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Protein Molecules as Robotic Mechanisms: An Interdisciplinary Project-Based Learning Experience at the Intersection of Biochemistry and Robotics

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Abstract

Increasingly, instructors are challenged by growing complexity in knowledge domains and the need to prepare students with specific skills relevant to an uncertain future. The speed of technological advance and shifting societal conditions make this ever more arduous. One of the promises of project-based learning (PBL) is to cultivate many of the most important student qualities for facing such an uncertain world by exposing them to cross disciplinary problems. Indeed, providing the students with a plethora of perspectives from seemingly unrelated fields enhances their creative problem solving skills and enables them to better adapt to complex scenarios.

This paper describes a multidisciplinary effort between faculty from the Electrical and Computer Engineering Department at the University of Michigan-Dearborn and the Department of Chemistry and Biochemistry at the Worcester Polytechnic Institute (WPI). The project involved students modeling protein folding as a robotic mechanism and studying the problems associated with this complex system from multiple perspectives. After providing a brief technical background about the robotics-based approaches to the problem of protein folding/unfolding, this paper elaborates on the pedagogical elements of the project. Assessment results and student feedback highlight the learning outcomes and perspectives on this interdisciplinary, and intercollegiate project-based learning endeavor. The authors comment on challenges and opportunities associated with such PBL efforts and provide suggestions for disseminating these types of impactful PBL initiatives.

Introduction

The human labor market, which is facing technological advancements and shifting societal conditions, will encounter uncertain prospects while revolving around three categories of work in the age of artificial intelligence [1]: finding solutions to problems with unstructured characteristics, working with unfamiliar information subject to complex communication constraints, and performing manual tasks that are non-routine. Facing these unprecedented changes, instructors are challenged by growing complexity in knowledge domains. Furthermore, they need to prepare their students with specific skills relevant to an uncertain future affected by the advent of advanced AI and societal shifts. A signature paradigm for higher education that can prepare students for the uncertain labor market of the future, according to Bass [2, 3], should be driven by inclusive excellence and integrative learning, which are the two innovative drivers of

higher education.

Having its roots in John Dewey's philosophical thought [4], project-based learning (PBL) has proven to be a beneficial student-centered pedagogy over the years. Long-lasting and deep learning outcomes, improved communication skill set, and engaging students with critical and proactive thinking experience are among the many proven pedagogical advantages of PBL[1]. Being attentive to inclusive and integrative practices, PBL falls within 'the first quadrant' of the matrix depicted in Figure 1. Hence, "as machines get better at being machines", Bass [2] argues that "the primary purpose of higher education has to be helping humans get better at being human".

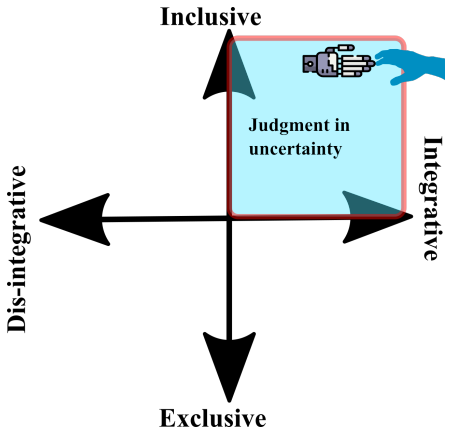


Figure 1: Being attentive to inclusive and integrative practices, PBL falls within 'the first quadrant' of the matrix [2]. Accordingly, PBL prepares the students for the uncertain prospects of the future labor market facing automation and technological advancements.

One of the promises of PBL, which falls within the upper right portion of matrix of 'the first quadrant' (see Figure 1), is to cultivate many of the most important student qualities for facing an uncertain world affected by technological advance and shifting societal conditions through exposing them to cross disciplinary problems. Indeed, PBL has the potential to enhance students' creative problem solving skills and enables them to better adapt to complex scenarios by providing them with a plethora of perspectives from seemingly unrelated fields.

With their PBL roots in First Robotics [5] and VEX [6], the interconnected fields of robotics and mechatronics have been extensively utilized for launching innovative PBL initiatives ranging from K1-12 to undergraduate STEM programs in the past decade (see, e.g., [7, 8]). There have also been several PBL initiatives for enhancing learning outcomes in general chemistry courses and engineering student retention rates (see, e.g., [9, 10]). Nevertheless, to the best of the authors' knowledge, there have been few if any prior PBL-based multidisciplinary approach lying at the intersection of the two seemingly unrelated fields of robotics and biochemistry.

This paper describes a multidisciplinary effort between faculty from the Electrical and Computer Engineering Department at the University of Michigan-Dearborn and the Department of Chemistry and Biochemistry at the Worcester Polytechnic Institute (WPI). This multidisciplinary

[1]See the Buck Institute for Education PBLWorks website for a rich collection of resources: `https://www.pblworks.org/`.

project effort involves students modeling protein folding as a robotic mechanism and studying the problems associated with this complex system from multiple perspectives. After providing a brief technical background about the robotics-based approaches to the problem of protein folding/unfolding, this paper elaborates on the pedagogical elements of the project. Furthermore, the authors comment on challenges and opportunities associated with such PBL efforts and provide suggestions for disseminating these types of impactful PBL initiatives.

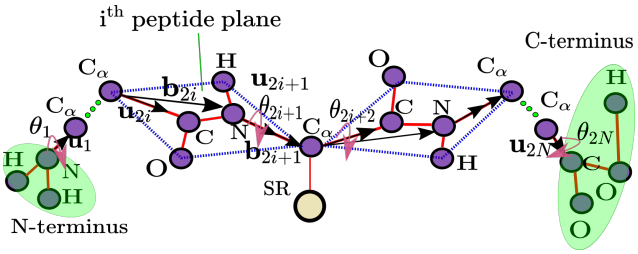
Technical Background

This section provides a quick overview of the technical foundation and driving force behind our collaborative PBL project. Protein engineering, drug development, and studying disorders like Alzheimer's at the molecular and cellular levels all depend on computer-aided prediction of the folded structure of a protein molecule [11]. The linear amino acid (AA) sequence of a protein molecule, also referred to as the primary sequence, plays a major role in determining its 3D structure. Many researchers in biochemistry including those involved with designing viral medicines that cause misfolding in virus proteins need to study folding mechanisms of protein molecules and their underlying folding pathways [12].

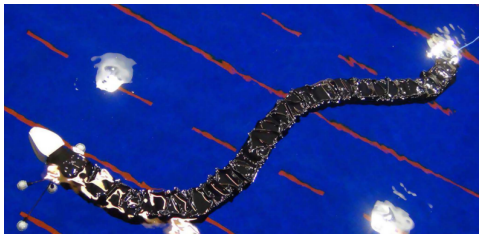
To solve the challenging problem of protein folding and compute the folding/unfolding pathways numerically, there are various robotics-inspired approaches in the literature that model protein molecules as hyper-redundant mechanisms, in which the molecule peptide planes are considered as rigid links and the alpha-Carbon and their bonded Nitrogen atoms are treated as revolute joints (see, e.g., [13–16]). The assumption of coplanarity of the atoms C_α, CO, NH, and C_α, which form each of the peptide planes (see Figure 2), is based on the results from high resolution X-ray crystallographic experiments (see, e.g., [17]). Intriguingly, such protein kinematic model depicted in Figure 2a has the exact same structure as manipulators with hyper degrees-of-freedom as described in the work of Mochiyama et al. (see, e.g., [18]). This type of kinematic modeling has also been used for multisection continuum robots (see, e.g., [19]).

As demonstrated in Figure 2a, each peptide plane, which consists of six coplanar atoms, can be considered as a linkage in the protein kinematic mechanism [20]. Central carbon atoms, which are denoted by C_α and commonly known as the alpha-Carbon atoms, act as hinges connecting peptide planes together. The red-colored line segments in Figure 2a depict the covalent chemical bonds between the peptide plane atoms. Each alpha-carbon atom is bonded to four other chemical components including the three atoms C, N, and H, and a variable side chain shown with SR. The first alpha-Carbon of the protein chain structure is bonded to N-terminus, which is an amino group, as well as one peptide plane. Similarly, the last C_α atom is chemically bonded to the C-terminus, which is a carboxyl group, as well as one other peptide plane. The backbone conformation[2] of the protein molecule kinematic structure consisting of the subchain $-\mathrm{N}-\mathrm{C}_\alpha-\mathrm{C}-$, is described by a collection of bond lengths and a set of pairs of dihedral angles, namely, the angles representing the rotations around the covalent bonds $\mathrm{C}_\alpha-\mathrm{C}$ and $\mathrm{N}-\mathrm{C}_\alpha$ (see Figure 2).

[2]In the biochemistry literature, 'conformation' is the standard word for describing the geometry of the protein molecule kinematic structure. In the robotics literature, on the other hand, the terminology 'configuration' is frequently used to describe the kinematic structures of robots. In this paper, unless otherwise stated, we use the two words 'conformation' and 'configuration' interchangeably.



(a) The protein molecule kinematic mechanism.



(b) A swimming snake robot with many degrees-of-freedom [21].

Figure 2: The protein molecule kinematic mechanism consisting of peptide planes as rigid links and alpha-Carbon atoms acting as hinges. Under the assumption of rigidity of the peptide planes, the underlying kinematics of a protein molecule backbone chain is exactly the same as hyper-redundant robotic mechanisms such as snake robots.

To compute the sequence of dihedral angles from an unfolded to a folded conformation and vice versa, the kinetostatic compliance method (KCM) for modeling the protein folding/unfolding process can used. The KCM framework pioneered by Kazerounian and collaborators is based on the well-established fact that the essential folding dynamics can be explained by neglecting the inertial forces (see, e.g., [13]). Instead, the protein chain dihedral angles vary kinetostatically under the effect of the interatomic force fields. Consequently, the dihedral angles at each conformation of the protein molecule change in proportion to the effective torques acting on the peptide chain. With this insight, it is possible to efficiently compute physically meaningful inputs for the protein backbone chain model as a hyper-redundant nano-mechanism using tools from control systems literature (see, e.g., [15, 16] for further details).

Project Development

As the first implementations of this PBL initiative, we wanted to expose senior year students who were taking the courses “Biochem 4110–Protein Structure and Function” at WPIf and “ECE 4641–Mobile Robots” at the University of Michigan-Dearborn to the robotics-inspired methods for solving the protein folding/unfoldfing problem. Furthermore, we wanted to ensure that the students could achieve the project objectives using publicly available online molecular simulation tools without having to program in languages such as Python or MATLAB. Finally, we wanted to ensure that the students could compare the results from the molecular dynamics (MD) simulations to a simplified and yet accurate model of protein chain extension in response to mechanical forces from devices such as optical tweezers and atomic force microscopes. Consequently, instead of relying on relatively complicated KCM-based models (see, e.g., [14, 16]), we chose the wormlike chain (WLC) model, whose continuum behavior is similar to certain types of soft robots such as one degree-of-freedom pneumatic bending robots [22]. In what follows, we provide the desired learning outcomes expected from our designed project, the description of the project tasks, and the questions associated with the project tasks.

Introduction and Desired Learning Outcomes

Devices such as optical tweezers and atomic force microscopes enable the manipulation of a single protein molecule and the ability to apply a mechanical force. This technique of mechanical unfolding of protein molecules yields significant information about the free energy landscape and

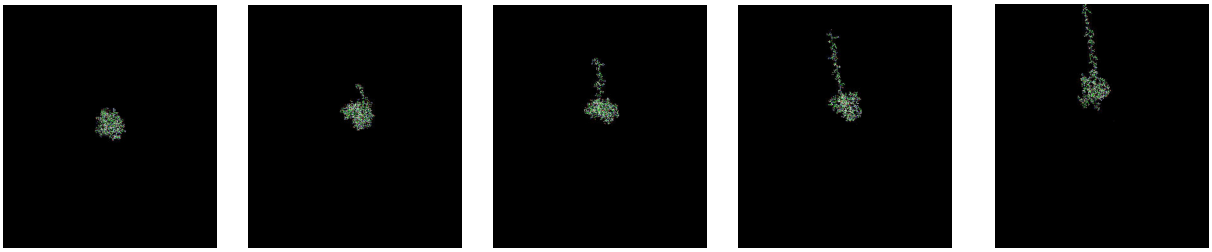


Figure 3: Snapshots of the animation of a sample unfolding numerical simulation using the "Forced Protein Unfolding" toolkit performed on the protein molecule Barnase through the tool [23] hosted on `https://nanohub.org`.

the folding intermediates of protein molecules. In this project, we asked the students to investigate the mechanical unfolding of the protein molecule Barnase since the forced unfolding of this molecule is relatively well-studied in the literature.

As described earlier, this project was to be done primarily on the Web, using publicly available programs. By the time the students finish this assignment they should be able to apply the publicly available online molecular simulation tools to study the problem of protein unfolding, relate the protein chain extension to the external force applied to it, synthesize numerical functions that can describe the average extension of a protein molecule as a function of the applied force to them, and assess the impact of forced unfolding on the structure of proteins.

Task 1: Forced protein unfolding toolkit on NanoHub
To use the protein unfolding simulator, students first needed to create an online account on `https://nanohub.org`. After creating their online account, they could start their molecular dynamics simulations using the "Forced Protein Unfolding" toolkit developed by Martini, Rafferty, and Flohr from Purdue University [23]. This toolkit enables users to easily perform non-equilibrium molecular dynamics simulations of single protein molecules subject to an external force and then analyze their simulation results both quantitatively and through animations of the protein dynamics. The three proteins currently implemented in this version of the Forced Protein Unfolding toolkit are RNase H (RNH), Barnase, and Ubiquitin. These three proteins present contrasting structural forms: Barnase has five central antiparallel β strands with small peripheral α helices; RNase H is larger containing more extensive α helices.

After accessing the unfolding tool web page and under the Protein Selection menu, the students would choose Barnase (1BNR) and set the unfolding simulation parameters including "Simulation time", "Unfolding force", and "Output points" using the Input Parameters options. After choosing these parameters, the students could launch their unfolding all-atom MD simulation. The NanoHub website would then submit their simulation request to a remote server. Due to the queue delays, their request could take several hours depending on the remote server usage. After running the simulation, the students would get the following results from their simulation: "Plot: End-to-end extension", "Plot: Secondary Structure vs. Extension", "Plot: Hydrogen Bonds", "PDB file", "GROMACS mdrun log", "Sequence: Hydrogen bond map", "Sequence: Ramachandran plot", "Chart: Secondary structure vs. Time", "Chart: Secondary structure vs. Extension", and "3D Animation" (see Figure 3).

As a complementary reading material, we asked the students to read the work by Daggett and collaborators [24]. In some of the questions associated with this project, the students would compare their findings from their simulation studies on nanoHub platform against the findings reported in [24].

Task 2: Investigating the worm-like chain model of protein molecules
The worm-like chain model is a simple continuum model for the statistical mechanics of a protein molecule subject to an external force [25]. Indeed, the mechanical properties of a protein in the folded and unfolded states are expected to be different—a folded protein has collapsed to its native structure with a conformational space of reduced order (i.e., a lesser number of degrees-of-freedom), whereas an unfolded protein has a larger number of degrees-of-freedom.

In this part of the project, the students would observe how a simple mathematical model known as the wormlike chain (WLC) model can be used for finding the relationship between the length of a protein molecule and the force applied to it. The seminal article "Entropic Elasticity of λ-Phage DNA" [26], whose validity has been experimentally verified in various protein molecule chains (see, e.g., [24]), provides the relationship between the extension of protein molecules and the forces applied to them using a very simple equation.

The students were asked to use an online graphing calculator[3] to draw the graph of the WLC equations. They were also asked to compare their results against the extension-force graph reported by [26]. Furthermore, the students were introduced to an interesting online tool called the WebPlotDigitizer[4], which also had an online YouTube video tutorial[5]. The semi-automated WebPlotDigitizer enables students to reverse engineer images of data visualizations to extract the underlying numerical data reported in scientific articles.

Questions associated with the tasks
We asked our students to answer the following two questions after performing Tasks 1 and 2.

Question 1) The following plots from a sample Barnase unfolding simulation Barnase demonstrate the number of hydrogen bonds per time (the left figure) and the number of amino acids participating in helical (blue) and beta sheet (red) secondary structures per extension of the protein molecule. You should be able to see the same patterns within your own unfolding simulations. Why do you see such patterns during unfolding? How do these patterns relate to your knowledge about the process of protein folding? Not only can you watch the animation of your protein unfolding simulation on NanoHub but also you can see the dynamic changes in the Ramachandran plots as your protein unfolds during this pulling process. How can you relate the dynamic changes in the Ramachandran plots to the following two figures?

Question 2) Valerie Daggett when studying the forced unfolding of Barnase in her paper (see Remark 1) used the worm-like chain model proposed in "Entropic Elasticity of lambda-Phage DNA" (you did some work on this model in Task 2). Use the worm-like chain model with the

[3] https://www.desmos.com/calculator
[4] https://automeris.io/WebPlotDigitizer/
[5] https://www.youtube.com/watch?v=Mv5nqAPCKA4

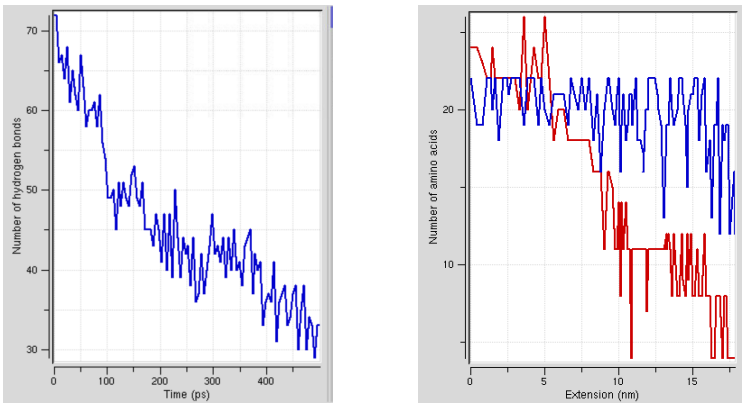


Figure 4: The number of hydrogen bonds per time (the left figure) and the number of amino acids participating in helical (blue) and beta sheet (red) secondary structures per extension of the protein molecule (the right figure).

parameters that are reported in Daggett's paper and compare the drawn curves using the online graphing calculator. How do these plotted graphs differ from the ones obtained from the nanoHub simulations?

Discussion

Followup presentation and student Q&A

We had a followup presentation for the students who were involved with this PBL module where the first author did a presentation on the research efforts that lie at the intersection of robotics and the problem of protein folding/unfolding. One of the interesting moments in this presentation was when the students got excited when hearing about the fact that some of the underlying optimization, path planning, and control algorithms that are utilized for solving challenging robotics and autonomous vehicle control problems can also play an integral role for guided numerical simulation of protein folding/unfolding processes. In addition to the presentation, the students had the chance to inquire about some of the tools that they were asked to work with in performing the project tasks.

Challenges and opportunities

One of the main challenges in the first implementation of this PBL initiative was trying to expose senior year students who were taking the course "Biochem 4110– Protein Structure and Function" at WPI to the robotics-inspired methods for solving the protein folding/unfolding problem. The students had little or even no prior exposure to robotics, complex nonlinear dynamical models capturing the relationship between external force and protein molecule extension, and molecular dynamics simulations. Furthermore, we wanted to ensure that the students could achieve the project objectives using publicly available online molecular simulation tools without having to program in languages such as Python, MATLAB, and molecular dynamics simulation programs such as GROMACS. To overcome this challenge, we decided to use the powerful molecular dynamics simulation tools provided on the NanoHub platform.

The challenge for implementation of the PBL initiative in the course "ECE 4641–Mobile Robots" at the University of Michigan-Dearborn was that the students had forgotten the basics of general chemistry, a course which they either take in their first year of college or as an AP course in their

final high school year. To overcome this challenge, the author from the University of Michigan-Dearborn held an additional lecture and reviewed the basic concepts of chemistry needed to complete the project.

Another challenge was to choose a simplified and yet accurate model where the students could compare the results from the molecular dynamics (MD) simulations to a simplified and yet accurate model of protein chain extension in response to mechanical forces from devices such as optical tweezers and atomic force microscopes. Consequently, instead of relying on relatively complicated KCM-based models, we overcame this challenge by choosing the wormlike chain (WLC) model, whose continuum behavior is similar to certain types of soft robots such as one degree-of-freedom pneumatic bending robots.

Finally, we were facing the issue of remote collaboration and coordination between the two faculty involved in designing the PBL module. We could overcome this challenge through working on shared documents and frequent email exchanges. We would like to remark that willingness and dedication of faculty to such collaborative initiatives is one the most important necessary conditions for the success of such efforts. Another effective solution that we came up with was to hold the followup presentation and student Q&A session.

Student Feedback and Reflections

Based on our interaction with the students through the followup and Q&A session as well as the written feedback/reflection statements provided by the students, we believe that this PBL initiative has been quite successful in its initial launching phase. Here is a sample feedback that we received from a group of four students at WPI: “Using the Nanohub software was a very educational experience, particularly in conjunction with Daggett’s paper and the paper by Bustamante et al. The myriad of graphs produced by the simulation were interesting to investigate and allowed for the corroboration of several trends that could be seen during protein unfolding. The animated gif of protein unfolding was also quite helpful and gave a unique look at how protein unfolding by extension could occur.” Another sample feedback that we received from a group of three ECE students at the University of Michigan-Dearborn was as follows: “I felt excitement exploring a problem at the intersection of biochemistry and robotics! This is a fascinating and exciting field that holds a lot of promise for the future of medicine, biotechnology, and beyond.”

Despite this positive experience, the students had also run into certain issues with the remote servers running the molecular dynamics simulations on NanoHub. Here is a sample feedback: “The difficulties with the tool came after running the simulation, however. The simulation frequently failed to run (majority of simulations crashed), producing the error message “No such file or directory” as seen in Figure 15 [from the student’s project report, see Figure 5 for a copy] below. The website also occasionally logged a user out, which would cause the simulation to fail.”

The first author had also run into similar occasional technical issues with these remote servers. Nevertheless, both the students and the first author had been able to obtain the results from NanoHub after a few failed runs. One remark based on the observations of the first author is that the time of day at which the requests are submitted to NanoHub remote servers and their computational queue length were playing an important role in determining the success or failure of the simulations. The other alternative would be asking the students to run their own molecular

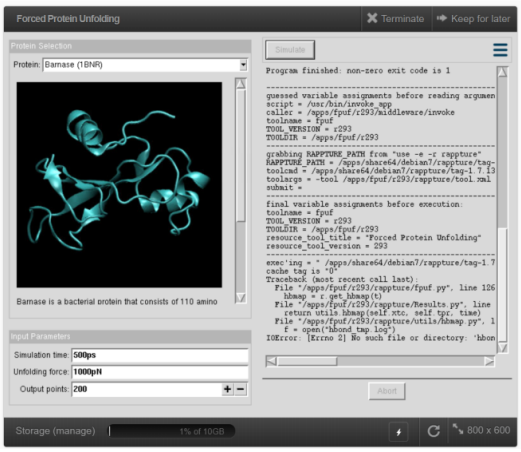


Figure 15: Error message on Nanohub's Forced Protein Unfolding tool.

Figure 5: The figure of the NanoHub error message pointed out in the student's final project report.

dynamics (MD) simulations using GROMACS (see, e.g., [27]). In this case, the students will need to learn some basics of MD simulations, to prepare the needed MD files, and to run them on their own computers or university local clusters.

Student Assessment

We performed two collections of assessments in the second implementation of our PBL initiative (namely, for the group six ECE students at the University of Michigan-Dearborn). The first assessment was based on ABET Outcome 1 [28], which is focused on assessing students on "an ability to identify, formulate, and solve complex engineering problems by applying principles of engineering, science, and mathematics". Complex engineering problems according to ABET [28] "include one or more of the following characteristics: involving wide-ranging or conflicting technical issues, having no obvious solution, addressing problems not encompassed by current standards and codes, involving diverse groups of stakeholders, including many component parts or sub-problems, involving multiple disciplines, or having significant consequences in a range of contexts". Involving multiple disciplines and having several sub-problems, the project can be considered as a complex engineering problem according to the ABET definition of complex engineering problems.

To assess the students' projects based on ABET Outcome 1 (i.e., our first assessment), we followed the guidelines proposed by Battistini and Kitch [29]. In particular, we assessed our students based on the following key performance indicators (KPIs): identify specific facts of engineering, science, and mathematics needed for a given situation; formulate the problem and identify key issues/variables, model real world situation; and, solve complex engineering problems.

For the aforementioned KPIs, we used the level of achievements proposed by Battistini and Kitch [29]: (1) Beginning: student fails to submit work or work is seriously flawed; (2) Developing: student work is weak, generic, and/or lacking detailed calculations or explanations; (3) Proficient: student work is mostly correct with accurate assumptions, calculations, and explanations; and, (4) Exemplary: student work is correct, organized, detailed and thoroughly

explained.

Figure 6 depicts the result of our assessment of the key performance indicators (KPIs) on ABET Outcome 1. As remarked earlier, involving multiple disciplines and having several sub-problems, our proposed project can be considered as a complex engineering problem according to the ABET definition. As it can be seen from Figure 6, the majority of the students except for one had a Proficient or Exemplary level of achievement in delivering their projects.

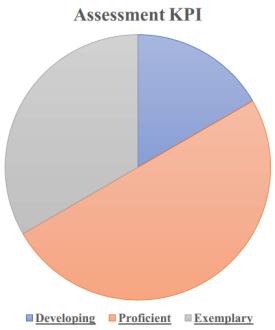


Figure 6: The result of assessment of key performance indicators (KPIs) on ABET Outcome 1.

In the second assessment, which closely follows the assessment proposed by Wilkerson *et al.* [7] in their robotics PBL initiative, we utilized an initial survey to gauge the students' prior knowledge of the topics and an exit survey that asked the same questions. Despite the fact that providing such data can be subjective at best, Wilkerson *et al.* [7] argue that "it seems prudent to have some measure, from the student perspective, of what was accomplished" for novel PBL initiatives.

The results of the initial and final surveys are depicted in Figures 8 and 6, respectively. Following Wilkerson *et al.* [7], a "1" on the scale represents a student having no prior knowledge and a "10" represents a student being fully educated in the topic's uses and interworkings.

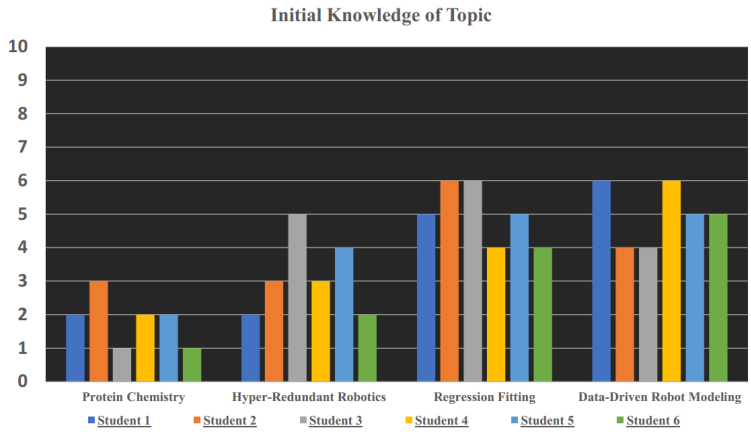


Figure 7: Student survey on their prior knowledge of the topic (i.e., the initial survey).

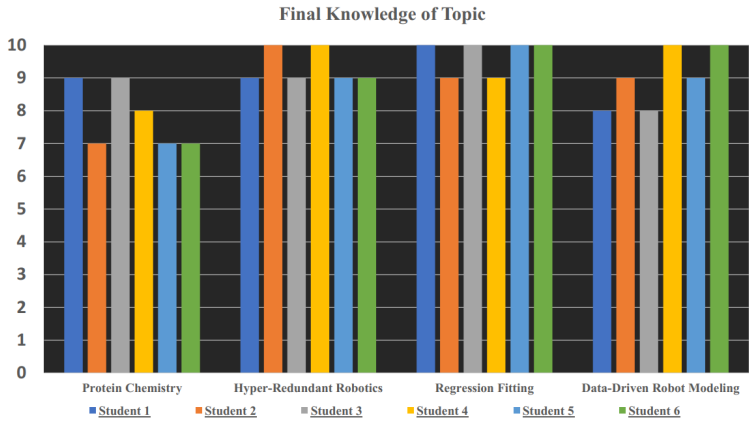


Figure 8: Student survey on their final knowledge of the topic after delivering the project (i.e., the exit survey).

Conclusion

In this paper we presented a multidisciplinary effort between faculty from the Electrical and Computer Engineering Department at the University of Michigan-Dearborn and the Department of Chemistry and Biochemistry at the Worcester Polytechnic Institute (WPI). The project involved students modeling protein folding as a robotic mechanism and studying the problems associated with this complex system from multiple perspectives. In the first implementations of this interdisciplinary PBL effort, we designed a PBL module for groups of eight and six students taking a biochemistry course at WPI and a senior year robotics course at the University of Michigan-Dearborn. The authors comment on challenges and opportunities associated with the presented PBL effort and provided suggestions for disseminating these types of impactful PBL initiatives.

Acknowledgments

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