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Many undergraduate students in introductory biochemistry courses find it challenging to understand how different levels of protein structure relate to each other. To address this problem, we introduced an inquiry-based laboratory exercise in which students are challenged to explain how the effects of mutations on different levels of protein structure lead to changes in protein function and ultimately to genetically-inheritable diseases. The implementation of this exercise in a large, second-year undergraduate, introductory biochemistry course led to a high level of student satisfaction and a more integrated view of biochemistry and genetics.

Firstpage

**Keywords**: protein structure, biochemistry, genetics, inquiry-based learning

**Introduction**

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**Secondary Heading**

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*Tertiary Heading*

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Quaternary heading

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**Student Outline**

**Objectives**

Use bioinformatics tools

Evaluate DNA sequence variations in specific genes

Describe molecular basis for inherited diseases

**Introduction**

As first demonstrated in a classic paper by Linus Pauling and co-workers (1949), mutations in hemoglobin lead to changes in protein structure, which in turn lead to a molecular explanation for the development of an important human disease, sickle-cell anemia. Since this classic study, many other papers have described examples of mutations that lead to changes in protein structures, and which in turn lead to the development of diseases (Steward et al. 2003). Over the next few weeks, you will have the opportunity to gain, using various bioinformatics tools, a structural perspective on the molecular basis of genetically-inherited diseases. As you saw in your introductory genetics course, human genetically-inherited diseases are caused by DNA sequence variations. Although disease-causing DNA sequence variations can occur in both non-coding and coding regions of the genome, the majority of characterized mutations occur in the coding region of genes. Since they can be found in the coding region of genes, these mutations often affect the structure and function of proteins. For this laboratory exercise, we will focus on genetically-inheritable diseases that are caused by this type of mutation. More specifically, we will focus on genetically-inheritable diseases that result from a missense mutation. Recall that a missense mutation is a change in the nucleotide sequence of a gene, where one or more nucleotides is or are replaced by another. This mutation results in a new codon, which causes a different amino acid to be inserted into the growing polypeptide chain during translation. For this laboratory exercise, you will be asked to work with your laboratory partner. You and your laboratory partner will be guided in the use of various bioinformatics tools to study the effects of disease-causing mutations on protein structure and function. We will specifically focus on different levels of protein structure and how they are intimately related to one another in the formation of the final, fully-folded protein. At the end of this exercise, you and your laboratory partner will be asked to orally present your results to the other members of your laboratory session via a 10-minute Power Point presentation.

**Methods and Data Collection**

*Part A: Selecting Your Topic*

 The first part of this project involves selecting your topic. There are eleven topics from which to select, and only one pair per laboratory section can work on each topic. So, topic selection is first come, first served. All eleven available topics are listed in Appendix A. Also included in Appendix A are the protein structure coordinates for the wild-type protein and a file with a “.pse” file name extension. You will need this file for your work with the protein visualization software PyMOL. Appendix A also contains one seed reference for each disease, to help you get started in locating background information on your topic as well as structural information and the disease-causing mutation.

*Part B: Studying the Protein Structure and Physiochemical Properties*

To help you complete your project, you will be guided through all of the steps using the K-Ras protein, which has been implicated in lung cancer. To make it easier for you, screenshots using the K-Ras example have been inserted in the text below.

Data Analysis

 Insert text as appropriate.

**Discussion**

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**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 students. LCD projector and computer are required for student presentations.

Often, this section will consist of a list of materials, equipment and supplies required conduct your laboratory study with a typical class of 20-30 students. Provide vendor information and current costs as appropriate.

**Notes for the Instructor**

One of the major challenges that we faced in implementing an inquiry-based exercise in a large class of over 500 students was to organize the exercise in a way that maximized the inquiry experience of each student without placing excessive demands on the limited time and resources of a small team of graduate teaching assistants, librarians and instructors.

Several design elements of the exercise were specifically chosen to meet this significant challenge. First, an introductory computer-based workshop session is conducted during a regularly scheduled, weekly laboratory section of the introductory biochemistry course. The relatively small groups of students in individual laboratory sections (approximately 22 students in each of 24 laboratory sections) facilitated the interactive nature of the computer- based exercises by providing opportunities for one-on-one interactions with teaching assistants and librarians, as well as peer-to-peer learning. Following this introductory session, students are given six weeks to complete the remaining self-guided exercises and to prepare their Power Point presentation, before the final student presentations.

One of the most difficult challenges facing this project was to devise a way to evaluate how students performed in the inquiry-based exercises. Since the oral presentation was designed to be the culmination of the student-initiated inquiry-based learning process, the overall performance of the students in this exercise was evaluated by marking the quality of the oral presentations for each pair of students. To standardize the evaluation of students in a large number of separate laboratory sessions, we developed a detailed marking rubric that provided specific guidance to the graduate teaching assistants regarding the grading of the final student presentations (Appendix A).

The marking rubric was carefully designed to emphasize the importance of creativity and inquiry, as opposed to a nonselective listing of information. Students were informed well in advance of their presentations that they would be marked for their creativity and the quality of their presentation, as well as for the scientific accuracy and completeness of information. As a result, students needed to master basic concepts and apply them in a meaningful way to prepare a successful presentation.

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**About the Authors**

Author's name has been an Instructor at the University of Calgary since 2006, where she teaches large courses in genetics and biochemistry, primarily at the second-year

**Appendix A**

**Mission, Review Process & Disclaimer**

The Association for Biology Laboratory Education (ABLE) was founded in 1979 to promote information exchange among university and college educators actively concerned with teaching biology in a laboratory setting. The focus of ABLE is to improve the undergraduate biology laboratory experience by promoting the development and dissemination of interesting, innovative, and reliable laboratory exercises. For more information about ABLE, please visit **http://www.ableweb.org/.**

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