InteraChem: Virtual Reality Visualizer for Reactive Interactive Molecular Dynamics

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Abstract

Interactive molecular dynamics in virtual reality (IMD-VR) simulations provide a digital molecular playground for students as an alternative or complement to traditional molecular modelling kits or 2D illustrations. Previous IMD-VR studies have used molecular mechanics to enable simulations of macromolecules such as proteins and nanostructures for the classroom setting with considerable success. Here, we present the INTERACHEM molecular visualizer, intended for reactive IMD-VR simulation using semiempirical and *ab initio* methods. INTERACHEM visualizes not only the molecular geometry, but also 1) isosurfaces such as molecular orbitals and electrostatic potentials, and 2) two-dimensional graphs of time-varying simulation quantities such as kinetic/potential energy, internal coordinates, and user-applied force. Additionally, INTERACHEM employs speech recognition to facilitate user interaction and introduces a novel "atom happiness" visualization using emojis to indicate the energetic feasibility of a particular bonding arrangement. We include a set of accompanying exercises that we have used to teach chemical reactivity in small molecular systems.

Keywords

High School/Introductory Chemistry < Audience, First-Year Undergraduate/General < Audience, Physical Chemistry < Domain, Computer-Based Learning < Pedagogy, Hands-On Learning/Manipulatives < Pedagogy, Computational Chemistry < Topics, MO Theory < Topics, Quantum Chemistry < Topics, Theoretical Chemistry < Topics

Introduction

Traditional molecular representations perform well for pedagogical purposes on small model systems but may struggle to accurately depict the full breadth of possible chemical reactions or the dynamic nature of molecules. For example, Kekule-Lewis structures and arrow-pushing mechanisms are widely used to conceptualize organic chemistry reactions, but fail to emphasize the three-dimensional nature of the structures. Conversely, modeling kits provide a spatial representation of molecules, but physical limitations (such as the number and placement of holes in each atom) can make it difficult to describe some motions or chemical reactions and impossible to describe exotic species (for example, CH_5^+). Students can overcome these obstacles with training, but advances in modern technology suggest more direct approaches such as the use of virtual reality (VR).[1-2] The rise of relatively affordable commodity VR headsets in the last few years (e.g. the Oculus Quest 2 is available for $299) has seen the development of a plethora of VR-enabled molecular visualizers.[3-5] This has in turn fueled the growth of VR applications and activities for chemical education.[6-11] Several studies have featured interactive molecular dynamics (IMD) simulations, where the user is immersed in a molecular movie with the ability to grab and pull molecules and observe how the system responds in real time. Haptic controllers allow control over translations and rotations and additionally have force-feedback capabilities, making them the traditional choice of peripheral for IMD.[12-14] However, these controllers have a limited range of motion, are prohibitively costly (> $1000) for most classrooms, and do not have the same widespread familiarity and versatility as VR headsets. Therefore, IMD in VR (IMD-VR) simulations seem to be a promising alternative for increasing the accessibility and impact of these simulations throughout chemical education.

Smooth real-time simulations necessitate updates to the molecular geometry at least several times a second; therefore, evaluating the forces on the atoms must be done on the order of a tenth of second or faster. As a result, molecular mechanics (MM) are the most popular choice, enabling IMD to be applied to large macromolecules such as proteins and carbon nanotubes.[4, 11, 15] However, MM force fields are not well-suited for studying chemical reactivity as bonds cannot be created or broken; therefore, semiempirical and *ab initio* methods are needed for reactive IMD simulations. The density functional tight binding[16] (DFTB) method has been used to facilitate nanostructure construction and study chemical reactivity in systems with over 100 atoms.[17-18] The use of consumer-grade graphical processing units (GPUs) enabled *ab initio*

IMD (AI-IMD) for systems with dozens of atoms.[19] Reactive IMD-VR simulations have been reported previously,[4] but their potential impact for chemical education has not been fully explored.

Here, we present the INTERACHEM molecular visualizer and a set of exercises developed with reactive IMD-VR simulations for both high school and undergraduate chemistry students. The exercises cover a variety of topics, including molecular geometry and structure, molecular bonding and orbitals, conformational changes, and acid-base and organic reactivity. A large focus was placed on the visualization of quantum mechanical quantities (e.g. bond order, molecular orbitals, electron density) as these quantities are not well-described with traditional molecular modelling kits or MM-based IMD-VR simulations. The INTERACHEM visualizer and an accompanying worksheet that we have used in previous classroom demos are both available for free online.[20]

INTERACHEM – Virtual Reality Interactive Reactive Molecular Dynamics

INTERACHEM is built with the UNITY game engine[21] and can be deployed to a wide variety of peripherals. Our primary development was done with the Oculus Rift S, although the Oculus Rift and Quest (in tethered mode via Oculus Link) have also been used.[22] Several stereoscopic (i.e. 3D) displays and projectors have been tested as well. The Rift S boasts "inside-out" tracking, meaning that no additional cameras or sensors are needed. This makes the INTERACHEM system fairly portable, which was useful as all three of our demonstrations required moving our simulation setup to a classroom. Additionally, haptic controllers such as the GEOMAGIC Touch[23] are supported through the OPENHAPTICS UNITY plugin[24-25] and can be used

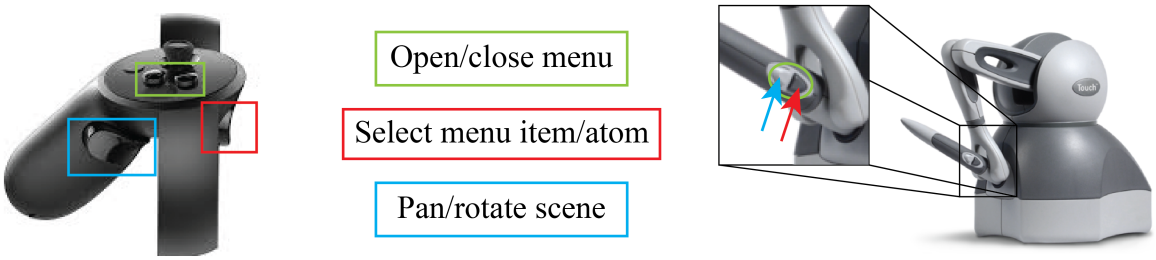

Figure 1. Basic control scheme for both VR (left) and haptic (right) controllers. Voice control can be accessed via the X button on the Oculus Touch controllers or the S key on the keyboard.

alongside a VR headset. This gives the advantages of both systems (i.e. 3D perception and force feedback), but the haptic controller's limited range of motion is still a major disadvantage compared to the freedom of the VR controllers.

A minimal control scheme was implemented with three functionalities: opening the menu (which pauses the simulation), selecting menu items or atoms, and panning/rotating the scene. The mappings of this scheme onto the VR handsets and haptic controllers are shown in Figure 1. Menu management (particularly drop-down menus for molecule and orbital selection) can be challenging for users in VR. Table 1 lists a series of available voice commands using UNITY's built-in voice recognition module which has been added to circumvent some of these issues. Most notably, the "[load | get] molecule" command (where "molecule" is a specific molecular common name such as benzene or phenol) fetches a geometry via PubChem's Power User Gateway (PUG) REST API,[26] avoiding the onerous task of navigating a file explorer menu to start new simulations. The built-in recognition has some difficulty recognizing chemical names,

Table 1. InteraChem voice commands

Phrase	Effect[a]
help	List all recognizable phrases
[pause|stop]	Pause the simulation
[play|resume]	Resume the simulation
temperature <T>	Set temperature to <T> Kelvin
[multiply|increase|scale] force by <factor>	Set user-applied force multiplier to <factor>
[load|get] molecule <name>	Fetch a molecular geometry via PubChem REST API
[optimize|minimize]	Optimize geometry of current structure
normal mode <mode>	Visualize mode <mode> (listed in descending order by frequency, only available after minimization)
select [bond|bond length]	Begin bond length selection for a new plot
select [angle|bond angle]	Begin bond angle selection for a new plot
select [dihedral|dihedral angle|torsion angle]	Begin dihedral angle selction for a new plot
orbital <n>	Visualize isosurface for canonical orbital <n> (in ascending energy order)
[highest occupied|lowest unoccupied] molecular orbital	Visualize HOMO/LUMO
electron density	Visualize electron density isosurface
electrostatic potential	Visualize electrostatic potential on electron density isosurface
[orbital|density] isovalue <value>	Set isovalue of orbital or electron density isosurfaces

[a]Square braces separated by a pipe (|) indicate interchangeable keywords. Trailing question marks indicate optional keywords. Angle braces denote input variables.

and further work to resolve these issues and expand the capabilities of voice commands in InteraChem is ongoing.

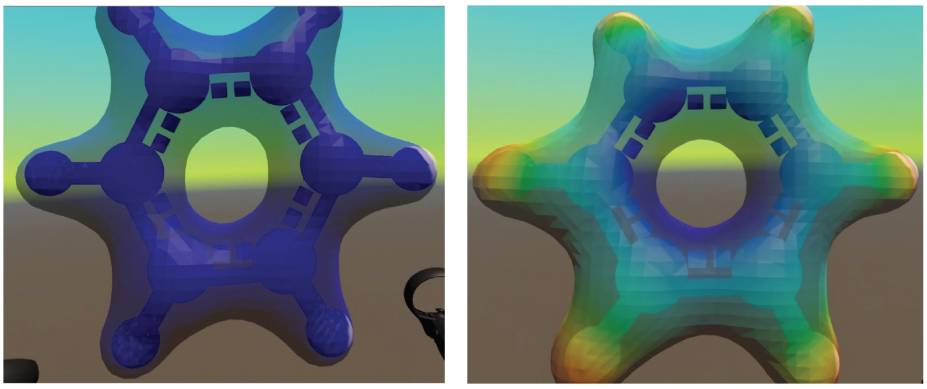

Figure 2. Electron density (left) and electrostatic potential (right) isosurfaces for benzene. The electrostatic potential uses the density isosurface but colors according to charge (blue for negative, red for positive).

Molecules are visualized using standard ball-and-stick representations, with the bond order dynamically updated by rounding the corresponding entries of the Mayer bond order matrix[27] to the nearest half-integer. Atoms are highlighted when the controller hovers on them, and a yellow tether is displayed to indicate which atom is currently selected by the user. Isosurfaces for molecular orbitals, the full electron density, or the electrostatic potential can be displayed in real-time as shown in Figure 2. The user can request plots for kinetic and potential energy, temperature, or any internal coordinate (e.g. bond distance, angle, or torsion), as shown in Figure 3. These plots can be moved to any location in the VR scene, which we have found to be an excellent use for the additional space in the user's peripheral vision.

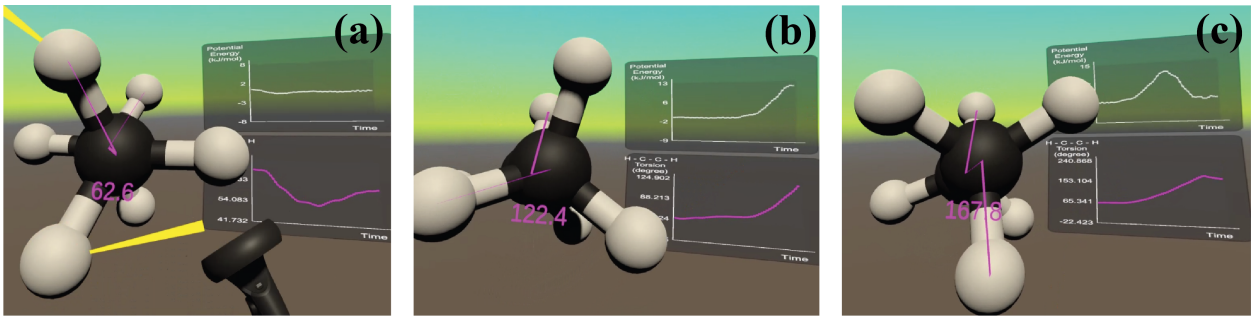

Figure 3. Ethane torsion showcasing potential energy in upper white plot and H-C-C-H torsion in lower purple plot for (a) staggered conformation at 60°, (b) eclipsed at 120°, and finally (c) staggered again at 180°. Note the plot y-axes change automatically rescale from (a) to (b) to fit the new range of values.

As an additional heuristic to aid and engage students, a "happiness" mode was added where happy and angry emojis were attached to each atom based on the local bonding environment, as demonstrated in Figure 4. The target number of bonds for first and second row elements is the difference between the number of valence electrons and the nearest full shell of electrons. For third row elements, hypervalency is possible and the set of allowed bonds ranges from the ideal number described above to the total number of valence electrons in increments of 2 (as each electron in a lone pair forms a new bond). We define the difference between the target number of bonds and the current number of bonds as

$$\Delta N_i = \left| N_{\text{ideal}} - \sum_{j \neq i} BO_{ij} \right| \tag{1}$$

where N_{ideal} is the closest ideal number of bonds and BO_{ij} is the Mayer bond order between atoms i and j. The "mood" of an atom is then determined by

$$\text{mood}_i = \begin{cases} \text{happy} & \Delta N_i < 0.15 \\ \text{neutral} & 0.15 < \Delta N_i < 0.30 \\ \text{angry} & \Delta N_i > 0.30 \end{cases} \tag{2}$$

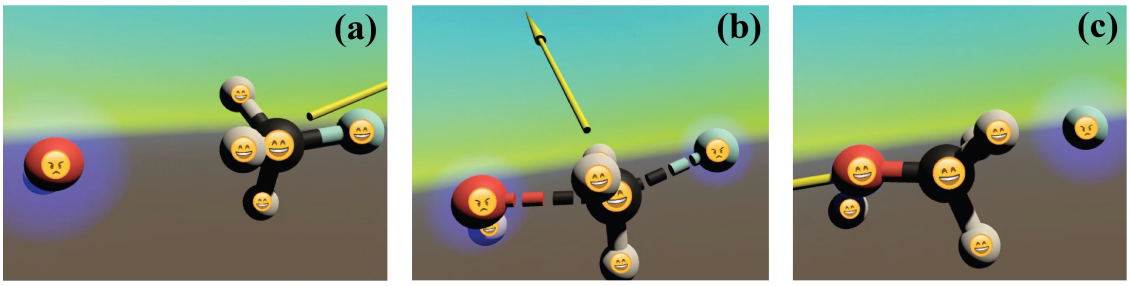

Figure 4. Atomic charge and emojis representing the local environment via "happiness". The yellow arrow is the molecular dipole, the blue aura represents negative charge, and an atom is labeled as happy/angry based on a bond saturation heuristic. This S_N2 reaction starts with (a) the negatively charged oxygen as unhappy, (b) both the nucleophile and leaving group are unhappy at the transition state as negative charge is transferred, and (c) the fluoride ion is unsaturated upon reaction completion.

The partial atomic charges (determined via Mulliken population analysis) and total molecular dipole are also shown in this mode, which can be activated by holding both triggers on the two VR controllers simultaneously.

The INTERACHEM visualizer is currently interfaced with two electronic structure packages. The xTB package[28] is linked into the executable and provides the GFN2-xTB semiempirical

method.[29] *Ab initio* methods such as Hartree-Fock (HF), density functional theory (DFT), configuration interaction singles (CIS), and complete active space configuration interaction (CASCI) are available from the TERACHEM electronic structure package via the recently developed TERACHEM Protocol Buffer (TCPB) interface.[30-31] The TERACHEM server currently needs to be run on a separate machine from the INTERACHEM visualizer as TERACHEM does not currently support Windows, but further work is ongoing to resolve this technical issue. The majority of the exercises below can be performed with either backend; however, the GFN2-xTB method from the xTB package is used by default as it is faster and therefore provides a consistently smooth user experience. The details of these interfaces and benchmarking of the electronic structure methods for reactive IMD-VR purposes will be described in an upcoming publication.

The reactive IMD simulations use velocity Verlet integration, a Bussi-Parrinello Langevin thermostat,[32] and a multiple timestep scheme incorporating the user force as in the AI-IMD work.[19] We intentionally use a fast frictional relaxation time of 50 fs in the thermostat (i.e., this is a "strong" thermostat) to compensate for the large forces (on the molecular scale) that are often induced by user interaction. By promoting fast energy dissipation, the possibility of molecular rupture due to unintentionally large user forces is minimized. A spherical reflecting boundary ensures that atoms are not lost when molecules do rupture after being subjected to high forces. All simulations are carried out in the gas phase, although implementations for the generalized Born/surface area[33-34] (GB/SA) and several conductor-like polarization models[35-38] are available in xTB and TERACHEM, respectively, paving the way for solvent phase reactive IMD in the future. The user-applied force is implemented as a spring between the selected atom and the controller. The default spring constant is set to comfortably manipulate internal motions (e.g. angles, dihedrals), and the user can scale the spring constant by a multiplicative factor to break bonds or move more massive atoms. In addition to reactive IMD, one can also perform geometry optimization via an internal BFGS[39-42] optimizer. Normal modes can be visualized from an optimized structure. Atoms can be frozen in space to run constrained dynamics or optimizations, or directly moved while the simulation is paused.

Teaching Chemistry with INTERACHEM – Overview of Sample Exercises

We have developed a series of exercises for reactive IMD-VR designed to be taught by one instructor with a single INTERACHEM-enabled station. Our demonstrations used a gaming laptop, the Oculus Rift S headset, and a few modelling kits. This portable solution allowed us to visit classrooms easily. Students take turns completing exercises while the remaining students observe the simulation on a second display or projector (usually already available in the classroom). We noticed that the observing students also benefit, formulating their own strategies for their turn with the headset and calling out ideas to the student in VR. This setup allows us to engage the entire class with a single VR headset, which helps to keep the equipment costs down. In our experience, it works well for up to 30 students at a time (and might be scalable to 50 students with some careful planning). Scaling VR instruction beyond 50 students at a time is an open challenge and we currently recommend that it be used in the context of laboratory sections (which tend to involve fewer students than the lecture section of lower-level chemistry classes).

The exercises begin with several basic molecular geometry tasks, such as attempting to distort tetrahedral methane, the umbrella flip motion in ammonia, or pseudorotations in trigonal bipyramidal complexes such as PF_5. These serve as a general introduction to VR and IMD, and also provide a launching pad for instructor-led discussions of chemical bonding concepts like Valence Shell Electron Pair Repulsion (VSEPR) theory[43] and the pitfalls of Kekule-Lewis structures and physical modelling kits. The next theme is reactivity and molecular orbitals, involving challenges such as comparing C-C torsion for ethane vs. ethene, visualizing σ and π orbitals in ethene and benzene, and promoting the ring opening of cyclobutene (as showcased in Figure 5). Several exercises focus on benzene and cyclohexane, including a discussion of molecular planarity, aromaticity and the π system in benzene (in which students attempt to throw

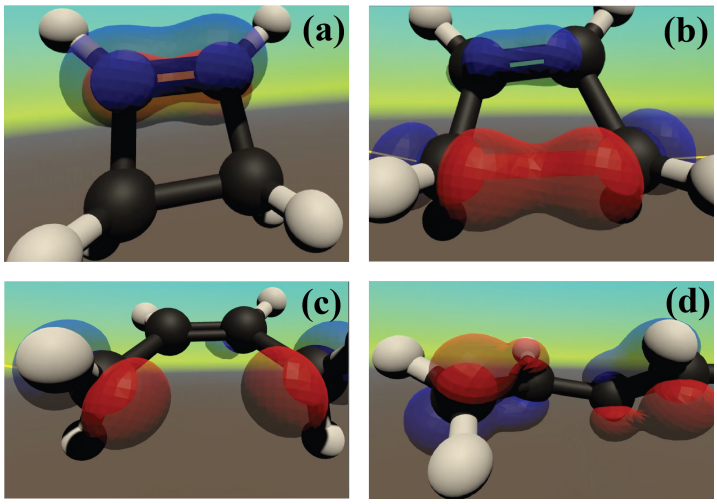

Figure 5. Ring opening of cyclobutene to butadiene displaying the highest occupied molecular orbital (HOMO), which starts as (a) a pi bond, (b) migrates to the breaking sigma bond as force is applied, (c) splits into individual *p* orbitals near the transition state, and (d) forms the new pi system of butadiene. Orbitals are prone to fluctuating over the course of the simulation and these snapshots are curated to demonstrate general trends in the evolution of the HOMO.

a hydrogen atom through the ring), and converting between the chair and boat conformers of cyclohexane. Finally, chemical reactivity is first shown through proton transfers in several acid-base systems and then through standard organic reactions such as nucleophilic substitution and elimination reactions. Links for videos depicting each exercise can be found listed in Table 2 and a full discussion of the exercise goals, typical outcomes, and talking points can be found in the Supporting Information.

Table 2. Video Demonstrations of IMD-VR Exercises

Video	Exercise	URL
1	Distorting tetrahedral methane	https://youtu.be/DJVWA8hyiLU
2	Umbrella flip in ammonia	https://youtu.be/vHSqrbgNxuI
3	Pseudorotations of PF_5 and PH_3F_2	https://youtu.be/xKiVzd3kifc
4	Ethane C-C torsion	https://youtu.be/3UpAGv0GDhU
5	Ethene C=C torsion	https://youtu.be/VDNtnQqWpEE
6	Ring opening of cyclobutene	https://youtu.be/WtIQXeA7PDY
7	H atom through benzene ring	https://youtu.be/Qn0v3rTVFRA
8	Cyclohexane chair⇔boat	https://youtu.be/b5H-Dn26lZ0
9	H^+ transfer in carbonic acid + water	https://youtu.be/E1B6gkPECKA
10	S_N2 of methyl fluoride + hydroxide	https://youtu.be/iVll4L8yWHY
11	E1 of t-butyl fluoride + hydroxide	https://youtu.be/evF5GoAOkHU
12	High force decomposition	https://youtu.be/Hq6JD33OpBo

We first presented these exercises to 15 undergraduate students in a section of Chem 173 at Stanford University, the physical chemistry class introducing quantum mechanics. Together, the students completed the majority of the exercises in the 50-minute section and spent roughly equal time becoming comfortable with the VR setup as performing the exercises. The discussion was tailored to build on their chemical and mathematical background. For example, harmonic oscillators as models of vibration were included in the context of normal mode analysis and molecular mechanics. Additionally, wavefunction-related concepts such as the nodes and energy ordering of molecular orbitals and the electron density were highlighted.

We also demonstrated reactive IMD-VR to high school students on two occasions. A total of 46 high school students (primarily 11th and 12th graders) were split over four 50-minute sessions as class C7382 at Stanford SPLASH Fall 2019. These sessions had two INTERACHEM stations and three instructors, giving small groups with five or six students per setup. Only half the exercises were run with a higher focus on molecular geometry (e.g. ammonia umbrella flip, cyclohexane conformers) and single vs. double bonds (e.g. ethane vs ethene torsion). The final challenge was setup as competition between the two teams with the goal to perform an S_N2 reaction in a hydroxide and methyl fluoride system. Most groups were able to discover the mechanism in reactive IMD-VR after three or four tries despite having no organic chemistry instruction. Finally, an extended 1.5-hour workshop was run for 17 high school students from 9th to 12th grade with one INTERACHEM setup. Four of these students evidently had previous exposure to VR headsets and were immediately comfortable in the simulation. In general, the high school students quickly acclimated to VR environment but spent longer completing each exercise compared to the undergraduates; from our experiences, high school students need at least two hours to complete all exercises that the undergraduates completed in 50 minutes.

We found the energy plots and molecular modeling kits to be valuable complementary tools for the instructor and external students. The instructor can point out energy barriers and relative stability of the conformers in real time, while the modeling kits provided reference structures to anchor students to their previous lessons. For students who completed exercises quickly, the challenges were further "gamified" by adding additional constraints, such as only allowing them to touch certain atoms or reducing the user-applied force. In the future, these concepts could be quantified to provide a numerical score for each challenge, where the lowest score represents the

discovery of the minimum energy mechanism with the smallest amount of external force. Conversely, students also greatly enjoyed using high forces to easily pull apart molecules. In addition to increasing student interest, relevant discussion can be generated by focusing on the recombination products in these scenarios.

Conclusion

IMD-VR simulations provide an excellent complement to traditional modeling kits by allowing students to visualize and interact with molecules in a 3D digital playground. Previous work has used molecular mechanics in IMD-VR simulations to expose students to proteins and nanostructures with great success. The use of semiempirical and *ab initio* molecular dynamics enables reactive IMD-VR simulations on system sizes typically taught in general and organic chemistry, providing an alternative way for students to study chemical reactivity without resorting to heuristics or rote memorization from textbooks. The IMD simulations may even occasionally appear to disagree with the textbooks, leading into discussions on advanced topics such as solvation effects to stabilize charged species in the nucleophilic substitution exercises.

INTERACHEM is a UNITY-based visualizer with interfaces to the xTB and TERACHEM quantum chemistry programs designed for reactive IMD-VR simulations. As a result, INTERACHEM focuses on visualization of wavefunction information in the form of adaptive bond order and molecular orbital or electron density isosurfaces that are not available in MM-based IMD-VR. A set of exercises for reactive IMD-VR have been developed and demonstrated for almost 80 students across both high school and undergraduate levels. In general, both groups of students responded well to the VR simulations, although high school students took longer to complete the exercises. However, this does not mean the high school students had a less successful experience; on the contrary, the high school students had animated discussions and provided creative (even if unintended) solutions. We welcome the development of further exercises by INTERACHEM users and we would be happy to host these on the software web page for community usage if they are sent to the corresponding author of this paper.

Although not quantified here, the concept of "gamification" for reactive IMD-VR simulations in the form of minimizing the user-applied force or constraining which atoms can be manipulation emerged naturally during our demonstrations. Gamification has seen significant success for both increasing participation and providing creative solutions to scientific problems

such as protein folding.[44-45] Further study is warranted on whether the gamification of reactive IMD-VR simulations leads to increased student participation or greater completion of learning objectives.

Associated content

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.XXXXXXX.

Student Worksheet with sample exercises (PDF)

Discussion of sample exercises for instructors (PDF)

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