Nonlinear Dynamic Models for Single-Cell Time-Lapse Microscopy

Jarad Niemi[1], Cheemeng Tan[2], Lingchong You[2,3], Mike West[1,3]

[1] Department of Statistical Science, [2] Department of Biomedical Engineering, [3] Institute for Genome Sciences and Policy

Nonlinear Dynamic Models

Observations (data)

Observation error

System noise

$$y_{c,t} = f(x_{c,t}) + \nu_{c,t}$$
$$x_{c,t} = g_c(x_{c,t-1}) + \omega_{c,t}$$

Unobserved true state

$f(\cdot)$ Observation function

$g_c(\cdot)$ State evolution function

Unknown parameters in:
- observation function,
- state evolution function,
- observation error, and
- system noise.

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Goal: Inference about unknown parameters based on data.

Bayesian Inference

$$p(\theta, x_{1:C,1:T} | y_{1:C,1:T})$$

$$\theta = (\theta_1, \theta_2, \ldots, \theta_p)'$$

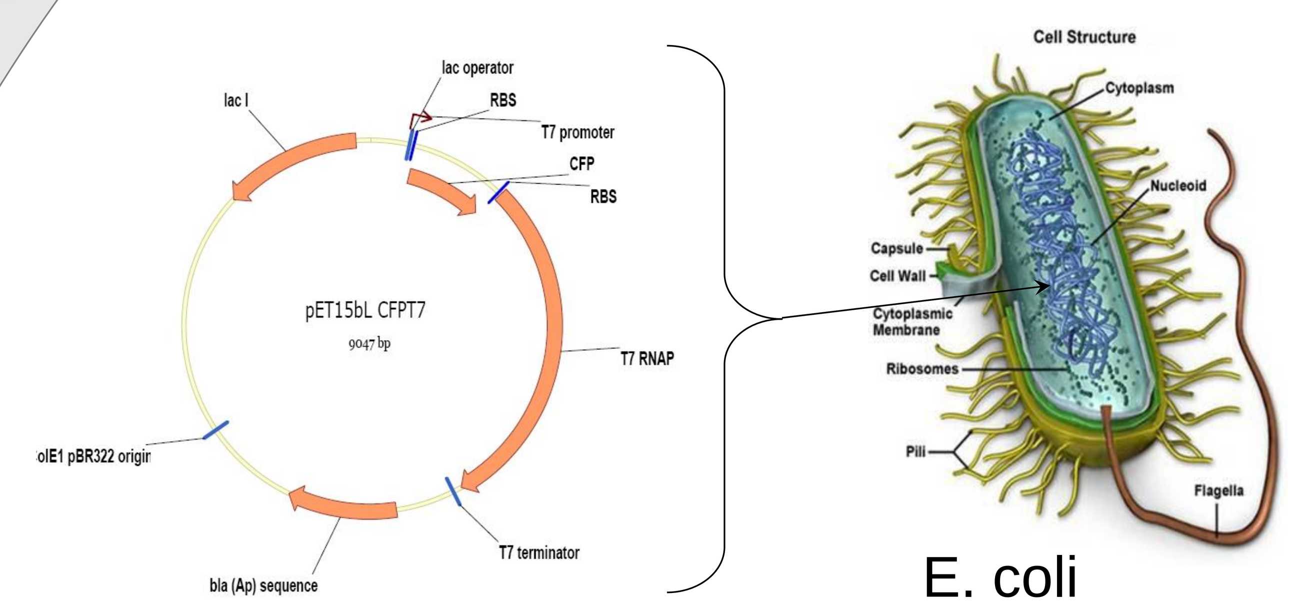
Markov chain Monte Carlo

AM4

$$x_{1:C,1:T} \sim p(\cdot|\theta, y_{1:C,1:T})$$
$$\theta_1 \sim p(\cdot|\theta_{-1}, y_{1:C,1:T}, x_{1:C,1:T})$$
$$\theta_2 \sim p(\cdot|\theta_{-2}, y_{1:C,1:T}, x_{1:C,1:T})$$
$$\vdots$$
$$\theta_p \sim p(\cdot|\theta_{-p}, y_{1:C,1:T}, x_{1:C,1:T})$$

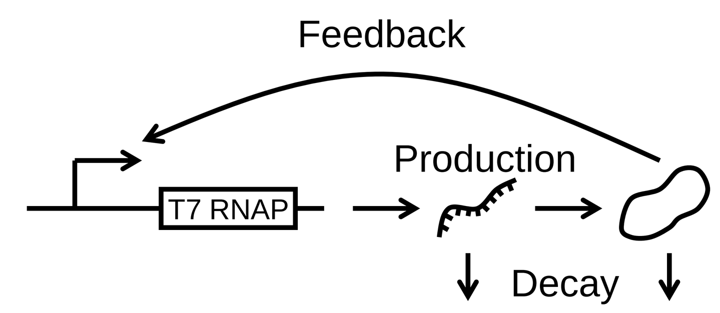
Case Study: T7 RNA polymerase bistability

Hypothesis: T7 RNAP level is driven by effective degradation rate.



E. coli

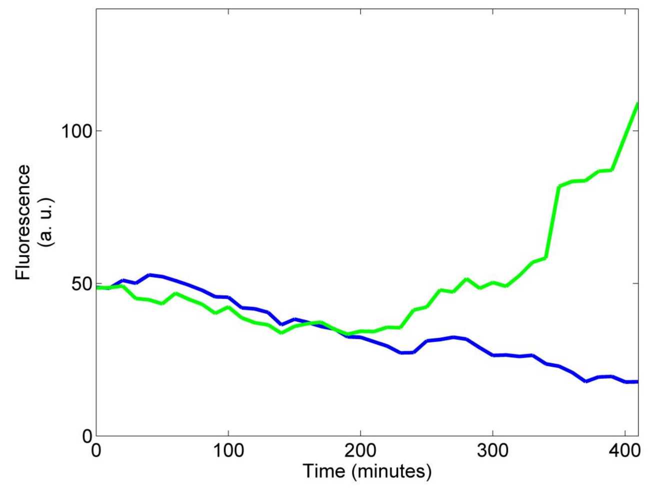
Circuit Schematic



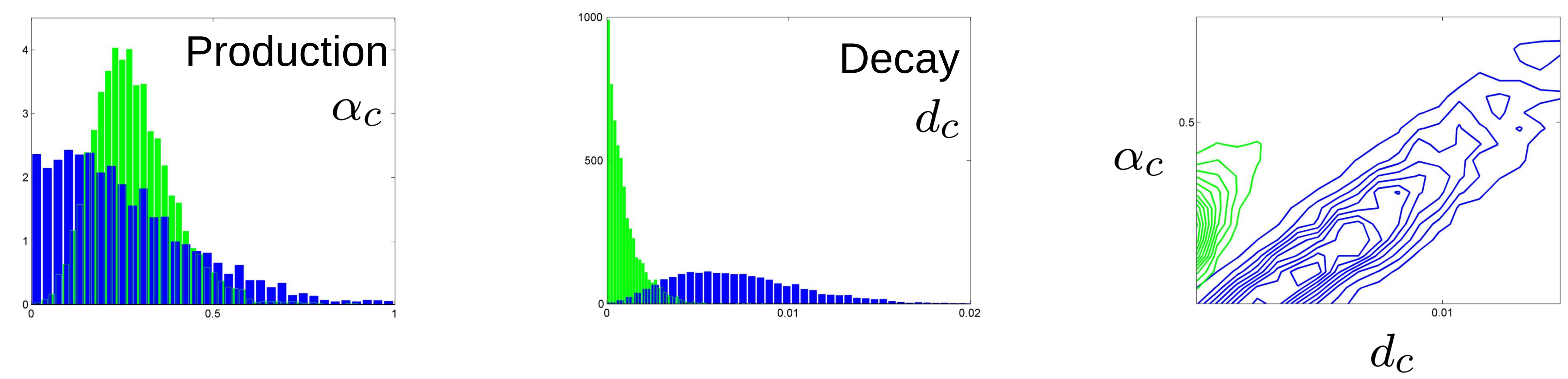
Positive-Feedback Model

$$f(x) = x$$
$$g_c(x) = x + \frac{k_c + \alpha_c x}{\beta_c + x} - d_c x$$

Data



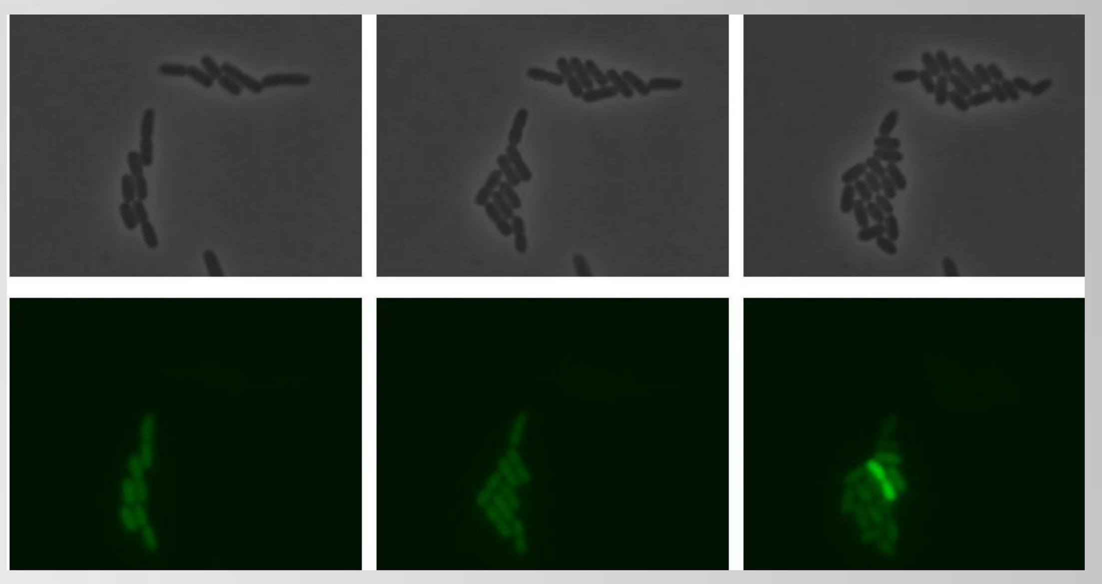
Results



Conclusions:

- Time-lapse fluorescent microscopy allows for studying in vitro cellular processes.
- Dynamic models with Bayesian methods are powerful tools for understanding these processes.
- Case study: T7 RNAP level appears driven by decay rate, although the combination of production and decay is important.

Time-Lapse Fluorescent Microscopy



Phase Image (top row):
- Used for imaging as described below

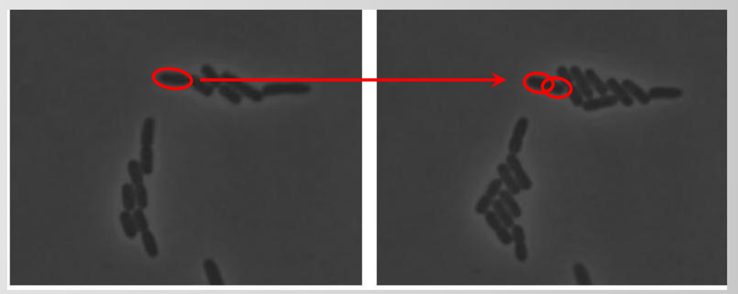
Fluorescent Image (bottom row):
- Provides a measure of the level of the target protein in the system.

Details:
- Pictures taken every 10 minutes to avoid photobleaching
- Recorded for ~7 hrs
- Multiple proteins simultaneously

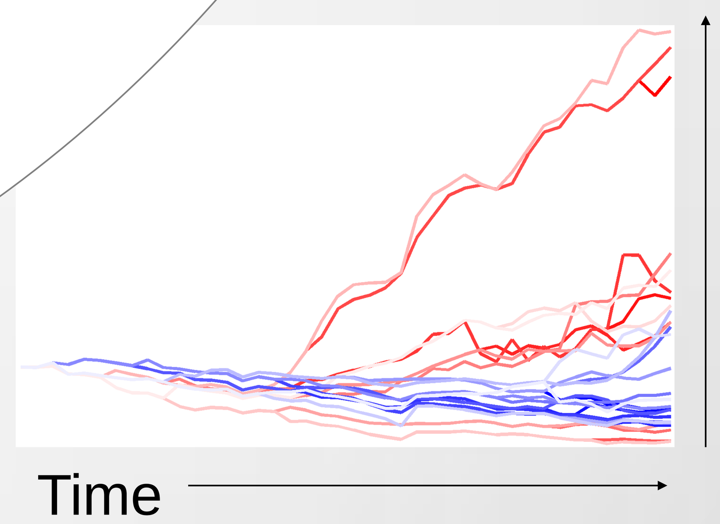
Imaging by CellTracer

Segmentation

Tracking



Lineage Reconstruction



Color indicates descension from a common ancestor.