

# Predicting Spatiotemporal Fluctuations of Gene Expression

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Presented at the 2015 q-bio Summer School  
Fort Collins (7/6); San Diego (7/22); Albuquerque (7/23)



# q-bio Summer School

## Three Campuses:

Albuquerque, NM (July 6-21)

San Diego, CA (July 13-28)

Fort Collins, CO (July 13-28)

## Eight Focus Areas:

Stochastic Gene Regulation

Cancer Dynamics

Complex Biological Dynamics

Cell signaling

Viral dynamics

Biomolecular simulations

Membrane biology

Computational Synthetic Biology

Experimental Synthetic Biology

Visit us at online at:

<http://q-bio.org>



## The 2015 q-bio Summer School (Albuquerque, San Diego, Fort Collins)

Applications are now being accepted for the Ninth Annual q-bio Summer School. Applications will be due on **Monday, February 16 at 11:59pm (MST)**. Submitted applications may be revised until that time. To apply now, please visit the application website: <https://www.openconf.org/qbioss2015/openconf.php>  
**Scholarships are available.**

The 2015 q-bio Summer School will be held on different dates at three different campuses

- 1) July 6-21, 2015 at the Colorado State University in Fort Collins, CO
- 2) July 13-28, 2015 at the University of New Mexico in Albuquerque, NM
- 3) July 13-28, 2015 at the University of California in San Diego, CA.

### School Overview:

The q-bio Summer School is an annual event intended to advance predictive modeling of cellular regulatory systems by exposing participants to a survey of work in quantitative biology and by providing in-depth instruction in selected techniques, with an emphasis on techniques useful for modeling cellular regulatory networks. Certain data analysis techniques and experimental methods will also be covered.

Lectures will be offered at **three campuses**. At the **San Diego campus**, the focus will be on synthetic biology. At the **Albuquerque and Fort Collins campuses**, the focus will be on different aspects of systems biology. Students will each work on a mentored project. Participants will attend daily core lectures, project-specific lectures, journal clubs, and computer and experimental labs. The summer school is designed for graduate students, postdocs, or anyone with a quantitative background who is new to modeling cellular regulatory systems/networks.

At the School students will attend 20-25 hours of core lectures, 20-25 hours of course-specific lectures, 10-15 hours of computational and experimental labs, and 10-15 hours of student presentations. There will also be 20-30 hours of mentored project work, which may include some simple experiments, theoretical developments and/or real data analyses.

### The main topics of the 2015 summer school are:

Biomolecular Simulations (Albuquerque, NM), Cell Signaling (Albuquerque, NM), Membrane Biology (Albuquerque, NM), Viral Dynamics (Albuquerque, NM), Cancer Dynamics (Fort Collins, CO), Stochastic Gene Regulation (Fort Collins, CO), Complex Biological Dynamics (Fort Collins, CO), Experimental Synthetic Biology (San Diego, CA), and Computational Synthetic Biology (San Diego, CA)

### Organizers:

S. Gnanakaran, *New Mexico Consortium, Los Alamos*, Jeff M. Hasty, *University of California, San Diego*, William S. Hlavacek, *New Mexico Consortium, Los Alamos*, Marek Kimmel, *Rice University, Houston*, Brian Munsky, *Colorado State University, Fort Collins*, Ashok Prasad, *Colorado State University, Fort Collins*, Douglas Shepherd, *University of Colorado, Denver*, Patrick Shipman, *Colorado State University, Fort Collins*, Mara P. Steinkamp, *University of New Mexico, Albuquerque*, Lev S. Tsimring, *University of California, San Diego*

### For inquiries about the scientific content at the summer school, please contact:

Brian Munsky (Fort Collins Campus): [munsky@engr.colostate.edu](mailto:munsky@engr.colostate.edu)  
Bill Hlavacek (Albuquerque Campus): [wshlavacek@gmail.com](mailto:wshlavacek@gmail.com)  
Lev Tsimring (San Diego Campus): [Itsimring@ucsd.edu](mailto:Itsimring@ucsd.edu)

### Point of Contact:

Shannan Yeager, q-bio Program Manager, [syeager@newmexicoconsortium.org](mailto:syeager@newmexicoconsortium.org)

For more information, please visit the school wiki at:  
[http://q-bio.org/wiki/The\\_Ninth\\_q-bio\\_Summer\\_School](http://q-bio.org/wiki/The_Ninth_q-bio_Summer_School)

- 1. Introduction - Information from transcript fluctuation**
2. Measuring and modeling single-cell and single-molecule responses
3. Case studies:
  - i. Kinase-activated gene transcription in budding yeast.
  - ii. Kinase-activated gene transcription in human cells.
4. Concluding remarks

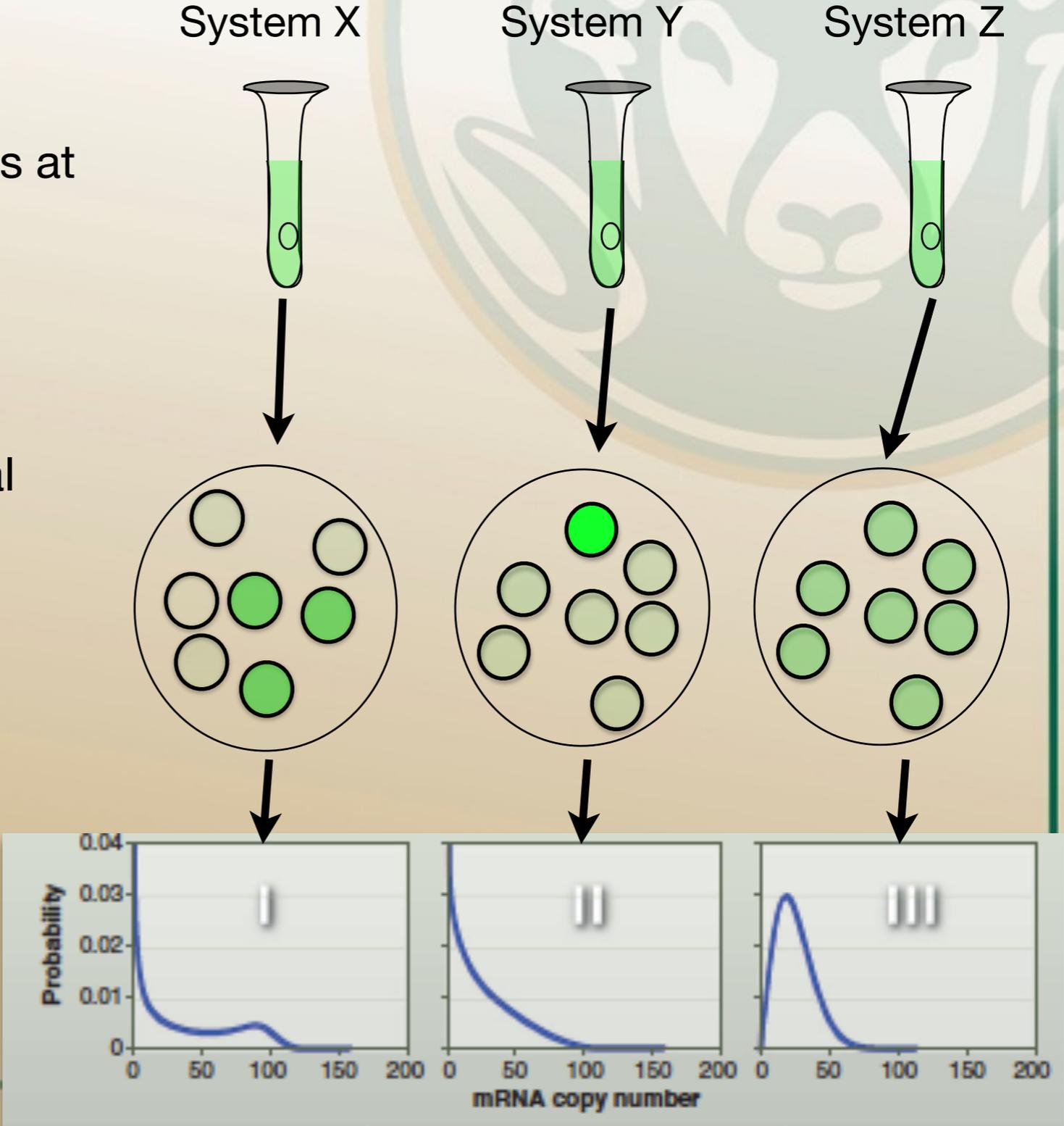


# Information in fluctuation

Different systems (species, inputs, mechanisms, ...) may express genes at equal *average* levels.

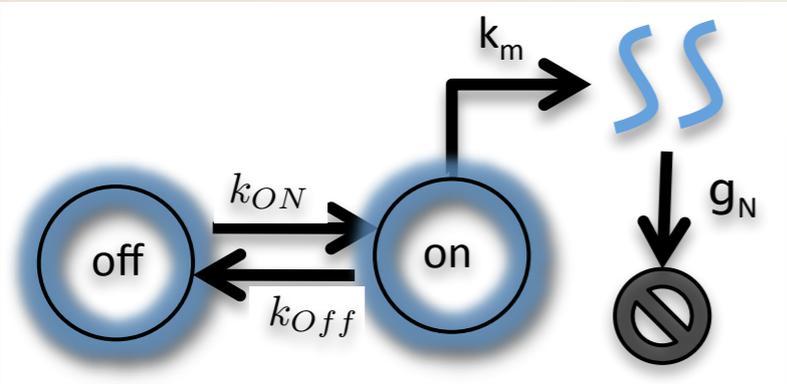
Single-cell measurements may reveal hidden response differences.

Collective responses can exhibit distinctive “fluctuation fingerprints”.



# Fluctuations may indicate gene regulation mechanisms

- Consider the bursting gene expression model:



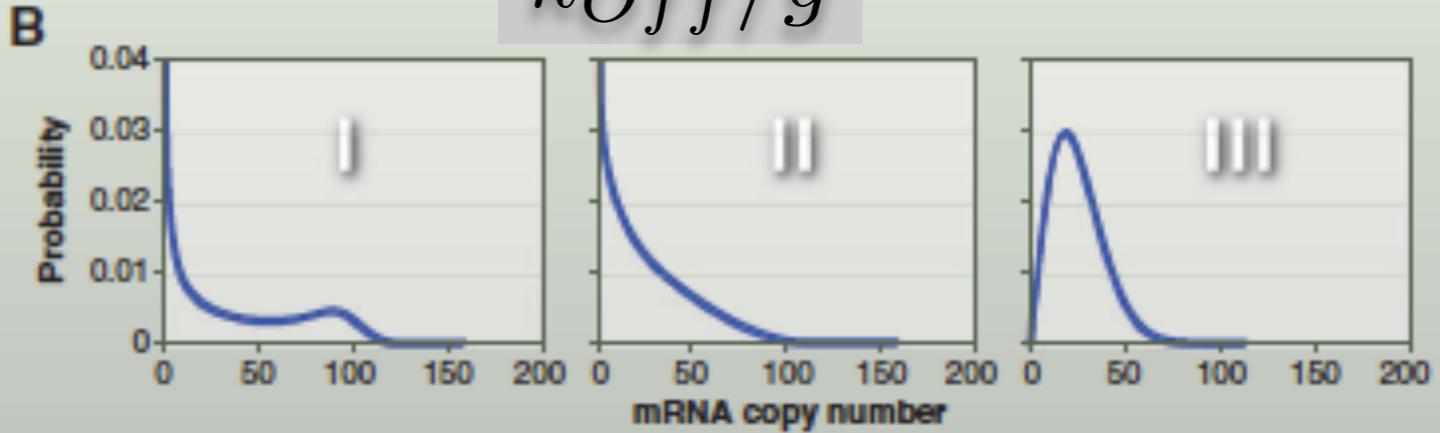
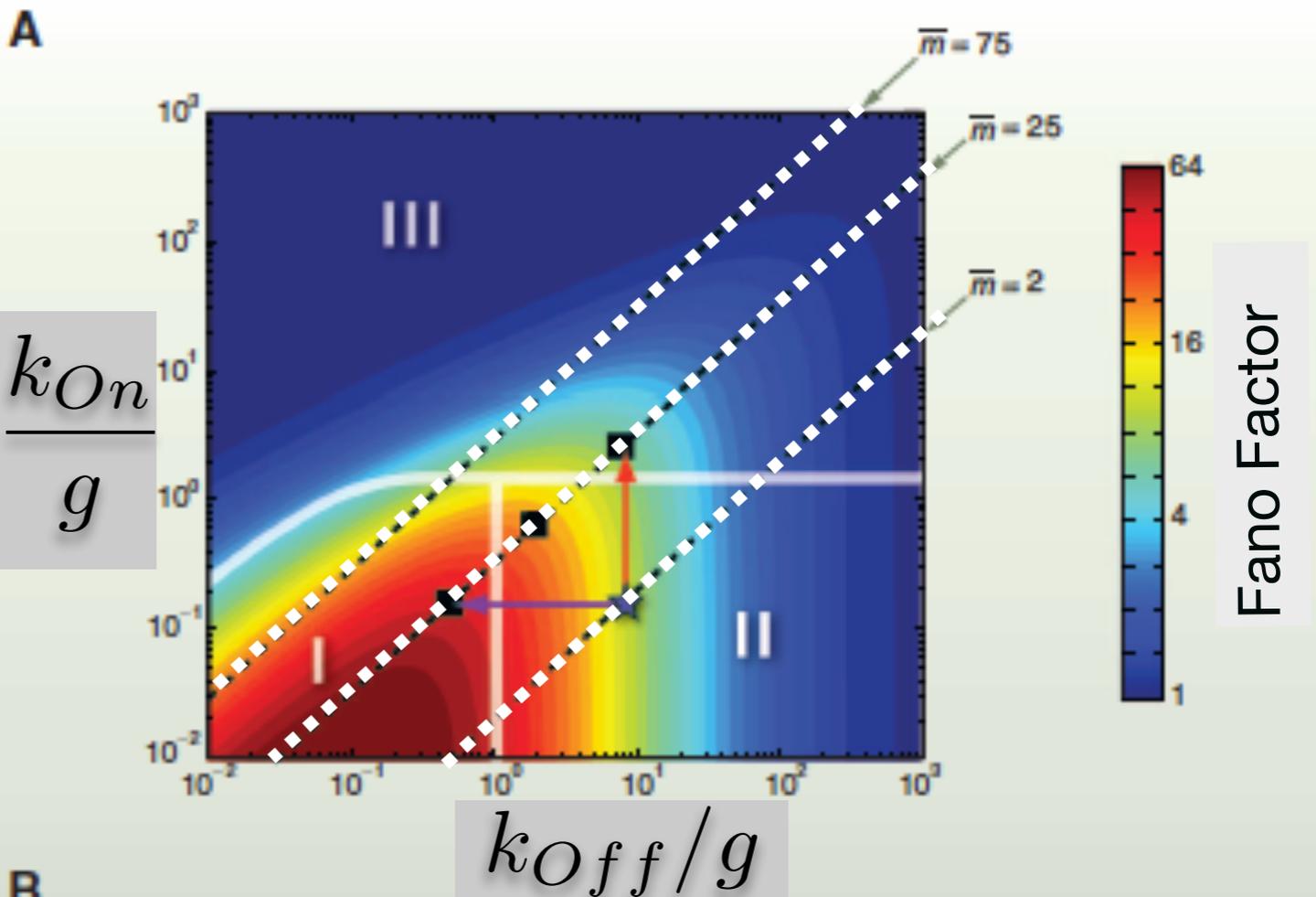
- Compute the expression mean and variability as functions of all parameters.

$$f_{on} = \frac{k_{ON}}{k_{ON} + k_{OFF}}$$

$$\mu = f_{on} \frac{k_m}{g_m}$$

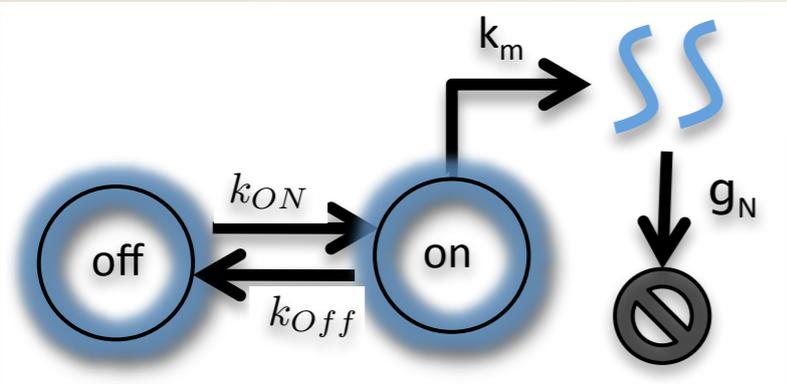
$$\frac{\sigma^2}{\mu} = 1 + \frac{(1 - f_{on}) k_m}{k_{ON} + k_{OFF} + g_m}$$

Expression 'Noise' versus parameters



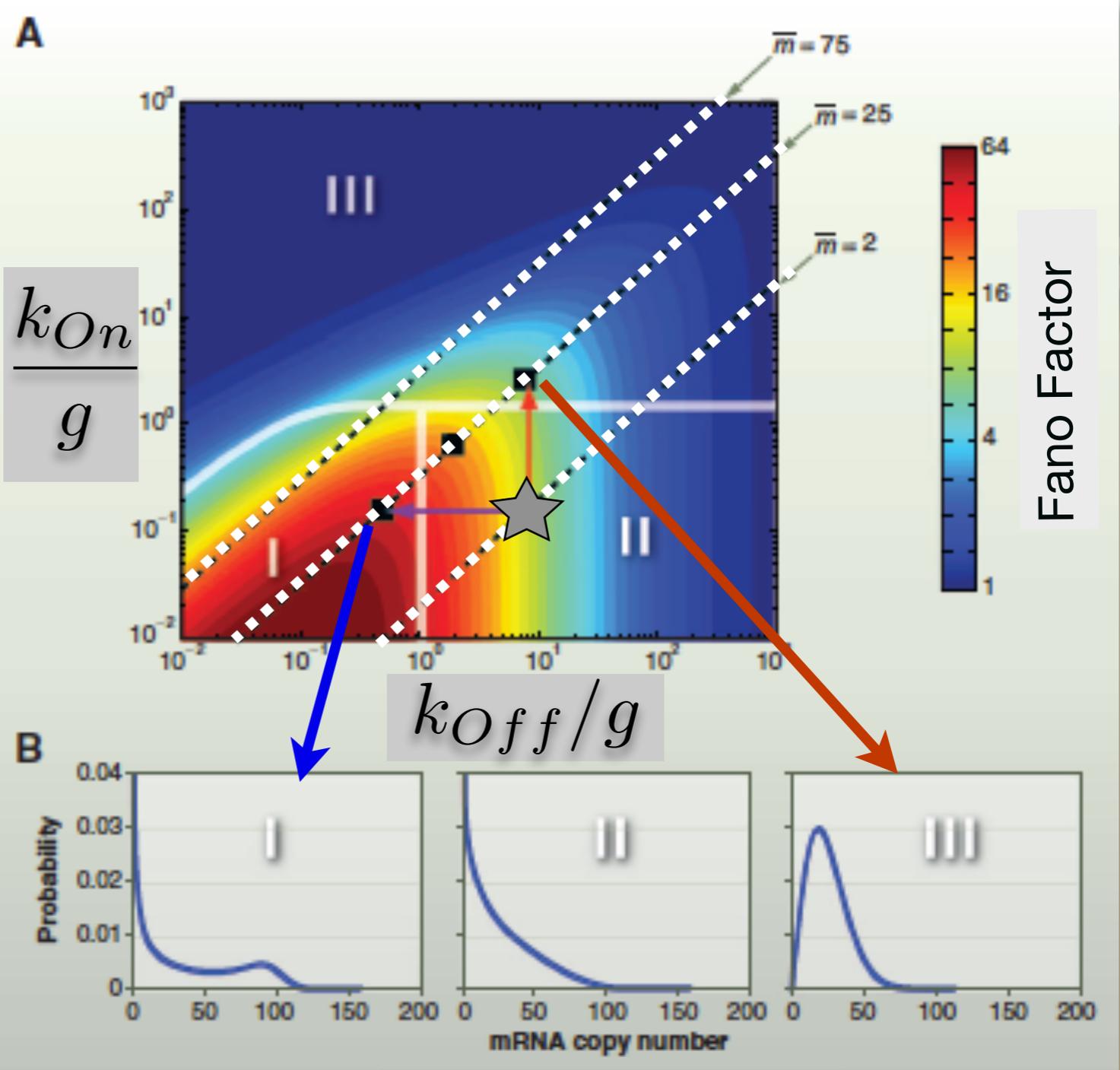
# Fluctuations may indicate gene regulation mechanisms

- Consider the bursting gene expression model:



- Compute the expression mean and variability as functions of all parameters.
- Tuning  $k_{Off}$  or  $k_{On}$  can increase expression, but:
- Tuning  $k_{Off}$  increases variability.**
- Tuning  $k_{On}$  decreases variability.**

Expression 'Noise' versus parameters



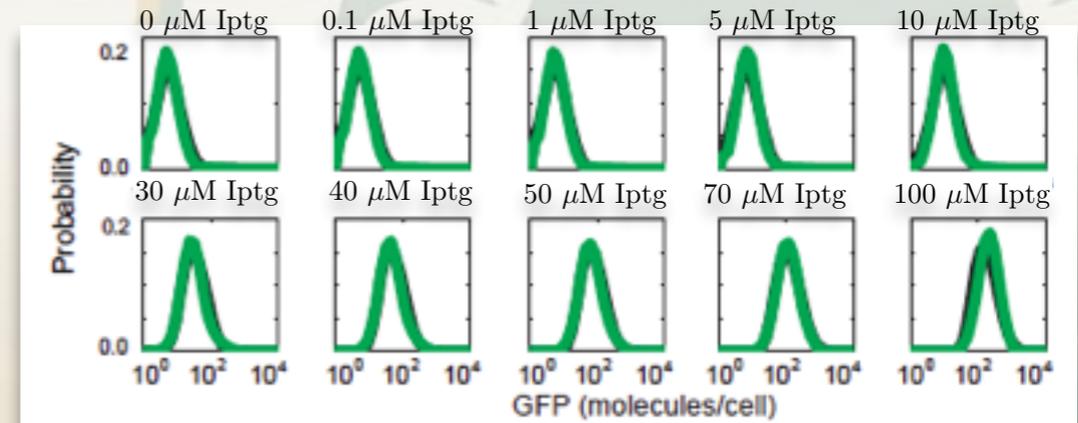
1. Introduction - Information from transcript fluctuation
- 2. MEASURING and modeling single-cell and single-molecule responses**



# Experimental tools for single-cell analyses

## Flow Cytometry

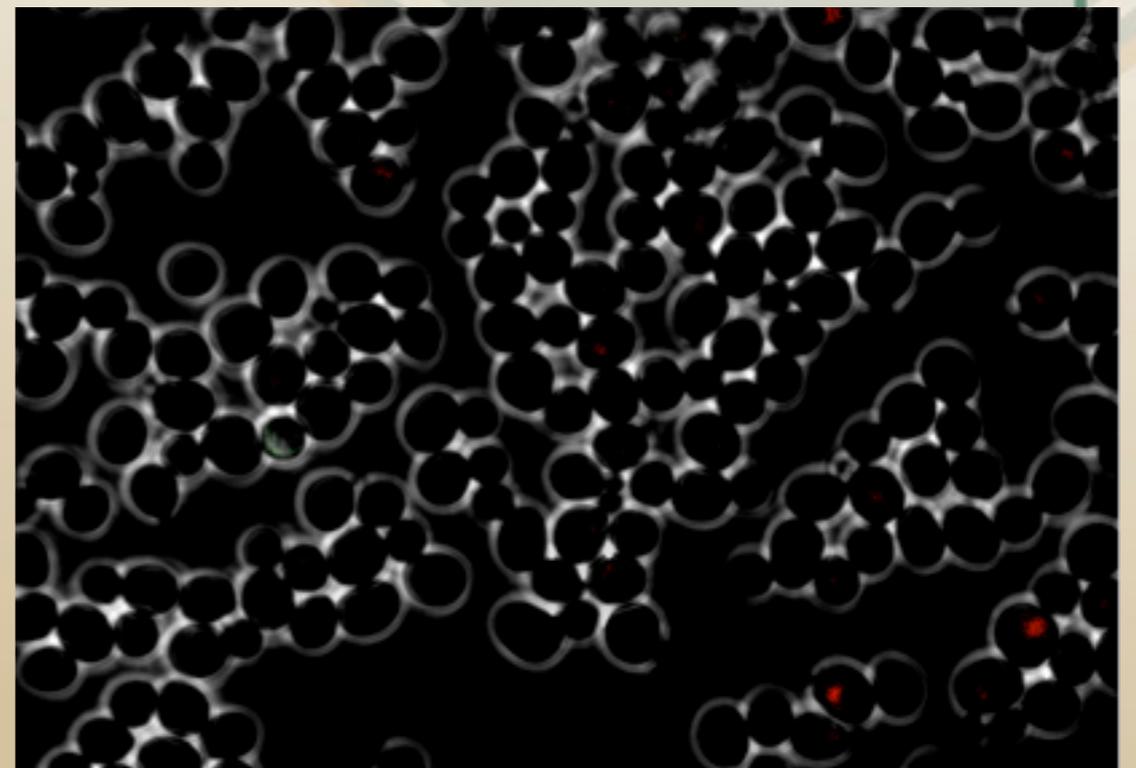
- Measure expression with fluorescent proteins or antibody labels for thousands of cells per second.



Lou, et al, *Nature Biotechnology*, 2012

## Time Lapse Fluorescence Microscopy

- Measure spatial and temporal properties of fluorescent protein responses.

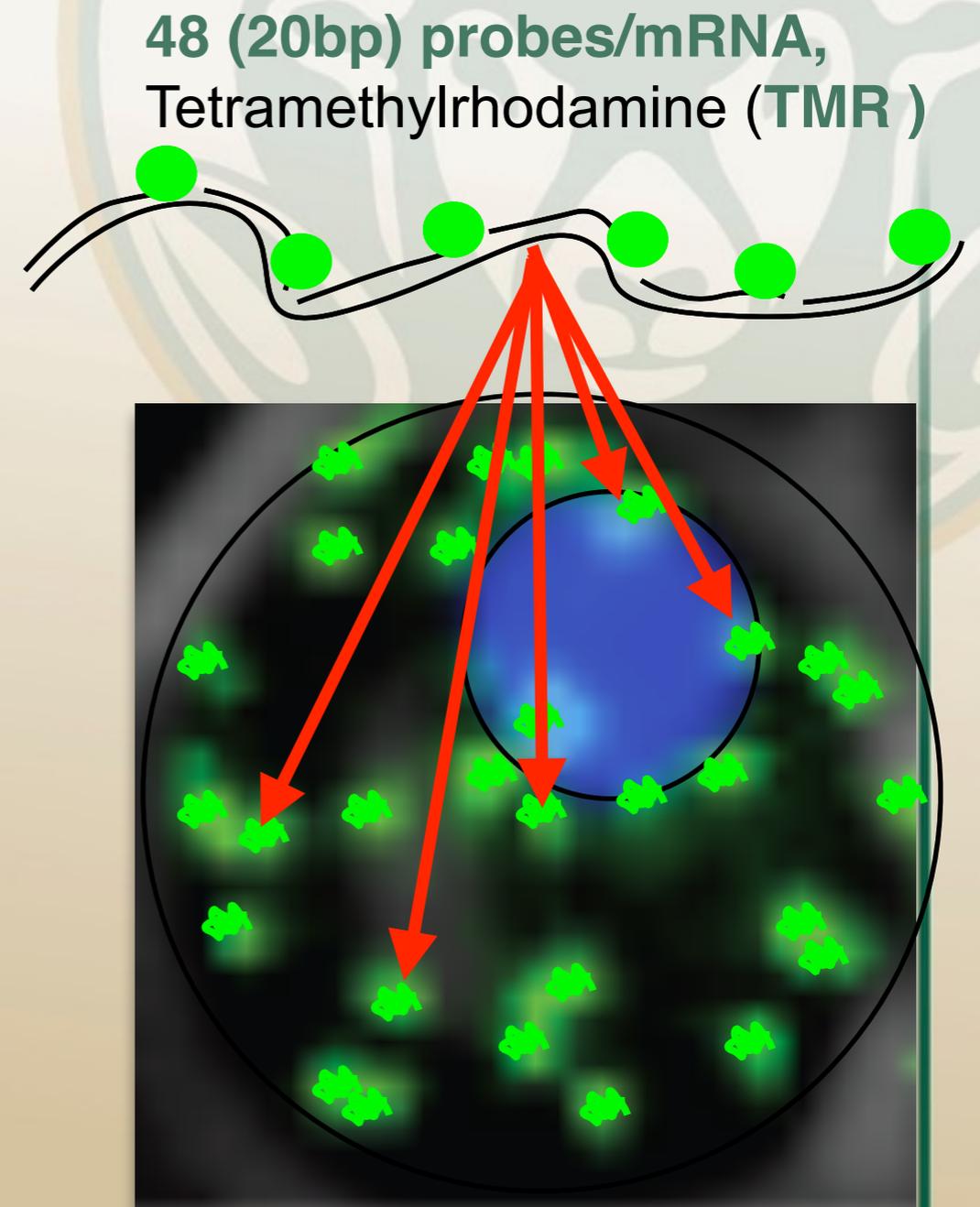


(Neuert, Munsky, et al, 2013)



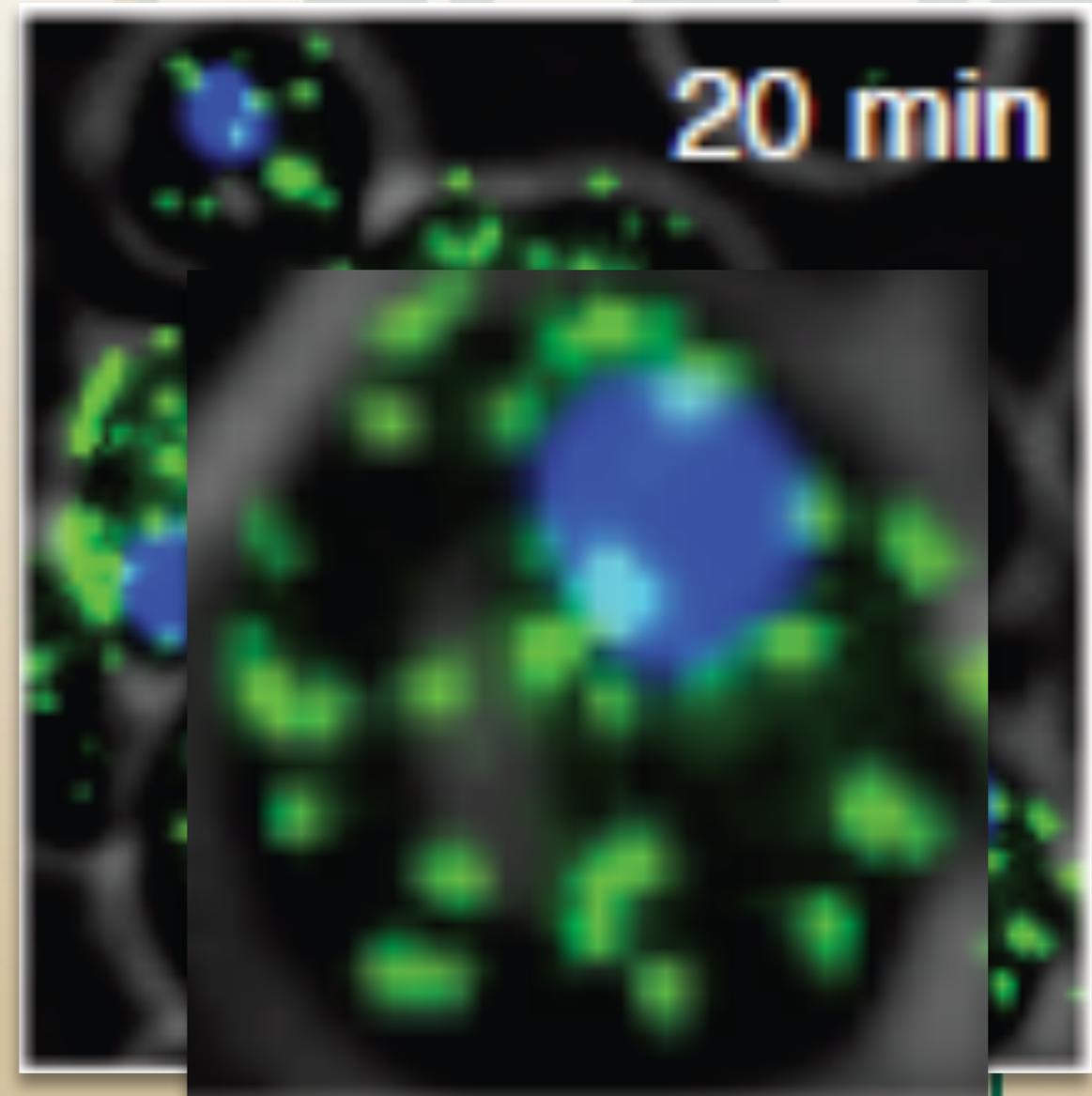
# Single-Molecule FISH (smFISH)

- Endogenous mRNA's can be labeled with single molecule Fluorescence *in situ* Hybridization (smFISH--Femino, 1998, Raj, 2008).
- Many probes (~50) are attached to endogenous mRNA.
- High signal-to-noise ratio enables single-molecule detection.



# Single-Molecule FISH (smFISH)

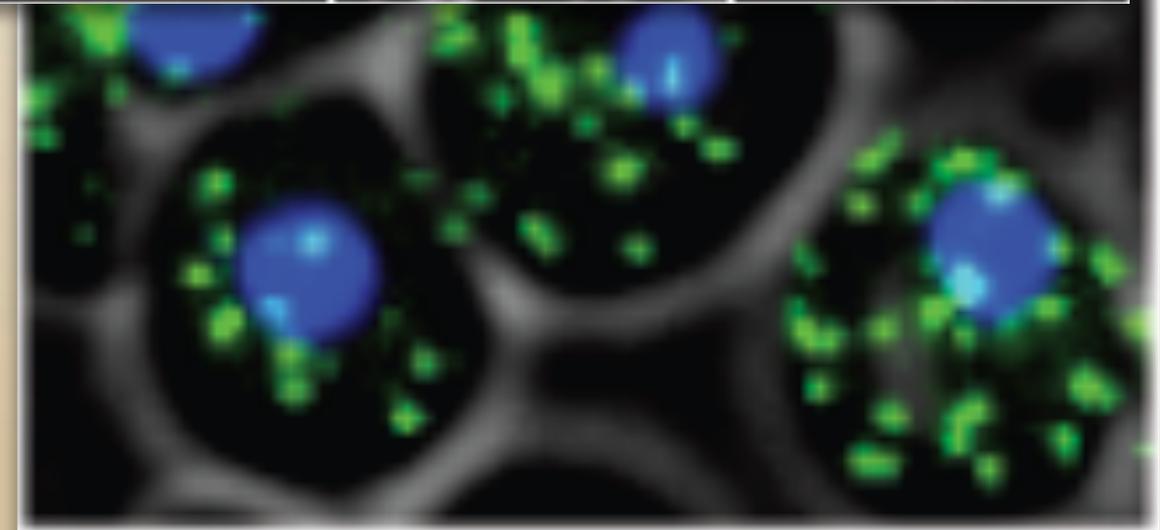
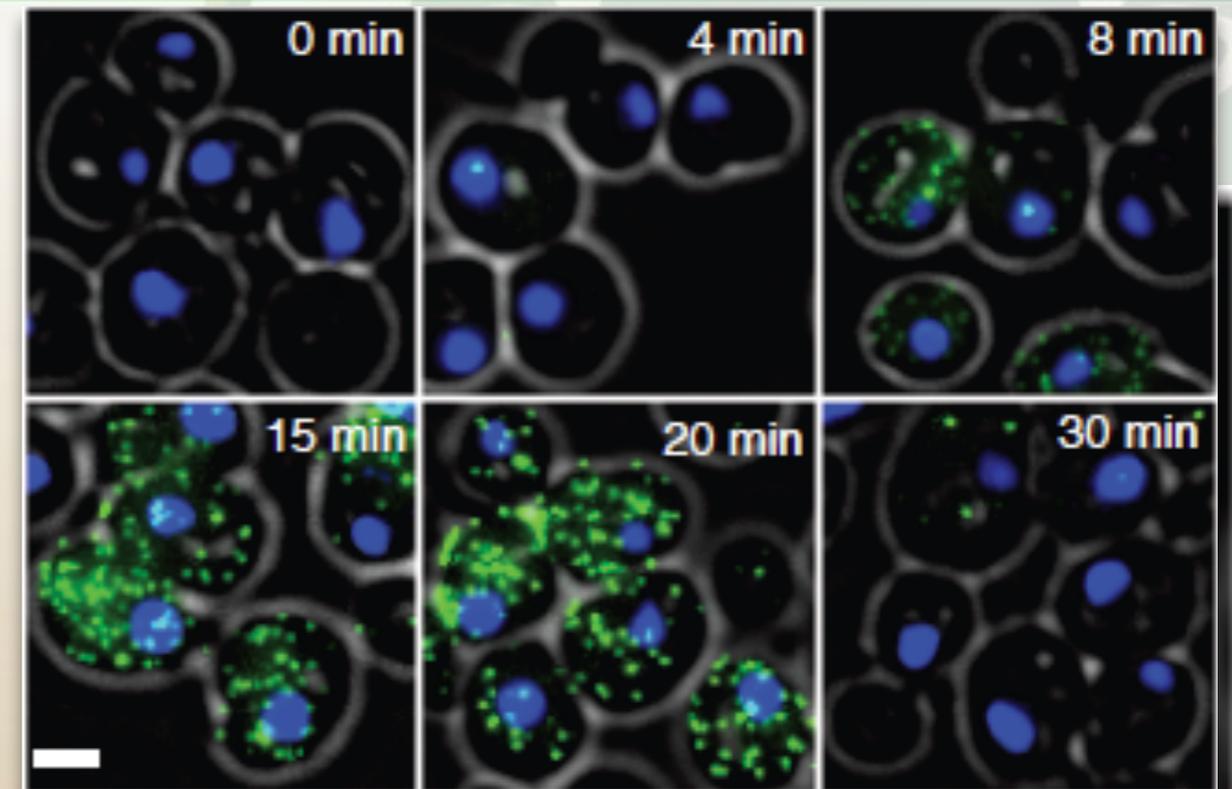
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Colorado State University

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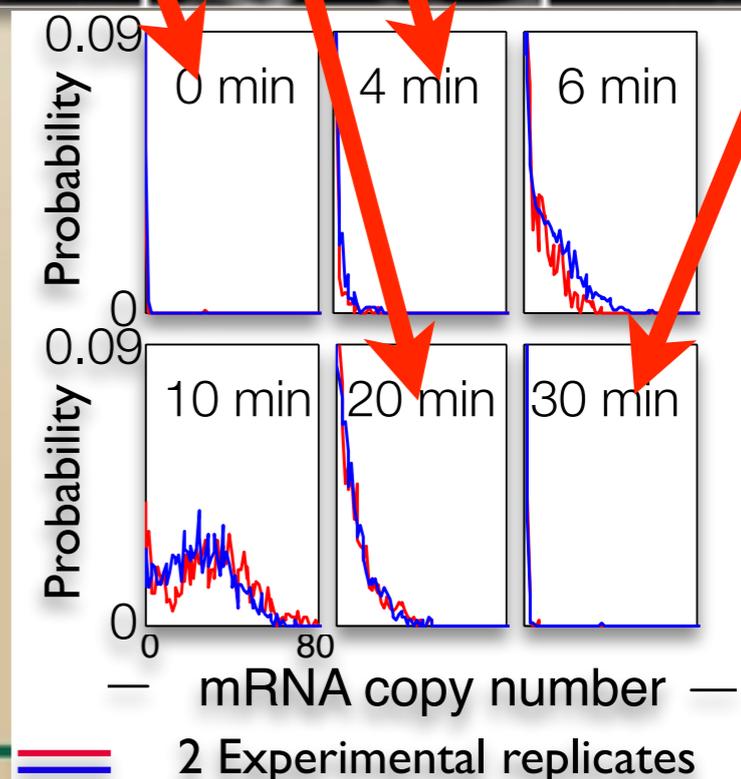
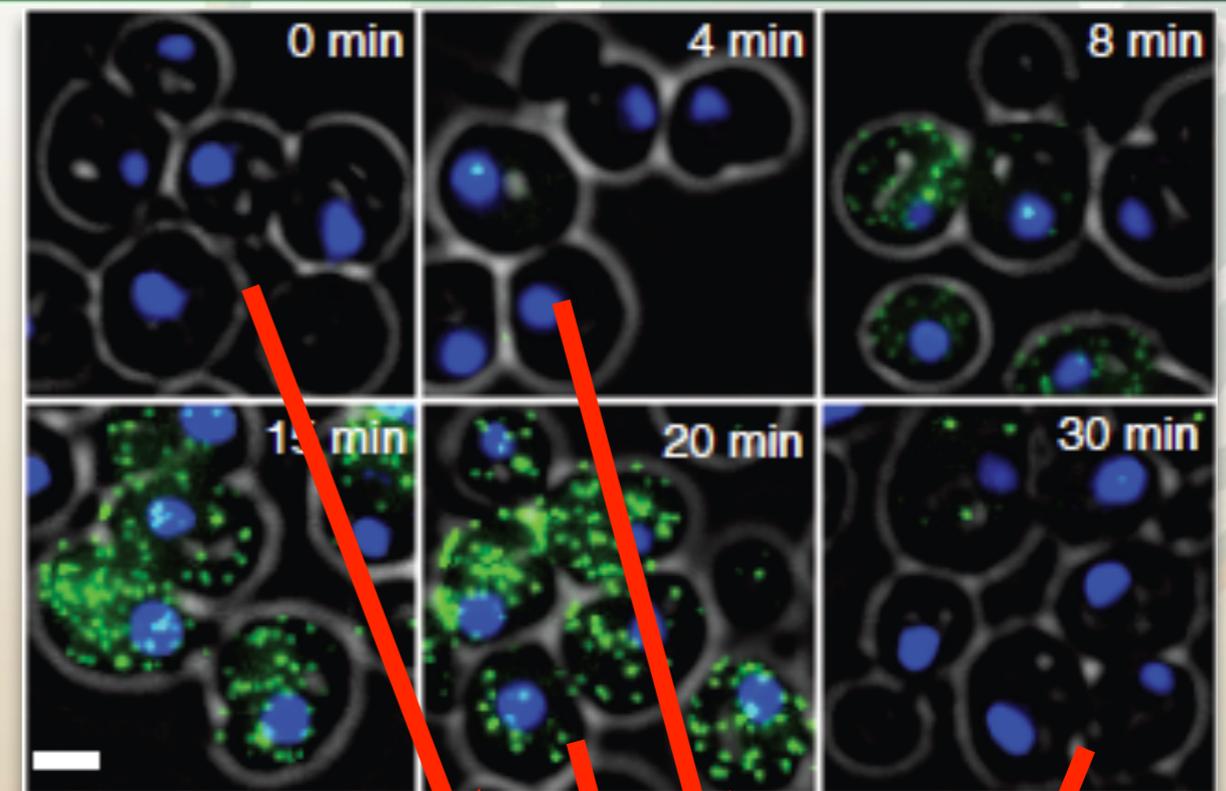


(Neuert, Munsky, *et al*, 2013)

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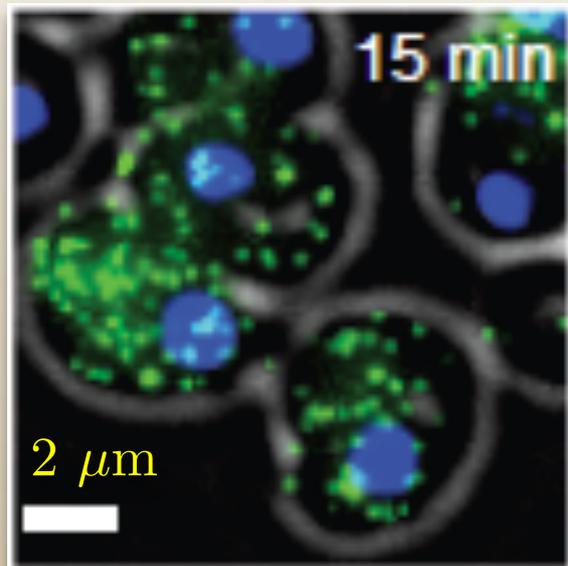


(Neuert, Munsky, *et al*, 2013)

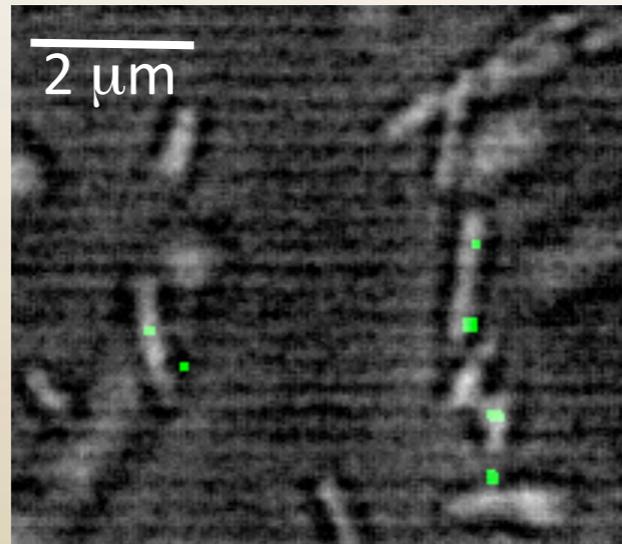
**Statistics are repeatable and therefore predictable!**



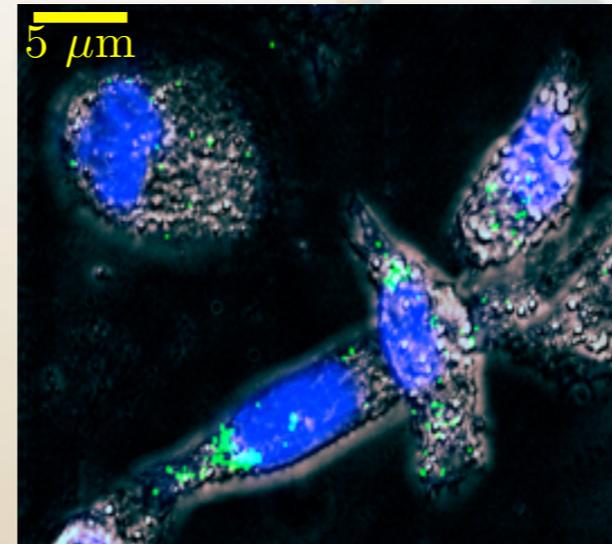
# Single-Molecule FISH (smFISH)



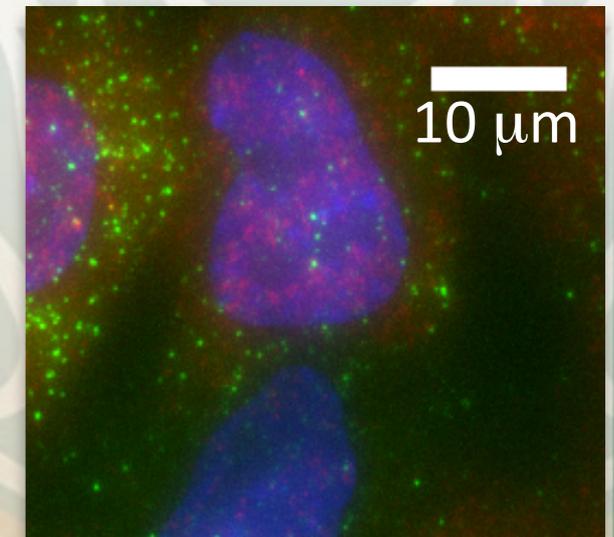
STI1 mRNA in *Saccharomyces cerevisiae* (budding yeast)  
-G. Neuert (VU)



Ysr35 sRNA in *Yersinia Pseudotuberculosis* (339nt)  
-D. Shepherd (CU Denver)



Traf6 mRNA in THP1 cells  
-D. Shepherd (CU Denver)



c-Fos mRNA (green) and p-p38 kinase (red) in U2OS cells  
-A. Senecal (CNRS)

*smFISH has been applied to many different RNA in many different organisms*

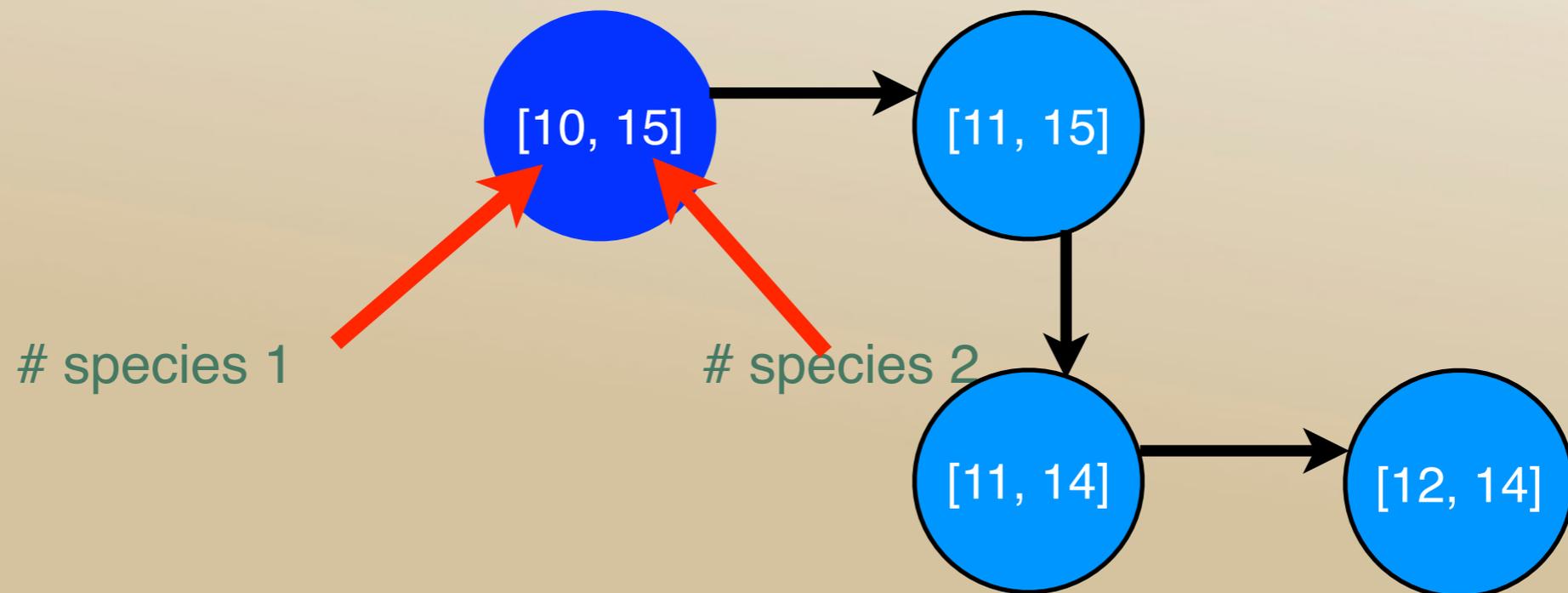


1. Introduction - Information from transcript fluctuation
- 2. Measuring and MODELING single-cell and single-molecule responses**



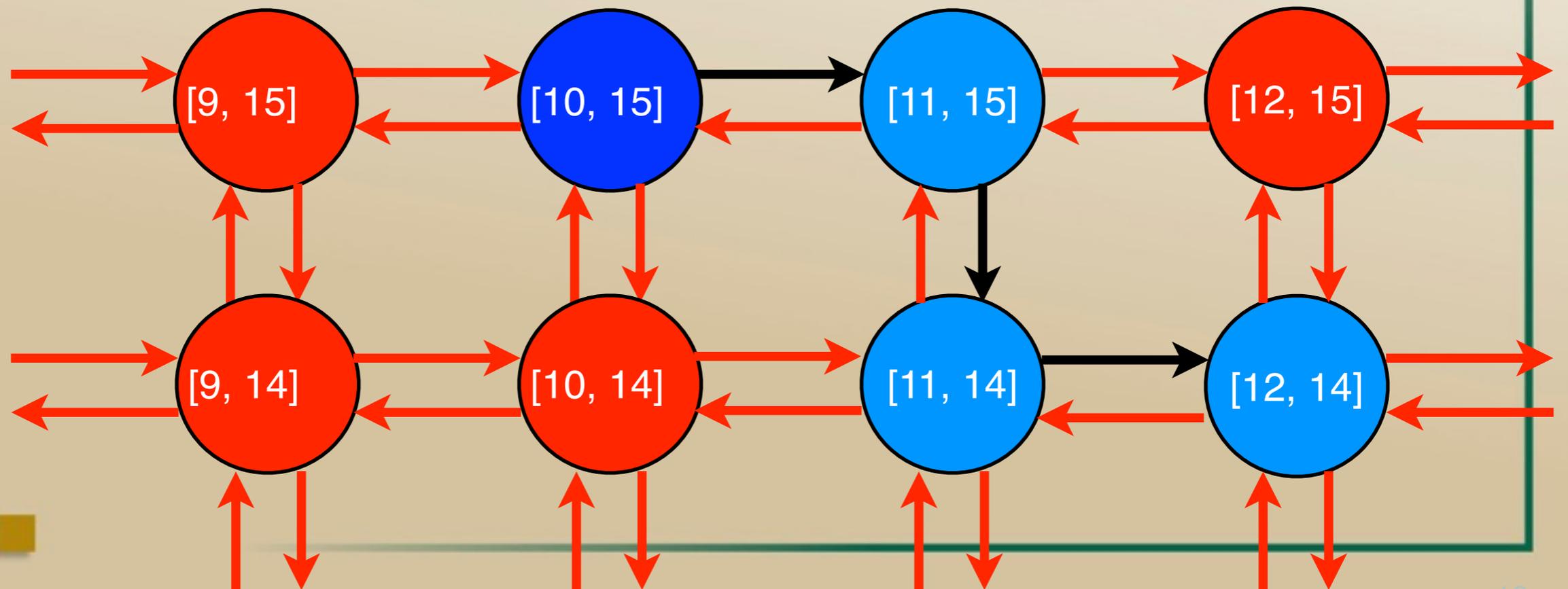
# A Markov description of single-cell gene regulation

- At any time, the state of the system is defined by its integer population vector:  $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another:

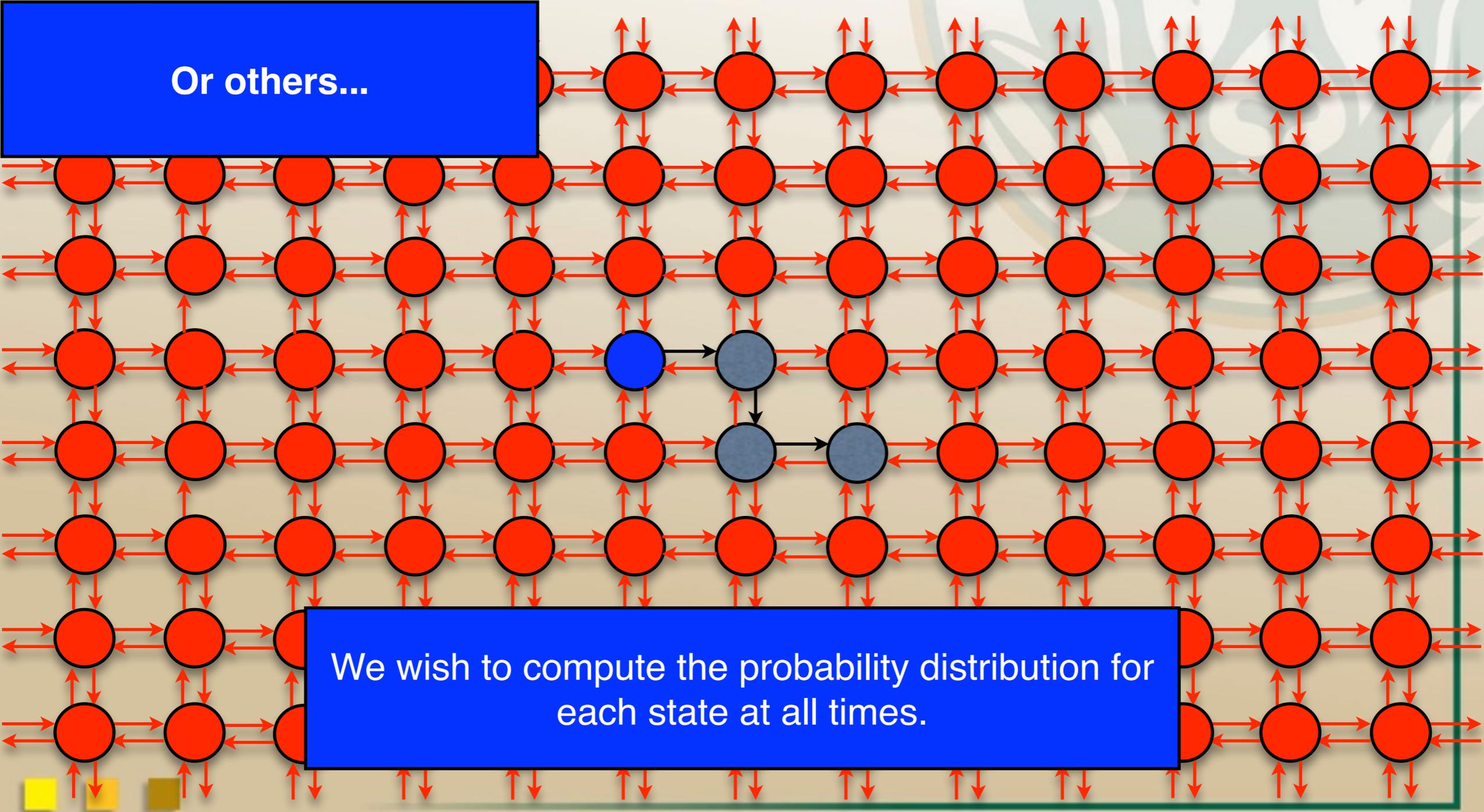


# A Markov description of single-cell gene regulation

- At any time, the state of the system is defined by its integer population vector:  $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another.
- These reactions are random, others could have occurred:

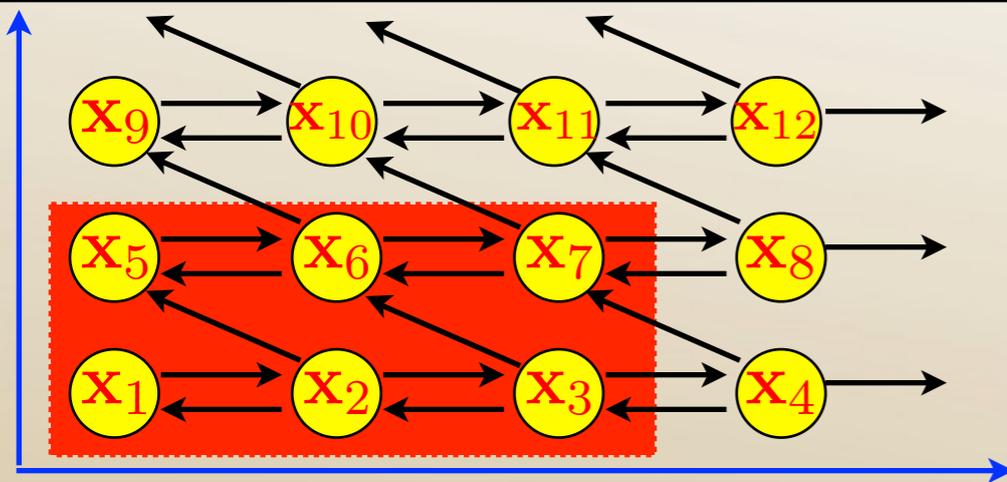


# A Markov description of single-cell gene regulation

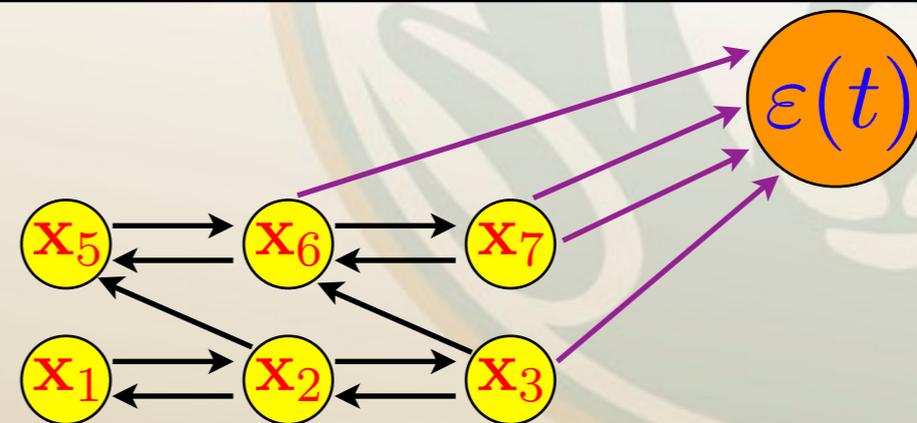


# The finite state projection approach

The Full System



The Projected System (FSP)



Full Master Equation

$$\begin{bmatrix} \dot{\mathbf{P}}_J \\ \dot{\mathbf{P}}_{J'} \end{bmatrix} = \begin{bmatrix} \mathbf{A}_J & \mathbf{A}_{JJ'} \\ \mathbf{A}_{J'J} & \mathbf{A}_{J'} \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(t) \\ \mathbf{P}_{J'}(t) \end{bmatrix}$$

Dimension =  $\#(J) + \#(J') = \text{Infinite}$

FSP Master Equation

$$\begin{bmatrix} \dot{\mathbf{P}}_J^{FSP} \\ \dot{\epsilon} \end{bmatrix} = \begin{bmatrix} \mathbf{A}_J & \mathbf{0} \\ -\mathbf{1}^T \mathbf{A}_J & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J^{FSP}(t) \\ \epsilon(t) \end{bmatrix}$$

Dimension =  $\#(J) + 1 = 7$

## The FSP Theorem

(Munsky, JCP '06)

$$\mathbf{P}_J(t) \geq \mathbf{P}_J^{FSP}(t) \text{ and}$$

$$\left\| \begin{bmatrix} \mathbf{P}_J(t) \\ \mathbf{P}_{J'} \end{bmatrix} - \begin{bmatrix} \mathbf{P}_J^{FSP}(t) \\ \mathbf{0} \end{bmatrix} \right\|_1 = \epsilon(t)$$

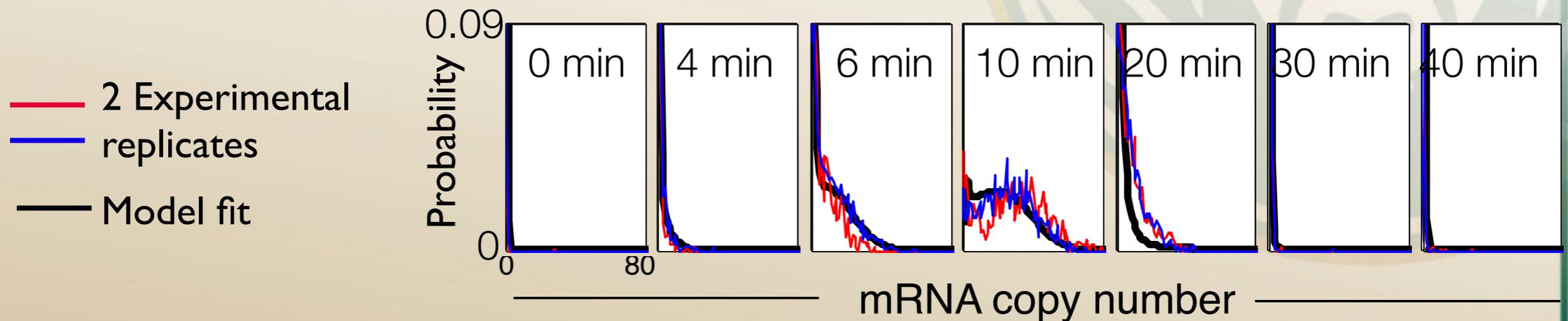


Software and tutorial available at:

<http://www.engr.colostate.edu/~munsky/Software.html>

# Inferring parameters from single-cell measurements.

Although single-cell reactions may be **Stochastic**, their statistics follow a **Deterministic** set of ODE's (i.e., the CME).



*We can fit and potentially predict these statistics.*

Fitting metrics:

Low cell counts --> maximum likelihood.\*

$$\log L(\{n_i\}|\Lambda) = \sum_{i=1}^N \log p_{n_i}(\Lambda) = \sum_{j=0}^{\max\{n_i\}} m_j \log p_j(\Lambda)$$



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- 3. Case Studies:**
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  - ii. Quantitative modeling for c-Fos mRNA burst dynamics in U2OS cells.

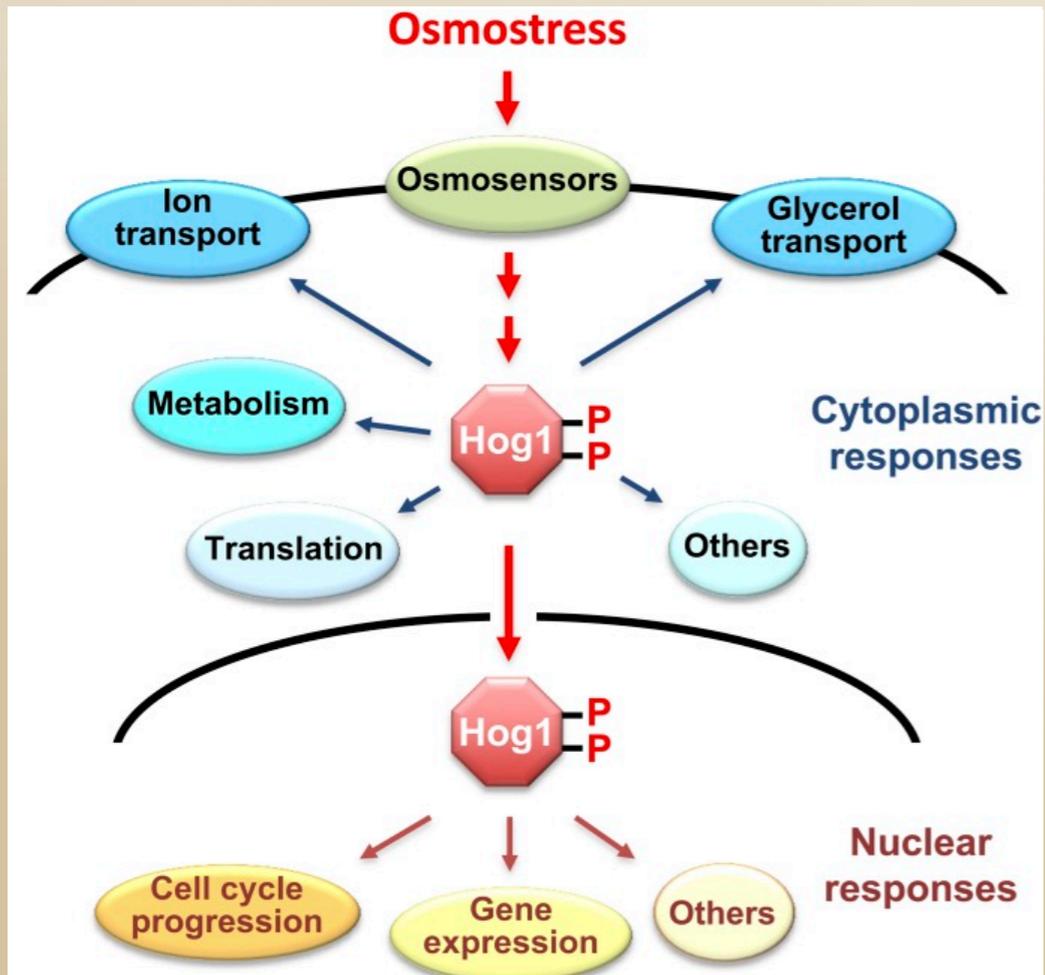


# Signal-activated gene regulation

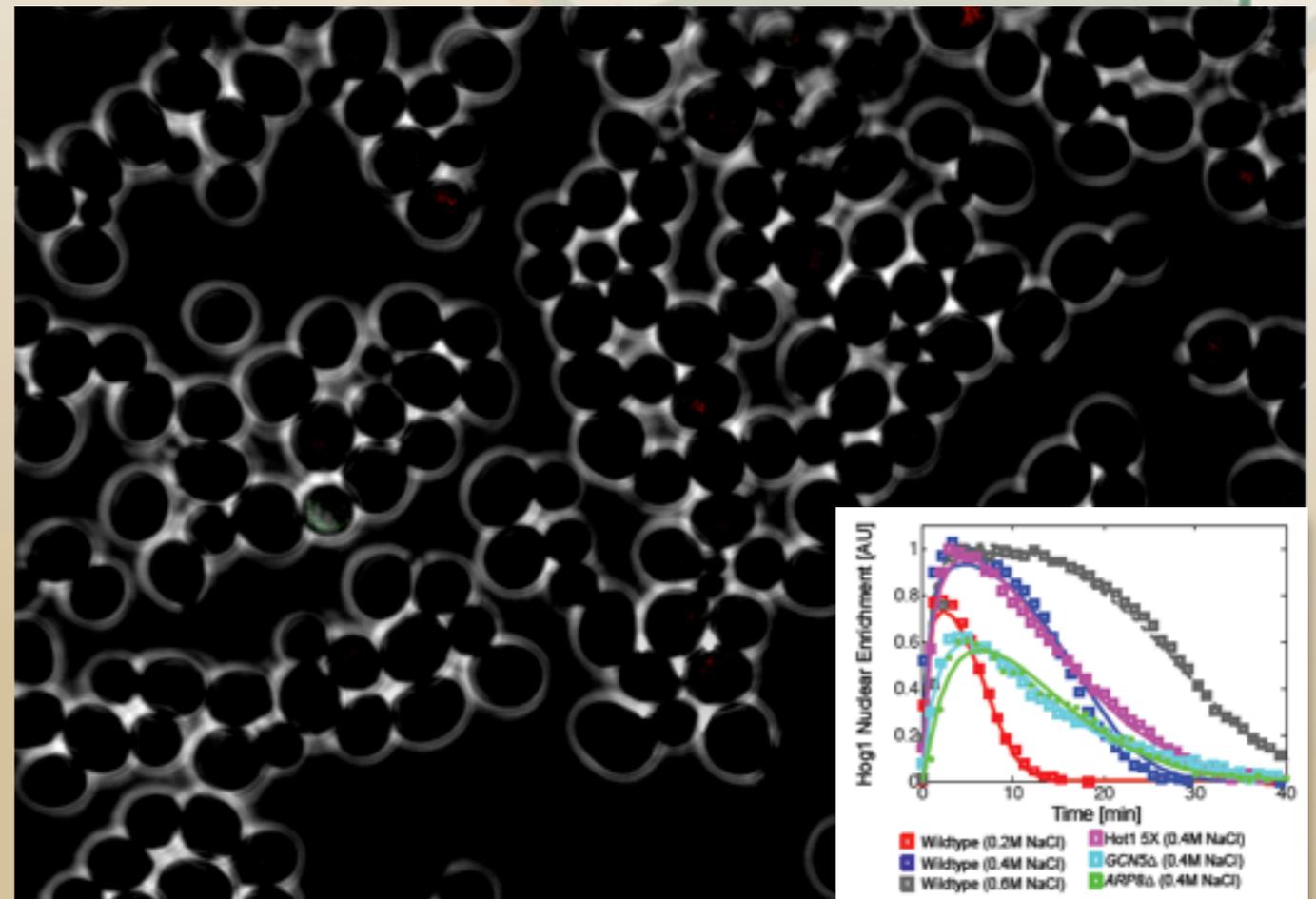
## (Osmotic shock response in yeast)

Colorado State University

- 0.2M NaCl is added at t=0.
- Hog1 (red) activates in 1-2 min.
- ... and remains active for ~12 min.



Osmotic-Adaptation, Activation and Localization of Hog1p, (Saito, Posas, *Genetics*, 2012)



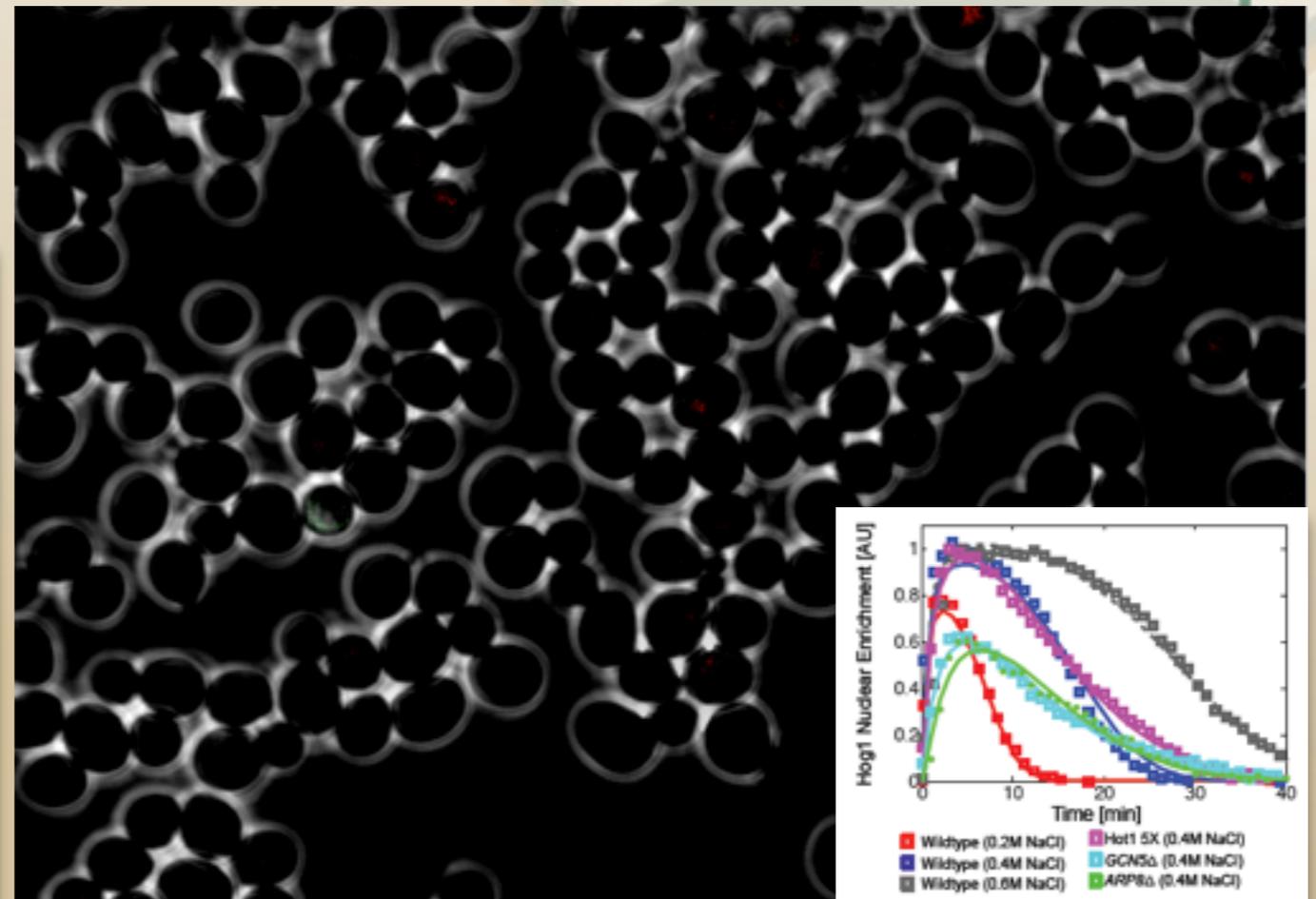
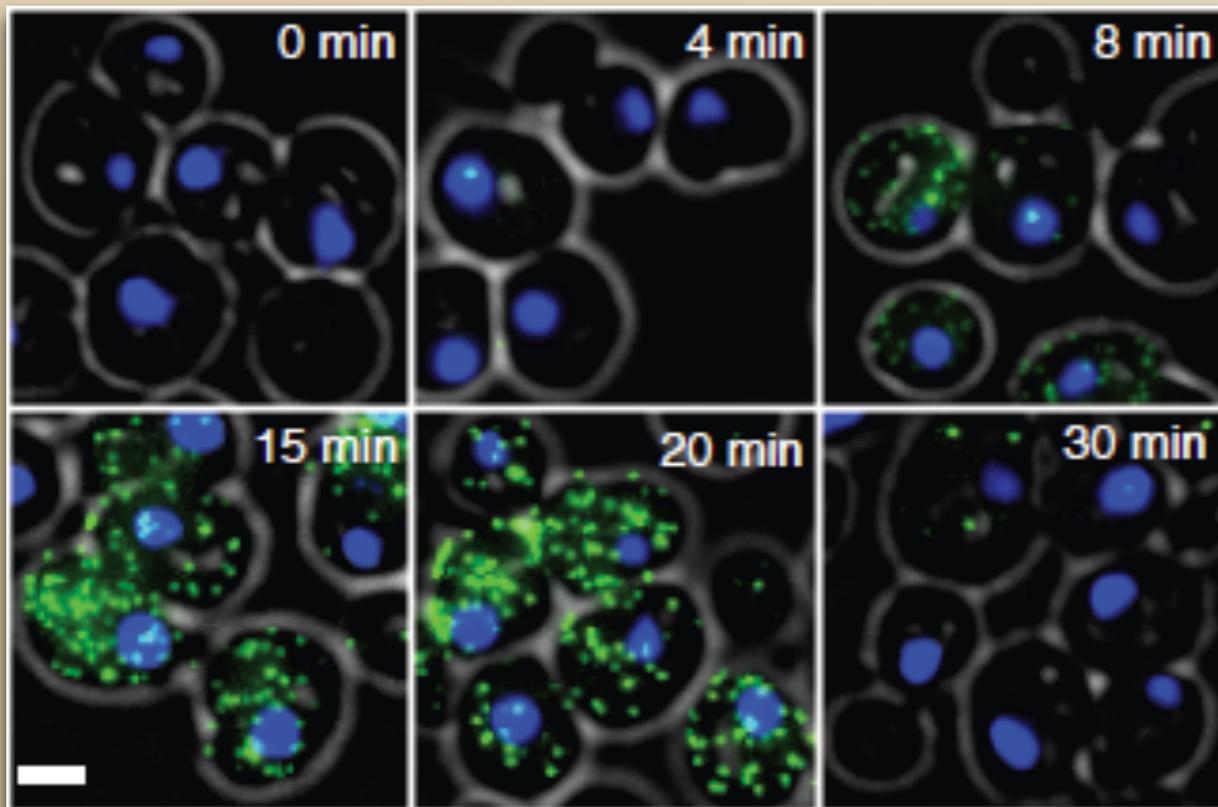
0-20 minutes after 0.2M NaCl shock (Neuert, Munsky, et al, 2013)

# Signal-activated gene regulation

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- 0.2M NaCl is added at t=0.
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- *Stl1* mRNA appear at 4 min.
- ... and are gone by 25 min.



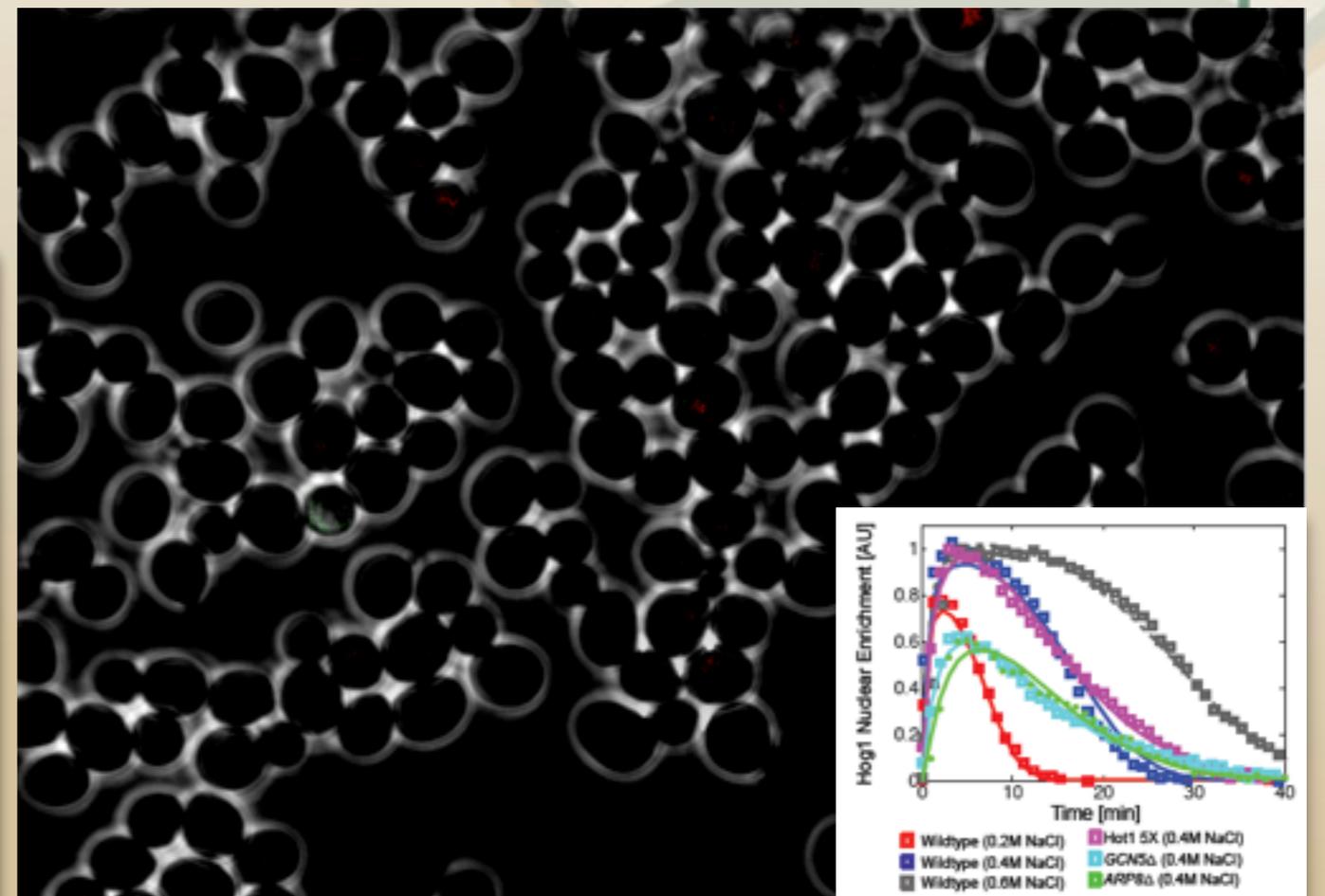
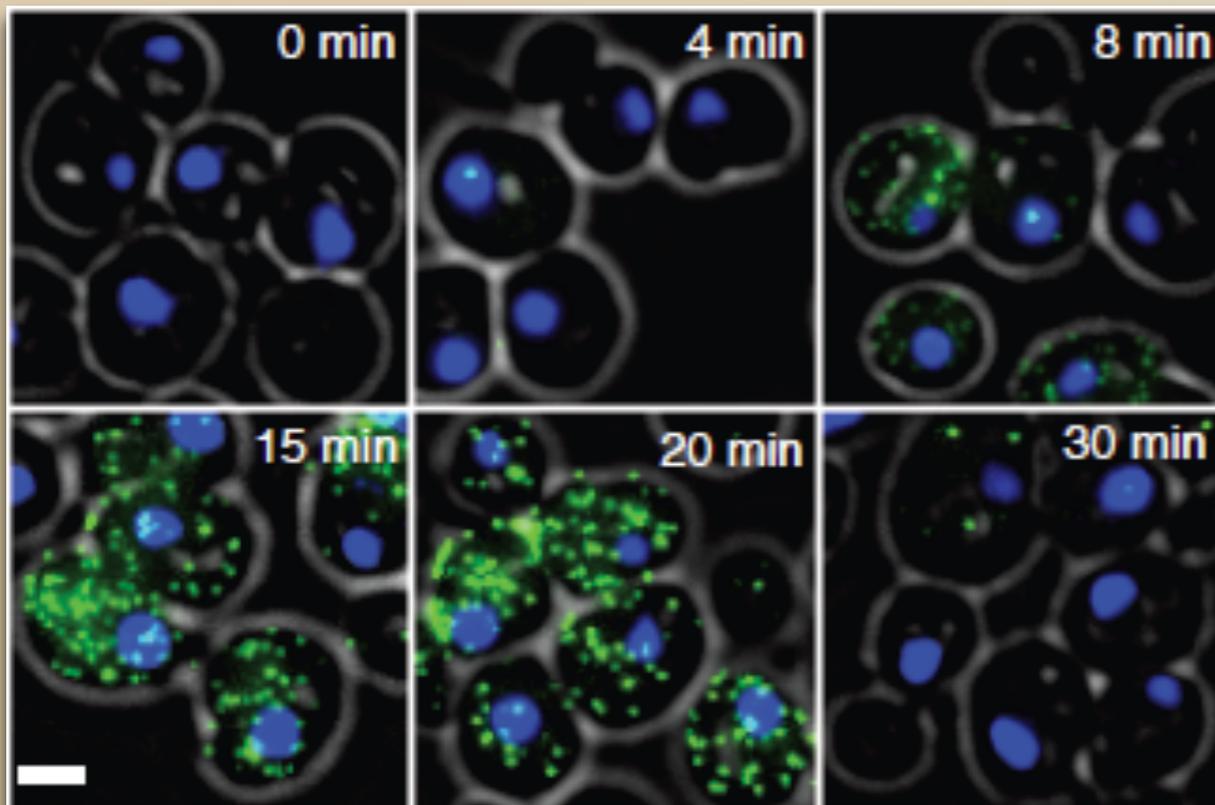
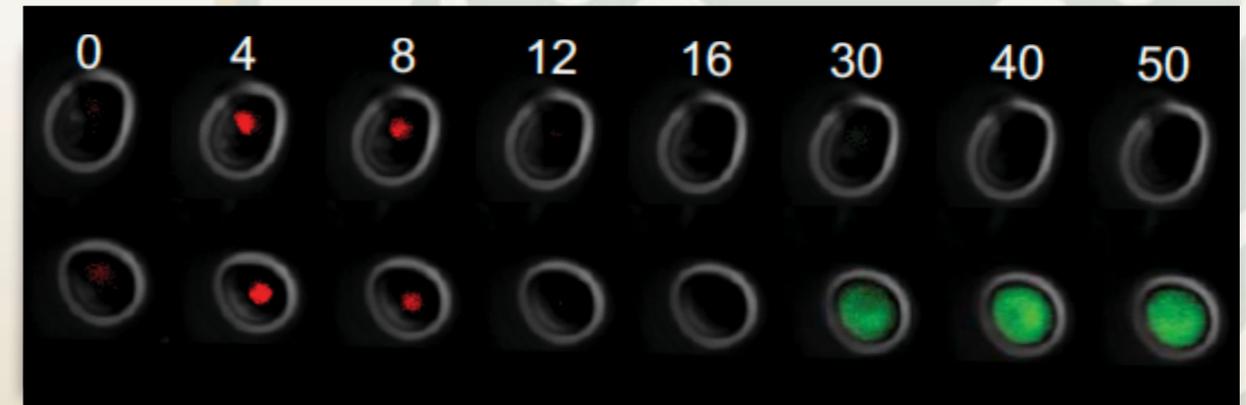
0-20 minutes after 0.2M NaCl shock  
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- *Stl1* mRNA appear at 4 min.
- ... and are gone by 25 min.
- *Stl1*-GFP appear at ~30 min.

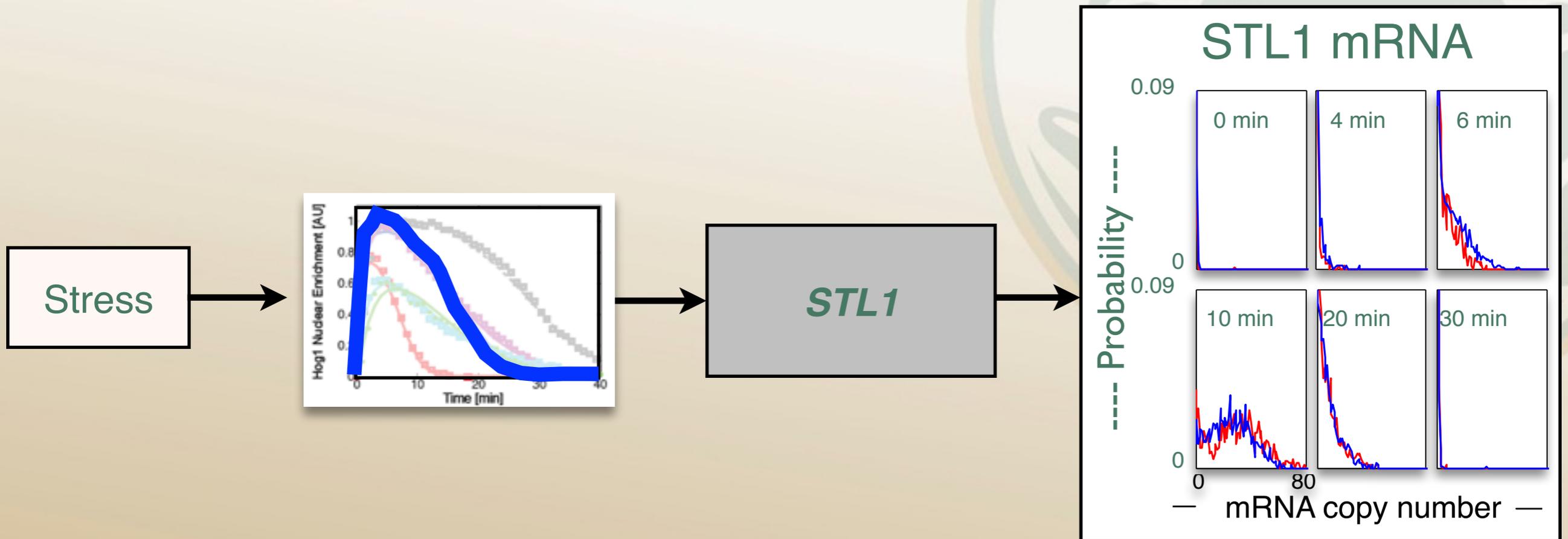


0-60 minutes after 0.2M NaCl shock  
(Neuert, Munsky, et al, 2013)

# Signal-activated gene regulation

(Osmotic shock response in yeast)

Colorado State University

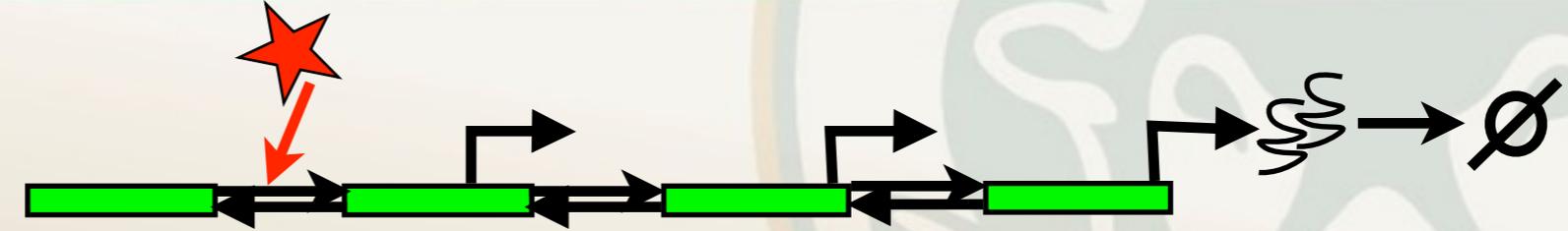


Our goal is to identify the mechanisms and parameters of *STL1*



# Possible model structures:

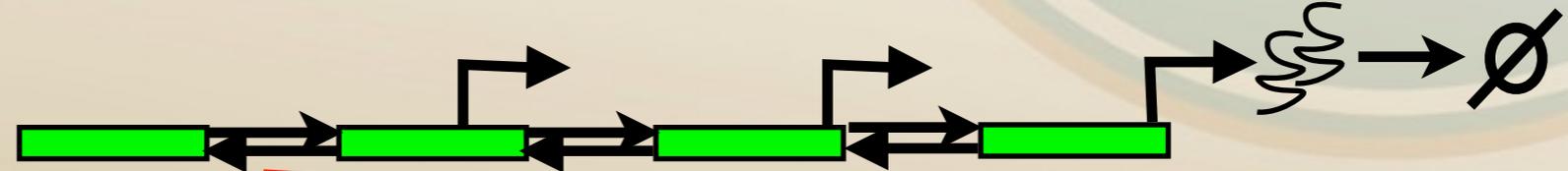
Is it the first of a cascade of activation events?



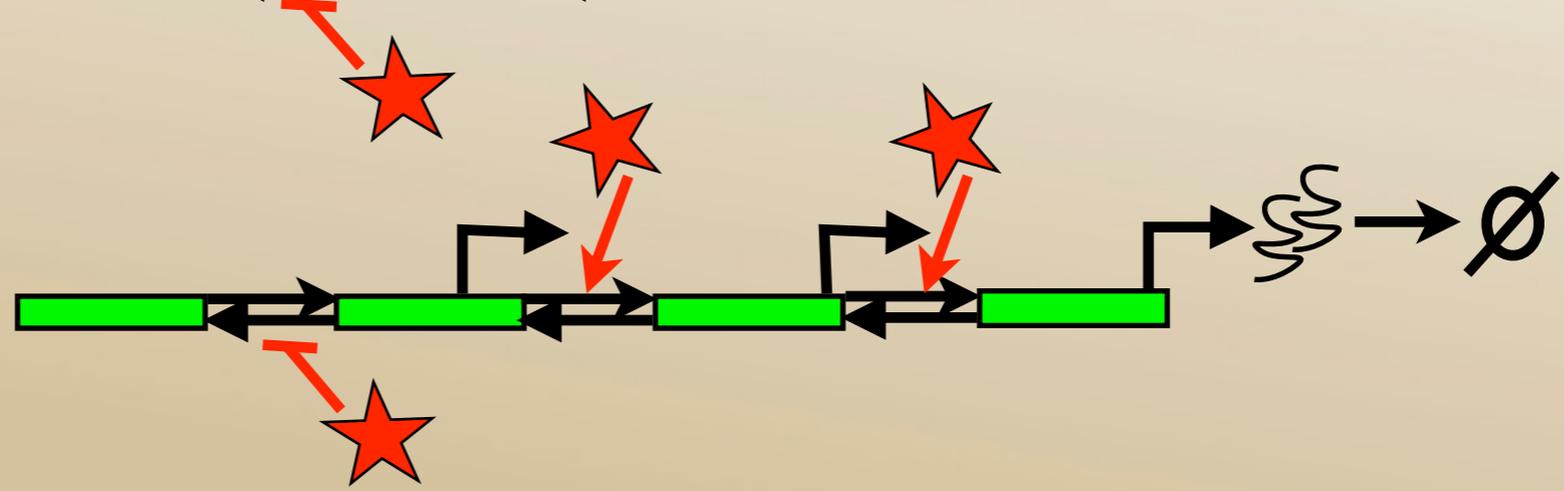
...the last activation event?



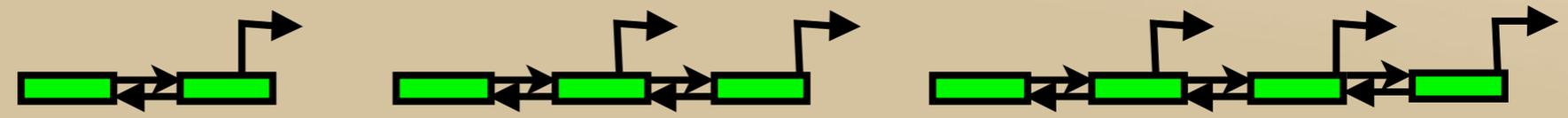
Does it repress a deactivation event?



Are there multiple effects?



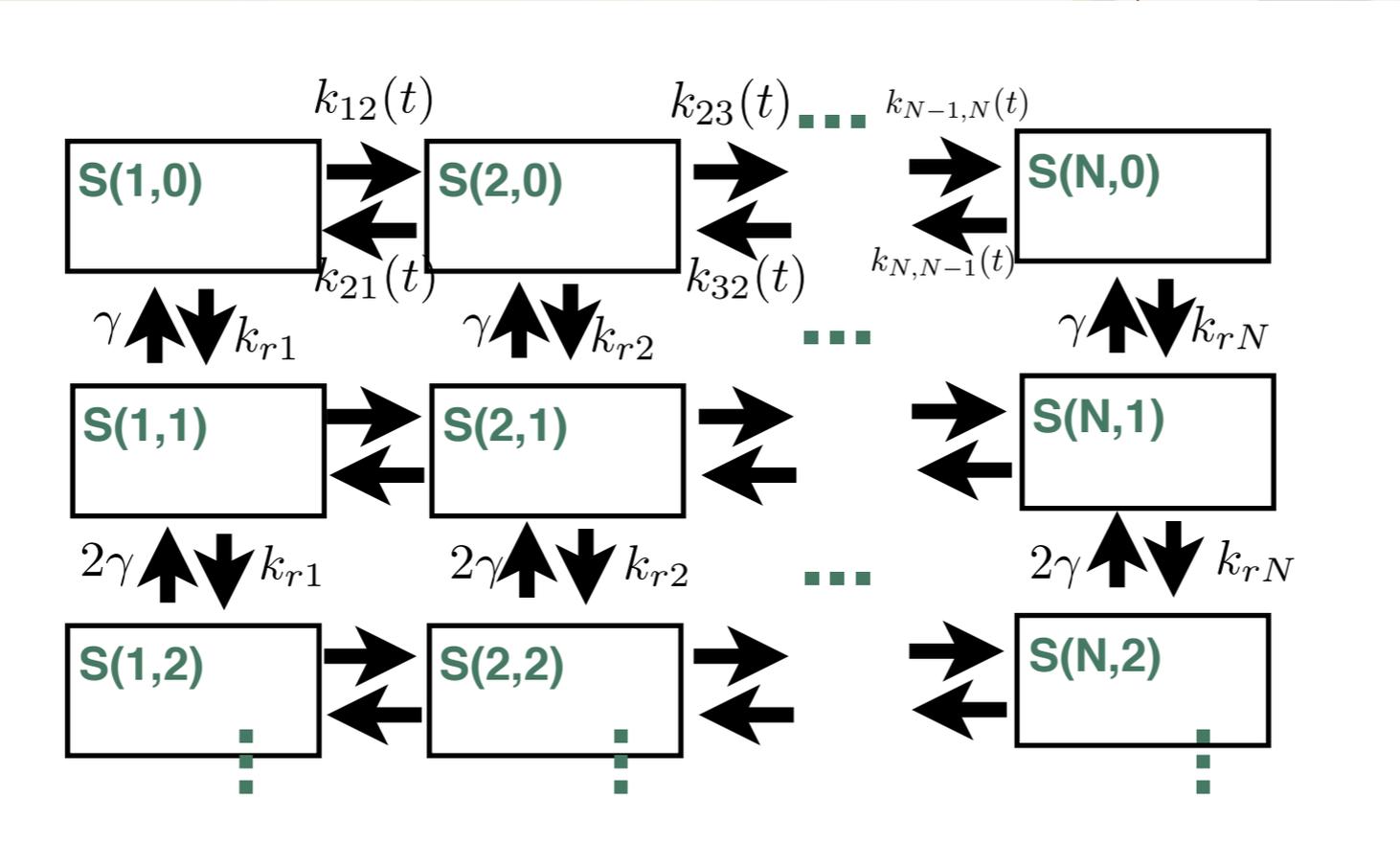
How many states are needed?



# Each structure defines a hidden Markov Model

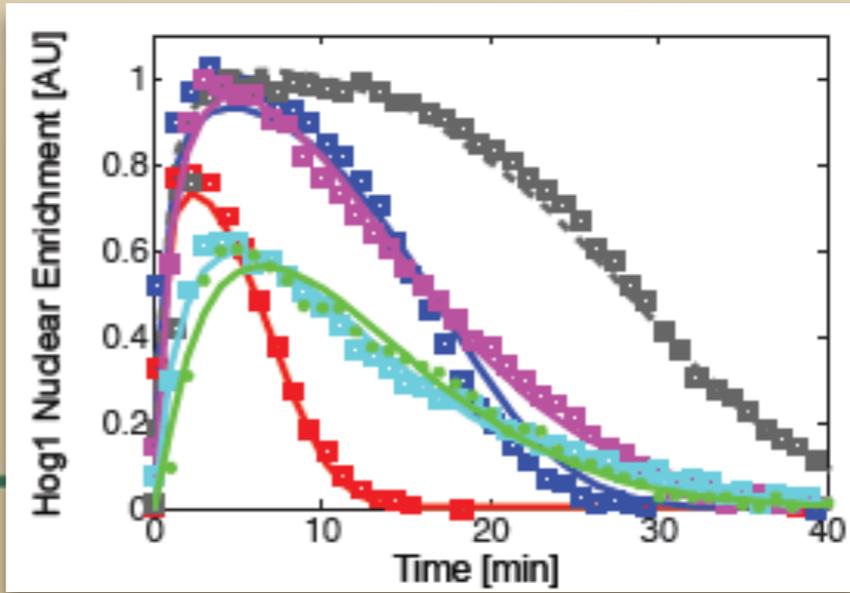
**HIDDEN:**  $N = \{2, 3, \dots\}$  possible gene states

**OBSERVABLE:** Integer number of mRNA



State-transition rates may vary in time, with experimental conditions, and/or with genetic mutations.

$$k_{ij} = k_{ij}(\text{Hog1}) = k_{ij}(t)$$



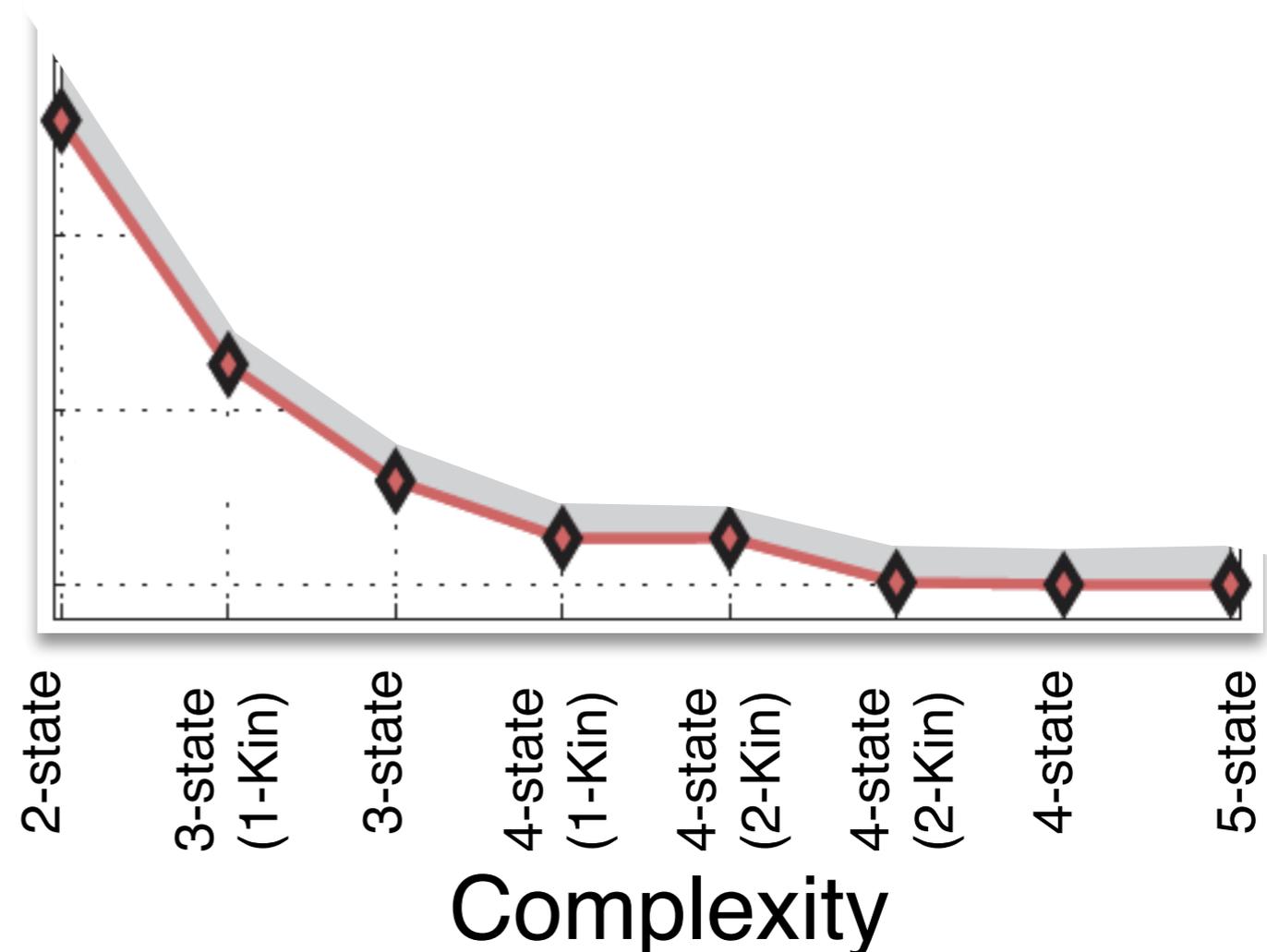
# Evaluating model structures of varying complexity

Colorado State University

We fit different 2-, 3-, 4- and 5- state model structures to wild-type data at 0.4M osmotic shock.

More states (and parameters) yield better fits,...

Fit, Uncertainty, and  
Prediction Errors



# Evaluating model structures of varying complexity

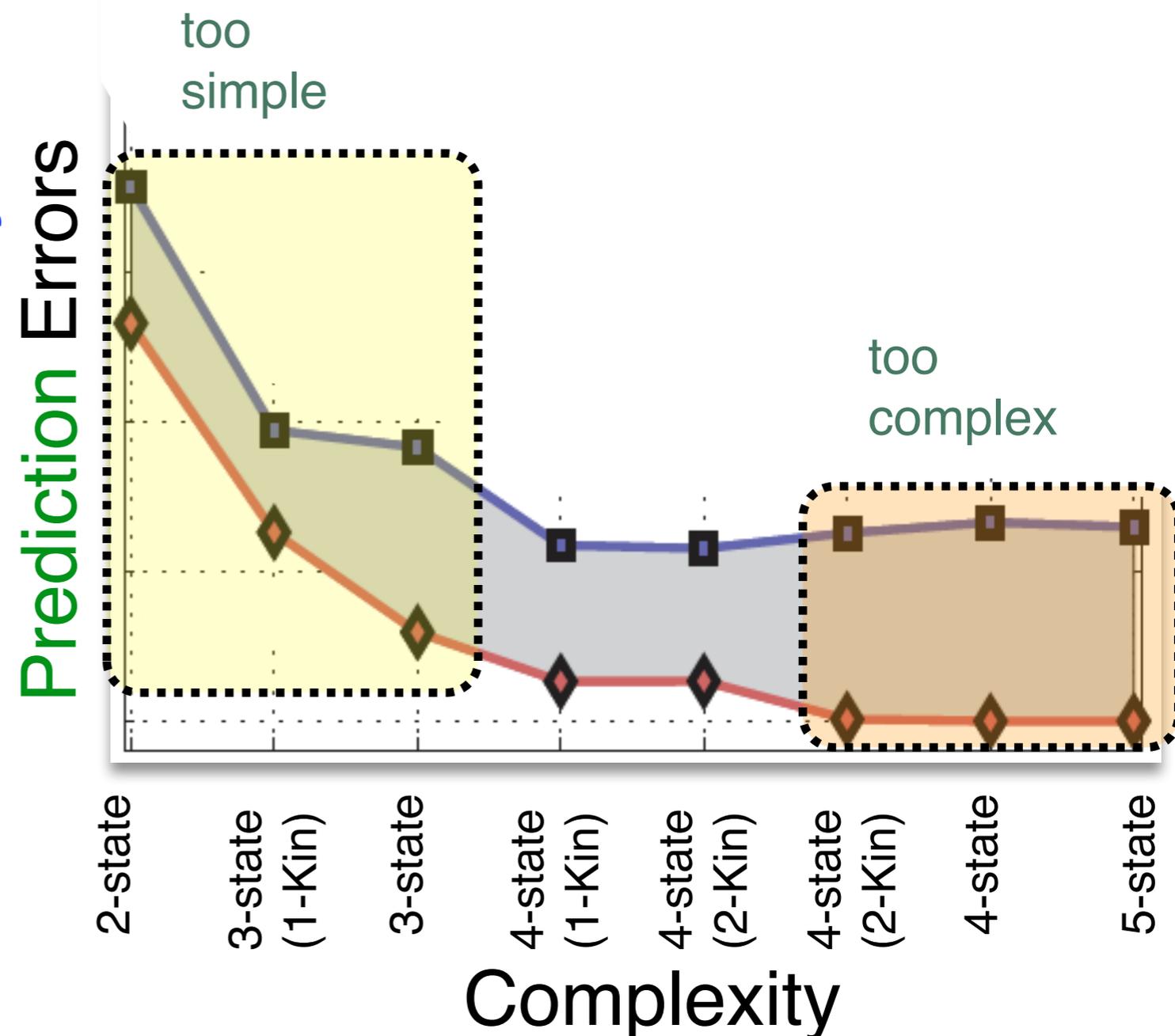
Colorado State University

We fit different 2-, 3-, 4- and 5- state model structures to wild-type data at 0.4M osmotic shock.

More states (and parameters) yield better fits,...

but they also give rise to greater uncertainty.

Fit, Uncertainty, and Prediction Errors



# Evaluating model structures of varying complexity

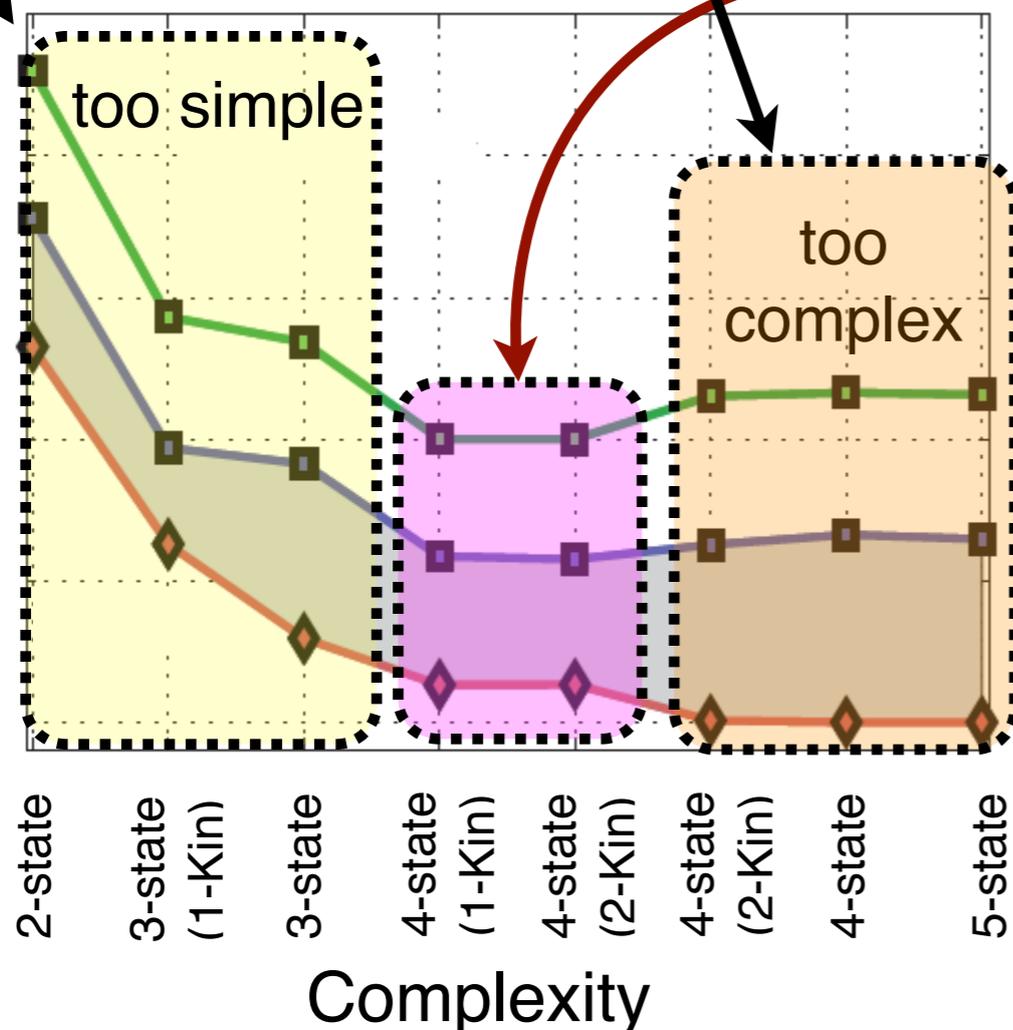
Overly-simple models cannot match the data.

Overly-complex models are poorly constrained.

Inaccurate predictions.

Imprecise predictions.

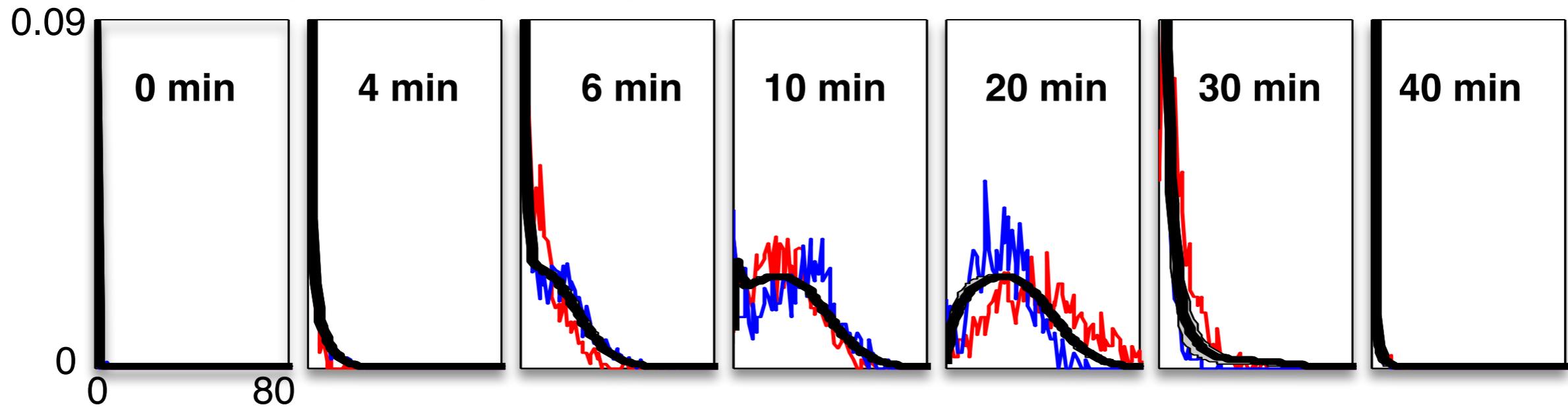
Fit, Uncertainty, and Prediction Errors



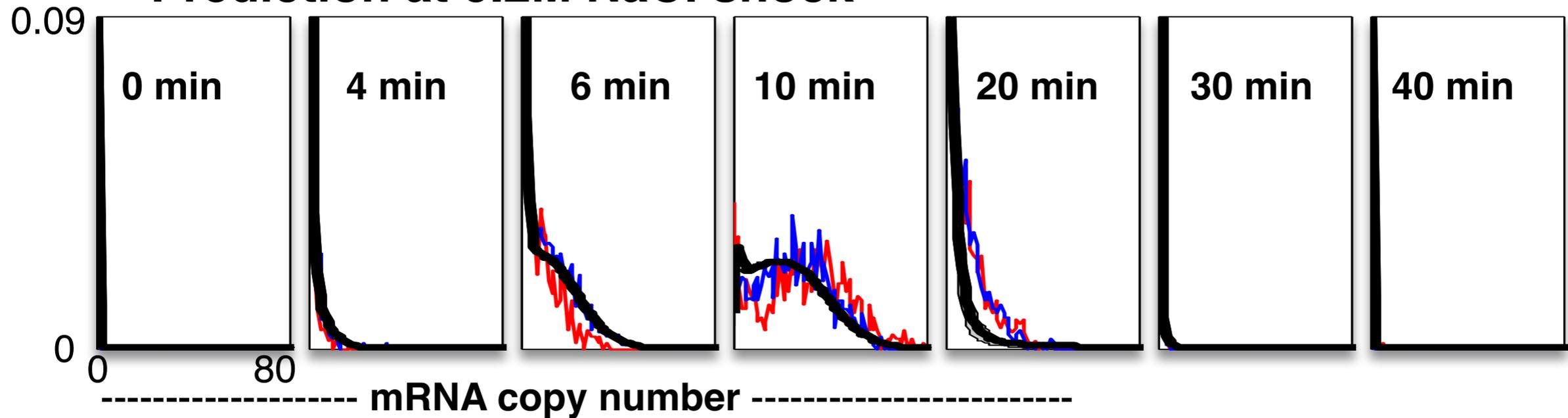
**Cross-validation analysis provides an excellent a priori estimate of predictive power.**

# Fits and predictions for *STL1* regulation

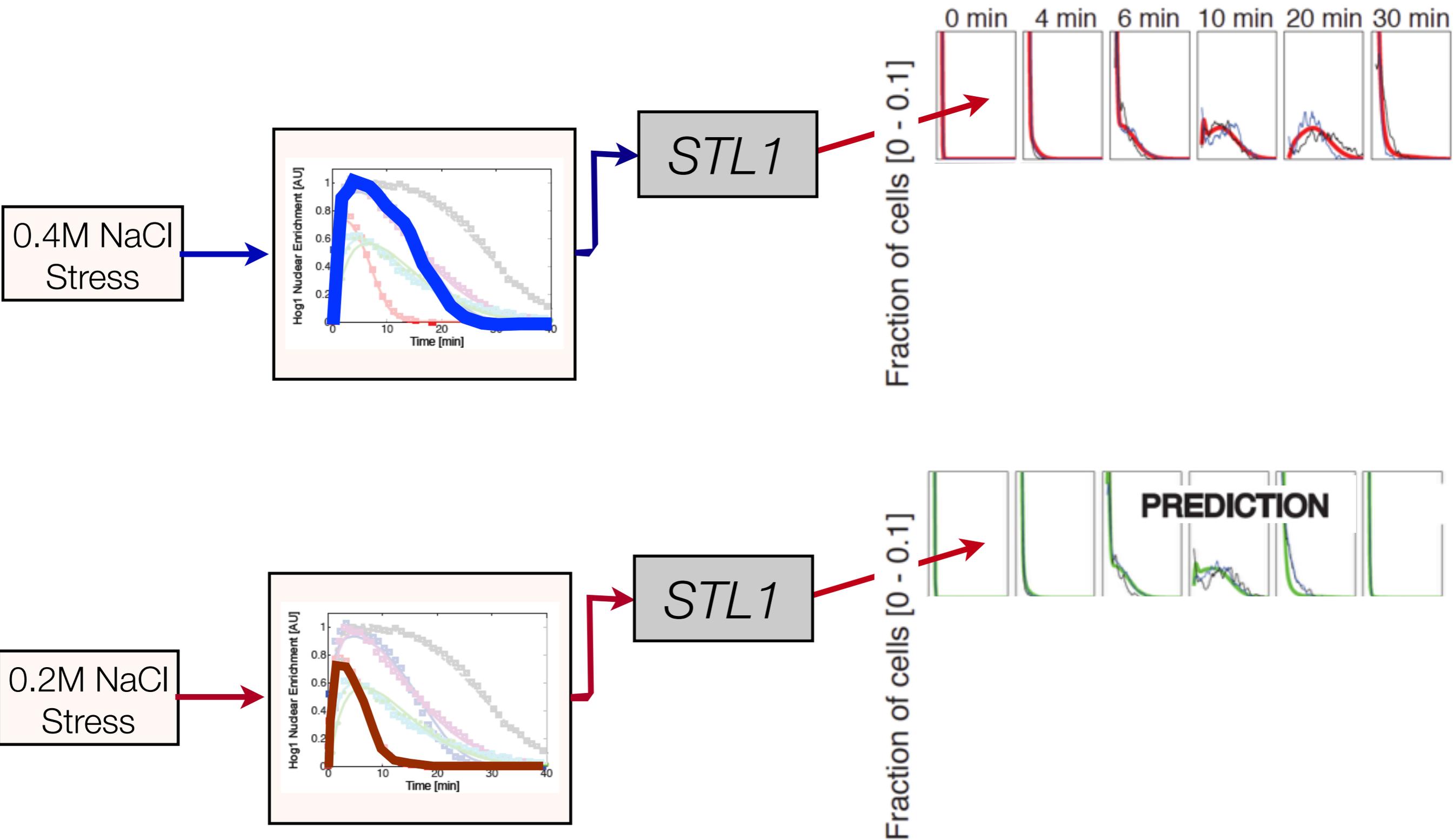
## Fit at 0.4M NaCl shock



## Prediction at 0.2M NaCl shock

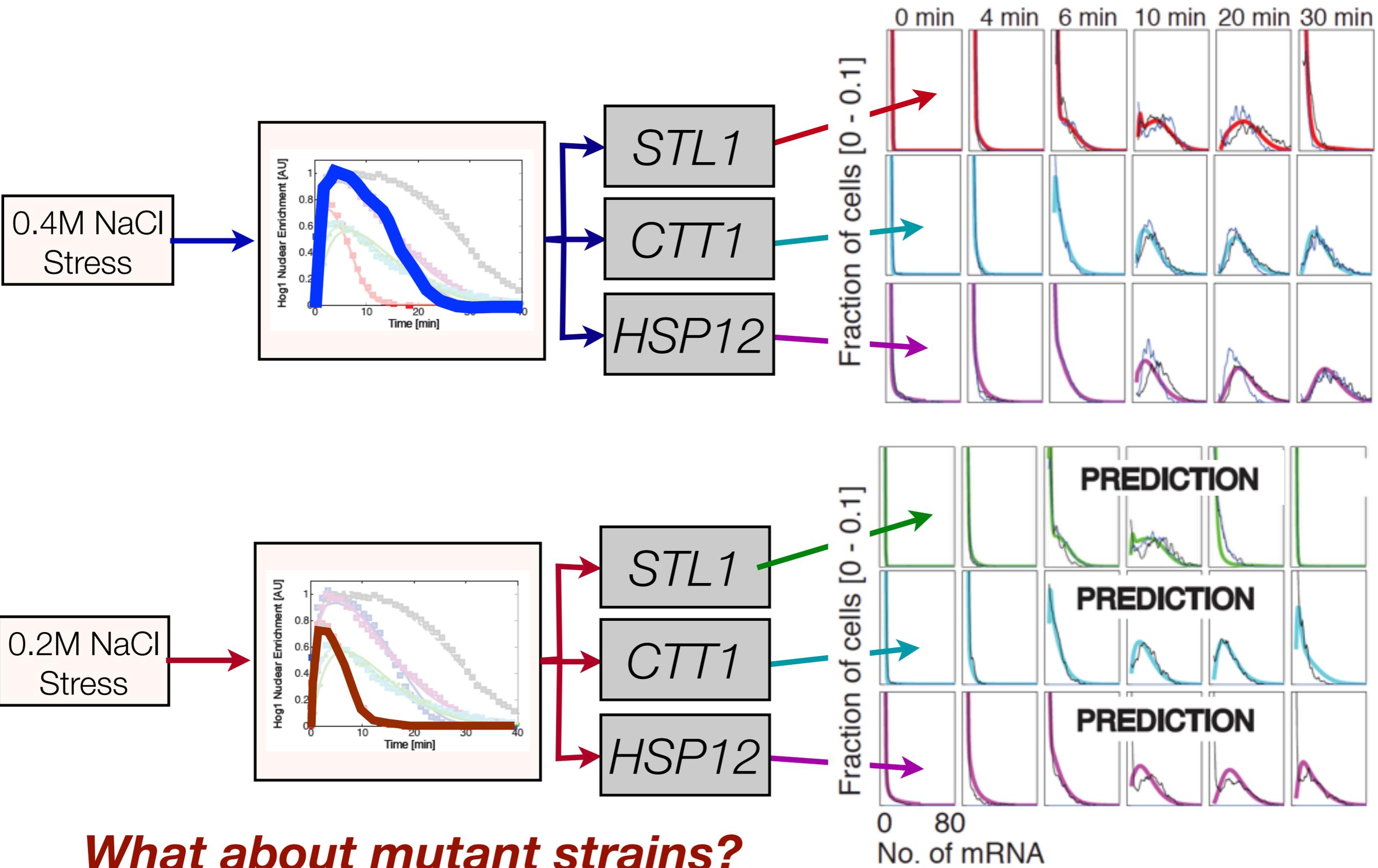


# The model can capture and predict WT mRNA dynamics for *STL1*



***What about other genes?***

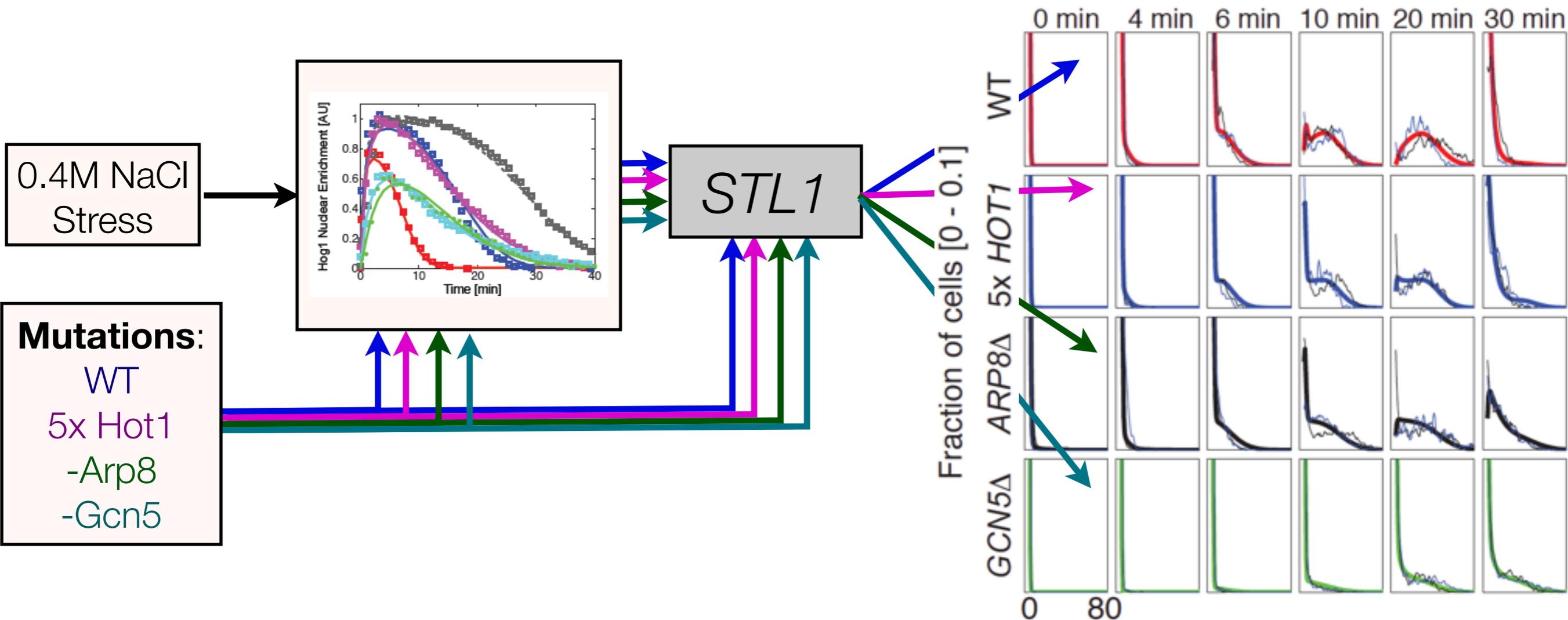
# The model can capture and predict WT mRNA dynamics for *STL1*, *CTT1* and *HSP12*



***What about mutant strains?***

# The model can capture and predict WT mRNA dynamics for *STL1*, *CTT1* and *HSP12*

It also captures *STL1* mRNA dynamics in **Wild Type**, **Hot1 over expression** and **Arp8** or **Gcn5** deletion strains

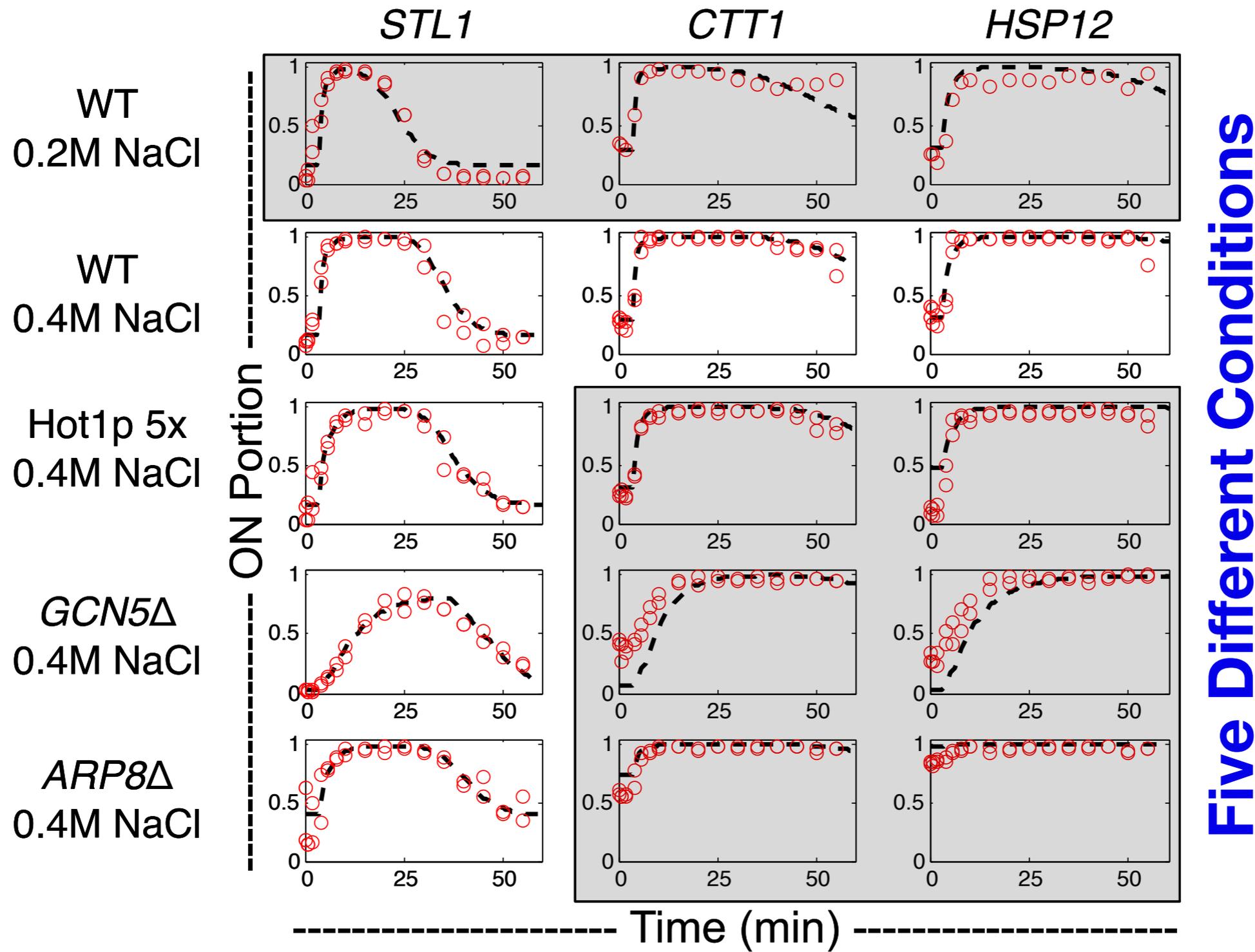


***What about new combinations of different genes and mutant strains?***



# Fitting and Predicting the Probability of ON Cells

## Three Different Genes



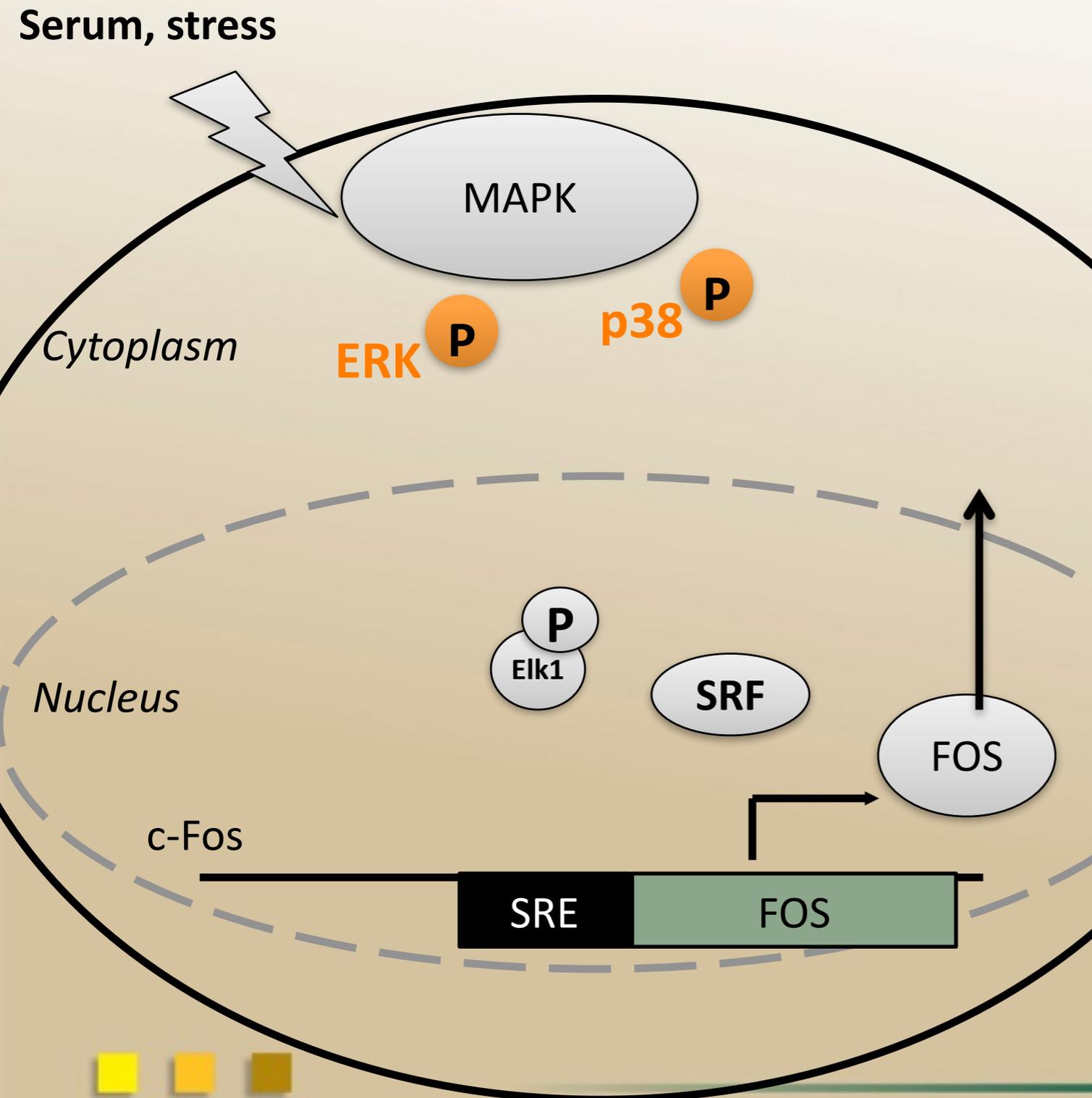
Five Different Conditions

**Predictions** with NO Free Parameters

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  - ii. Quantitative modeling for c-Fos mRNA burst dynamics in U2OS cells.**



# A glance at the activation of c-Fos

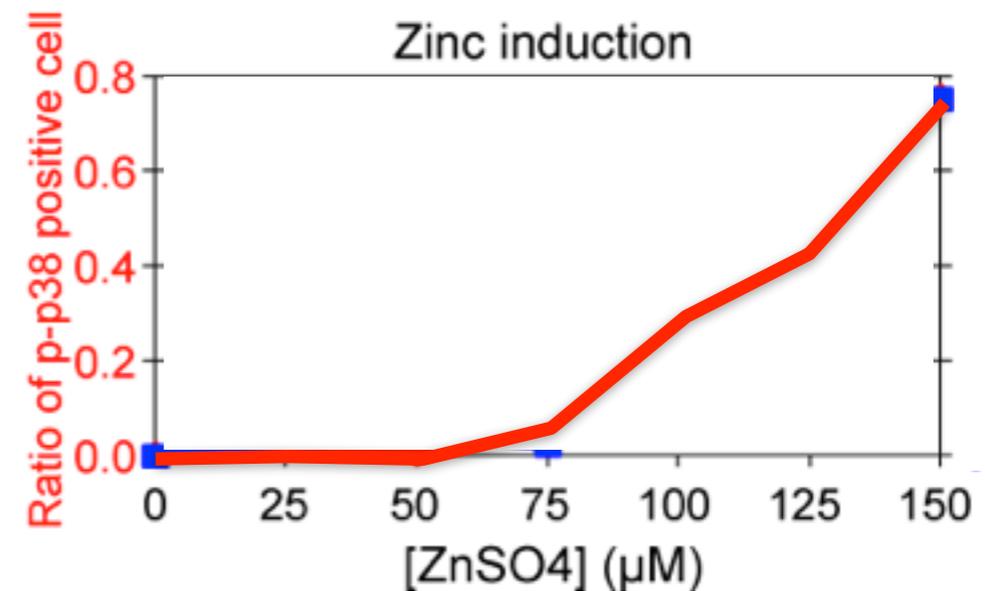
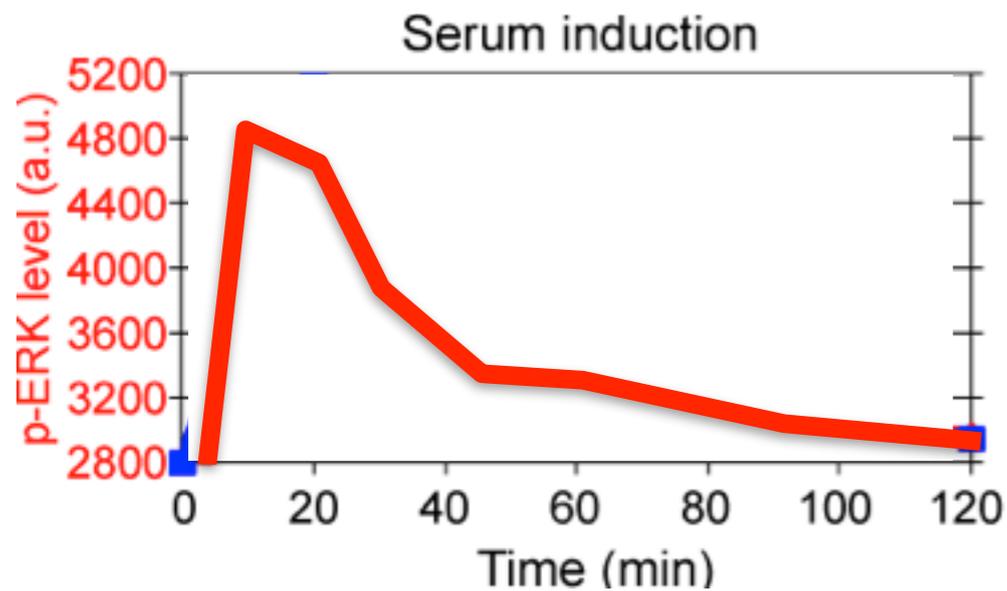
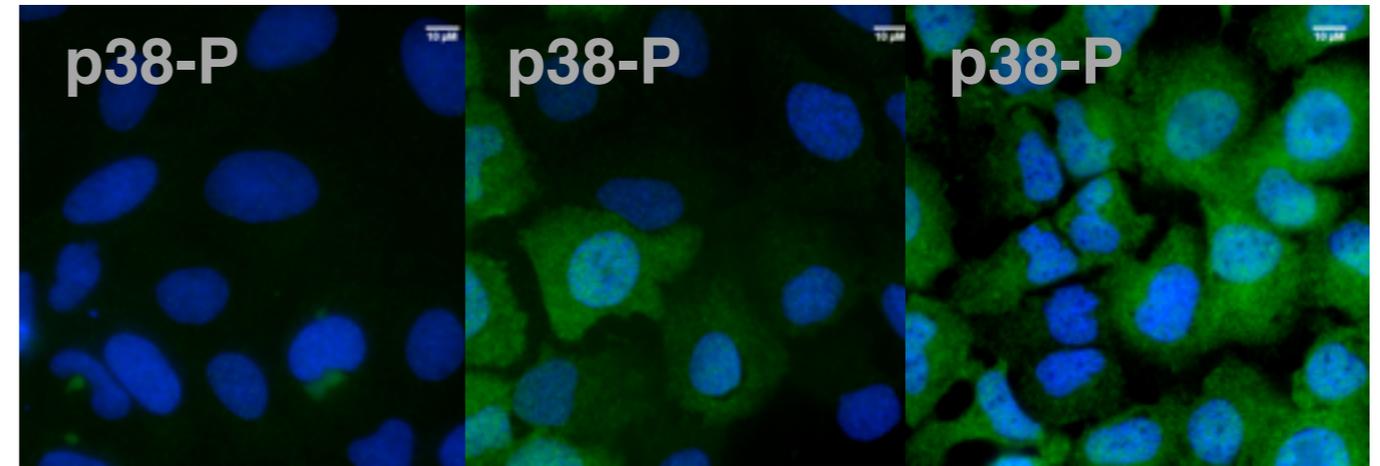
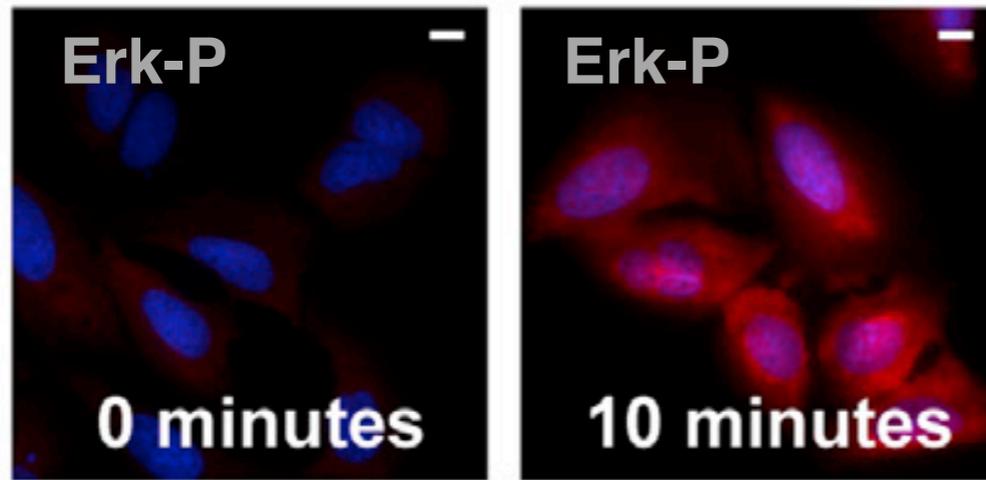


## Chain of events:

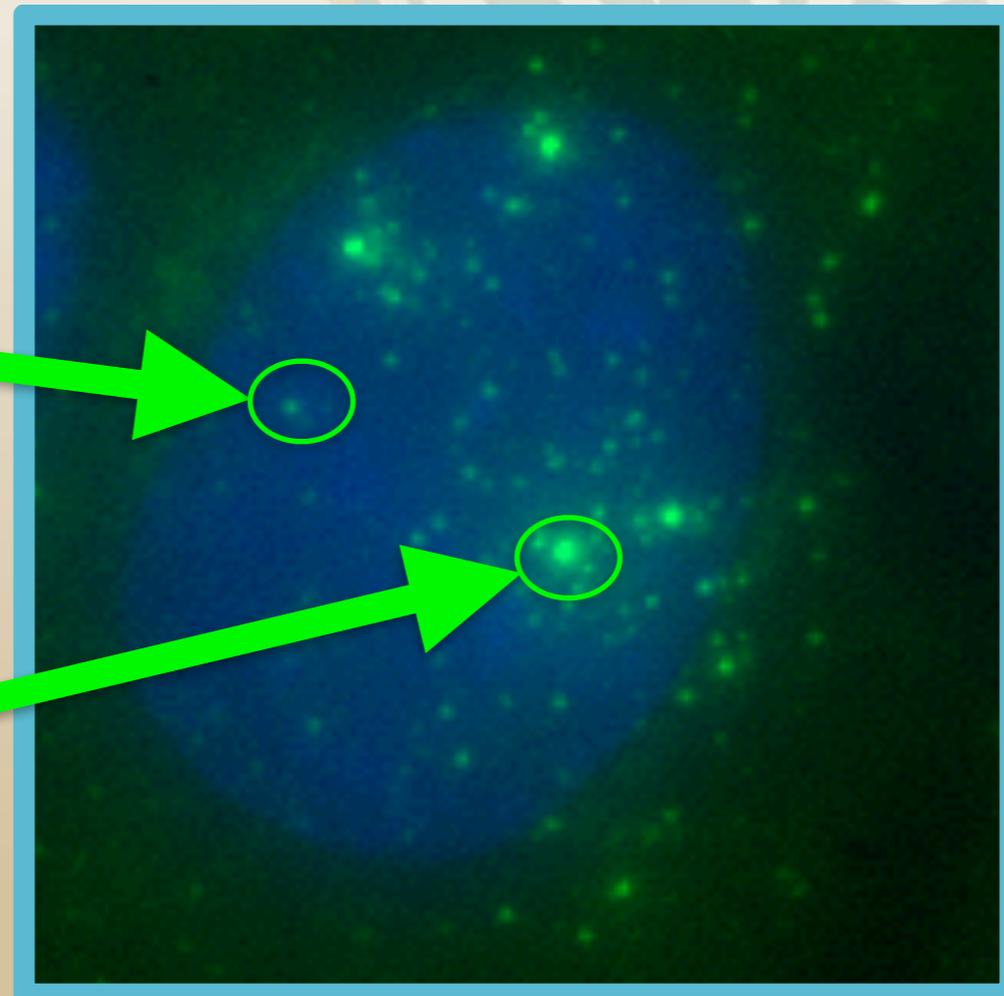
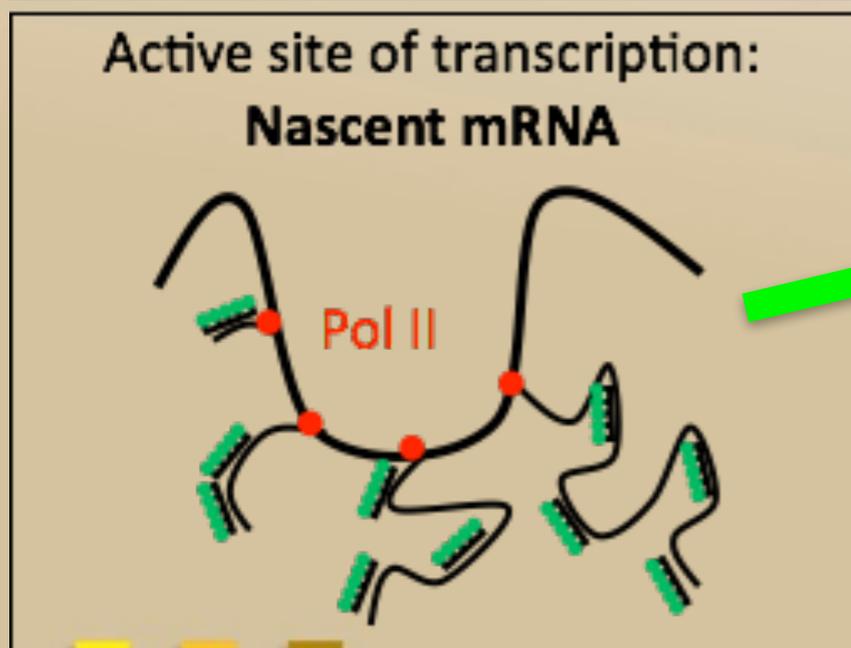
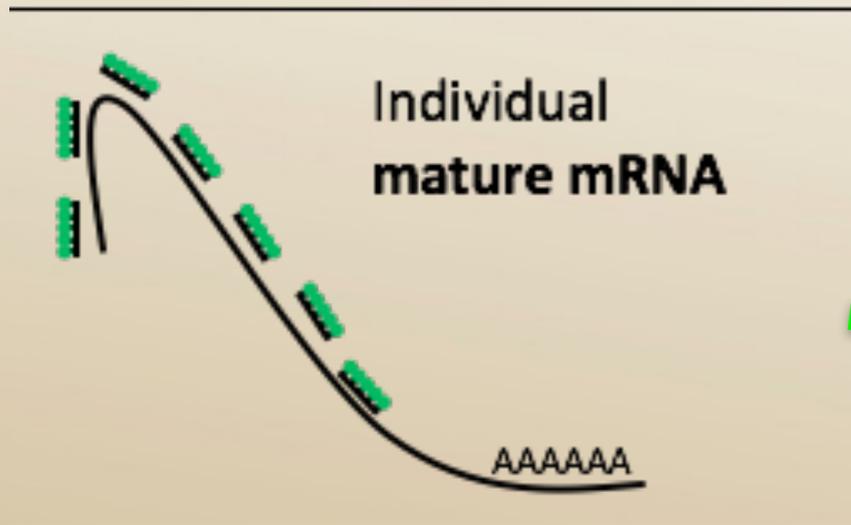
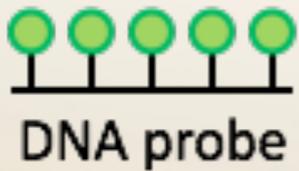
- Serum (zinc stress) activates phosphorylation of ERK (p38).
- ERK/p38 translocate to nucleus & phosphorylate Elk1.
- Elk1 and serum response factor (SRF) bind to serum response element (SRE).
- The activated promoter now transcribes c-Fos mRNA.
- c-Fos affects differentiation, proliferation, survival, ...



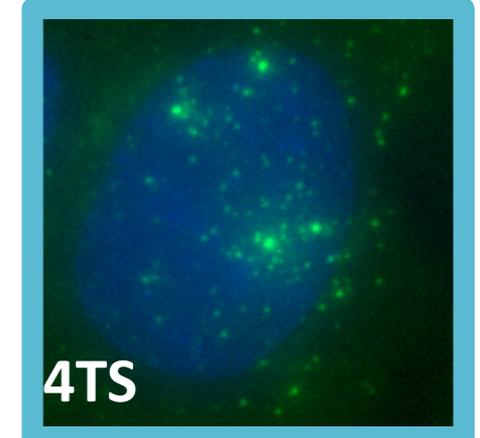
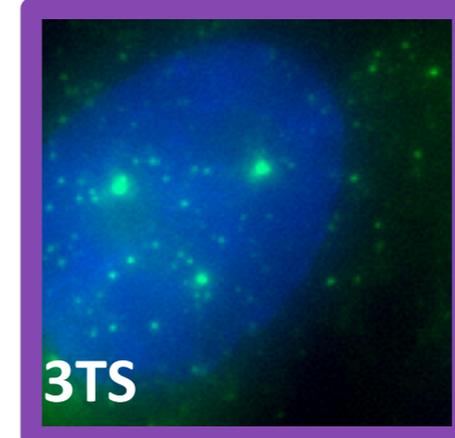
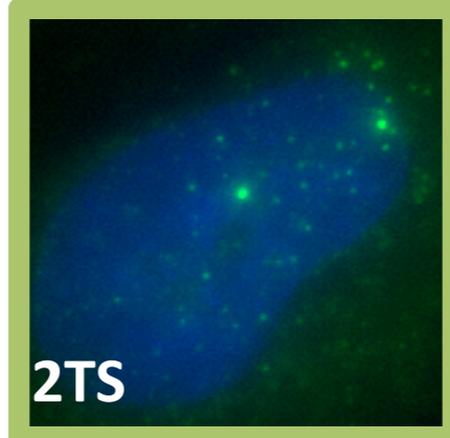
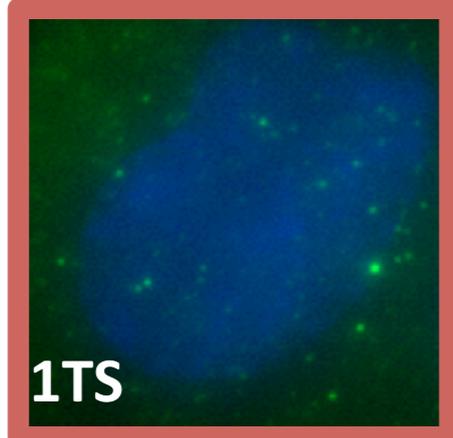
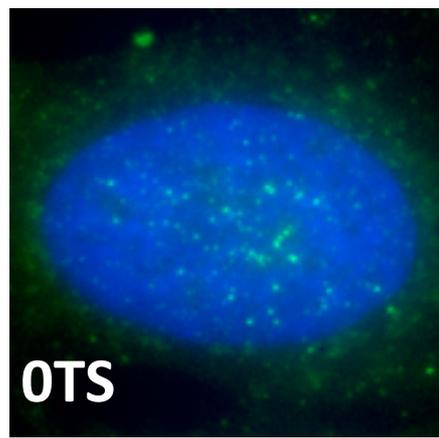
## Erk and p38 phosphorylation following stimulus



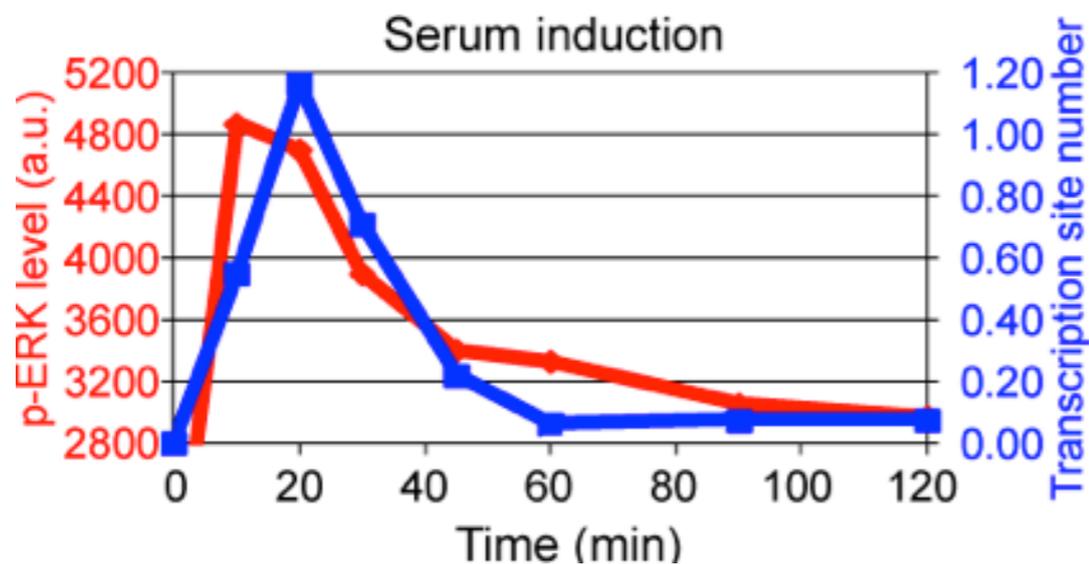
# Measuring c-Fos Activity at the Single Transcript Level



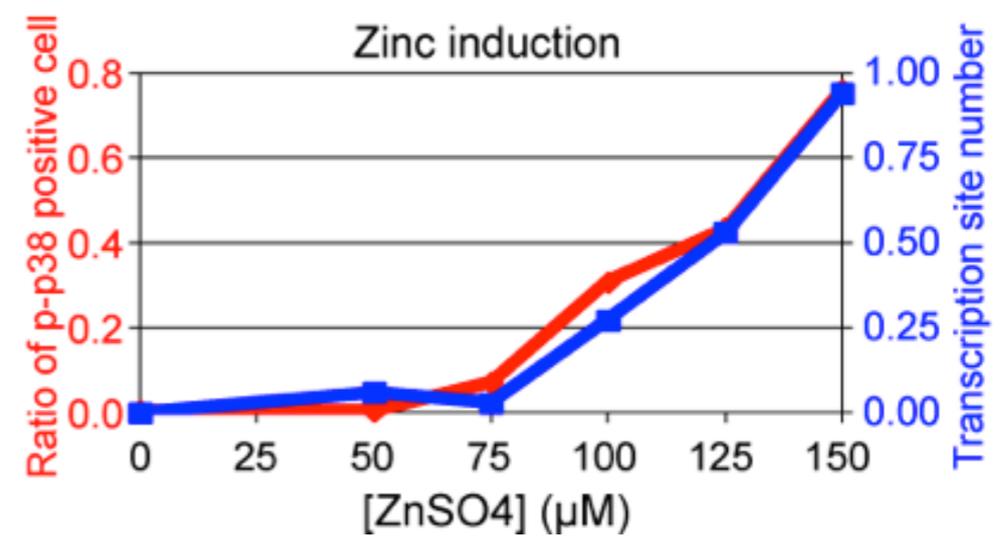
# Signaling Affects Transcription Site Activation



The number of ATS's varies randomly from cell to cell.  
The *average* number of ATS's tracks MAPK induction dynamics.



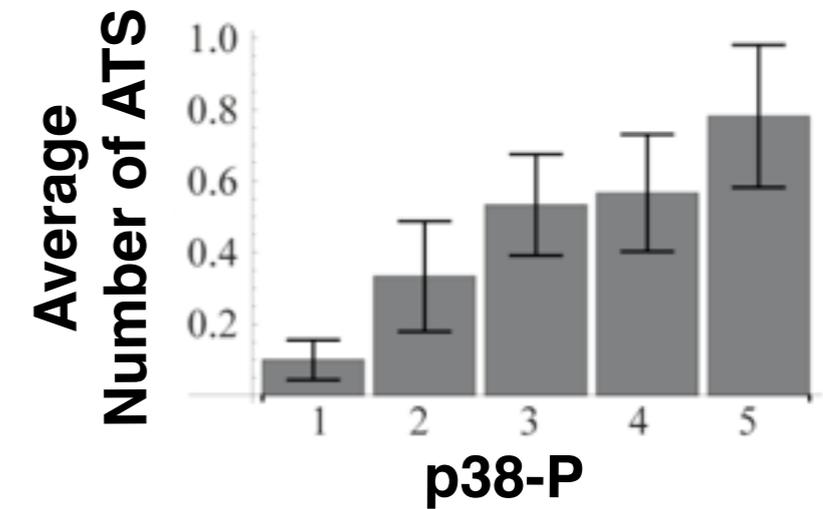
**Serum activation**



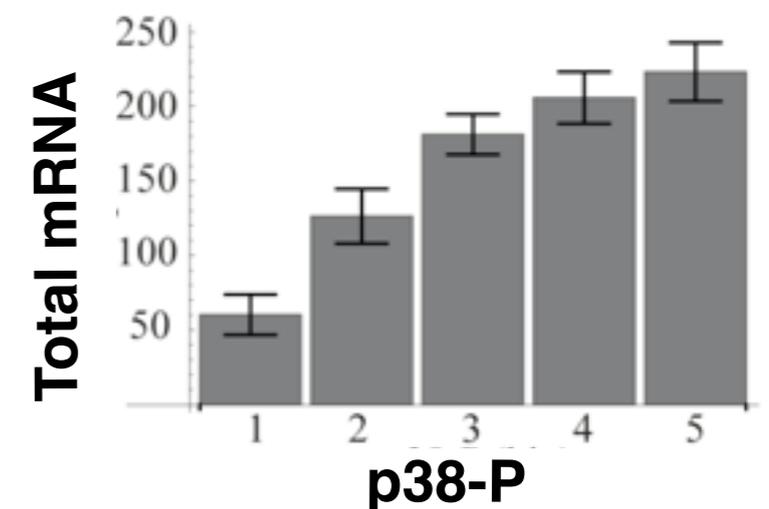
**Zinc activation**

# Signaling Affects Number of *Mature* mRNA.

The *average* number of ATS's tracks MAPK induction dynamics.



The *average* number of mature mRNA tracks MAPK induction dynamics.

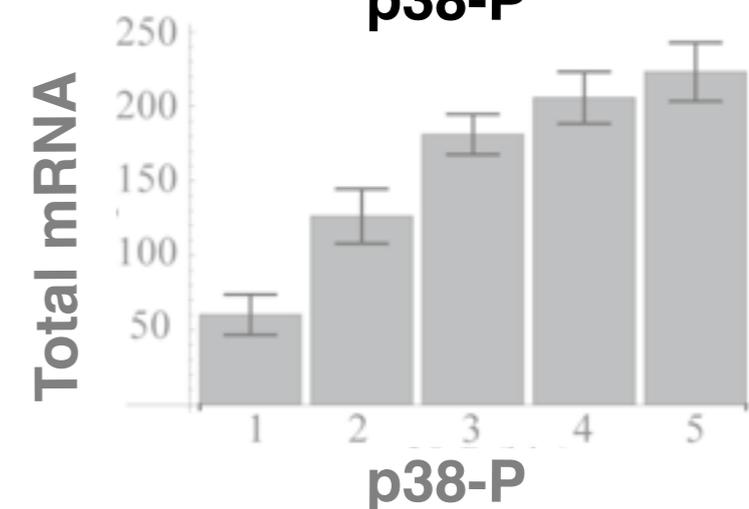
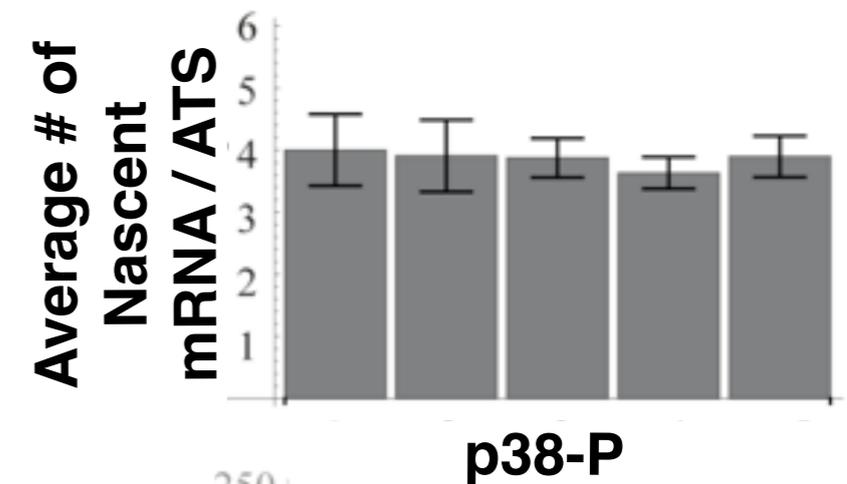
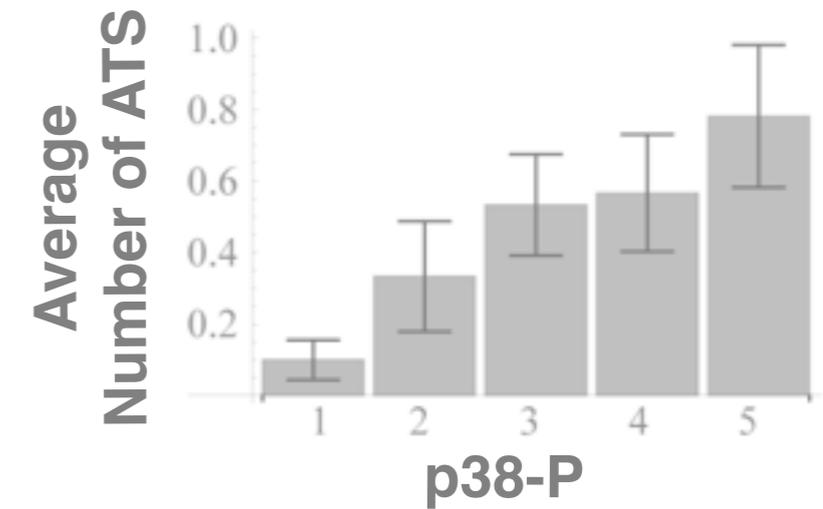


# Signaling does *not* affect *Nascent mRNA* numbers!

The *average* number of ATS's tracks MAPK induction dynamics.

**The average number of nascent mRNA per ATS is independent of MAPK.**

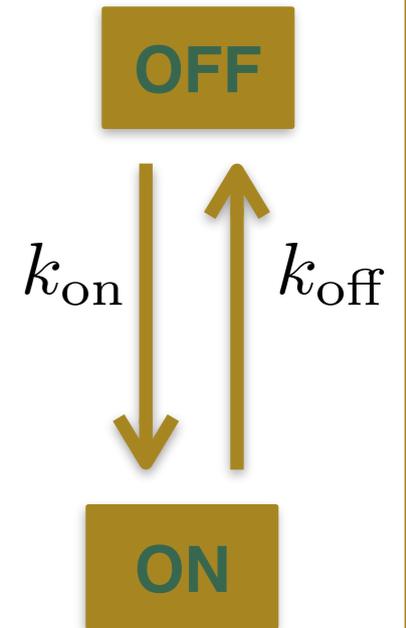
The *average* number of mature mRNA tracks MAPK induction dynamics.



# Models for c-Fos burst behavior



Transcription Factors (bind and unbind)



# Models for c-Fos burst behavior



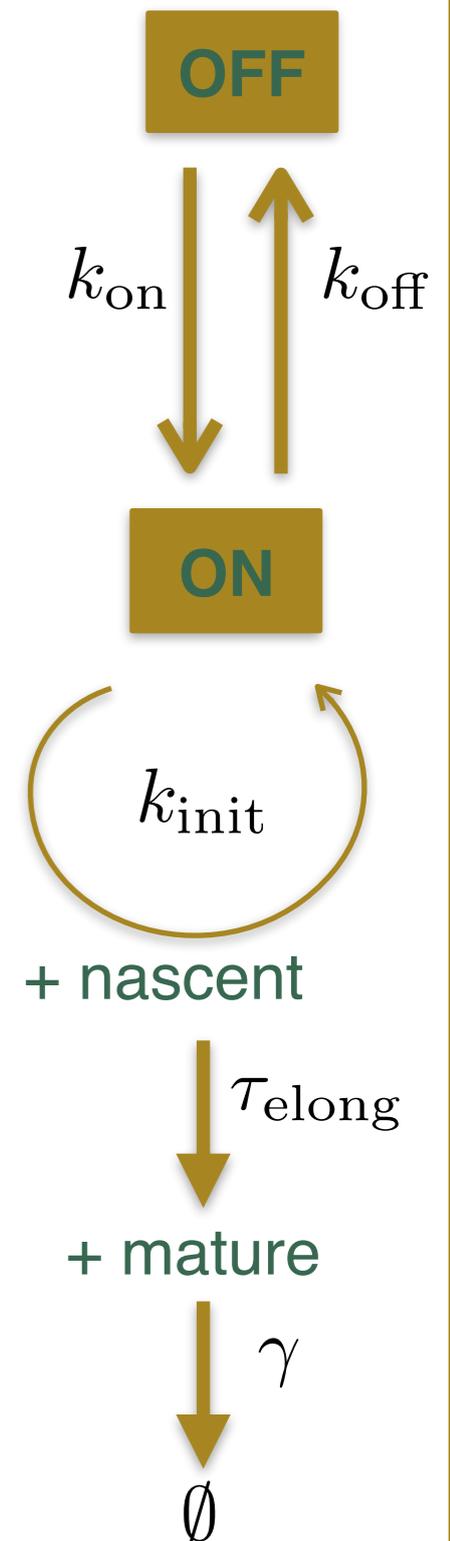
Transcription Factors (bind and unbind)



RNA Polymerase II (initiate and elongate)



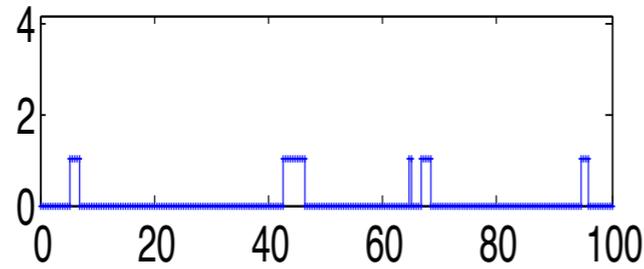
Mature mRNA (complete and degrade)



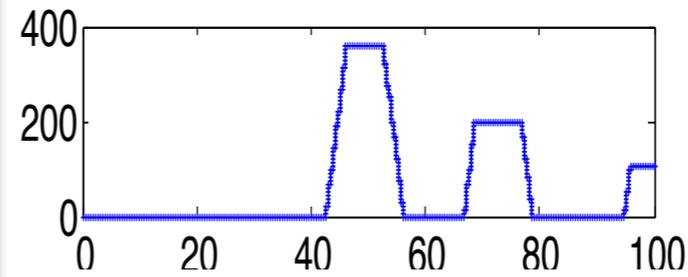
# Trajectories from Alternate c-Fos Burst Models

**1) Rare Isolated bursts**

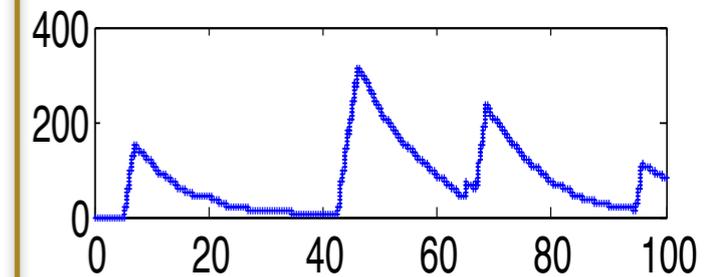
# Active TS



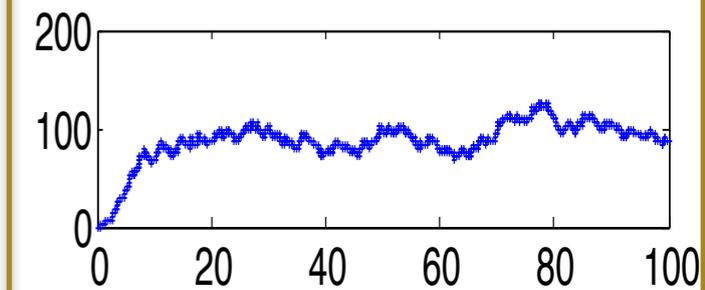
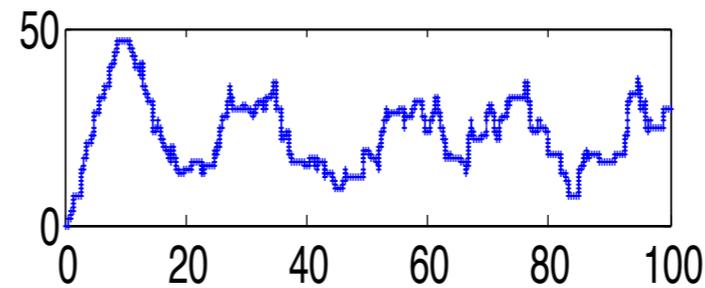
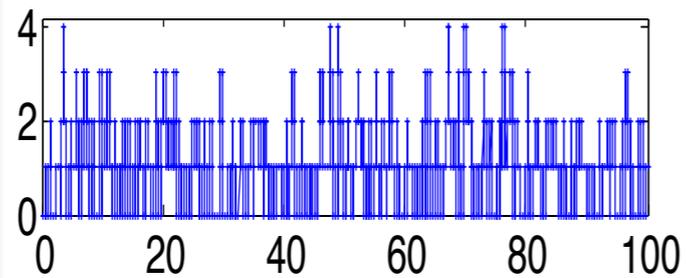
Nascent mRNA per TS



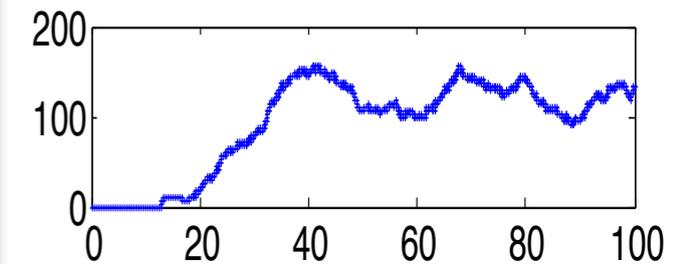
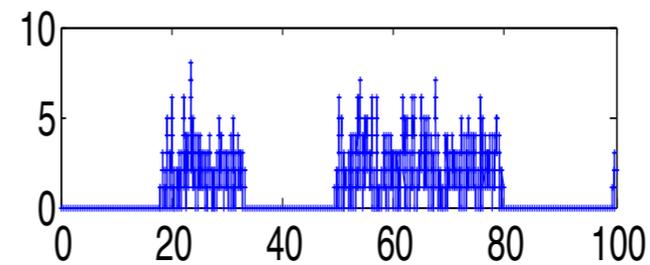
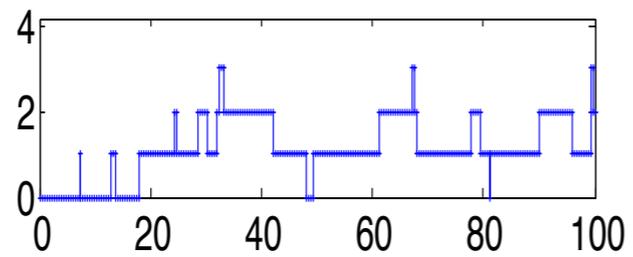
\*Mature mRNA



**2) Frequent Merging bursts**



**3) Rare Saturated bursts**



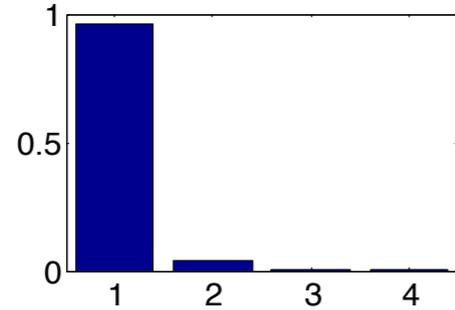
\*All models tuned to produce an average of 100 mature mRNA at equilibrium.  
Representative trajectories from Stochastic Simulation Algorithm (Gillespie, 1976).



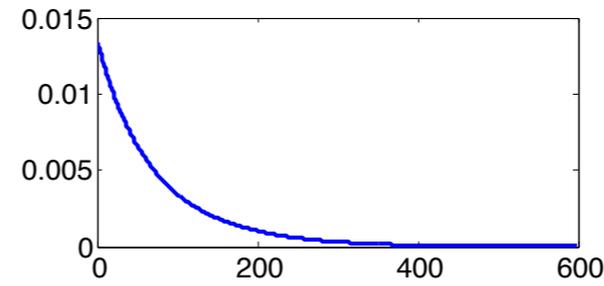
# Distributions from Alternate c-Fos Burst Models

**1) Rare Isolated bursts**

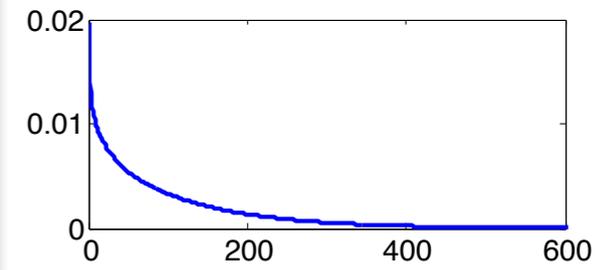
Active TS



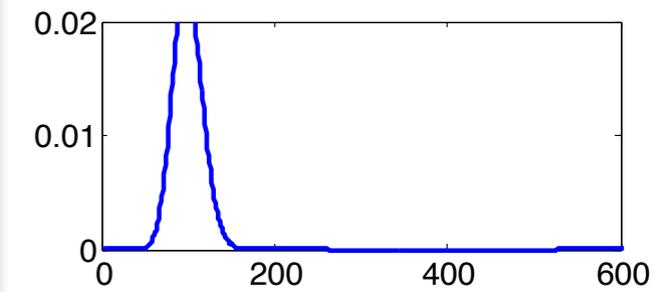
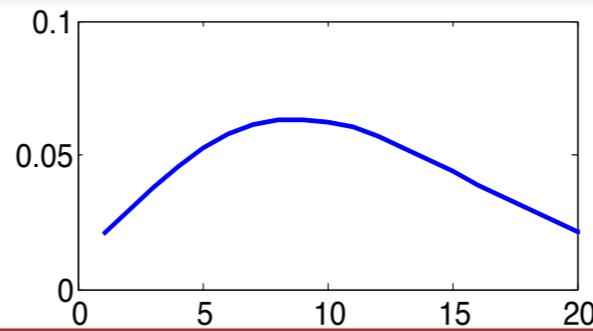
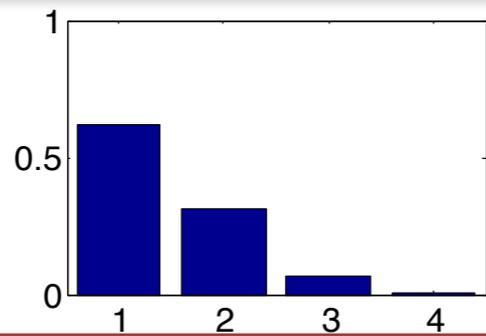
Nascent mRNA



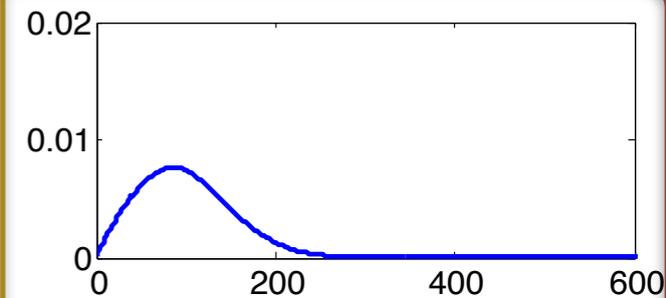
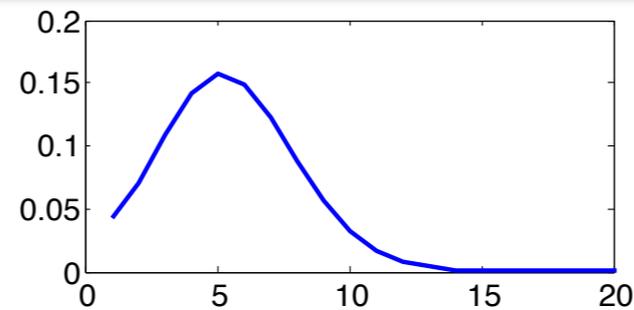
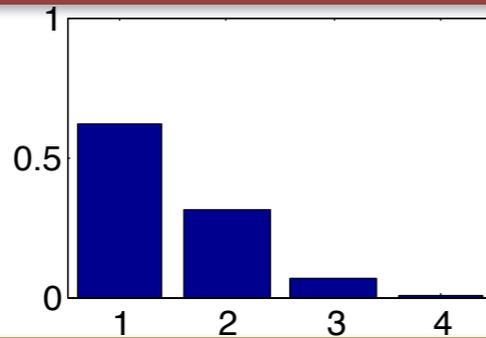
Mature mRNA



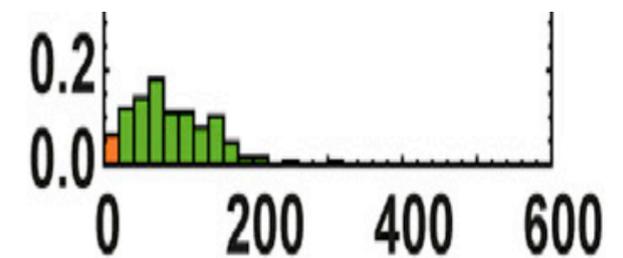
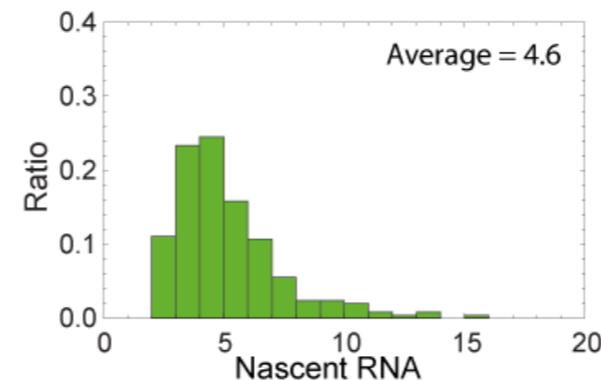
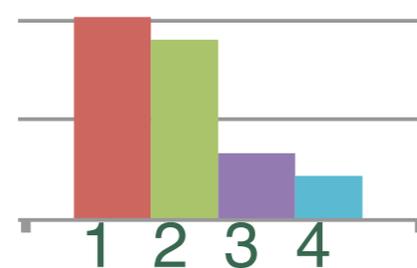
**2) Frequent Merging bursts**



**3) Rare Saturated bursts**

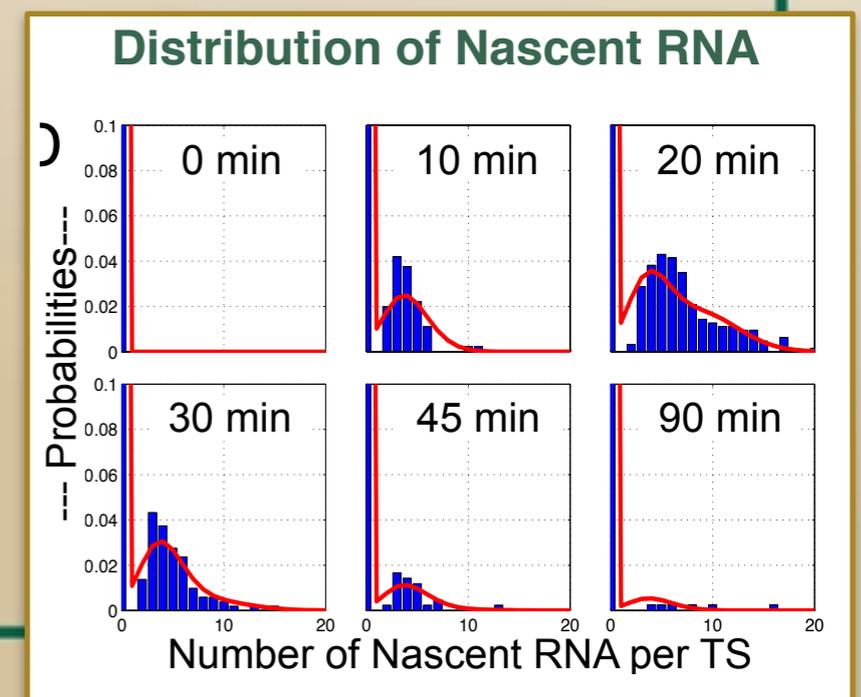
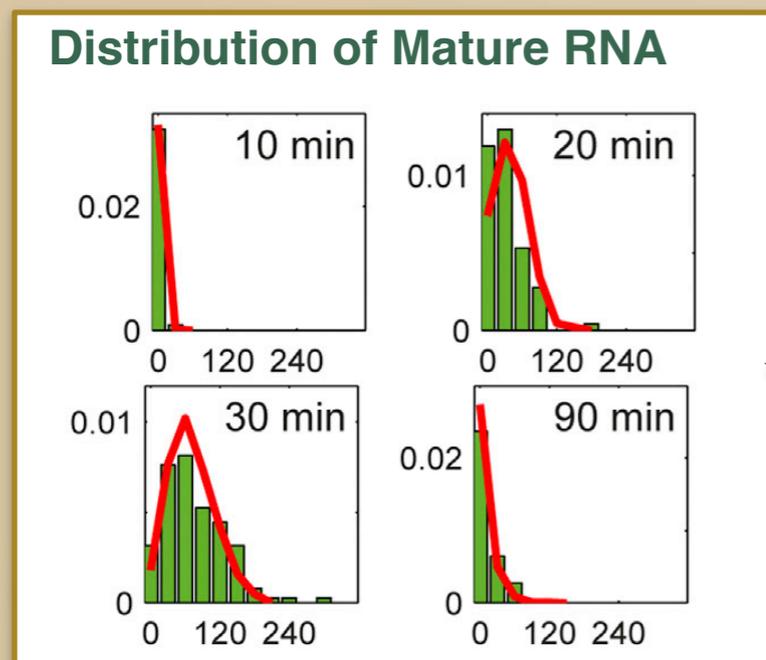
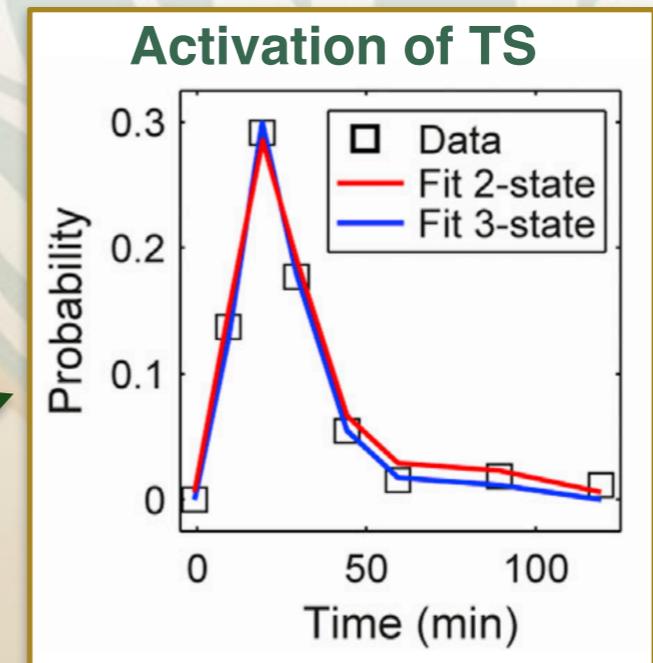
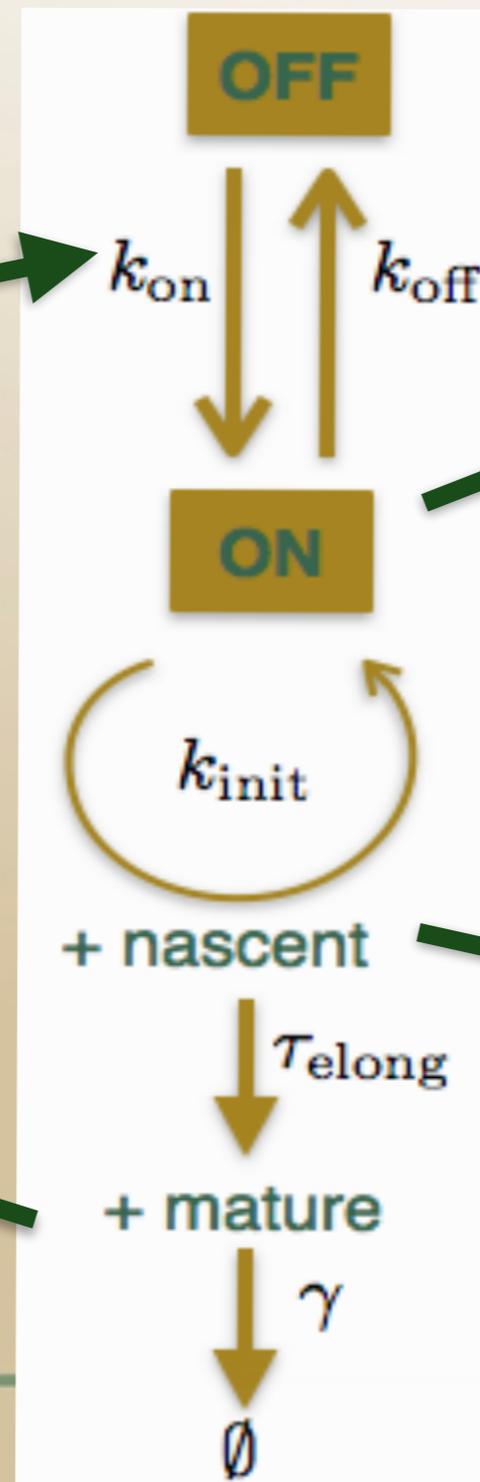
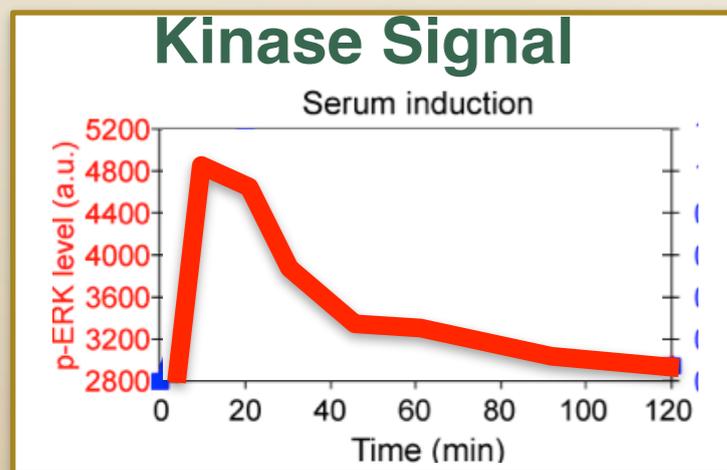


**Experimental Data**



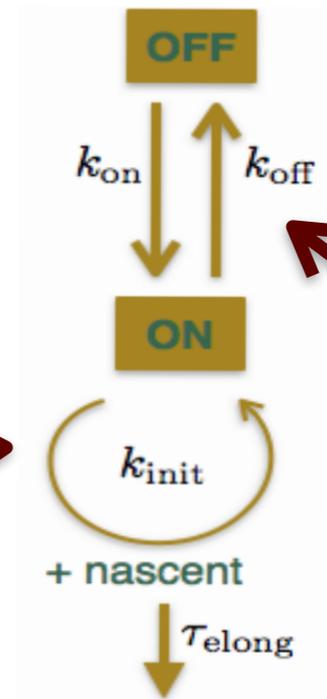
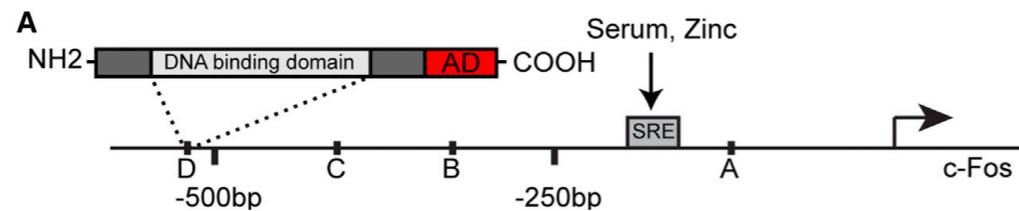
# Quantitative fits to signal-activated transcription dynamics

- Burst saturation model accurately captures c-Fos dynamics.

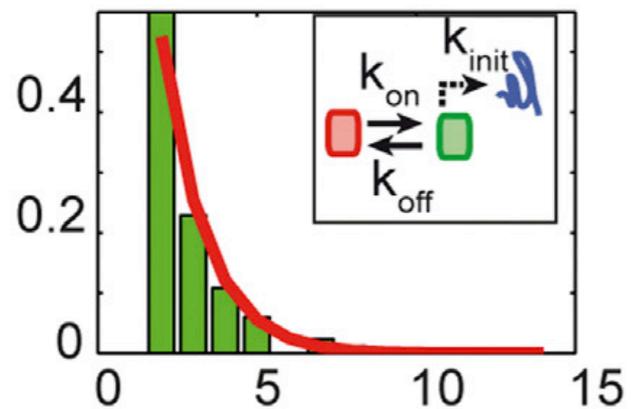


# Transcription Factor Modification of Burst Dynamics

- Transcription Factor (TF) properties alter burst dynamics.
- We probe these changes using the transcription activator-like effector (TALE) approach (Perez-Pinera et al, 2013)

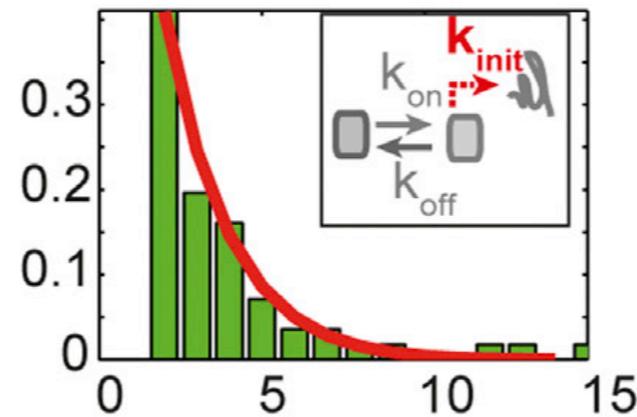


VP16



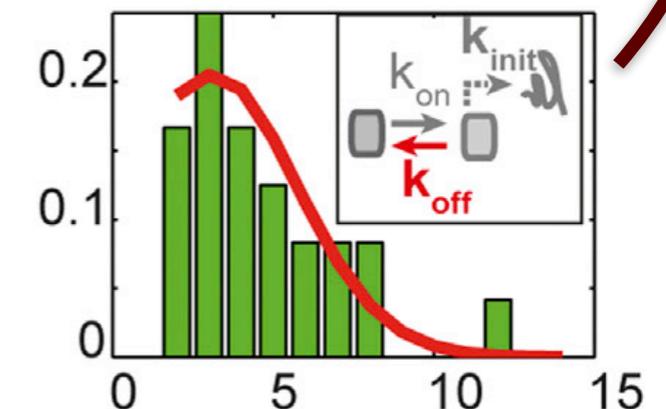
Single weak TF  
Small isolated bursts

VP64



Single strong TF  
Larger isolated bursts

4xVP16



Multiple weak TF's  
Longer saturated bursts

The same model captures all TF activators with only one parameter change.

1. Introduction - Information from transcript fluctuation
2. Measuring and Modeling single-cell and single-molecule responses
3. Case Studies:
  - i. Predicting kinase-activated gene regulation dynamics in *Saccharomyces cerevisiae* (budding yeast)
  - ii. Quantitative modeling for c-Fos mRNA burst dynamics in U2OS cells.

## 4. Conclusions



# Summary and Conclusions

## **Stochastic, temporal, and spatial fluctuations affect single-cell dynamics**

These complicate modeling and disrupt transcription control.

## **But statistics of these fluctuations follow deterministic rules:**

Cells exhibit distinct, measurable 'fluctuation fingerprints'.

Can reveal subtle gene regulation mechanisms & parameters.

Can be predicted with high accuracy and precision.

**Uncertainty Quantification** reveals when models are too simple, too complex, or just right (i.e., the Goldilocks Model).

We have identified **predictive quantitative models** of transcription regulation for many natural and synthetic genes in several organisms.

**Prediction is the first step toward design, optimization and control.**



## ...wherein dynamic stimuli and single-cell measurements reveal gene regulation mechanisms

1. \*Munsky, \*Neuert, van Oudenaarden, Using Gene Expression Noise to Understand Gene Regulation, **Science**, **336**:6078, 183–187, 2012.
2. \*Neuert, \*Munsky, *et al*, Systematic Identification of Signal-Activated Stochastic Gene Regulation, **Science**, **339**:6119, 584-587, 2013.
3. Senecal, Munsky, *et al*, Transcription Factors Modulate c-Fos Transcriptional Bursts, **Cell Reports**, **8**:1, 75-83, 2014.



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Chris Voigt, MIT  
Brynne Stanton, MIT  
Ying-Ja Chen, MIT

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Xavier Darzacq, UC Berkeley  
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Christophe Zimmer, Institut Pasteur

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Nan Li, LANL  
Sofiya N. Michva-Viteva, LANL

## The PAP Switch:

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David Low, UCSB  
Mustafa Khammash, ETH

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Kumkum Ganguly, LANL  
Babetta Marrone, LANL  
Taraka Dale, LANL

## Team at CSU:

### *Postdocs:*

Vijay Gupta

### *Graduate Students:*

Zachary Fox

### *Undergrads:*

Lucas Suazo

Michael May

Graduate Research  
Positions available  
in predictive  
modeling and  
experiment design.



# q-bio Summer School

## Three Campuses:

Albuquerque, NM (July 6-21)

San Diego, CA (July 13-28)

Fort Collins, CO (July 13-28)

## Eight Focus Areas:

Stochastic Gene Regulation

Cancer Dynamics

Complex Biological Dynamics

Cell signaling

Viral dynamics

Biomolecular simulations

Membrane biology

Computational Synthetic Biology

Experimental Synthetic Biology

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<http://q-bio.org>

## The 2015 q-bio Summer School (Albuquerque, San Diego, Fort Collins)

Applications are now being accepted for the Ninth Annual q-bio Summer School. Applications will be due on **Monday, February 16 at 11:59pm (MST)**. Submitted applications may be revised until that time. To apply now, please visit the application website: <https://www.openconf.org/qbioss2015/openconf.php>  
**Scholarships are available.**

The 2015 q-bio Summer School will be held on different dates at three different campuses

- 1) July 6-21, 2015 at the Colorado State University in Fort Collins, CO
- 2) July 13-28, 2015 at the University of New Mexico in Albuquerque, NM
- 3) July 13-28, 2015 at the University of California in San Diego, CA.

### School Overview:

The q-bio Summer School is an annual event intended to advance predictive modeling of cellular regulatory systems by exposing participants to a survey of work in quantitative biology and by providing in-depth instruction in selected techniques, with an emphasis on techniques useful for modeling cellular regulatory networks. Certain data analysis techniques and experimental methods will also be covered.

Lectures will be offered at **three campuses**. At the **San Diego campus**, the focus will be on synthetic biology. At the **Albuquerque and Fort Collins campuses**, the focus will be on different aspects of systems biology. Students will each work on a mentored project. Participants will attend daily core lectures, project-specific lectures, journal clubs, and computer and experimental labs. The summer school is designed for graduate students, postdocs, or anyone with a quantitative background who is new to modeling cellular regulatory systems/networks.

At the School students will attend 20-25 hours of core lectures, 20-25 hours of course-specific lectures, 10-15 hours of computational and experimental labs, and 10-15 hours of student presentations. There will also be 20-30 hours of mentored project work, which may include some simple experiments, theoretical developments and/or real data analyses.

### The main topics of the 2015 summer school are:

Biomolecular Simulations (Albuquerque, NM), Cell Signaling (Albuquerque, NM), Membrane Biology (Albuquerque, NM), Viral Dynamics (Albuquerque, NM), Cancer Dynamics (Fort Collins, CO), Stochastic Gene Regulation (Fort Collins, CO), Complex Biological Dynamics (Fort Collins, CO), Experimental Synthetic Biology (San Diego, CA), and Computational Synthetic Biology (San Diego, CA)

### Organizers:

S. Gnanakaran, *New Mexico Consortium, Los Alamos*, Jeff M. Hasty, *University of California, San Diego*, William S. Hlavacek, *New Mexico Consortium, Los Alamos*, Marek Kimmel, *Rice University, Houston*, Brian Munsky, *Colorado State University, Fort Collins*, Ashok Prasad, *Colorado State University, Fort Collins*, Douglas Shepherd, *University of Colorado, Denver*, Patrick Shipman, *Colorado State University, Fort Collins*, Mara P. Steinkamp, *University of New Mexico, Albuquerque*, Lev S. Tsimring, *University of California, San Diego*

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[http://q-bio.org/wiki/The\\_Ninth\\_q-bio\\_Summer\\_School](http://q-bio.org/wiki/The_Ninth_q-bio_Summer_School)