Teaching enzyme catalysis using an open source framework for interactive molecular dynamics in virtual reality

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The reemergence of virtual reality (VR) in the last few years has led to affordable commodity hardware that can offer new ways to teach, communicate and engage with difficult concepts, especially those which involve complicated 3D motion and spatial manipulation. In a higher education context, these immersive technologies make it possible to teach complex molecular topics in a way that may aid or even supersede traditional approaches such as molecular models, textbook images, and traditional screen-based computational environments. In this work we describe a study involving 24 third-year UK undergraduate chemistry students who undertook a traditional computational chemistry class complemented with an additional component utilising real-time interactive molecular dynamics simulations in VR (iMD-VR). Exploiting the flexibility of an open-source iMD-VR framework which we recently described,[1] and building on recent work where we demonstrated the ability to use this framework to run 'on-the-fly' density functional theory in VR at interactive speeds,[2] we designed three tasks for students to complete in iMD-VR: (1) interactive rearrangement of the chorismate molecule to prephenate using forces obtained from 'on-the-fly' density functional theory calculations; (2) unbinding of chorismate from the active site chorismate mutase enzyme using molecular-mechanics forces calculated in real-time; and (3) docking of chorismate with chorismate mutase using real-time molecular mechanics forces. A survey indicated that most students found the iMD-VR component more engaging than the traditional approach, and also that it improved their perceived educational outcomes and their interest in continuing on in the field of computational sciences.

INTRODUCTION

The teaching of chemistry inherently relies on models to represent the underlying molecular processes, structures, properties, interactions, behaviors, and physics which drive phenomenological chemical change. In a chemistry context, the importance of models derives from the fact that atomic level molecular changes are usually not possible to observe directly. In constructing a model, the choice of representation depends on the size and complexity of the molecular structure being examined; as complexity grows, it is increasingly important to have compact models for abstracting the structure to make it intelligible. Early in their chemical education, students are taught to use Lewis structures as molecular representations, which are shortly thereafter replaced by skeletal structures as the molecules become more complex. In typical first-year undergraduate classes, students are introduced to new representations, such as Newman projections, which are designed to capture 3D information in 2D.[3] In the teaching of molecular symmetry, it is common to rely on physical 3D molecular model construction kits, which can be used to intuitively illustrate symmetry operations in a fashion that engages 3D spatial reasoning. In structural biology, coarse representations called ribbon or cartoon diagrams (also called Richardson diagrams)[4] are used to help simplify the visualisation of protein secondary structure.

All these representations are useful in certain contexts, but they share a common drawback insofar as they lack time resolution. As a result, then often lack a connection to the continuous motion which characterizes molecules, obscuring the critical role of dynamics and entropy in understanding chemical thermodynamics. University-level chemistry tends to be taught using static, time-independent representations such as skeletal structures. When molecular dynamics is directly tackled, it is often described in the form of mathematical representations. For example, the partition function, which forms one of the key concepts in statistical mechanics and transition state theory, is an integral over all the different ways that a molecule can translate, rotate, and vibrate. Similarly, entropy is fundamentally connected to a molecule's flexibility. However, understanding the microscopic basis for dynamics and entropy are difficult concepts for students to grasp, which may be a consequence of the fact that the bulk of chemistry teaching focuses on static molecular representations. An approach which incorporates dynamical representations has the potential to make these difficult concepts easier to convey in an intuitive way.

New technological paradigms have been adopted in recent years to move beyond static representation approach to university-level chemical education,[5-6] offering alternative ways for students to understand molecular science outside the wet lab. For example, computational chemistry can provide students with the ability to watch screen-based movies of molecular motion or build structures for subsequent post-processing using specialist codes, as well as introducing them to the power of computational workflows for understanding molecular processes. However, few tools enable students to

intuitively interact with the rigorous 3D dynamics that governs molecular motion. In the past few years, research within psychology and neuroscience has shown that multi-sensory processing increases attention.[7] Inspired by findings like these, our group has actively been developing immersive technologies for enabling multisensory perception of nanoscale dynamics, exploring perceptual channels beyond vision, including audio, touch, and proprioception.[8-10] In this work, we illustrate the use of research-grade simulation tools to enable interactive molecular dynamics simulations in VR (iMD-VR), which can be used to create multi-person interactive dynamics environments to help students learn about molecular motion and dynamics. In utilizing state-of-the-art tools like those described herein, students not only increase their understanding of chemical structure and dynamics, but they also gain fluency in using sophisticated visualization tools, providing benefit in the form of transferable skills and computer literacy which is practically useful beyond their university education. As a research field, computational chemistry is increasingly essential, providing insight into molecular physics, structural biology and materials science, and driving progress in areas such as drug design, catalysis and biochemistry,[11-14] where it routinely provides molecular-level insight into experimental results, and enables the investigation of areas which are difficult to study using standard laboratory and analytic tools.[15]

Important challenges arise in teaching computational chemistry techniques and tools during undergraduate degrees. Because of the complexity of the field, most courses allot little time to the teaching of these tools as well as the required computer literacy. Moreover, given the wide range of domains where computational tools can be applied, it is not often possible to give more than a cursory introduction to some of the tools and the physical insight that they can provide. For example, training in one area, such as classical molecular dynamics using a forcefield approach, does not necessarily provide students with the tools to tackle other computational chemistry areas, such as electronic structure calculations. The difficulty is compounded by the fact that many computational tools are legacy scientific codes, and therefore offer a user experience which feels dated compared to the sorts of apps and media experiences to which students are often accustomed. For example, problems arise from the fact that molecular dynamics packages often require students to deal with bespoke (and often dated) input formats and bash scripting for the first time. Many computational chemistry codes are not user-friendly, requiring specialist training to acquire familiarity with each code and its associated jargon, in part because several popular molecular dynamics simulation packages were designed prior to the availability of modern human-computer interaction technologies (CHARMM[16] for example can trace its origins back to the time of FORTRAN punch cards). Over the past several years, we have run computational chemistry classes teaching students how to use these powerful but highly specialised legacy tools, and we have often found that it can be difficult to convince students that learning to use such tools is preparing them to cope with the workflows of the future.[17-19]

Most common molecular viewer interfaces used for teaching chemistry require the user to interact with molecules through the traditional 2D interface. For complex 3D structures, such interfaces have clear limitations. The more popular molecular visualisers of the last 30 years provide a 2D perspective on what are naturally 3D structures and processes, and also suffer co-location issues.[20] In a recent paper by O'Connor *et al*, we described this so-called 'co-location problem' in detail.[21] Briefly, perfect co-location arises when the interaction site in physical space is perfectly aligned with the interaction site in digital virtual space. For example, touchscreens achieve perfect co-location in 2D because the interaction site in physical space is identical to the interaction site in virtual space. This is a significant reason why children at a very young age find it straightforward to navigate a touchscreen. Programs such as Gaussview[22] or VMD[23] which are primarily built to utilize a mouse and screen interface do not represent co-located forms of interaction. For understanding and manipulating complex 3D structures, the constraints of this type of interaction can lead to unintended motions (e.g., moving an atom out of a molecular axis by accident) and can be frustrating for students.

Open source iMD-VR represents an intuitive set of computational research tools that solve the problem of 3D co-location, as shown in the video at vimeo.com/244670465. In this article we have utilized iMD-VR in traditional higher-education laboratory modules to train students in computational approaches to molecular science, and also as a compliment to understanding the fundamentals responsible for observations made during wet-lab work. We demonstrate how our open-source iMD-VR framework can be used to aid teaching about molecular interactions, molecular forces, enzymology,[24] mechanism generation, and protein-ligand docking. We show that students have a favorable response to this technology,[19, 25] which enables them to learn about dynamical aspects of molecular behavior they often find difficult to understand. The iMD-VR software we use for the real-time dynamical interactivity, Narupa,[26] is a state-of-the-art open source project[1] which enables multiple participants to cohabit the same iMD-VR environment to 'reach out and touch' real-time research-quality molecular dynamics simulations, 'feeling' their dynamical responses, and manipulating their motion in real-time. The source code is available at gitlab.com/intangiblerealities[26] along with a stable beta executable at irl.itch.io/narupaxr.[27] Narupa builds on the capabilities of the proof-of-principle framework which we recently described,[21] including several key upgrades, enabling users to: (1) cohabit the same iMD-VR environment with other users; (2) set up their own quantum chemistry or molecular mechanics simulations using a flexible force API;[1-2] (3) run the VR client and force server on local networks, avoiding problems associated with network latency; and (4) access a range of tools (e.g., a flexible selection interface) which streamline the use of iMD-VR for complex applications. In designing Narupa, we have actively engaged with designers, artists, and human-computer interaction (HCI) experts, in order to create a framework which not only has scientific utility, but which represents best HCI practice, and which is aesthetically compelling.

At present, there are a wide array of relatively distinct technologies which are often referred to as 'virtual reality', and which can sometimes be a source of confusion for those unfamiliar with the area. Broadly speaking, different VR technologies can be distinguished according to the level of immersion they offer. VR pioneers such as Jaron Lanier have emphasized this point, highlighting the fact that frameworks which are often referred to as 'virtual reality' enable

participants to do little more than "just looking around in a spherical video".[28] Lanier, along with other HCI researchers, has made a point to distinguish those technologies which afford reaching out to touch the virtual world versus those that do not: *If you can't reach out and touch the virtual world and do something to it, you are a second class citizen within it... a subordinate ghost that cannot even haunt.* Mel Slater schematizes different VR technologies *according to the level of immersion which they offer*[17] – i.e., any VR technology's level of immersion can be defined relative to another VR technology by determining whether its affordances enable it to simulate in principle (or not) the experiences enabled by an alternative VR technology. So a specific VR technology A is 'more immersive' than another VR technology B so long as A could be designed (in principle) to simulate the experience of using B.

Our efforts to date have focused primarily on the HTC Vive, because its design affordances enable one to 'reach out and touch' simulated realities like 'on-the-fly' molecular physics. According to Slater's definition, the HTC Vive (which utilizes sensors on the headset and controllers to allow real-time motion tracking) is amongst the most immersive commodity frameworks, in the sense that it could be designed to simulate the vast majority of other VR technologies (e.g., a CAVE, a Samsung Gear headset, a Playstation headset, etc.), but not *vice versa*. Our software implementation permits multiple individuals to simultaneously cohabit the same simulated virtual reality space, enabling collaborative classes to be run using a room-scale setup in which students can walk around, interacting with one another and with simulated molecular objects in the virtual world, all of which is perfectly co-located in 3D. We believe that this immersive framework, which enables molecular interaction with atomically resolved precision, is more effective for teaching complex concepts than less immersive frameworks.

ENZYME CASE STUDY

Over the last 8 years, we have run a class for 3rd year chemistry majors at the University of Bristol, which uses the CHARMM[16] molecular simulation package to teach students about the rearrangement of chorismate to prephenate, first in vacuum, and then catalysed by chorismate mutase. Chorismate mutase is a biosynthetic enzyme that is part of the pathway that results in the production of tyrosine,[29] and is found in various non-animal species. The chemical mechanism of the reaction involves a Claisen rearrangement, illustrated in Figure 1, and is characterized by distinct conformational changes in the ring as the reaction progresses from reactant to transition state, and then to product. Progress along the reaction coordinate is straightforward to track visually by inspecting the cleavage of the ether bond as well as changes in the ring conformation. Transition state stabilization is an important factor in catalysis in this enzyme and the stabilization provided by the enzyme along the reaction coordinate can be calculated using standard quantum mechanical/molecular mechanical (QM/MM) techniques.[15, 30-36] By comparing their own results to those of their peers, the students are able to relate the degree of transition state stabilisation to the conformation of the enzyme, and thereby gain insight into the role that transition state stabilization plays in catalysis.

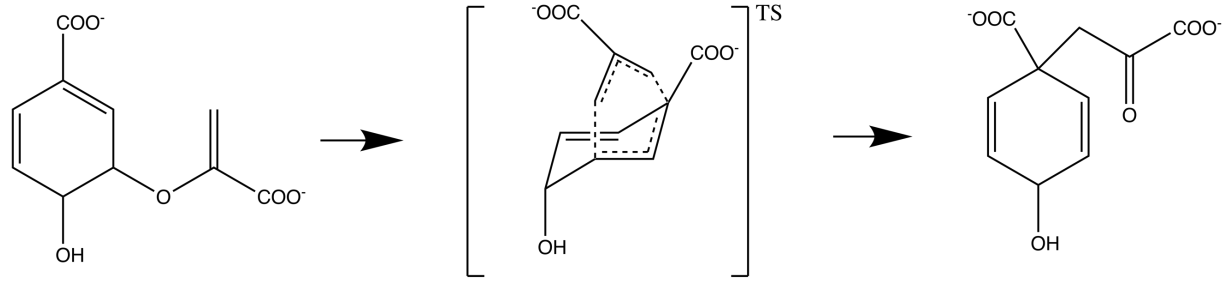

Figure 1: Reaction scheme for the rearrangement of chorismate into prephenate

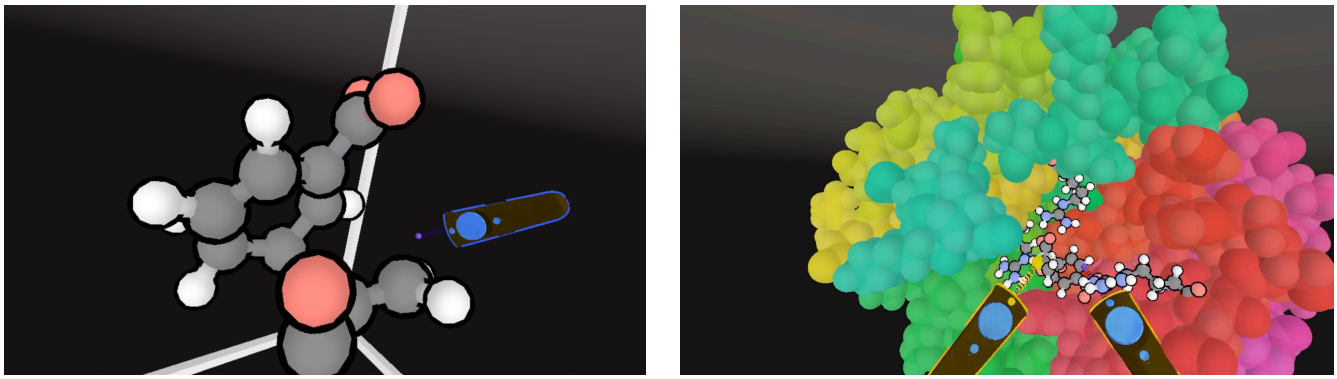

Figure 2: A student's first-person view from within Narupa's iMD-VR environment as they interact with the alpha carbon with respect to the ring carboxylate of chorismate to perform the Claisen rearrangement. Right: A student reaching into chroismate mutase with two controllers

DESIGN OF THE CLASS

Our hypothesis when designing this education experiment was that iMD-VR would enable better learning outcomes and a better experience of computational molecular modelling and simulation techniques. Our experience over the last several years has shown that a number of students found the standard CHARMM/VMD class frustrating due to a lack of familiarity with its text-based input syntax. We integrated iMD-VR into the aforementioned third-year undergraduate computational chemistry class, which is conducted over two days. The intended learning outcomes for this class are that the students should understand: (1) the importance of protein-transition state stabilization for biomolecular catalysis, (2) how to calculate the stabilisation energy provided by the enzyme; and (3) how enzyme conformational changes affect reactivity. The class also aims to teach the students the difference between quantum mechanical (QM) and molecular mechanical (MM) calculations and how these methods are combined in a powerful hybrid method called QM/MM (recognised in the 2013 Nobel Prize).[37-38] The wider skills which we intend the students to learn during this class include an understanding of: (1) the command prompt (bash), (2) the CHARMM molecular dynamics program and its input syntax, and (3) the use of the visualisation program VMD.[23, 39] Through introducing iMD-VR, we set out to understand the utility of a new simulation, interaction, and visualization technology for studying reactive conformations of chorismate and chorismate mutase, in comparison to the more traditional CHARMM/VMD approach we have utilized over the years.

The CHARMM/VMD lab is run in a standard computer room, equipped with PCs, with one post-doctoral demonstrator managing two postgraduate assistants who all can answer questions and deal with technical issues as they arise. For the purposes of this experiment, we ran the iMD-VR component in a separate room, to ensure that each student's iMD-VR starting point was similar. The students were taken to the iMD-VR room individually and introduced to the controllers. We described to students how the buttons on the real-world controls corresponded to actions in the iMD-VR simulation. For this study the students only needed to operate each controller's 'trigger', enabling them to exert a force on a targeted atom, and manipulate its dynamics and motion. Each student was then provided a brief overview of the series of chemical tasks that they would be conducting, and given up to ten minutes in iMD-VR to accomplish these tasks. Each student was offered an opt-out and nausea warning before they attempted the iMD-VR section, although zero students opted out and zero reported any discomfort. The three tasks which we instructed the students to undertake are shown in a video available at vimeo.com/320188113, and included the following:

A. Claisen rearrangement of chorismate to prephenate via a cyclic transition state, as shown in Figure 1 and part A of the supporting video. The reaction was conducted in a vacuum using real-time forces obtained from a semi-empirical quantum mechanical method called density functional theory tight binding (DFTB).[40] This technique was chosen because it is one of the fastest quantum chemistry methods available, and so allows students to undertake real-time interaction with the molecules to simulate chemical reactions.
B. Removing the chorismate substrate from a setup in which the chorismate was bound to chorismate mutase, as shown in part B of the supporting video. In undertaking this unbinding procedure, students were instructed to minimise perturbation to the enzyme's structure by exercising precision and care, so as not to destroy protein secondary structure in the vicinity of the active site. For this purpose, we highlighted in advance three arginine sidechains which we know to be important for the binding of chorismate (shown in the right hand panel of Figure 2). This allowed us to highlight to the students those residues which required particular care.
C. Starting with chorismate unbound to chorismate mutase, students were asked to dock chorismate into the chorismate mutase active site so that it remained in a bound pose. An example is shown in part C of the supporting video. Again, part of the challenge here is to utilize sufficient care and precision so as to not disrupt the secondary structure of the protein by not introducing too much energy into the chorismate molecule along its docking trajectory.

After all the students had completed the iMD-VR component and the CHARMM component, they were required to fill out a 22-question digital questionnaire about their experiences which was integrated into an online form hosted on the Bristol School of Chemistry Digital Laboratory Manual (DLM).[41] The 22 questions were designed to gauge the student sentiment regarding the more traditional CHARMM/VMD approach compared to the iMD-VR component, and also to assess their prior experience with gaming, VR and CHARMM/VMD. Twenty of the questions asked gathered responses using a Likert scale and the final two (Q21 and Q22) collected long-form feedback.

SIMULATION SETUP

The simulations experienced (and driven) by the students used the following computational and physical conditions: Task 1 was run with a temperature of 300 Kelvin and a time step of 0.25 fs. The MIO parameter set[42] was used in combination with a version of the DFTB+ code[40] that was modified to act as a library callable from within NarupaXR, taking advantage of its flexible API. Tasks 2 and 3 used a temperature of 300K, a time-step of 0.50 fs and the amber ff99SB forcefield.[43] A Berendsen thermostat[44] was used throughout to maintain the target temperature. The graphical representation of the enzymes was chosen to remove some of the complexity from the secondary structure by using a space-filling Van der Waals representation for the backbone of the enzyme, with only the chorismate and three arginine resides shown in an all-atom representation, as shown in Figure 2 and parts B and C of the supplementary video. Detailed installation instructions for NarupaXR which include example enzymatic systems can be found at https://irl.itch.io/narupaxr.

RESULTS AND DISCUSSION

The survey results collected from the students are presented below, with the raw data included in the SI. We have selected the most significant results for graphical display and discussion in the main body of the text.

		CHARMM/VMD		iMD-VR	
Q#	Question	Median	Interquartile range	Median	Interquartile range
1	I enjoyed using [Platform]	2	1.00 - 3.00	5	4.00 - 5.00
2	I found [Platform] simple to use	2	1.00 - 3.00	4	4.00 - 4.25
3	[Platform] improved my understanding of molecular structure and movement	3.5	3.00 - 4.00	5	4.00 - 5.00
4	[Platform] helped me understand the difference between quantum mechanical and molecular mechanical calculations	2	1.00 - 3.00	4	3.00 - 4.25
5	When answering the marked lab quiz [Platform] played a dominant role in my visual recall of the enzyme	3	2.00 - 4.00	3	3.00 - 4.00
6	Visualising Chorismate/Chorismate mutase in [Platform] aided my understanding of the reaction	3.5	2.00 - 4.00	4	4.00 - 5.00
7	Working with [Platform] has increased my interest in working with the computational sciences	2	1.75 - 3.25	4	3.00 - 4.25

Table 1: Median values and interquartile ranges that show the 25% and 75% quartile ranges, where [Platform] is either CHARMM/VMD, or iMD-VR. This data is represented further in Figure 3.

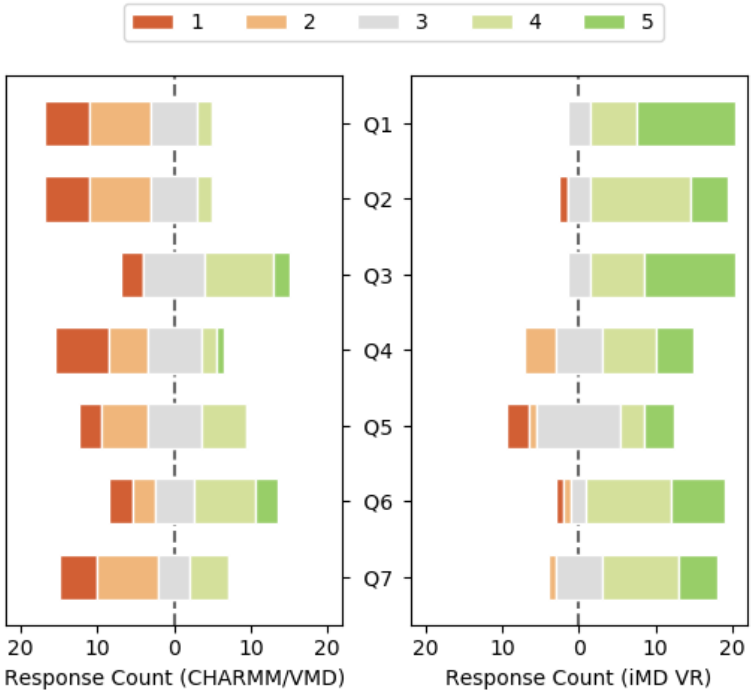

Figure 3: A divergent bar plot showing a comparison of student attitudes towards the CHARMM/VMD and VR platforms. Responses are given on a 5 point Likert scale, where 1 represents strong disagreement and 5 represents strong agreement. Plots that are skewed to the right (and green) are answers in agreement to the question, whereas questions skewed to the left (and red) of three indicate disagreement. The left-hand plot shows the results for CHARMM/VMD and the right-hand plot shows the results for iMD-VR

Prior experience

We specifically set out to assess whether the prior experience of students in iMD-VR and computational chemistry correlated with their preference for either platform. The participants reported not having any familiarity with VR, on a scale of none (1) to extensive (5). The median value obtained was 1, with an interquartile range of 1-2. Their reported familiarity with computational chemistry was higher, with a median value of 2.5 and interquartile range of 2-3. The survey asked the participants if they agreed with the statement "I play video games in my spare time". This question aimed to gauge their overall familiarity with computer games, which we suspected could prime their expectation on how to interact with 3D systems and prepare them for non-mouse interaction. One a scale of disagree (1) – agree (5), the students reported a median of 3 and an interquartile range of 2-4. This distinctly average result suggests a relatively even spread of experience with gaming.

Platform comparison

The student sentiment from the survey comparing CHARMM/VMD to iMD-VR has been collated in Table 1, with corresponding statistics for each of the 14 platform comparisons. The questions posed in this section ask a student if a given platform was enjoyable or simple to use and other qualitative questions; a response of 5 on the scale indicates a positive response in agreement with the question. These questions were asked using a Likert scale between disagree (1) or agree (5). This table presents both the median values and the interquartile values showing where the lowest 25% and highest 75% responses fall as a measure of answer skew. Figure 3 shows a visualization of the response data, utilising a divergent stack plot centered around Likert Scale value 3 (between agree and disagree) to help illustrate the differences in student impression of iMD-VR compared to CHARMM/VMD. We have also colour coded the answers where a value of 1 (disagree) is in red and a value of 5 (agreement) is green. A red bar with a skew to the left on figure 3 is indicative that the question resulted in disagreement by the participants and a green bar with a skew to the right is indicative of an agreement. Inspection of Fig 3 shows that students answered more agreeably (and positively) for iMD-VR than they did for CHARMM/VMD.

The question that resulted in the most similar distribution for the two platforms was question 5, which asked students whether a platform played a dominant role in their visual recall. Table 1 shows that for this question the median value for both platforms are 3; however, the interquartile ranges indicate that iMD-VR had fewer disagreement responses (range 3-5 compared to 2-5 for CHARMM/VMD). In interpreting the responses to this question, an important fact to bear in mind is that the students only had ten minutes in iMD-VR whereas they had 12 hours to work with CHARMM/VMD. This provides some indication of how powerful even a small amount of time in iMD-VR may be for influencing visual recall. Questions one and two asked students if they found the platforms enjoyable and easy to use, and figure 3 shows that participants agreed that iMD-VR was easy to use, whereas they found CHARMM/VMD generally harder to use. For these questions, iMD-VR showed agreement responses with median values of 4 and 5 whilst CHARMM/VMD resulted in values of 2. These responses indicate that iMD-VR was more appealing for students to work with compared to CHARMM/VMD and suggests that iMD-VR is a tool that may improve student engagement. Question 7 also indicates that iMD-VR may attract students to the computational sciences, with Figure 3 showing many more responses indicating agreement with the question for iMD-VR, with the median of these responses being 4, whereas CHARMM/VMD had a median of only 2. In combination with the earlier two questions measuring enjoyment and degree of simplicity, there seems to be a strong indication that the students have a positive perception of iMD-VR. The Figure 3 results highlight the potential for state-of-the-art immersive tools like iMD-VR to have a profound effect on the student outlook in computational fields.

The participants indicated that iMD-VR was better at helping them understand molecular structure and movement (Q3) with a median value of 5 and an interquartile range of 4-5 compared to CHARMM/VMD, which had a median of 3.5 with a range of 3-4, despite only having a short time in iMD-VR (although the novelty effect cannot be discounted without further research). The immersion in a dynamic simulation, in this case, appears to have a clear effect on the students' perspective on the nature of molecular motion. An unexpected result was that iMD-VR seemed to help students better understand the difference between QM and MM calculations compared to CHARMM/VMD. When asked about the utility of iMD-VR and CHARMM/VMD for helping participants understand the difference between QM and MM calculations, the median value was 4 for iMD-VR and only 2 for CHARMM/VMD. This we found particularly surprising because the CHARMM/VMD section of the class explicitly demonstrated how students could go about setting up a QM/MM calculation. The response to this question may indicate that, despite understanding the terminology, the experiential difference played an important role in enhanc their understanding – i.e., iMD-VR connected to 'on-the-fly' molecular mechanics in tasks B and C did not enable students to break and make bonds, whereas iMD-VR connected to an 'on-the-fly' density functional theory in task A enabled students to experience interactively breaking and making bonds. When asked if a platform aided the understanding of the reaction in Q6 the survey indicated that the participants found iMD-VR to help their visualisation more than CHARMM/VMD. iMD-VR obtained a median value of 4 whereas CHARMM/VMD has a median of 3.5. Despite the similarity of these values, there is a marked difference in their interquartile spreads. CHARMM/VMD has values between 2 and 4 and iMD-VR has values between 4-5, indicating more consistency for the iMD-VR responses compared to the CHARMM/VMD responses.

iMD-VR task completion

The rate of scientific task completion is as important as student preference in showing that iMD-VR is a viable tool in university-level chemistry education. Figure 4 shows students' reports on their ability to complete each of three iMD-VR tasks. All three tasks showed medians above 4, and 25% quartile ranges above 3.5 indicating high rates of task completion. In particular, the participants reported being able to dock/bind chorismate into the highlighted active site (leftmost panel) with a median value of 5 and a lower quartile value of 4 indicating near total completion of this molecular

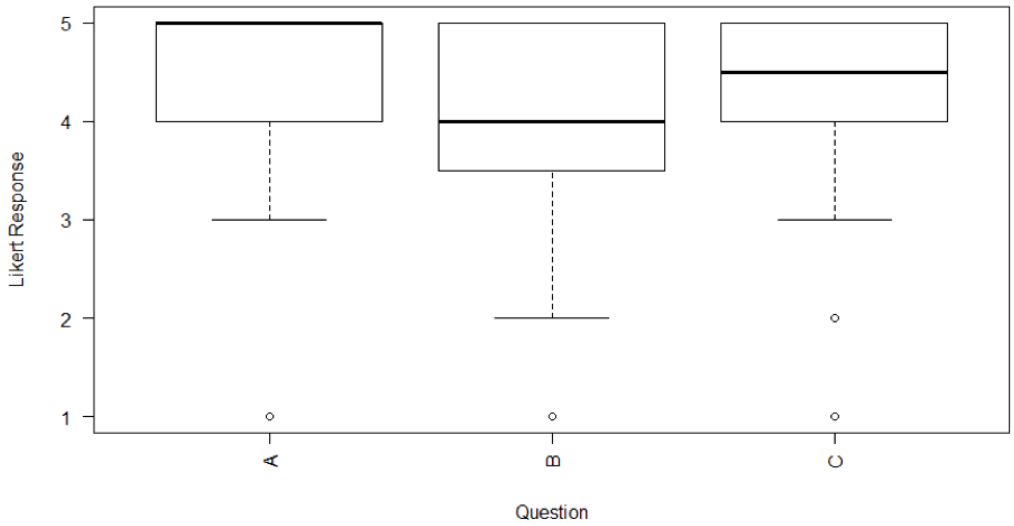

Figure 4: Responses of students to questions relating to their ability to perform biomolecular manipulation tasks in VR, given on a 5 point Likert scale, where 1 represents strong disagreement and 5 represents strong agreement. The questions were as follows: (A) I was able to bind Chorismate into Chorismate Mutase in VR, (B) I was able to recognise the orientation of Chorismate in Chorismate Mutase in VR, (C) I was able to rearrange the Chorismate molecule in VR

binding objective. This task is of particular interest in domains such as structure-based drug design, or protein-protein docking, both of which are important in a pharmaceutical context. The ability of students without prior experience in either docking or iMD-VR to perform this task quickly shows the power that iMD-VR tools may have in accelerating important biomolecular research tasks. These results suggest that students could perform such actions early on in their studies and improve their understanding of pharmacological problems. Data from such classes could potentially be collected and studied with the aim of generating ensemble starting points for high-quality statistical data to analyze binding energies, mechanisms, and poses. Column C in Figure 4 refers to the quantum rearrangement of chorismate to prephenate; the results show that the students felt that they were able to manipulate the chemical system. Anecdotally, we observed during these simulations that students struggled to recognise the functional groups of chorismate, despite having been furnished with structure diagrams as shown in Figure 1. This may indicate that their familiarity with 2D projected structural diagrams does not transfer into an ability to recognize 3D chemical structures, and more broadly suggests that 2D training in molecular visualization is not immediately transferable to 3D spatial reasoning, potentially affecting the way that students approach chemical problems. This is a point which we intend to study in further detail in future studies.[45]

Long form answers

The participants were also asked to give long-form answers on their impressions on both platforms (full responses are given into the SI). For iMD-VR, the comments were nearly entirely positive with comments such as "interesting", "good fun", and "great experience". For CHARMM/VMD, the sentiment was less enthusiastic, with comments such as "lots of fiddling", "infuriating" and "a touch confusing". As an approximate measure of sentiment, we utilised Microsoft azure cognitive analysis[46-47] on the collected text answers obtained for both platforms. This model uses a machine learning approach to analyze text-based input and detect sentiment, scaling it between a value of 100% for positive and 0% as negative. iMD-VR resulted in a value of 100% and CHARMM/VMD as 2%. Google cloud[48] offers a similar set of tools, and gauges sentiment between -1 (negative) and +1 (positive). Using these tools, the CHARMM/VMD exercise scored as -0.3, whereas iMD-VR obtained a score of 0.9. Neither of these models are exact measures of sentiment; however they are broadly indicative that the sentiment for iMD-VR appears to be much more positive than for CHARMM/VMD.

CONCLUSIONS

To date, there are few studies examining the use of iMD-VR as a chemistry teaching tool in higher education. Its effects on both student sentiment towards computational science and its ability to support learning objectives is worth further investigation. The work we have presented here shows that iMD-VR is an effective and practical tool for undergraduate computational chemistry teaching. Our work also shows that iMD-VR improves students' impression of computational molecular science and their overall sentiment toward molecular simulations, but that it also has a positive effect on their own perceived learning outcomes. With the changing landscape of undergraduate education, it is important that chemistry and other scientific domains keep up with state-of-the-art technological developments and enable students to become comfortable with emerging simulation and visualization approaches that are becoming increasingly ubiquitous across several fields beyond chemistry.[17] The results discussed herein indicate that iMD-VR has the potential to form an important part of this process. Narupa enables students to interact with molecular motion, molecular dynamics, and chemical reactions. This open-source immersive environment not only enhances learning, but also allows students to perform complex molecular operations such as docking of substrate or inhibitor molecules into enzymes, and driving conformational and chemical changes. Clearly iMD-VR has the potential to contribute to education in all disciplines that involve studying microscopic molecular

structures, spanning for example materials science, structural biology, biochemistry, and related disciplines. iMD-VR could have profound effects on changing what is achievable within undergraduate courses. As we carry on developing the open-source Narupa project, we plan to explore the extent to which training students with 2D models transfers to 3D intuition, and also evaluate the effects of group iMD-VR work compared to individual work. In particular, we will carry out studies designed to evaluate the pedagogical relationships that arise when instructors cohabit the iMD-VR environment alongside students – e.g., understanding how such environments impact instructors' ability to guide students through molecular modelling tasks, demonstrate important physical principles and reaction mechanisms, and answer student questions as they arise.

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SUPPLEMENTARY INFORMATION

Questions:

1. I would rate my familiarity with using VR prior to this lab as: (none - extensive)
2. I would rate my familiarity with using computational chemistry prior to this lab as: (none - extensive)
3. I enjoyed using CHARMM (agree - disagree)
4. I enjoyed using VR (agree - disagree)
5. I found CHARMM simple to use (agree - disagree)
6. I found VR simple to use (agree - disagree)
7. I regularly play video games in my spare time: (agree - disagree)
8. I was able to bind chorismate into chorismate mutase in VR: (agree - disagree)
9. I was able to recognise the orientation of chorismate in chorismate mutase in VR: (agree - disagree)
10. I found was able to rearrange the chorismate molecule in VR (agree - disagree)
11. VR improved my understanding of molecular structure and movement: (agree - disagree)
12. VMD improved my understanding of molecular structure and movement: (agree - disagree)
13. VR helped me understand the difference between quantum mechanical and molecular mechanical calculations (agree - disagree)
14. CHARMM helped me understand the difference between quantum mechanical and molecular mechanical calculations (agree - disagree)
15. When answering the marked lab quiz VR played a dominant role in my visual recall of the enzyme (agree -disagree)
16. When answering the marked lab quiz CHARMM/VMD played a dominant role in my visual recall of the enzyme (agree -disagree)
17. Visualizing Chorismate/Chorismate mutase in VMD aided my understanding of the reaction (agree - disagree)
18. Visualizing Chorismate/Chorismate mutase in VR aided my understanding of the reaction (agree -disagree)
19. Working with CHARMM has increased my interest in working with the computational sciences (agree - disagree)
20. Working with VR has increased my interest in working with the computational sciences (agree - disagree)
21. Please write a sentence of how you found using CHARMM (long form)
22. Please write a sentence of how you found using VR (long form)

Answers:

Student	q1	q2	q3	q4	q5	q6	q7	q8	q9	q10	q11	q12	q13	q14	q15	q16	q17	q18	q19	q20
1	1	2	3	5	2	5	4	4	3	5	4	3	4	3	3	4	4	4	3	4
2	2	4	1	4	1	4	1	5	5	5	5	4	3	1	3	1	1	3	1	4
3	1	3	2	5	3	5	2	5	5	5	4	4	4	3	1	4	4	4	2	4
4	1	2	2	5	1	4	2	5	4	4	5	5	4	1	5	2	2	5	2	5
5	1	3	1	3	1	3	3	3	2	2	3	1	2	1	2	2	2	**2**	1	2
6	3	2	2	4	2	4	3	4	4	4	4	3	3	3	4	3	4	4	3	3
7	1	3	1	3	1	3	3	5	1	5	4	4	3	1	1	4	5	5	1	3
8	1	2	3	5	4	4	3	3	3	4	4	5	5	3	4	3	4	5	4	5
9	2	4	4	5	3	4	2	5	4	4	5	4	5	3	5	2	3	5	3	4
10	2	3	4	4	3	4	1	5	5	3	3	3	3	4	1	1	5	3	4	3
11	1	3	2	5	1	5	3	5	5	5	5	3	5	2	5	3	4	5	2	4
12	2	2	3	4	2	4	2	5	3	3	5	3	2	4	3	3	3	4	4	4
13	1	2	3	5	4	4	2	3	4	4	5	4	3	3	3	4	4	4	4	5
14	1	3	3	5	3	4	1	4	4	5	5	3	5	2	3	4	2	4	4	4
15	3	2	1	5	2	5	5	5	5	5	4	1	5	1	3	2	1	4	1	5
16	4	3	3	5	3	4	5	5	4	4	5	4	4	2	5	2	3	5	3	5
17	3	1	2	5	2	4	4	5	5	5	5	4	4	3	3	3	4	4	2	4
18	1	3	2	4	2	4	4	4	4	5	4	3	3	2	3	2	4	4	2	4
19	1	1	1	5	1	1	1	5	5	5	5	1	4	1	4	1	1	1	1	3
20	1	2	2	4	3	3		1	4	1	3	4	2	1	3	4	3	4	2	3
21	1	2	1	5	2	5	4	5	5	5	5	4	4	5	3	3	5	5	2	3
22	1	4	2	3	2	4	1	4	4	4	5	3	2	2	3	3	3	4	2	4

Long form answers:

Q21 (CHARMM/VMD):

1. Very confusing as I've never used command windows or anything similar. Wasn't massively well explained on the DLM either
2. Multiple different instructions in different places made it nearly impossible to use, I think the lab presumed a level of knowledge about a command line that nobody had and needed straightforward instructions with an explanation of what each thing di
3. Hard at first, but once the first one had been run, it becomes quite intuitive once you know what you are doing
4. Difficult to understand how to use commands
5. Difficult, boring and uninspiring
6. Frustrating at first due to lack of instructions, but was fairly intuitive after that
7. Difficult to understand and dull.
8. Okay
9. Was difficult to use as it required a lot of fiddling in directories which was difficult as it is not something I have experienced before
10. It was confusing at first, but easy afterwards.
11. Not at all intuitive, could not use without extensive help
12. Found it difficult to use for the first couple of hours, but was then okay
13. Fine, a touch confusing but fine
14. very difficult to set up at first but rewarding and liked learning how to code
15. All explanations of how to use the programme were incomplete, contradictory and confusing it made the workshop take far longer than necessary and in general caused it to be boring and infuriating. The list of useful commands is terrible
16. Complicated at times but learning a little bit of 'coding' language was interesting
17. difficulties arose as the commands to use CHARMM were not clear. After understanding which commands to use and how to properly use them CHARMM became easier to use
18. With no prior knowledge of using this sort of program it was quite difficult to get to grips with.
19. Very difficult and confusing considering I have no experience of coding! I think a clearer explanation should be given on how to use the software.
20. Incredibly difficult
21. Very difficult as it wasn’t intuitive and didn’t come naturally to me
22. Instructions on how to code were not good, once I understood the basics it was ok but still slightly confusing to use.

Q22 (iMD-VR)

1. A fun novelty and really interesting to see things in the real time/upclose
2. Very interesting, can see the potential.
3. I really enjoyed it, but I did it right at the end, so already understood what the reaction looked like. Had I done it at the start I probably would have helped me understand what I was doing when using CHARMM
4. Really aided visualisation of the enzyme and was memorable
5. unnecessary at undergrad
6. Impressive, user interface was good but took a little getting used to
7. Fun.
8. Really interesting
9. Really easy to use and a great visual aid to understand what was going in in regards to the enzyme active site and the interaction with the arginine on the enzyme
10. It was interesting.
11. Very good at helping visualise the process being studied
12. It was very interesting and helpful for visualising the reaction
13. yeah good fun
14. Great new way to experience reactions, enjoyed it
15. The VR was a welcome break from the rest of the workshop as it was well explained, easy to use, interesting and visually stimulating. I learnt more in that 10 minutes the other 11 hours I've spent doing this workshop.
16. VR was very enjoyable to use. I found being able to walk around the molecule, and use intuitive rotating/moving controls really helped my visualisation of both the molecules and understanding the difference between QM and MM.
17. I found using VR interesting it added a completely new for of visualisation to the reaction and increased my understanding of the matter at hand
18. The VR was useful for visualising what was going on in the reaction and fun to use.
19. It was really fun to use and a great experience.
20. fun but slightly disorientating
21. Very easy. much easier to grasp than CHARMM
22. Good to visualize the reaction.