Planarian Regeneration: Connecting Lab Exercises & Scientific Modeling

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ABSTRACT
There are benefits to both laboratory exercises and scientific modeling, and connecting the two may allow for deeper understanding and interest. Laboratory exercises provide students with opportunities to experience phenomena, but without scientific modeling, students may still lack understanding of the mechanisms at play. This article describes an example of how a traditional laboratory exercise on planarian regeneration is enhanced with a modeling activity on cell signaling.

Key Words: cell differentiation; cell division; cell signaling; model; planaria; regeneration; stem cell.

Introduction
Laboratory exercises allow students to experience phenomena, and students benefit from this type of learning (Kolb, 2015). On the other hand, laboratory exercises often show the visible results of phenomena without illustrating the underlying mechanisms at play. Therefore, students can complete the steps of some exercises without understanding, for instance, how the laboratory method works (e.g., gel electrophoresis) or why a modification to an organism causes a visible change (e.g., slicing planaria resulting in tissue regeneration). Overcoming this dilemma includes the use of scientific modeling so that students can predict and draw the mechanisms at the molecular scale. This article describes an example of how modeling is incorporated into a traditional laboratory exercise.

Planaria, which are small flatworms found in freshwater and marine habitats, are known for their regenerative ability. In nature, some planarian species occasionally attach to a substrate and break themselves into one or more parts. Each part regenerates into a fully functioning individual within a few weeks (Handberg-Thorsager et al., 2008). In the laboratory, pieces as small as 1/279 of the organism develop into functioning individuals (Handberg-Thorsager et al., 2008). Molecular mechanisms at work include cell division, stem cell differentiation, and cell signaling. Because of their regenerative ability, relative ease of care, and low cost, planaria are commonly used in high school and college laboratory exercises for cell-division and gene-expression investigations (e.g., Rose & MacRae, 1969; Accorsi et al., 2017). These exercises involve making observations during and after regeneration, sometimes while testing for the effects of altering environmental factors, such as light or chemicals in the water. They provide visible results but fail to show the molecular causes, such as cells signaling for cell division. To address this dilemma, students create drawn models that link the concepts from the lab to molecular processes described in class.

Course Background
I implemented this activity in an introductory biology course sequence (two semester-long courses) for undergraduate science majors (Figure 1). Ideally, the lab exercise and associated modeling activity happen together; on the other hand, implementing them in different courses of a sequence allows for anecdotal observations.
regarding whether students needed the laboratory exercise to understand the modeling activity. In the first course of the sequence, students learn about organismal concepts, including life cycles and mitosis, and in the second course of the sequence, they learn molecular concepts, such as cell signaling.

During the first course, students completed a laboratory exercise in which they performed different types of cuts on planaria and observed their regeneration. We examined regeneration as a whole; that is, we did not explicitly consider that regeneration is occurring for multiple tissue types. The exercise followed similar procedures and data observations as HHMI BioInteractive’s “Planaria Regeneration Activity” (http://media.hhmi.org/biointeractive/activities/planaria/planaria_regen_activity.pdf). Students made observations for two weeks. Afterward, during lecture – which is taught in a flipped style so that students work in teams during the majority of the class time – we linked the lab exercise to life cycles by creating scientific models that explained variations from the “typical” animal life cycle that uses mitosis for growth and repair rather than for reproduction (see Khan Academy’s “Sexual Life Cycles” page for an example: https://www.khanacademy.org/science/biology/cellular-molecular-biology/meiosis/a/sexual-life-cycles). This activity can be expanded to address physiology objectives, such as organ system diversity. Planaria have simple organ systems, including an incomplete digestive tract (i.e., a tract with one opening), a ladder-type nervous system, and no specialized gas-exchange organ (i.e., diffusion only).

About one-quarter of the students in the second course also took my section of the first course of the sequence and were separated across the teams. I also taught this course using a flipped approach, and the in-class activities primarily involved creating models to explain molecular mechanisms. The course was separated into four equal units, and the third unit focused on proteins.

The following objectives are for this unit of the course:

1. Describe the molecular structures of protein.
2. Model and explain the functions of protein.
3. Explain how molecular structure determines molecular interactions and relates to the cellular functions of proteins.
4. Make predictions about the cellular functions of proteins based on their chemical properties.
5. Explain and model the relationship between a substrate and an enzyme.
6. Explain and model the functions of the active site and allosteric site of an enzyme.
7. Explain the ways in which cells communicate with each other.
8. Predict how cells communicate with each other after a stimulus.
9. Explain possible cellular responses of communication signals (e.g., DNA replication).
10. Explain and model communication within a cell, including the functions of a G protein (RAS is an example of a G protein), GDP, GTP, and kinases.
11. Predict how protein mutations and drugs influence communication between and within cells.

As part of this unit, students complete a case study on cell communication in planaria. The modeling activity described below is focused on objectives 7–9, which refer to cell communication. Prior to this activity, students created models for case studies that met objectives 1–6. All of the objectives for this unit are assessed at the end of the unit with a case study exam, including the creation of a model that links the objectives of this planaria activity (objectives 7–9) to within-cell signaling (objective 10).

Student Preparation for Modeling Activity

In preparation for this class period, students learn about cell communication by reading and viewing the following resources:

- Clark et al. (2018), 4.6: Connections between cells and cellular activities, https://openstax.org/books/biology-2e/pages/4-6-connections-between-cells-and-cellular-activities
- Clark et al. (2018), 9.1: Signaling molecules and cellular receptors, https://openstax.org/books/biology-2e/pages/9-1-signaling-molecules-and-cellular-receptors
- Learn Genetics, Genetic Science Learning Center, “The fight or flight response,” http://learn.genetics.utah.edu/content/cells/cellcom

As homework, students complete an open-note quiz that covers basic concepts from the resources listed above. Because most students did not experience the planaria lab, we introduced the idea of planarian regeneration during class by watching the HHMI BioInteractive video “Planarian Regeneration and Stem Cells” (https://www.biointeractive.org/classroom-resources/planarian-regeneration-and-stem-cells).

Modeling Activity

There are three main parts to this activity (see Figure 2 for worksheet). In the first part, students write out which processes take place for stem cells to divide via mitosis (DNA replication) and for cells to differentiate (epidermal growth factors act as signaling molecules to trigger protein synthesis). Then students write out their prediction on the relative location of cells that are producing the signals for cell division and differentiation. This has students practice different types of cell signaling while also using their understanding to predict which ones are at play. Answers vary; the goal is for students to provide plausible models. Of the student teams that uploaded their models to Google Drive team folders (which was an optional way for students to share their models with all team members), three teams predicted endocrine signaling and three others suggested paracrine signaling for DNA replication. For cell differentiation, two teams predicted each of the following: autocrine, paracrine, and endocrine. Finally, for part 3, students develop a model that uses their answers from parts 1 and 2 to draw and explain how cells are communicating during cell division and differentiation. Students’ models show the planaria being cut (i.e., the environmental stimulus) and the signaling processes that initiate DNA replication and then differentiation (Figure 3).

As students are working on the modeling activity, the instructor walks around the classroom, answering questions, checking
Today, we will model how regeneration occurs in an organism called planaria (a flatworm; phylum Platyhelminthes). Although many planaria species sexually reproduce, they will occasionally asexually reproduce by dividing their bodies in half and regenerating tissue in both halves to produce two organisms. They will also regenerate if they are injured or bisected.

Although scientists know that a variety of cuts can cause planaria to regenerate new tissue, there is still a lot that we do not know about how their cells signal to one another. In this activity, students are making predictions on how cell signaling works to cause regeneration.

Part 1
Two main steps will occur for planarian regeneration:
- Stem cell division via mitosis
- Cell differentiation

1. Which process will have to occur for cells to prepare for cell division?
2. The new cells are stem cells that will later differentiate into different tissues. Which process will occur as cells differentiate?

Part 2
1. Before cells can divide via mitosis, they undergo DNA replication. After the planarian is cut, signaling molecules bind to stem cells (which are located throughout the body). These signaling molecules bind to receptors. Once binding occurs, the receptor changes shape and causes a cascade of events that include activation of a kinase. These events cause DNA replication to occur.
   a. The signaling molecule is likely a common stress hormone, such as adrenaline or cortisol. Where do you think is the location of the cells that produce the signaling molecules?
   b. To answer the question above, consider the four main types of signaling from the reading:
      i. Autocrine (a cell targets itself)
      ii. Gap junction (a cell targets another cell that is connected to it by a channel)
      iii. Paracrine (a cell targets a nearby cell)
      iv. Endocrine (a cell targets a distant cell through the bloodstream)

2. Once the stem cells divide, most of them will differentiate into other tissue, such as digestive or nervous system tissue. A molecule called epidermal growth factor (EGF) will bind to EGF receptors on the stem cells. This causes a change in shape of the receptor which then activates a kinase and Ras cascade. These events trigger protein synthesis in the cell. Which proteins are synthesized will vary from cell to cell- producing different tissue types in the planaria.
   a. Like the question above, where is the signaling molecule (in this case, EGF) coming from? Use a different type of signaling from the previous question.

Part 3
1. Imagine that you have just cut a planarian in half, producing one fragment with a head and one fragment with a tail. What is happening to the tissue in the head fragment? (Note that we are only focusing on the head fragment because different signaling molecules are used to produce the brain.) It takes approximately two weeks for planarian regeneration to occur. Model what is happening to the planarian.

Your model should answer the following questions:
   a. Where is the signaling molecule coming from?
   b. What happens once the signaling molecule binds to the receptor? Note that you do not need to consider the cascade of events that occur within the cell to cause DNA replication or protein synthesis- just focus on the receptor and result for today.
   c. Which cells are undergoing DNA replication?
   d. Why are these cells undergoing DNA replication?
   e. When do the cells undergo cell differentiation?
   f. How do cells differentiate?
   g. What does the organism look like before and after cutting it- immediately and after regeneration is complete?

Figure Credit
Figure 1: Image attributed to Eduard Solà (2008) under Creative Commons Attribution-Share Alike 3.0 Unported license. https://commons.wikimedia.org/wiki/File:Dugesia_subtentaclata_1.jpg
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Figure 2. Student worksheet.
students’ models, and asking students how they selected the types of signaling. This gives the instructor an idea of how students are performing on the modeling activity. If consistent issues arise across teams, such as drawing general models of how the signaling type works and not relating it to the case study, the instructor can interrupt the class to clarify the issue for everyone. When most students are done with the modeling activity, select a few teams to present their models to the class—choose teams that vary in their signaling predictions. For a large class, use a document camera or take a photo of the model and project it to a screen. After students present their models, provide a brief wrap-up that explains that the purpose of the modeling activity was to create a biologically plausible prediction and that there was more than one possible scenario. For grading, I have students upload photos of their models to the institution’s online learning management system and give them a participation grade based on completeness. Students’ understanding of the concepts are summatively assessed at the end of the unit.

○ **Online Modifications**

This modeling activity is also ideal for hybrid or fully online courses. Rather than having students work in teams to create the model, each student works individually on the model and then posts the model to the online learning management system’s discussion board. Students then help each other on their models by responding to their peers with the following prompts:

- If there is a model that you notice may need some feedback and no one else has provided it, then go ahead! In your response, include which aspects of the model are done well and which aspects need improvement and why. Do not repeat information that someone else already posted to that model. This is a good reason why you should start engaging in the discussion board early in the week.
- If you realize that there is something incorrect in your model after looking at your peers’ models, then respond to your own model post with the revised model, a list of whose models helped you, and what you changed in the revised model. The models are still graded based on completeness. As a wrap-up to the activity, the instructor selects a few models and reposts them as an announcement with a description on why the instructor chose those models.

○ **Evaluation**

To evaluate the effectiveness of the modeling activity in promoting student understanding of cell signaling, I implemented and assessed the activity in a large-enrollment (n = 162), non-science majors course that did not have a laboratory component. In classes that followed this activity, students created models for neuron signaling and models that explain what happens within a cell once a signal is received. On an exam that was centered on a diabetes case study, students created models that assessed their understanding of the objectives of these three models by showing “the complete process of cell signaling from insulin to impact on glucose uptake,” including “How does a signal travel from the pancreas to cells throughout the body?” Most students (60%) correctly illustrated endocrine signaling by showing the pancreas cell, the bloodstream, and the receptor on the target cell. They were only required to draw it, not label it, but nearly half also labeled it as “endocrine.” Seventeen percent of students did not address this question in their model, only showing what happens once a cell receives a signal. Some students (16%) showed a standard signaling model with two cells next to each other—albeit a small number of these students were illustrating neuron signaling with presynaptic and postsynaptic neurons. Rarely, students drew models of autocrine signaling, paracrine signaling (and labeled it as such or labeled it as “endocrine” signaling), or drew a general model of endocrine signaling but did not refer to the case study (i.e., showed one cell far away from another cell and labeled it as endocrine signaling). Overall, among the students who attempted to show how the signal travels from the pancreas to the target cells, most demonstrated an understanding of cell-to-cell signaling. If this activity is used in a unit that includes neuron signaling, then it is essential to be explicit regarding how the two models differ.

○ **Conclusion**

There are benefits to both laboratory exercises and scientific modeling, and connecting the two may allow for deeper understanding and interest. This activity has students use a traditional laboratory exercise to visualize the results of molecular mechanisms and then learn how those mechanisms work via scientific modeling. During implementation of the modeling activity, I noticed that students from the first course of the sequence eagerly explained the laboratory exercise to their teammates, which suggests that doing the laboratory exercise may have increased their interest in the activity, but students who had not taken part in that exercise did not seem to struggle. This was further demonstrated in using this activity in a course with a non-laboratory component. Nonetheless, students applied concepts to a real scenario that they personally witnessed in lab to predict which molecular mechanisms are at work.
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