Communication

Necessity is the Mother of Invention: A Remote Molecular Bioinformatics Practical Course in the COVID-19 Era

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ABSTRACT: The COVID-19 pandemic has brought many challenges to human beings, related to not only health and way of life but also teaching because of the interruption of the standard training at universities imposed by lockdowns. Concerning the latter, the academic community had to reinvent itself, in many ways, to carry on with prepandemic education. This article focuses on the use of modern technology and software to create a virtual, highly interactive classroom where a remote but still hands-on course on molecular bioinformatics can be taught, motivating the university students and helping them learn the course contents without significant compromises imposed by successive lockdowns. We implemented such a virtual hands-on molecular bioinformatics course in the second semester of the 2020/2021 academic year. Furthermore, we compared the learning outcomes with those for the earlier editions of the same course in the pre-COVID-19 era, in which the more traditional teaching method was used where all teaching was delivered with physically present lecturers. The virtual classroom proposed here allowed the students to develop skills close to, although slightly below, those obtained with physically present learning.

KEYWORDS: *Graduate Education/Research, Biochemistry, Chemoinformatics, Laboratory Instruction, Computer-Based Learning, Biophysical Chemistry, Computational Chemistry, Enzymes, Hands-On Learning/Manipulatives, Distance Learning/Self Instruction*
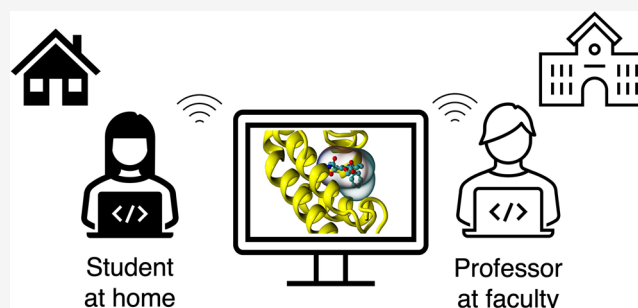
◼ INTRODUCTION

Molecular bioinformatics is a popular course among the students at the University of Porto in Portugal. Biochemists, biologists, bioinformaticians, biotechnologists, and even chemists or physicists choose it every year as an optional discipline to complement their knowledge. We usually cover areas such as homology modeling, molecular docking, virtual screening, and classical molecular dynamics. Homology modeling[1] is a technique to build a three-dimensional structure of a protein from the protein sequence and the 3D structures of other proteins that share a common ancestor with it. Molecular docking[2,3] is a technique that predicts the pose (or geometry of association) of two molecules on the basis of knowledge of the molecular structure of each one. This technique is widely used to predict the geometries of association of protein−ligand and protein−protein complexes, among other molecular complexes. Virtual screening[4−6] is a fundamental technique in the drug discovery process by which millions of ligand molecules are automatically evaluated in terms of their affinity to bind a therapeutic target molecule. We focus on its most common and efficient protocol, receptor-based virtual screening, although other variants are used when the receptor structure is unknown. Receptor-based methods, also called structure-based methods, evaluate the interaction

between the ligand and the receptor, trying to differentiate ligands that bind strongly to the target protein from ligands that do not. The main requirement for a receptor-based virtual screening campaign is the existence of the 3D structure of the target. This can be an X-ray crystallographic, NMR, or cryo-EM structure or even a homology modeling structure. Classical molecular dynamics[7,8] is a technique that allows for simulation of the time evolution of a molecular system by predicting the trajectory of the system's atoms through integration of Newton's equations of motion. Molecular dynamics is used to predict many structural, thermodynamic, and dynamic properties of a molecular system with atomic-level detail.

All of these subjects are directed at enticing the students toward drug discovery, which is presently a very important subject. We have been very successful in the recent past with this course from the point of view that our graduate students often come back for M.Sc. and/or Ph.D. theses on those

subjects. The molecular bioinformatics course that we have devised is primarily hands-on. We deliver the theory as required to solve the problems posed in the hands-on classes, intertwining it with practical protocols that the students follow and execute sitting at the computers of the Computational Biochemistry Laboratory. These classes are informal and lively. Unfortunately, when the SARS-CoV-2 virus struck during the second semester of the 2019/2020 academic year, the students could not attend the classes physically because of the imposed lockdown, and the course professors were not quick enough to respond with an optimal solution that would maintain the same sort of interest on the students' part. Moving from physically present to online teaching in a few weeks unleashed many different strategies with varying degrees of success across the globe. The case of chemistry is particularly challenging because of the central importance of hands-on experimental teaching (for an excellent collection of papers about this experience, see the special issue on Insights Gained While Teaching Chemistry in the Time of COVID-19 that was recently published by this *Journal*[9,10]). In our case, teaching was done through Zoom[11] classes, remote demonstrations, journal clubs, and article writing, which all have their purposes but certainly not the purposes of the University of Porto molecular bioinformatics course—to provide a solid, practical, hands-on component in addition to a theoretical background in bioinformatics in the specific fields of homology modeling, molecular docking, virtual screening, and molecular dynamics and, above all, to provide the student with competencies of independent modeling work and independent learning in this field so that their skills keep evolving and reacting to the vertiginous progress in molecular bioinformatics. Such goals can only be met with a solid practical component in the course.

However, necessity is the mother of invention, and therefore, predicting that a new lockdown would affect the second semester of the 2020/2021 academic year (which did happen!), we decided to reinvent the course in such a way as to deliver the course remotely while in lockdown but still maintain the core objectives, i.e., a hands-on course on molecular bioinformatics topics.

Remote teaching in chemistry has a long history, about which excellent, concise introductions can be found in the literature.[12] It was developed for students who voluntarily chose it because of distance or time constraints. It has been very much rooted in the theory of independent learning.[13] However, none of these circumstances were present in our experience. Our students have never chosen remote learning; they were forced to do it because of the pandemic. In addition, we never intended to change the bioinformatics course into an independent learning course; instead, we tried to keep the course as similar as possible to the physically present course that had been run before the pandemic and will follow after the pandemic through the use of communication technology.

Furthermore, as the practical work of the course is entirely computational (there are no wet-lab experiments in this course), the students can in principle develop the same practical protocols as their colleagues did during the pre-COVID-19 era, even though they do so remotely (i.e., not physically present in the classes), given that appropriate software infrastructure is assembled. This article is an account of how this distance learning course within a physically present paradigm was done and the impact of the remote "computational laboratory" classes on the development of the students' practical skills.

■ METHODOLOGY

During the 2019/2020 molecular bioinformatics course, the students worked from home as required by law during the lockdown period. However, the professors delivered the classes from inside the faculty. This means that each professor was physically present in the Computational Biochemistry Laboratory, delivering the computational class, while the students sat at home working at their laptops.

Like many universities, the University of Porto has a firewall that prevents access to the computers from the outside. Therefore, to access any computers inside the faculty's internal network, the molecular bioinformatics students first needed to install the faculty's VPN software on their laptops. Next, they had to access the actual computers of the laboratory to remotely see their desktops, have access to licensed software, and work as if they were physically present in the room. There is a highly well-priced (for educational institutions) software called *nomachine*[14] that is capable of providing just that, i.e., virtual machines with all the possibilities of the real ones, which we also adopted. Therefore, Zoom, VPN, and nomachine were all that we needed to recreate the Computational Biochemistry Laboratory in the students' homes. We emphasize that the core of our experiment is to improve the interactivity during remote learning and to evaluate whether such improved remote interactivity does improve remote learning and whether it is comparable to physically present classes. From this point of view, the software used is only a means to an end, i.e., to enhance the interactivity of remote learning.

Before starting the course, the professors provided videos to install the VPN and nomachine software and asked the students to follow them at home. Surprisingly, not a single student reported any problem or difficulty installing that software on their laptops.

During the course, in each 3 hour class, the needed theoretical background (half-hour) was taught using Zoom, after which the students started following the hands-on protocols to apply what they had learned.

The course was attended by 34 students of the first year of the M.Sc. programs in Chemistry, Biochemistry, Bioinformatics and Computational Biology, and Applications in Biotechnology and Synthetic Biology. The duration of the course was 42 h spread along the semester. The students were divided into three groups: one included the M.Sc. students in Chemistry and Biochemistry, another the M.Sc. students in Bioinformatics and Computational Biology, and the third the M.Sc. students in Applications in Biotechnology and Synthetic Biology. The division into groups was done to reduce the student/professor ratio to 15 or below. There were no relevant differences in the learning outcomes or interactivity between the groups.

Additionally, it allowed separation of the students with different academic backgrounds. For example, the M.Sc. students in Bioinformatics and Computational Biology and Applications in Biotechnology and Synthetic Biology mostly have B.Sc. degrees in Biology and Computer Science and lack in-depth formation in biological chemistry. Therefore, many concepts imply a deeper understanding of biological chemistry that needs to be taught, explained, or remembered in detail to them but not to the M.Sc. students in Chemistry and Biochemistry, who mostly have degrees in Chemistry,
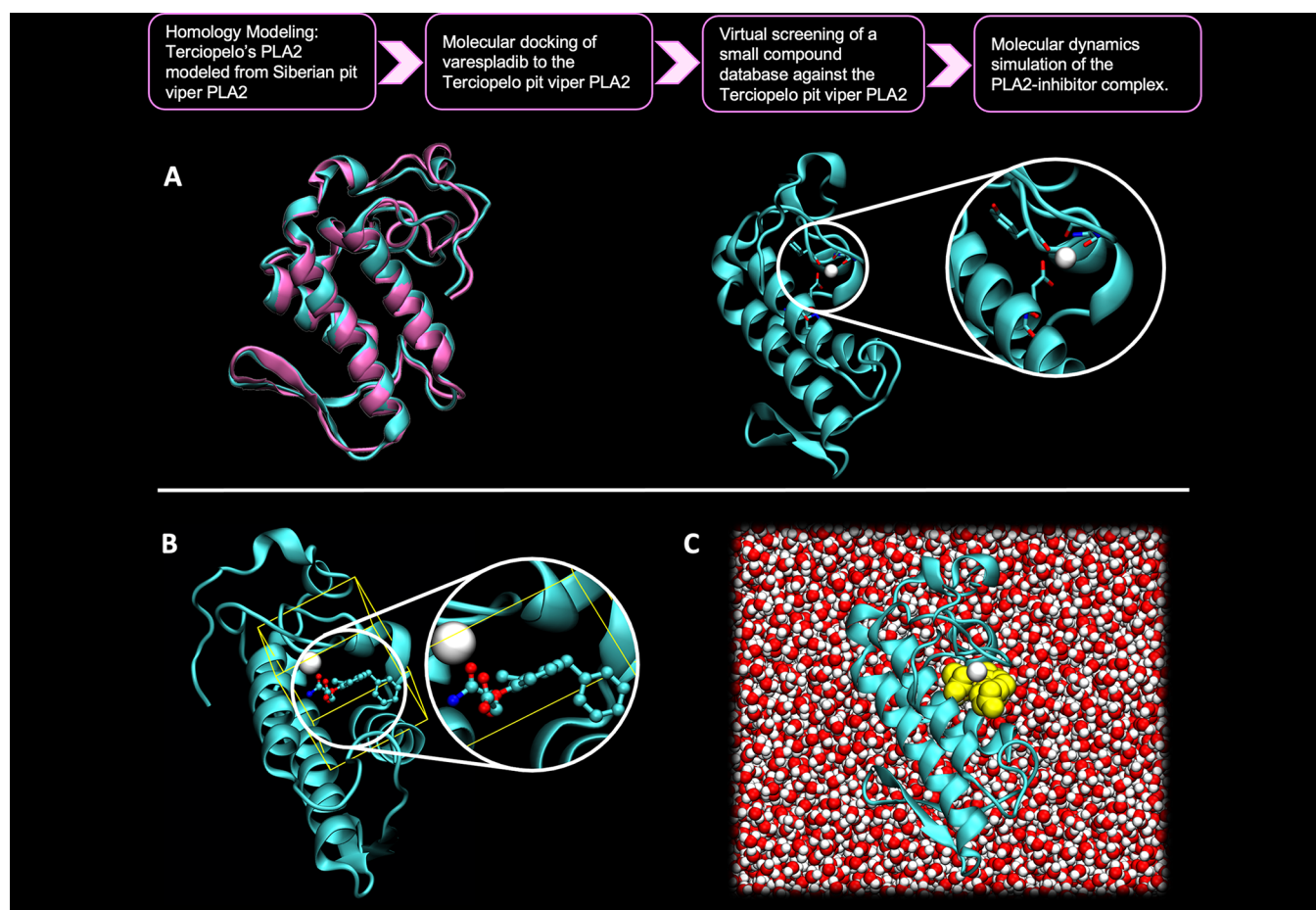
Figure 1. Workflow of the hands-on course. (A) (left) Representation of the 3D structure of Terciopelo pit viper PLA2 (magenta) modeled from the Siberian pit viper PLA2 structure (cyan) using the software SwissModel. The two structures are superimposed. (right) Detail of the active site of the Siberian pit viper PLA2 with the Ca^{2+} ion cofactor shown in white and the coordinating residues as sticks. (B) Docking of varespladib in the active site of Terciopelo pit viper PLA2 with the software vsLab.[3] The docking box is shown in yellow. (C) Molecular dynamics simulation of the Terciopelo PLA2−varespladib complex in aqueous solution to analyze the enzyme−inhibitor interactions. The simulation was done with the software package Amber.[17]

Biochemistry, Pharmaceutical Sciences, or related fields with excellent preparation in biological chemistry.

The entire course was delivered separately to the three groups of students.

■ RESULTS AND DISCUSSION

The practical component of the course focuses on a single problem: the discovery of new therapies against snakebite. Pursuing this goal leads the student to develop the desired molecular bioinformatics skills to solve that central problem. Moreover, the fact that the work focuses on an orphan disease that provokes immediate emotion in almost any individual motivates the student, who nurtures the hope of using science to alleviate the suffering of humanity.

The core subject of the course is a central toxin in the venom of almost all venomous snakes: the secreted enzyme phospholipase A2 (PLA2) (Figure 1). The specific snake studied is the Siberian pit viper (*Gloydius halys*), which was chosen because of the quality of its existing PLA2 crystallographic structures.[15]

In the first module of the course, on homology modeling, the student uses the Siberian pit viper PLA2 structure to model the Terciopelo viper (*Bothrops asper*) PLA2 structure, which is of fundamental medical importance in Central and South America (Figure 1A). First, the molecular modeling software SwissModel[16] is used. This research-level software, accessed through an open web server, is rigorous, pedagogical, and deep without being cryptic, and it has an excellent graphical interface. In the authors' opinion, it is one of the best modeling software for classroom use, and it is free, which facilitates subsequent independent usage by the student. The modeled structure is subsequently optimized with molecular mechanics software (Amber[17] in our case).

The structure of Terciopelo pit viper PLA2 has been obtained by X-ray crystallography and reported in the literature.[18] Thus, the students can compare their results with the experimental ones. The similarity is usually excellent, which allows the students to validate the predictive method by themselves without having to rely on the results of others, strengthening their self-confidence and confidence in molecular bioinformatics methods.

The second module aims at docking a clinically very promising inhibitor, varespladib, in the active center of Terciopelo pit viper PLA2. It is a competitive inhibitor under clinical trials for use against snakebite envenoming. The software used was vsLab, developed in-house, which combines the Autodock4 software[19] and the VMD molecular visualization software[20] in a graphical environment where molecular

Table 1. Organization of the Course, Including the Time Spent in Each Module, the Learning Outcomes, and the Software Used in Each of Them

Module	Hours	Learning/Pedagogical Goals	Software	Availability and Platform
Homology modeling	8	Learn how to model a protein structure from its sequence and evaluate the predicted structure's quality and reliability	SwissModel	Webserver, freeware
			VMD	Win/macOS/Linux, freeware
			Amber	Win/macOS/Linux, commercial (Gromacs is a freeware alternative)
Molecular docking	10	Learn how to model the structure of a protein−ligand complex and evaluate the quality and reliability of the predicted structure	vsLab	Win/macOS/Linux. Freeware
			VMD	Win/macOS/Linux, freeware
			Autodock4	Win/macOS/Linux, freeware
Virtual screening	12	Learn how to screen a ligand database for high-affinity binders of a target receptor and evaluate the quality and reliability of the predicted binders	vsLab	Win/macOS/Linux, freeware
			VMD	Win/macOS/Linux, freeware.
			Autodock4	Win/macOS/Linux, freeware
Molecular dynamics	12	Learn how to generate an ensemble of protein−ligand structures and analyze its time-dependent average properties	Amber	Win/macOS/Linux, commercial (Gromacs is a freeware alternative)
			VMD	Win/macOS/Linux, freeware

Figure 2. A professor helps a student to perform docking calculations. The student is working from home on computer LQT09. The figure also shows the sessions of the students at computers LQT07−LQT10. The professor moves from computer to computer in the classroom, working directly with the students during their computer sessions. Communication is made through Zoom (panel situated on the right-hand side wall of the lab, hidden in the photograph); the students can hear the professor from any place in the classroom. The laboratory dynamic is very much the same as during the pre-COVID-19 era, with the difference that the students sit at home!

docking and virtual screening can be performed intuitively and pedagogically. vsLab was explicitly developed for classroom use and is free of charge, just like Autodock4 and VMD. After performing molecular docking, the students analyze the interactions between varespladib and the enzyme (Figure 1B).

In the third module, the student moves on to virtual screening of high-affinity ligands of PLA2 within a small library of bioavailable compounds to find new PLA2 competitive inhibitors. The vsLab software is again used to perform the virtual screening within its pedagogical and intuitive graphical platform. The compound library is obviously too small for scientific standards but sufficient for students to learn the basic concepts of virtual screening. It consists of varespladib, four high-affinity inhibitors taken from the open binding database BindingDB,[21] and 45 compounds randomly taken from the ZINC compound database,[22] which is presently the most widely used open compound library for virtual screening. Because of the rarity of high-affinity inhibitors, the result of a random choice of inhibitors is that all or almost all of them will

be inactive. Therefore, we are left with a library of five active compounds and 45 inactive compounds (10%/90%) on which the virtual scan is performed. In the end, the students analyze the results, determining how well the method can identify the active compounds within the outnumbering inactive compounds and calculating the enrichment factor of the technique.

Finally, in the fourth and last module, the students choose the top-scoring inhibitor from the virtual screening campaign and perform a classical molecular dynamics simulation of the enzyme−inhibitor system in an aqueous solution (Figure 1C). The simulation is aimed to assess the stability and completeness of the previously determined enzyme−inhibitor structure with a more accurate technique involving conformational sampling. The professor provides the parameters for the ligand. The Amber software package is used, which also has an intuitive graphical user interface. This concludes the molecular bioinformatics course. The course protocol is freely available for download.[23] The organization of the course, its goals, and the software used are summarized in Table 1.

Table 2. Summary of the Strengths and Weaknesses of the Three Course Methods Discussed in This Work

Course Method	Strengths	Weaknesses
Physically present	Full interaction with the student; communication is straightforward	Difficult to implement in cases such as a pandemic or for courses provided to students that are very much geographically spread
	Practical-work problems are straightforward to solve and questions are easier to answer, as both the professor and student work on the same computer	Expensive, or sometimes not possible, for courses provided to international participants
	Nonverbal language helps the professor realize whether the student understands the work	
Remote with computer sharing	Straightforward to implement when geographical proximity is a problem or during a pandemic/lockdown	The nonverbal language is lost, making perception of the student's understanding more difficult.
	Reasonable interaction with the student	Communication through Zoom is less clear and lively than being physically present; the student loses focus more easily
	Easiness to understand and correct practical-work problems by intervening in the student's session	Solving practical-work problems is less straightforward
	Software performance is independent of the student's hardware	Internet connection stability is a vulnerability
	No need to install and manage scientific software on the student's computer	
Remote with screen sharing	Straightforward to implement when geographic proximity is a problem or during a pandemic/lockdown	Difficulty with understanding and correcting practical-work problems
	Reasonable interaction with the student	Software performance depends on the student's hardware
		Need to install and manage scientific software at the student's computer
		Internet connection stability is a vulnerability

By the end of the course, the students have acquired solid skills in molecular bioinformatics within a problem-centered learning paradigm, focused on a single problem, a central goal throughout the semester.

The fundamental difference of the remote technology we propose here is that the professor, who is physically present in the lab, shares the computer with the student and follows at the desktop of each computer everything that the students do remotely in their homes without the need for individual screen sharing, which may be troublesome for a class of this size (i.e., 15 students).

There are two significant advantages of computer sharing over screen sharing in an undergraduate course. The first is technical: computer sharing avoids the need for local installation of complex scientific software, much of which is licensed, and permits more homogeneous software performance because the differences in the students' experiences depend almost only on the Internet connection and not on the quality of the computer. Even though developing administration skills is important,[24] it might be an additional complexity in the unprecedented pandemic era.

The second is technical/pedagogical: computer sharing implies the existence of two screens, two mouses, and two keyboards acting at the same computer session, which permits the professor to take control over the session and intervene in the student's software session with full capabilities and without significant time delays to correct mistakes or help in the many computational problems the students face while developing the protocols, something that is very difficult to do only with screen sharing (Figure 2). The teacher's inability to control the student's session through the mouse and keyboard in computational chemistry courses was noted before as a limitation of distance learning,[25] and with our implementation this has been overcome. Tasks like rotating molecules, opening menus, and correcting text become straightforward with computer sharing but are slow and troublesome with screen sharing.

This simple aspect differentiates between a fully interactive, almost physically present-like course and a traditional remote course. In addition, eye and voice communication with the students can be constantly made via Zoom or any other reliable cloud platform for video and audio conferencing.

This level of interaction allowed the students to complete all of the protocols. After the students' evaluation, we concluded that the competencies they acquired were very close to those obtained by students that had the entire physically present course in the pre-COVID-19 era. However, limitations were still encountered, emphasizing that nothing replaces direct student−teacher contact. Communication is more straightforward when two persons are physically together than remotely. This is felt more when the teacher needs to explain and transmit complex concepts or help students correct errors. Table 2 summarizes the advantages and disadvantages of each of the discussed teaching strategies.

As the protocol is designed to be finished within the 42 h course, there is flexibility to recover delays in the next weekly class. Nevertheless, the students can still access the computers in the laboratory and work after class time, although without the teacher's support.

The evaluation of the students is a continuous assessment scheme with a final exam at the end of the course. The continuous assessment evaluates the students' performance in solving the protocols during the course. In addition, the professor checks the work of the students one by one in every class and discusses the work with the students, asking questions and evaluating the quality of the answers. Altogether, continuous evaluation provides a suitable means to measure student performance on the practical work. The distribution of students' marks at the end of the remote course provided by the continuous assessment was near but slightly below that of the previous physically present course in the pre-COVID-19 era before correction through normalization. The average ± standard deviation of the continuous evaluation marks in the remote course was 15.5 ± 2.0 (the minimum grade for approval is 10, and the maximum grade is 20), which was lower than that for the physically present course (17.1 ± 1.7). The marks of the remote course were normalized to fit the ones of the physically present course to correct the negative consequences of the COVID-19 pandemic. This means that even with all of our efforts, the lack of being physically present affected the development of practical skills.

Furthermore, when the students of the 2019/2020 academic year chose to undertake their M.Sc. theses with us, we were able to confirm while supervising them that their skills were well-developed, although slightly below the average of their colleagues of those academic years in which the teacher was physically present. However, the fully interactive course described in this technical report still provided very satisfactory hands-on competencies to the students.

The student/professor ratio of 15 was not ideal for the present course. There were times when the student had to wait longer than desired for the professor's assistance with the practical work. Computational protocols are prone to minor technical problems that the students find difficult to solve on their own, particularly in the first weeks of the course. Typical examples include difficulties in executing the tasks correctly using the Linux operating system and errors introduced in the complex input files of the molecular dynamics software. The software error messages are not straightforward to interpret, and the student has to deal with many errors and error messages that often need the professor's assistance.

Additionally, the continuous assessment is less enriching with a high student/professor ratio. On several occasions, we have taught with smaller student/professor ratios and concluded that the ideal ratio for this course is 10 or below. Unfortunately, however, the University of Porto does not have the resources to allow for such low ratios regularly.

Online courses have a long history. Almost every bioinformatics software has online tutorials, which the student can follow independently to become proficient. The software used here is no exception. Autodock4,[2,19] VMD,[20] Swiss Model,[16] and Amber[17] all have impeccable and pedagogical online tutorials that are freely available. However, these tutorials are not trivial to follow outside a research environment because of the typical lack of hardware facilities and software availability. The teaching of molecular bioinformatics faces intrinsic difficulties across the globe for the same reasons, in particular in universities with fewer resources, even unrelated to the COVID-19 era, such as a lack of computer classrooms that are adequate to run bioinformatics software because of either hardware limitations or the absence or difficulty of managing advanced specific software and Linux operating systems.[24,26] These difficulties might be overcome, at least in part, by the use of web-based software. However, the availability of free, pedagogical web-based software for bioinformatics is limited, at least for some of its areas. These difficulties are aggravated by online teaching insofar as the course relies upon the students' equipment, creating further obstacles and inequalities in the learning process.[27]

The subject of teaching bioinformatics courses in the COVID-19 era has been addressed before. At the core of most distance-learning methods is overcoming the above-mentioned fundamental problems. For example, Ramírez-Sarmiento and co-workers described an elegant scheme for overcoming them through cloud computing.[28] At the core of their protocol is a cloud-based system in which the students access all software and tutorials through their computer's web browser and run the calculations using cloud computing resources instead of their resources, supported by the teacher via Zoom sessions.

We favored using our physical computing lab instead of a cloud-based lab because of the intense interactivity that sharing the student's computer session provides, which is the decisive advantage of the method proposed here and the core of our approach—it is what makes our approach different from the preceding ones. A computer-session-sharing system allows complete and almost real interactivity between teacher and student rather than the performance of protocols in a cloud-based environment supported by the teacher via a Zoom session. Our system allows for the development of bold protocols where the student's imagination and originality can be unleashed because of the continuous online support the teacher provides in real-time. There is evidence that extensive interactivity is fundamental for the learning process and for keeping the students motivated. For example, a study involving COVID-19-imposed remote learning in third- and fourth-year students of a 5 year program in Chemistry, Environment, and Chemical Engineering in France showed that the most interactive strategies had the highest preference among the students and, conversely, the less interactive solutions were the most disliked.[12]

The computer-sharing system has vulnerabilities, as it depends on the student and institution connection speed. However, the author's institution checked whether all students had suitable conditions (computer, internet connection) to attend the remote classes and took measures in the few cases where these conditions were lacking. In the case of this course, such problems did not emerge, fortunately.

In general, the internet connections were fast enough for the work to run smoothly and stably. Overall, the experience was excellent. Although it was not quite the same as being in the classroom (e.g., there was always a tiny lag when moving molecules), it was perfectly manageable.

Our experience opens new horizons for the remote teaching of hands-on computer courses, in particular in the field of molecular bioinformatics. Physically present teaching is the unrivaled method to achieve a high level of proficiency. However, there are circumstances where it is not practical, viable, or even intended to do so, such as the courses at Open University, courses targeting international students with fewer resources to move abroad, and courses open to students of many backgrounds in a large number of countries. New ways of distance learning will always find their public and broaden innovative teaching approaches. This report is a validated step in this direction.

◼ CONCLUSION

We have reported a remote hands-on course on molecular bioinformatics within a highly interactive environment. The professor and the students use and share the same computer sessions, simultaneously using the mouse and keyboard to command the same software applications. This level of interaction leads to the development of skills that are close to (but still not as good as) those obtained with physically present teaching. Our protocol opens ways to implement distance-based hands-on courses when needed with minimal loss of learning quality.

It was fulfilling to be able to offer a course to our students and teach it as a hands-on course as per usual. We could not have done it without all of the nearly open software that many people generously share, helping to overcome the difficult times in which we are living.

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Notes

The authors declare no competing financial interest.

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