

Augmented Reality in Undergraduate Biology Classroom

Swati Agrawal

University of Mary Washington, Department of Biology, 1301 College Ave, Fredericksburg VA
22401 USA

(sagrawal@umw.edu)

Three dimensional characteristics of protein and DNA molecules are important in aiding student comprehension of almost any biological structure or process that are taught in introductory as well as advanced biology classes. Most of this content is currently presented to students in the form of two-dimensional schematics and projections. However, in depth understanding of structure-function dynamic relationship cannot be performed without the concepts of 3-D objects and 3-D processes. Here we describe a method for the production of 3-D interactive images that can be manipulated in real time through the use of augmented reality software. Two activities presented here were conducted in a Cell Biology class using the MERGE Cube. The first activity compares the protein structure of GFP and dsRed to explain the nuances in primary, secondary, tertiary and quaternary structure of the protein and how these structures contribute to function. There are many ways in which such lessons can be adapted for more inquiry-based classes. One such activity that has been successfully used, illustrates the properties of membrane proteins that make them suitable for their specific function in the plasma membrane. A second learning activity was used to teach the concepts of mitosis and cell cycle regulation. 3-D models of cells were built using an easily accessible and free platform. These models were then projected in virtual space using the MERGE Cube to show different phases of mitosis. Consistent with the published data we found that even in the upper level classes students had misconceptions regarding the concepts of ploidy and chromosome structure and the above activity helped answer some of those misconceptions. This activity provided a way to effectively communicate molecular and genetic aspects of chromosomes to the students in an engaging way.

Keywords: augmented reality, protein structure, mitosis, MERGE Cube.

Introduction

Understanding how macromolecules are structured; the interplay between surface topology, molecular flexibility, charge, and hydrophobicity--can be overwhelming for students. The challenges of understanding macromolecular structures are magnified when studying their interactions. To grasp how cells work, students must become very comfortable using molecular visualizations to gain insight into molecular binding interactions and reactions.

Augmented and virtual reality (AR/VR) tools have gained popularity in a number of medical and molecular research applications. For example, a number of AR/VR platforms for structure-based drug design approaches have recently been published with the promise to allow acceleration of drug discovery process making the process faster and more cost

effective (Richardson et al. 2013). Bringing this technology to biology classrooms can transform the way we teach these topics and will prepare and inform students on how to use this technology. To-date most courses that cover topics in structural biology rely on 2-D representations or a handful of 3-D models to teach these topics. In rare cases when molecular visualization is used in courses it is most often used in demonstrations. While a limited number of augmented reality apps have been explored in higher education, the major obstacles seem to be the cost of the available programs, ease of application, and most importantly the limited number of models available (Garcia-Bonete et al. 2019). We have developed an easy-to-use instructional technology using augmented reality to view molecular structures and interactions that is cheap and effective and which can be used to view any of the 140 structures currently available in the Protein Data Bank (PDB). Here we propose a model where

students are not only introduced to molecular visualization programs but they also gain confidence over time in navigating the tools used routinely in structural and molecular biology research such as PDB and PyMOL (Rigsby and Parker 2016).

The protein activity presented here can be scaled up or down in its nature of complexity depending on the class being taught. For example in introductory or general education classes, visualization of protein and DNA on the MERGE Cube in 3-D has been helpful in giving students

something tangible to look at and be able to interact with. In upper level classes such as Biochemistry or Cell Biology, instructors might choose to integrate additional learning modules on PDB and PyMOL followed by visualization in AR on the MERGE Cube. A 50-minute lecture period provides sufficient time if one intends to only use the MERGE Cube for the first activity i.e comparison of GFP and dsRed structures for teaching concepts in protein structure. For the mitosis activity a 3-hour lab period is typically ideal.

Student Outline

Learning Goals

Upon completion of this activity students will be able to:

- Efficiently navigate the Protein Data Bank (PDB) and research a protein of interest.
- Confidently view proteins on PyMOL and explore different representations of the protein to display and highlight the protein structural elements at the secondary, tertiary and quaternary levels.
- Understand how vastly different amino acid sequences can yield very similar structures, and similar sequences can sometimes yield very dissimilar structures.

Introduction

The first activity described here is for viewing 3-D structures of green fluorescent protein (GFP) and dsRed protein in virtual space. This activity aims at illustrating the various levels of protein structure and the bonds responsible. The second activity aims at understanding different kinds of transmembrane proteins (receptors, enzymes, transporters, and anchors). Each group of two students will be given a protein to research and a list of questions to answer. Then you will look at the protein in PyMOL followed by AR visualization.

Protein Structure Activity I

- Open the Object Viewer app on your iPads (or iPhones or Android phones).
- One by one pull up the following object codes in the app on the iPad.

GMJK92, LVGX0Q and R6DE82

1. For each of the proteins identify the most predominant secondary structure in the protein in front of you

Object Viewer code GMJK92 Secondary structure _____

Object Viewer code LVGX0Q Secondary structure _____

Object Viewer code R6DE82 Secondary structure _____

2. Compare the structures GMJK9 and R6DE82 and write down your observation at the level of quaternary structure

Protein Structure Activity II

For the next activity we are going to use PyMOL to view and modify protein structures. PyMOL is computer software, a molecular visualization system created by Warren Lyford DeLano. Researchers use PyMOL to produce high-quality 3-D images of small molecules and biological macromolecules, such as proteins, for scientific publication. PyMOL can also be used for homology modeling model in order to model the structure of an unknown molecule using a known protein with structural similarity as a template.

To open structures on PyMOL we will use the protein structures available on PDB. PDB is the Protein Data Bank, a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy, and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member

organizations (PDBe, PDBj, and RCSB). The PDB is overseen by an organization called the Worldwide Protein Data Bank, wwPDB. The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, now require scientists to submit their structure data to the PDB. Many other databases use protein structures deposited in the PDB. For example, SCOP and CATH classify protein structures, while PDBsum provides a graphic overview of PDB entries using information from other sources, such as Gene Ontology. We have talked about a large class of membrane proteins that have many diverse functions in our Cell Biology class. Membrane proteins may fall in one of the categories listed below. You will be assigned a type of protein from the list above. Find an example on PDB and answer the questions from information you found on PDB before coming to the class

Transporters: Glucose transporter, SGLT, Na⁺-K⁺ pump, Ca²⁺ pump

Anchors: Spectrins, Bcl2

Receptors: GPCR, Ligand-gated acetylcholine receptor

Enzymes: Tyrosine kinase, adenyl cyclase

- Note the PDB ID
- Protein name and type of protein
- What organism is the protein from?
- How many amino acid residues are there?
- What is the function of protein in the cell?
- What is the predominant secondary structure present?
- What are some recognizable domains in your protein (e.g. kinase, phosphatases, ATPase, specific ligand binding domains etc.)?
- Can you predict from the structure of the protein whether it is an integral membrane protein or peripheral protein?
- How many transmembrane passes does the protein have?
- Anything else known about the proteins like diseases that especially affect these proteins or drugs that especially target the protein.

We will look at your protein in on the MERGE Cube in class. Follow the steps below to view the proteins in PyMOL , upload the file to Object Viewer and view the protein structure on Object Viewer.

1. Register and download the educational license for PyMOL on your computer <https://pymol.org/edu/?q=educational/> (already done for you)
2. Open the protein file on PyMOL by typing fetch _____ (PDB ID here).
3. Click the cartoon representation of the structure. (in right hand panel, click S > cartoon).
4. You can explore PyMOL and change the color of the chains. Distinguish individual chains by different colors. Try to distinguish some important domains in the protein by giving the residues different color.
5. Save the file in collada or .dae format (give it a name that you will be able to recognize).
6. Now depict structure as 'Surface' (all > S > surface).
7. Repeat step 6 again and save as a distinct .dae files.
8. Login to Miniverse using your account login and password

9. <https://www.miniverse.io/experience?e=object-viewer-for-merge-cube>

10. Upload both files and note down the two object codes here

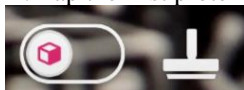
Cartoon file _____

Surface file _____

In class:

11. Enter the object code from Miniverse on the app on the iPad.

12. Tap the first protein on iPad/iPhone and tap stamp. Align the white target box on a place on your work table.



15. Tap the stamped image now. You can scale it, rotate it, or move it by using the tools that show up at the bottom.



13. Now rotate to your right to the next group's protein. Enter the next group's object code to bring up an image of the second transmembrane protein. Follow steps 1-2 to place the two proteins next to each other.

14. What similarities and differences do you notice when comparing your protein to another protein? Record your observations in the table provided below for each of the proteins you observe.

Name of the protein	PDB ID and miniverse ID	No. of amino acids	Most prominent secondary structure	Integral or peripheral protein?	How many transmembrane passes

Augmented Reality Mitosis Review

Part A:

Every stage of the cell has a separate 3-D image and hence an individual object code. Here are the object codes that you will need for the first part:

NVY 4VM

XK0 LD5

Follow the instructions below to bring up the two different stages so the cell in the virtual space in front of you.

1. Enter the first object code in the app on the iPad and tap stamp. You can then remove the MERGE Cube and the model of the first cell will remain.



2. Tap the stamped image now. You can scale it, rotate it, or move it by using the tools that show up at the bottom.



3. Repeat this process for the second object code so that you can compare the two cells side-by-side.

Q 1. Compare the two cells. Identify the parent (undivided) and daughter (divided) cells from the two models. Write down the object code next to the following:

- Parent:
- Daughter :

Q 2. Is the cell shown haploid or diploid? _____

Q 3. Explain how you arrived at the answer:

Part B:

For the next part you are going to identify cells at various stages of mitosis: prophase, prometaphase, metaphase, anaphase and telophase. Here are the object codes in jumbled up order:

Object Code	Phase
55L 8PB	
GMJ KR4	
WKR 51N	
QDK MGK	
GMJ KRM	

View each of the 5 models for the phases by entering the object code in the app and examining the cell model on the MERGE Cube.

Q 3. Identify which phase each model represents and note it above.

Part C:

Next, you will order the models so that they are in order of the five stages of mitosis by placing them in order in virtual space.

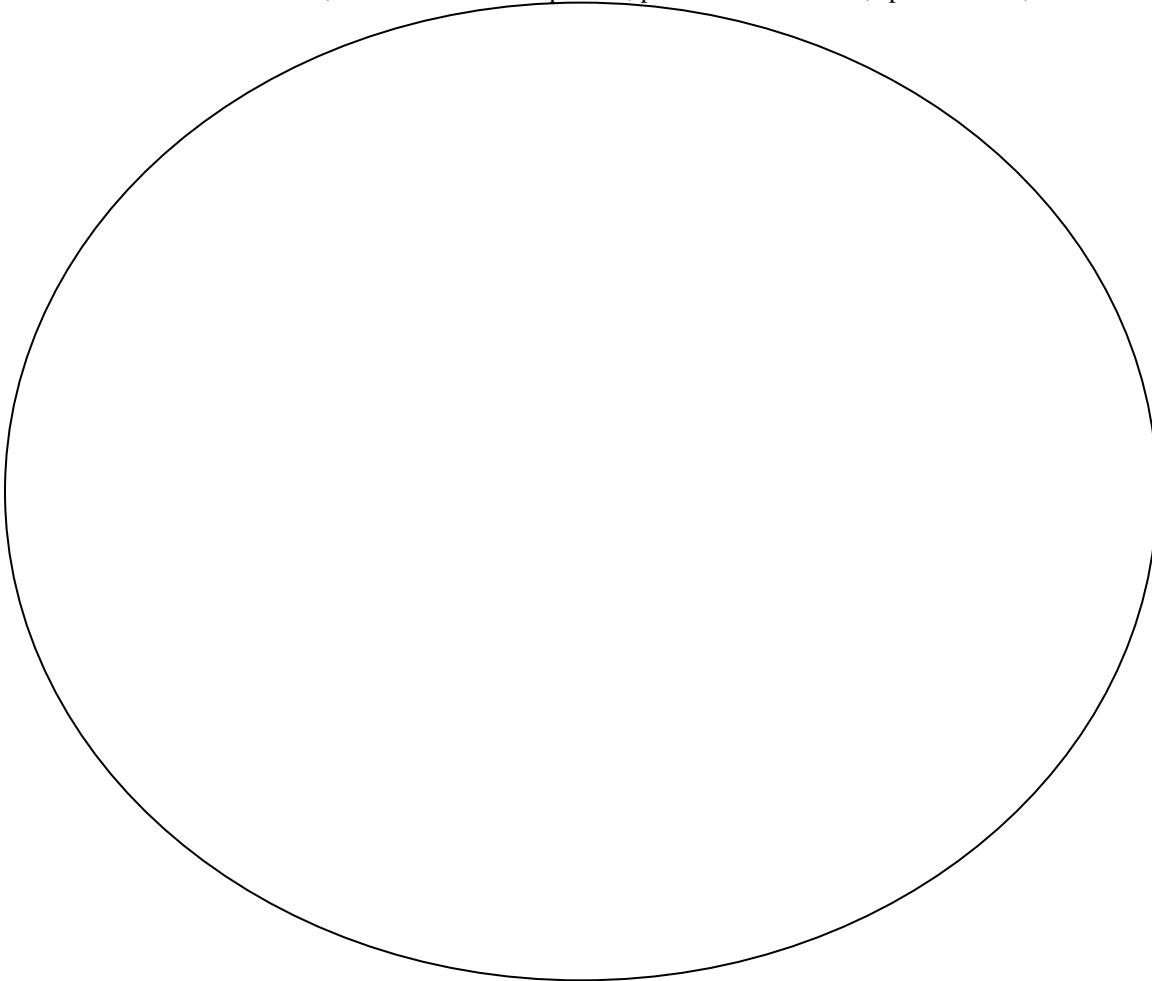
To do so:

- Line up your worksheets in order from phase 1 to phase 5.
- Enter the object code for the first phase in the app.
- Tap the model and tap “stamp”.
You can then remove the MERGE Cube and the model of the first cell will remain.
- Repeat this process until you have all the five stages in the virtual space.
- Now arrange the phases in the right order in the virtual space starting from the first identifiable stage in cell division to the most complete stage.
- Once you have put them in order, fill out the worksheet for each of the phases.

(A separate identical sheet is provided to the students for prophase, prometaphase, metaphase, anaphase and telophase)

1. Number of chromosomes in the cell:
2. Nuclear envelope present?

3. Centrioles duplicated?
4. Spindle fibers formed?
5. Position of chromosomes with respect to equator of the plate?
6. What is the key feature that helps you identify the stage?
7. Draw a cell with four pairs of chromosomes in _____ phase in the space given below. Make sure your diagram shows different chromosomes, sister chromatids if present, position of centrioles, spindle fibers, and nuclear envelope.



Materials

A computer with Internet access and the PyMOL program (educational version freely available for download from <http://pymol.org/educational/>) is required for each pair of students. LCD projector and computer are required for student presentations.

- Computer with Internet connection and PyMOL downloaded on it
- MERGE Cube (available on Amazon.com for \$15)

Access to an iPad or iPhone with MERGE Cube object viewer app (this is the 3-D viewer device and is free download)

Notes for Instructors

According to our observation the use of augmented reality appeared to increase the time students spent observing and learning the material. Although PyMOL (alone without AR) and other computer visualization methods have been used in the classroom, the immersive nature of the activity showed a major positive shift in the attitude of students toward this complex topic. 3-D models have been used previously by other instructors, however typically only a few models are presented to the students and it is mostly for demonstration purposes. The process of researching a membrane protein of their choice on PDB, followed by tweaking the protein in PyMOL meant that students spent more time interacting with these structures. Indeed according to feedback received from the students, the use of AR to study a protein helped develop a much deeper understanding of the structure and function of the protein in a biochemical and physiological context.

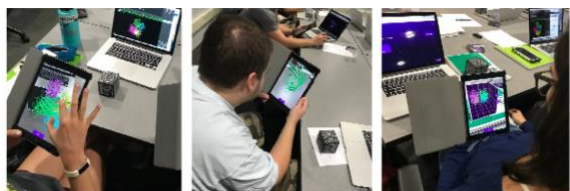


Figure 1. Students in Cell Biology class at Washington College looking at protein structure on MERGE Cube.

These lessons were prepared for students in the Cell Biology and Genetics courses at Washington College during Fall 18 and Spring 19 semester. The average class size was 16 and all the activities mentioned below were conducted during a 3-hour lab period. The length of the three activities vary and it is possible to combine a wet lab activity along with any of these activities. In our experience students really enjoyed the relaxed lab atmosphere which

encouraged one-on-one discussions between the students, instructor and the Library Academic Technologist. The activity was conducted in pairs which facilitated peer-to-peer collaboration with room for exploration of concepts beyond the curriculum.

Laptops, iPads and the MERGE Cubes provided to the students were purchased by the College. PyMOL was already installed and ready for use by the students at the start of the activity. A class Miniverse account was created to provide a common space where all PyMOL and mitosis cell models were uploaded. During the ABLE workshop some participants experienced restricted use for certain features on the MERGE Object Viewer app. This problem was not experienced in the classroom with students, hence it is advised that anyone intending to use the app checks its compatibility with the available devices (Android vs Apple) before the start of the lesson. If possible it is best to provide students with iPads/iPods purchased through the institution.

One of the major challenges of the protein activity was student comfort in navigating PyMOL. We recommend several short assignments for students especially in upper level classes dedicated to PyMOL so they can be comfortable with the program. PyMOL wiki is a great resource for all new users trying to learn basic features of PyMOL (<https://pymolwiki.org/>). We suggest that the instructors share this resource with the students.

This activity can easily be scaled for any instructional level and for any courses that teach concepts in protein structure and function. Some other examples of application of augmented reality in classroom would be exploration of protein-protein interaction, protein-DNA interaction, the effect of different mutations on protein function by inducing conformational change, and changes in binding affinities for other reactants.

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Acknowledgments

I want to thank Raven Bishop (Instructional Technologist at Washington College) for introducing me to MERGE Cube and helping me develop these lessons. I would also like to thank the students of Washington College and the participants of the ABLE 2019 workshop for their valuable feedback on this activity.

About the Author

Swati Agrawal is currently an Assistant Professor at University of Mary Washington where she teaches Introductory Biology and Cell Biology. These lessons were developed at Washington College for introductory Cell Biology and Genetics courses. She continues to use these lessons at UMW in a 300 level Cell Biology course.

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Citing This Article

Agrawal S. 2020. Augmented Reality in undergraduate biology classroom Article 1 In: McMahon K, editor. *Advances in biology laboratory education*. Volume 41. Publication of the 41st Conference of the Association for Biology Laboratory Education (ABLE). <https://doi.org/10.37590/able.v41.art1>

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