INTRODUCTION

Students learn best when engaged, for example with student-centered learning strategies that allow them to experience concepts through multiple modes, including kinesthetically (1–4). In STEM fields, easy access to tools such as 3D printers and open-source molecular structure viewers has provided affordable and practical alternatives to engage students by allowing them to model biologically relevant entities—including molecules and electron orbitals—and their functions (5–15).

In this report, we describe the combined use of 3D-printed macromolecular models and Jmol (an open-source Java 3D molecular structure viewer) to facilitate students' engagement with molecular concepts in cancer biology. While the literature has demonstrated the individual utility of 3D-printed models and Jmol exercises in the undergraduate classroom, we chose to combine these complementary activities to deepen students' understanding of the relationship between structure and function of macromolecules through multimodal learning (16–18). This report's modules focus on the biology, structure, and function of the human p53 protein, a tumor suppressor molecule famous for coordinating DNA repair, senescence, and apoptosis and for its frequent mutation in many different types of human cancers (19). The role of p53 as a transcription factor that binds DNA and activates target gene expression exemplifies the close relationship between macromolecular structure and cellular function. Student engagement is also encouraged by the relevance and relatability of the content, including the importance of p53 to human disease states that have touched many of their lives at a personal level.

PROCEDURE

Materials

Students require access to an instructional handout (Appendix 1 or 2; answer keys for instructors are available from the authors upon request), a white 3D-printed model of p53 bound to DNA (see Appendix 3 for detailed instructions and tips), and different color paints and a brush to paint the model as indicated. Students receive their own 3D-printed p53 bound to DNA model kit (Fig. 1). Students also need a computer for access to relevant Jmol sites.

Below we describe not only the two contexts in which we have implemented these modules but additional alternatives for course implementation.

Upper-Level Undergraduate Course: Cell Biology

Our module (Appendix 1) was used as a beginning-of-the-semester take-home assignment so that students could review concepts they had learned previously through foundational biology courses, setting the stage for subsequent discussions of new cell biology course content. The worksheet was introduced and assigned during the very first class period and covered macromolecules, protein and DNA structure, and basic cellular functions. During the 2-week period provided to complete it, students reached out to the instructor for assistance as needed, kicking off the semester with open communication and conversations between instructor and students. Students ultimately turned in their assignments through the online course management system.
system and orally presented their findings to the class (see Appendix 1 for presentation details and options). At the end of the activity, students were encouraged to keep their 3D model to use it as a study aid for future discussions and content. We referred back to p53 several times during the course to help segue between topics or units, for example, to transition from basic macromolecular structure to how different macromolecules (e.g., proteins, DNA) can interact with one another to generate new functionalities in cellular processes, such as transcription. Other content segue examples that benefitted from this exercise included transitions from transcription to control of gene expression, from intracellular compartments to systems like nuclear protein transport, and from cell cycle and cell death to cancer. Students’ engagement in the exercise provided them with a wealth of information to refer to as they strived to make connections between new content and fundamental principles of macromolecular structure and function. Some of these details are reflected in the student comments provided in Appendix 4.

**Graduate Biology Course: Molecular Mechanisms of Cancer**

This is a graduate-level course modeled after a published Course-Based Undergraduate Research Experience (CURE) (20). In brief, students worked in pairs to analyze different p53 missense mutations identified in one or more human tumors but not yet fully characterized. This activity (Appendix 2) was implemented in the third week of the course, after students were introduced to the molecular mechanism of p53 function. The introduction period focused on p53 regulatory elements required for transactivation and provided training in qualitative and quantitative assays (growth fitness, beta-galactosidase filter assays) to assess the ability of each p53 mutant to transactivate expression of reporter genes. The mutants worked on by the students presented different transactivation defects, enabling the students to develop hypotheses for why their mutant was defective. During the activity, students conducted DNA sequence alignments on their mutant versus normal p53 and determined the amino acid identity of their missense mutation. They then used online molecular modeling software (Jmol) to view the published structure of p53 binding to DNA. As part of this exercise, each student received their own 3D-printed p53 bound to DNA model kit (Fig. 1) and located their mutation on the painted models.

Interestingly, mutations that mapped directly to the p53/DNA interface were easily interpreted by the students as clear DNA binding defects, using either visualization software or 3D-printed models. On the other hand, mutations merely in close proximity to the DNA interface proved difficult to interpret using visualization software alone, and students only recognized the potential of these mutations to indirectly influence DNA binding upon visualizing them on their 3D-printed models. Additionally, students used their models throughout the semester to discuss their results during mock lab meetings as well as during their final poster presentations. Students found their models particularly useful during poster presentations, because they provided an easier platform for discussing their findings (Appendix 4).

**Alternative Applications**

This activity could benefit students enrolled in introductory courses. It could be implemented as an in-class lab.

**Safety Issues**

None

**CONCLUSION**

Coupling macromolecule 3D-printed models and online molecular viewing provides students with two learning tools that immediately engage them in questions of structure and function in a visual, memorable, and kinesthetic way while also providing downstream benefits following the activity. We found that the two components complemented one another well, providing opportunities for students to recall prior knowledge and apply it to novel situations.

**SUPPLEMENTAL MATERIALS**

Appendix 1: Instructional handout for undergraduate students
Appendix 2: Instructional handout for graduate students
Appendix 3: Step-by-step guide
Appendix 4: Table S1, student feedback from two pilot institutions
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REFERENCES

1. Carlson S. 2005. The Net generation goes to college. Chron High Educ 52:A34.
2. Jenkins H. 2006. Convergence culture: where old and new media collide. New York University Press, New York, NY.
3. Tapscott D. 2009. Growing up digital: how the Net generation is changing your world. McGraw-Hill, New York, NY.
4. Baepler P, Walker JD, Brooks DC, Saichaie K, Petersen CI. 2016. A guide to teaching in the active learning classroom: history, research, and practice. Stylus Publishing, LLC.
5. Da Veiga Beltrame E, Tyrwhitt-Drake J, Roy I, Shalaby R, Suckale J, Pomeranz Krummel D. 2017. 3D printing of biomolecular models for research and pedagogy. J Vis Exp (121):55427.
6. Cooper AK, Oliver-Hoyo MT. 2017. Creating 3D physical models to probe student understanding of macromolecular structure. Biochem Mol Biol Educ 45:491–500.
7. Babilonia-Rosa MA, Kuo KH, Oliver-Hoyo MT. 2018. Using 3D printed physical models to monitor knowledge integration in biochemistry. Chem Educ Res Pract 19 (4): 1199–1215. doi:10.1039/C8RP00075A
8. Meyer SC. 2015. 3D printing of protein models in an undergraduate laboratory: leucine zippers. J Chem Educ 92(12):2120–2125.
9. Tavousi P, Amin R, Shahbazmohamadi S. 2018. Assemble-and-match: a novel hybrid tool for enhancing education and research in rational structure based drug design. Sci Rep. doi:10.1038/s41598-017-18151-8
10. Griffith KM, Cataldo RD, Fogarty KH. 2016. Do-it-yourself: 3D models of hydrogenic orbitals through 3D printing. J Chem Educ 93(9):1586–1590.
11. Batiza A, Colton S, Franzen M, Goodsell DS, Herman T, Morris J, Patrick M. 2006. Tactile teaching: exploring protein structure/function using physical models. Biochem Mol Biol Educ 34(4):247–254.
12. Brown A. 2015. 3D printing in instructional settings: identifying a curricular hierarchy of activities. TechTrends 59(5):16–24.
13. Mendez JD, Smiar K. 2016. Creating and using interactive, 3D-printed models to improve student comprehension of the Bohr model of the atom, bond polarity, and hybridization. J Chem Educ 93(9):1591–1594.
14. Herraez A. 2006. Biomolecules in the computer: Jmol to the rescue. Biochem Mol Biol Educ 34(4):255–261.
15. Howell ME, Van Dijk K, Booth CS, Helikar T, Couch BA, Roston RL. 2018. Visualizing the invisible: a guide to designing, printing, and incorporating dynamic 3D molecular models to teach structure–function relationships. J Microbiol Biol Educ 19(3). doi:10.1128/jmbe.v19i3.1663
16. Cass ME, Rzepa HS, Rzepa DR, Williams CK. 2005. The use of the free, open-source program Jmol to generate an interactive web site to teach molecular symmetry. J Chem Educ 82(11):1736.
17. Nouri, J. 2018. Students’ multimodal literacy and design of learning during self-studies in higher education. Technol Knowl Learn 24(5):1–16.
18. Harris MA, Peck RF, Colton S, Morris J, Chaibub NE, Kallio J. 2009. A combination of hand-held models and computer imaging programs helps students answer oral questions about molecular structure and function: a controlled investigation of student learning. CBE Life Sci Educ 8(1):29–43.
19. Vieler M, Sanyal S. 2018. p53 isoforms and their implications in cancer. Cancers 10(9):288.
20. Hekmat-Scafe DS, Brownell SE, Seawell PC, Malladi S, Imam JF, Singla V, Bradon N, Cyert MS, Stearns T. 2017. Using yeast to determine the functional consequences of mutations in the human p53 tumor suppressor gene: an introductory course-based undergraduate research experience in molecular and cell biology. Biochem Mol Biol Educ 45(2):161–178.