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HAL Authorization

# Bursting in gene expression model

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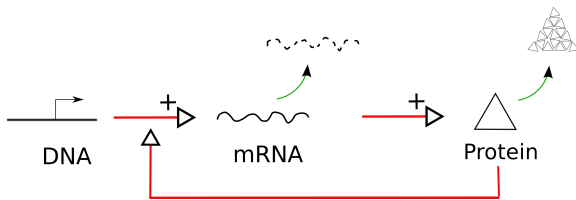
Goodwin's deterministic model

Stochastic gene expression model

Analytical results on a reduced model

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*Crick (1958)* : Central Dogma.

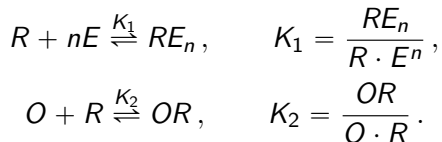
*Jacob, Perrin, Sánchez, Monod (1960)* : Operon.

$$\left\{ \begin{array}{l} \frac{dM}{dt} = \lambda_1(E) - \gamma_1 M, \\ \frac{dI}{dt} = \lambda_2 M - \gamma_2 I, \\ \frac{dE}{dt} = \lambda_3 I - \gamma_3 E. \end{array} \right. \quad (1)$$

*Goodwin (1965), Griffith (1968), Othmer (1976), Selgrade (1979)...*

# The transcription rate function $\lambda_1$

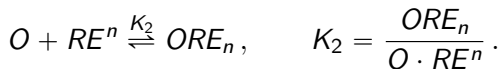
- ▶ **Inducible Operon** : Repressors  $R$  interacts with both the Operator  $O$  and the Effector  $E$ ,



With **QSSA**, and if  $O_{tot} \ll R_{tot}$ ,

$$\lambda_1(E) \sim \frac{O}{O_{tot}} = \frac{1 + K_1 E^n}{1 + K_2 R_{tot} + K_1 E^n}. \quad (2)$$

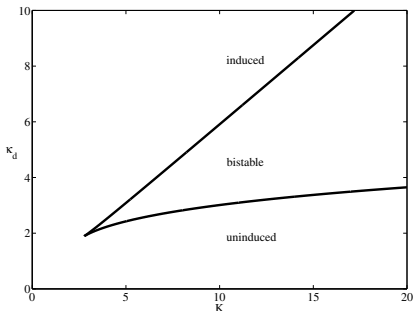
- ▶ **Repressible Operon** : Similar but



and we get

$$\lambda_1(E) \sim \frac{O}{O_{tot}} = \frac{1 + K_1 E^n}{1 + (K_1 + K_2 R_{tot}) E^n}. \quad (3)$$

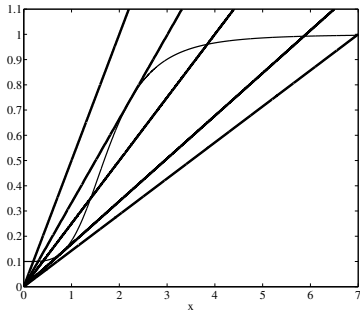
## Bifurcation analysis in ODE



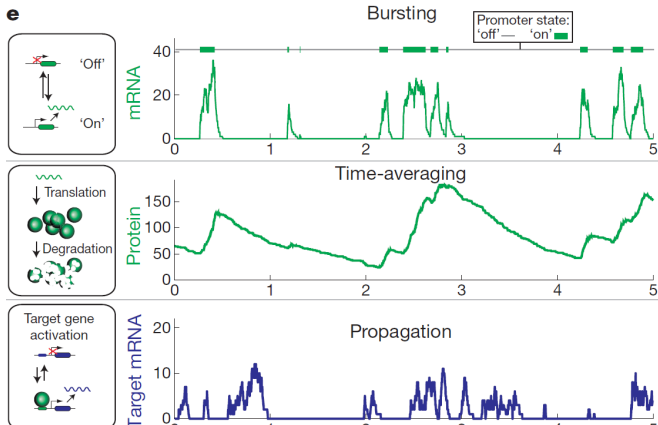
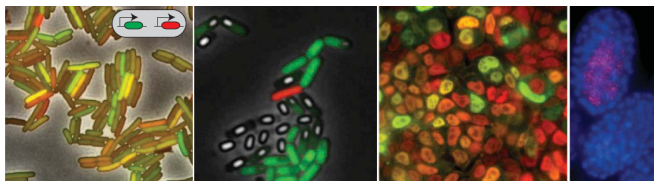
- ▶ **Inducible** : Mono-stability or Bi-stability.
- ▶ **Repressible** : Mono-stability or limit cycle.

$$\begin{cases} \frac{dx_1}{dt} = \gamma_1[\lambda_1(x_3) - x_1], \\ \frac{dx_2}{dt} = \gamma_2(x_1 - x_2), \\ \frac{dx_3}{dt} = \gamma_3(x_2 - x_3). \end{cases} \quad (4)$$

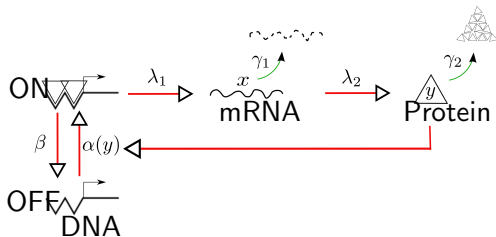
Here  $\lambda_1(x) = \kappa_d \frac{1 + x^n}{K + x^n}$ .



## Eldar and Elowitz (Nature 2010)



## 'New' Central dogma



Novick & Weiner (1957), Ko et al. (1990), Ozbudak et al. (2002), Elowitz et al. (2002), Raser & O'Shea (2004)...

$$\left\{ \begin{array}{l} \frac{dx}{dt} = G(t)\lambda_1(y(t)) - \gamma_1 x(t), \\ \frac{dy}{dt} = \lambda_2 x(t) - \gamma_2 y(t), \\ (G = 0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G = 1). \end{array} \right. \quad (5)$$

Rigney & Schieve (1977), Berg (1978), Peccoud & Ycart (1995), Thattai & Van Oudenaarden (2001)...

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# Can we perform a systematic bifurcation theory on such systems ?

- ▶ We are interested in long time behavior.
- ▶ We want to know how many modes has the stationary distribution.
- ▶ This requires in practice 'analytical' solution.

A subclass of the 'three-stage' (DNA, mRNA, Protein) model is the 1D-bursting model (Storage model)

$$Lf(x) = -\gamma(x)f'(x) + \lambda(x) \int_0^{\infty} (f(x+y) - f(x))h(x,y)dy \quad (6)$$

where  $h$  is the *burst size distribution*,  $\int_0^{\infty} h(x,y)dy = 1$ . If  $h(x,y) = -\frac{\nu'(x+y)}{\nu(x)}$ ,  $\nu \searrow$  and  $\nu \rightarrow_{\infty} 0$ ,

$$Lf(x) = -\gamma(x)f'(x) + \frac{\lambda(x)}{\nu(x)} \int_x^{\infty} f'(z)\nu(z)dz \quad (7)$$

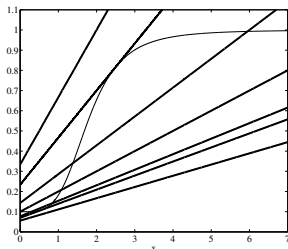
Any stationary distribution satisfies  $\int_0^{\infty} Lf(x)u^*(x)dx = 0$ , so that

$$\int_0^{\infty} \left[ -\gamma(x)u^*(x) + \nu(x) \int_0^x \frac{\lambda(y)}{\nu(y)} u^*(y)dy \right] f'(x)dx = 0. \quad (8)$$

Hence

$$u^*(x) = \frac{\nu(x)}{C\gamma(x)} \exp \left( \int^x \frac{\lambda(y)}{\gamma(y)} dy \right) \quad (9)$$

## Bifurcation analysis in SDE

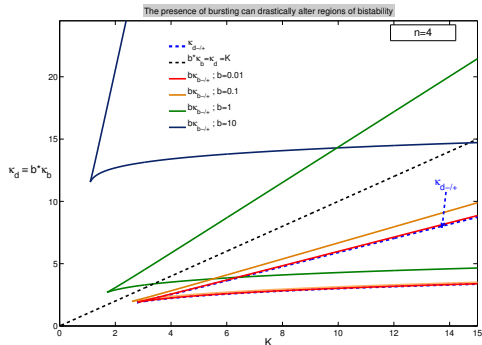


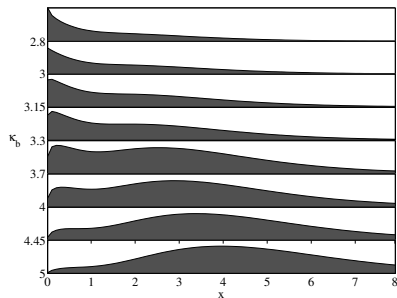
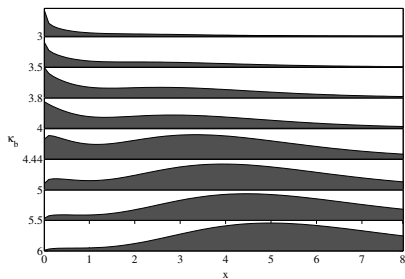
- ▶ **Inducible :**  
Uni-modal or Bi-modal.
- ▶ **Repressible :**  
Uni-modal.

(under technical assumptions...)  
 $u(t, x)dx = \mathbb{P}\{x(t) \in [x, x + dx)\}$   
 converges as  $t \rightarrow \infty$  (in  $L^1$ ) towards  $u^*$ ,

$$\frac{du^*}{dx} = \left[ \lambda(x) - \gamma \left(1 + \frac{x}{b(x)}\right) \right] \frac{u^*(x)}{\gamma x}.$$

with  $b(x) = -\frac{\nu(x)}{\nu'(x)}$  and  $\gamma(x) = \gamma x$ .



Stationary distribution  $(\lambda, \gamma, b) \Rightarrow (u^*)$ 

Here  $\lambda(x) = \kappa_b \frac{1 + x^n}{K + x^n}$  and  $b(x) = b$  ( $\nu(x) = \exp(-x/b)$ ).

# From the 3-stage to the bursting model

$$\left\{ \begin{array}{l} \frac{dx}{dt} = G(t)\lambda_1(y(t)) - \gamma_1 x(t), \\ \frac{dy}{dt} = \lambda_2 x(t) - \gamma_2 y(t), \\ (G=0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G=1). \end{array} \right. \quad (10)$$

- ▶ If the mRNA lifetime is short ( $\gamma_1 \rightarrow \infty$ ), we can perform an **adiabatic** reduction ( $x(t) \approx G(t) \frac{\lambda_1}{\gamma_1}(y(t))$ ):

$$\left\{ \begin{array}{l} \frac{dy}{dt} = G(t) \frac{\lambda_2 \lambda_1}{\gamma_1}(y(t)) - \gamma_2 y(t), \\ (G=0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G=1). \end{array} \right. \quad (11)$$

$$\left\{ \begin{array}{l} \frac{dy}{dt} = G(t) \frac{\lambda_2 \lambda_1}{\gamma_1} (y(t)) - \gamma_2 y(t), \\ (G = 0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G = 1). \end{array} \right. \quad (12)$$

- ▶ If the Gene active periods are short ( $\beta \rightarrow \infty$ ), we obtain the **bursting** model

$$\frac{dy}{dt} = Z(t) - \gamma_2 y(t), \quad (13)$$

where  $Z = \sum_i Z_i \delta_{T_i}$  is a jump process, of jump rate  $\alpha(y(t))$  and jump size cumulative distribution **of separated form**

$$\mathbb{P}\{y(T_i^+) \geq z \mid y(T_i^-) = y\} = \exp\left(-\int_y^z \frac{\gamma_1 \beta}{\lambda_1 \lambda_2}(w) dw\right).$$

### Remark

For a constitutive gene,  $b := \frac{\lambda_1 \lambda_2}{\gamma_1 \beta}$  is the average number of proteins produced per Gene activation event.

## Remark

For the '2-stage' model (Telegraph),

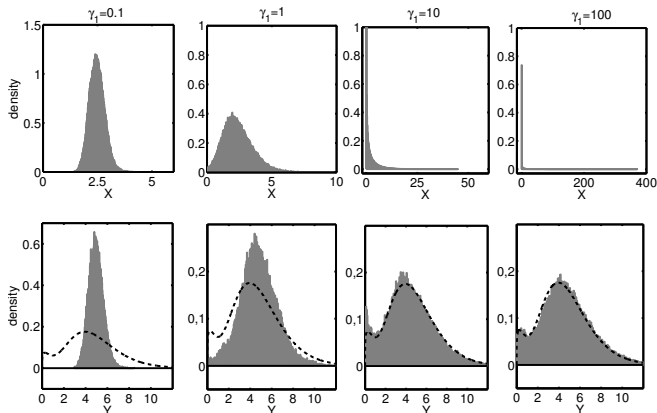
$$\left\{ \begin{array}{l} \frac{dx}{dt} = G(t)\lambda(x(t)) - \gamma x(t), \\ (G = 0) \xrightleftharpoons[\beta(x(t))]{\alpha(x(t))} (G = 1). \end{array} \right. \quad (14)$$

we have (See Boxma et al. 2005)

$$\frac{du^*}{dx} = \left[ \frac{\alpha(x)}{\gamma x} - \frac{\beta(x)}{\lambda(x) - \gamma x} - \frac{\lambda(x)/x - \gamma + \gamma x(\lambda'(x) - \gamma)/(\lambda(x) - \gamma x)}{\lambda(x)} \right] u^* \quad (15)$$

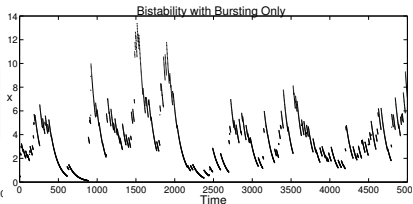
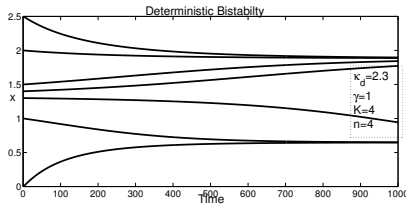
## Small recap' on the forward problem (1/2)

- ▶ We performed an adiabatic reduction to make the problem analytical tractable.
- ▶ We solved the reduced problem for arbitrary coefficients at equilibrium.
- ▶ We performed an (deterministic-analogous) bifurcation study.



## Small recap' on the forward problem (2/2)

- ▶ Careful! The two notions of deterministic bistability and 'stochastic bistability (bimodality) are in fact quiet different



- ▶ (mean) Switching time : can quantify the 'stability' of each state.

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Similar results may be obtained for a 'bursting-division' model.

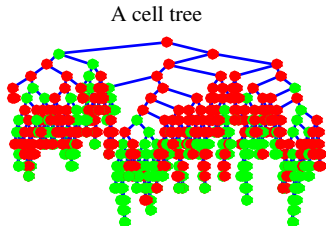
$$Lf(x) = d(x) \int_0^x (f(y) - f(x))\kappa(x, y)dy + \lambda(x) \int_0^\infty (f(x+y) - f(x))h(x, y)dy$$

For instance, with uniform repartition kernel ( $\kappa(x, y) = 1/x$ ), constant division rate  $d$  and constant exponential burst size ( $h(x, y) = \exp(-y/b)$ ),

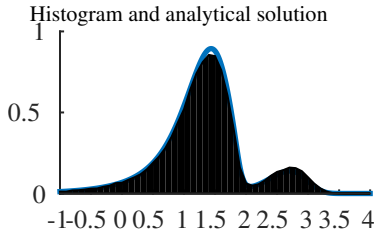
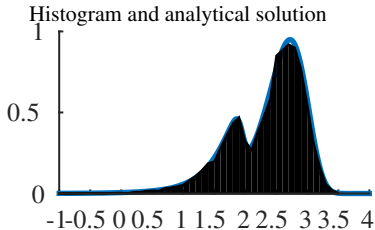
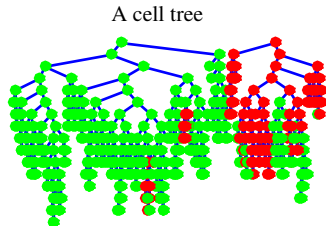
$$\frac{d}{dy}u^* = \left[ -\frac{\lambda'(y) + d}{\lambda(y) + d} + \frac{\lambda(y)}{\lambda(y) + d} \left( \frac{1}{x} + \frac{1}{b} \right) - \frac{xb^2}{bx + 1} - \frac{1}{x} \right] u^*(y)$$

This may be used to predict the long time behavior of a dividing cell population

scenario 1



scenario 2



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# Inverse Problem : $(u^*) \Rightarrow (\lambda, \gamma, b)$

For a constitutive gene, we can infer the burst rate (in protein lifetime unit)  $\frac{\lambda}{\gamma}$  and the mean burst size  $b$  from the first two (stationary) moments

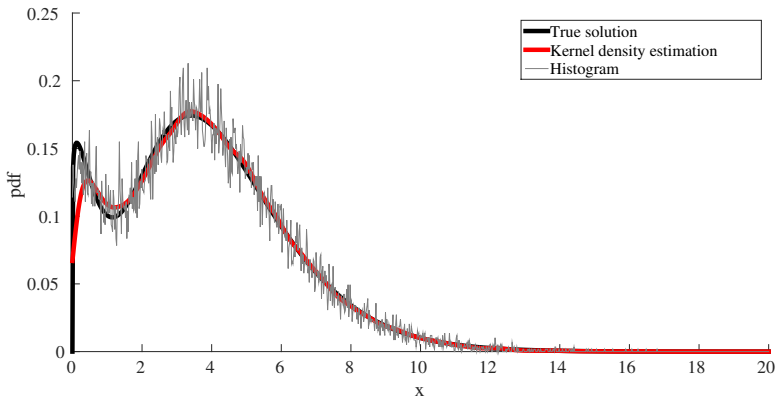
$$\frac{b\lambda}{\gamma} = \mathbb{E}[X],$$
$$b = \frac{\text{Var}(X)}{\mathbb{E}[X]}.$$

For an auto-regulated gene, we can inverse the formula for the stationary pdf :

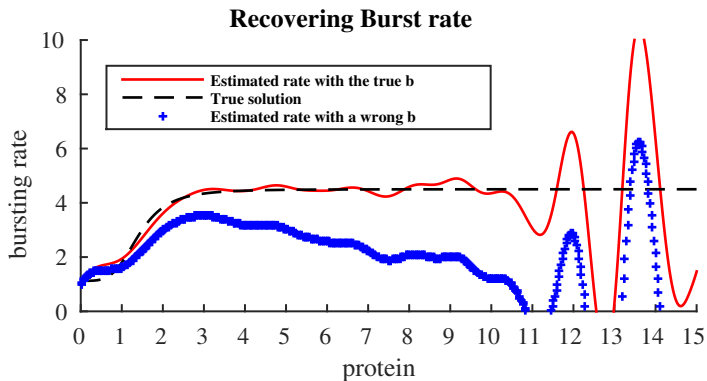
$$\frac{(xu^*(x))'}{u^*(x)} = \frac{\lambda(x)}{\gamma} - \frac{x}{b(x)}.$$

# Simulated data

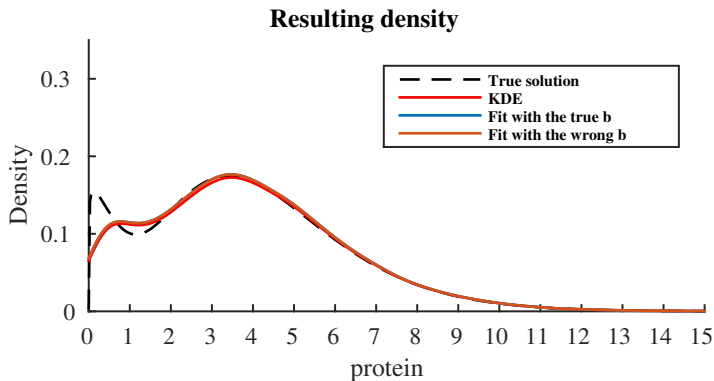
## Density reconstruction by Kernel Density Estimation



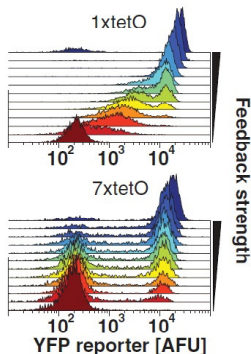
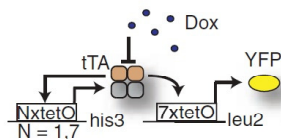
## Inferred bursting rate



# Resulting Probability Density Function



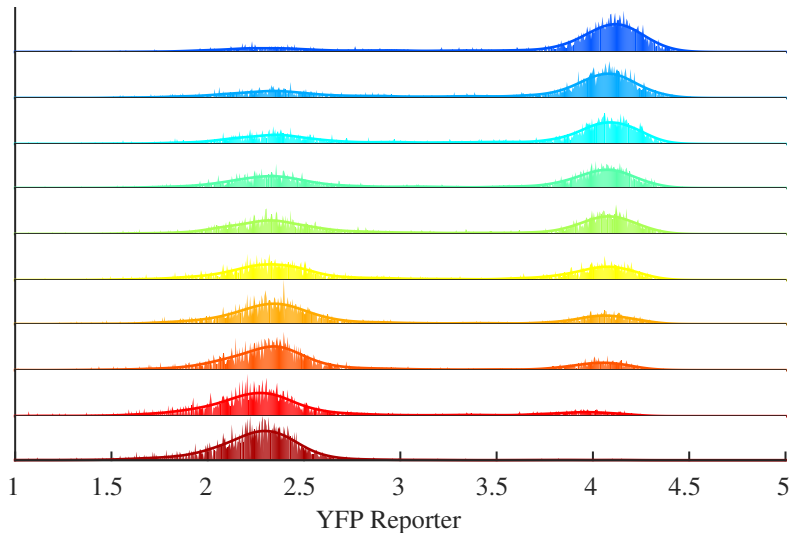
## Single cell data on self-regulating gene



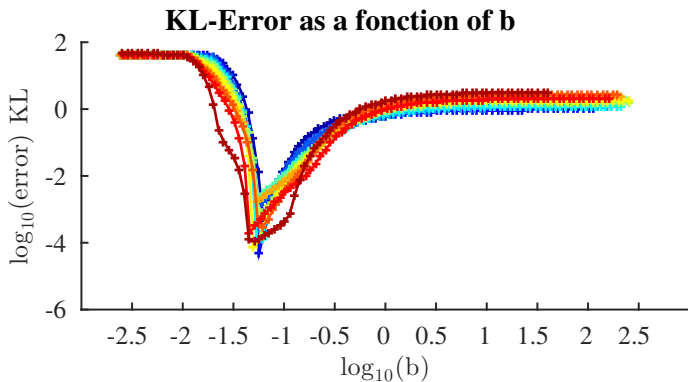
**Noise Can Induce Bimodality in Positive Transcriptional Feedback Loops Without Bistability**  
 Tsz-Leung To, *et al.*  
*Science* **327**, 1142 (2010);  
 DOI: 10.1126/science.1178962

- ▶ Synthetic Tet-Off in budding yeast.
- ▶ Feedback modulated by an external parameter (doxycycline)

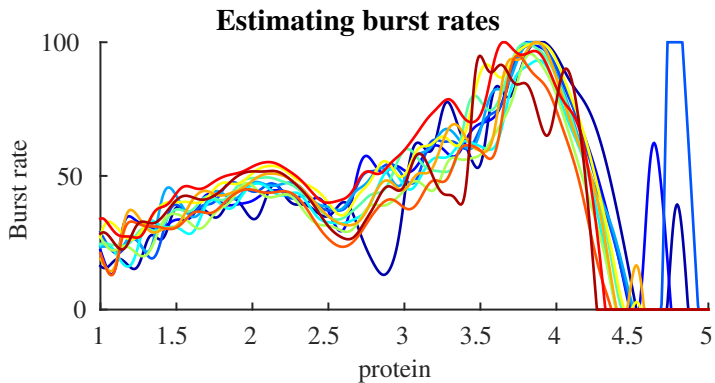
# 1) Kernel Density Estimation



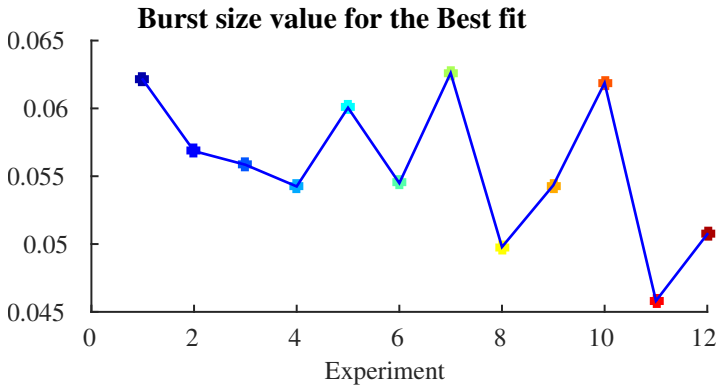
## 2) Finding the 'best' mean burst size (KL distance)



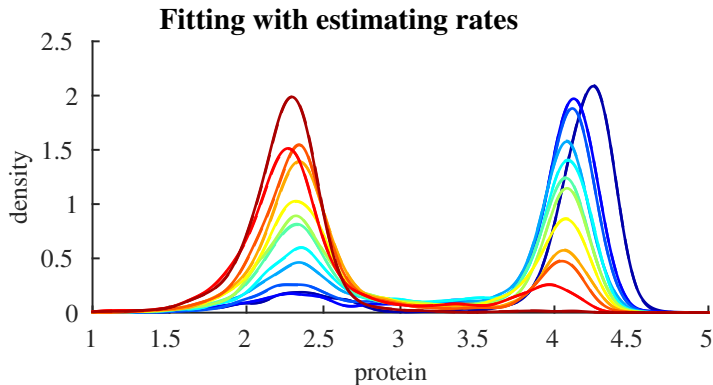
### 3) Inferred burst rate



### 3) Inferred mean burst size



## 4) Resulting Probability Density Function



## Small recap' on the inverse problem

- ▶ With the help of the full solution, we obtained a formula to find the parameter functions from the stationary density.
- ▶ We applied this on simulated and real data.
- ▶ The inverse problem is generally ill-posed (cannot find burst size  $b$  and burst rate  $\lambda$  at the same time).
- ▶ Although the resulting pdf does usually 'fit' the data.
- ▶ Work still on progress...

Merci de votre attention !

- ▶ *Molecular distributions in gene regulatory dynamics*, M.C Mackey, M. Tyran-Kamińska and R.Y., *Journal of Theoretical Biology* (2011) 274 :84-96
- ▶ *Dynamic Behavior of Stochastic Gene Expression Models in the Presence of Bursting*, M.C Mackey, M. Tyran-Kamińska and R.Y., *SIAM Journal on Applied Mathematics* (2013) 73 :1830-1852
- ▶ *Adiabatic reduction of a model of stochastic gene expression with jump Markov process*, R.Y., C. Zhuge, J. Lei, M.C Mackey, *Journal of Mathematical Biology* (2014) 68 :1051-1070