Mechanisms of Gene Expression

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Course website: https://zach-hensel.github.io/gem2023/

Objectives

- To familiarize students with some mechanisms of regulating gene expression at the transcription and post-transcription levels including production and degradation processes;
- To offer study of selected topics at the cutting edge of advancing knowledge on gene expression;
- To teach critical analysis of original experimental data and the scientific literature;
- To familiarize students with peer review of gene expression literature;
- To introduce stochastic simulation and machine learning techniques that can be applied by non-expert scientists and used to inform experimental design;
- To demonstrate how knowledge of gene expression mechanisms is being deployed in synthetic biology.

Lectures

T1 – Introduction: One point-of-view on history of research in genetics and evolution, molecular studies, and developments in post-transcriptional regulation

T2 – The operon and transcriptional regulation: Transcription factors and other aspects of gene regulation in bacteriophage lysis/lysogeny

T3 – Bacterial gene expression mechanisms – size, activation, translation, degradation

T4 – Insights into gene expression from single-molecule studies

T5 – Synthetic biology: How do we get from simple gene circuits to engineering synthetic organisms?

T6 – Machine Learning: How are machine learning techniques changing studies of gene expression?

Optional exercise 1: Machine learning tutorial "TensorFlow, Keras and deep learning, without a PhD"

T7 – Topics in eukaryotic gene regulation: chromatin folding at different scales and predicting binding from sequence using machine learning

T8 – Stochastic simulations: an easy (really!) method that can be applied to almost any problem in biology

Optional exercise 2: Perform a stochastic simulation of a simple gene circuit using Tellurium

T9 – Gene editing update with excerpts from *The Scientist: The Race for the Repressor* (ABC News; provided by CSHL Library), *Decoding Watson* (PBS), *Make People Better* (Rhumbline Media)

Team Project 1 – Described on next page

Team Project 2 – Described on next page

Team Project 3 – Described on next page

Team Project 4 – Described on next page

Evaluation: A passing grade requires (1) active participation in class discussions, (2) participation in the team projects, and (3) attending all lectures.

Team Projects

Overview: Teams will work on small exercises in groups of 4 in the afternoons on different topics and present their results in the mornings starting on Tuesday. There is no expectation that presentations be polished!

Before starting: Discuss with team members to identify team members' strengths (subject background, knowledge of techniques, etc). Making an outline and assigning tasks ahead of time will help work more efficiently. It would be good to focus on a topic that more than one team member has some familiarity with. It is OK to change topics along the way if you come to a dead end.

Team Project 1 — Identify *the critical research paper* generally accepted to have proven or discovered some molecular gene expression/regulation mechanism. This can be old or new, but older papers *may* have a smaller scope and be easier to work with. In a short presentation (less than 10 minutes), describe the work; presentations could focus on:

1. What were the key known and unknown facts at the time this work was conducted and published?
2. Identify the specific hypothesis that was tested.
3. Describe the experimental method(s) used. How does the experiment work? What was quantified? How was the data analyzed?
4. Put the work in historical context. Were the authors of the research paper in competition with anyone? What was enabled by this result?
5. Making a figure/schematic to summarize the paper (*e.g.* graphical abstract) may be useful.

Team Project 2 — Preprint journal club. Identify a preprint (*e.g.* on bioRxiv or medRxiv) that is at least loosely related to the topic of the first days' project. Read the abstract closely and break it down to identify (1) the claimed big-picture significance of topic the work, (2) the methodology used, (3) key results, and (4) conclusions. Prepare presentations of about 10 minutes, including time for questions. Guides on how to present your conclusions in the form of a preprint journal club can be found here: https://asapbio.org/preprint-journal-clubs

Preprint requirements and suggestions

- Must NOT be published in a peer reviewed journal (bioRxiv and medRxiv list if articles are already published)
- To be manageable, articles should be, roughly, "letter" length: 1500–2500 words, 3–5 figures (not including supplements)

Team Project 3 — Protein complex structure prediction to investigate gene regulation. Identify protein-protein interactions relevant to the topic of your project that have high confidence to exist and some described mutant phenotypes, but without complete experimental data in the PDB. Using tips/tools discussed in class, predict the structure of monomers and protein complexes. Your preliminary presentation can focus on both negative and positive results.

Before class, one or more team members should install a program for visualizing protein structures such as:

- ChimeraX (easy to install) https://www.cgl.ucsf.edu/chimerax/download.html
- PyMol (easy to use; registration required) https://pymol.org/edu/

Team Project 4 — Continue work from the previous day and develop a research project proposal to test specific hypotheses arising from your investigation of predicted structures and relevant literature. The goal is to develop 15-minute (including time for questions) presentations of an experimental research proposal, addressing:

- What is your hypothesis? What is your evidence that it might be proven? What would be the significance if so (understanding basic science, drug development, understanding disease mechanisms, etc)?
- What is your specific experimental plan (techniques used, variables tested, outcomes measured)?
- If the plan has multiple steps, what do you and what will you do if an intermediate step fails?