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Bursting in gene expression model

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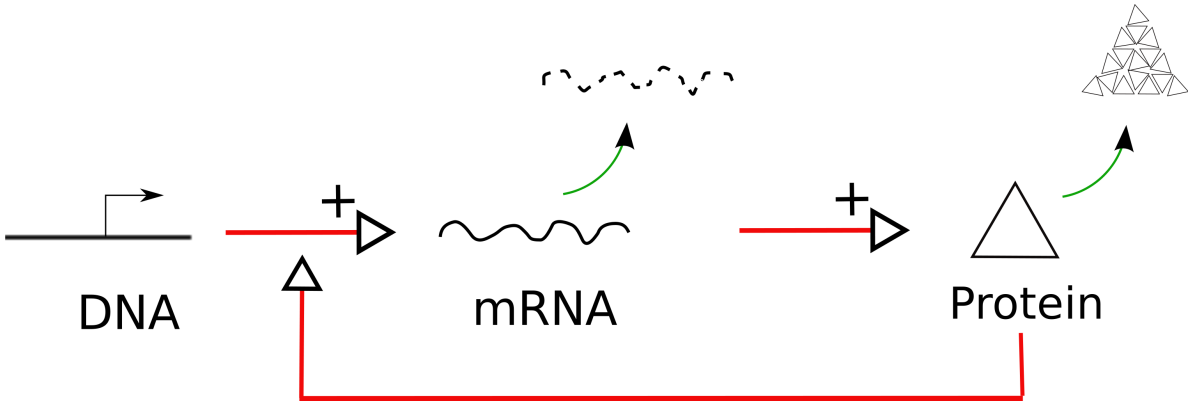
[4]Tsinghua University, China.

Goodwin's deterministic model

Stochastic gene expression model

- Analytical results on a reduced model
- Ongoing work 1) Taking into account division
- Ongoing work 2) Recovering the burst statistics



Crick (1958) : Central Dogma.
Jacob, Perrin, Sánchez, Monod (1960) : Operon.

$$\begin{cases} \dfrac{dM}{dt} &= \lambda_1(E) - \gamma_1 M\,, \\ \dfrac{dI}{dt} &= \lambda_2 M - \gamma_2 I\,, \\ \dfrac{dE}{dt} &= \lambda_3 I - \gamma_3 E\,. \end{cases} \tag{1}$$

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

The transcription rate function λ_1

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

$$R + nE \overset{K_1}{\rightleftharpoons} RE_n\,, \qquad K_1 = \frac{RE_n}{R \cdot E^n}\,,$$

$$O + R \overset{K_2}{\rightleftharpoons} OR\,, \qquad K_2 = \frac{OR}{O \cdot R}\,.$$

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

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

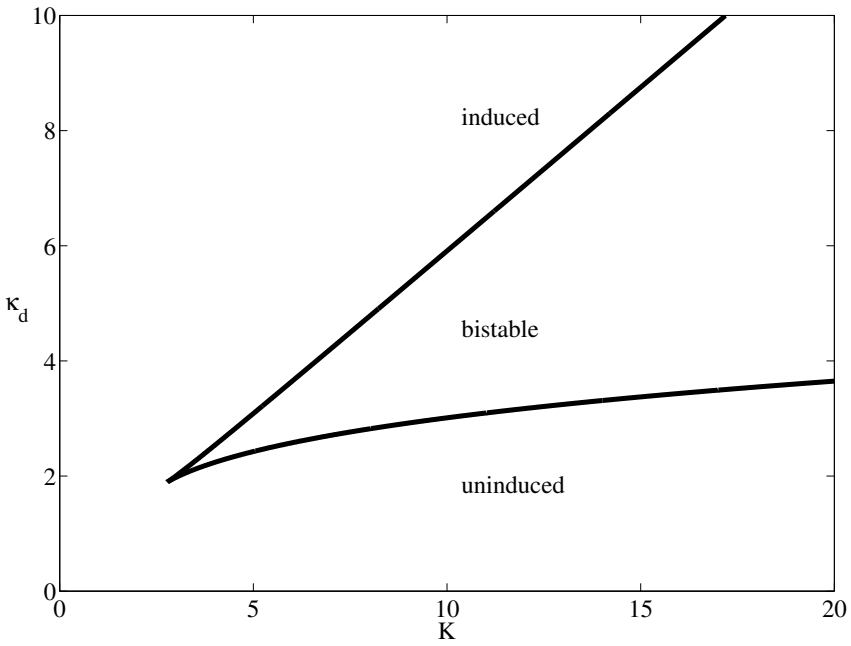
- **Repressible Operon :** Similar but

$$O + RE^n \overset{K_2}{\rightleftharpoons} ORE_n\,, \qquad K_2 = \frac{ORE_n}{O \cdot RE^n}\,.$$

and we get

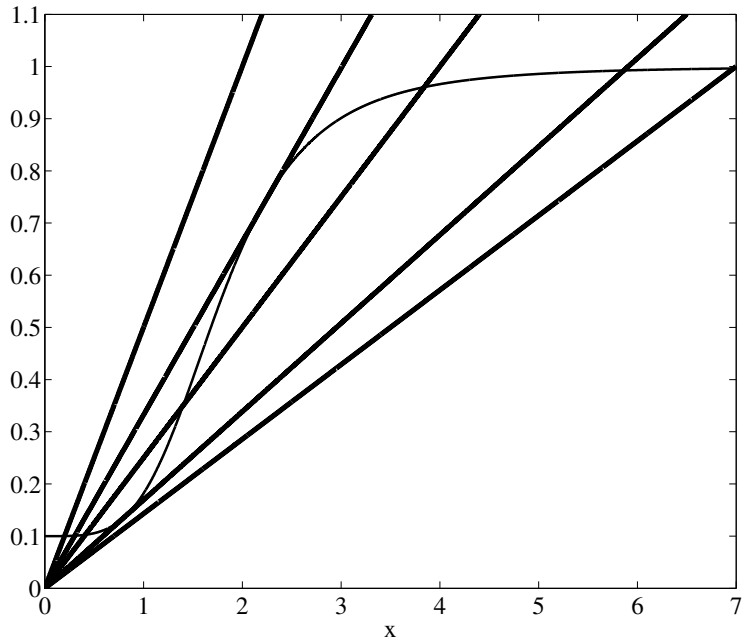
$$\lambda_1(E) \sim \frac{O}{O_{tot}} = \frac{1 + K_1 E^n}{1 + (K_1 + K_2 R_{tot}) E^n}\,. \tag{3}$$

Bifurcation analysis in ODE



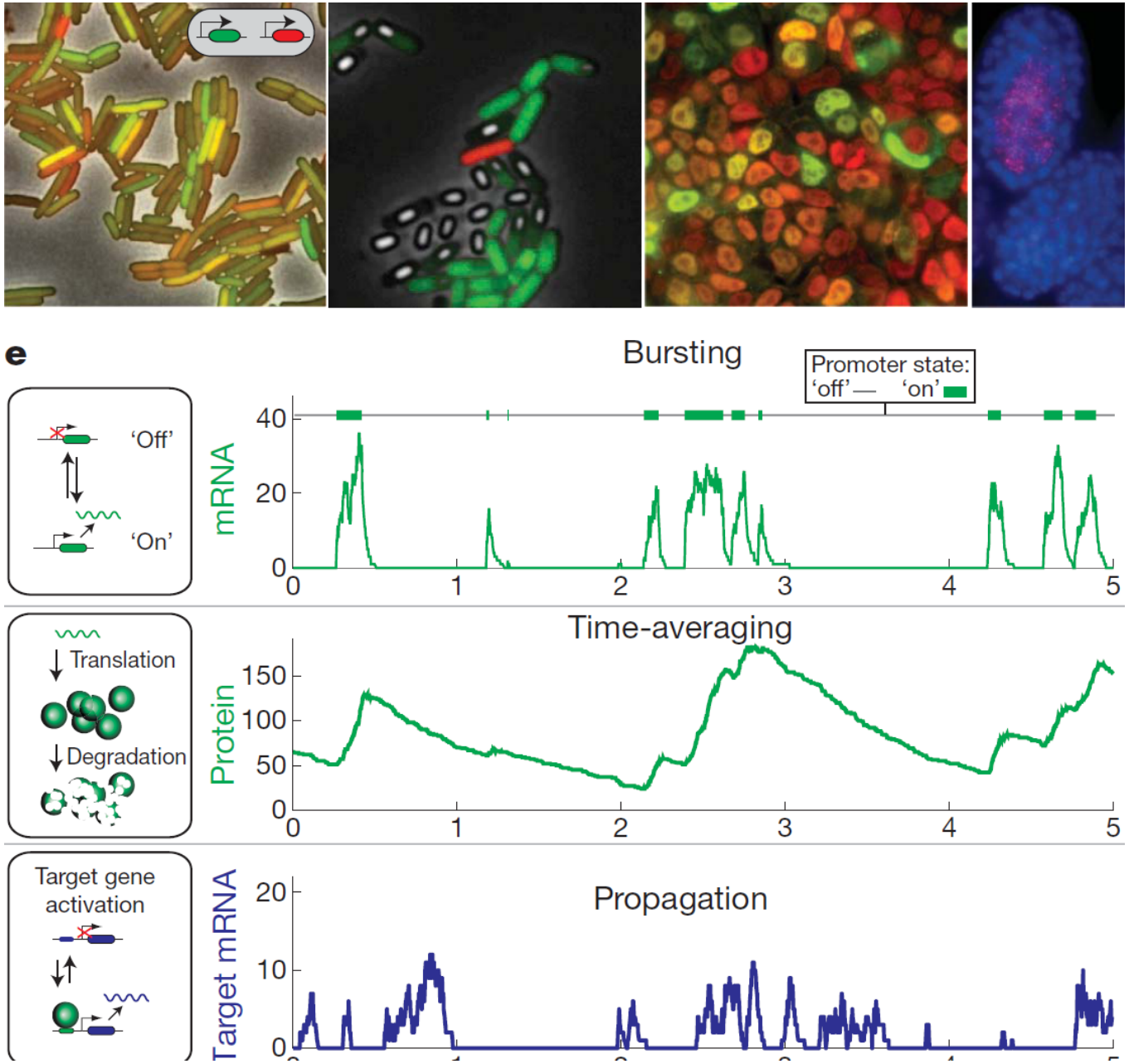
$$\begin{cases} \dfrac{dx_1}{dt} &= \gamma_1[\lambda_1(x_3) - x_1]\,, \\ \dfrac{dx_2}{dt} &= \gamma_2(x_1 - x_2)\,, \\ \dfrac{dx_3}{dt} &= \gamma_3(x_2 - x_3)\,. \end{cases} \tag{4}$$

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

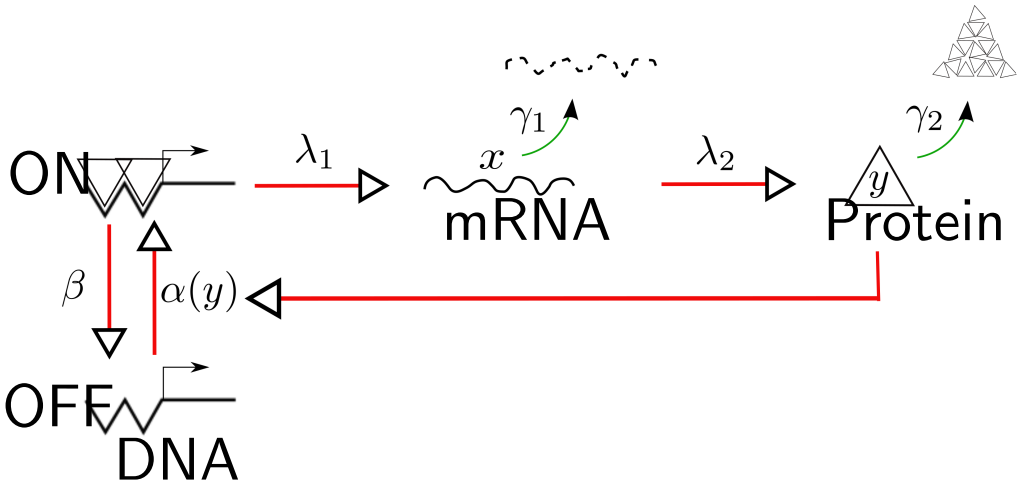


- **Inducible :** Mono-stability or Bi-stability.
- **Repressible :** Mono-stability or limit cycle.

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)...

$$\begin{cases} \dfrac{dx}{dt} = G(t)\lambda_1(y(t)) - \gamma_1 x(t)\,, \\ \dfrac{dy}{dt} = \lambda_2 x(t) - \gamma_2 y(t)\,, \\ (G=0) \underset{\beta(y(t))}{\overset{\alpha(y(t))}{\rightleftharpoons}} (G=1)\,. \end{cases} \tag{5}$$

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

Outline

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Stochastic gene expression model

- Analytical results on a reduced model
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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 $\nu \to_\infty 0$,

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

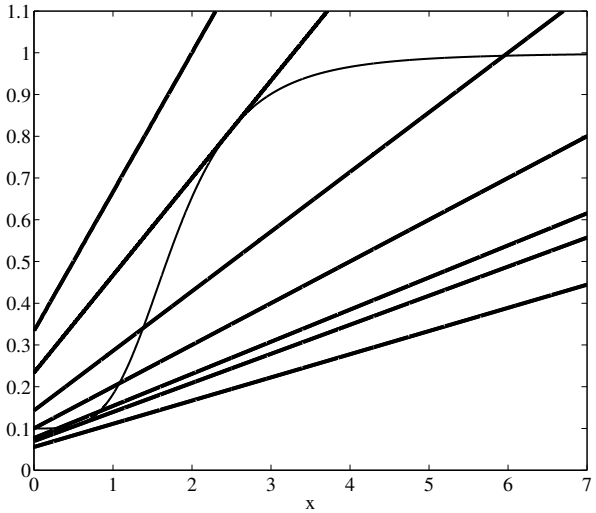
Any stationary distribution satisfies $\int_0^\infty Lf(x)u^*(x)dx = 0$, so that

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

Hence

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

Bifurcation analysis in SDE

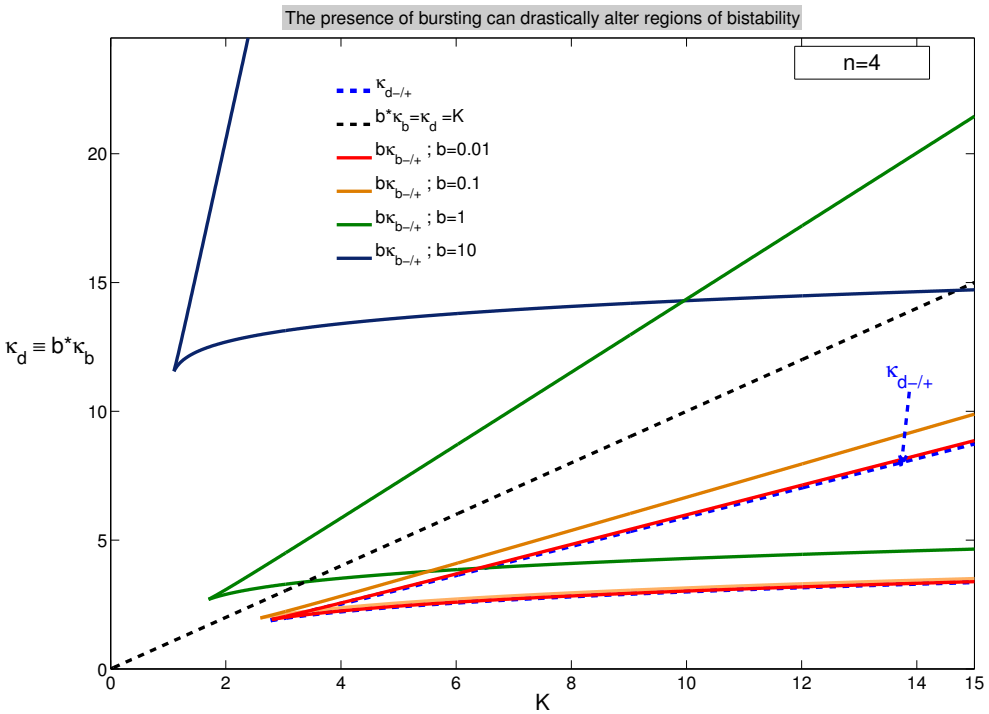


(under technical assumptions...)
$u(t,x)dx = \mathbb{P}\{x(t) \in [x, x+dx)\}$
converges as $t \to \infty$ (in L^1) towards u^*,

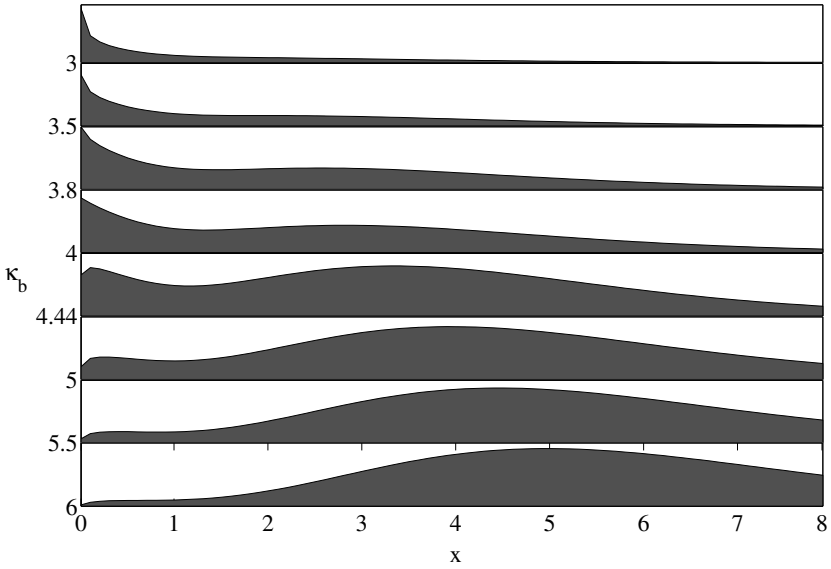
$$\frac{du^*}{dx} = \left[\lambda(x) - \gamma(1 + \frac{x}{b(x)})\right] \frac{u^*(x)}{\gamma x}.$$

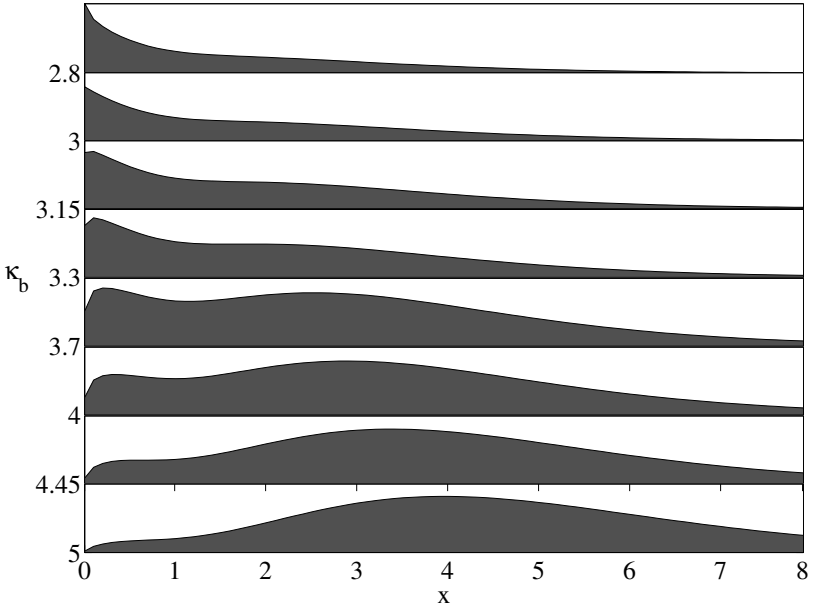
with $b(x) = -\frac{\nu(x)}{\nu'(x)}$. and $\gamma(x) = \gamma x$.

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



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





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

From the 3-stage to the bursting model

$$\begin{cases} \dfrac{dx}{dt} & = & G(t)\lambda_1(y(t)) - \gamma_1 x(t)\,, \\ \dfrac{dy}{dt} & = & \lambda_2 x(t) - \gamma_2 y(t)\,, \\ (G=0) & \underset{\beta(y(t))}{\overset{\alpha(y(t))}{\rightleftharpoons}} & (G=1)\,. \end{cases} \tag{10}$$

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

$$\begin{cases} \dfrac{dy}{dt} & = & G(t)\frac{\lambda_2\lambda_1}{\gamma_1}(y(t)) - \gamma_2 y(t)\,, \\ (G=0) & \underset{\beta(y(t))}{\overset{\alpha(y(t))}{\rightleftharpoons}} & (G=1)\,. \end{cases} \tag{11}$$

$$\begin{cases} \dfrac{dy}{dt} & = & G(t)\frac{\lambda_2\lambda_1}{\gamma_1}(y(t)) - \gamma_2 y(t)\,, \\ (G=0) & \underset{\beta(y(t))}{\overset{\alpha(y(t))}{\rightleftharpoons}} & (G=1)\,. \end{cases} \tag{12}$$

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

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

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**

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

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),

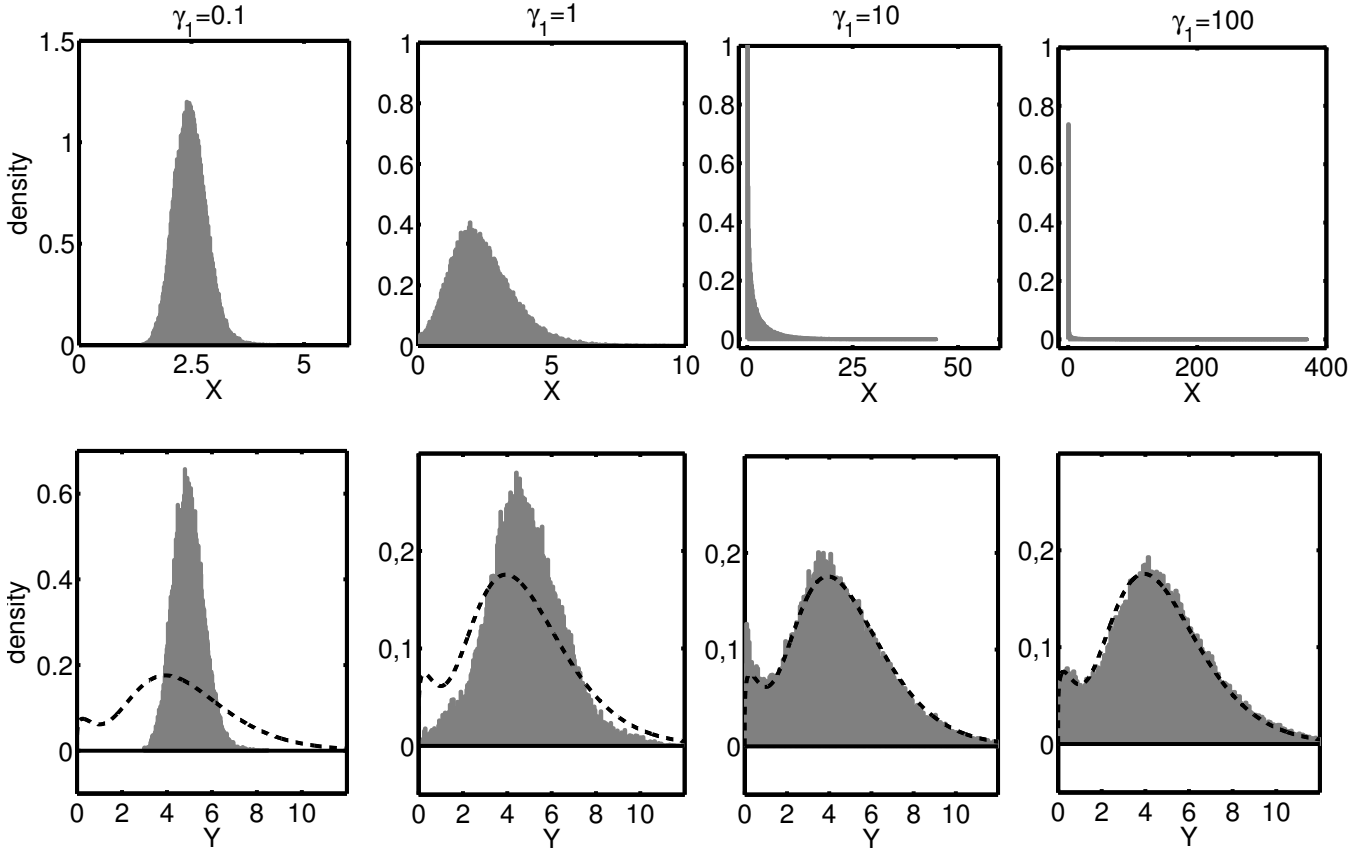
$$\begin{cases} \dfrac{dx}{dt} & = & G(t)\lambda(x(t)) - \gamma x(t)\,, \\ (G=0) & \underset{\beta(x(t))}{\overset{\alpha(x(t))}{\rightleftharpoons}} & (G=1)\,. \end{cases} \tag{14}$$

we have (See Boxma et al. 2005)

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

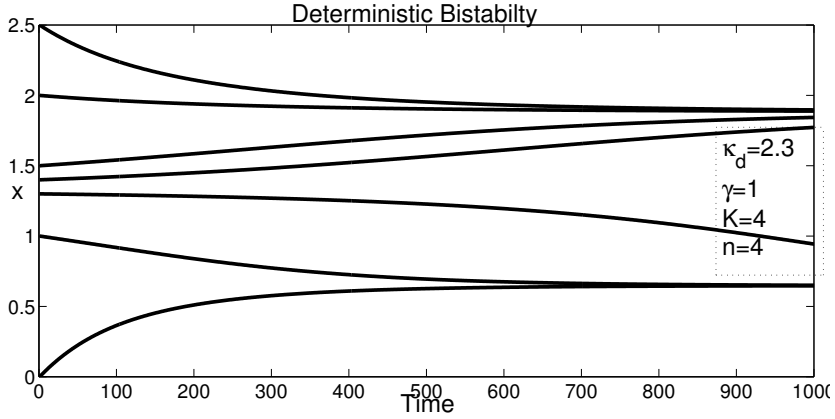
Small recap' on the forward problem (1/2)

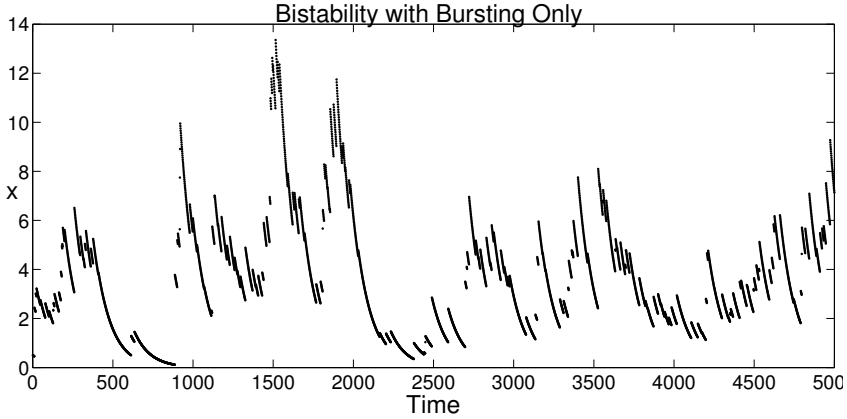
- We performed an adiabatic reduction to make the problem analytical tractable.
- We solved the reduced problem for arbitrary coefficients at equilibrium.
- We performed an (deterministic-analogous) bifurcation study.



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.

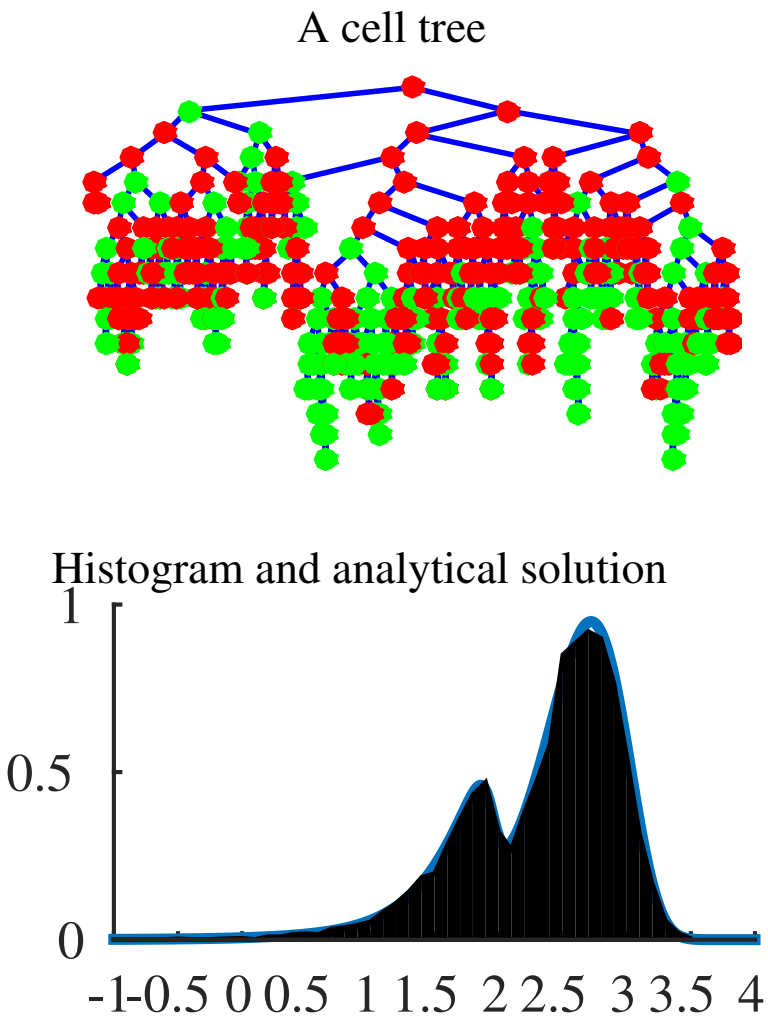
$$Lf(x) = d(x)\int_0^x (f(y) - f(x))\kappa(x,y)dy + \lambda(x)\int_0^\infty (f(x+y) - f(x))h(x,y)dy$$

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

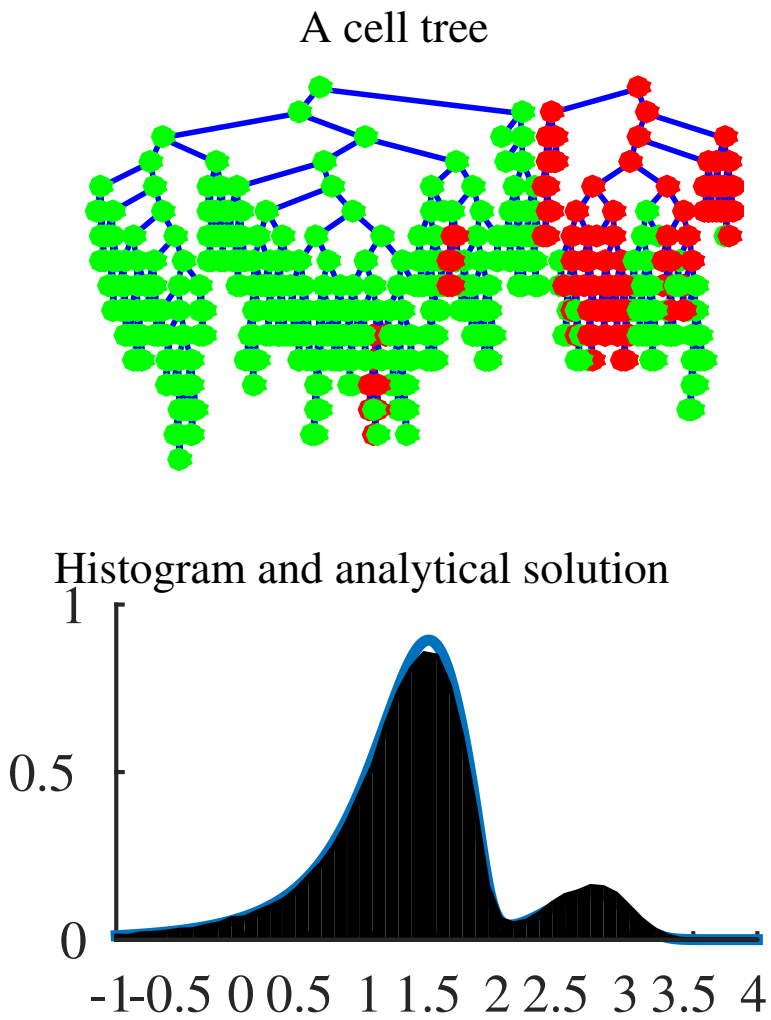
$$\frac{d}{dy}u^* = \left[-\frac{\lambda'(y)+d}{\lambda(y)+d} + \frac{\lambda(y)}{\lambda(y)+d}\left(\frac{1}{x}+\frac{1}{b}\right) - \frac{xb^2}{bx+1} - \frac{1}{x}\right]u^*(y)$$

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

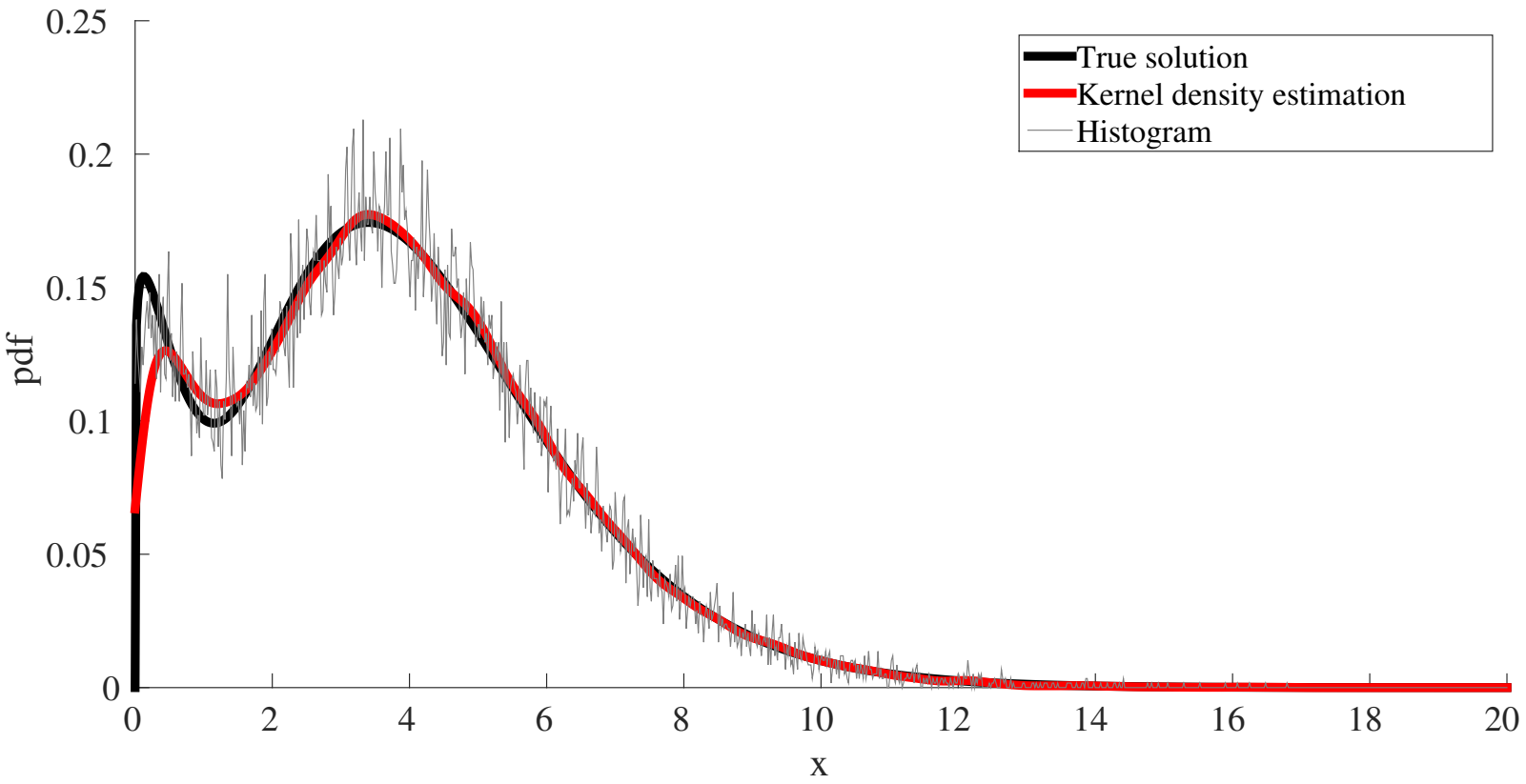
$$\frac{b\lambda}{\gamma} = \mathbb{E}\big[X\big]\,,$$
$$b = \frac{Var(X)}{\mathbb{E}\big[X\big]}\,.$$

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

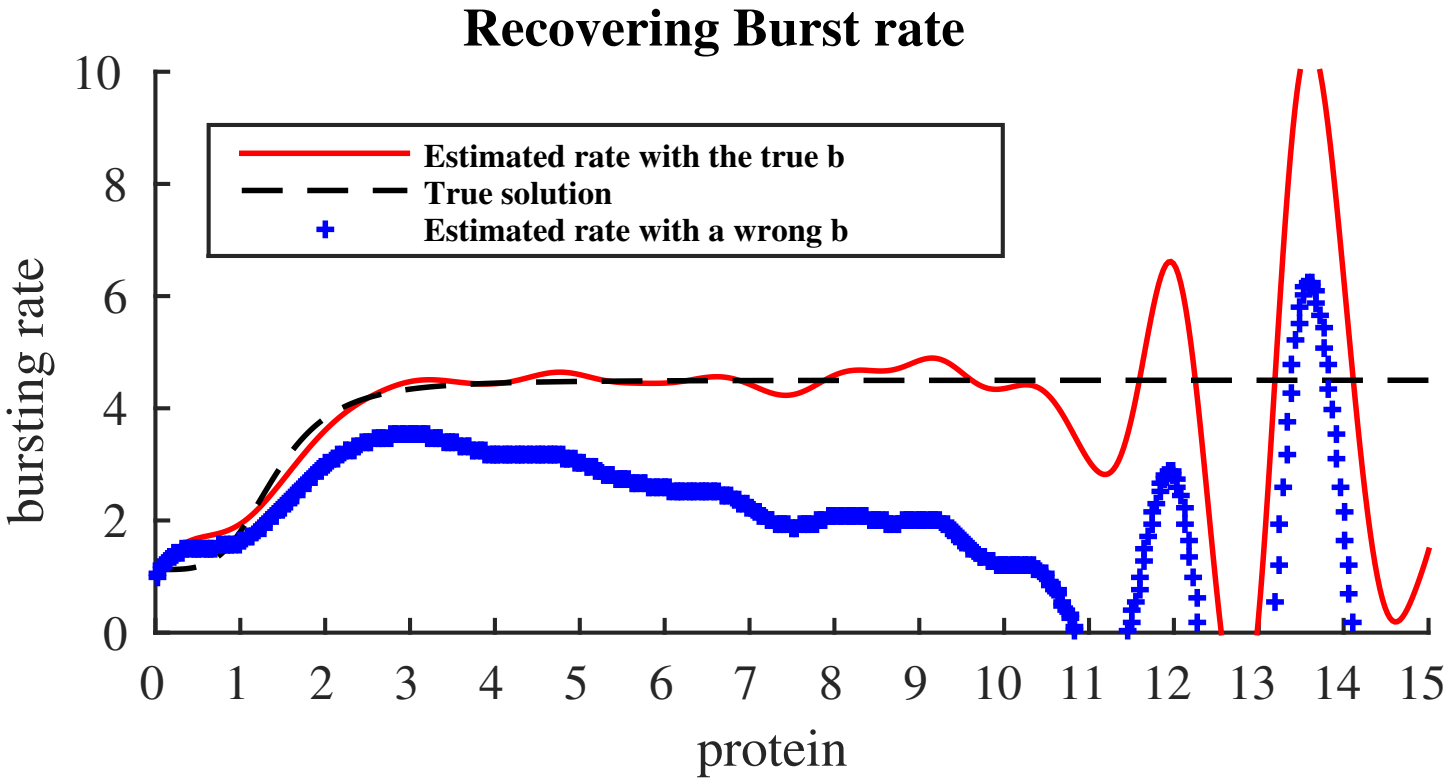
$$\frac{(xu^*(x))'}{u^*(x)} = \frac{\lambda(x)}{\gamma} - \frac{x}{b(x)}\,.$$

Simulated data

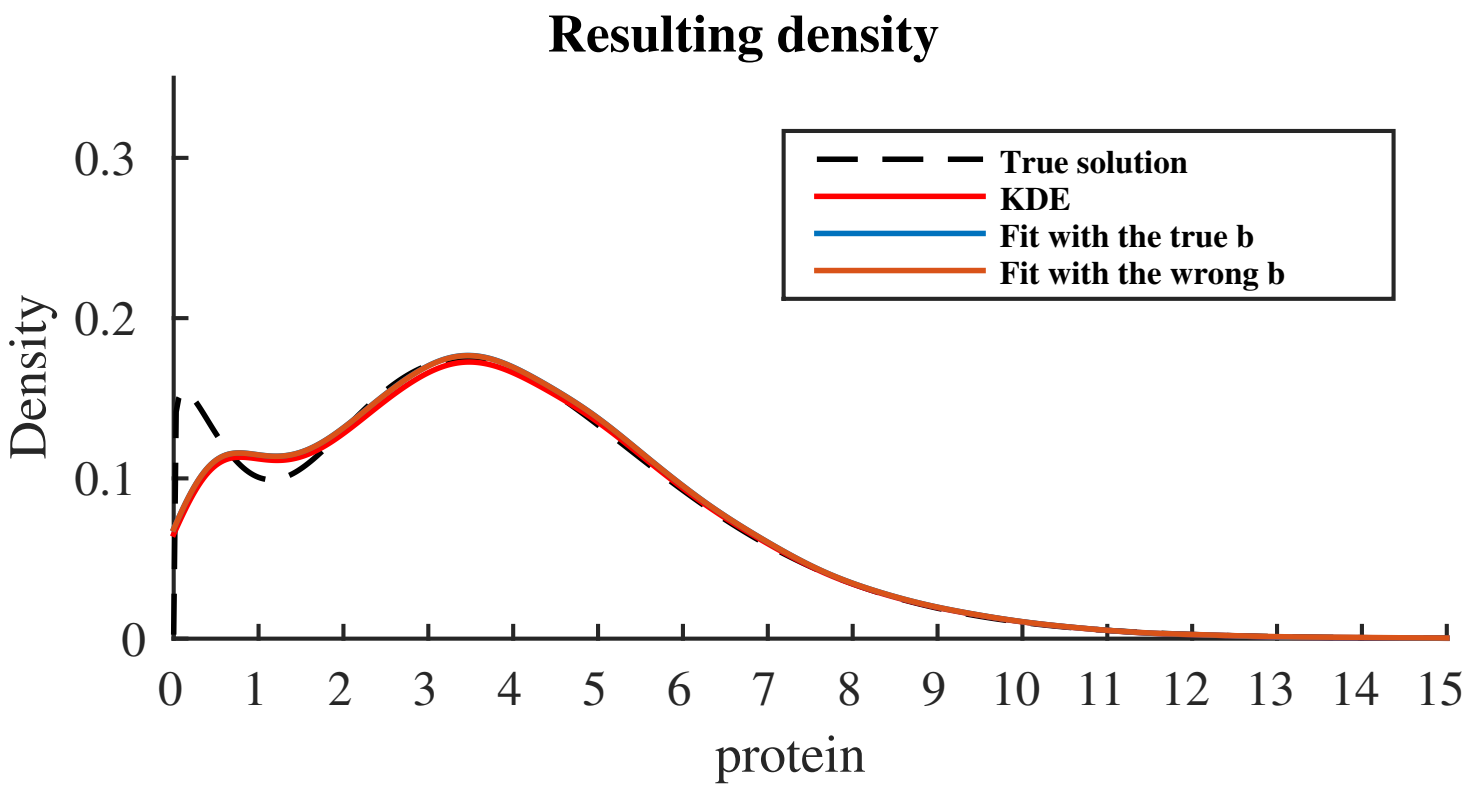
Density reconstruction by Kernel Density Estimation



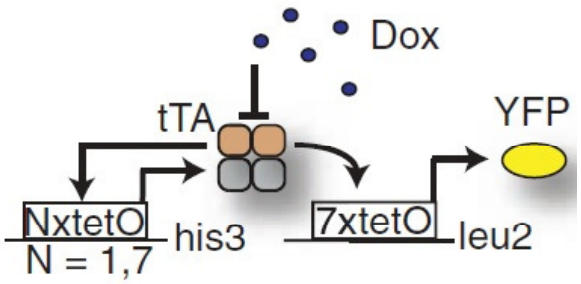
Inferred bursting rate

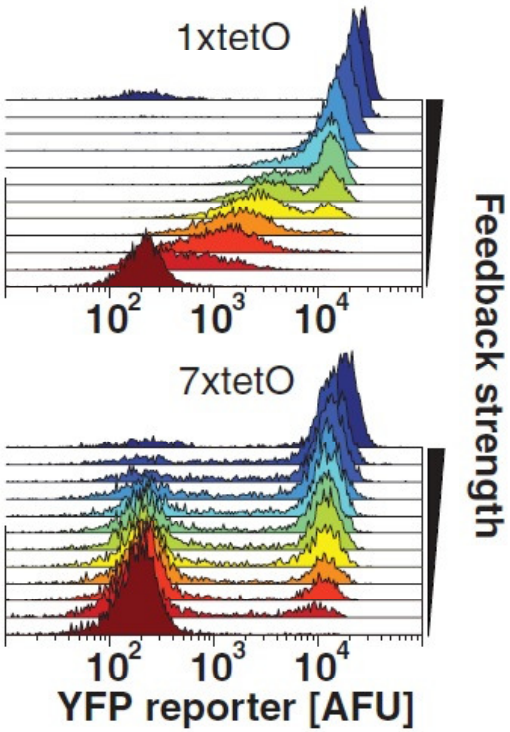


Resulting Probability Density Function



Single cell data on self-regulating gene

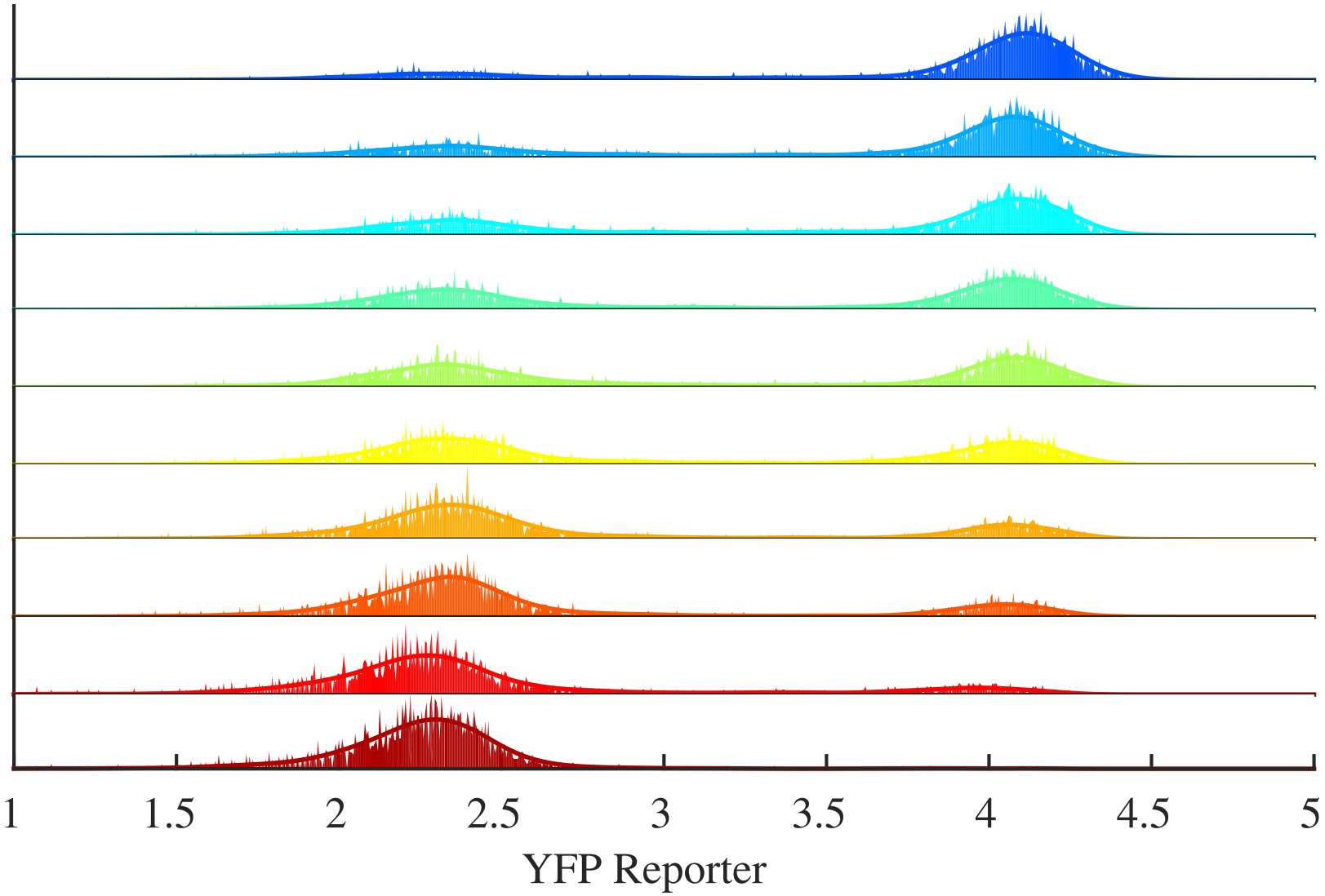




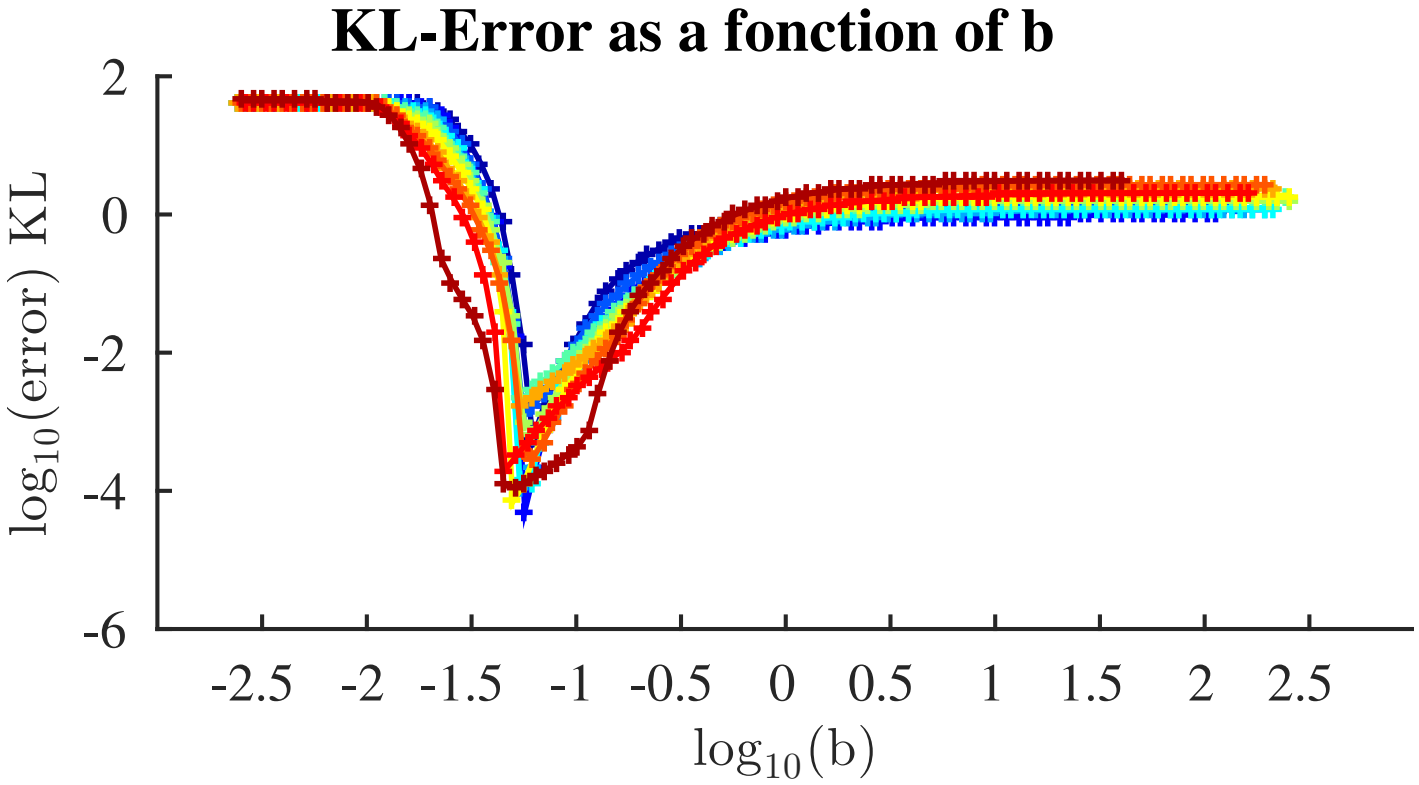
Noise Can Induce Bimodality in Positive Transcriptional Feedback Loops Without Bistability
Tsz-Leung To, *et al.*
Science **327**, 1142 (2010);
DOI: 10.1126/science.1178962

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

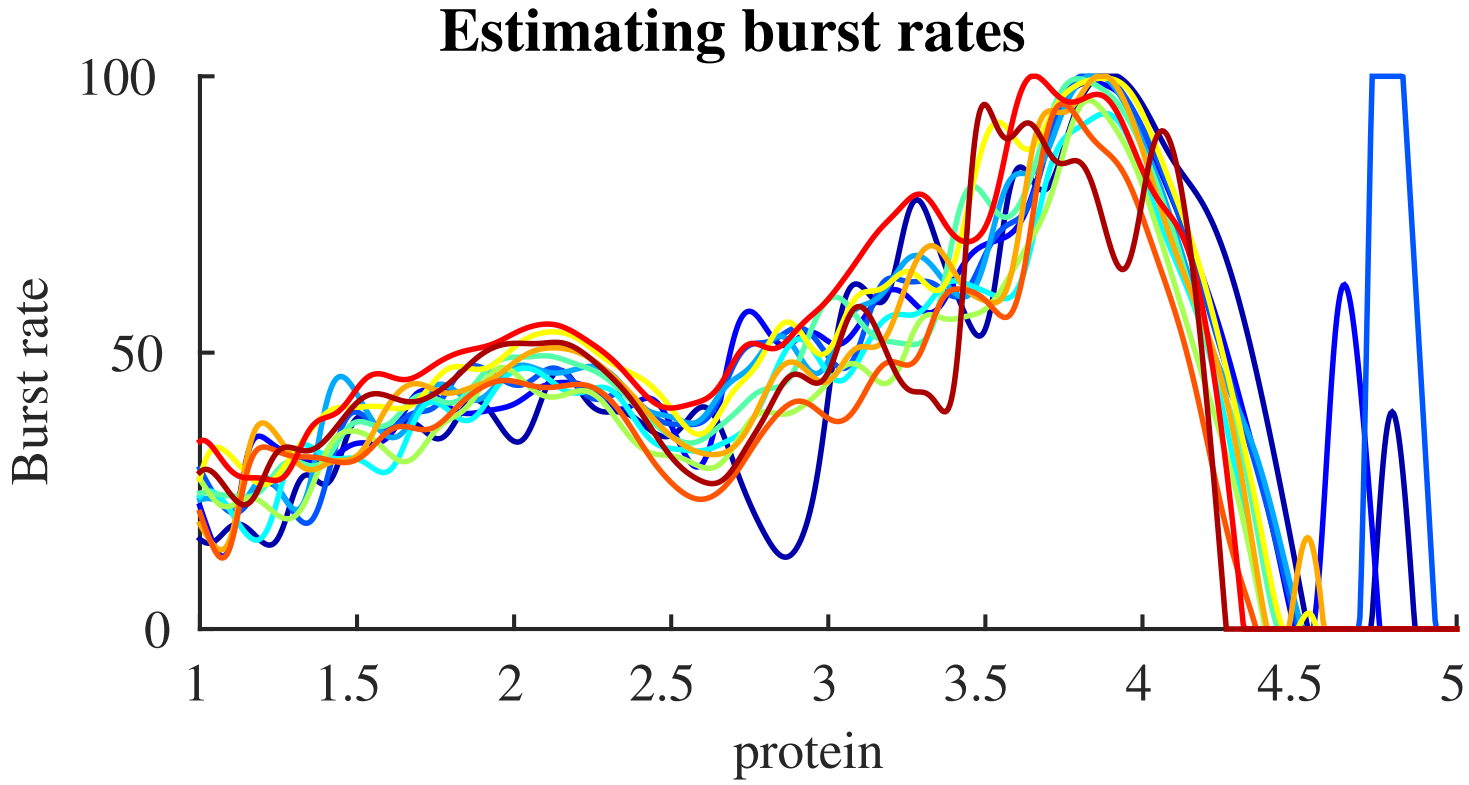
1) Kernel Density Estimation



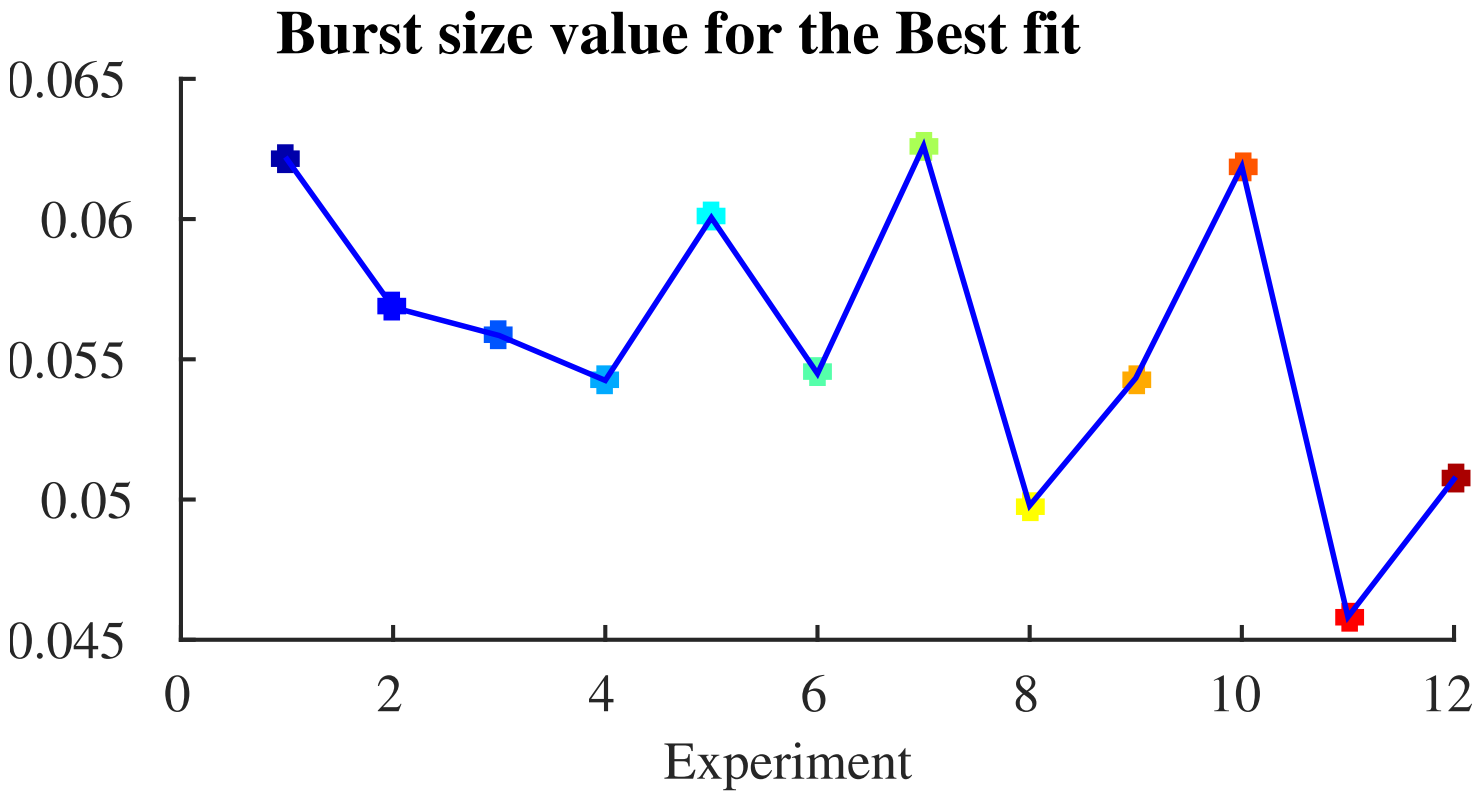
2) Finding the 'best' mean burst size (KL distance)



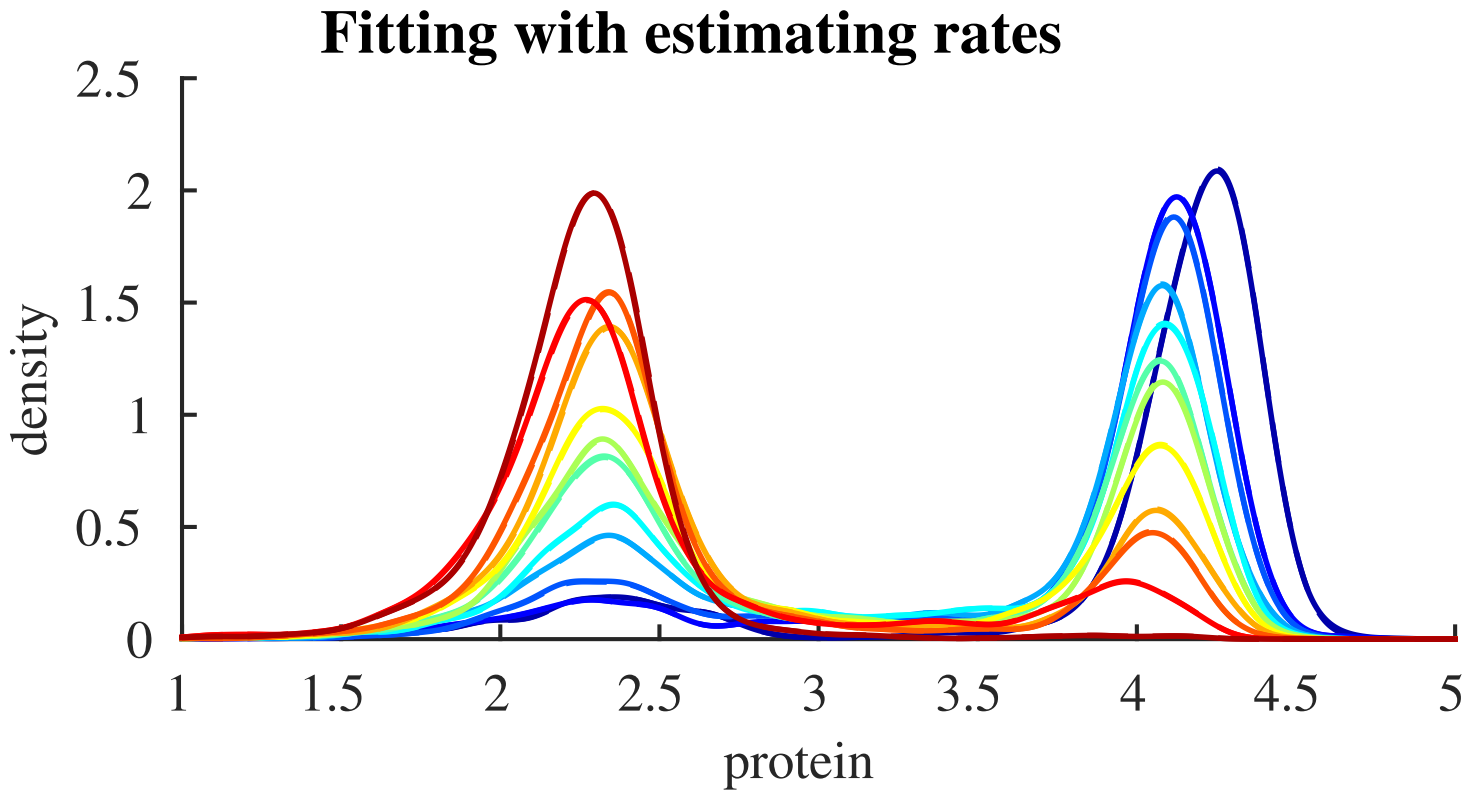
3) Inferred burst rate



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 λ at the same time).
- Although the resulting pdf does usually 'fit' the data.
- Work still on progess...

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