Title: The Molecular Case Study Cycle

Author:

Shuchismita Dutta, Ph.D.; Scientific Educational Development Lead, RCSB Protein Data Bank; Associate Research Professor, Institute for Quantitative Biomedicine; Member, Cancer Pharmacology, Cancer Institute of New Jersey; Rutgers, The State University of New Jersey

Abstract

Molecular visualization and structure-function discussions present a valuable lens for research, practice, and education in chemistry and biology. Currently, molecular structural data, visualization tools and resources are underutilized by students and faculty. A new community, Molecular CaseNet, is engaging undergraduate educators in chemistry and biology to collaboratively develop case studies for interdisciplinary learning on real world topics. Use of molecular case studies will help biologists focus on chemical (covalent and non-covalent) interactions underlying biological processes/cellular events and help chemists consider biological contexts of chemical reactions. Experiences in developing and using molecular case studies will help uncover current challenges in discussing biological/chemical phenomena at the atomic level. These insights can guide future development of necessary scaffolds for exploring molecular structures and linked bioinformatics resources.

Introduction

Visualizing shapes and analyzing interactions of biological macromolecules have inspired research, discovery, and technology design in both chemistry and biology. To prepare students for contributing to these fields “Structure and Function” features prominently in various community-determined education standards in both disciplines. For example, it is included in the American Chemical Society (ACS) Guidelines for Bachelor’s Degree Programs (ACS Committee on Professional Training 2015); in American Society for Biochemistry and Molecular Biology (ASBMB)’s “Concept Driven Teaching” (Tansey, Baird et al. 2013); as Threshold Concepts in Biochemistry (Loertscher, Green et al. 2014); and as a core concept in “Vision and Change” for undergraduate biology education (AAAS 2011). Undergraduate educators are constantly looking for suitable lessons/activities that meet the respective disciplinary community standards.

In the past two decades, collaborative efforts among chemistry and biology educators have made significant progress in incorporating molecular structure-function discussions in undergraduate education. The “Molecular Visualization in Science Education” workshop (NSF 2001) recommended incorporation of molecular visualization into undergraduate chemistry curricula. Inspired by the molecular visualization and pedagogical discussions in the workshop, a series of projects developed courses and assessment strategies for using molecular visualization in chemistry education (Jones, Jordan et al. 2005). These pedagogical approaches and tools have yet to be extensively adapted for biology education. More recently, the BioMolViz group has developed and published a Biomolecular Visualization Framework (Dries et al., 2017) defining themes, goals, and learning objectives for molecular visualization of biomolecules along with relevant assessment instruments. Although many biochemistry and biology courses engage students in interactive biomolecular visualization exercises, rarely do they integrate biology and chemistry knowledge in order to get a deeper understanding of the topic being discussed.

Exploring biomolecular structures in real world contexts can provide opportunities for interdisciplinary learning. Visualizing and discussing biomolecular interactions in atomic detail can provide chemistry students a context for applying chemical knowledge, while biology students can learn how the shapes, properties, and interactions of specific molecular components can provide mechanistic explanations for cellular behavior (van Mil, Boerwinkel et al. 2013, van Mil, Postma et al. 2016). In fact, experts from different subdisciplines in biology explain molecular and cellular mechanisms slightly differently, based on methods used, biological context, analogies, and narration of stories (Trujillo, Anderson et al. 2015). Molecular case studies provide a convenient way to engage students in analyzing challenging real-world problems at the interface of chemistry and biology. Biomolecular structure-function discussions can provide a platform for integrating knowledge and interdisciplinary discussions.

Objectives

Molecular CaseNet brings together a community of undergraduate educators to collaboratively develop and use molecular case studies at the interface of biology and chemistry. It was initiated in 2018 as part of an NSF RCN-UBE Incubator project (NSF DBI-1827011) to create a few examples of molecular case studies, pilot them, and gather feedback on their usability and relevance in multiple curricular contexts. The main motivation for developing molecular case studies is to engage students in applying 3D spatial reasoning and their knowledge of biology and chemistry. The cases can engage chemistry students in exploring "Biological Structures and Interactions" as part of conceptual topics in biochemistry curricula and introduce biology students to specific core concepts e.g., "Structure and function"; and "Information flow, exchange, and storage" (Brownell, 2017).

Another motivation for developing molecular case studies was to help students learn about science practices. In order to keep up with current science, besides learning about scientific concepts, it is also critical for students to learn about how scientists learn about new systems and topics. The molecular case studies can introduce students to many public biological data resources and help students learn navigate through them to learn about gene and protein sequence data archives [e.g., GenBank (Benson, Cavanaugh et al. 2013), UniProt (UniProt Consortium 2019)]; protein function and interactions with ligands, inhibitors, drugs [e.g., PubMed, DrugBank (Wishart, Feunang et al. 2018), BRENDA (Jeske, Placzek et al. 2019)]; visualize and analyze biomolecular structures available from the Protein Data Bank (Berman et al., 2003); and integrate information from all of these bioinformatics resources and the scientific literature to synthesize new knowledge and/or solve problems. Thus, molecular case studies can introduce students to various science practices and skills (e.g., "process of science", "modeling", "interdisciplinary nature of science" and "communication and collaboration") (Clemmons et al., 2020).

Project Description

The Molecular CaseNet steering committee collaborated on developing the first molecular case study. Discussions began with trying to understand two things: (a) what would educators want their students to learn from the molecular case studies? and (b) how would the cases be incorporated in current curricula? Even in the early phase of these discussions it became clear that chemistry and biology educators (and students) had different interests, expectations, and preparations for navigating through the cases. While chemistry educators did not have a lot of time in their curricula to discuss the central dogma of biology and related concepts, biology educators did not have a lot of time in their courses to review chemical interactions that form the foundation for molecular case studies. To fully participate in case discussions students (and educators) would need scaffolds to learn discipline specific and/or case theme related vocabulary and concepts. Additionally, to engage multidisciplinary educators and students in use of molecular case studies the cases needed to be modular, and open-ended so that they can be adapted to different curricular contexts.

Considerations in Developing a Molecular Case Study

The first molecular case study, “Nicholas’ Story” (Dutta et al., 2020), was written collaboratively by the seven-member steering committee. Discussions and considerations while writing the case guided the development of a general format for molecular case studies. Key components, resources, tools, and conceptual frameworks considered in developing the first case are described here.

a. Case theme: this engages the students and educators provides a real-world context for the case study. In order to make it easy to incorporate in the curricula a theme that is common to both biology and chemistry curricula was selected for the first case study. In subsequent cases a broad range of topics were selected to match curricular interests.
b. A hook: such as a video, narrative, image, story, scientific report, biological phenomenon, newspaper article etc. related to the case theme had to be identified to engage students in the case. The actual case discussion focused on explaining an observation, answering questions, and/or solving a problem posed in the case, all in molecular detail.
c. Getting to the structure(s): No assumptions were made about students’ prior knowledge of the case theme. So, they were either directly introduced to molecules playing a role in the case or guided through the scientific literature to identify them. Following this, students were asked to identify 3D structures of case-related proteins and complexes in the Protein Data Bank. If no suitable structures were found, structures of molecules that are similar in amino acid sequences, 3D structures, and/or functions, were identified for exploration. A number of public bioinformatics data resources and tools were included in the case to help identify molecules related to the topic of interest. Instructions for how to access and use these bioinformatics resources were included within the case.
d. Molecular exploration: A number of free molecular visualization software/platforms are available to explore biomolecular structure(s), e.g., Jmol/JsMol (Jmol Development Group 2008), UCSF Chimera (Pettersen, Goddard et al. 2004), Pymol (DeLano 2002), or iCn3D (NCBI Resource Coordinators 2017). In some instances, the Online Macromolecular Museum (OMM, callutheran.edu/BioDev/omm/gallery.htm) offered pre-made interactive

visualizations. In curricular contexts where limited time is available for active hands-on visualization, pre-made OMM exhibits (if available) were used for molecular exploration. For active visualization and exploration, a web-based tool such as iCn3D was preferred to minimize additional requirements for downloading and installing software. Instructions for accessing and using relevant visualization tools were included within the case.

e. Modeling: in order to discuss the molecular structure and interactions and answer the case questions students may have to consult the scientific literature and other data resources. By combining information from the literature, various public bioinformatics data resources/tools, and structural explorations, answers for the case study questions can be synthesized.

Experiences from developing the first case underscored the need for a framework to tie together these elements in a molecular case study.

Format for Molecular Case Studies

The Molecular Case Study Cycle was created as a framework for developing, using, and discussing cases at the interface of biology and chemistry. The cycle can help educators and researchers with varied experiences and expertise to meaningfully use and contribute to the case study collection. It can also help authors of molecular case studies organize parallel sets of discipline specific instructions for implementing the case in various curricular settings.

In its current rendition, the Molecular Case Study Cycle (Figure 1) has two halves - one representing the concepts, data resources, and skills commonly discussed in biology curricula (colored pink), while the other half represents knowledge and skills required for discussing and applying chemical concepts (colored blue). Molecular structures are conveniently positioned at the interface of the two halves of this cycle and provide a platform for discussing molecular mechanisms of observations on either side of the cycle. The Molecular CaseNet Steering Committee decided that each molecular case study should be guided by the molecular case study cycle and engage students in navigating through the complete cycle at least once.

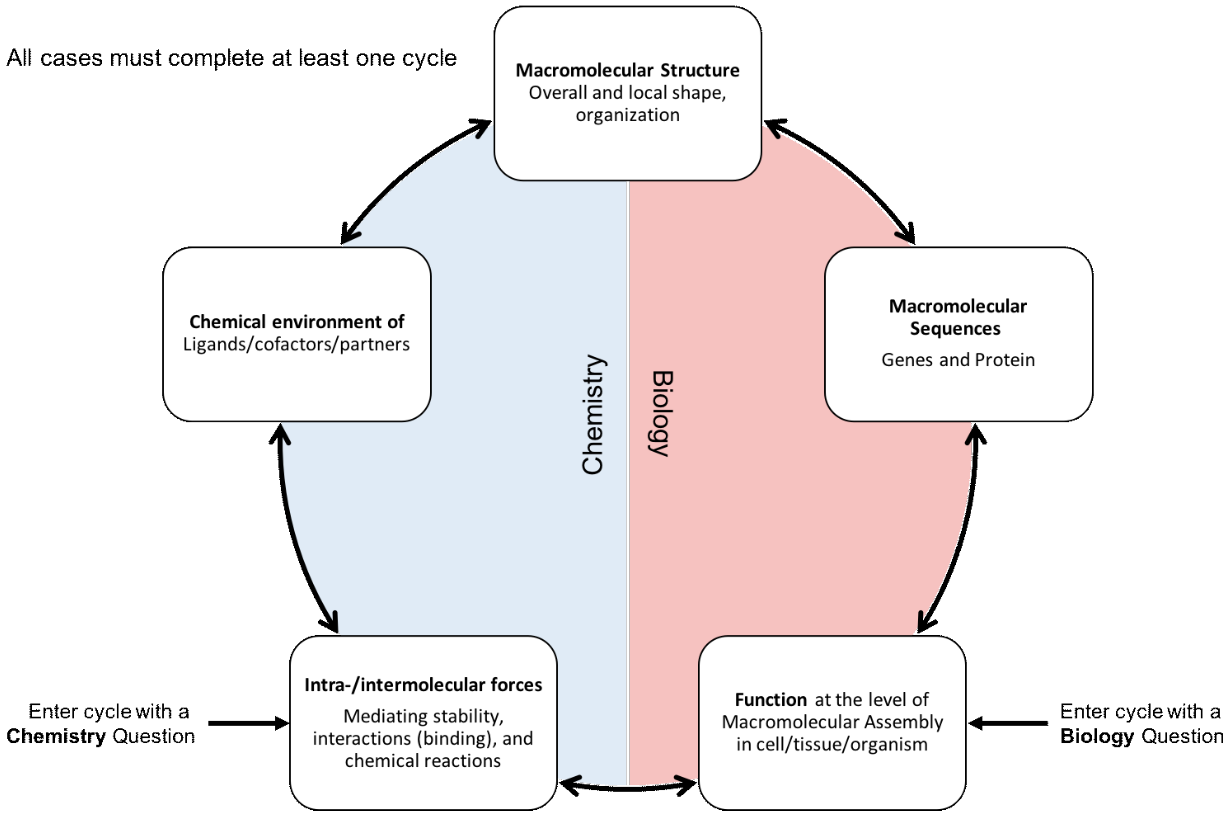

Figure 1: Molecular Case Study Cycle showing the biological phenomenon and information about it on the right (colored pink) and chemical interactions and discussions on the left (colored blue).

The Molecular Case Study Cycle was presented at various meetings and workshops to gauge interest in undergraduate educators for developing and using molecular case studies. Within the past year ~10 undergraduate chemistry, biochemistry, and biology educators have collaborated with Molecular CaseNet Steering Committee members to write seven case studies on a variety of topics. All the case studies developed so far, begin with a question related to a biological process, phenomenon, or problem. Initial discussions in the case focus on identifying the protein(s) and/or complexes that play a role in the process/problem being explored in the case. In some instances when the 3D structures of the case specific proteins or complexes are not available, structures of related proteins (e.g., from another organism) may be chosen for case discussion. Once one or more relevant PDB structures are identified the overall 3D shapes and interactions of the molecule can be examined using specific visualization tools and used for explaining cellular, and organismal level functions in molecular detail.

Findings

The molecular case studies were pilot tested to find out if they were useful and relevant to different curricular contexts. In Spring 2020 Molecular CaseNet collaborated with the Quantitative Biology Education and Synthesis (QUBES) network to host a Faculty Mentoring Network (FMN).

A group of fifteen undergraduate educators, teaching in a variety of curricular settings, participated in the semester long FMN. They provided feedback on the cases, adapted them to meet their specific curricular needs and used them in their classrooms. Some of these educators used the cases in small classrooms (~5 students), while others in a large classroom (over 100 students). Educators teaching introductory courses had to scaffold the cases they chose to meet their students' needs, while more advanced students engaged in exploring additional sections developed by the educator teaching the case. A couple of new cases were also written during this FMN. After incorporating feedback from the FMN participants these cases were published on the QUBES platform. The various adaptations that the FMN faculty created were also published on QUBES. The cases themselves are freely available from the Molecular CaseNet website (https://molecular-casenet.rcsb.org/) for anyone to use and adapt.

Conversations with chemistry and biology faculty has begun to shed light on barriers that may be preventing educators from using molecular structures in teaching and learning. Informal discussions in various workshops and meetings uncovered the need for developing scaffolds to help students (and educators) learn some discipline specific vocabulary, foundational concepts and skills in order to fully participate in case discussions. For example, introductory chemistry students need to understand concepts in biology such as the central dogma in order to meaningfully navigate through and integrate information from a variety of public biological data resources. Similarly, biology students need a refresher on the properties of covalent and various non-covalent interactions that stabilize biomolecular structures and form the foundation of molecular interactions. Both chemistry and biology faculty and students need to learn about the contents, navigation, and use of data from various bioinformatics resources (including 3D structural data from the PDB). Inclusion of scaffolds may help educators with limited prior experience with molecular structures to gain confidence in teaching their disciplinary content in molecular detail.

Selected members of Molecular CaseNet have initiated a process for addressing the need for scaffolds in facilitating broad use of molecular case studies. In Fall 2020, as part of the Biome Institute organized by QUBES, a small group of undergraduate educators reviewed various education standards in chemistry and biology to identify knowledge gaps and common misconceptions in chemistry and biology instructions. The group has begun developing scaffolds for students (and educators) that can be used in preparation for and/or during the case discussions. Quick refreshers and scaffolds developed here will be suitably integrated with the published molecular case studies at different points of Molecular Case Study Cycle. The and training materials will also be shared on the Molecular CaseNet website for being included in cases developed in the future and/or inclusion in teaching and learning outside of the molecular case studies.

Conclusion

The Molecular CaseNet community is growing. Several undergraduate educators have joined the community and participated in developing/using the cases in a variety of curricular contexts. The Molecular Case Study Cycle provides a foundation for educators to engage in interdisciplinary collaborations to develop and use case studies. It also helps identify and organize knowledge gaps/misconceptions in both disciplines. Use of molecular case studies and creation of training material for explorations at the interface of chemistry and biology will strengthen the foundations for interdisciplinary learning. In addition to learning specific disciplinary contents, use of molecular case studies will help train participating students (and educators) in navigating various public data resources and using bioinformatics tools to acquire skills/experiences that better prepare them for learning, teaching, and research.

The Molecular Case Study Cycle provides a framework for key elements necessary for developing a molecular case study. Some of the important ones include a hook or a story to engage the student/ case study participant; motivation (e.g., observation, question, problem) and guidance (scaffolds) to navigate through relevant biological data resources to learn about and gather information related to the case; PDB structures relevant for the case discussion; and appropriate visualization/analysis tools for modeling the system and discussing the molecular basis of the case theme. Currently, all cases available from the Molecular CaseNet website are motivated by a biological process, question, or problem. Through the case discussions students explain the process, answer the question, or begin solving the problem in molecular detail. However, molecular case studies may begin at any point in the Molecular Case Study Cycle. For example, the motivation for the case may be a chemistry or even a molecular structural observation or question. The Molecular CaseNet welcomes chemistry, structural biology, and other disciplinary educators to collaborate in developing and piloting new case studies for the collection.

Requesting a Key

All molecular case studies and related resources are freely available online (https://molecular-casenet.rcsb.org/). Educators can access accompanying teaching notes by requesting for an account by writing to the author (sdutta@rcsb.rutgers.edu).

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References

- (2008). "Jmol: an open-source Java viewer for chemical structures in 3D." from http://www.jmol.org/.
- AAAS (2011). Vision and Change in Undergraduate Biology Education: A Call to Action. Washington, DC.
- ACS Committee on Professional Training (2015). "Undergraduate Professional Education in Chemistry: ACS Guidelines and Evaluation Procedures for Bachelor's Degree Programs."

- Benson, D. A., M. Cavanaugh, K. Clark, I. Karsch-Mizrachi, D. J. Lipman, J. Ostell and E. W. Sayers (2013). "GenBank." Nucleic Acids Res **41**(Database issue): D36-42.
- Berman, H. M., K. Henrick and H. Nakamura (2003). "Announcing the worldwide Protein Data Bank." Nat Struct Biol **10**(12): 980.
- Brownell, S.E., Freeman, S., Wenderoth, M.P., and Crowe, A.J., (2014), “BioCore Guide: A Tool for Interpreting the Core Concepts of Vision and Change for Biology Majors” CBE—Life Sciences Education **13** (2): 200-211
- Clemmons, A.W., Timbrook, J., Herron, J.C., and Crowe, A.J., (2020) “BioSkills Guide: Development and National Validation of a Tool for Interpreting the Vision and Change Core Competencies” CBE—Life Sciences Education **19**(4)
- DeLano, W. (2002). "The PyMOL molecular graphics system, http://www.pymol.org."
- Dries, D. R., D. M. Dean, L. L. Listenberger, W. R. Novak, M. A. Franzen and P. A. Craig (2017). "An expanded framework for biomolecular visualization in the classroom: Learning goals and competencies." Biochem. Mol. Biol. Educ. 45(1): 69-75.
- Dutta, S., Cortes, K. L., Jakubowski, H. V., Lenahan, M., Marcey, D., Marsteller, P., Terrell, C. (2020). “Nicholas' Story” QUBES Educational Resources. doi:10.25334/H82J-3C28
- Jeske, L., S. Placzek, I. Schomburg, A. Chang and D. Schomburg (2019). "BRENDA in 2019: a European ELIXIR core data resource." Nucleic Acids Res **47**(D1): D542-D549.
- Jones, L., K. D. Jordan and N. A. Stillings (2005). "Molecular visualization in chemistry education: the role of multidisciplinary collaboration " Chemical Education Research and Practice **6**: 139-149.
- Loertscher, J., D. Green, J. E. Lewis, S. Lin and V. Minderhout (2014). "Identification of threshold concepts for biochemistry." CBE Life Sci Educ **13**(3): 516-528.
- NCBI Resource Coordinators (2017). "Database Resources of the National Center for Biotechnology Information." Nucleic Acids Res. **45**(D1): D12-D17.
- NSF (2001). Molecular Visualization in Science Education. NCSA Access Center, Arlington, VA NSF.
- Pettersen, E. F., T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng and T. E. Ferrin (2004). "UCSF Chimera--a visualization system for exploratory research and analysis." J Comput Chem **25**(13): 1605-1612.
- Tansey, J. T., T. Baird, Jr., M. M. Cox, K. M. Fox, J. Knight, D. Sears and E. Bell (2013). "Foundational concepts and underlying theories for majors in "biochemistry and molecular biology"." Biochem. Mol. Biol. Educ. **41**(5): 289-296.
- Trujillo, C. M., T. R. Anderson and N. J. Pelaez (2015). "A Model of How Different Biology Experts Explain Molecular and Cellular Mechanisms." CBE Life Sci Educ. **14**(2): ar20.
- UniProt Consortium (2019). "UniProt: a worldwide hub of protein knowledge." Nucleic Acids Res **47**(D1): D506-D515.
- van Mil, M. H. W., D. J. Boerwinkel and A. J. Waarlo (2013). "Modelling Molecular Mechanisms: A Framework of Scientific Reasoning to Construct Molecular-Level Explanations for Cellular Behaviour." Science and Education **22**(1): 93-118.
- van Mil, M. H. W., P. A. Postma, D. J. Boerwinkel, K. Klaassen and A. J. Waarlo (2016). "Molecular Mechanistic Reasoning: Toward Bridging the Gap Between the Molecular and Cellular Levels in Life Science Education." Science Education **100**(3): 517-585.

- Wishart, D. S., Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, D. Le, A. Pon, C. Knox and M. Wilson (2018). "DrugBank 5.0: a major update to the DrugBank database for 2018." Nucleic Acids Res **46**(D1): D1074-D1082.