

# Predictive spatial models of gene regulation via Bayesian inference

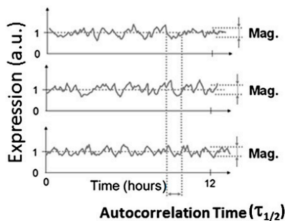
Clayton W. Seitz

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# Gene expression is stochastic and non-constitutive

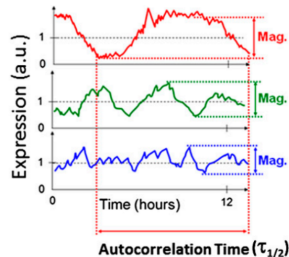
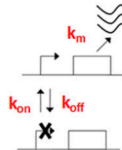
A

**Constitutive  
gene expression**



B

**Episodic 'bursty'  
gene expression**



## Single-state models

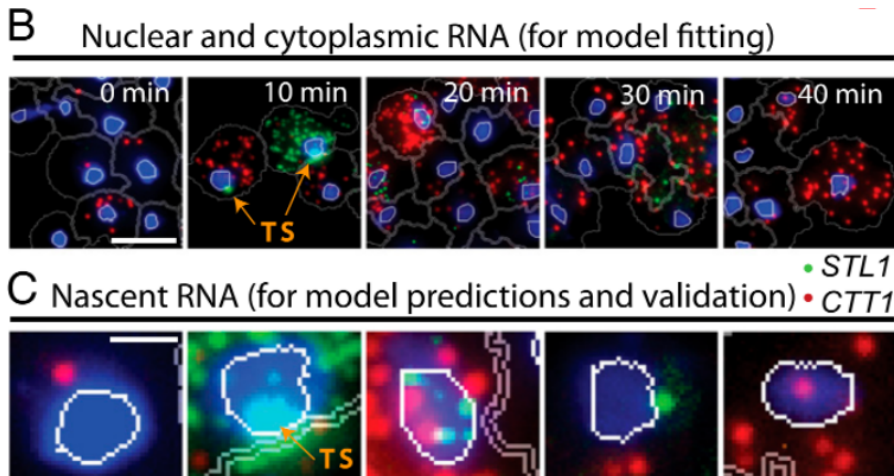
- ▶ Transcription occurs at a fixed rate
- ▶ mRNA counts are Poisson
- ▶ Underestimates variance in mRNA counts

## Two-state models

- ▶ Promoter can be on or off
- ▶ mRNA counts are not Poisson

Chromatin structure is complicated e.g., loops. Multiple *cis*-regulatory elements can contribute to promoter switching and transcription control

# STL1/CTT1 induction with NaCl in yeast



**Figure 1:** Munsky et al., PNAS 2018

## A quick note on ergodicity and ensemble snapshots

- ▶ **Ergodicity** = statistics of the ensemble and a single process are the same
- ▶ Implies the parameters of the process are the same for every cell
- ▶ Ensemble snapshots useful due to experimental constraints (multiplexing)

$$\lim_{N \rightarrow \infty} \frac{1}{N} \sum_{i=1}^N (x_i - \mu)^n = \int (x - \mu)^n p(x) dx$$

# A compartment model for spatial gene expression

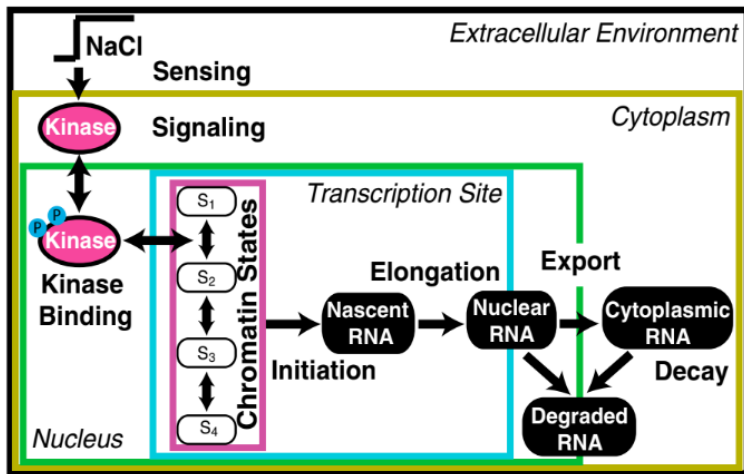
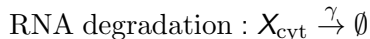
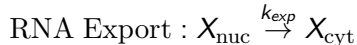
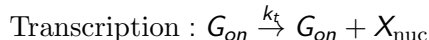
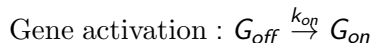


Figure 2: Munsky et al., PNAS 2018

## A compartment model for spatial gene expression

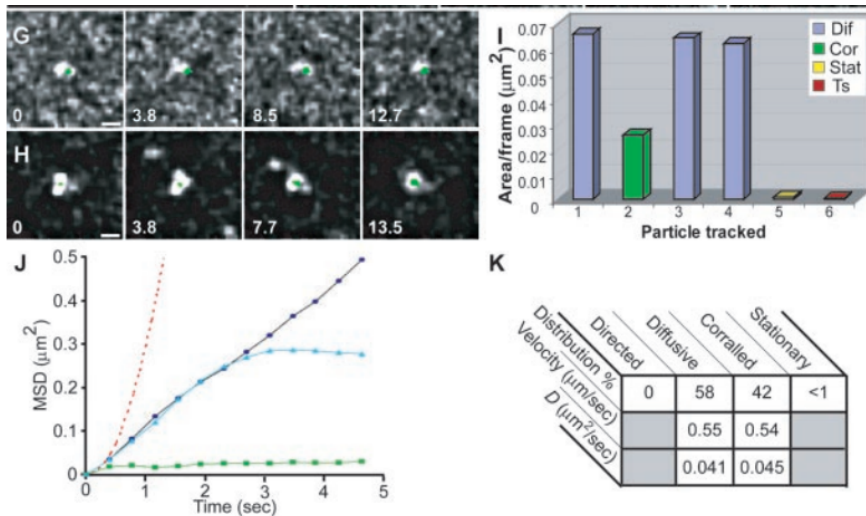
Let  $X$  represent an arbitrary RNA transcript of gene  $G$



Raw data collected post induction can be used to infer parameters

$$\theta = (k_{\text{on}}, k_{\text{off}}, k_t, k_{\text{exp}}, \gamma)$$

# Brownian RNA transport in the nucleus



**Figure 3:** Shav-Tal et al., Science 2004

## Rate of nuclear export is determined by diffusion

Particles have been shown to be distinguishable (non-ergodic dynamics)

The probability current  $J(r, t)$  determines the rate of RNA export

Even if diffusion is Brownian motion, the export rate parameter is not constant:

$$\frac{dP(x, y, t)}{dt} = D \cdot \nabla^2 P = D \frac{dJ(x, y, t)}{dt}$$

There is also the birth of new particles affecting the density



## An Ising model of promoter switching

Promoter activation often requires chromatin reorganization, binding of specific TF combinations. We can imagine a random (?) walk through the binding phase space

$$\mathcal{H} = -\frac{1}{2} \sum_{i,j} J_{ij} x_i x_j - \sum_j h_j x_j \quad P(\mathbf{x}) = \frac{1}{Z} \exp(-\beta \mathcal{H}(\mathbf{x}))$$

We know  $p(x_j = 1) = \exp(-\beta H(x_i = 1))$ . Then, we define

$$h_j = -\frac{1}{\beta} \log p(x_i = 1) = -\frac{1}{\beta} \log \frac{[x_j]}{K_j + [x_j]}$$

Suppose that there is a single state or set of states  $\mathbf{x}^*$  for which the promoter is active

$$\lambda = \frac{Z_{on}}{Z_{on} + Z_{off}} \rightarrow P(n|\mu) = \frac{\mu^n}{n!} \exp(-\mu)$$

with  $\mu = \lambda t$

# Bayesian parameter inference using ensemble snapshots

Suppose we have a series of ensemble snapshots of an *in-vitro* population:

$$\mathbf{x} = \{\mathbf{x}_0, \dots, \mathbf{x}_t\} \quad \mathbf{y} = \{\mathbf{y}_0, \dots, \mathbf{y}_t\}$$

with  $\mathbf{x}_t = \{x_1, \dots, x_n\}$  and similarly for  $\mathbf{y}$ . Under perfect measurements  $\mathbf{x} = \mathbf{y}$

We would like to use  $\mathbf{x}$  to fit a dynamical model  $\mathcal{M}(\theta)$ . Bayesian inference lets us infer  $\theta$  from  $\mathbf{x}$  while quantifying the uncertainty in our estimate:

$$P(\theta|\mathbf{x}) \propto f(\mathbf{x}|\theta)\pi(\theta) = \pi(\theta) \prod_t f(\mathbf{x}_t|\theta)$$

The likelihood  $f(\mathbf{x}_t|\theta)$  is often difficult to define or intractable to compute due to the curse of dimensionality, making even MLE a challenge

## Kolmogorov's forward equation (chemical master equation)

Dynamics on biochemical reaction networks are inherently stochastic and the state space is discrete. We can only write probabilities over the state space

$$\begin{aligned}P(\mathbf{x}_i, t) &= \sum_j T_{ji}(\mathbf{x}_i, t | \mathbf{x}_j, t - \Delta t) P(\mathbf{x}_j, t - \Delta t) \\&= \sum_k T_k(\mathbf{x}_i, t | \mathbf{x}_i - \nu_k, t - \Delta t) P(\mathbf{x}_i - \nu_k, t - \Delta t)\end{aligned}$$

where  $T_k$  is the probability of a reaction channel  $k$  firing in the interval  $(t, t + \Delta t)$ .

Taking the limit  $\Delta t \rightarrow 0$  one can derive the forward Kolmogorov equation or chemical master equation (CME)

$$\frac{dP(\mathbf{x}, t | \mathbf{x}_0)}{dt} = \sum_k T_k(\mathbf{x} - \nu_k) P(\mathbf{x} - \nu_k, t) - T_k(\mathbf{x}) P(\mathbf{x}, t)$$

# References I