

# Stochastic single gene expression model

**Romain Yvinec<sup>1</sup>, Michael C. Mackey<sup>2</sup>, Marta Tyran-Kamińska<sup>3</sup>, Changjiing Zhuge<sup>4</sup>, Jinzhi Lei<sup>4</sup>**

<sup>1</sup>BIOS group, INRA Tours, France.

<sup>2</sup>McGill University, Canada.

<sup>3</sup>University of Silesia, Poland.

<sup>4</sup>Tsinghua University, China.

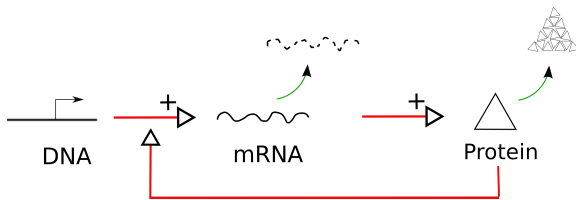
Goodwin's deterministic model

Stochastic gene expression model

Reduced model

Inverse problem

Future work : Taking into account division



*Crick (1958)* : Central Dogma.

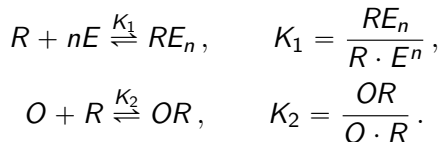
*Jacob, Perrin, Sánchez, Monod (1960)* : Operon.

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

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

# The transcription rate function $\lambda_1$

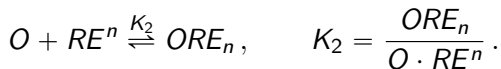
- ▶ **Inducible Operon** : Repressors  $R$  interacts with both the Operator  $O$  and the Effector  $E$ ,



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

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

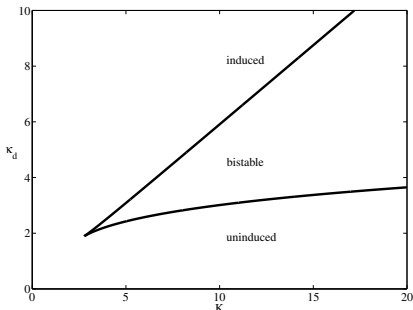
- ▶ **Repressible Operon** : Similar but



and we get

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

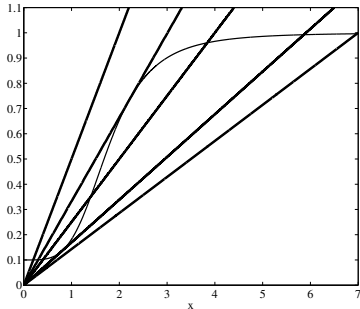
## Bifurcation analysis in ODE



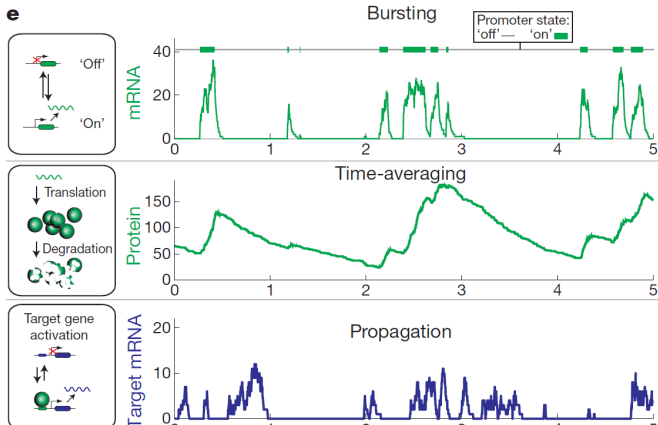
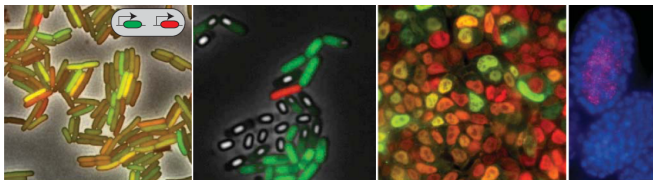
- ▶ **Inducible** : Mono-stability or Bi-stability.
- ▶ **Repressible** : Mono-stability or limit cycle.

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

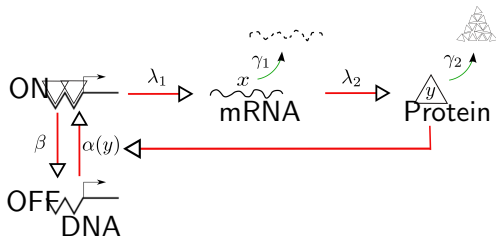
Here  $f(x) = \kappa_d \frac{1 + x^n}{K + x^n}$ .



## 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)...

# Outline

Goodwin's deterministic model

Stochastic gene expression model

Reduced model

Inverse problem

Future work : Taking into account division



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

- ▶ If the gene switching rates are fast ( $\alpha, \beta \rightarrow \infty$ ), we recover the Goodwin's model (no gene noise).
- ▶ If the mRNA lifetime is short ( $\gamma_1 \rightarrow \infty$ ), we can perform an **adiabatic** reduction ( $x(t) \approx G(t) \frac{\lambda_1}{\gamma_1}(y(t))$ ) :

$$\left\{ \begin{array}{l} \frac{dy}{dt} = G(t) \frac{\lambda_2 \lambda_1}{\gamma_1}(y(t)) - \gamma_2 y(t), \\ (G = 0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G = 1). \end{array} \right. \quad (6)$$

$$\left\{ \begin{array}{l} \frac{dy}{dt} = G(t) \frac{\lambda_2 \lambda_1}{\gamma_1} (y(t)) - \gamma_2 y(t), \\ (G = 0) \xrightleftharpoons[\beta(y(t))]{\alpha(y(t))} (G = 1). \end{array} \right. \quad (7)$$

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

$$\frac{dy}{dt} = Z(t) - \gamma_2 y(t), \quad (8)$$

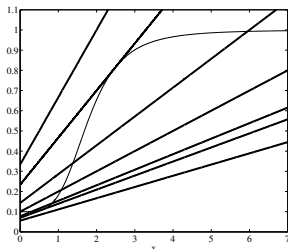
where  $Z = \sum_i Z_i \delta_{T_i}$  is a jump process, of jump rate  $\alpha(y(t))$  and jump size distribution

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

### 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.

## Bifurcation analysis in SDE

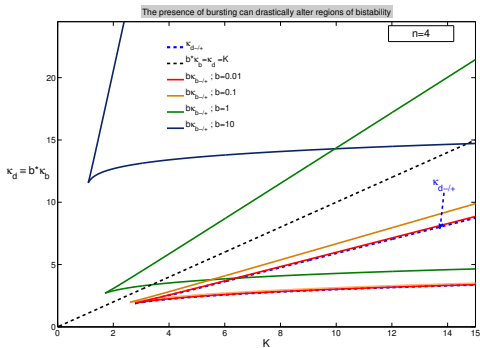


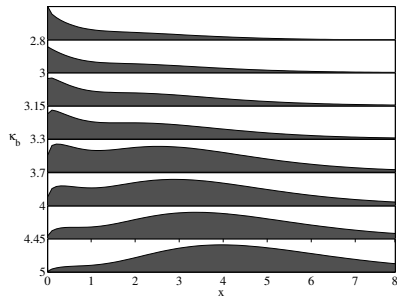
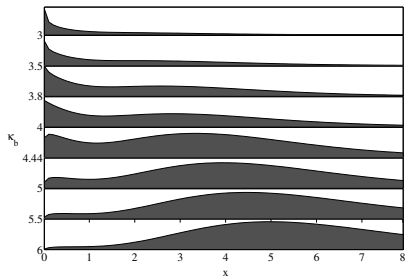
- ▶ **Inducible :**  
Uni-modal or Bi-modal.
- ▶ **Repressible :**  
Uni-modal.

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

$$\frac{du^*}{dy} = \left[ \alpha(y) - \gamma_2 \left(1 + \frac{y}{b(y)}\right) \right] \frac{u^*(y)}{\gamma_2 y}.$$

Here  $\alpha(y) = \kappa_b \frac{1 + y^n}{K + y^n}$ , and  $b(y) = b$ .

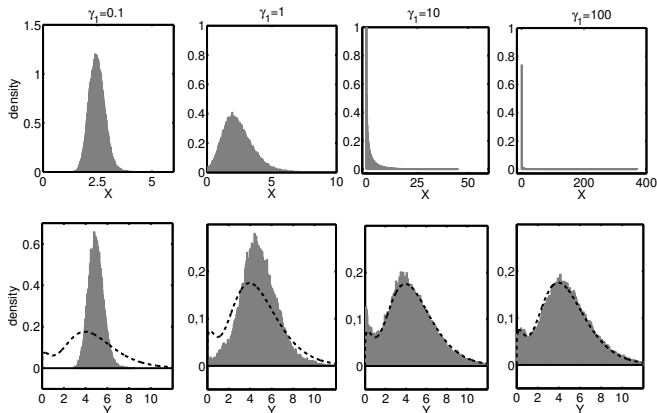


Stationary distribution  $(\alpha, \gamma, b) \Rightarrow (u^*)$ 

Here  $\alpha(y) = \kappa_b \frac{1 + y^n}{K + y^n}$  and  $b(y) = b$ .

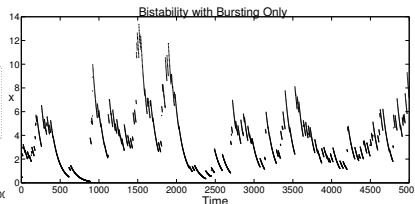
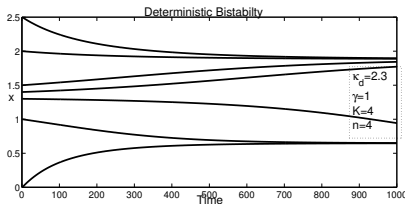
## Small recap' on the forward problem (1/2)

- ▶ 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 bimodality are in fact quite different



Goodwin's deterministic model

Stochastic gene expression model

Reduced model

**Inverse problem**

Future work : Taking into account division

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

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

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

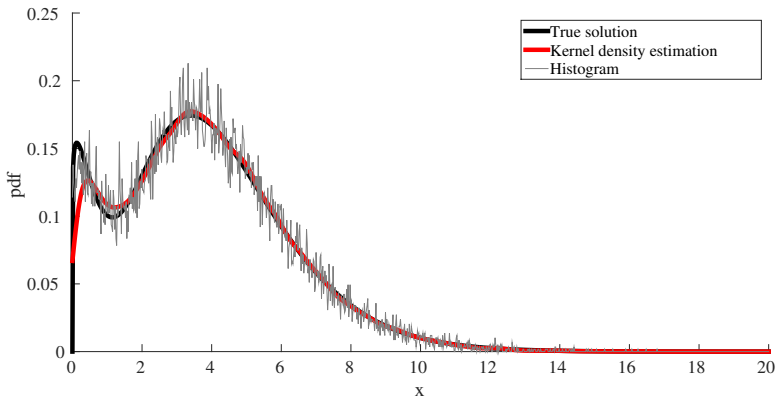
For an auto-regulated gene, we can inverse the formula for the stationary pdf :

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

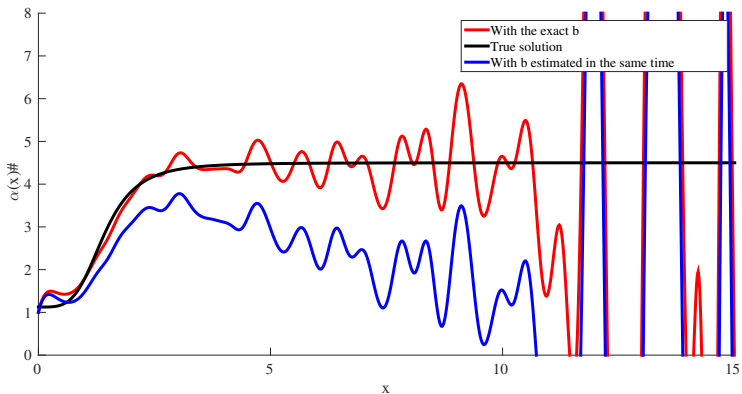


# Simulated data

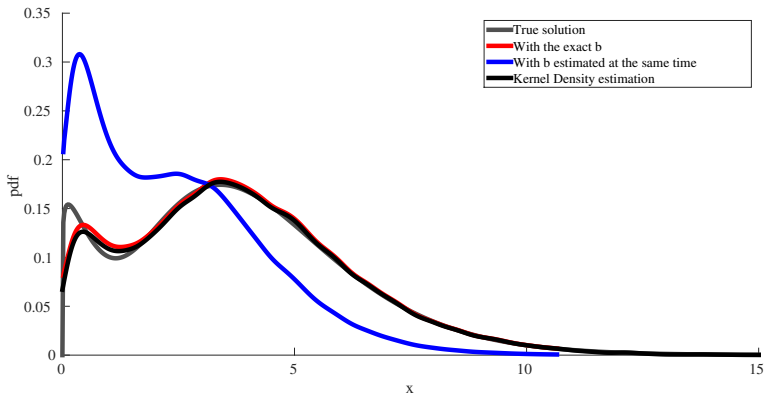
## Density reconstruction by Kernel Density Estimation



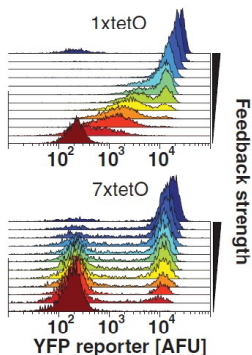
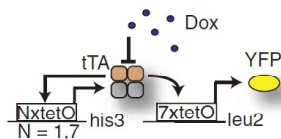
# Inferred bursting rate



# Resulting Probability Density Function



## Single cell data on self-regulating gene



### Noise Can Induce Bimodality in Positive Transcriptional Feedback Loops Without Bistability

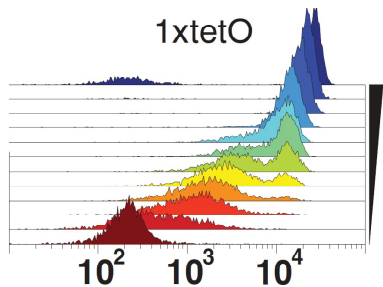
Tsz-Leung To, *et al.*

*Science* 327, 1142 (2010);

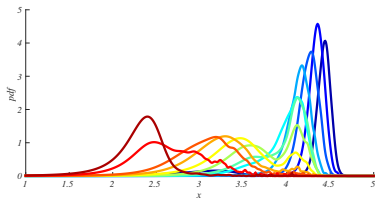
DOI: 10.1126/science.1178962

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

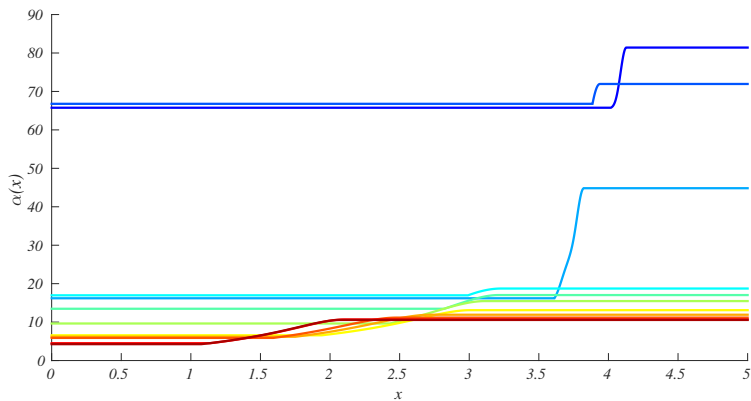
Single cell data on  
self-regulating gene



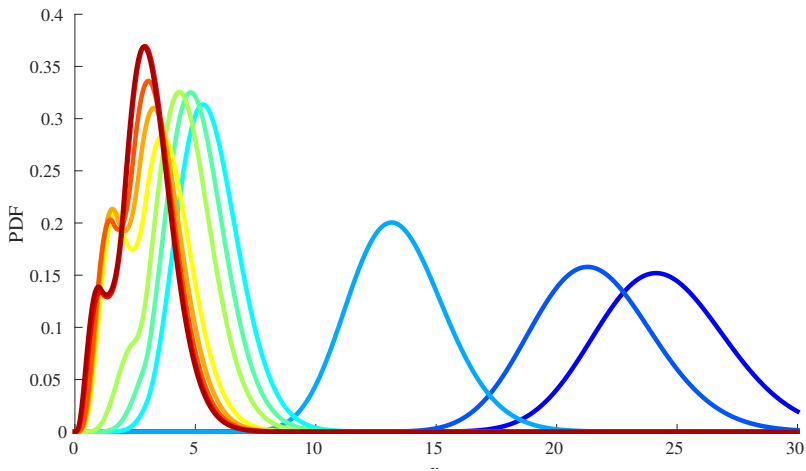
Smoothed pdf obtained by  
kernel density estimation



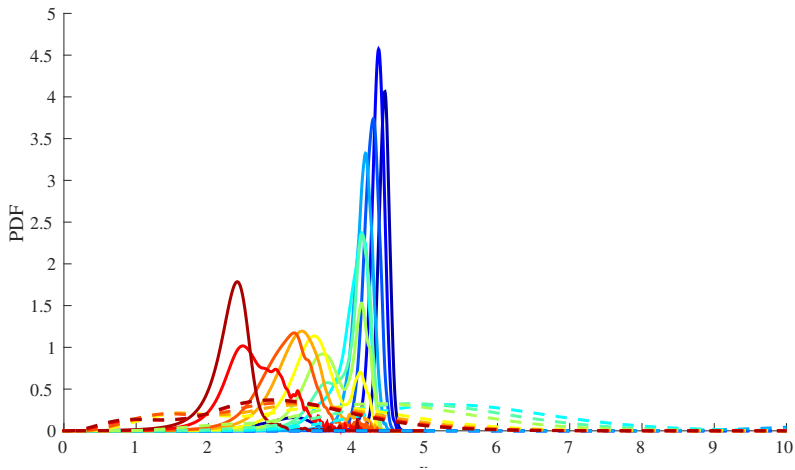
# Inferred bursting rate



# Resulting Probability Density Function



# Does that Fit? Can do better!





## 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 seems generally ill-posed (cannot find burst size  $b$  and burst rate  $\alpha$  at the same time).
- ▶ If the resulting pdf does not 'fit' the data, it may be a good reason to rule out this model.
- ▶ Work still on progress...

# Outline

Goodwin's deterministic model

Stochastic gene expression model

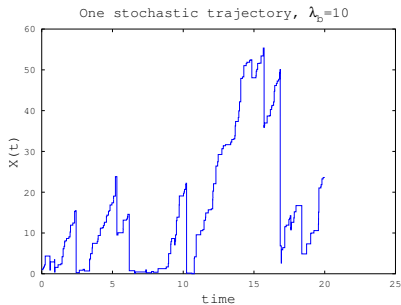
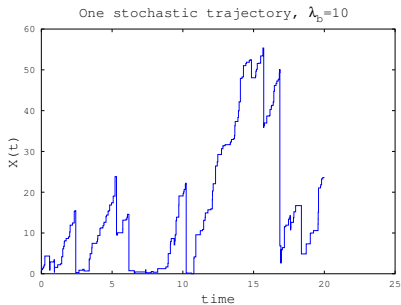
Reduced model

Inverse problem

Future work : Taking into account division

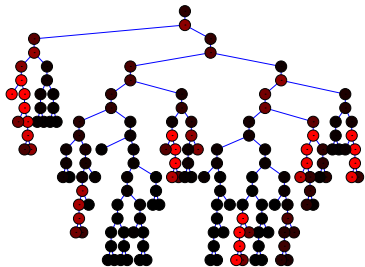
Similar results may be obtained for a continuous growth division model or a bursting-division model. For instance, with uniform repartition kernel, constant division rate  $d$  and constant burst size  $b$ ,

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

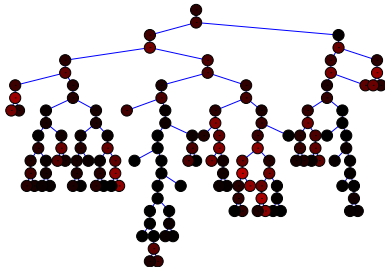


This may be used to predict the long time behavior of a dividing cell population

A cell tree,  $\lambda_D=10$

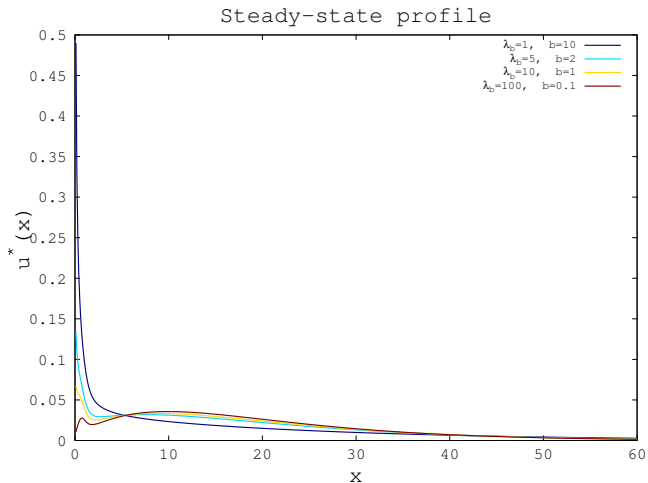


A cell tree,  $\lambda_D=100$



- ▶ Inverse problems may be adapted to genealogical tree data (*Doumic et al. 2014, Krell 2014*)

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



- ▶ Such framework can be used to study **non-linear** population model...

Vielen Dank !

- ▶ *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