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Engaging Complexity: Learning about Biological Systems via Construction of and Interaction with Computational Models

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Strategies to teach and learn about complex biological processes are often reductionist, aiming primarily at memorization of system components. This approach often falls short of developing in students an understanding of the integration of the components towards a coherent and dynamic system. We present a lesson designed in our software, Cell Collective (https://learn.cellcollective.org) to enable students to learn about biological processes and their dynamic nature by building and simulating computational models. In the lesson, students gain an understanding of regulation of the *lac* operon as determined by a system of interconnected molecules and complexes and how negative feedback loops produce oscillations by interacting with a pre-constructed model of the lac operon and editing a simpler, incomplete model to replicate known system behaviors. All skills which students build through this lesson (model navigation, simulation, construction) are useful across Cell Collective modules on a variety of traditional biology topics.

Keywords: gene regulation, lac operon, modeling, networks, simulation, systems thinking

Introduction

What underlies regulation of *lac* operon expression is a system of interconnected molecules and molecular complexes. This lesson provides students opportunities to manipulate and thereby appreciate the parts of the system, their interconnectedness, and the consequences of the system's structure for its overall behavior. In the simulation portion of the lesson, students simulate wild-type and mutant versions of the system under various environmental conditions and are prompted to predict, explain, observe, and explain the system's behavior. In the model construction portion of the lesson, students formally capture their own understanding of a simplified version of the system in a computational model.

Learning Goals

- Students will be able to describe the network of molecules and molecular complexes that makes the expression of the *lac* operon responsive to environmental conditions.
- Students will be able to create logical models of dynamic systems.

Learning Objectives

- Students will be able to recognize the main direct role of each part of the *lac* operon system in regulation of *lac* operon expression.
- Students will be able to list the conditions, such as levels of various nutrients (e.g. glucose and lactose) and/or mutations, which would yield a desired state (e.g. cycling, stably high, or stably

off/low) of some part of a given regulatory network, such as the *lac* operon.
- Students will be able to predict the state (e.g. cycling, stably high, or stably off/low) of a component of a regulatory network, such as the *lac* operon, given a set of conditions, such as levels of various nutrients (e.g. glucose and lactose) and/or gene/protein mutations.
- Students will be able to explain through which components and interactions of a regulatory network some given conditions, such as levels of various nutrients (e.g. glucose and lactose) and/or mutations, affect the state of some other part of the network (e.g. cycling, stably high, or stably off/low).

Intended Audience

This lesson in its current form is most suitable for upper-level undergraduate laboratories. With modifications, it can be implemented in first-year laboratories. A variant of this lesson has been implemented with first-year students and upper-level biochemistry students at a large research university and second-year students at a small liberal arts college.

Required Learning Time

The complete lesson, including assessment, takes less than 3 hours. If less time is available, parts may be omitted or assigned as homework.

Prerequisite Student Knowledge

Students should be familiar with the concepts of biomolecules (specifically carbohydrates and proteins, and nucleic acids), catalysis by enzymes, gene expression, and the cell.

Prerequisite Teacher Knowledge

Instructors should be familiar with the regulation of *lac* operon expression, feedback loops, and simulation and construction of Cell Collective models.

Materials

A computer with connection to the Internet, preferably through Chrome or Firefox browser, is required for each student. Blank paper or whiteboards may also be useful.

Notes for the Instructor

Here are some tips to correct common errors in model construction and simulation activities:

- During model simulation (e.g., Section 6 of the Model Simulation form), students must set the Sliding Window at 1.
- During model construction, students must specify dominance. When there is a positive and negative edge going into a single component, the student must specify whether or not he/she wants the effect of the negative regulator to dominate over the effect of the positive regulator. The student may specify dominance by clicking on the target node and then clicking on dominance in the Regulatory Mechanism panel.
- During model construction, students must save their models after any changes they make, by clicking the disk icon in the upper left.

Acknowledgments

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About the Authors

Lara Appleby is a Preceptor at the University of Delaware, facilitating integrated introductory Biology and Chemistry for first-year students. Previously, as a Postdoctoral Research Associate at the University of Nebraska – Lincoln, she developed this and other computational modeling-based lessons and assessments. She earned her Ph.D. in Biology from the University of Houston, studying the ecology and evolution of harvester ants and her M.Phil. in Genetics from Yale University for her contributions to a computational model of *C. elegans* development. Dr. Appleby works to engage students, especially in introductory biology courses, through clear, skill-focused curricula aligned with national standards.

Heather Bergan-Roller is an Assistant Professor in the Department of Biological Sciences at Northern Illinois University. Her research focuses on understanding how undergraduate students think about, learn, and communicate about biology. Previously as a Postdoctoral Research Associate at the University of Nebraska – Lincoln, she developed computational modeling-based lessons and measured their impact on student learning. Dr. Bergan-Roller earned her Ph.D. in Cell and Molecular Biology from North Dakota State University

Joseph Dauer is an Assistant Professor of Life Sciences in the School of Natural Resources at the University of Nebraska-Lincoln. He studies student learning of biological systems through modeling, qualitative and quantitative. He is interested in how students store and retrieve knowledge and whether knowledge connectivity can support learning. Dr. Dauer earned his M.S. and Ph.D. in Ecology from the Pennsylvania State University.

Audrey Crowther is a research assistant at the University of Nebraska - Lincoln. Her focus is on developing computational model-based lessons and in compiling a comprehensive database of computational research models that are based in Boolean algebra. Ms. Crowther earned her Bachelors in Microbiology from the University of Nebraska - Lincoln.

Tomas Helikar received his Ph.D. from the Department of Pathology and Microbiology at the University of Nebraska Medical Center in 2010. From 2010 to 2013, he completed his postdoctoral work in the Mathematics department at the University of Nebraska at Omaha. Since 2013, Dr. Helikar has been an Assistant Professor in the Department of Biochemistry at the University of Nebraska at Lincoln (UNL), where he also holds a courtesy appointment at the Department of Computer Science and Engineering. Dr. Helikar's research efforts center around the development of computational biology methods. He also utilizes computational modeling and simulations to understand the dynamical nature of biological processes, as well as interactive pedagogical methods to teach about biological systems to life sciences students. Dr. Helikar develops and teaches courses on computational biology and modeling. Dr. Helikar's work is currently being supported by several NSF grants, an NIH grant, and Google. In 2016, Dr. Helikar received UNL's Dinsdale Award for Excellence in Research, Teaching, and Service.

Appendix A
Lesson Plan and Links

We recommend that students first complete the **pre-lab** which orients students to the *lac* operon, systems thinking, and, through a training exercise (**https://goo.gl/forms/82aTfUP51rz0UNuQ2**), the modeling software which students will use throughout the rest of the lab.

After the pre-lab, students should be ready to complete the **Model Construction** activity followed by the **Model Simulation** activity. The **Inventory** can be administered both before and after the rest of the module as a pre-test and a post-test. The inventory is hard, so take that into consideration if you use it for a grade.

<table>
<tr><th>Activity</th><th>Completion setting</th><th>Estimated completion time (mins)</th><th>Working unit</th><th>Primary delivery method</th></tr>
<tr><td>Inventory:
https://goo.gl/oCufgn</td><td>in class</td><td>10</td><td>individuals</td><td rowspan="6">Google form
(link in column 1)</td></tr>
<tr><td>pre-lab: https://goo.gl/K8gx6Q</td><td>homework</td><td>30</td><td>individuals</td></tr>
<tr><td>Model Construction:
https://goo.gl/JffCdz</td><td rowspan="3">in class</td><td>40</td><td rowspan="2">groups of 2
(or 3)</td></tr>
<tr><td>Model Simulation:
https://goo.gl/H4LjT2</td><td>40</td></tr>
<tr><td>Inventory:
https://goo.gl/G8chIZ</td><td>10</td><td>individuals</td></tr>
<tr><td>Survey:
https://goo.gl/forms/jsKglBpBI1G5H8rj2</td><td>any</td><td>5</td><td>individuals</td></tr>
</table>

Sending Google Forms to Students

1. Within your form, click “Send”, on the top right.
2. Share the link provided with your students.

Setting an Automatic Due Date on Google Forms

1. Within your form, click the vertical three dots, on the top right.
2. Click “Add-ons”.
3. Search for formLimiter.
4. Install formLimiter.
5. Within your form, click on the puzzle piece icon.
6. Click on formLimiter, and set your due date.

Appendix B
Answer Key

Scenario 1: Control

Observations

- *lac* operon mRNA: cycles
- internal glucose: cycles

Explanation

In a normal E. coli cell in the absence of glucose, intracellular glucose and *lac* operon mRNA both cycle because the absence of glucose increases levels of cAMP, which in turn binds to CRP, forming CAP, which in turn binds to the *lac* promoter. Presence of lactose leads to the presence of allolactose, which in turn binds the *lac* repressor, preventing the repressor from binding to the *lac* operator. With no repressor on the operator and with CAP on the promoter, RNA polymerase *can* bind to the promoter and produce *lac* mRNA. *lac* operon mRNA is translated into B-galactosidase, which in turn takes lactose and yields glucose. This glucose then, through the pathway described above, causes transcription of the *lac* operon to stop.

Scenario 2: Loss of Function CRP Mutation

Observations

- *lac* operon mRNA: stably non-existent
- internal glucose: stably non-existent

Explanation

In a CRP loss-of-function mutant, internal glucose and *lac* operon mRNA are both stably non-existent because with a mutation in CRP, the CAP that is formed when glucose is absent is not be able to bind to the *lac* promoter, so RNA polymerase is also not able to bind to the *lac* promoter. Therefore there will be no *lac* operon transcription. Without *lac* operon transcription, there is no B-galactosidase, and so none of the available lactose can be converted into glucose.

Scenario 3: Loss-Of-Function Lacz Mutation

Observations

- *lac* operon mRNA: stably high
- internal glucose: stably non-existent

Explanation

In a *lacZ* loss-of-function mutant, internal glucose is stably non-existent because translation of such a transcript would yield dysfunctional B-galactosidase. With dysfunctional B-galactosidase, none of the available lactose would be broken down to yield glucose. In this mutant, the *lac* operon mRNA would be stably high, though, because lack of glucose would still lead to high levels of cAMP, which would in turn bind to CRP to form CAP, which would in turn bind to the promoter. Presence of lactose would still cause presence of allolactose which would bind to the *lac* repressor, preventing the *lac* repressor from binding to the *lac* operator. Thus, RNA polymerase would bind to the *lac* promoter and produce *lac* operon mRNA.

Appendix C
Model Notes and Links to Student Forms

Cell Collective Models

- The lac operon system

  Notes:
  - This model does not include permease; lactose internalization is modeled as occurring automatically when lactose is present outside of the cell.
  - In this model, CAP binds directly to the promoter, though in reality it binds to a part of the *lac* operon immediately upstream of the promoter.
  - Allolactose is modeled as automatically resulting from the presence of internal lactose.

- The lac operon system - build

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