Discovering Cellular Respiration with Computational Modeling and Simulations

Heather E. Bergan-Roller†, Nicholas J. Galt‡, Joseph T. Dauer†, Tomáš Helikar*

1School of Natural Resources, University of Nebraska-Lincoln, Lincoln, NE 68583
2Department of Science, Valley City State University, Valley City, ND 58072
3Department of Biochemistry, University of Nebraska-Lincoln, Lincoln, NE 68588
†Authors contributed equally to this work

Abstract

Cellular respiration, a common topic among introductory and cellular biology curricula, is a complex biological process that exemplifies core biological concepts, including systems, pathways and transformation of energy, and structure and function relationships. Unfortunately, many students struggle to understand cellular respiration and its associated concepts. To help students with their understanding of cellular respiration, we developed a lesson that uses computational modeling and simulations through an on-line modeling platform, Cell Collective (learn.cellcollective.org). Computational models and simulations allow students to observe and influence the dynamics of complex biological systems not observable in static diagrams from textbooks. In our lesson, students explore different aspects of cellular respiration by making changes to the system. For each perturbation, students investigate the underlying mechanistic causes by iteratively predicting the mechanism, testing their prediction with simulations, interpreting and reporting on their findings, and reflecting upon their prediction until they can accurately describe the underlying mechanism. Because the lesson is self-contained and requires little guidance from the teacher, the lesson can be implemented in a wide-variety of settings without the need for many changes to existing curricula.

Citation: Bergan-Roller, H.E., Galt, N.J., Dauer, J.T., and Helikar, T. 2017. Discovering Cellular Respiration with Computational Modeling and Simulations. CourseSource. https://doi.org/10.24918/cs.2017.10

Editor: Jessamina Blum, University of Minnesota, Minneapolis, MN

Received: 09/01/2016; Accepted: 01/26/2016; Published: 05/11/2017

Copyright: © 2017 Bergan-Roller, Galt, Dauer, and Helikar. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited. No permission is required from the authors or the publishers for noncommercial use of the published materials.

Conflict of Interest and Funding Statement: This work was supported by the National Science Foundation under Grant No. IUSE #1432001 to Tomáš Helikar and Joseph Dauer. Tomáš Helikar is serving or has served as a scientific advisor and/or consultant to Discovery Collective (1905 Harney St, Suite 1, Omaha, NE 68102).

Supporting Materials: S1. Cellular Respiration Simulations-Background Reading, S2. Cellular Respiration Simulations-Pre-class Assignment, S3. Cellular Respiration Simulations-Lecture Presentation Slides, and S4. Cellular Respiration Simulations-Discovering Cellular Respiration Activity Packet.

*Correspondence to: 1901 Vine Street, Lincoln, NE 68588-0664 Email: thelikar2@unl.edu

Learning Goal(s)

Students will:

• Understand the steps of cellular respiration.
• Discover how computational modeling can be used to observe and semi-quantitatively measure the dynamics of biological macromolecules involved in cellular respiration.
• Understand how biological activity of macromolecules are regulated.
• Understand how cells transform energy and cycle matter.

Learning Objective(s)

Students will be able to:

• Describe how changes in cellular homeostasis affect metabolic intermediates.
• Perturb and interpret a simulation of cellular respiration.
• Describe cellular mechanisms regulating cellular respiration.
• Describe how glucose, oxygen, and coenzymes affect cellular respiration.
• Describe the interconnectedness of cellular respiration.
• Identify and describe the inputs and outputs of cellular respiration, glycolysis, pyruvate processing, citric acid cycle, and the electron transport chain.
• Describe how different energy sources are used in cellular respiration.
• Trace carbon through cellular respiration from glucose to carbon dioxide.
INTRODUCTION

Thinking about biological phenomena from a systems perspective has been defined as essential for all students, from kindergarten through undergraduate (1,2). Cellular respiration is a complex biological process that involves molecules (e.g., glucose, ATP, NADH, pyruvate) that dynamically interact in space and time and collectively result in usable energy for cellular functions. As such, cellular respiration should be studied and understood systemically. Cellular respiration is commonly taught in secondary and undergraduate biology courses and is a foundational topic for understanding larger-scale biological activities such as digestion and food webs (3,4), as well as core biological concepts such as matter and energy transformation and conservation (5-7). However, cellular respiration is a difficult topic for learners (4,8).

Traditional methods for teaching the concepts of cellular respiration rely heavily on memorization. Despite good intentions from teachers, students have memorized common scenarios (e.g., lack of oxygen) and can easily answer “why” these scenarios arise and what happens as a final result. However, students fail to explain the mechanisms of “how” biological events occur (9). To address these issues, we created this lesson to help students gain a systems perspective of cellular respiration. The lesson helps students understand the dynamic mechanisms regulating the cellular respiration system by applying computational modeling and simulations. This lesson was designed using evidence-based best practices in support of science learning (10) to facilitate conceptual understanding and development of core competencies (e.g., process of science, modeling, and simulation) (1). During the lesson, students predict, test, record, reflect upon, and consolidate their mechanistic understanding of the respiration using a web-based modeling platform, Cell Collective (learn.cellcollective.org). In the computational model, model components correspond to biological components such as glucose and ATP, and these components are connected based on their mechanism of regulation. These regulatory mechanisms are described with mathematical rules (based on Boolean algebra) (11,12).

We have implemented this lesson in three semesters of introductory biology for biology majors at a large research university during a single discussion (i.e. dry laboratory) period lasting two to three hours. Students were organized into groups of three to four at the beginning of the semester and remained in those groups throughout. Within the group, students work individually on this lesson, but consult as necessary with their group. The lesson is self-contained: students receive all the needed instructions and prompts in the printout and can progress through the lesson without the help of the instructor. The lesson is modular, providing flexibility to adjust lesson timing for particular needs. The modules include: 1) concise background information and images on cellular respiration; 2) reading comprehension questions; 3) introduction to computational models; 4) introduction to the web-based modeling platform, Cell Collective (learn.cellcollective.org); 5) investigations of cellular respiration. We implemented the lesson with Modules 1 and 2 as pre-class assignments and Modules 1, 3-5 grouped together as an in-class activity, which we call, Discovering Cellular Respiration. Module 1, the background reading, is included in both the pre-class and in-class portions of the lesson. The background reading is included in the pre-class assignment to provide a basic introduction to the system so that the lesson does not rely on a textbook or lectures. Additionally, the background reading is included in the in-class portion of the lesson to encourage students to refer back to this information as they go through the lesson.

Intended Audience

This lesson was designed for undergraduate biology students at the introductory level. The lesson could be used for higher-level courses by setting higher expectations for responses.

Required Learning Time

This lesson was designed to be taught in-class during a discussion period and lasts about two hours. The Discovering Cellular Respiration activity packet (Supporting File S4) could also be implemented as a homework assignment outside of class.

Pre-requisite Student Knowledge

Prior to embarking on the lesson, students should understand: the chemical nature of biology (i.e. matter consists of elements and compounds, chemical bonding between atoms, chemical reactions, hydrogen bonding), the structure and functions of cells (i.e. organelles and extracellular components in prokaryotic and eukaryotic cells), structure and function of macromolecules, and have an introduction to metabolism (i.e. thermodynamics, endergonic and exergonic reactions, enzyme function and regulation). These topics are commonly discussed in introductory biology prior to cellular metabolism. In addition to content knowledge, students should have basic computer and internet skills. For example, students should be able to open and navigate within a web browser, point and click, type short text and numbers, and recognize “play” and “pause” symbols.

Pre-requisite Teacher Knowledge

Prior to conducting the lesson, you should have a thorough understanding of the same content and skills described above for students. In addition, you should have an understanding of cellular respiration including the processes involved (i.e. glycolysis, pyruvate processing, citric acid cycle, electron transport chain, and fermentation), major molecules involved in each process, the cellular locations of processes and molecules, and regulatory mechanisms governing cellular respiration. We provide much of this information in the background reading section of the lesson. In addition to content, you should be familiar with the Cell Collective on-line learning platform (learn.cellcollective.org). This knowledge will allow you to facilitate student learning during the lesson. Fortunately, you can attain much of this knowledge, both content and skills, by simply working through the activities prior to class. Additionally, you should be comfortable with explaining what cellular mechanisms are and how they apply to cellular respiration. You can attain this information by reviewing the provided lecture slides (Supporting File S3) that you will present at the beginning of the in-class portion of the lesson.

SCIENTIFIC TEACHING THEMES

Active learning

Students take an active role in all parts of the lesson. In the activities outside of class, students read about the cellular respiration system and computational models using the
provided background information. During the class, students investigate the impacts of changes to cellular respiration by predicting, observing, reporting, and reflecting upon cellular mechanisms. During all activities, students work independently on the simulations and write their individual answers, but they are encouraged to discuss in small groups.

**Assessment**

In the pre-class assignment, students answer reading comprehension questions based on background reading. During the in-class portion of the lesson, students engage in self-evaluations. Specifically, students are asked to predict the dynamics of a model, test their predictions with the simulation, report on their observations, and interpret the results in terms of a cellular mechanism. Students self-evaluate whether or not their prediction was correct before moving on. Finally, summative assessment can include grading responses to the questions in the lesson. Table 2 provides a detailed account of how parts of the lesson align with the learning objectives.

**Inclusive teaching**

This lesson supports inclusive teaching primarily in two ways. First, students work in small groups. This structure allows students to express their understanding and questions and get feedback from peers when individual instructor feedback is not frequently available. Second, the lesson applies modern technology (i.e. simulations) used in science research not typically experienced by introductory students. The computer-based learning medium may appeal to different students than traditional wet laboratories, lectures, and textbook reading. Simulations can show students how life sciences are related to computing and could help students to understand other model-based phenomena such as predicting the weather and understanding climate change.

**LESSON PLAN**

An overview and timeline for the lesson plan are provided in Table 1.

**Before Class**

**Assign Reading and Pre-Class Assignment**

Prior to teaching the in-class portion of the lesson, assign students to read the background information (Supporting File S1) and complete the pre-class assignment (Supporting File S2). By reading the background information, students will get a concise introduction to the processes and important components of cellular respiration, regulation of cellular respiration, and computational models. The pre-class assignment ensures that students complete the reading and are prepared for the in-class portion of the lesson. We expect the reading and pre-class assignment to take students 30 minutes to an hour.

Additionally, students will need a computer to conduct the activity. When making the announcement about the pre-class reading and assignment, instruct your students to bring computers to class. Although it is ideal for every student to have his or her own computer, the activity is done in small groups. Therefore, if someone does not have a computer, they can work with other members of their group who do have computers. Alternatively, you could schedule the activity in a computer lab, if that is possible with your class size and your institution.

**Review In-Class Materials**

To prepare to lead the in-class portion, review the pre-class materials [i.e. background reading (Supporting File S1) and assignment (Supporting File S2)]; these resources introduce the content to be covered during class. Additionally, review the in-class materials (Supporting Files S3-S4). You will present the provided lectures slides (Supporting File S3) on mechanistic explanations to your students at the beginning of the class; therefore, you should have a thorough understanding of what mechanistic explanations are composed of and be able to explain that to your students. Finally, go through the Discovering Cellular Respiration activity packet (Supporting File S4) just as your students will. This activity will give you a deeper understanding of the content, develop your skills for navigating the Cell Collective platform, and help you prepare for potential issues and questions from your students. All of these materials (Supporting Files S1-S4) are provided in this article. Additionally, the Discovering Cellular Respiration activity packet (Supporting File S4) is available within the online software (learn.cellcollective.org). Answer keys are available from the authors by request so that students do not have easy access to the answers.

**Print In-Class Materials**

Each student will need a copy of the Discovering Cellular Respiration activity packet (Supporting File S4), which includes all background, instructions, and question prompts. Either the students will print their own copy to bring to class, or the instructor can provide copies for each student. The background reading materials are included in the packet so that students can reference this information as they complete the activity.

Instead of printing hard copies of the activity, the Discovering Cellular Respiration activity packet is available as a Google Form. The Google Form includes all of the same background text and images, instructions, and questions prompts as the Discovering Cellular Respiration activity packet (Supporting File S4). Students type their answers in Google Forms and the software conveniently and automatically generates a summary of the responses and organizes all responses into an Excel spreadsheet. The Google Form version of the Discovering Cellular Respiration activity packet is available upon request from the authors.

**In-Class**

**Collect Pre-Class Assignment**

Prior to beginning the in-class portion of the lesson, collect students’ pre-class assignments. The pre-class assignment primarily serves to ensure that students completed the background reading. Students will be investigating the content further within the Discovering Cellular Respiration activity.

**Present Mini-Lecture**

To inform and guide the students through the activity, we have provided lecture slides. We have found that this presentation helps to inform student expectations regarding the content and
length of the activity. Without the mini-lecture, students do not know what is coming next and sometimes expect to leave the class early. The lecture slides (Supporting File S3) include an itinerary, an outline of the Discovering Cellular Respiration activity, learning objectives, and a description of mechanistic explanations. You can describe the learning objectives to your students as a checklist that they should be able to complete by the end of the class. The mechanistic explanation slides define “mechanistic explanation,” explain its purpose, and provide an example in the context of cellular respiration. Additionally, the lecture slides include prompts that guide students through the activity including when to hand in assignments, when to discuss with group members, and approximately how much time should be spent on each portion of the activity. Furthermore, we provide commentary in the notes section of the slides to instruct you on what to do with each slide.

Facilitate the Discovering Cellular Respiration Activity

To begin the Discovering Cellular Respiration activity, hand out the packets (Supporting File S4) to all students or have students access the Google Form of the activity. Inform students that, as they go through the activity, they are responsible for filling out the questions in the packet individually but they’re welcome to discuss within small groups. The Discovering Cellular Respiration activity is self-contained, since the packet (Supporting File S4) provides students with all of the background information, directions, and question prompts they need to complete the activity successfully.

Exercise 1. Matching

In the first part of the activity, students complete a matching exercise to align cellular respiration inputs to their function. This exercise serves to re-engage students with the content because it may have been a few days since they read the background reading. The mini-lecture guides students to complete this portion and discuss with their group.

Exercise 2. Set up computational simulations

In the second part of the activity, students take out their computers, access Cell Collective (learn.CellCollective.org), create an account, and open the Discovering Cellular Respiration model. The activity then provides detailed instructions on how to set up the simulations to monitor the components and processes of the cellular respiration computational model. Simulation settings (e.g., sliding window size of 100) have been optimized to provide clear visuals for students. Students may need to refer back to these instructions during later parts of the activity.

The quantitative values of components (e.g., glucose set to 95%) do not directly correspond to a specific biological measurable property such as concentration because the mathematical framework underlying the utilized computational model of cellular respiration in Cell Collective is based on stochastic logical modeling (12). Instructors and students can interpret values (e.g., 95%) of external components (e.g., glucose) semi-quantitatively. For example, glucose set to 95% can be interpreted as “high amounts of glucose” and 10% as “low amounts of glucose.” Additionally, the activity level (y-axis of the simulation graph ranging from 0 to 100) of the model’s internal components (e.g., glycolysis) is determined by the regulatory mechanisms of other directly interacting components and also provides a semi-quantitative measure (as a probability of being active at a given time point) to describe the relative activity of a particular model component in response to environmental signals and/or perturbations in the model (12).

Exercise 3. Investigate the impact of changes to cellular respiration

In the third part of the activity, students investigate the impact of changes that affect cellular respiration using the computational model of cellular respiration in what we call Investigations. Because the computational model of cellular respiration is based on stochastic logical modeling (described above), students and instructors should focus on whether and how the activity of a given component is increased or decreased (as opposed to specific values) in response to mechanistic changes in the modeled system. This approach is similar to the interpretation of the output of many biological experiments, including Western Blots, differential gene expression analysis, and similar experimental methods.

The content of each Investigation is unique in that it closely examines only a portion of cellular respiration at a time. In the first Investigation, students examine how the processes of cellular respiration in brain cells, which rely on primarily glucose, are affected when glucose is not available. In the second Investigation, students explore how an alternative fuel (i.e., fatty acids) affects cellular respiration. In the third Investigation, students evaluate how a drug that inhibits the citric acid cycle affects carbon dioxide output. In the fourth Investigation, students examine how the inhibition of pyruvate processing affects glycolysis and fermentation. In the fifth Investigation, students explore how the absence of oxygen affects the processes of cellular respiration.

In each Investigation, we refer students back to basic content that is required to answer the questions. Students need to apply this information and use critical thinking skills to fully describe the mechanistic “how” of each perturbation. The mechanism addressed in Investigation 1 is relatively large (containing nine molecules and processes) because we provide most of the mechanism for the students to fill in as a scaffold (13) to help them writing their own mechanisms in subsequent Investigations. The mechanisms involved in Investigations 2-4 start small and progress in size and complexity. Finally, in Investigation 5, students are asked to consider almost the entire system of cellular respiration.

We facilitate critical thinking by having students achieve objectives for each Investigation. Investigations 1 and 3-5 have similar objectives that we break down into specific steps: A) making predictions; B) developing a mechanistic explanation of the prediction(s); C) testing the prediction using the simulation; D) recording the results of the simulation, E) evaluating the prediction; and F) improving the mechanistic explanation and retesting as necessary. For example, in Investigation 1, students are asked to predict how lack of glucose in a brain cell will affect cellular respiration processes. Students support their prediction with a mechanism based on the provided model. In Investigation 1, students are provided most of a mechanistic explanation and are asked to fill in blanks. This format provides scaffolding (13) for and engages students in building a high quality, accurate mechanistic explanation in the context of cellular respiration. This scaffolding is removed for Investigations 3-5 where Step B is open-ended. In Step C, students are provided with the settings for the simulation to test
their prediction. They should apply these settings and observe the simulation. In Step D, students report simulation results. In Step E, students evaluate their prediction as correct or incorrect based on the simulation results. If they are incorrect, students are directed to repeat steps A-E until their results match their prediction. Finally, in Step F, students attempt to describe the accurate mechanism of the perturbation. We designed these objectives, as recommended by best practices of using simulations to facilitate science learning (10), to have students:

- make explicit their conceptions as predictions (Step A),
- confront alternative conceptions with simulation results (Step D) (14),
- reflect on their prior knowledge (Step E), and
- use evidence (from simulation results) to support findings (Step F).

The objectives of Investigation 2 are slightly different. We designed Investigation 2 to address the known misconception that glucose is the only energy source used in cellular respiration (15). However, the concept did not align well with the aforementioned objectives and therefore comes with slightly different objectives.

Ways to facilitate the Discovering Cellular Respiration Activity

Although the activity is self-contained and driven primarily by the students, we encourage you to engage with your students as they navigate the learning process. We suggest that your role is to 1) be available for questions and issues from the students; 2) check in with the students to confirm that they are simulating the perturbations correctly; and 3) ensure that students understand and are executing mechanistic explanations. To confirm that students are adjusting and simulating perturbations correctly, observe which Investigation they are working on and verify that their settings align with given instructions in Step C of the Investigation. To ensure that students are applying mechanistic explanations, read over their answers to Steps B and F of each Investigation and look for two or more components, their interactions, and an explanation of how the phenomena described in the prompt occurs. You can also use the answer key (available upon request from the authors) to facilitate this formative assessment. We suggest checking in initially with one student per small group at a time then encourage that student to discuss with their group. This check-in provides some feedback to all students in the group, even if only indirectly, when all students cannot be reached directly. Additionally, it helps promote peer instruction.

Common areas of difficulty and solutions

- Students may want to skip over Exercise 1 and go straight to the Cell Collective portion of the activity. However, we see that many students are not in the right frame of mind to investigate the details of cellular respiration without any priming immediately before investigating the simulations of cellular respiration. We find that the activity is most successful when done in the order that is provided in the activity packet.
- Students may haphazardly make changes to the simulation settings which made lead to incorrect simulation results. These mistakes may prevent students from confronting their alternative conceptions (14) with correct simulation results. Therefore, it is essential for you to mediate this activity by verifying that students are adjusting the simulation settings correctly.
- Many times students will skip over detailed instructions and become confused or frustrated with the simulations. If you suspect frustration from a student, have him or her go back to carefully read and apply the instructions. This review commonly provides clarity and productive engagement with the simulations.

Below is a list of materials that are necessary and/or useful for teaching the lesson, all of which are provided as supporting materials, links to websites, or by request from the authors.

- Background reading (Supporting File S1)
- Pre-class assignment (Supporting File S2)
- Pre-class assignment answer key (request by contacting the authors)
- In-class lecture slides (Supporting File S3)
- Discovering Cellular Respiration activity packet (Supporting File S4)
- Discovering Cellular Respiration activity packet answer key (request by contacting the authors)
- Discovering Cellular Respiration Google Form (request by contacting the authors)
- Cell Collective (accessible at learn.CellCollective.org)

TEACHING DISCUSSION

Effectiveness in Achieving the Learning Objectives

The lesson provides frequent opportunities to assess student achievement of the learning objectives. Alignment of learning objectives, assessments, and achievement on assessments (results) from one of our implementation are detailed in Table 2. The data on effectiveness were collected from a sample of all consenting students from three class sections during the fall of 2015 implementation (n = 24). All student-generated data were collected with institutional review board approval. Achievement of a learning objective was defined as a student receiving 65% of available points on the assessment aligned to that learning objective. Students performed well on most learning objectives that focused on demonstrating understanding of concepts, namely identifying and explaining the role of components (e.g., glucose) of cellular respiration. Additionally, students were able to successfully trace carbon through cellular respiration from glucose to carbon dioxide, a concept that is difficult, yet beneficial for introductory biology students (7). Students successfully interacted with the simulations although some students had difficulties either applying the proper settings and/or interpreting the simulations. The aspect of the lesson that students struggled with the most was describing the cellular mechanisms. Students had more difficulty with longer mechanisms compared to shorter mechanisms. Others have shown that students have difficulty generating mechanistic explanations (9). Nevertheless, we suspect that providing frequent opportunities for students to practice forming mechanistic explanations will help them develop this skill.

Student Reactions to the Lesson

Student reactions to the lesson were determined by
interviews with 11 teaching assistants (TAs) who facilitated the lesson during the fall of 2015. All TAs felt the lesson was very engaging because the computer simulations allowed the students to see effects in “real time,” which is difficult if not impossible during wet laboratory activities. TAs reported that their students, especially intermediate-performing students, were more engaged with the content during this lesson compared to the other activities they used previously. Representative comments are presented below.

“They thought it was a cool, easy way to visualize what was happening. Interest was high.” (TA 3)

“They were pretty receptive... seemed more receptive to that than even the real labs.” (TA 8)

Possible Adaptations

Although this lesson was used in an introductory biology discussion section for majors at a large research university, it could be easily applied in other courses and settings. For example, this lesson could be applied to a mid-level cell biology or biochemistry course by placing more emphasis on the cellular mechanisms rather than the basic components of cellular respiration. Additionally, the lesson could be implemented as a homework assignment as it is self-contained. Finally, this lesson would likely be successful at other types of institutions such as community colleges and liberal arts colleges.

Based on our experience with the lesson, we provide some opportunities for potential adaptations. For example, the pre-class assignment could be implemented in class to ensure students complete it. However, we still recommend that students do the background reading before class. Otherwise, students tend to skip over the background reading. Although the lesson is designed to be self-driven and inquiry-based, some instructors and students are more comfortable with a more traditional introduction to the material. Therefore, instructors could add additional readings and/or lecture on cellular respiration prior to engaging in the lesson. Many students and even TAs struggled with creating a mechanistic description, despite the lecture slides and scaffolded answer in Investigation 1. We suggest having students practice creating a simple mechanistic explanation and receive feedback (16) by both peers and the teacher before independently trying to describe cellular respiration mechanistically for the in-class activity. A post-assessment sometime after this lesson would help to reveal what information students retained from the lesson. The post assessment could focus on cellular respiration concepts as well as mechanistic descriptions of a system other than cellular respiration.

SUPPORTING MATERIALS

• S1. Cellular Respiration Simulations-Background Reading
• S2. Cellular Respiration Simulations-Pre-class Assignment
• S3. Cellular Respiration Simulations-Pre-class Assignment
• S4. Cellular Respiration Simulations-Lecture Presentation Slides
• S5. Discovering Cellular Respiration with Computational Modeling and Simulations

Respiration Activity Packet

ACKNOWLEDGMENTS

We thank Dr. Steven Harris, James Buescher, and the teaching assistants for their assistance in implementation and their feedback on the lesson. We thank Xin Wang and John Sutton of RMC for conducting and analyzing interviews with teaching assistants. We thank Audrey Crowther for her help editing the lesson and Taylor Uhrlir for editing the manuscript. This work was supported by the National Science Foundation under Grant No. IUSE #1432001 to T. Helikar and J. T. Dauer.

REFERENCES

1. AAAS. 2011. Vision and Change in Undergraduate Biology Education: A Call to Action. Washington, D.C.
2. NRC. 2012. A Framework for K–12 Science Education: Practices, Crosscutting Concepts, and Core Ideas. National Academies Press, Washington, D.C.
3. Anderson CW, Sheldon TH, Dubay J. 1990. The effects of instruction on college nonmajors’ conceptions of respiration and photosynthesis. J Res Sci Teach 27:761-776.
4. Brown MH, Schwartz RS. 2009. Connecting photosynthesis and cellular respiration: Preservice teachers’ conceptions. J Res Sci Teach 46:791-812.
5. Jin H, Zhan L, Anderson CW. 2013. Developing a Fine-Grained Learning Progression Framework for Carbon-Transforming Processes. Int J Sci Educ 35:1663-1697.
6. Lin C-Y, Hu R. 2003. Students’ understanding of energy flow and matter cycling in the context of the food chain, photosynthesis, and respiration. Int J Sci Educ 25:1529-1544.
7. Wilson CD, Anderson CW, Heidemann M, Merrill JE, Merritt BW, Richmond G, Sibley DF, Parker JM. 2006. Assessing Students’ Ability to Trace Matter in Dynamic Systems in Cell Biology. CBE-- Life Sci Educ 5:323-331.
8. Flores F, Tovar ME, Gallegos L. 2003. Representation of the cell and its processes in high school students: An integrated view. Int J Sci Educ 25:269-286.
9. Abrams E, Southerland S. 2001. The how’s and why’s of biological change: How learners neglect physical mechanisms in their search for meaning. Int J Sci Educ 23:1271-1281.
10. Smetana LK, Bell RL. 2012. Computer Simulations to Support Science Instruction and Learning: A critical review of the literature. Int J Sci Educ 34:1337-1370.
11. Helikar T, Cutucache CE, Dahlquist LM, Herek TA, Larson JI, Rogers JA. 2015. Integrating Interactive Computational Modeling in Biology Curricula. PLoS Comput Biol 11:e1004131.
12. Helikar T, Kowal B, McClenathan S, Bruckner M, Rowley T, Madrahimov A, Wicks B, Shrestha M, Limbu K, Rogers JA. 2012. The Cell Collective: toward an open and collaborative approach to systems biology. BMC Syst Biol 6:96.
13. Pea RD. 2004. The Social and Technological Dimensions of Scaffolding and Related Theoretical Concepts for Learning, Education, and Human Activity. J Learn Sci 13:423-451.
14. Duit R, Treagust DF. 2003. Conceptual change: A powerful framework for improving science teaching and learning. Int J Sci Educ 25:671-688.
15. Haslam F, Treagust DF. 1987. Diagnosing secondary students’ misconceptions of photosynthesis and respiration in plants using a two-tier multiple choice instrument. J Biol Educ 21:203-211.
16. Bell B, Cowie B. 2001. The characteristics of formative assessment in science education. Sci Educ 85:536-553.
## Table 1. Discovering Cellular Respiration - Teaching Timeline

| Activity                        | Description                                                                 | Time               | Notes                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------|
| **Preparation for Class**       |                                                                             |                    |                                                                      |
| Background reading and assignment | 1. Share the background reading and pre-class assignment with students at least a few days to a week before the in-class activity  
2. Instruct students to complete background reading and pre-class assignment before coming to class the day of the activity  
3. Instruct the students to bring computers to the class for the activity | < 5 min            | • Background reading is provided in file S1  
• Pre-class assignment is provided in file S2  
• It is ideal if each student has a computer. If they do not, students can share computers as they will be discussing in groups. Be sure at least one person in each group has a computer. |
| Review in-class materials       | 1. Review the provided lecture slides and student activities  
2. Familiarize yourself with cellular respiration content  
3. Familiarize yourself with learn.CellCollective.org  
4. Prepare for questions and issues students may have during class | 1-2 hours depending on expertise on cellular respiration content and comfort with the modeling platform | • Lecture slides are provided in file S3  
• You may use the same background reading you provided to the students to familiarize yourself with the content (S1)  
• Go through the Discovering Cellular Respiration Activity Packet (S4) |
| Print off in-class activity packets | Print off one activity packet per student | Depends on number of students and printer speed | Alternatively, use the Google Forms version of the activity packet (contact authors for access) |
| **In-Class Events**             |                                                                             |                    |                                                                      |
| Collect pre-class assignment    |                                                                             | < 5 min            |                                                                      |
| Mini-lecture on itinerary and mechanisms | Lecture on the itinerary and the structure of mechanistic explanations | ~5 minute          | Lecture slides are provided in file S3                              |
| Facilitate Discovering Cellular Respiration Activity (S4) | 1. Hand out the Discovering Cellular Respiration activity packets to all students  
2. Instruct students to begin and go at their own pace  
3. Walk around the room to be available for any questions  
4. Allow students to discuss in pairs/small groups but do their own work  
5. Collect student work | 2 hours            | Discovering Cellular Respiration activity packet is provided in file S4  
Alternatively, use the Google Forms version of the activity packet (contact authors for access) |
## Table 2. Lesson Alignment and Results

| Focus | Learning Objective | Assessment | Results |
|-------|--------------------|------------|---------|
| **Demonstrating understanding of concepts** | Identify and describe the inputs and outputs of cellular respiration, glycolysis, pyruvate processing, citric acid cycle, and electron transport chain | Pre-class assignment | Mean score was 10.3 out of 15 points (SD=1.65, range 6-12). |
| | | Exercise 1- input function matching | Mean score was 4 out of 5 points (SD=1.17, range 2-5). |
| | Describe *how* different energy sources are used in cellular respiration | Investigation 2 | Mean score was 1.4 out of 5 points (SD=0.95, range 0-3). |
| **Interacting with the simulation** | Trace carbon molecules through cellular respiration from glucose to carbon dioxide | Investigation 3 | Mean score was 6 out of 9 points (SD=1.85, range 2-9). |
| **Writing mechanisms** | Perturb and interpret a simulation of cellular respiration | Observe that students apply the correct settings to all Investigations Part D. “Report your simulation results” | Based on how students reported their results, 9 out of the 24 students incorrectly applied simulations settings in at least one investigation. Mean score was 3.5 out of 4 points (SD=0.9, range 0-4). |
| | Describe cellular mechanisms regulating cellular respiration | Part B. “Provide a mechanistic prediction” for Investigations 1, 3-5 | Student mechanisms were graded on a three-point scale, from no mechanism (0), components of the mechanism (1), and components and relationships of the mechanism (2). Out of 24 students, 5 provided full mechanisms for all Investigations, 14 provided partial mechanisms, and 5 provided almost no mechanism. |
| | Describe *how* changes in cellular homeostasis affect metabolic intermediates | Part F. “Accurately describe the mechanism” in Investigations 1, 3-5 | Mean score was 5.3 out of 16 points (SD=3.8, range 0-13). |
| | Describe *how* glucose and oxygen affect cellular respiration | Pre-class assignment question 5 (oxygen) Parts A and F in Investigation 1 (glucose) and Investigation 5 (oxygen) | 19 out of 24 of students correctly described when fermentation is active. 23 out of 24 students predicted how glucose affects cellular respiration correctly. When describing the details of how glucose affects cellular respiration, the mean score was 1.67 out of 3 points (SD=1.21, range 0-3). 17 out of 24 students predicted how oxygen affects cellular respiration correctly. When describing the details of how oxygen affects cellular respiration, the mean score was 1.5 out of 6 points (SD=2.14, range 0-6). |
| | Describe the interconnectedness of cellular respiration | Parts B and F in Investigations 1, 3, and 5 | When combining the activities, the mean score was 7.5 out of 17 points (SD=4.0, range 2-17). |