


Fluctuating-rate model of single-cell dynamics and its applications



Hao Ge (葛颢)

haoge@pku.edu.cn

¹Beijing International Center for Mathematical Research

²Biodynamic Optical Imaging Center

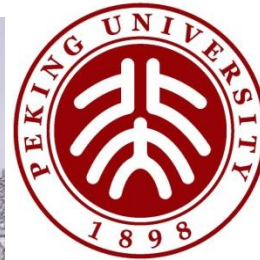
Peking University, China

<http://bicmr.pku.edu.cn/~gehao/>

BICMR: Beijing International Center for Mathematical Research



BIOPIC: Biomedical Pioneering Innovation Center



BIOPIC

北京大学生物医学前沿创新中心



<http://biopic.>

Summary of Ge group

JSP06,08,17
PRE09,10,13,14,16,18
JCP12; JSTAT15

**Stochastic theory of
nonequilibrium
statistical mechanics**

JPCB08,13,16; JPA12; SPA17
Phys. Rep. 12
Science13; Cell14; MSB15
PlosCB18

**Stochastic modeling of
biophysical systems**

**Stochastic
Biophysics
(Biomath)**

**Nonequilibrium
landscape theory
and rate formulas**

**Statistical machine
learning of single-cell
data**

PRL09,15
JRSI11; Chaos12

Theory

Providing analytical tools



Providing scientific problems

Applications

Interactions among math, physics, chemistry and biology

Notices

of the American Mathematical Society

November 2015

Volume 62, Number 10

Mathematical Biology is Good for Mathematics
page 1172

Fruit Flies and Moduli: Interactions between Biology and Mathematics
page 1178

Geometry of Data and Biology
page 1185

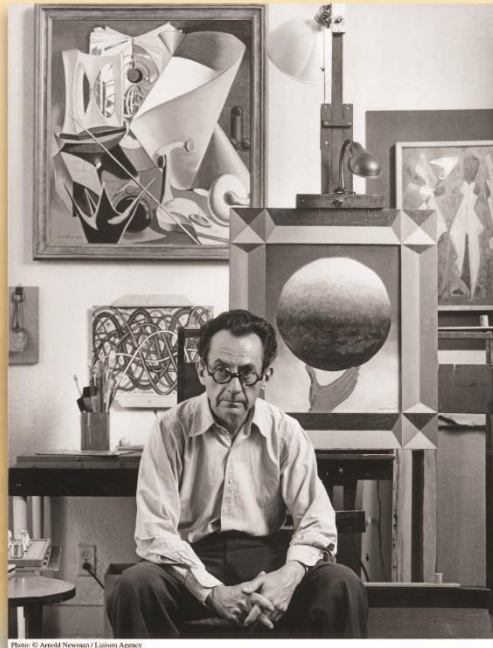


Photo: © Arnold Newman / L'Espresso Agency

 **AMS**
AMERICAN MATHEMATICAL SOCIETY

About the cover: Dada Mathematics? (see page 1207)

science & society

feature

Biology is the new physics

The increasing use of mathematics in biology is both inspiring research in mathematics and creating new career options for mathematical biologists

Philip Hunter

Biology has long been the stepchild of the natural sciences. Compared with mathematical proofs, physical formulae and the molecules of chemistry, biology, like life itself, has often seemed unquantifiable, unpredictable and messy. Yet, scientists have striven gallantly to pin biology down through the application of the other natural sciences. Ever since Gregor Mendel (1822–1884) formulated the laws of heredity, biology has slowly transformed itself into a ‘hard’ science. In fact, research in biology and medicine depends increasingly on mathematics and computation, with profound consequences for those fields and for the skills needed to conduct research and clinical development. The conversion of biology into a more quantifiable science will continue to the extent that it might even become the main driving force behind innovation and development in mathematics. This, at least, is the view of Michael Mackey, President of the Society for Mathematical Biology, which aims to foster international interactions between the two fields.

The conversion of biology into a more quantifiable science will continue to the extent that it might even become the main driving force behind innovation and development in mathematics

“For many years the inspiration for innovation in applied mathematics has come from physics, but in my opinion, in this century it will come from the biological sciences, broadly defined,” Mackey explained, adding that this switch has been taking place slowly over several decades. While physics has stagnated, waiting for new theoretical insights to make progress against fundamental problems such as quantum gravity, Mackey argued, theoretical biology has emerged as a new source

of inspiration for mathematicians. “In my 40 plus years of research, I have found that problems in biomathematics almost always uncover unexplored and undeveloped areas of mathematics,” he said. “These are areas that mathematicians have not even thought about exploring. New mathematics.”

In some cases, new mathematical techniques have been developed to tackle specific problems, but biology has also stimulated fundamental progress in mathematics, according to Jürgen Jost, Director of the Max Planck Institute for Mathematics in the Sciences in Leipzig, Germany. Jost cited the field of information geometry, which first emerged as a method to combine geometry and statistical probability theory to tackle problems in other scientific fields including physics and economics. “The new field of information geometry draws a lot [of] inspiration from information processing in biological systems, from the cell to the brain,” he explained.

Information geometry is increasingly applied across a range of biology disciplines at different scales of time and space. For example, in proteomics, it is used to analyse interactions between macromolecular complexes; in modelling epidemics, it is able to account for more complex and subtle differences in quantities, such as rates of infection among populations, than previous approaches. Indeed, the reason for the growing use of information geometry across biological and medical research is that it is capable of allowing for non-uniformity in the systems under study, whether at the scale of a protein, cell, pathway or ecosystem. In essence, information geometry combines geometry with probability theory to model changing, complex and nonlinear systems.

Other techniques have evolved alongside information geometry to analyse interactions between processes that operate across a huge range of spatiotemporal scales. The human immune system, for example,

involves events at the level of individual gene expression or protein interactions that take place in nanoseconds; cellular mechanisms or body-wide events that can take minutes, hours or days; and interactions between people or even whole populations that last months and years. Trying to understand these systems involves bridging different layers and scales, and this need, Jost points out, has driven developments in mathematical biology.

The application of mathematics to biology itself is hardly new and dates back at least to Mendel and his work on the inheritance of traits in the mid-nineteenth century. This led eventually to the theory of Mendelian inheritance as the foundation of modern genetics for all sexually reproducing organisms, which assumes that traits are passed down as whole units on a digital basis, rather than being watered down in an analogue fashion. In this case, the mathematics was straightforward: simple probability theory applied to trait inheritance. The difference in the present relationship between biology and mathematics is that there is now a two-way trade in ideas and research, which leads to more complex tools and applications in and across both sciences.

...mathematical biology is now spreading beyond fundamental questions and is starting to yield practical benefits

Another difference is that mathematical biology is now spreading beyond fundamental questions and is starting to yield practical benefits. It is being applied widely in cancer research, for instance, to both model the growth and metastasis of tumours and to understand why treatment sometimes fails. According to Mark Chaplain, Head of the Mathematics Division at the University of Dundee in the UK, the application of mathematical techniques has led to substantial progress in three key areas of cancer research.

The first is a series of developments in modelling tumour induced angiogenesis – the process by which new blood vessels are formed as the tumour grows. This was previously poorly understood and, according to Chaplain, involves irregular small-scale processes that cannot be tackled with

Voice on Cell

Cell

Leading Edge
Voices

Expanding the Biology Toolkit

Fun with Chemistry



Carolyn Bertozzi
Stanford University & HHMI

Whether you call it biochemistry, molecular pharmacology, or chemical biology, one thing we can agree on is that chemists have long sought to advance the biological sciences. Through development of reagents, instruments, algorithms, and technologies, chemistry brings to biology the ability to drill down to molecules, bonds and atoms—the scale of matter at which all living things converge on common principles. But one often hears the dogma that “you can teach a biologist to be a chemist, but this is not so easy to teach a chemist to be a biologist.”

Mathematical Laws of Randomness

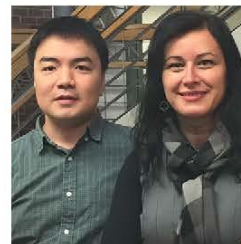


Hao Ge
Peking University

The stochastic processes of transcription and translation inside cells can be described mathematically by a Chemical Master Equation (CME) model, typically simulated by the Gillespie algorithm. Recently, a simple two-state CME model combined with the in vitro single-molecule experiments has revealed the molecular basis for the transcriptional burst under an induced condition in prokaryotic cells (Chong, S., et al., *Cell* 158, 314–326).

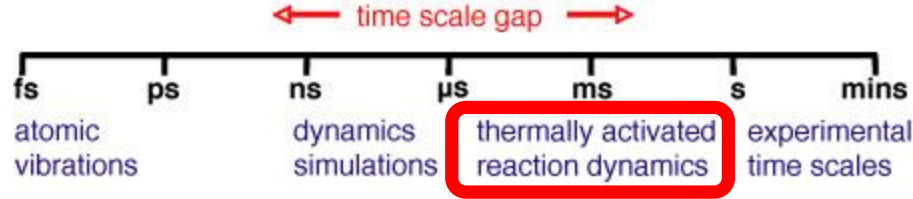
The large deviation principle, a highly sophisticated mathematical theory, clearly and

Computing Power for Genomics



Jian Ma and Olga Milenkovic
University of Illinois at Urbana-Champaign

Genomics research is undergoing a paradigm shift thanks to the development of a myriad of new high-throughput systems for massive data acquisition. These data come with the promise of unprecedented insights into fundamental molecular and cellular mechanisms and the potential for developing models that explain how genomes and regulatory networks function during development and how they differ across species and change in disease state.



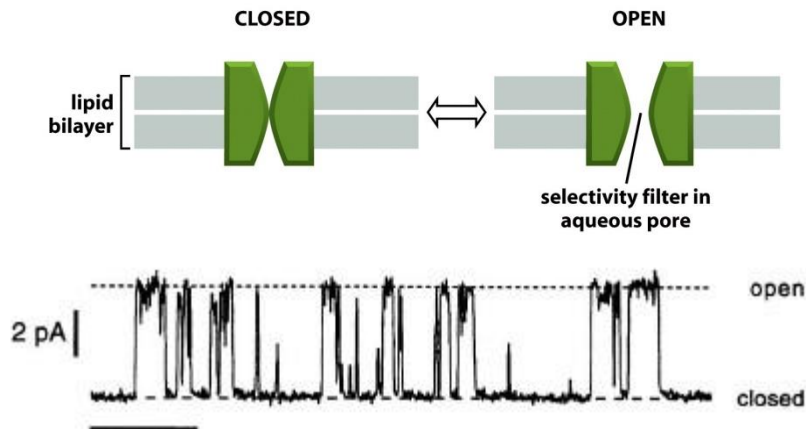
Which kind of physical/chemical processes can be described by stochastic processes?

- **Mesoscopic scale (time and space)**
- **Single-molecule and single-cell (subcellular) dynamics**
- **Trajectory perspective**

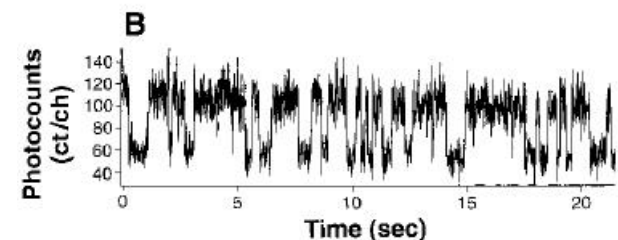
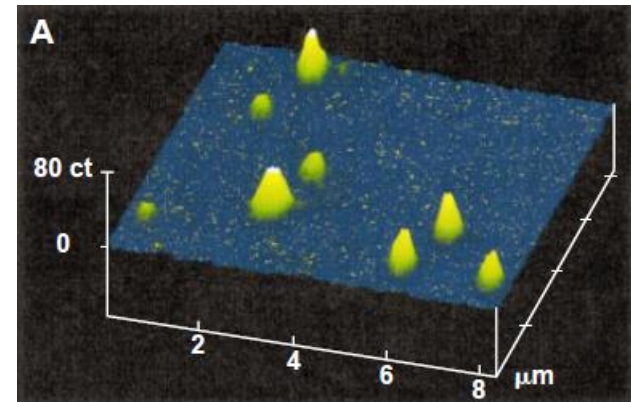
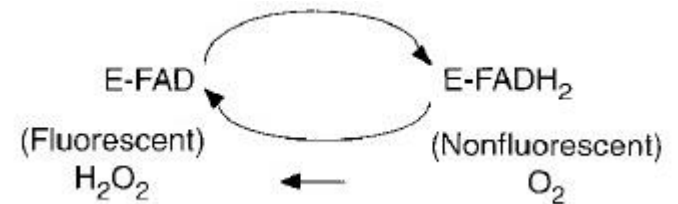


Single-molecule experiments

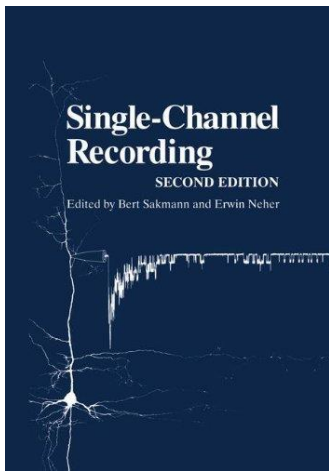
Single Ion channel



Single-molecule enzyme kinetics

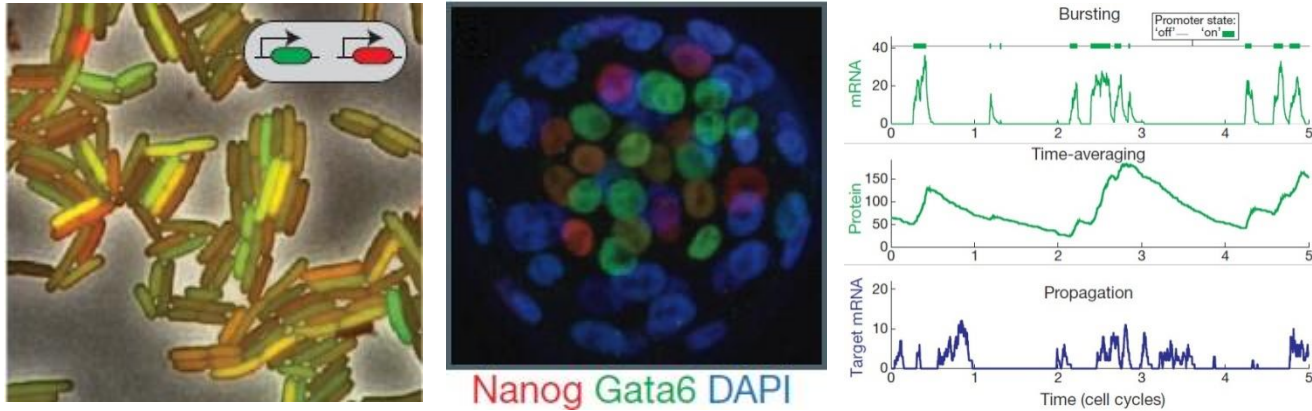


Lu, et al. *Science* (1998)

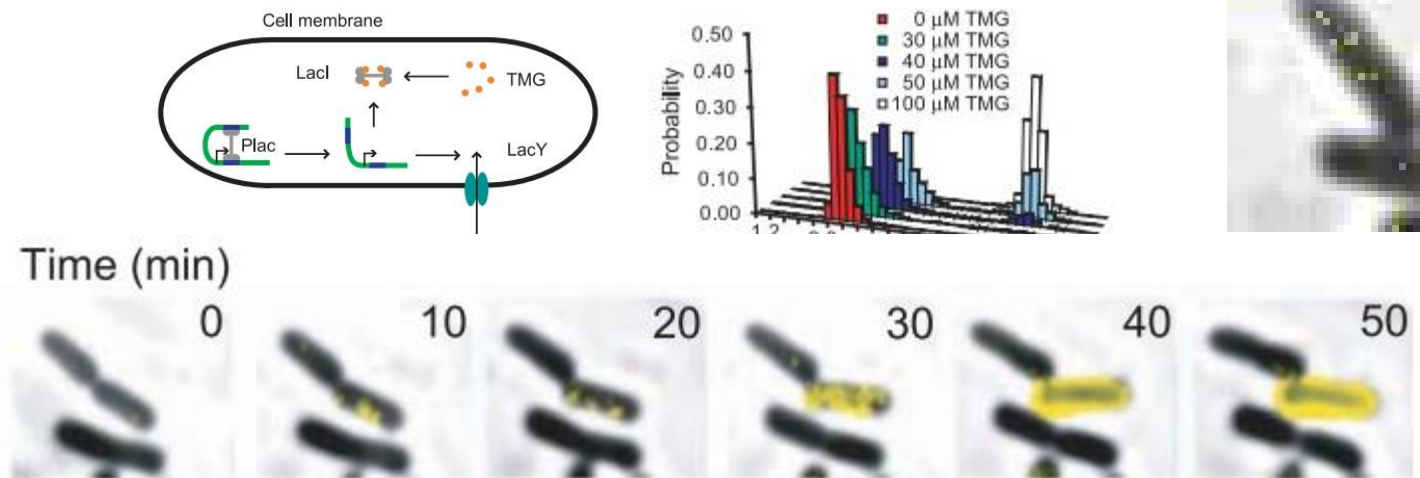


E. Neher and B. Sakmann
Nobel Prize in 1991

Single-cell dynamics (in vivo)

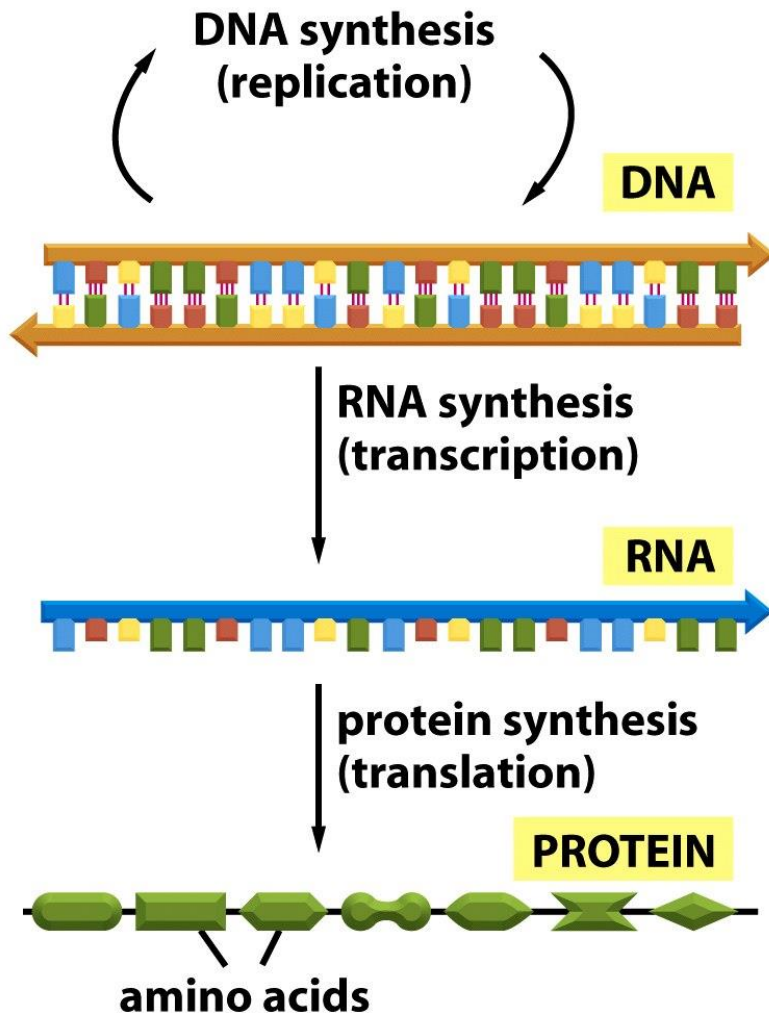


Eldar, A. and Elowitz, M. *Nature* (2010)



Choi, et al. *Science* (2008)

Central Dogma

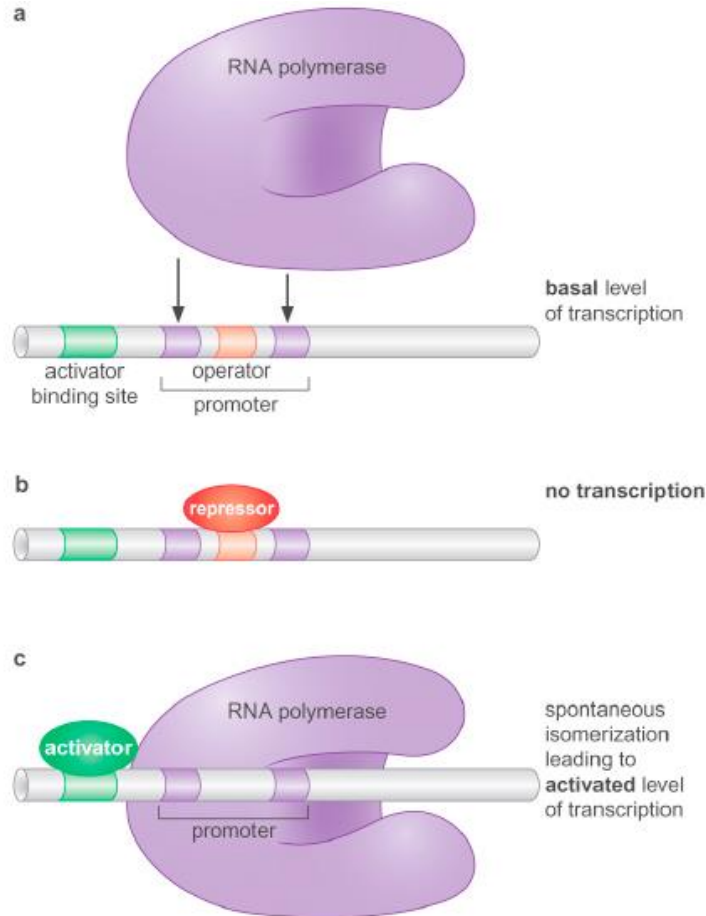


Copy numbers in a single cell

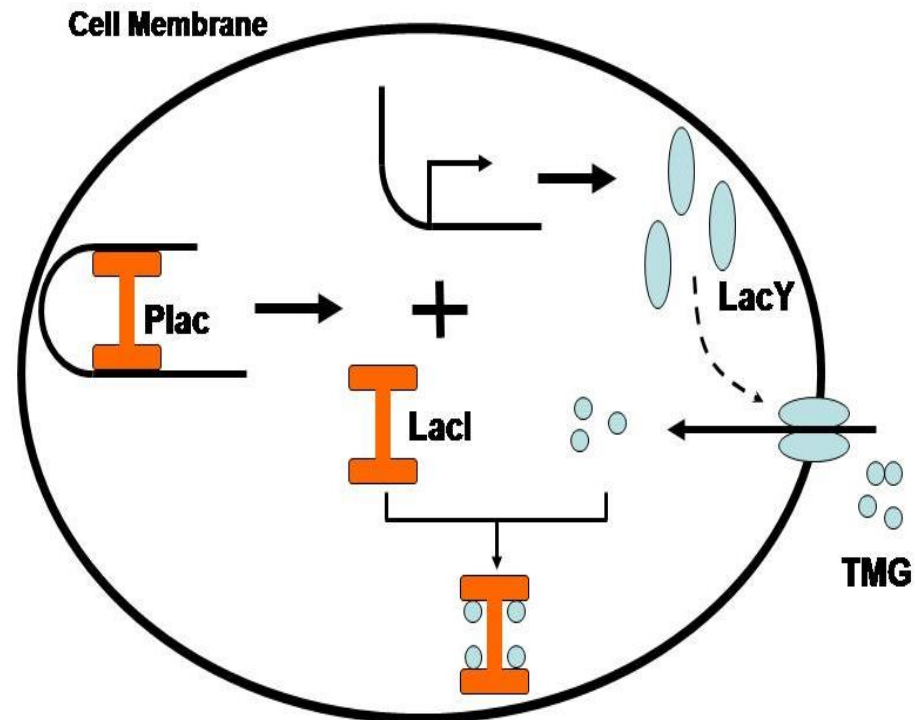
	Bacteria	Eukaryotic cells
DNA	1 or 2	~2
mRNA	A few	1 - 10 ³
Protein	1 - 10 ⁴	1 - 10 ⁶

Not enough attention has been paid to this fact.

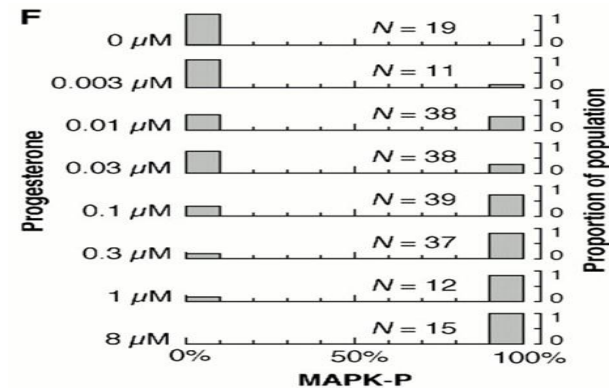
Regulation of gene expression



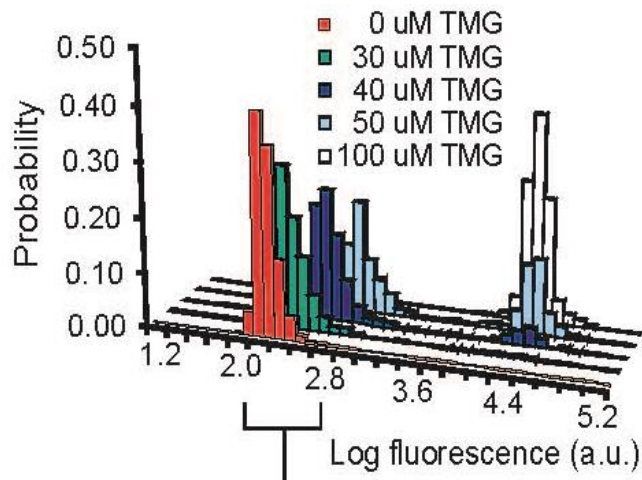
An example of gene circuit with positive feedback: Lac operon



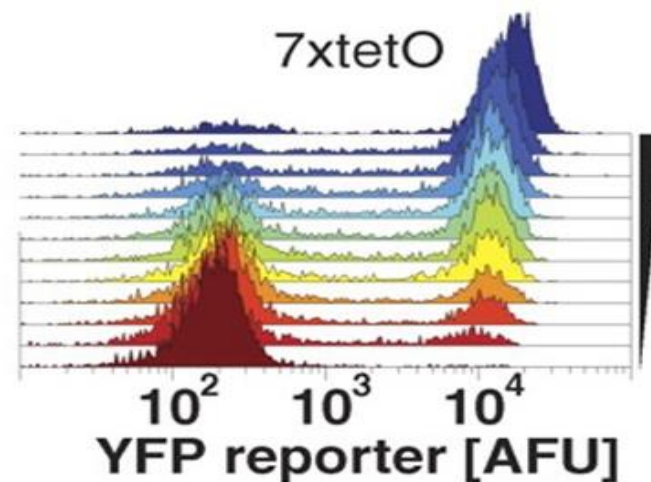
Bimodal distributions in biology: multiple phenotypic states



Ferrell, J. and Machleder, E. *Science* (1998)



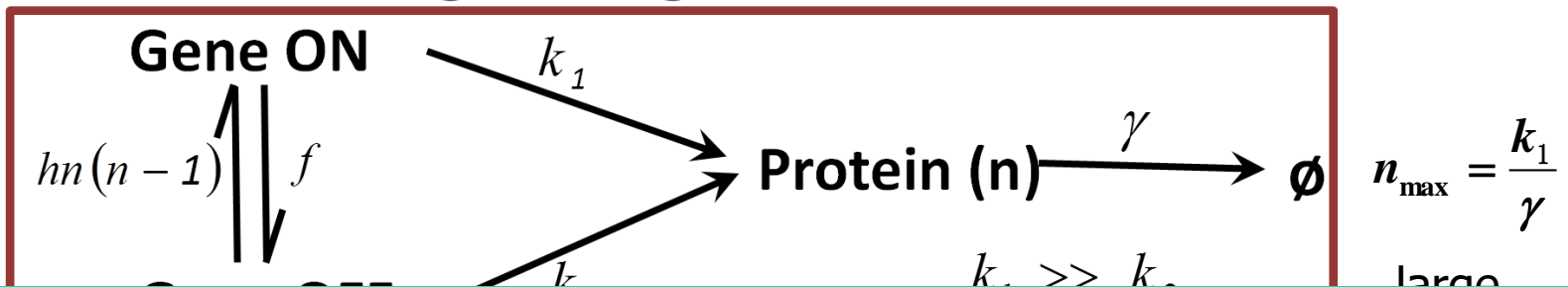
Choi, et al., *Science* (2008)



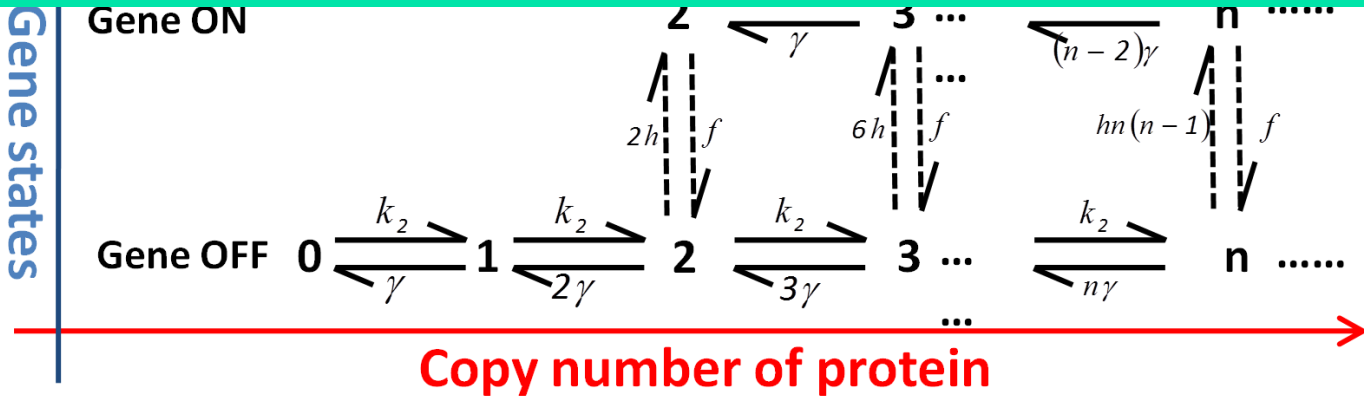
To, T. and Maheshri, N. *Science* (2010)

Two-state model with positive feedback

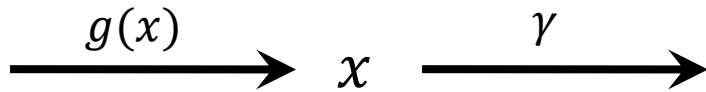
(A) A minimal gene-regulation network



The analytical results introduced here can be applied to any self-regulating module of a single gene, while the methodology is valid for a much more general context.

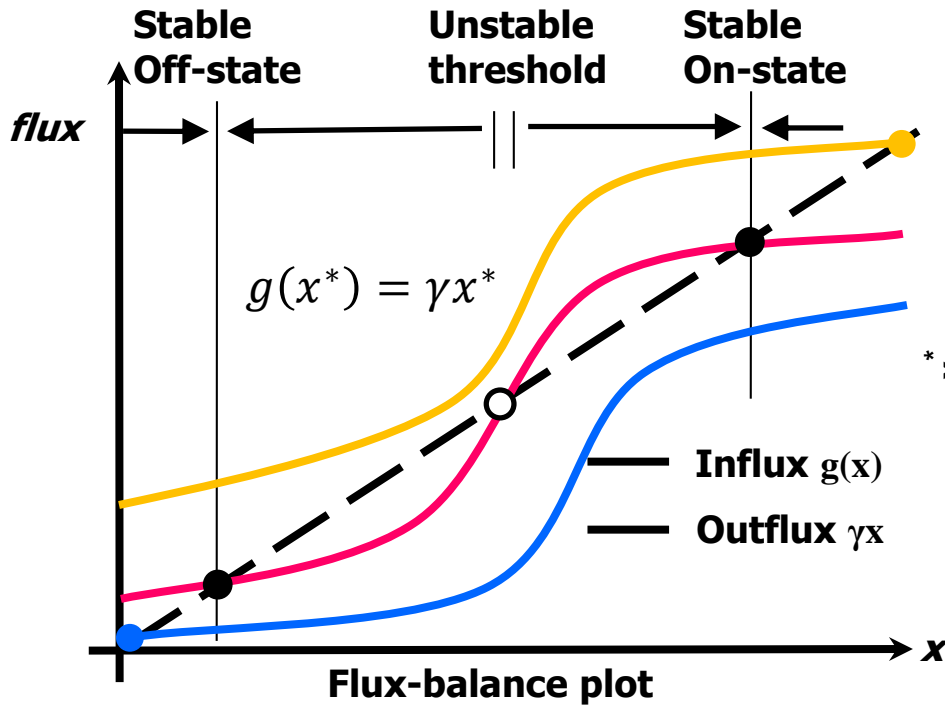


Mean-field deterministic model with positive feedback

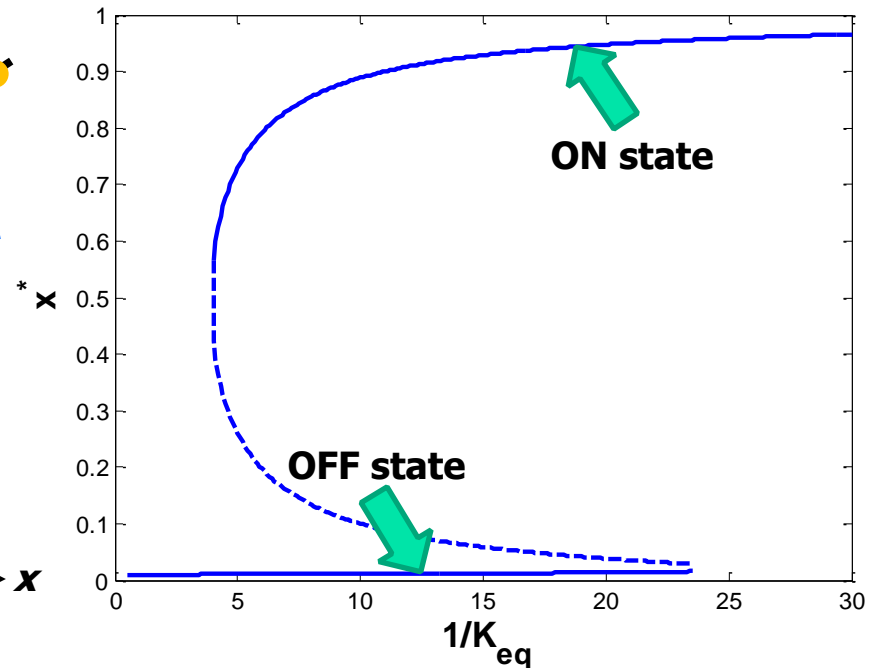


$$\frac{dx}{dt} = g(x) - \gamma x \quad x = \frac{n}{n_{max}}$$

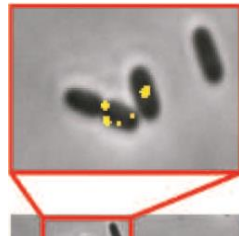
\uparrow
Sigmoidal influx



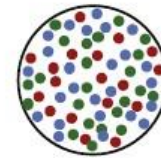
Bifurcation diagram



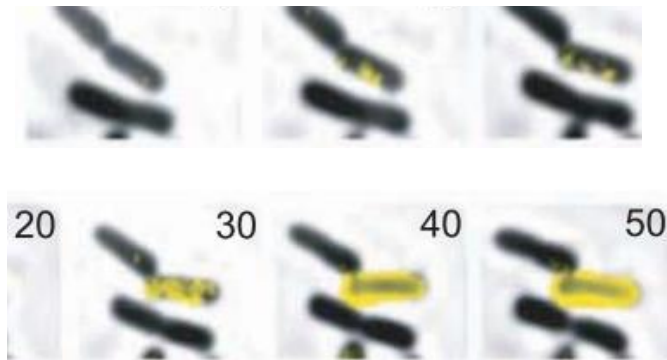
Interconversion of different phenotypic states



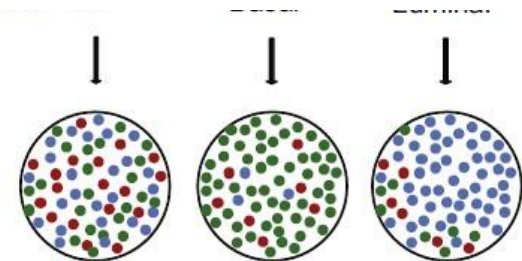
Parental population



How to quantify the transition rates between different phenotypic states, provided their existence?



Choi, et al., *Science* (2008)



Expanded subpopulations

Gupta, et al., *Cell* (2011)

Three time scales and three different scenarios

(i) : *cell cycle* (γ)

(ii) : *gene - state switching* ($f, hn(n-1)$)

(iii) : *synthesis rate of protein* (k_1)



When stochastic gene-state switching is extremely rapid

(i)

(iii)

(ii)

Ao, et al. (2004);
Huang, et al. (2010);...

When stochastic gene-state switching is extremely slow

(ii)

(i)

(iii)

Qian, et al. (2009);
Wolynes, et al. (2005);...

When stochastic gene-state switching is relatively slow

(i)

(ii)

(iii)

Wolynes, et al. (2005);
Ge, et al. (2015)

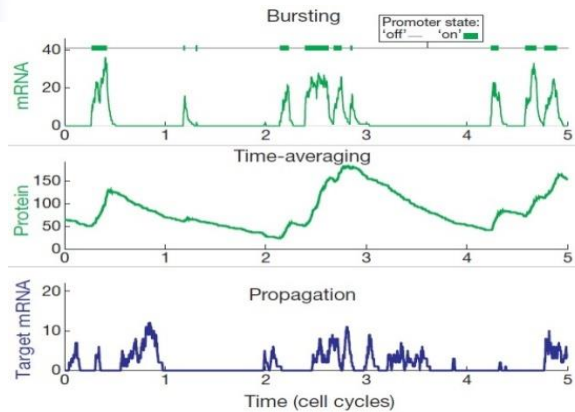
When the time scales of (ii) and (iii) are comparable

(i)

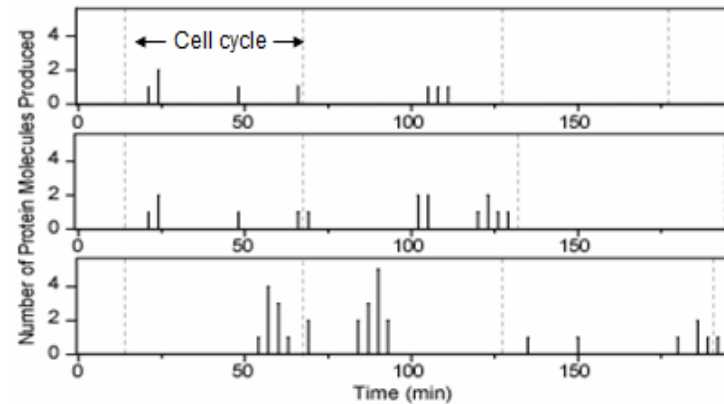
(ii) (iii)

Assaf, et al. (2011);
Li, et al. (2014)

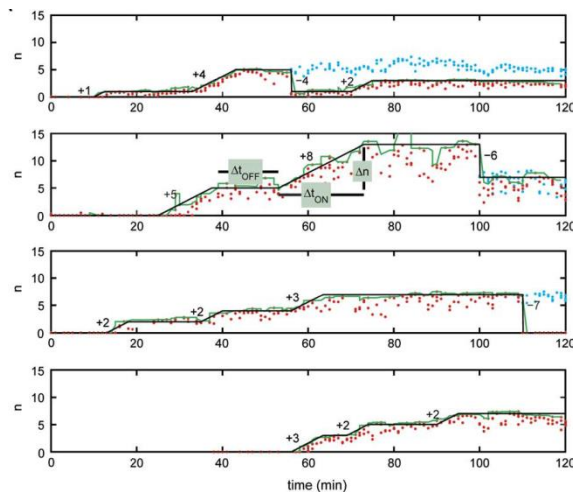
Bursty dynamics and relatively slow gene-state switching



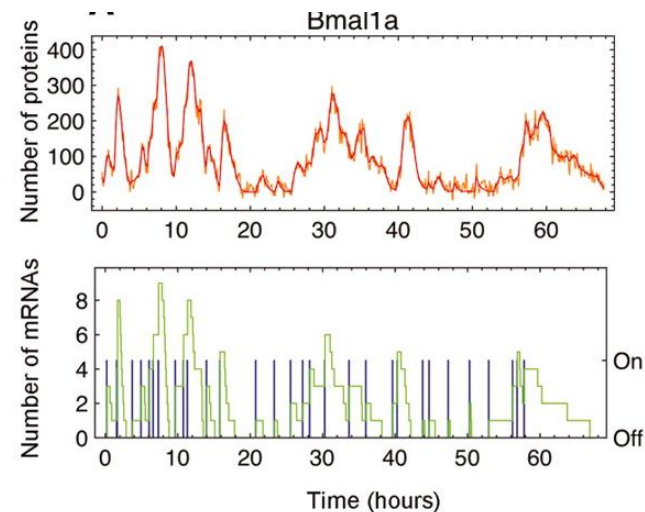
Eldar, A. and Elowitz, M. *Nature* (2010)



Cai, et al. *Science* (2006)



Golding et al. *Cell* (2005)



Suter, et al. *Science* (2011)

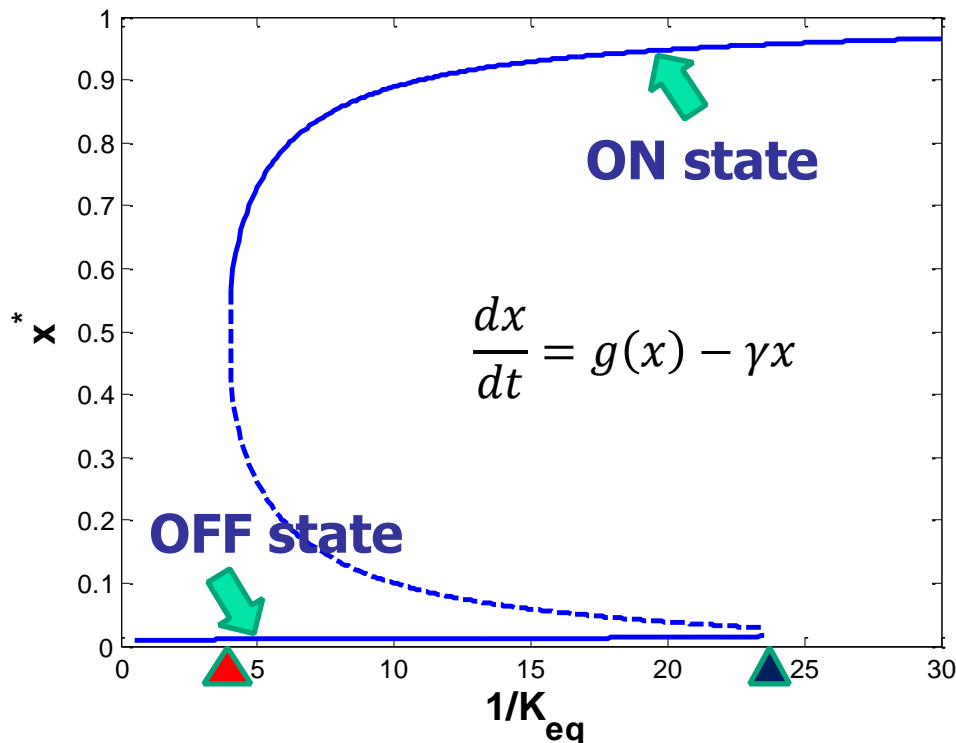
A single-molecule fluctuating-rate model is derived

Rescaled dynamics

(A) $k_1, f, \bar{h} \gg \gamma$

(B) $k_1 \gg f, \bar{h}, \gamma$

**Continuous Mean-field limit
Bifurcation diagram**



**Fluctuating-rate model
(Piecewise deterministic Markov process)**

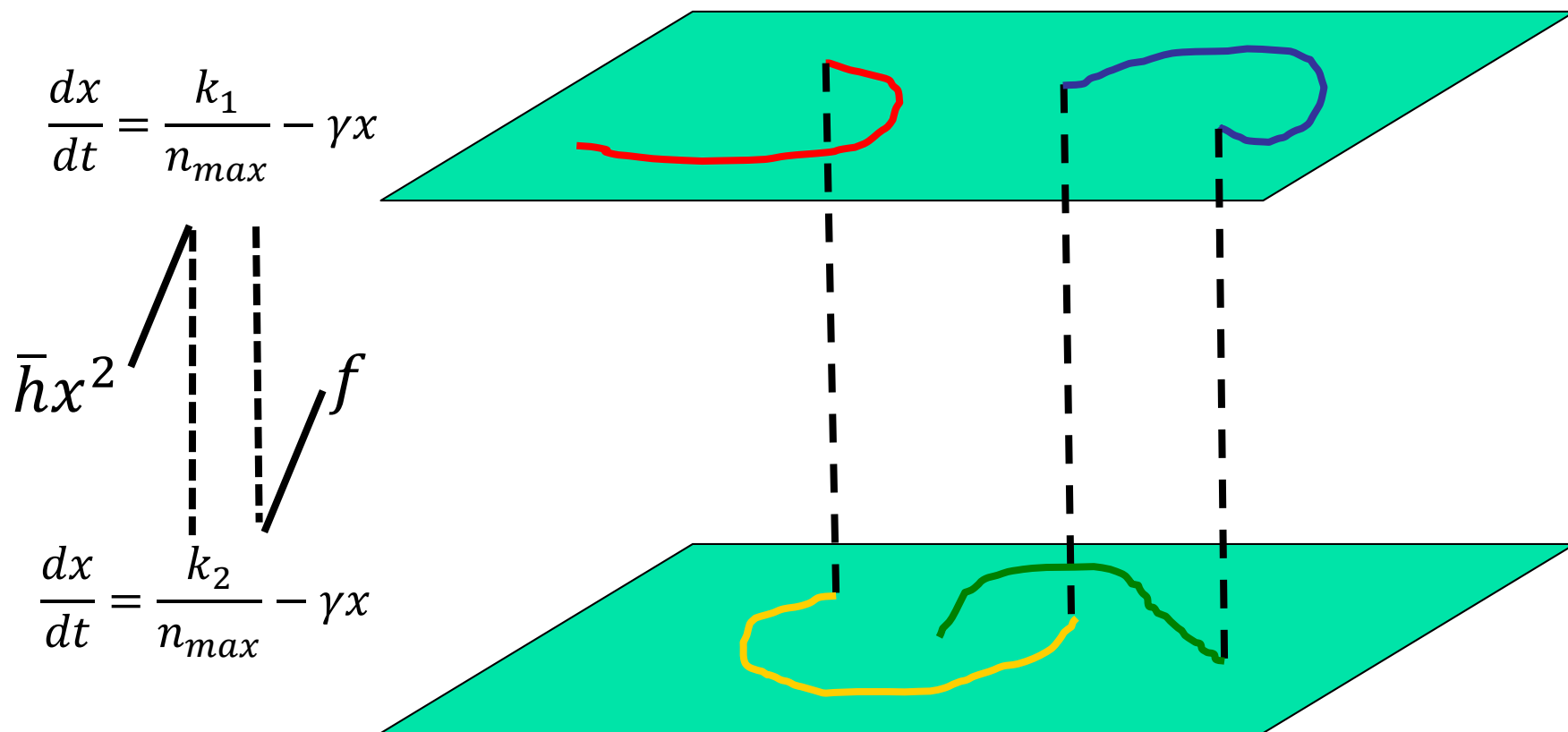
$$\frac{dx}{dt} = \frac{k_1}{n_{max}} - \gamma x$$

$$\frac{dx}{dt} = \frac{k_2}{n_{max}} - \gamma x$$

$$x = \frac{n}{n_{max}}$$

$\bar{h}x^2$ (upward transition rate)
 f (downward transition rate)

Stochastic dynamics of fluctuating-rate model



Nonequilibrium landscape function emerges

As gene-state switching is much faster than the cell cycle

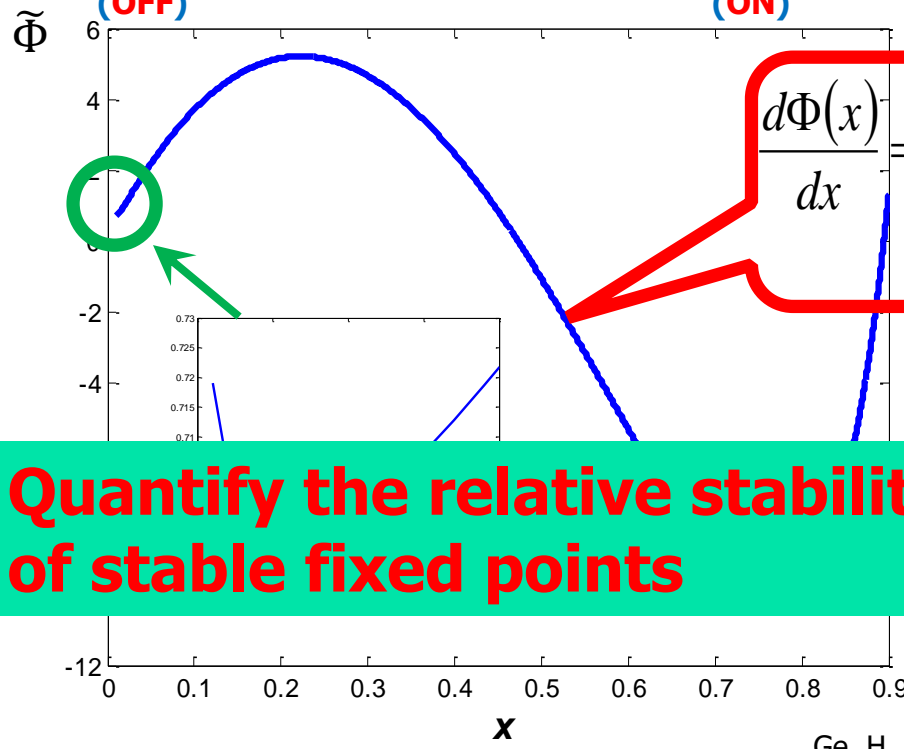
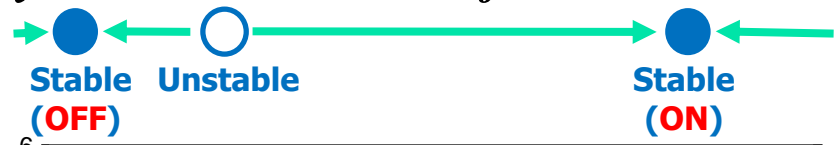
Landscape function

$$p^{ss}(x) \propto e^{-\Phi(x)}$$

analog to energy function at equilibrium case

$$\frac{dx}{dt} = g(x) - \gamma x$$

Dynamics in the mean field limit model



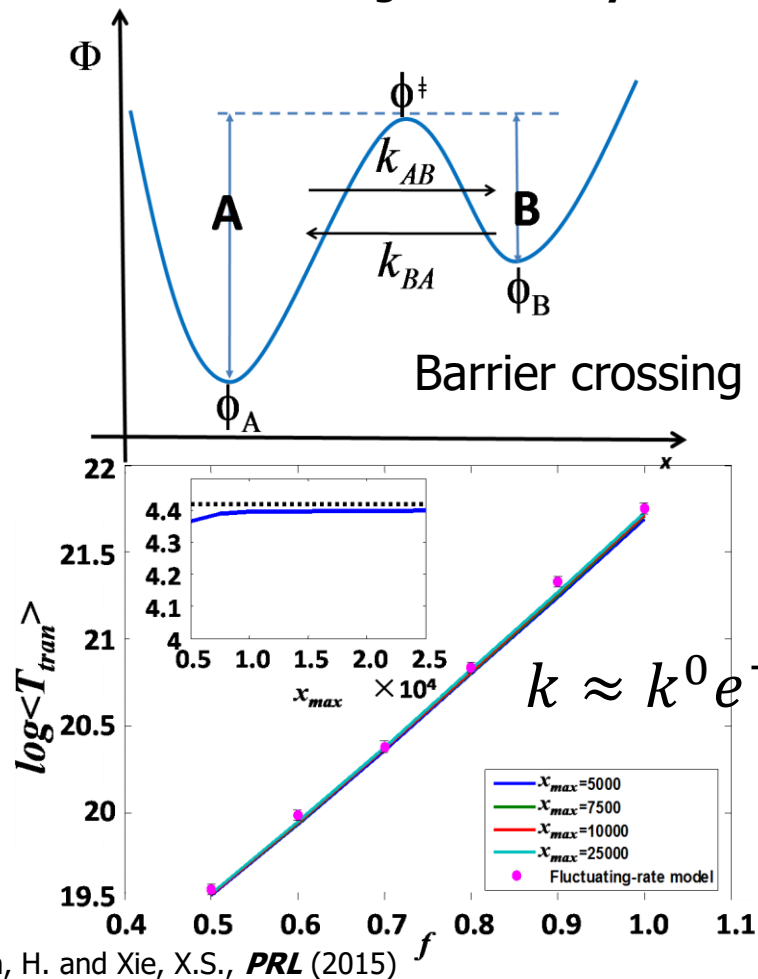
$$\frac{d\Phi(x)}{dx} = \frac{f}{\frac{k_1}{n_{\max}} - \gamma x} + \frac{\bar{h}x^2}{\frac{k_2}{n_{\max}} - \gamma x}$$

Quantify the relative stability of stable fixed points

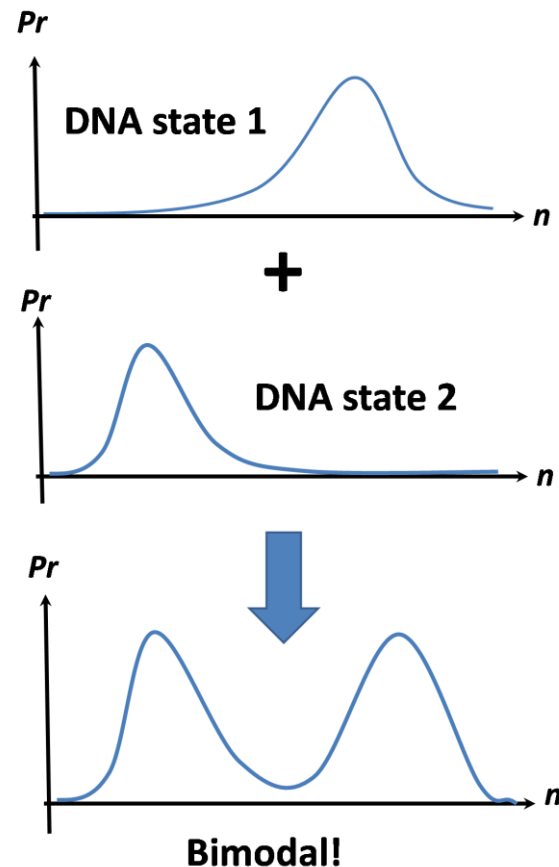
$$\tilde{\Phi} = \Phi / f$$

Rate formulae associated with the landscape function

Gene-state switching is relatively slow

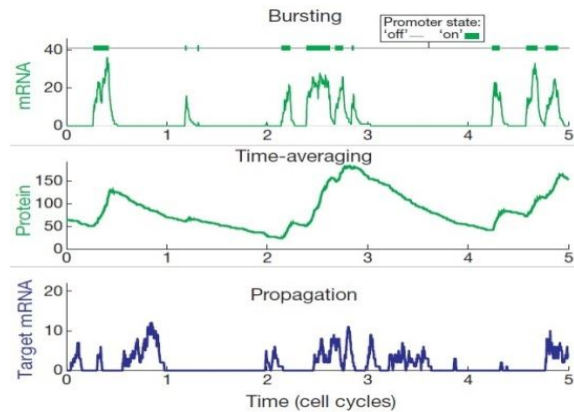


Gene-state switching is extremely slow

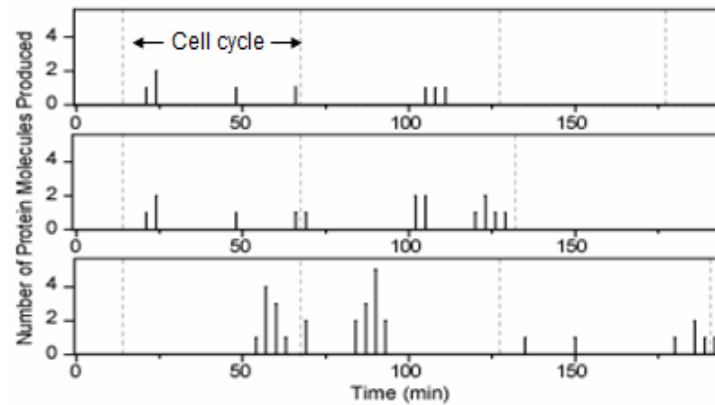


k linearly depend on gene-state switching rates

Compared to previous rate formulae for bursty dynamics



Eldar, A. and Elowitz, M. *Nature* (2010)



Cai, et al. *Science* (2006)

Burst size

$$b \approx \frac{1}{f} \left(\frac{k_1}{n_{\max}} - \gamma x_{\text{off}} \right) \approx \frac{\gamma}{f}$$

If $\frac{d\Phi(x)}{dx} \approx \frac{1}{b}, x \leq x^\ddagger$ \longrightarrow $k \approx k^0 e^{-\frac{x^\ddagger - x_{\text{off}}}{b}}$

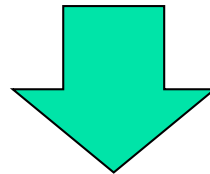
Rigorous analysis: quasi potential in LDP



Local: The Donsker-Varadhan large deviation theory for Markov process



Global: The Freidlin-Wentzell large deviation theory for random perturbed dynamic system



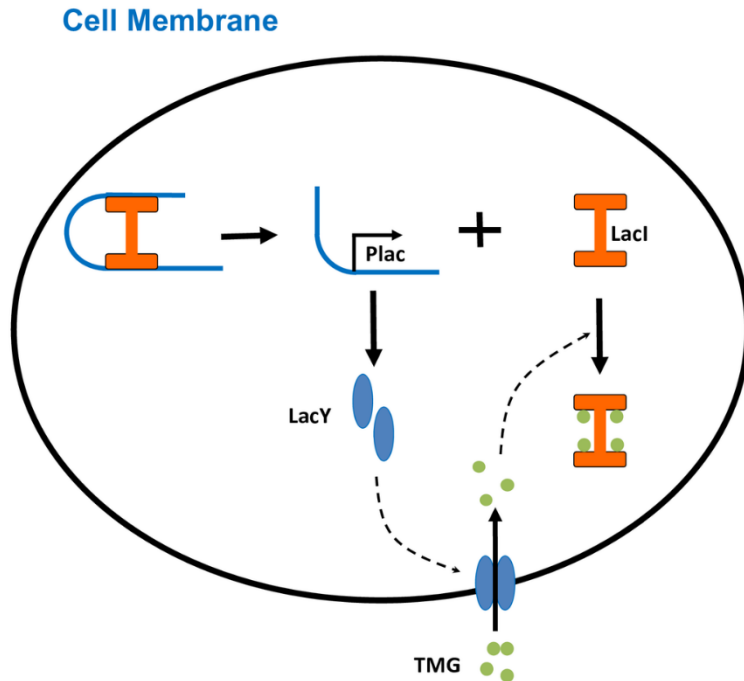
LDT of Fluctuating-rate model (Switching ODE)

See Chapter 7 in Freidlin and Wentzell: Random Perturbations of Dynamical Systems (2nd Ed). Springer 1984

Faggionato A. et al.: Non-equilibrium thermodynamics of piecewise deterministic Markov processes, *JSP* (2009)

Fluctuating-rate model for Lac operon

(A) **Positive feedback (PF)
+ multiple gene states**

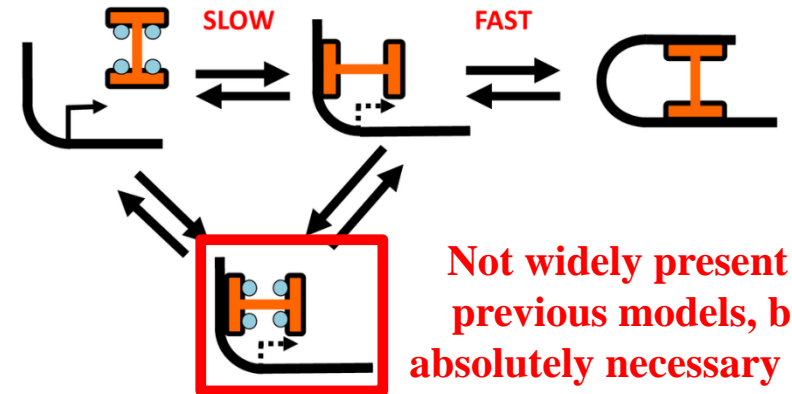


$$\begin{aligned} \frac{dM}{dt} &= Dk_M \eta \leftarrow k_M M, \\ \frac{dY}{dt} &= k_Y M - \gamma_Y Y, \\ \frac{dI}{dt} &= \alpha k_I Y \beta (I_e) - \gamma_I I + c(I_e - I). \end{aligned}$$

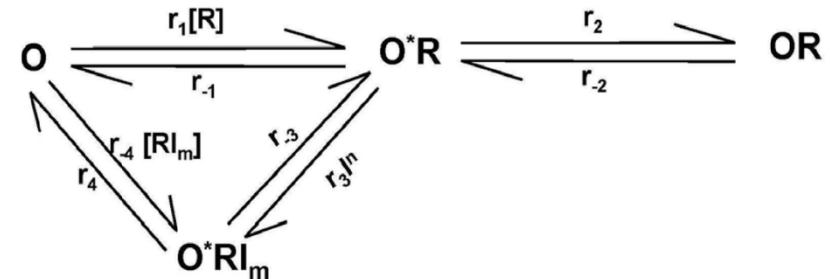
Stochastic variable for the state of operon

Inspired by Choi, et al. *Science* (2008)

(B)



(C)



Single-molecule fluctuation broadens bistability with PF

Mean-field model

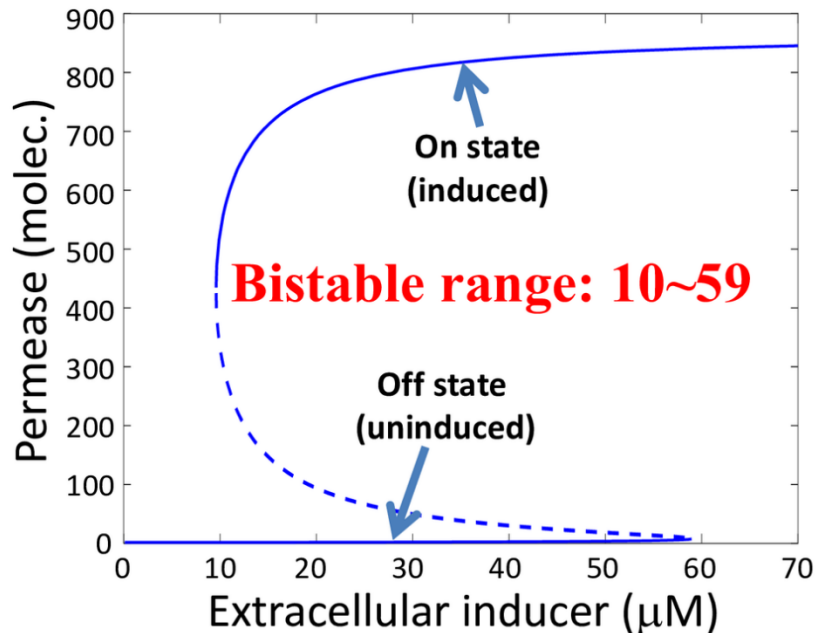
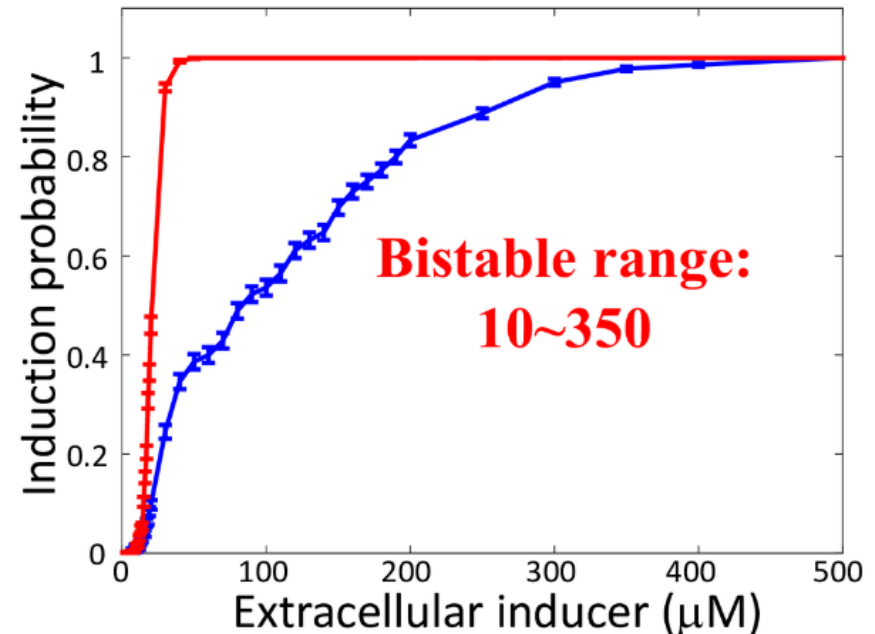


Diagram for **deterministic bistability**

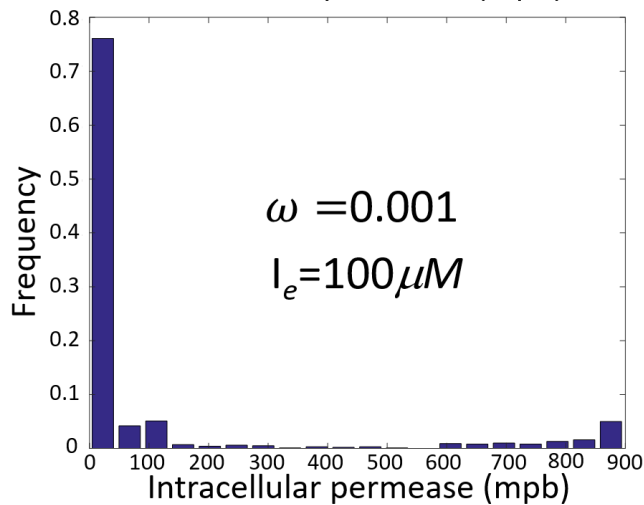
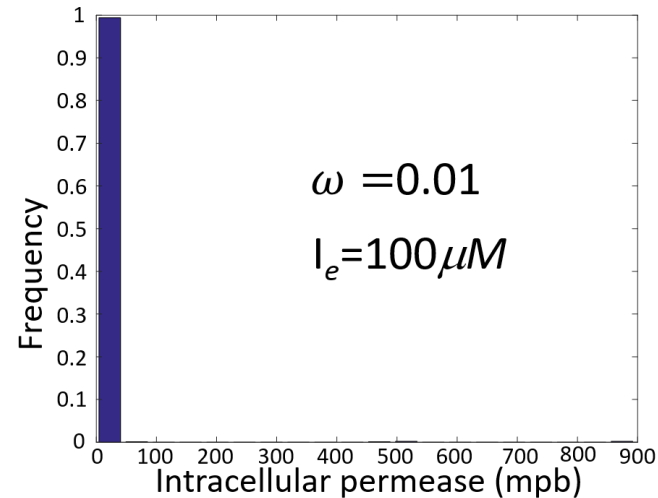
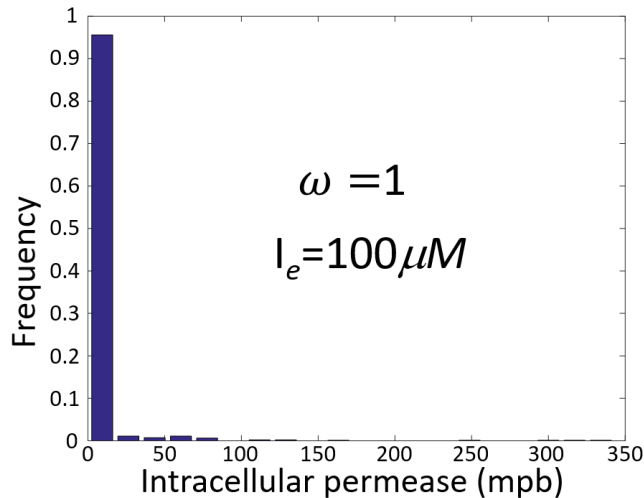
Steady-state hysteresis



Broadened bistability: emergence of stochastic bistability

Stochastic bistability without PF is impossible

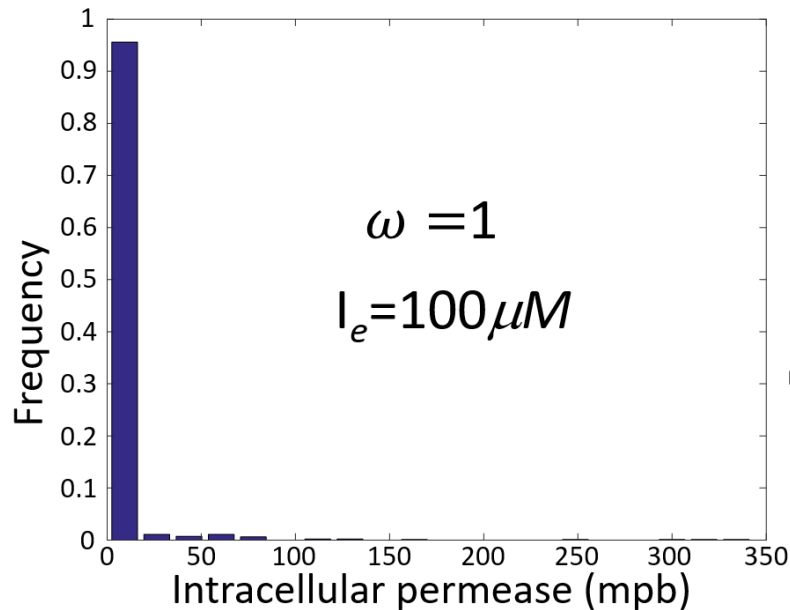
ω : the ratio of operon-state switching rates with respect to the wild-type cells



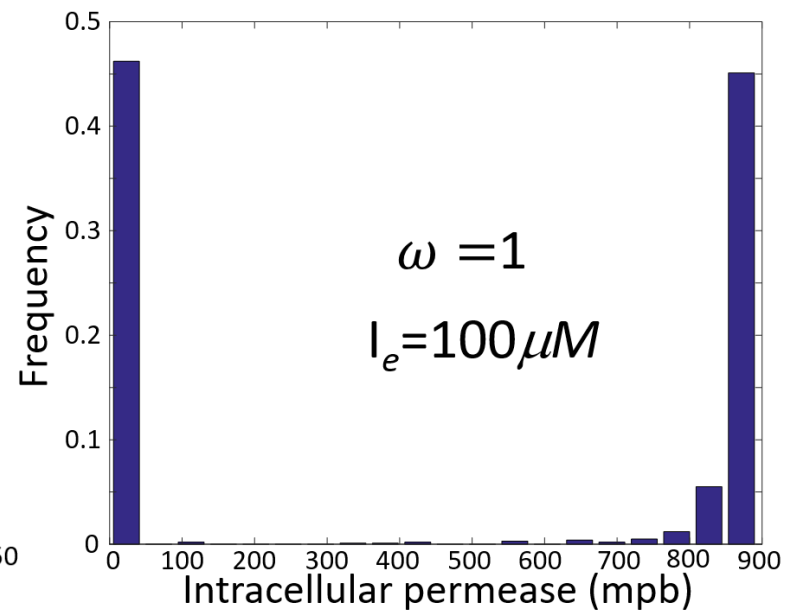
Slow gene-state switching is necessary for stochastic bistability; But has to be extremely slow in the absence of positive feedback!

Stochastic bistability with PF: stabilizing the induced state

Without feedback

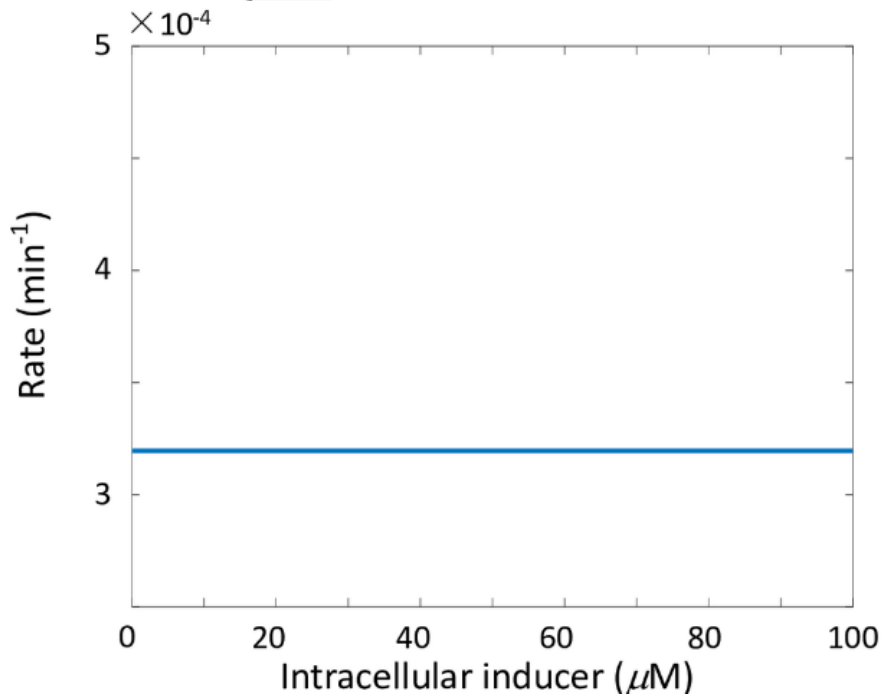


With feedback

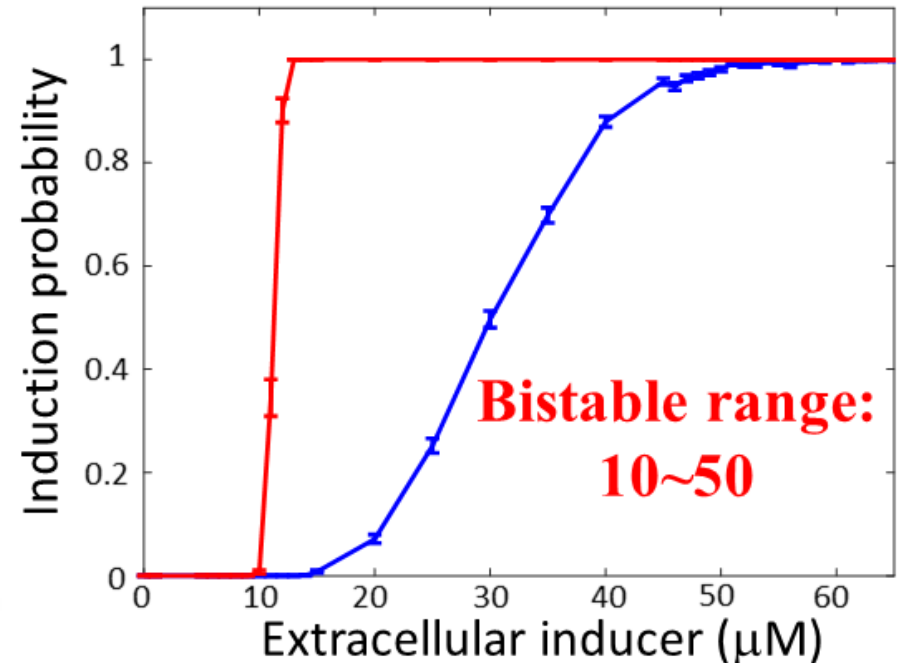


**With the help of PF, gene-state switching
does not have to be extremely slow!**

Slow operon-state switching: stabilizing the uninduced state

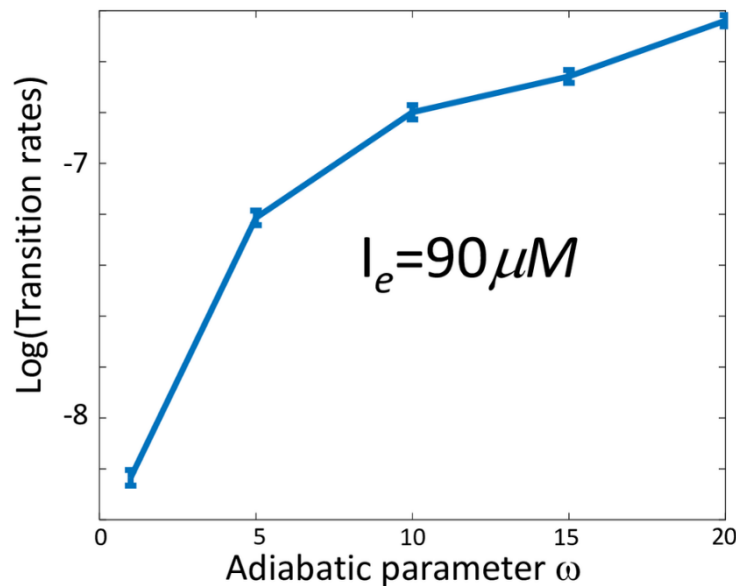


$$\omega = 20$$

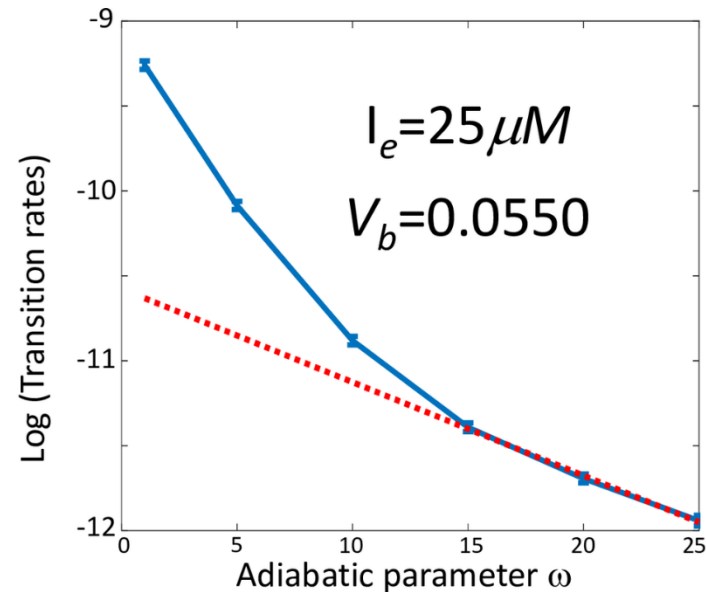


Transition rates distinguishing two categories of bistability

Increasing the gene-state switching rates



k_{ij} increases and finally saturates
Stochastic bistability



$k_{ij} \approx k_{ij}^0 e^{-\omega V_{ij}}$
Deterministic bistability



Summary

- **Stochastic processes become more and more popular to model the mesoscopic biophysical dynamics, especially in single-cell biology.**
- **We proposed a single-molecule fluctuating-rate model in an intermediate scenario, which is significantly simpler than the full Chemical-Master-Equation description. Also we derived an associated saddle-crossing rate formula for the phenotype.**
- **We apply the fluctuating-rate model to Lac operon system, showing why and how the stochastic gene-state switching broads the parameter region for bistability.**

Acknowledgement



Prof. Hong Qian
University of Washington



Prof. Sunney Xiaoliang Xie
Harvard University
and now Peking University

Fundings: NSFC, MOE of PRC



Thanks for your attention!
