Stochastic modelling of gene regulatory networks

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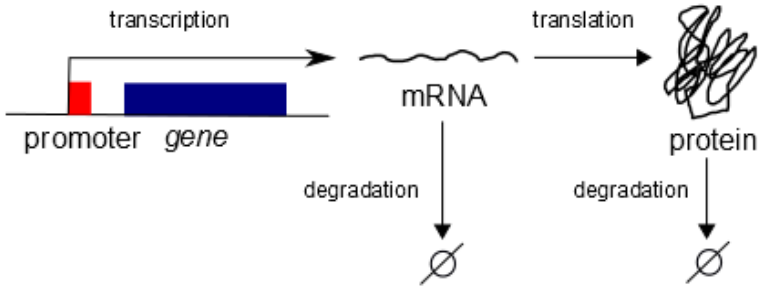
Gene expression

- Typically, and simplifying quite a bit, **gene expression** in bacteria involves:
  - Transcription by RNAP (mRNA)
  - Translation by ribosomes (proteins)
  - Degradation of mRNA and protein

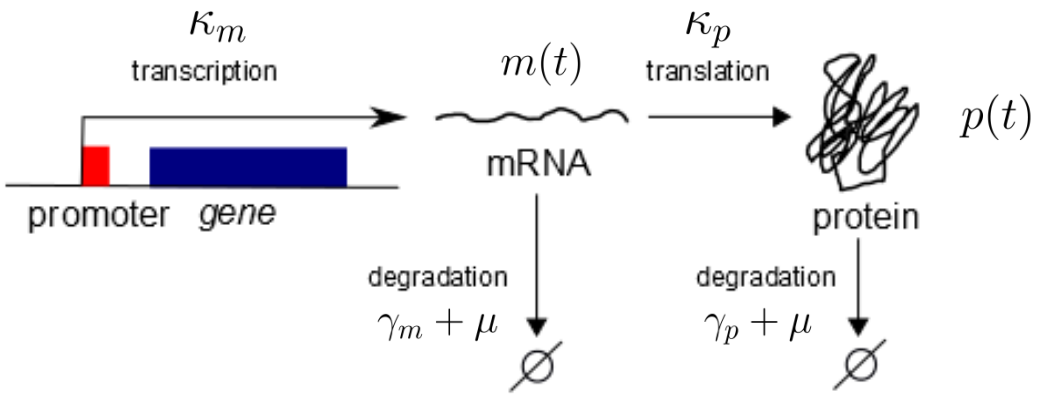


Modeling of gene regulatory networks

- ODE model of gene expression, distinguishing **transcription** and **translation**

$$\dot{m} = \kappa_m - (\gamma_m + \mu)\, m$$

$$\dot{p} = \kappa_p\, m - (\gamma_p + \mu)\, p$$



$m(t) \geq 0$, concentration mRNA

$p(t) \geq 0$, concentration protein

$\kappa_m, \kappa_p > 0$, synthesis rate constants

$\gamma_m, \gamma_p > 0$, degradation rate constants

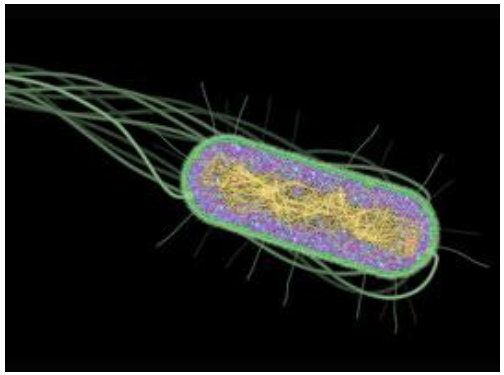
$\mu \geq 0$, growth rate

Stochasticity in gene expression

- ODE models make abstraction of underlying biochemical reaction processes involved in gene expression that may not be warranted

Kaern *et al.* (2005), *Nat. Rev. Genet.*, 6(6):451-464

- Gene expression is **stochastic** instead of **deterministic** process
  - Underlying biochemical reactions are stochastic processes
  - Probability of reaction to occur depends on random encounters of molecules in cell



Goodsell (2010), *The Machinery of Life, Springer,* 2nd ed.

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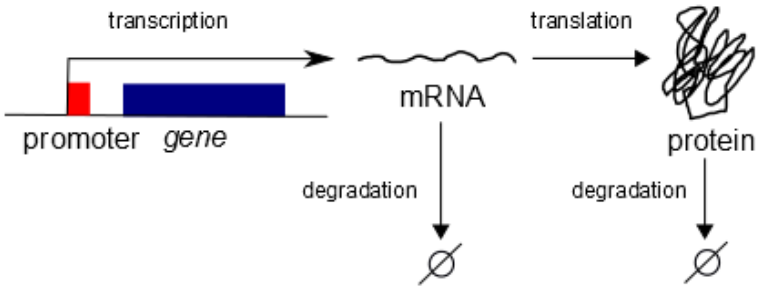
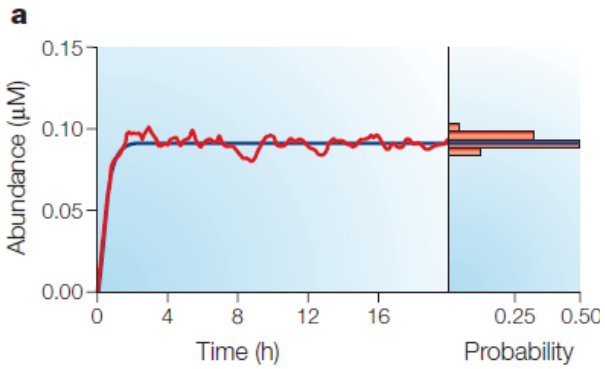
- **Discrete** number of molecules of reaction species, instead of **continuous** concentrations

  Some reactions species involved in gene expression have very low copy numbers (1-10)

Stochasticity in gene expression

- Stochasticity in gene expression leads to **noise**
  - Fluctuations in mRNA and protein concentrations





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Stochasticity in gene expression

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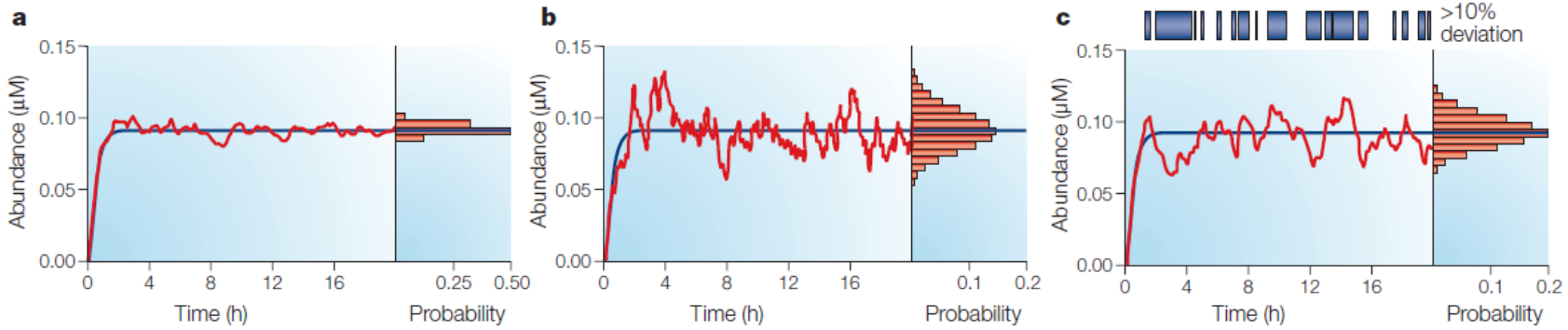
  - Fluctuations in mRNA and protein concentrations
- Noise amplified by small number of molecules



Decrease in number of mRNA and protein molecules wrt **a**

Decrease in number of mRNA molecules wrt **a**, for same number of protein molecules

Kaern *et al.* (2005), *Nat. Rev. Genet.*, 6(6):451-464

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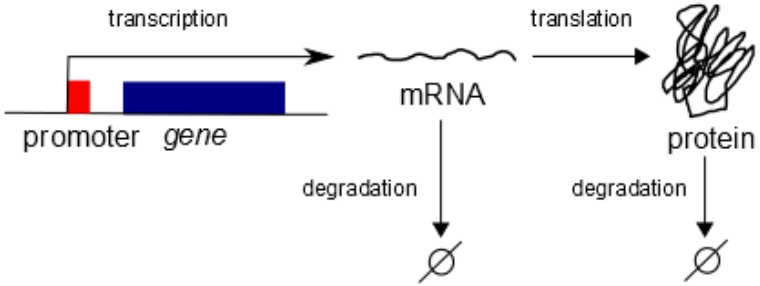

- Different types of noise:
  - **Intrinsic noise:** fluctutations due to stochasticity of processes involved in gene expression (transcription, translation, …)

Stochasticity in gene expression

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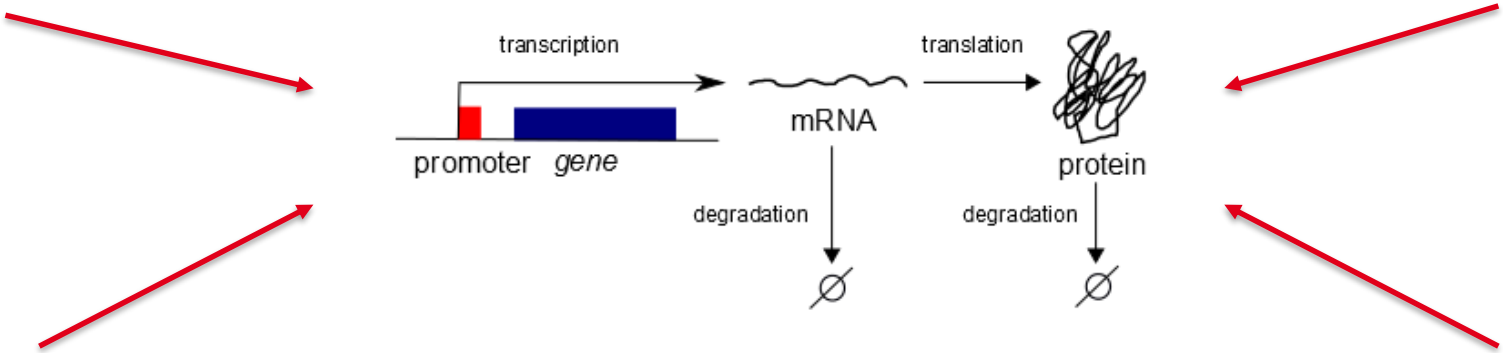
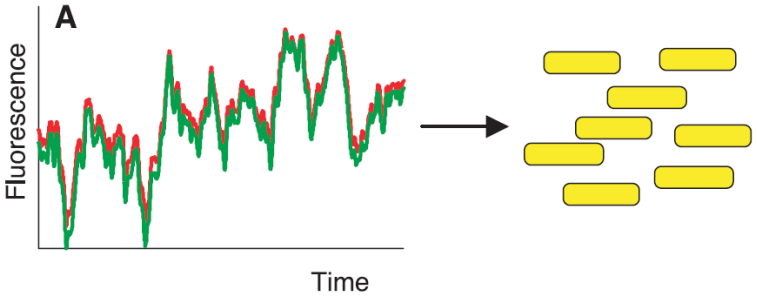


- Different types of noise:
  - **Intrinsic noise:** fluctutations due to stochasticity of processes involved in gene expression (transcription, translation, …)
  - **Extrinsic noise:** fluctuations due to variability in external factors (temperature, ribosome availability, …). Impact on rate constants.

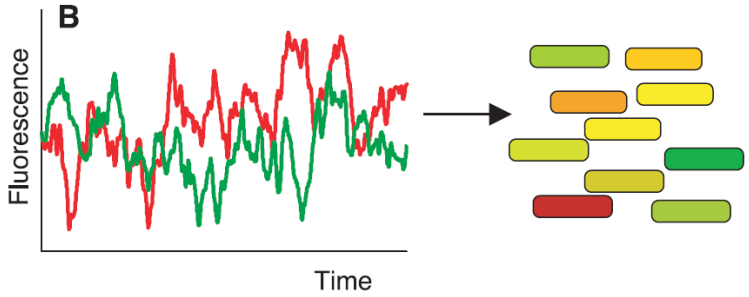
Stochasticity in gene expression

- Experimental discrimination between intrinsic and extrinsic noise

  Expression in a single cell with two different reporter genes (*gfp* and *cfp*) controlled by same promoter



No intrinsic noise, so relative amount of both proteins is constant over time and across individual cells in population



Intrinsic noise, so relative amount of both proteins varies over time and across individual cells in population

Elowitz *et al.* (2002), *Science*, 297(5584):1183-6

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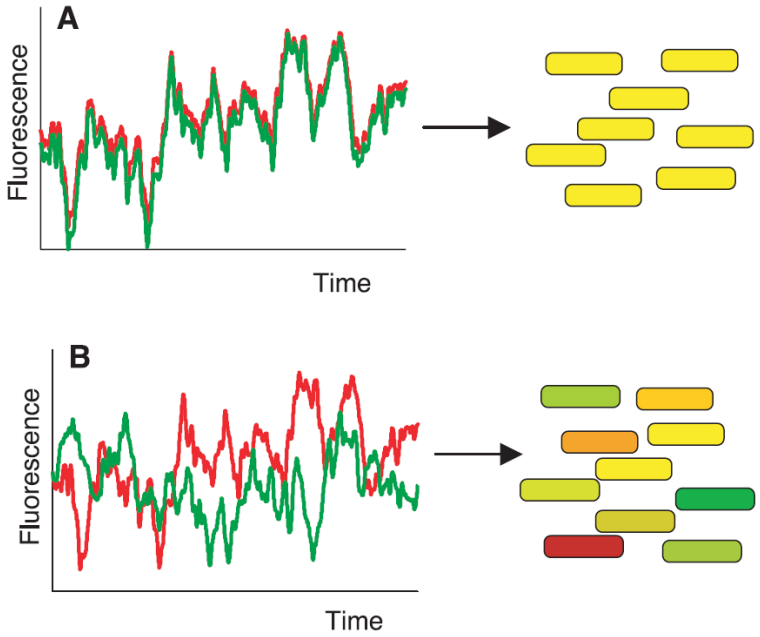

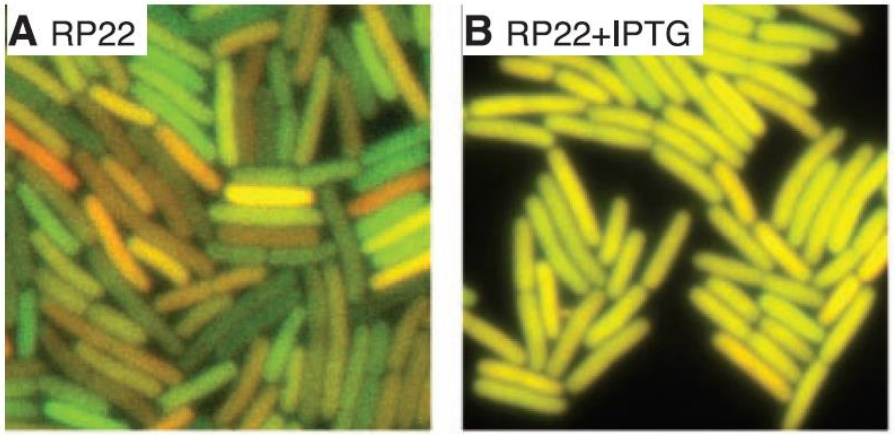

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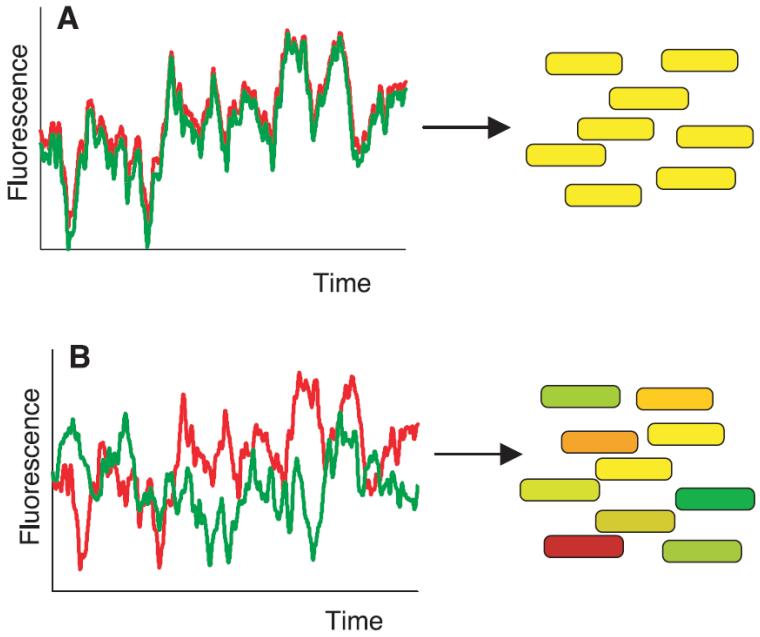
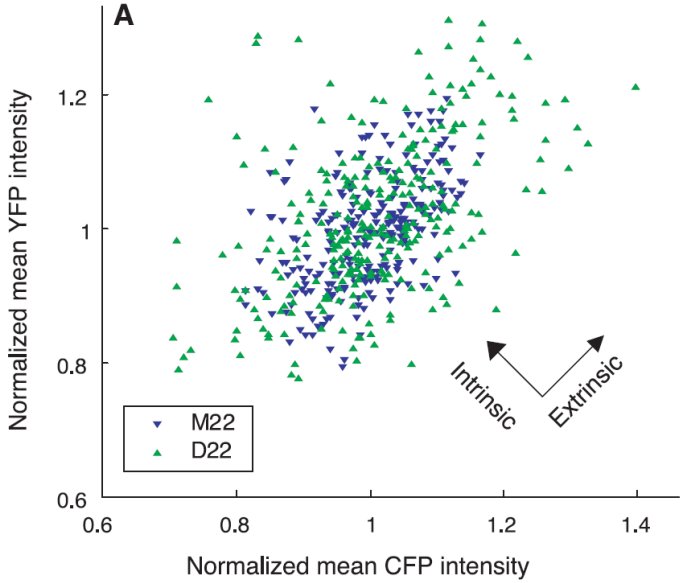




Elowitz *et al.* (2002), *Science*, 297(5584):1183-6

Stochasticity in gene expression

- Major question is how cells both **tolerate and exploit** noise.

  Rao *et al.* (2002), *Nature*, 420(6912):231-237

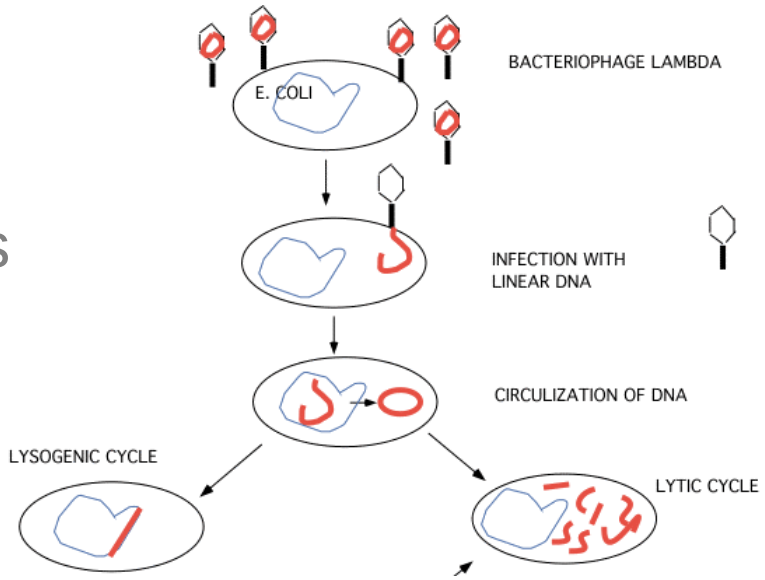
  Raj and van Oudenaarden (2008), *Cell*, 135(2):216-26

- Most cellular processes are **robust** to noise, despite stochasticity of underlying system of biochemical reactions

- Sometimes, intracellular noise drives **population heterogeneity** that may be beneficial for a species

  After infection, only fraction of cells lyse

- ODE models are not suitable for studying origin and effects of noise



Stochastic models

- **Stochastic models** of gene regulation are more appropriate
- Number of molecules of each species i at time-point t represented by discrete variable $X_i(t) \in \mathbb{N}$

X_1 X_2 X_3 X_4

Stochastic models

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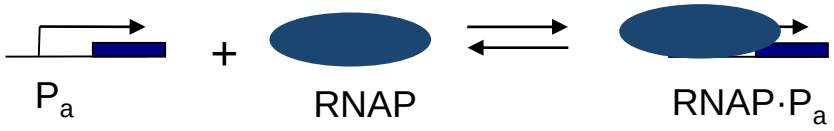
- Number of molecules of each species i at time-point t represented by discrete variable $X_i(t) \in \mathbb{N}$
- Reactions between molecular species lead to change in state of system from $\boldsymbol{X}(t)$ to $\boldsymbol{X}(t+\Delta t)$ over time-interval Δt, where $\boldsymbol{X} = [X_1, \ldots, X_n]'$

  Change of state by reaction k described by vector $\boldsymbol{\nu}_k$

Reaction 1: $\boldsymbol{\nu}_1 = [-1\ -1\ 1\ 0]$



Reaction 2: $\boldsymbol{\nu}_2 = [1\ 1\ -1\ 1]$

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$X_1 = 1$ $X_2 = 7$ $X_3 = 0$ $X_4 = 10$

Reaction 1: ν_1 = [-1 -1 1 0]

$X_1 = 0$ $X_2 = 6$ $X_3 = 1$ $X_4 = 10$

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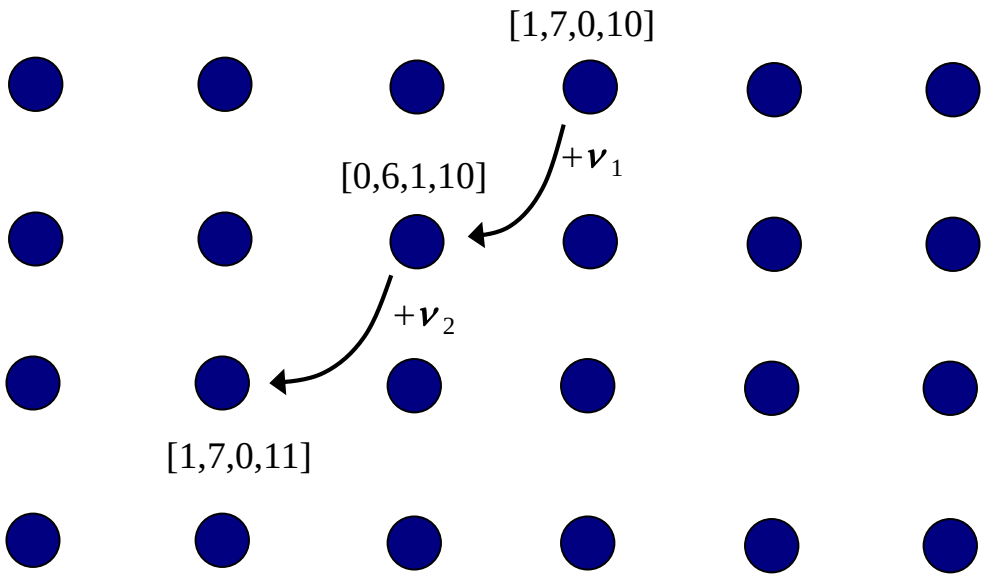
$X_1 = 0$ $X_2 = 6$ $X_3 = 1$ $X_4 = 10$

Reaction 2: ν_2 = [1 1 -1 1]

$X_1 = 1$ $X_2 = 7$ $X_3 = 0$ $X_4 = 11$

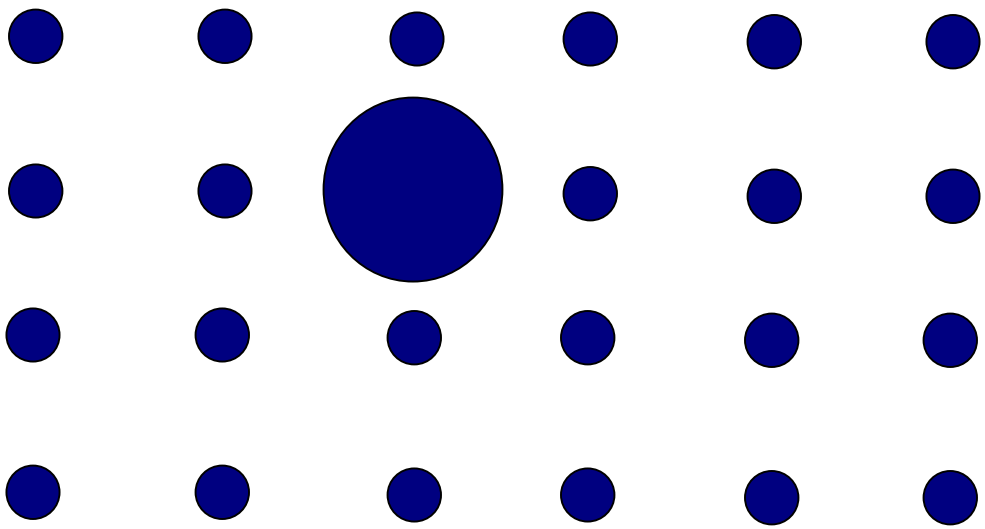
Stochastic models

- Possible states are given by possible value combinations for variables: $\boldsymbol{X} = \boldsymbol{V}$, with $\boldsymbol{V} = [V_1, \ldots, V_n]'$
- Transitions between states are given by possible reactions k



Stochastic models

- Probability distribution $\mathrm{p}[\boldsymbol{X}(t)=\boldsymbol{V}]$ describes probability that at time-point t there are $\boldsymbol{V}=[V_1,\ldots,V_n]'$ molecules



Time t_0

Stochastic models

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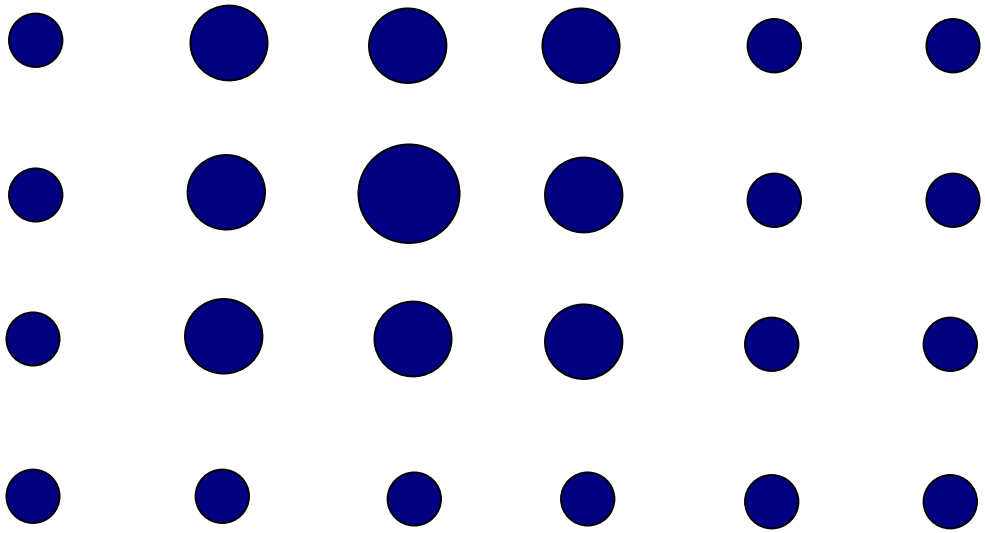

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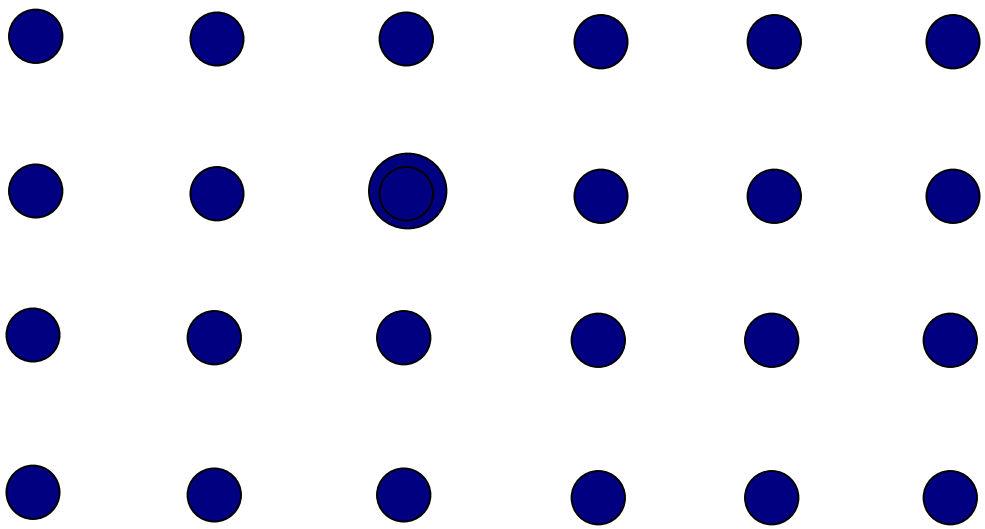

Time t_2

Stochastic master equation

- Evolution of probability distribution $p[\boldsymbol{X}(t)=\boldsymbol{V}]$ given by

$$p[\boldsymbol{X}(t+\Delta t)=\boldsymbol{V}] = p[\boldsymbol{X}(t)=\boldsymbol{V}](1-\sum_{j=1}^{m}\alpha_j \Delta t) + \sum_{k=1}^{m} p[\boldsymbol{X}(t)=\boldsymbol{V}-\boldsymbol{\nu}_k]\,\beta_k \Delta t$$

  - m is the number of reactions that can occur in the system
  - $\alpha_j \Delta t$ is the probability that reaction j will occur in $[t, t+\Delta t]$ given that $\boldsymbol{X}(t)=\boldsymbol{V}$
  - $\beta_k \Delta t$ is the probability that reaction k will bring the system from $\boldsymbol{X}(t)=\boldsymbol{V}-\boldsymbol{\nu}_k$ to $\boldsymbol{X}(t+\Delta t)=\boldsymbol{V}$ in $[t, t+\Delta t]$

Van Kampen (1997), *Stochastic Processes in Physics and Chemistry*, Elsevier

Stochastic master equation

- For $\Delta t \to 0$ we obtain **stochastic master equation**

$$\mathrm{d}\mathrm{p}[\boldsymbol{X}(t)=\boldsymbol{V}] / \mathrm{d}t = \sum_{j=1}^{m} \mathrm{p}[\boldsymbol{X}(t)=\boldsymbol{V}-\boldsymbol{\nu}_j]\, \beta_j - \mathrm{p}[\boldsymbol{X}(t)=\boldsymbol{V}]\, \alpha_j$$

- Probabilities α_j, β_j are defined in terms of kinetic constants of reactions and number of reactant molecules
- Unimolecular reaction j : $S_1 \rightarrow$ product(s)

$$\alpha_j = k_j X_1$$

- Bimolecular reaction j : $S_1 + S_2 \rightarrow$ product(s), $2S_1 \rightarrow$ product(s)

$$\alpha_j = k_j X_1 X_2/\Omega\,, \quad \alpha_j = k_j X_1 (X_1\text{-}1)/\Omega \qquad \Omega \text{ : cell volume}$$

Gillespie (2007), *Annu. Rev. Phys. Chem.*, 58:35-55

Stochastic master equation

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- Probabilities α_j, β_j are defined in terms of kinetic constants of reactions and number of reactant molecules
- Analytical solution of master equation is not possible in most situations of practical interest

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Stochastic simulation

- Analytical solution of master equations is not possible in most situations of practical interest
- **Stochastic simulation** generates sequences of reactions that change state of system, starting from initial state $\boldsymbol{X}(0) = \boldsymbol{V_0}$
  - Stochastic simulation samples joint probability density function

    $$\mathrm{p}[\tau, j | \boldsymbol{X}(t) = \boldsymbol{V}]$$

    τ = time until occurrence of next reaction

    j = index of next reaction
  - **Interpretation:** $\mathrm{p}[\tau, j | \boldsymbol{X}(t) = \boldsymbol{V}]\mathrm{d}\tau$ is probability, given $\boldsymbol{X}(t) = \boldsymbol{V}$, that next reaction will occur in $[t+\tau, t+\tau+\mathrm{d}\tau]$ and is reaction j

Gillespie (2002), *J. Phys. Chem.*, 81(25): 2340-61

Gillespie (2007), *Annu. Rev. Phys. Chem.*, 58:35-55

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    τ = time until occurrence of next reaction

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  - Probability density function defined in terms of α_j, β_k (reaction constants)

Gillespie (2002), *J. Phys. Chem.*, 81(25): 2340-61

Gillespie (2007), *Annu. Rev. Phys. Chem.*, 58:35-55

Stochastic simulation

- Analytical solution of master equations is not possible in most situations of practical interest
- **Stochastic simulation** generates sequences of reactions that change state of system, starting from initial state $\boldsymbol{X}(0) = \boldsymbol{V_0}$
- Sampling of $\mathrm{p}[\tau, j|\boldsymbol{X}(t) = \boldsymbol{V}]$ yields sequences in exact accordance with stochastic master equations:
- Repeating stochastic simulation many times (Monte-Carlo procedure) yields approximation of probability distribution $\mathrm{p}(\boldsymbol{X}(t) = \boldsymbol{V})$

Gillespie (2002), *J. Phys. Chem.*, 81(25): 2340-61

Gillespie (2007), *Annu. Rev. Phys. Chem.*, 58:35-55

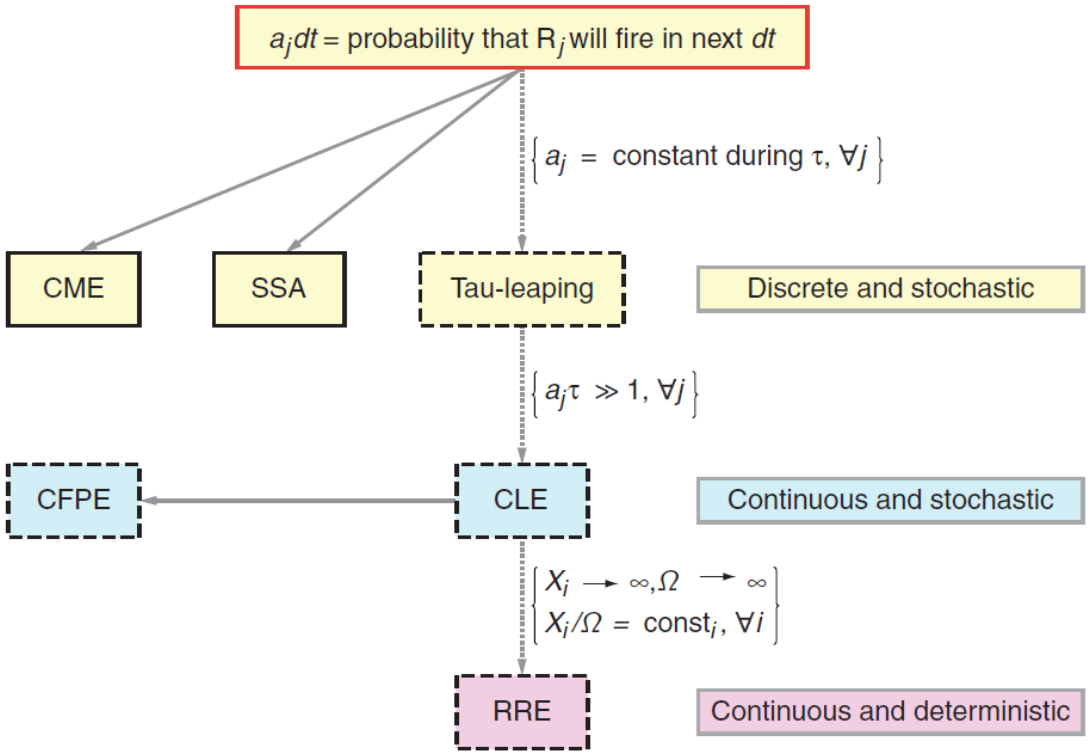
Stochastic simulation

- Analytical solution of master equations is not possible in most situations of practical interest
- **Stochastic simulation** generates sequences of reactions that change state of system, starting from initial state $\boldsymbol{X}(0) = \boldsymbol{V_0}$
- Various approximations of basic stochastic simulation algorithm, trading exactness for simulation speed:
  - Tau-leaping approaches: choose τ such that α_j, β_j remain approximately constant over time interval (encapsulate several reactions in one step)
  - Quasi-steady-state approximations (distinguish between slow and fast reactions)
  - …

Gillespie (2007), *Annu. Rev. Phys. Chem.*, 58:35-55

Stochastic simulation

- Relation of stochastic simulation models with other modeling approaches



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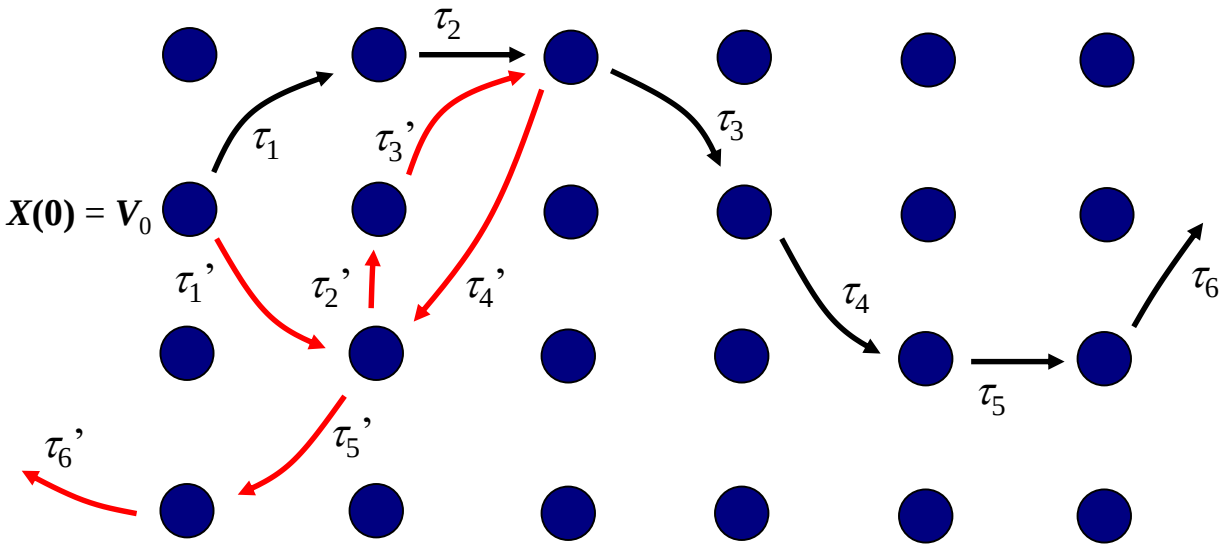
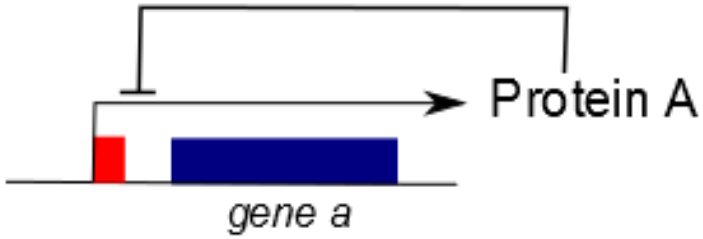


- Stochastic simulation may lead to different dynamical behaviors starting from identical initial conditions: **heterogeneity**

Auto-inhibition network

- **Auto-inhibition** network consists of a single gene, coding for transcription regulator inhibiting expression of its own gene

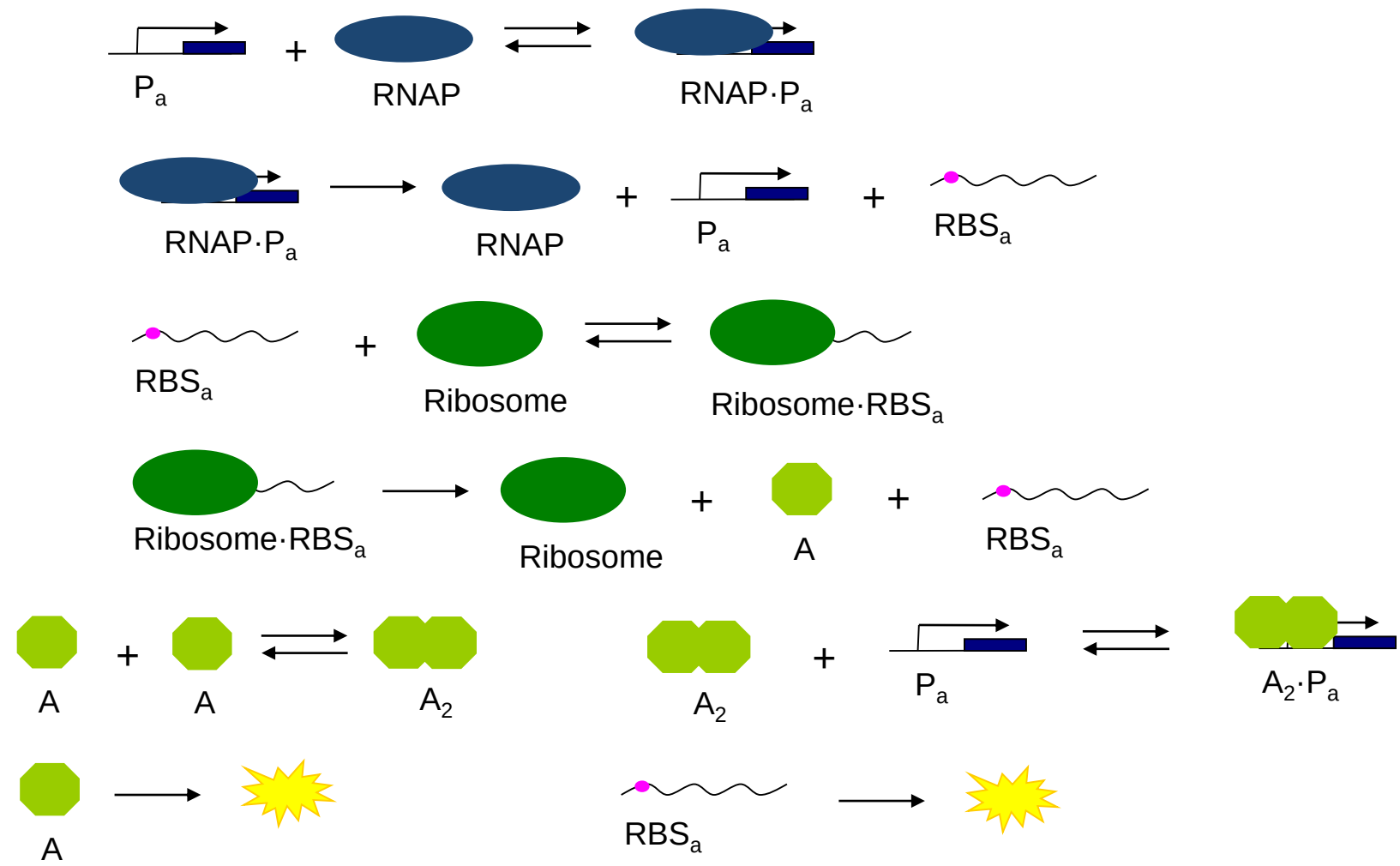


- Auto-inhibition is example of **negative feedback**, and frequently occurs in bacterial regulatory networks

Thieffry *et al*. (1998), *BioEssays*, 20(5):433-440

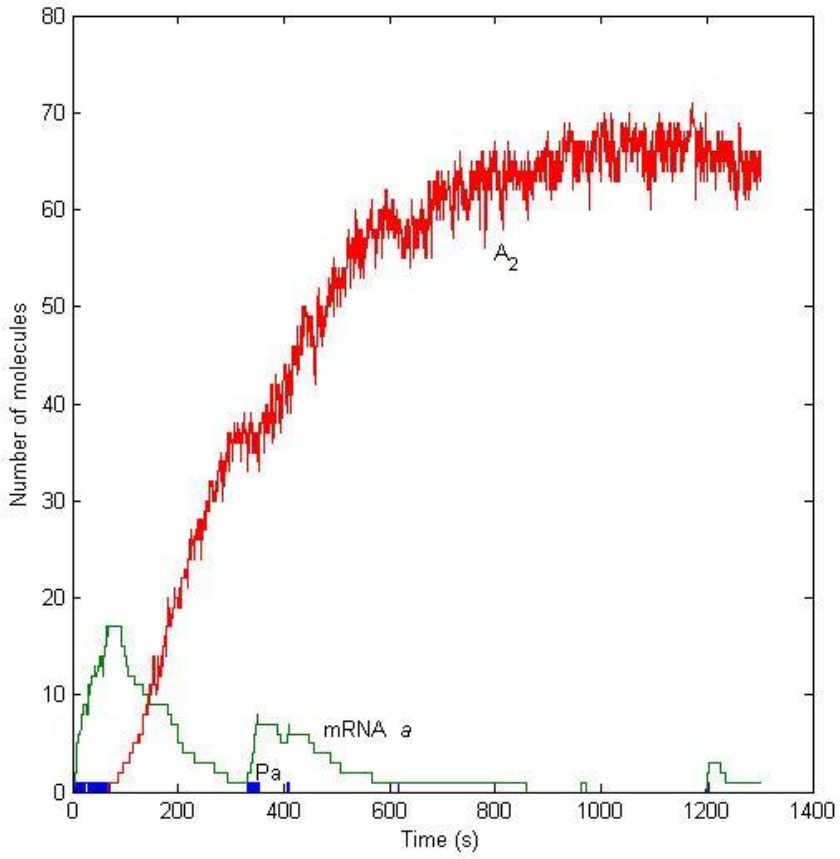
- Development of stochastic model requires list of species, reactions, and kinetic constants

Reactions and species



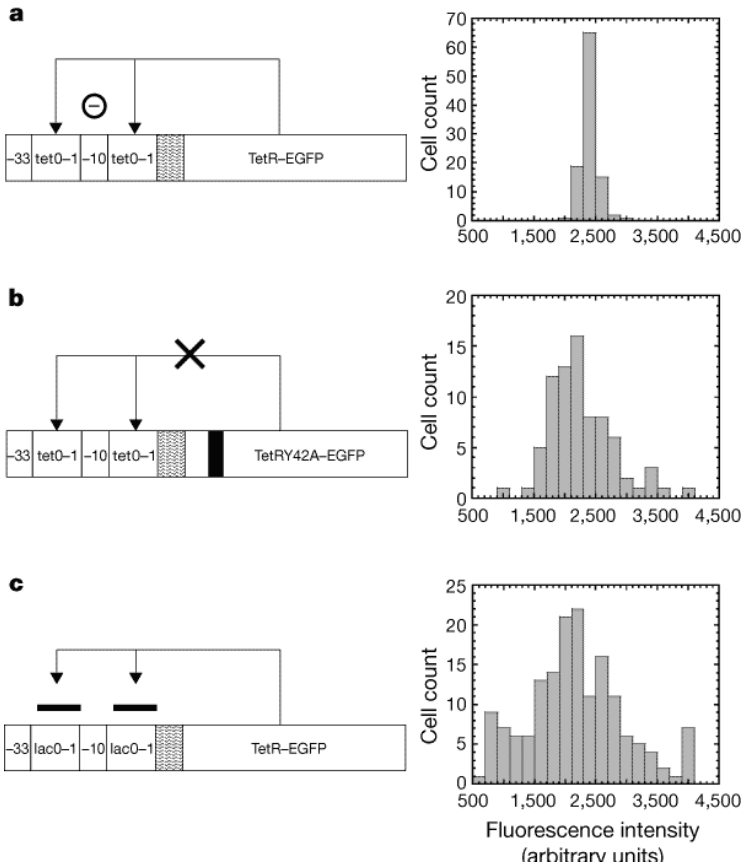
Stochastic simulation of auto-inhibition

- Occurrence of fluctuations and bursts in gene expression



Auto-inhibition and noise reduction

- Auto-inhibition reduces fluctuations in gene expression level

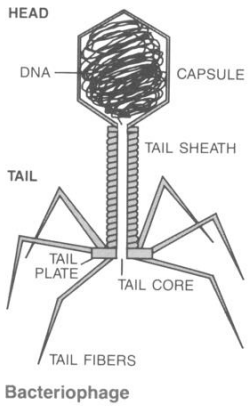


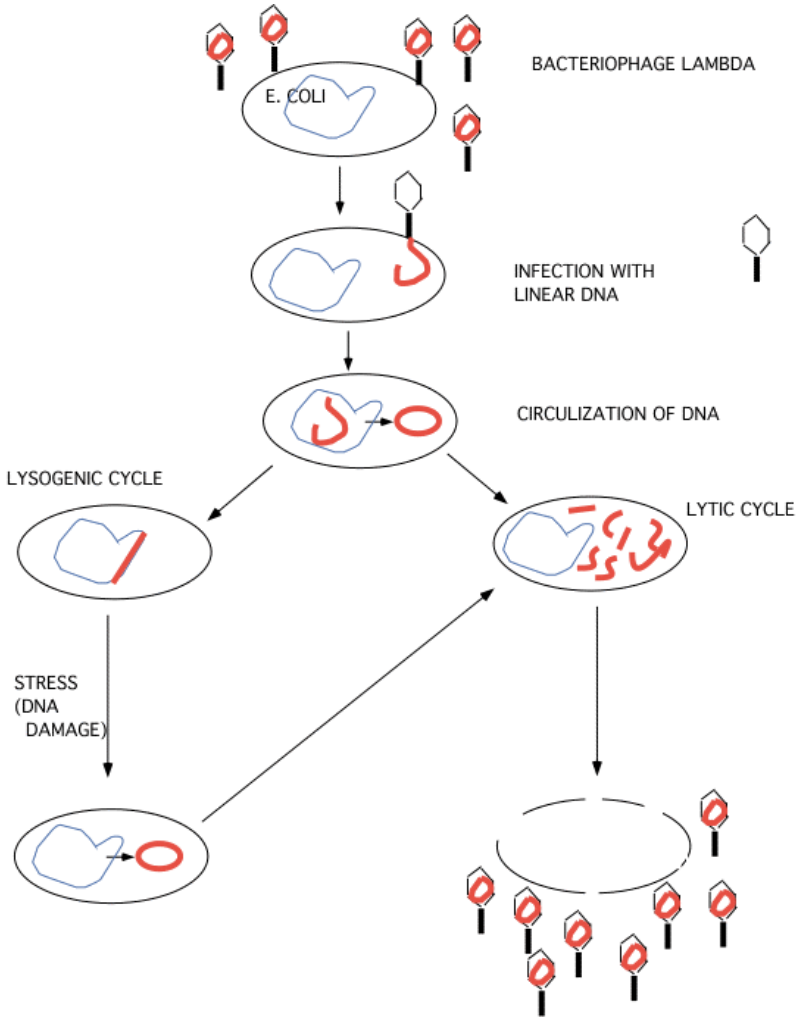
Becskei and Serrano (2000), *Nature*, 405(6785):590-591

Bacteriophage λ infection of *E. coli*

- Response of *E. coli* to phage λ infection involves decision between alternative developmental pathways: **lytic cycle** and **lysogeny**

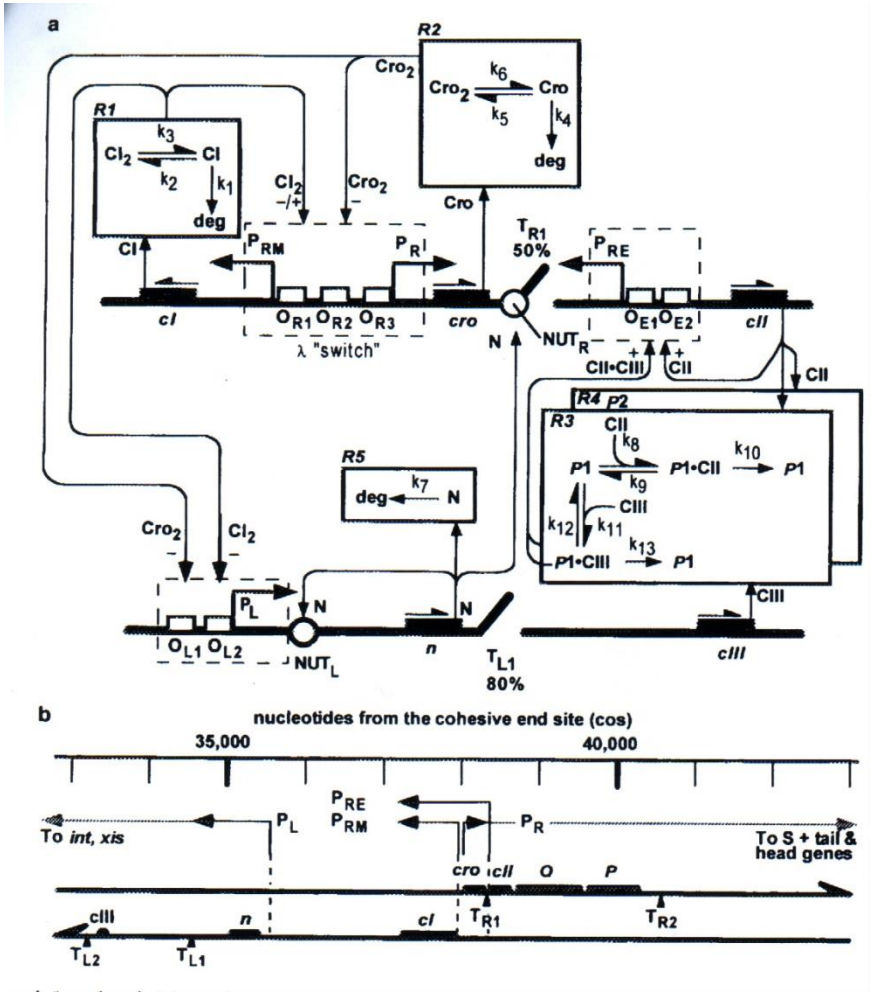
Ptashne (1997), *A Genetic Switch: Phage λ and Higher Organisms*, Cell Press





Stochastic analysis of phage λ infection

- Stochastic model of λ lysis-lysogeny decision network

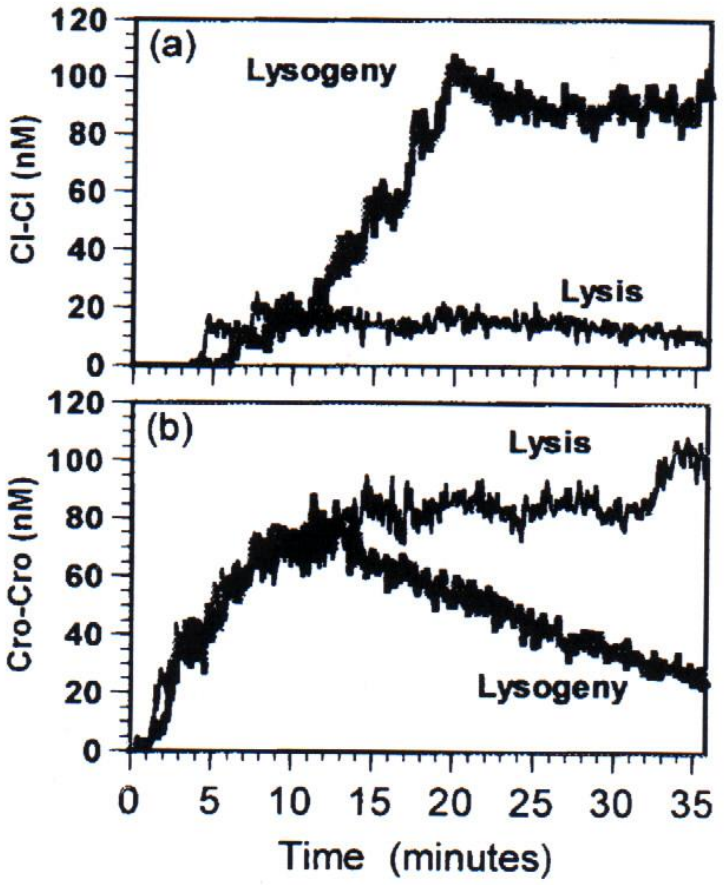


Arkin *et al.* (1998), *Genetics*, 149(4): 1633-1648

Stochastic analysis of phage λ infection

- Time evolution of Cro and CI dimer concentrations

- Due to stochastic fluctuations, under identical conditions cells follow one or other pathway (with some probability)



Arkin *et al.* (1998), *Genetics*, 149(4): 1633-1648

Comparison with deterministic approach

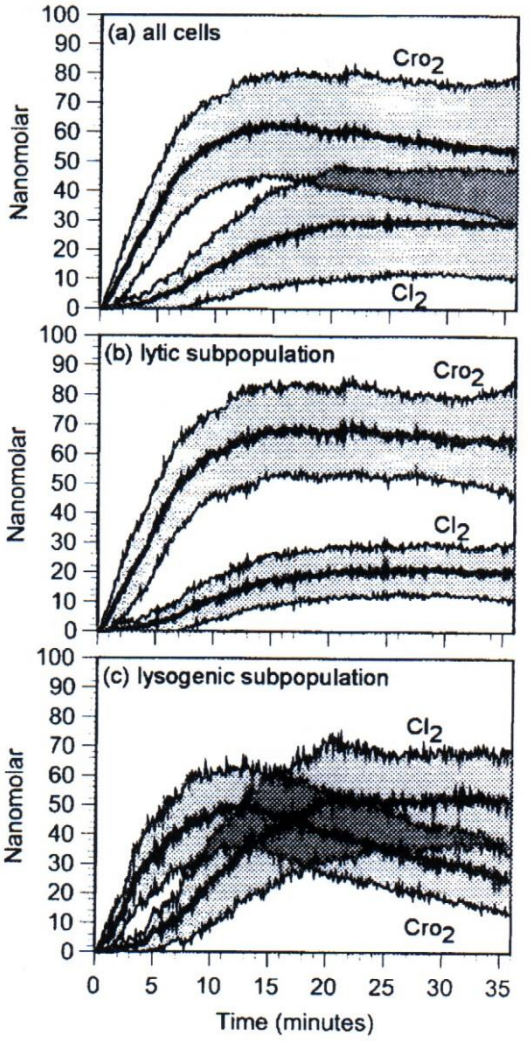
- Deterministic models can be seen as predicting **average behavior** of cell population

  Gillespie. (2000), *J. Chem. Phys.*, 113(1): 297-306

- Analysis of average behavior may obscure that one part of population chooses one pathway rather than another

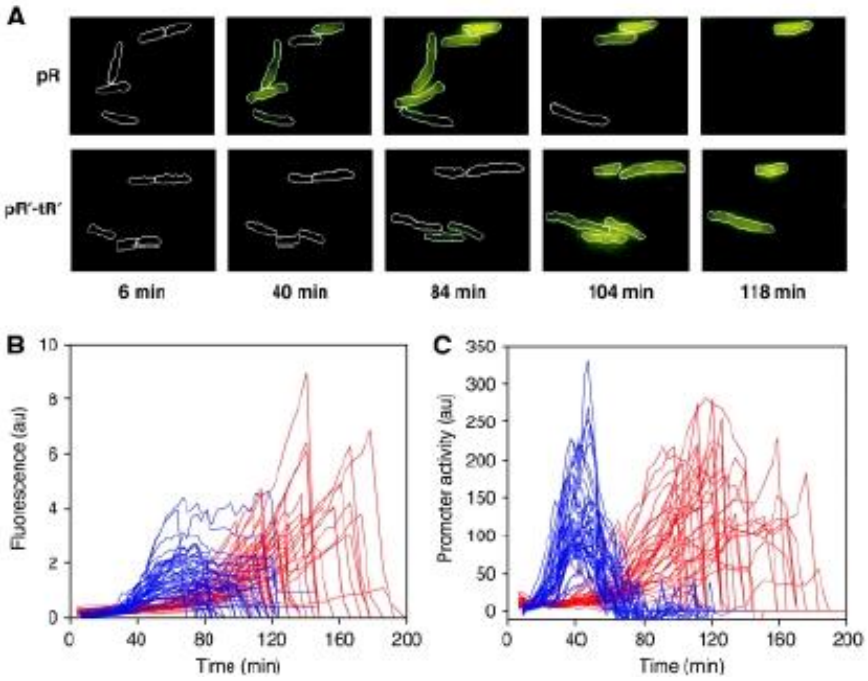
  Arkin *et al.* (1998), *Genetics*, 149(4): 1633-1648

- However, under some conditions deterministic models yield good approximation



Measurements of phage λ infection

- New measurement techniques allow real-time and *in-vivo* monitoring of the execution of lytic and lysogenic pathways in individual cells
  - Use of reporter genes in combination with fluorescence microscopy

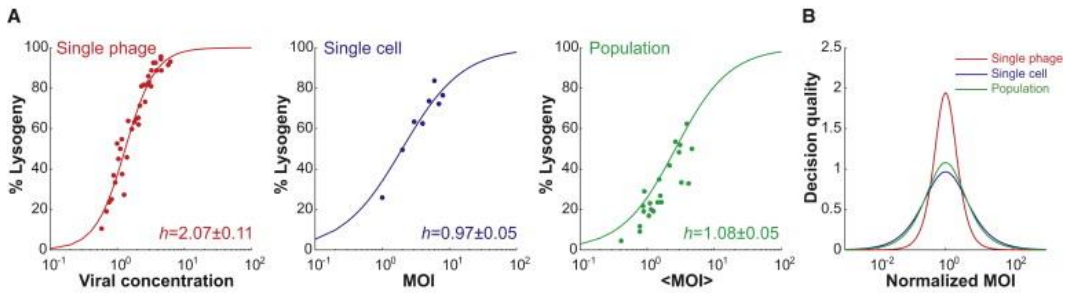


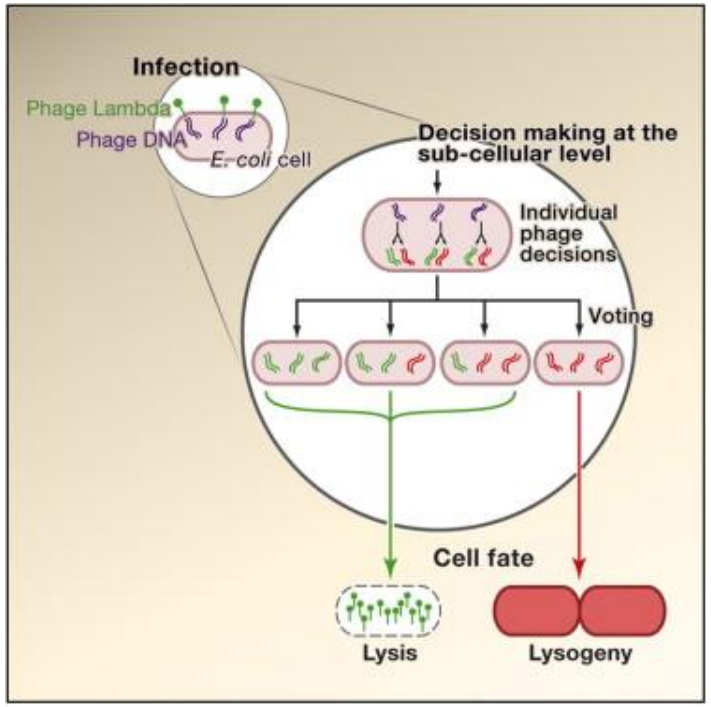
Amir *et al.* (2007), *Mol. Syst. Biol.*, 3:71

Stochasticity and hidden variables

- Is observed population heterogeneity entirely due to stochastic dynamics of biochemical reactions?
- **Hidden variables** that deterministically set outcome of what seems noisy decision process

  Deterministic voting of stochastic decision in single phages





Zeng *et al.* (2010), *Cell*, 141(4):682-91

Discussion

- Stochastic models provide more realistic picture of gene expression
- Difficulty of stochastic models is that required information on regulatory mechanisms on molecular level usually not available

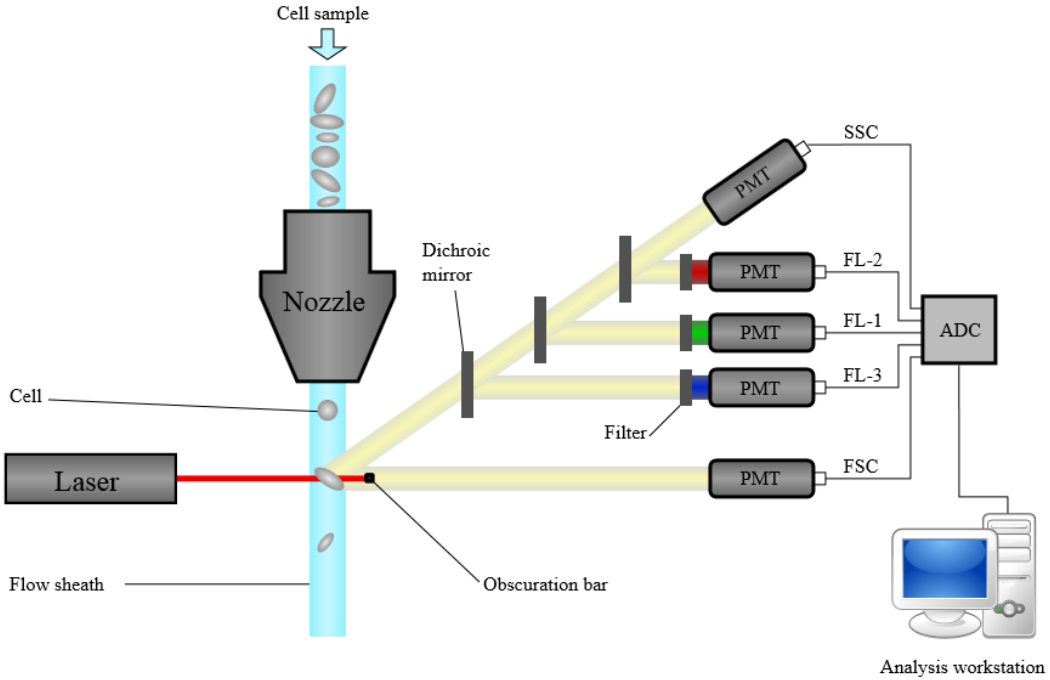
  Reaction schemes and kinetic constants are not or incompletely known
- Another difficulty is that stochastic simulation is computationally expensive

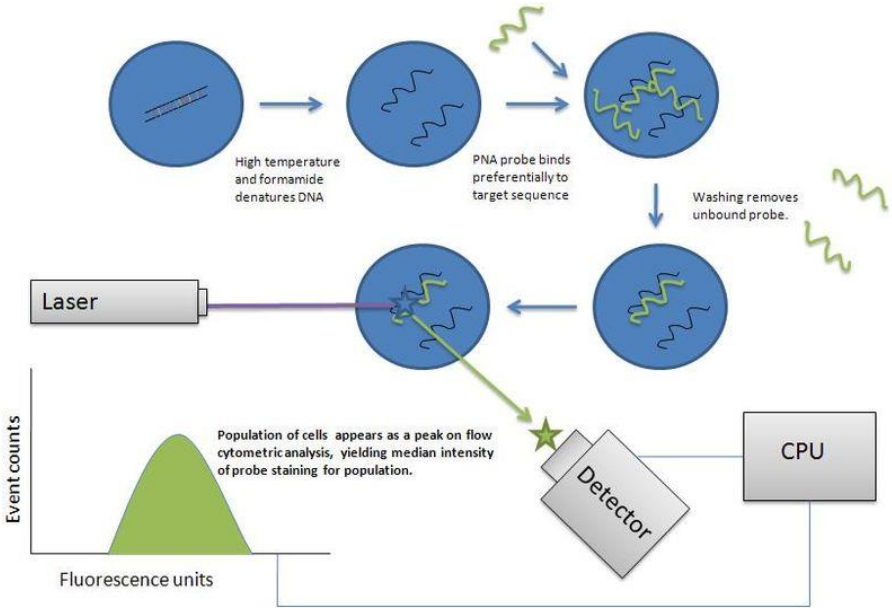
  Large networks cannot currently be handled, but a host of extensions and approximations have been developed

Identification of stochastic models

- Rate constants of a given reaction network are often unknown, and must be inferred from data
- Data for stochastic model identification need to provide information about variability
- Statistics predicted by the model need to be matched to the data to get parameters that explain observations
  - Requires trying many hypothetical parameter values
  - Need fast solution of the CME for a given parameter hypothesis
- Models should also be validated, to make sure that they are capable of good predictions in new conditions

Single-cell data: Flow-cytometry





(Wikipedia)

Single-cell data: Microfluidics

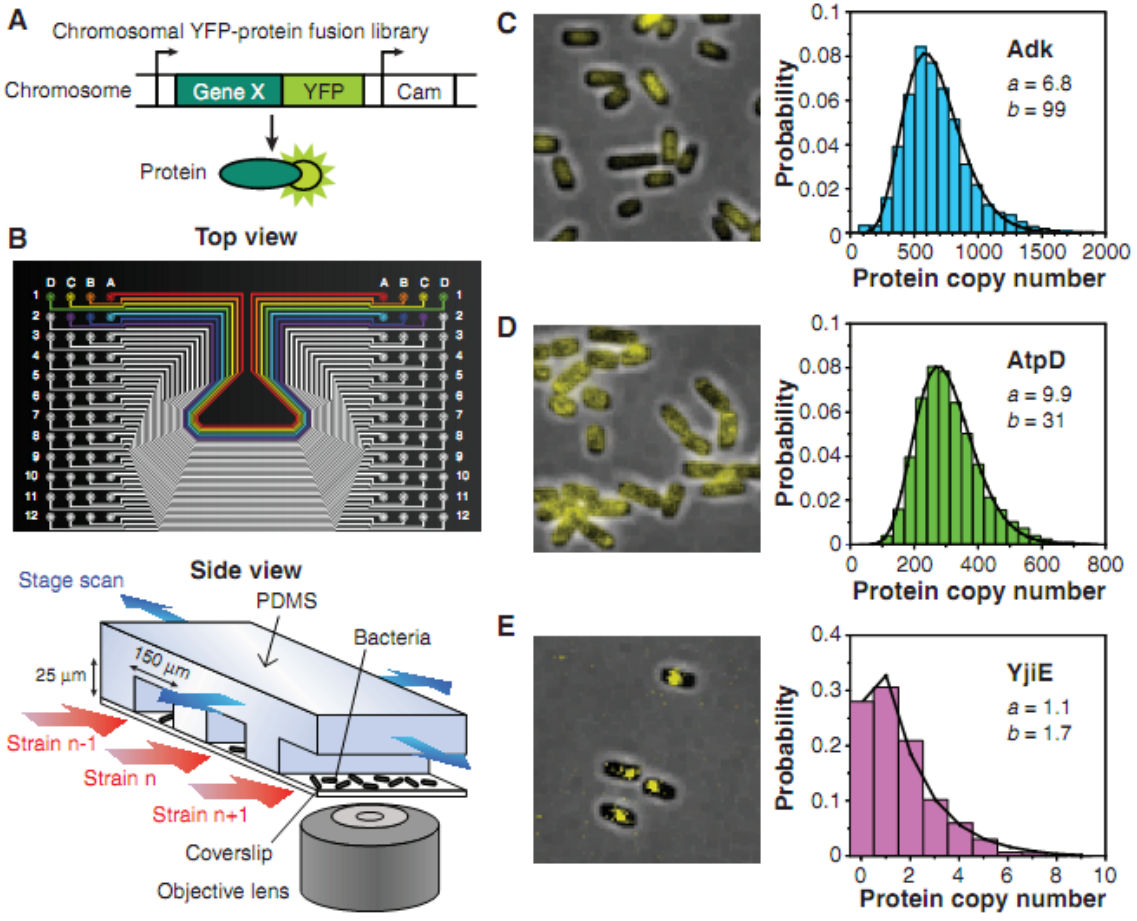
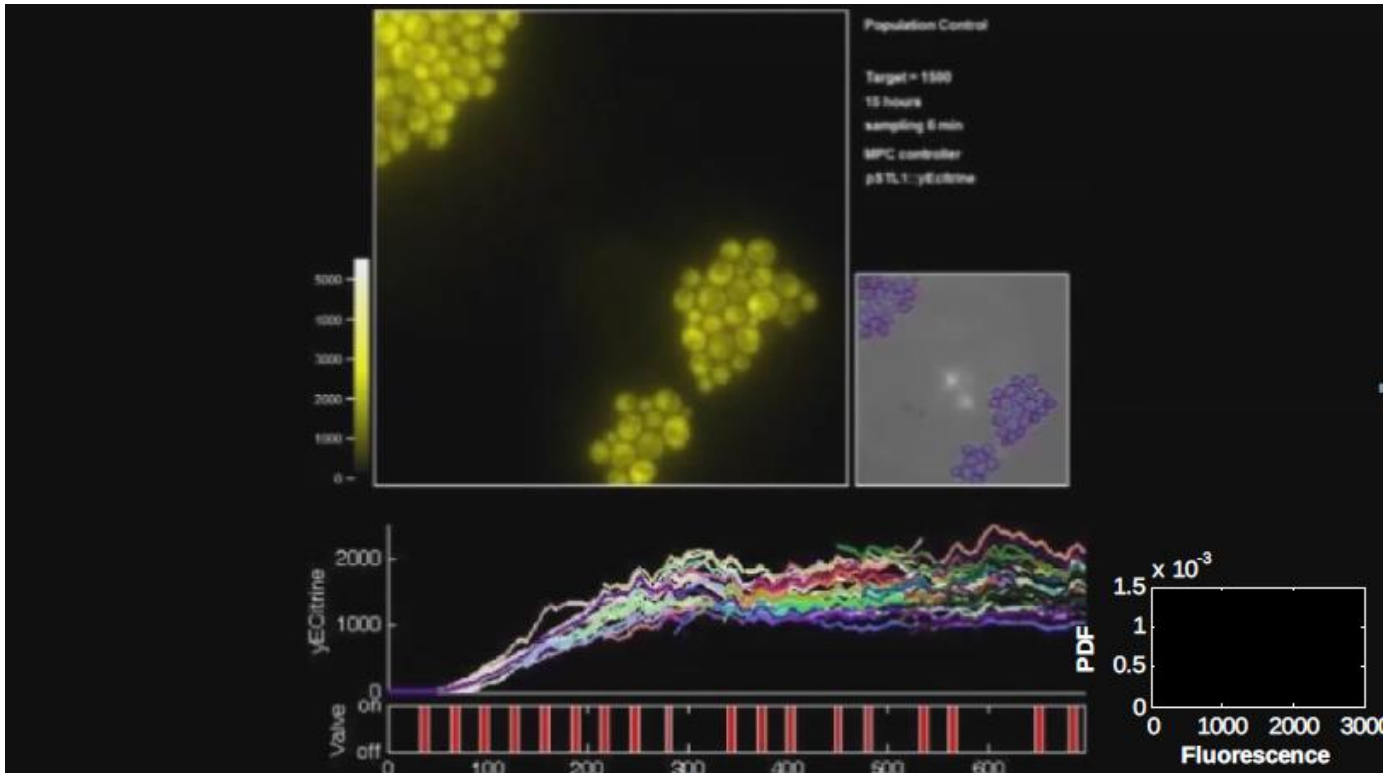


Fig. 1. Quantitative imaging of a YFP-fusion library. (**A**) Each library strain has a YFP translationally fused to the C terminus of a protein in its native chromosomal position. (**B**) A poly(dimethylsiloxane) (PDMS) microfluidic chip is used for imaging 96 library strains. *E. coli* cells of each strain are injected into separate lanes and immobilized on a polylysine-coated coverslip for automated fluorescence imaging with single-molecule sensitivity. (**C** to **E**) Representative fluorescence images overlaid on phase-contrast images of three library strains, with respective single-cell–protein level histograms that are fit to gamma distributions with parameters *a* and *b*. Protein levels are determined by deconvolution (*18*). The protein copy number per average cell volume, or the concentration, was determined as described in the main text and the SOM (*18*). (C) The cytoplasmic protein Adk uniformly distributed intracellularly. (D) The membrane protein AtpD distributed on the cell periphery. (E) The predicted DNA-binding protein YjiE with clear intercellular localization. Single YjiE-YFPs can be visualized because they are localized. Note that, unlike (C) and (D), the gamma distribution asymmetrically peaks near zero if *a* is close to or less than unity.

(Taniguchi *et al.*, Science 329, 533 , 2010)

Single-cell trajectories: Microfluidics cont'd

- Example: Osmotic shock response in yeast



(Uhlendorf *et al.*, PNAS 2012)

Approximate solution of the CME: The Finite State Projection method

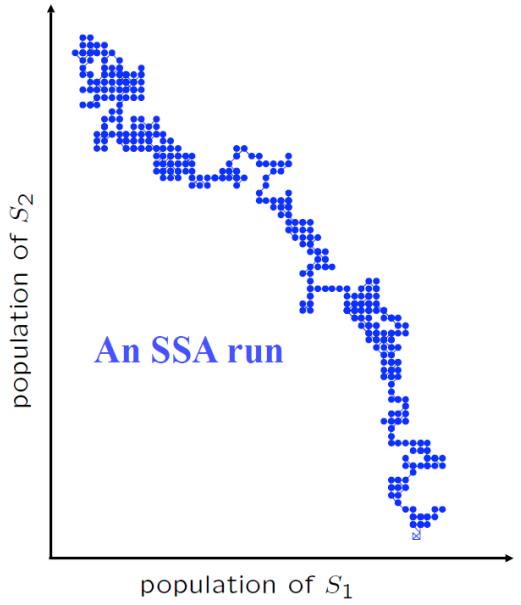
[The material on Finite State Projection in these slides is borrowed from

M.Khammash, "The Chemical Master Equation in Gene Networks: Complexity and Approaches"

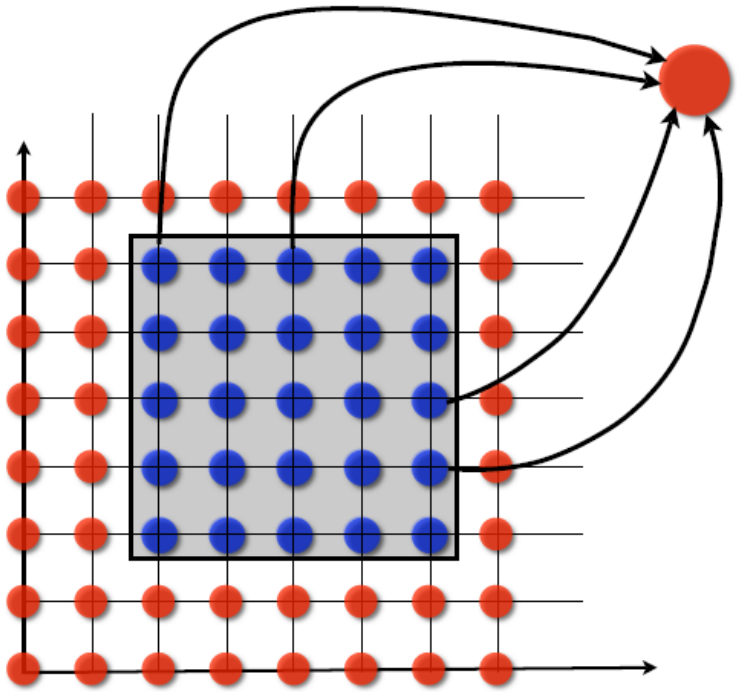
available at:

http://www.cds.caltech.edu/~murray/wiki/images/d/d9/Khammash_master-15aug06.pdf]

- The state of the system evolves on a lattice
- Each state value has a probability that evolves over time
- Some state values are traversed with larger probability than others
- Figure shows a simulated example for a system with two species



- How about restricting attention to the most probable states ?



- A finite subset is appropriately chosen
- The remaining (infinite) states are projected onto a single state (red)
- Only transitions into removed states are retained

The projected system can be solved exactly!

- Start from the (infinite) matrix representation of the CME

The states of the chemical system can be enumerated:

$$\mathbf{X} := [\mathbf{x}_1 \quad \mathbf{x}_2 \quad \mathbf{x}_3 \quad \dots \quad]^T$$

The *probability density state vector* $\mathbf{P}(\mathbf{X}, \cdot) : R \to \ell_1$ defined by:

$$\mathbf{P}(\mathbf{X}; t) := [p(\mathbf{x}_1; t) \quad p(\mathbf{x}_2; t) \quad p(\mathbf{x}_3; t) \quad \dots \quad]^T$$

The evolution of the *probability density* state vector is governed by

$$\dot{\mathbf{P}}(\mathbf{X}; t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}; t)$$

- One has the following result

Let $J = [m_1 \dots m_N]$ be an indexing vector. We define $\mathbf{A}_J$ to be the principle submatrix of $\mathbf{A}$ defined by J.

Theorem [Projection Error Bound]: Consider any Markov process in which the probability distribution evolves according to the ODE:

$$\dot{\mathbf{P}}(\mathbf{X}; t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}; t).$$

If for an indexing vector J: $\mathbf{1}^T \exp(\mathbf{A}_J t)\ \mathbf{P}(\mathbf{X}_J; 0) \geq 1 - \epsilon$, then

$$\left\| \begin{bmatrix} \mathbf{P}(\mathbf{X}_J; t) \\ \mathbf{P}(\mathbf{X}_{J'}; t) \end{bmatrix} - \begin{bmatrix} \exp(\mathbf{A}_J t)\ \mathbf{P}(\mathbf{X}_J; 0) \\ 0 \end{bmatrix} \right\|_1 \leq \epsilon$$

Munsky B. and Khammash M., Journal of Chemical Physics, 2006

The FSP algorithm

- **Step 0.** Define the propensity functions and stoichiometry for all reactions.
  - Choose the initial probability density function $\mathbf{P}(\mathbf{X}, 0)$.
  - Choose the final time of interest, t.
  - Choose the total amount of acceptable error ϵ.
  - Choose an initial finite set of states: $\mathbf{X}_{J_0}$.
  - Set $i = 0$.

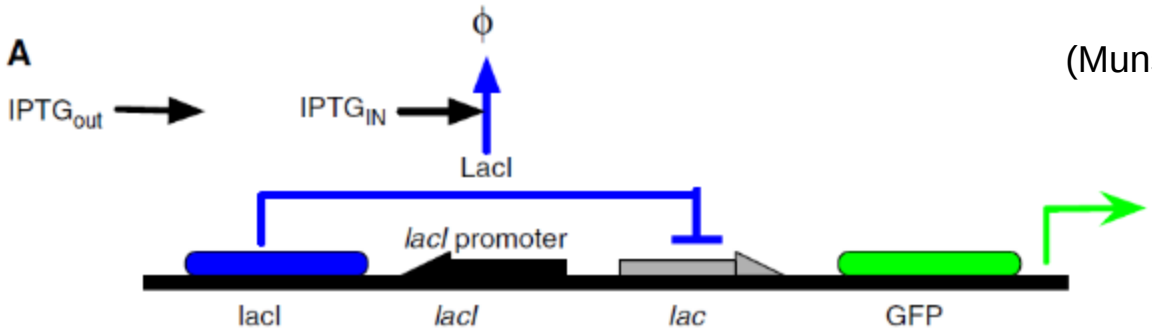
- **Step 1.** Form $\mathbf{A}_{J_i}$. Compute $\Gamma_{J_i} = \mathbf{1}^T \exp(\mathbf{A}_{J_i} t)\ \mathbf{P}(\mathbf{X}_{J_i}; 0)$.

- **Step 2.** If $\Gamma_{J_i} \geq 1 - \epsilon$: stop.

  $\exp(\mathbf{A}_{J_i} t)\ \mathbf{P}(\mathbf{X}_{J_i}; 0)$ approximates $\mathbf{P}(\mathbf{X}_{J_i}; t)$ to within ϵ.

- **Step 3.** Add more states to get $\mathbf{X}_{J_{i+1}}$. Increment i. Go to step 1.

Example: Identification of *E.coli* Lac operon



(Munsky *et al.*, Mol Syst Biol, 2009)

- Stochastic model:

$$[\mathrm{IPTG}]_{\mathrm{IN}}=[\mathrm{IPTG}]_{\mathrm{OUT}}\cdot(1-\exp(-\pi t)),$$

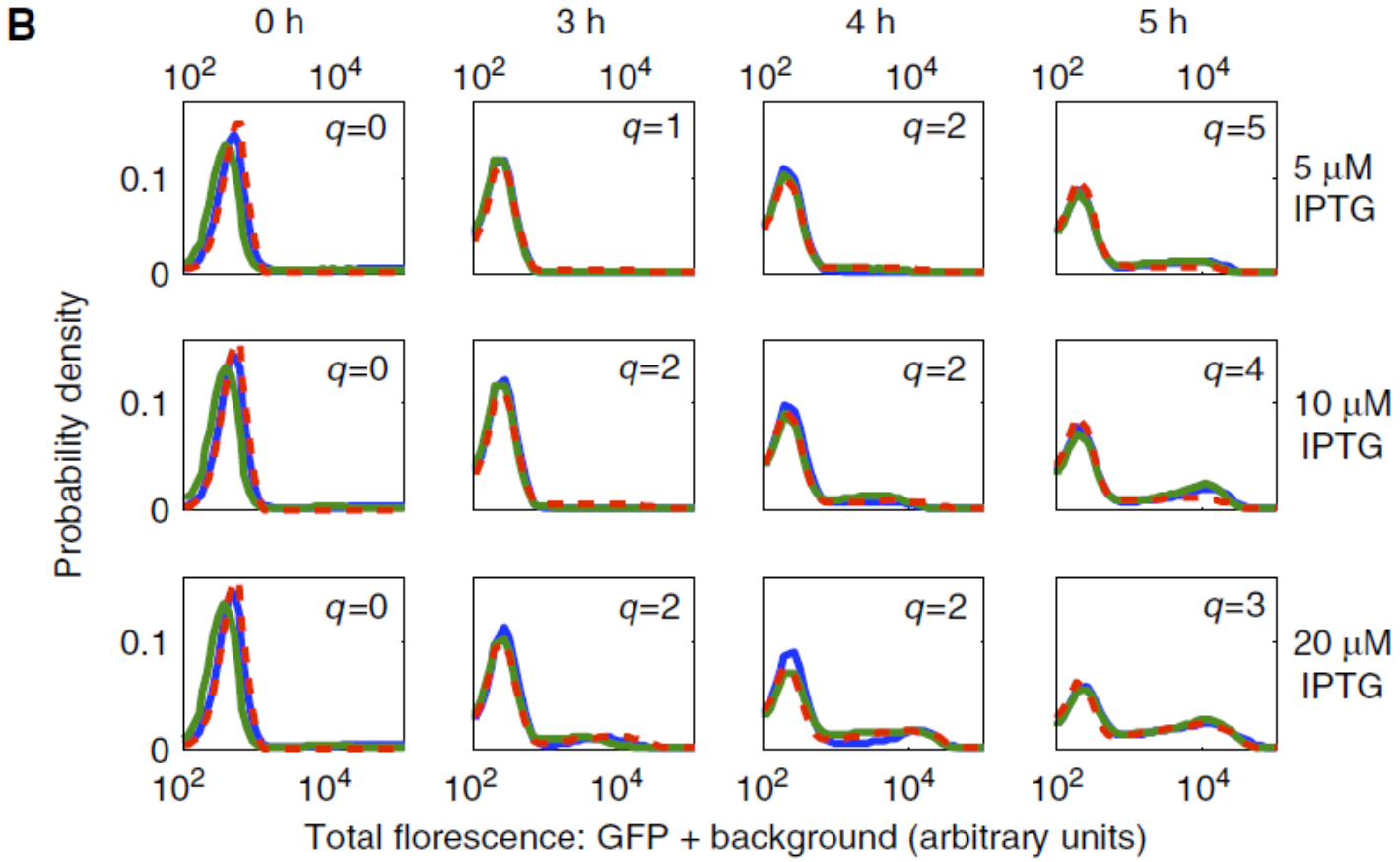
$$R_1:\phi\xrightarrow{w_1}\mathrm{LacI},\quad R_2:\mathrm{LacI}\xrightarrow{w_2}\phi,\qquad w_1=k_{\mathrm{L}},\qquad w_2=\delta_{\mathrm{L}}\cdot[\mathrm{LacI}],\quad \delta_{\mathrm{L}}=\delta_{\mathrm{L}}^{(0)}+\delta_{\mathrm{L}}^{(1)}[\mathrm{IPTG}]_{\mathrm{IN}}.$$

$$R_3:\phi\xrightarrow{w_3}\mathrm{GFP},\quad R_4:\mathrm{GFP}\xrightarrow{w_4}\phi\qquad w_3([\mathrm{LacI}])=\frac{k_{\mathrm{G}}}{1+\alpha[\mathrm{LacI}]^{\eta}}\qquad w_4=\delta_{\mathrm{G}}\cdot[\mathrm{GFP}],$$

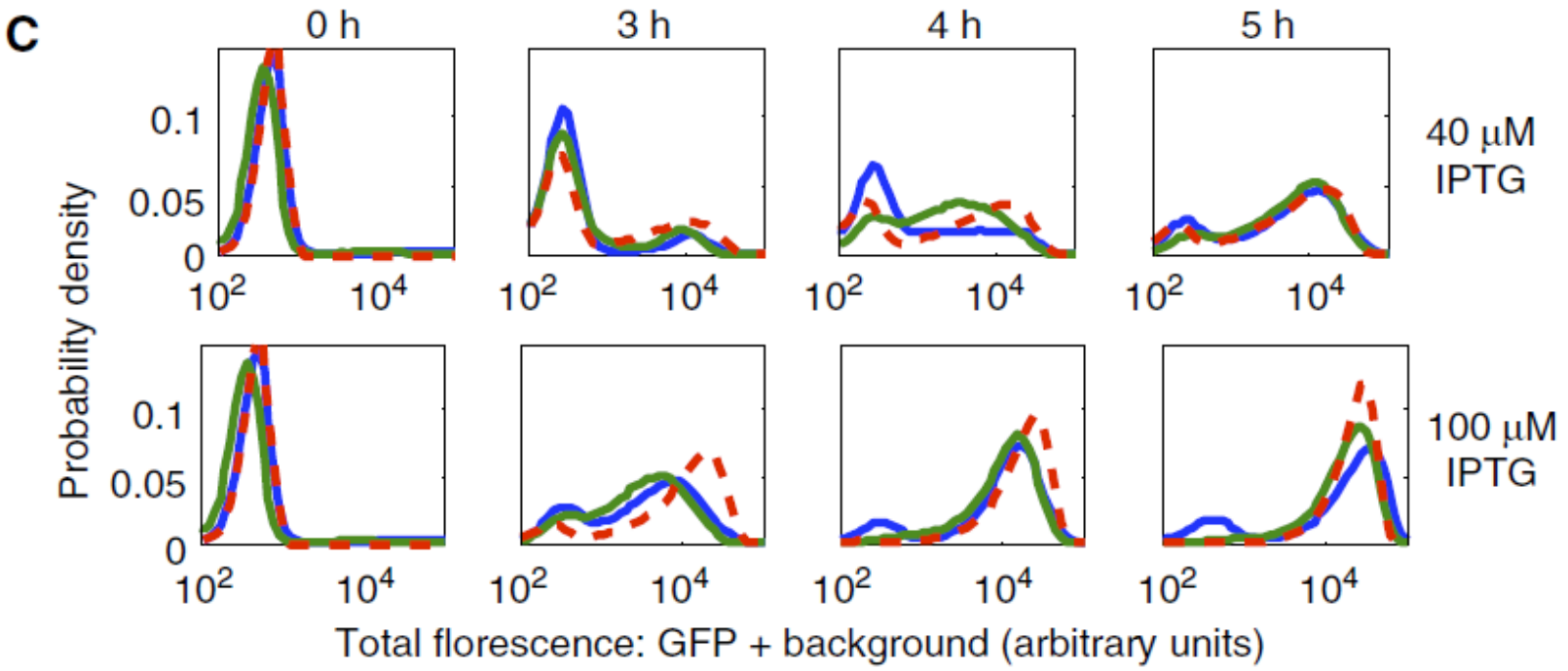
- Parameter identification by matching histograms with FSP

$$\Lambda^*:=\mathrm{argmin}_{\Lambda}\left\{\sum_i q_i\cdot\left\|f_{\mathrm{Meas}}^{(i)}-f_{\mathrm{Tot}}^{(i)}\right\|_1\right\}$$

- Fitting :


B
0 h
3 h
4 h
5 h
10^2
10^4
q=0
q=1
q=2
q=5
q=4
q=3
0.1
0
5 μM IPTG
10 μM IPTG
20 μM IPTG
Probability density
Total florescence: GFP + background (arbitrary units)

- Validation :


C
0 h
3 h
4 h
5 h
40 μM IPTG
100 μM IPTG
Probability density
0.1
0.05
0
10^2
10^4
Total florescence: GFP + background (arbitrary units)

Discussion

- Other approaches exist / are being developed
  - The method of moment equations (e.g. Zechner *et al.*, PNAS 2012)
  - Approximation of stationary distribution (steady-state data) (e.g. Taniguchi *et al.*, Science 2010)
- Stochastic model inference more instructive than ODE
  - Allows one to capture (variability and) bimodality
  - Allows for estimation of otherwise undistinguishable rate parameters
- Yet, stochastic model identification is computationally heavy and still requires specific solutions for specific problems
- And extrinsic noise ? Yet another chapter (hot topic)

… Thanks!

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