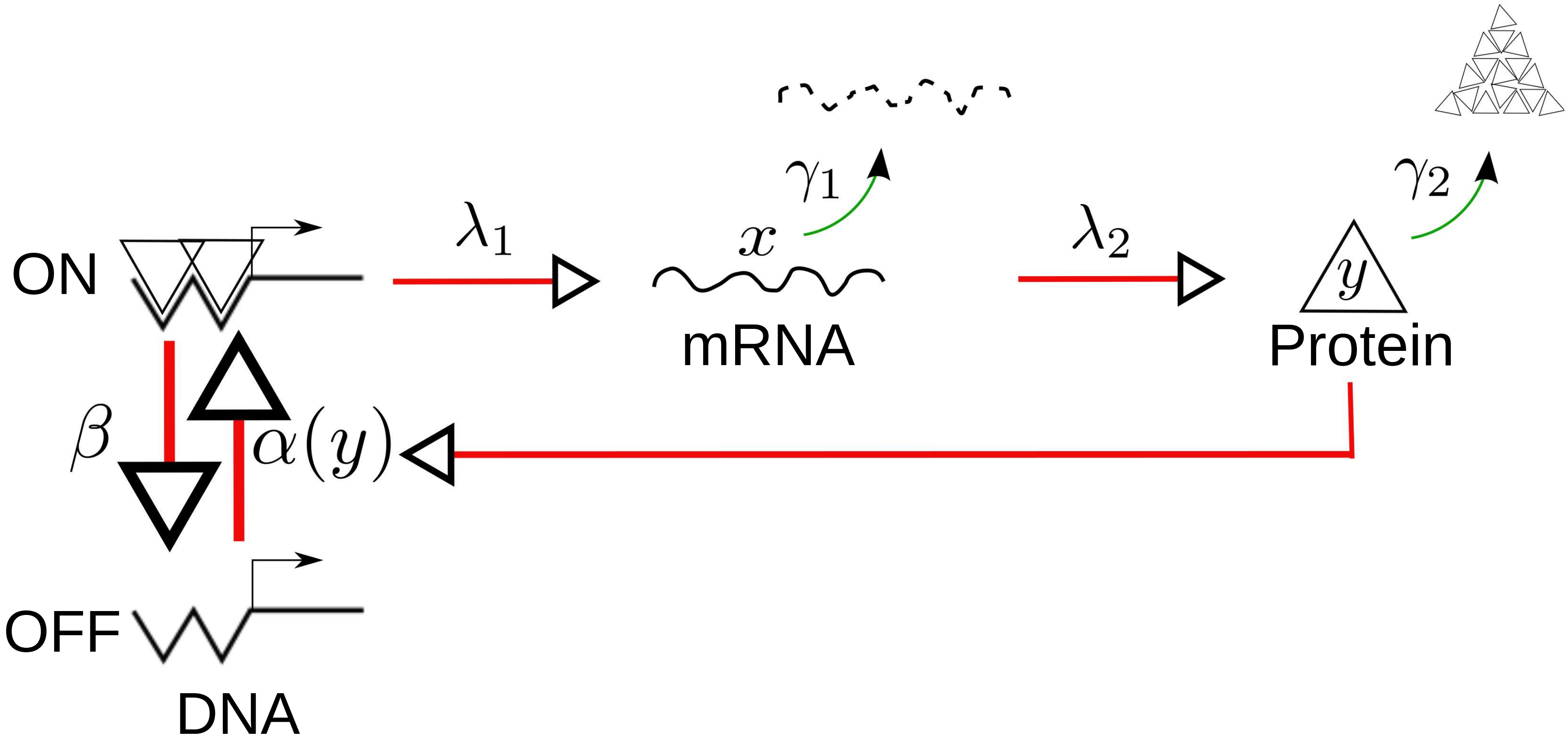


Yu et al. 06

Self-regulated gene

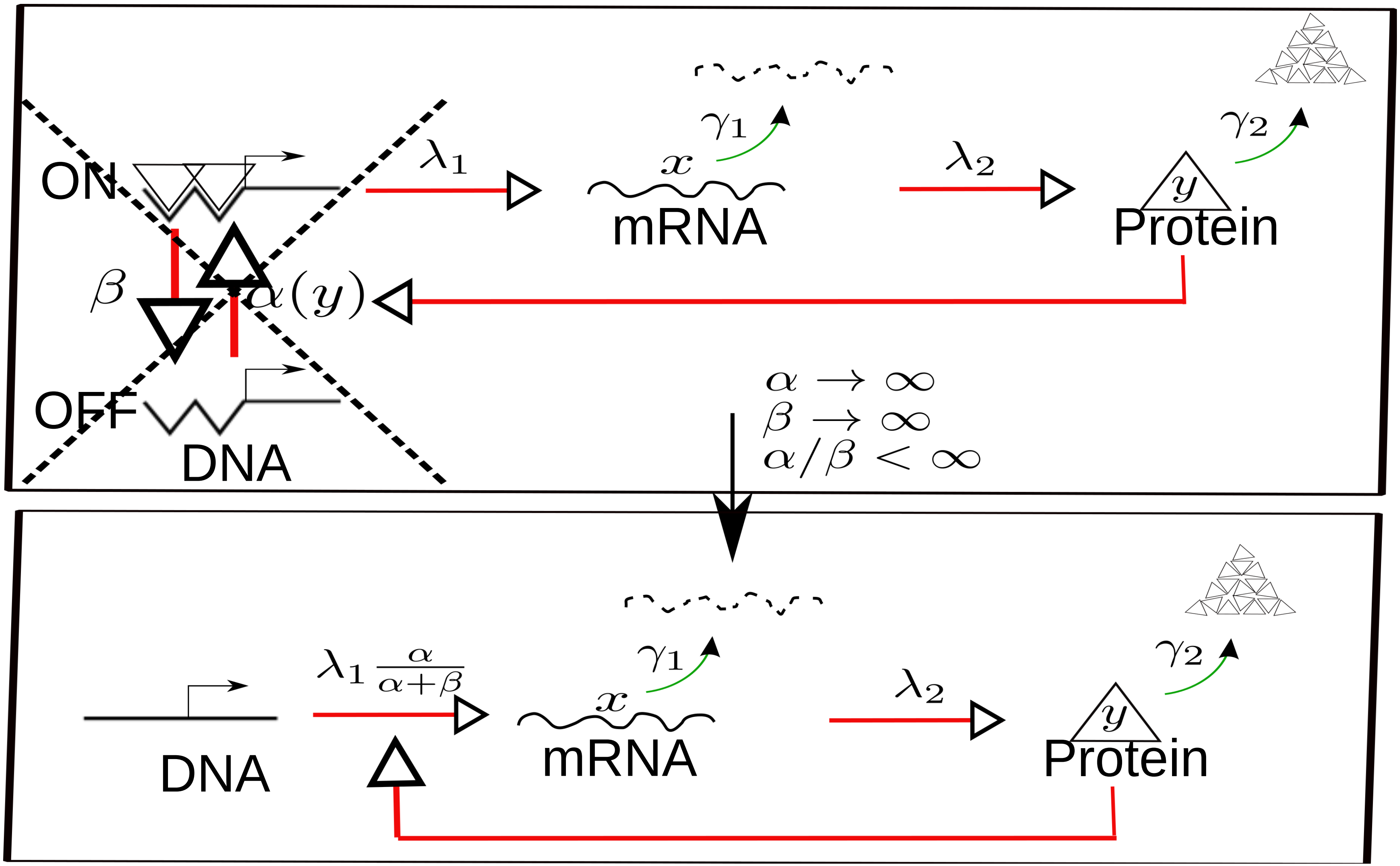


Reduction 1

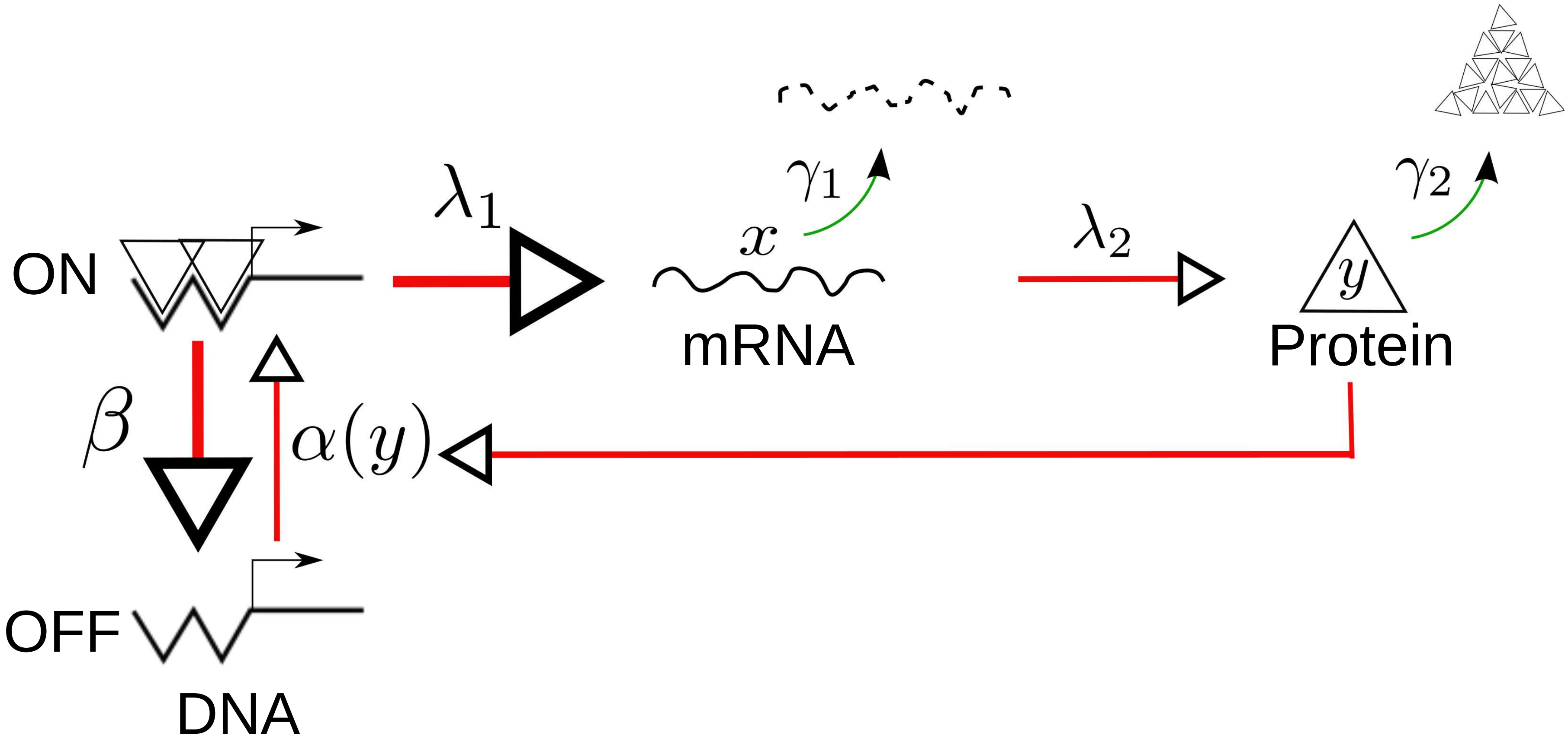


Bobrowski 06: Degenerate convergence of Semigroups.

Reduction 1

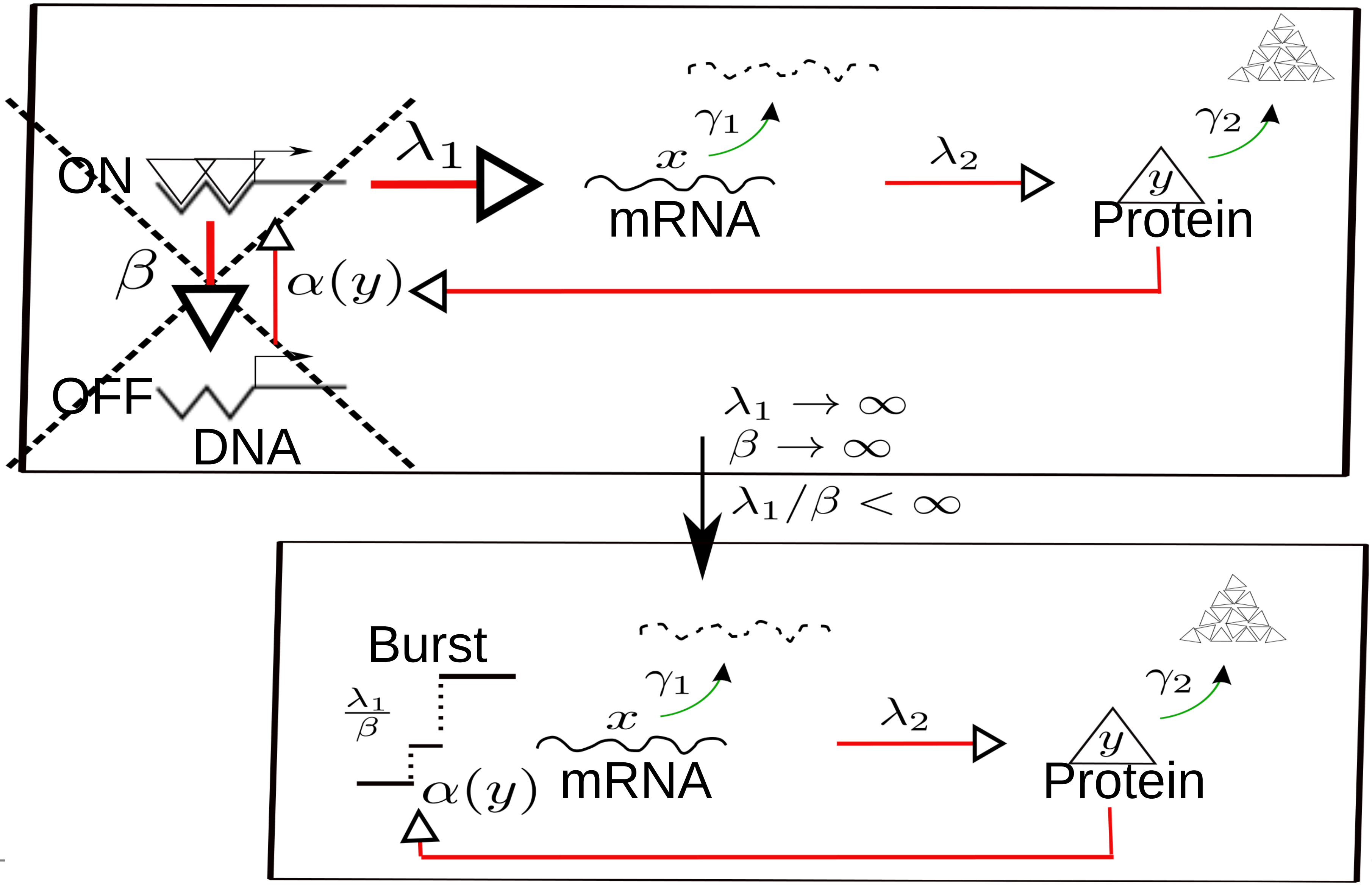

ON
OFF
DNA
λ_1
x
mRNA
γ_1
λ_2
y
Protein
γ_2
β
$\alpha(y)$
$\alpha \to \infty$
$\beta \to \infty$
$\alpha/\beta < \infty$
DNA
$\lambda_1 \frac{\alpha}{\alpha+\beta}$
x
mRNA
γ_1
λ_2
y
Protein
γ_2

Reduction 2



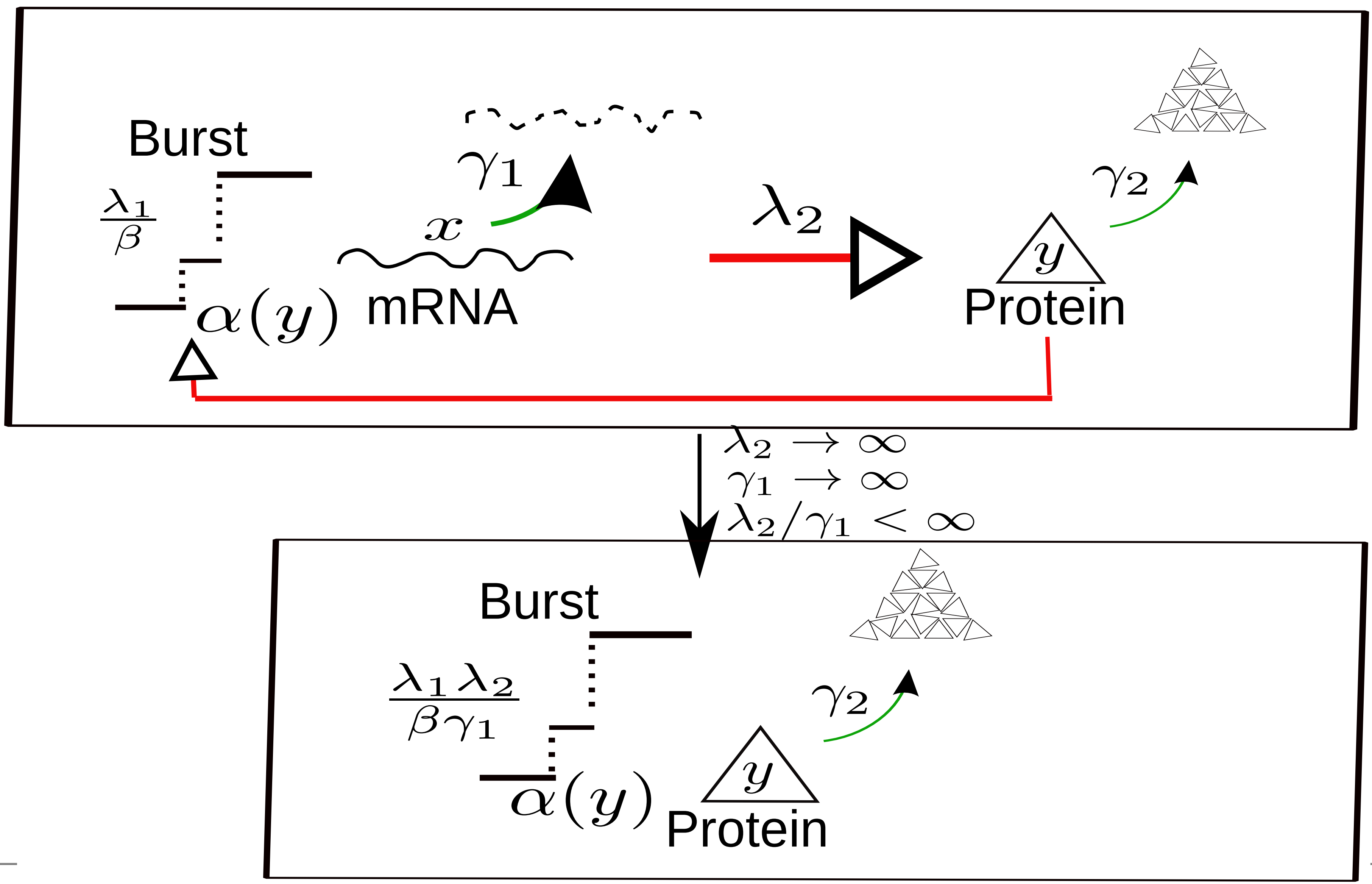
λ_1
γ_1
γ_2
λ_2
x
y
ON
mRNA
Protein
β
$\alpha(y)$
OFF
DNA

Reduction 2



ON
OFF
DNA
λ_1
β
$\alpha(y)$
x
mRNA
γ_1
λ_2
y
Protein
γ_2
$\lambda_1 \to \infty$
$\beta \to \infty$
$\lambda_1/\beta < \infty$
Burst
$\frac{\lambda_1}{\beta}$
$\alpha(y)$
x
mRNA
γ_1
λ_2
y
Protein
γ_2

Reduction 3


Burst
$\frac{\lambda_1}{\beta}$
γ_1
x
$\alpha(y)$
mRNA
λ_2
γ_2
y
Protein
$\lambda_2 \to \infty$
$\gamma_1 \to \infty$
$\lambda_2/\gamma_1 < \infty$
Burst
$\frac{\lambda_1 \lambda_2}{\beta \gamma_1}$
γ_2
$\alpha(y)$
y
Protein

Sketch of the proof

Initial process

(1)
$$\frac{dX}{dt} = \xi - \gamma X$$

where ξ is a dichotomous random process, which takes the values 0 or $\lambda > 0$ and switches at rate $\alpha(X)$ and β.

Final process, when $\beta \to \infty$**,** $\lambda \to \infty$**,** $\beta/\lambda \to b < \infty$

(2)
$$dX = dN(\alpha(X), h) - \gamma X$$

where N is a compound poisson process, of intensity $\alpha(X)$ and jump h exponentially distributed of mean b.

Semi-group proof

Let's define the semigroup $T_t f(x) = \mathbb{E}_x f(X_t)$ then the Dynkin's formula reads $T_t f(x) - f(x) = \int_0^t T_s \mathcal{A} f(X_s) ds$. For any test function f *in the domain of* A

$$\frac{d}{dt}\int_0^\infty p_t^0(x) f^0(x) + p_t^1(x) f^1(x) dx = -\gamma \int_0^\infty x p_t^0(x) \frac{df^0}{dx} dx$$

$$- \int_0^\infty (\gamma x - \lambda) p_t^1(x) \frac{df^1}{dx} dx + \int_0^\infty (\alpha(x) p_t^0(x) - \beta(x) p_t^1(x))(f^1(x) - f^0(x)) dx$$

For any test function such that $f^0(x) = f^1(x) = f(x)$,

$$\frac{d}{dt}\int_0^\infty (p_t^0(x) + p_t^1(x)) f(x) dx = - \gamma \int_0^\infty x(p_t^0(x) + p_t^1(x)) \frac{df}{dx} dx$$

$$+ \lambda \int_0^\infty p_t^1(x) \frac{df}{dx} dx$$

A particular choice for a test function

For any test function such that $f^0(x) = 0$, $f^1(x) = g(x)$,

$$\begin{aligned}\frac{d}{dt}\int_0^\infty p_t^1(x)g(x)dx &= -\gamma\int_0^\infty xp_t^1(x)\frac{dg}{dx}dx + \lambda\int_0^\infty p_t^1(x)\frac{dg}{dx}dx \\ &+ \int_0^\infty \alpha(x)p_t^0(x)g(x)dx - \beta\int_0^\infty p_t^1(x)g(x)dx\end{aligned}$$

One can perform a ***quasi steady-state approximation***, which gives

$$\begin{aligned}\lambda\int_0^\infty p_t^1(x)g(x)dx &= -\frac{\gamma\lambda}{\beta}\int_0^\infty xp_t^1(x)\frac{dg}{dx}dx + \frac{\lambda}{\beta}\int_0^\infty \alpha(x)p_t^0(x)g(x)dx \\ &+ \frac{\lambda^2}{\beta}\int_0^\infty p_t^1(x)\frac{dg}{dx}dx\end{aligned}$$

Iterating

Iterating the process, one can find,

$$\int_0^\infty \lambda p_t^1(x)\frac{df}{dx}dx = \sum_{i\geq 1}\left(\frac{\lambda}{\beta}\right)^i \int_0^\infty \alpha(x)(p_t^0(x)+p_t^1(x))\frac{d^i f}{dx^i}$$

$$- \quad \sum_{i\geq 1}\left(\frac{\lambda}{\beta}\right)^i \int_0^\infty \gamma x p_t^1(x)\frac{d^i f}{dx^i} - \sum_{i\geq 1}\left(\frac{\lambda}{\beta}\right)^i \int_0^\infty \alpha(x) p_t^1(x)\frac{d^i f}{dx^i}$$

The first sum give the jump kernel

$$\int_0^\infty \alpha(x)(p_t^0(x)+p_t^1(x))\left(\int_x^\infty h(y-x)f(y)dy - f(x)\right)dx,$$

where h is a distribution whose moments are given by

$$\mathcal{E}^i[h] = i!\left(\frac{\lambda}{\beta}\right)^i$$

The two others sum are shown to be arbitrary small.□

summary

- The same is working in a discrete formalism
- Powerful tools to perform adiabatic reduction in Hybrid systems
- The "full-model" can now be analysed according its different limit behaviour.
- Other scaling are to be investigated

Thank you for your attention!