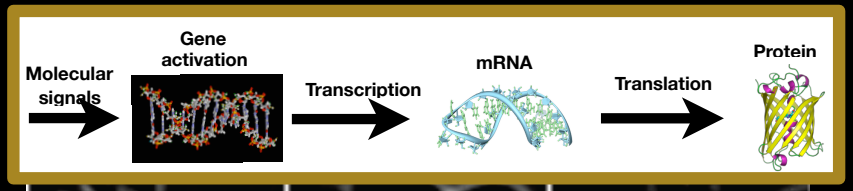
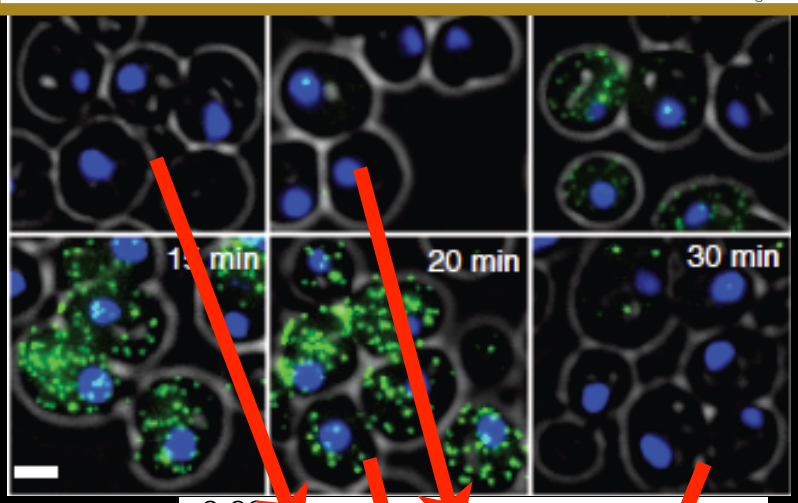
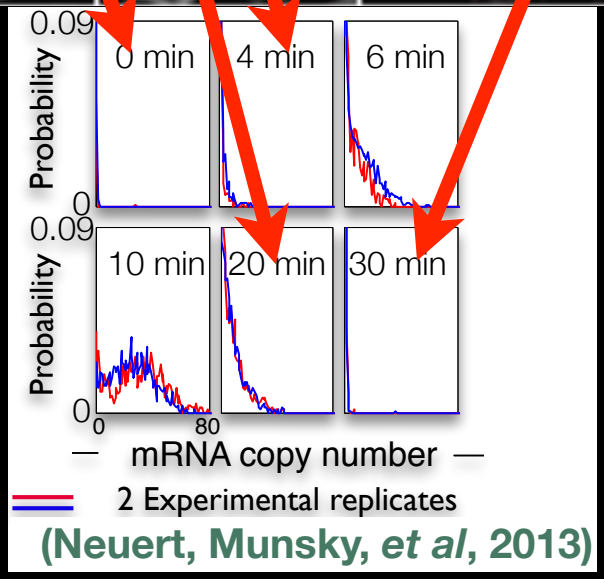
Project 1 — FSP tools for interpretation, prediction and design of single-cell experiments.

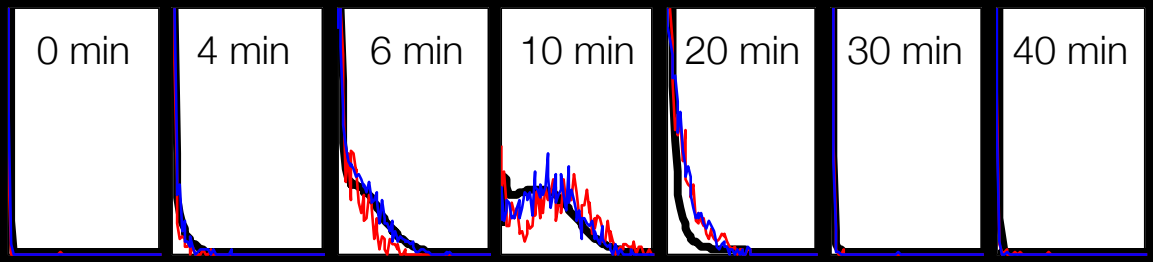






(Neuert, Munsky, *et al*, 2013)

- **Modern single-cell experiments make it possible to quantify the number of important genes/mRNA/Proteins per cell.**
- **Although each individual cell's behavior is stochastic, the statistics of populations is quantifiable and reproducible.**
- **The Chemical Master Equation (CME) and Finite State Projection (FSP) provide means to compare gene expression models with single-cell gene expression data.**



Project 1 — FSP tools for interpretation, prediction and design of single-cell experiments.

In this project students will:

1. **Formulate the CME for various models of gene regulation.**
2. **Solve the FSP approximation for the CME for transient times.**
3. **Understand the use of the FSP to compute first passage times and decision probabilities for non-linear, and non-stationary processes.**
4. **Compute the likelihood that measured data has come from a given FSP model.**
5. **Maximize that likelihood using gradient and non-gradient based methods.**
6. **Use MCMC to quantify parameter space around the maximum likelihood estimate.**
7. **Use the model and FSP analysis to perform parametric sensitivity analysis.**
8. **Use the FSP to compute the Fisher Information Matrix to quantify an experiment design's capability to resolve key model parameters.**
9. **Explore and explain how different experiments are expected to result in more or less information about model mechanisms and parameters.**

Project 1 — FSP tools for interpretation, prediction and design of single-cell experiments.

Before getting started, students should:

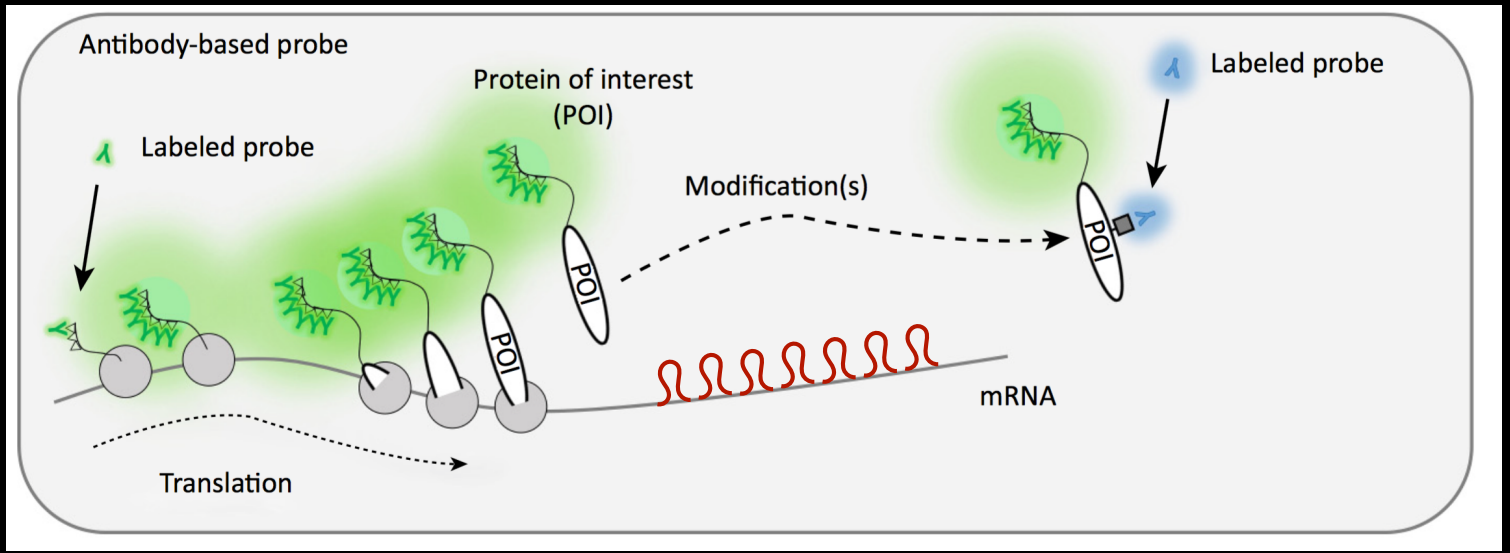
1. **Get familiar with the stochastic simulation algorithm (SSA) and the concepts of "stoichiometry" and "propensity functions".**
2. **Install Matlab or Python and implement an SSA (on your own or with a partner).**
3. **Refresh your memory (or read on wikipedia) about the solution of simple linear systems:**

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x}$$

4. **Implement a numerical solution for such a linear system for some vector, 'x', and some matrix, 'A'.**
5. **Read up a little on the integration of stochastic models and single-cell data (e.g., see the review at Munsky et al, Science 2012).**
6. **If you have model in mind, try to write out the stoichiometry and propensities for that model.**
7. **If you have single-cell data already, write a script to load that data into Matlab/Python and make a histogram.**
8. **Brainstorm to think about what changes you could make in a single-cell experiment (e.g., different environmental inputs, different image analyses, different fluorescence reporters, different measurement times, etc…)**

Project 2 — Modeling Dynamics of Single-mRNA Translation Experiments.

- **New experiments make it possible to quantify the translation of nascent proteins from single copies of mRNA.**
- **When integrated with mechanistic models, these can reveal different effects of frame shifting, codon usage, pauses, etc.**

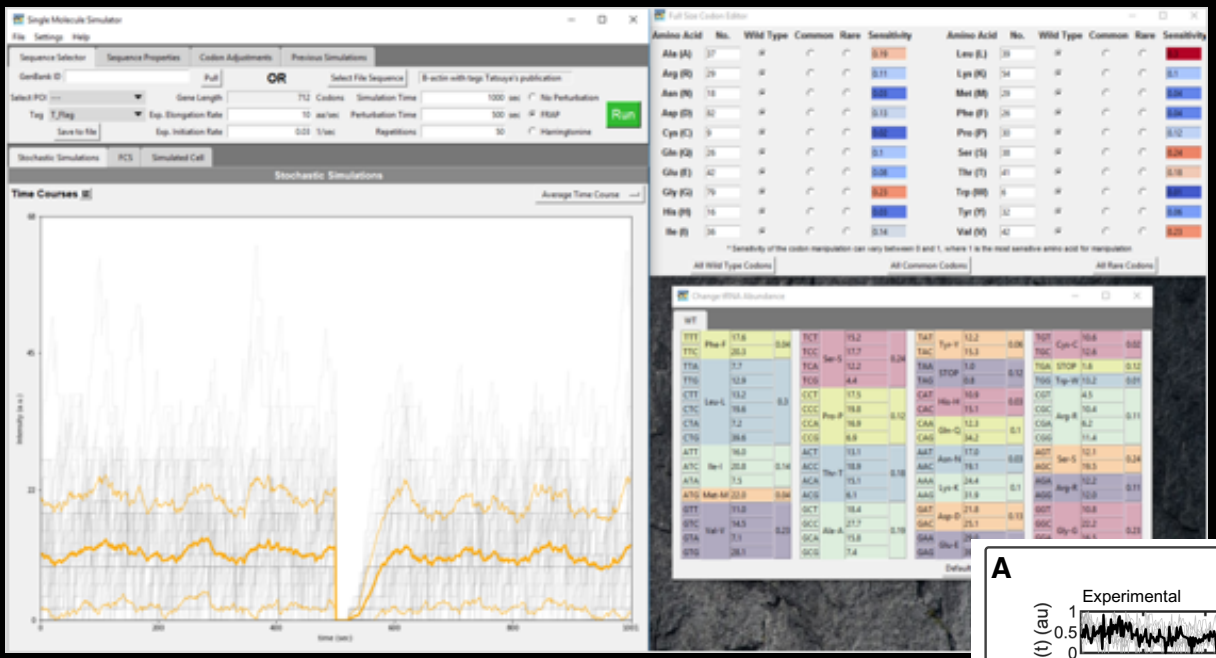


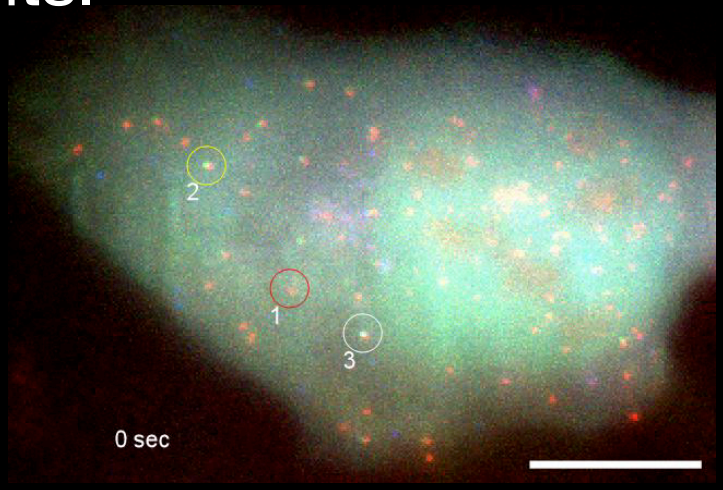
Project 2 — Modeling Dynamics of Single-mRNA Translation Experiments.

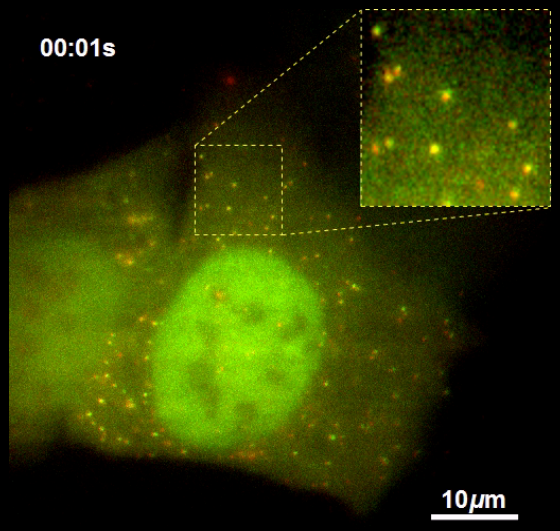
In this project students will:

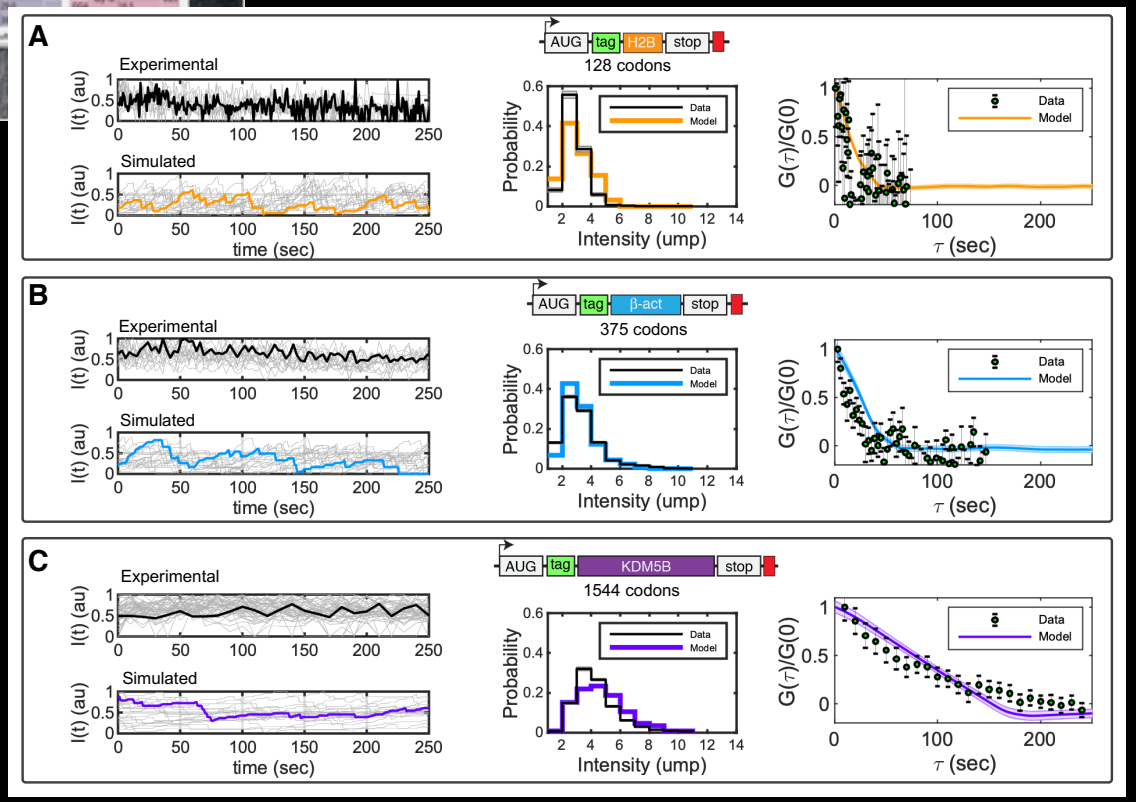
1. **Formulate a generalized model of translation elongation dynamics.**
2. **Simulate ribosome motion and single-mRNA translation dynamics with this model for various assumptions of codon-dependent translation rates.**
3. **Convert simulations of ribosome movement to fluorescence outputs to simulated time-lapse experiments.**
4. **Explore how different genetics, different probe designs, and different mechanisms affect the observable translation dynamics.**
5. **Compare results from models of translation dynamics to experimental data in the recent literature.**

Project 2 — Modeling Dynamics of Single-mRNA Translation Experiments.









Project 2 — Modeling Dynamics of Single-mRNA Translation Experiments.

Before getting started, students should:

1. Read about some of the newest experiments for single-mRNA translation analysis:
https://science.sciencemag.org/content/352/6292/1425
https://www.sciencedirect.com/science/article/abs/pii/S0168952517300343
https://www.sciencedirect.com/science/article/abs/pii/S1097276519303557
https://www.sciencedirect.com/science/article/pii/S0092867419304994

2. Familiarize yourself with modeling tools used for such processes by reading:
https://www.biorxiv.org/content/10.1101/659987v1.abstract

3. Get familiar with the stochastic simulation algorithm (SSA) and the concepts of "stoichiometry" and "propensity functions"
4. Install Python (preferred) and Matlab and implement an SSA (on your own or with a partner).