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ABSTRACT

The emerging fields of citizen science and gamification reformulate scientific problems as games or puzzles to be solved. Through engaging the wider non-scientific community, significant breakthroughs may be made by analyzing citizen-gathered data. In parallel, recent advances in virtual reality (VR) technology are increasingly being used within a scientific context and the burgeoning field of interactive molecular dynamics in VR (iMD-VR) allows users to interact with dynamical chemistry simulations in real time. Here, we demonstrate the utility of iMD-VR as a medium for gamification of chemistry research tasks. An iMD-VR "game" was designed to encourage users to explore the reactivity of a particular chemical system, and a cohort of 18 participants was recruited to playtest this game as part of a user study. The reaction game encouraged users to experiment with making chemical reactions between a propyne molecule and an OH radical, and "molecular snapshots" from each game session were then compiled and used to map out reaction pathways. The reaction network generated by users was compared to existing literature networks demonstrating that users in VR capture almost all the important reaction pathways. Further comparisons between humans and an algorithmic method for guiding molecular dynamics show that through using citizen science to explore these kinds of chemical problems, new approaches and strategies start to emerge.

I. INTRODUCTION

In recent years, the closely related concepts of "gamification"[1–3] of scientific problems and utilizing "citizen scientists"[4] to gather data have become increasingly used as research tools in the molecular science literature. Significant work in this regard came from Cooper *et al.* with the Foldit program[5,6] in which the protein folding problem was recast as a computer game with tutorials, scoring system, and other game-like attributes. Chiefly, Foldit was designed to create an enjoyable experience for the public and thus drive user engagement. An early paper by Cooper *et al.*[6] demonstrated that the users of the game, the "citizen scientists," were able to spot and create favorable folding conformations, often more efficiently than computer-based algorithms designed to complete the same task. Subsequently, this framework has been extended and data from the users have been directly used to accomplish research tasks involving protein/enzyme design[7] and crystal structure identification.[8] Another promising strand to this type of citizen science study involves formalizing the strategies used by human users for algorithm development.[9] Detailed studies in this regard have shown that citizen scientists can explore different areas of the solution surface for a given scientific problem and can potentially find minima in solution space, which are different to those found by existing algorithms.[8,9] The growing body of work in this field clearly demonstrates that if scientific problems are formulated in the right way and the game is engineered to engage a lay audience with these questions,

then utilizing data from the public can be highly effective.

Another emerging tool in the molecular sciences is the use of virtual reality (VR) technologies,[10–21] and the manner in which VR can aid the teaching/learning of computational chemistry tasks has been well documented.[22,23] Recent developments in such technologies have been leveraged in the Narupa software.[24–27] In Narupa, "players" use a VR headset to enter a real-time molecular dynamics simulation. Within VR, they are able to reach out with hand-held controllers and "pull" atoms in order to perturb or direct the dynamics of the molecular system around them. This "interactive" molecular dynamics approach[25,28–30] extended to virtual reality (iMD-VR) has been described in several recent papers.[27,31] It has been shown that a VR environment offers an intuitive way for non-experts to understand and manipulate molecular motion, and it was demonstrated that users in a 3D VR environment were significantly more efficient at performing complex computational chemistry tasks when compared to a 2D mouse-based or touchscreen interface.[27] The utility of this iMD-VR framework has been demonstrated in other applications: It has been shown to be effective at sampling drug binding poses[32] and has recently been utilized for a study on SARS-CoV-2 docking,[33] it has been used to aid the sampling of molecular geometries for fitting to a neural network,[34,35] and the enhanced perception of users in iMD-VR toward subtle dynamical changes in molecular simulations is an area of ongoing research.[36,37] Other work has explored the addition of sonic elements to add another perceptive layer to users' experience in VR.[38] These successes coupled with the user interface (UI) elements and the immersive experience afforded by VR and potential sonification make iMD-VR an ideal basis for a gamification interface.

When looking at a problem to gamify, one area attracting substantial research interest is the automatic generation of chemical reaction networks.[39–48] There are a wide range of fields in which one wishes to model the chemical evolution of a system of competing reactions and transformations. These range from gas phase modeling of the chemistry in the Earth's atmosphere[49] or in a combustion engine[45,47] to the modeling of organometallic complexes[44] or homogeneous catalysis.[50] Given the ubiquity of this type of problem, there have been several recent software packages designed to automatically map the network of chemical reactions within a chemical system.[42,43,46] This leaves the two open questions: Whether "citizen scientists" could efficiently explore chemical networks and what differences in strategy might emerge between human- and computer-guided mechanism generation. The reaction network initiated by the OH + propyne reaction is a key step in the combustion of natural gas, and the network of possible reactions has been extensively characterized by both automated methods[51] and by manual transition state searching.[52] This system presents itself as an ideal candidate for proof-of-concept studies for a reaction finding "game." Of the two comprehensive literature mechanisms, the automated (Kinbot) study by Zador[51] made efforts to prune the mechanism down to those reactions that are relevant under combustion conditions and lower temperature conditions and for this reason used as the primary benchmark of "known important reactions" in the rest of this paper.

In this paper, we detail the design and implementation of an iMD-VR game where the aim is to find reactions between two molecules. We evaluated this iMD-VR game with a prospective user study where non-experts were tasked with playtesting the game. Each player was given the C_3H_5O atomic system starting with the OH and propyne moieties for the reasons given above. This paper aims to explore whether this iMD-VR based game is an effective tool for mechanism generation, and we will be using two metrics to assess this: Do the users discover the known reactions for a well-studied system and do the users find novel reaction pathways. The secondary aim of this paper is to begin to compare molecular trajectories guided by humans and those guided by some algorithmic acceleration method with the aim of highlighting strategic differences. This paper is organized as follows: Secs. II and III detail the methods with Sec. II detailing new elements in this work that create a game-like iMD-VR environment, and Sec. III detailing the design and evolution of the user test experience. The results from these user tests are presented in Sec. IV, where we analyze the reaction game data in the context of three separate questions: Does the user-generated reaction network capture the important process that has been identified in the literature, does the user-generated network find anything new, and can we identify any difference in strategy between human-guided molecular dynamics and molecular dynamics biased through some algorithmic method.

II. REACTION GAME INFRASTRUCTURE

The reaction game used for the user tests in the current work is based on the Narupa iMD-VR framework and in particular makes use of the efficient interface between Narupa and the Scine Sparrow electronic structure package,[53] allowing for real-time quantum evaluation of the forces of the system. This is essential for exploring reactive changes (bond breakage and formation) of a system in Narupa.[52]

An interactive Narupa iMD simulation is run through two applications, a Python backend dynamics engine and the frontend Narupa iMD program. The "backend" runs the molecular dynamics while also acting as a server, sending simulation data to the Narupa iMD application on-the-fly. The communication between these two applications allows users to cohabit the "VR space" where the MD data are visualized in full 3D and in real time. Within this environment, users can reach out with the hand-held VR controllers and interact with the atoms around them; when grabbing an atom in this way, the user is applying an external force into the system; hence, the atoms will react to this input. These additional forces are relayed back to the Python backend that incorporates them into the MD calculations. Through this feedback look, a fully immersive and interactive simulation in VR is realized. (https://vimeo.com/312963823)

To facilitate a "game-like" experience and to incentivize the discovery of chemical reactions, a number of additions were made to the core Narupa framework. These additions can be loosely grouped into three different categories: additional infrastructure to allow automated identification, bookmarking, and scoring of chemical reactions, the addition of audio elements to the game to engage another layer of the user's perception and to impart more, real-time, information to the users such as the energy of the system, and added user interface (UI) elements to aid users in navigating the network of reactions they had discovered. This section details the elements that were used for the final set of user participation tests. The "reaction game" was refined over three separate sets of user tests, and this design process and the evolutions of the user test process are described in Sec. III.

A. Reaction finding and bookmarking

To function as a mechanism generation tool, it was necessary to have an automated way of identifying when a reaction had occurred. This is a problem encountered in other (automated) mechanism generation approaches based on molecular dynamics, and for this work, we implemented a version of the TSSCDS algorithm of Martínez-Núñez,[40] for tracking when a reaction may have occurred. For the starting OH + propyne Cartesian coordinates, we created a connectivity matrix ($\boldsymbol{C}$) describing the bonding structure of the system. This was an N by N matrix where N is the number of atoms in the system (9 in the current case), and each matrix element signified whether atoms ij were bonded (1) or nonbonded (0) based on whether the current interatomic distance was less than some ideal bond distance for that atom pair (Table S1 of the supplementary material).

At each subsequent time step, the current interatomic distances d_{ij} of the system were then compared with the reactant bonding structure (given by $\boldsymbol{C}$) to monitor the reaction. Specifically, a reaction was then considered to occur if for an atom i,

$$\max(\delta_{in}) > \min(\delta_{ik}); \delta_{ij} = \frac{d_{ij}}{d_{ij}^{REF}}. \tag{1}$$

Here, index n runs over atoms bonded to i ($\boldsymbol{C}_{ij}$ matrix elements equal to one) and index k runs over atoms that do not have a bond to i ($\boldsymbol{C}_{ij}$ matrix elements equal to zero). Once a reaction occurred and the product was identified, the connectivity matrix $\boldsymbol{C}$ was updated to describe the new bonding structure of the system.

Upon reaction, the product geometry was determined by propagating the system for a further 80 MD steps to give the system a chance to fully enter the "product" region of configurational space. A steepest descent minimization was then performed for 50 iterations. For each reactive event, the potential energies of the system at the reactant structure, transition point, and product structure were stored, and a SMILES string was associated with the reactant and product geometries using a newly implemented canonical SMILES algorithm.[54] The SMILES served a dual purpose: They allowed the system to identify whether a user had repeated a reaction sequence that they had already performed, and they served a convenient label for initial bookkeeping such that users could get some idea of the structures they had formed in real time. For all the post analysis performed in this paper, independent minimization and SMILES generation routines were used to refine the raw data as described in Sec. IV.

Given the combinatorially large number of possible chemical reactions, we introduced a scoring mechanism to give users feedback on the relative kinetic importance of the different channels they found and to incentivize finding reactions with lower barriers. The SMILES codes were used to ensure that a user did not get any score for repeating a reaction that they had already performed. How important a given reaction is to the overall mechanism is determined by the free energy barrier for that reaction relative to other possible reactions from the same reactant structure. While it was not practical to determine the free energy for the reactions in real time, the potential energy of the transition point relative to the reactant was used as an indicator of the reaction favorability. The scores were calculated according to the following equation:

$$Score = 2.5 \times (400 - Ea), \tag{2}$$

where Ea is the transition point potential energy relative to reactants in kJ mol^{-1}. It was decided that a barrier of over 400 kJ mol^{-1} represented a reaction that was unlikely to be kinetically important and thus returned a score of zero. A factor of 2.5 was used to place the scores on a scale from 0 to 1000 to make the range more end-user intuitive. This scoring mechanism was viewed very much as a first iteration and is likely to be subject to improvement in future studies.

B. Sonification

Much of the game related elements we added to Narupa were designed to encourage "players" to react to the simulation and to preferentially explore lower energy conformation space available to the system. The potential energy of the system was not a quantity that was easily amenable to visualization, and instead, an auditory representation of the potential energy of the system was used. Given the amount of visual stimulus the "players" were already subjected to, it was hoped that this information might be better portrayed to the "players" through sonification. The sonification was created using the Wwise game audio engine.

The potential energy was sonified using a one-to-many mapping strategy, and the single value of the potential energy was mapped to multiple audio parameters with the aim of creating a sense of tension and urgency as the energy increased. A looping drone sound and a rhythmic pulse sound were triggered upon the energy exceeding a certain threshold. The source audio for the drone has a fairly static frequency content. This was then modulated with effects to reflect changes in the potential energy. The sound was passed through a parametric equalizer (EQ) with a high gain and narrow bandwidth (producing a sharp spike around its center frequency). The potential energy was set to modulate the center frequency of the spike between 100 Hz and 3 kHz. This was then passed to a delay unit, whereby the amount of feedback (the proportion of the output signal fed back to the input) increased proportionally with the potential energy. Finally, the audio signal was increasingly distorted with increases in potential energy. The combination of an EQ spike and a delay with a feedback loop meant that the longer the "players" stayed in a high energy state, the louder and more distorted the sound would become.

In addition to the sonification of the potential energy, "earcons" (short musical passages whose features are designed to represent some data feature) were added in order to categorize the types of reaction a "player" had performed. We grouped reactions into three types: association where the number of molecular fragments in the systems was reduced upon reaction, dissociation where the number of molecular fragments in the system increased upon reaction, and isomerization where the number of molecular fragments remained constant upon reaction. These three reaction types will be discussed more in Sec. III, but it was noticed in early tests that "players" had a preference for performing some reaction types over others. The earcons were designed to serve two purposes: to emphasize a reaction event and provide a sense of achievement and to encourage users to explore the different types of earcons by performing the different classes of reactions.

The sounds for all three reaction types were created using the same synthesis method to provoke a sense that they all pertain to the

FIG. 1. Left panel: User in VR using the controllers to apply force to two separate atoms. Interacting atoms are designated by white circles surrounding them. Right panel: UI elements showing the current score and a popup menu with a history of previously discovered species.

same category of event. The association earcon consists of a three-note chord that sustains for four bars, after which, a further two, higher notes are added in order to connote the idea of two things joining. The disassociation earcon consists of a five-note chord, which sustains for two bars, at which point three of the notes stop, leaving only two notes to sustain for the final two bars to connote the idea of something thinning out or splitting.

In order for the isomerization earcon to be linked to the others and yet stand out as a special case, it uses the same note classes but is different in its form. It consists of a fast arpeggio rising over four octaves using shorter, more percussive notes. The intention here is that this earcon stands out as a special case and would therefore encourage players to explore more of this type of reaction in order to trigger the more unusual/interesting sound event.

Examples of the sonification elements can be found in the tutorial video of the supplementary material.

C. UI additions

A number of visual UI elements were added to the VR front end of Narupa to create the game-like experience we desired. A dialogue box was used to indicate when a reaction had been detected. This box displayed a "Minimizing" message while the simulation briefly paused to determine the reaction score and to minimize the product geometry. This dialogue box was briefly replaced by one displaying the reaction score once the analysis was complete, before this dialogue box also disappeared allowing the users to continue exploring the reactivity of the system. The total cumulative score was continually displayed on the outside of the simulation box. In addition to these game related notifications, we also introduced a new menu for users in the game, displaying screenshots of the different product species they had discovered so far and allowing users to select one of these screenshots to reset the simulation geometry to that of the chosen product. This allowed users to rewind if they found that they had followed a sequence of reactions into an unreactive "cul-de sac" state. The screenshots of the player view from the reaction game are shown in Fig. 1.

III. USER TEST DESIGN

Prior to the final set of user tests described here, the test design evolved over several phases of tests. The use of iMD-VR as a platform for a reaction finding game was particularly motivated by the dynamic nature of the simulations. Visualizing such simulations offers far more information than a static representation of the chemistry: As the dynamic simulation is fully responsive to input, we surmise that iMD-VR can give real-time insights into systems being studied. For example, a favorable reaction will seem to "snap" into place, whereas trying to pull a molecule into an unfavorable conformation will be met with resistance. A strong user interface is key to making this principle obvious to the end-user. Thus, the testing experience was designed to maximize the perceptual feedback received from the simulation to help participants intuit favorable reactions.

The first round of user tests consisted of 30 undergraduate chemists given 5 min in a reactive OH + propyne simulation. It was apparent in these initial tests that users were highly adept at guiding multiple molecular fragments together to form a larger species (adduct). However, players were less successful when it came to promoting complex unimolecular or rearrangement reactions of the adduct atoms. From the literature benchmark for this system, it is known that the lowest energy and thus most kinetically important reactions in the OH + propyne system involve unimolecular rearrangement, such as hydrogen atom transfer from one atom to another. In the first tests, users demonstrated a propensity toward fragmenting the molecular adduct into smaller and smaller fragments, often imparting very large amounts of force into the system to achieve this. This is understandable from an entopic perspective: To perform a hydrogen transfer, at least three atoms need to be confined to be in a relatively small volume of configuration space, enabling the existing bond to break while simultaneously forming a new one. Conversely, a dissociation reaction simply required two atoms to be "pulled" apart with relatively few constraints on the configuration of the atoms. Even if a reaction scored zero due to the high energies involved, the user was then left with a system of molecular fragments that would rapidly associate together with little or no energy barrier. Future iterations aimed at reducing the bias toward entropically favorable reactions and encouraging users to consider the energetics of their interactions.

The second iteration of user tests was modified to encourage users to be more aware of the potential energy in the system. Primarily, the amount of force users could impart from their VR controllers was reduced providing a greater sense of "exertion" when users tried to break stable chemical bonds. This was emphasized by a reduction in the MD time step from 1 to 0.5 fs, which visually slowed

the simulation: A user should be free to break a stable bond without forming a new one, but it should take considerably more time and effort than doing so through a more stable transfer reaction. At this point, sonification elements were introduced to provide the users with additional sensory feedback about the energetic state of the system. This set of user tests consisted of 21 participants. The results from this second set of user tests showed a marked improvement over the first in terms of the extent to which users were able to reproduce the benchmark literature reaction network (see Fig. S1 of the supplementary material).

In this work, we focus on the results from the final iteration of user tests. These tests followed a similar format to the previous iteration with two exceptions: Users were guided through a more extensive tutorial and users were given 15 rather than 5 min to explore the reactivity of the OH + propyne system. These changes reflected our perception of there being a significant "learning curve" for users in the first two tests with regard to unfamiliarity with both the VR hardware and also the specific molecular simulation environment. The full tutorial video shown to each participant is given in the supplementary material, and this was followed by asking the users to accomplish a number of tasks for a separate isobutyl radical + O_2 simulation, which are as follows:

- "3 min to make as many different fragment combinations as you can, there must be no more than 3 H's unattached to a C at any one time."
- "3 min to carry out as many migrations either H or C as you can."
- "3 min to create as many cyclic products as you can."

Once these tasks were complete, users in VR were then given a full 15 min to sample different reactions in the OH + propyne system. 18 participants took part in this refined user test experience. The remainder of this paper will focus on the data gathered from this final set of user tests.

IV. RESULTS

A. User tests vs literature benchmark

The first metric that we use to assess the success of our crowd sourcing method for generating reaction is the extent to which the network generated by the final user tests reproduces the known network. As noted in the Introduction, the C_3H_5O (OH + propyne/OH + allene) system is unusually well characterized by the automated Kinbot study, and we take the resulting network from this study as representing a highly accurate description of the important chemistry. This Kinbot study involved some pruning of the full network such that only the reactions with low energetic barriers were considered, and Fig. 1 of the Kinbot study[47] further delineates the particularly important reactions by marking them as bold. Figure 2 shows the full network of nodes and edges discovered in the Kinbot study, and this network is colored according to whether the same reactions (edges) were found from analyzing the user test results. From Fig. 2, it can be seen that the "players" in VR discover all but four of the reactions from the benchmark and only miss one of the bold reactions. Furthermore, it is noted that the missing bold reaction was discovered in the second iteration of user tests (see Sec. S2 of the supplementary material). Given the limited scope of these tests, it is highly encouraging that a small cohort of users, each given 5 min with the system, can collectively cover the reaction network. With higher recruitment of participants, who would ideally have more than 5–15 min to explore a system, we anticipate that far reaching areas of a chemical landscape can be explored.

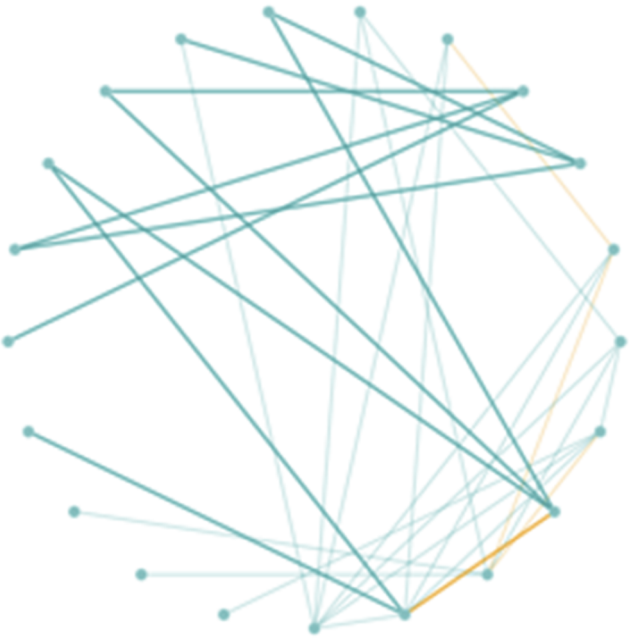


FIG. 2. Proportion of the benchmark Kinbot network captured by the final user tests. Orange signifies a species (node) or reaction (edge) present in the benchmark but not found in the user study. The bold lines are those reactions identified as particularly important by Kinbot.

Having demonstrated that the user test results provide good coverage of the important parts of the network, we turn to looking at an extended reaction network from the user test data with a view to analyzing the parts of the network discovered here, which are new or novel. In order to conduct this comparison fairly, it is necessary to recognize that all reaction chains in the literature mechanisms we compare to, terminate once a dissociation or fragmentation reaction takes place. For this reason, we have removed all bimolecular reactions from the user test data apart from those starting with the OH + propyne fragments. Figure 3 shows the resulting network covered by participants in the final user tests and indicates which nodes and edges were also found in the literature. Clearly, the space explored in the user tests is larger than that explored in the literature, and there are a range of new nodes discovered in the user test network, which do not appear in the literature. Many of these new nodes are "dead ends" with only one connecting edge and these typically represent fragmented products. There are other nodes found only in the user test, which are unimolecular and connected to a literature node by an isomerization process. Interestingly, there are also new edges (marked in cyan) showing new connections between existing literature nodes.

The second metric we wish to consider when assessing the success of the VR based crowd sourcing approach is whether the users identify any missing or novel reactions. Clearly, from Fig. 4, the user test data include many reactions that were not identified in the

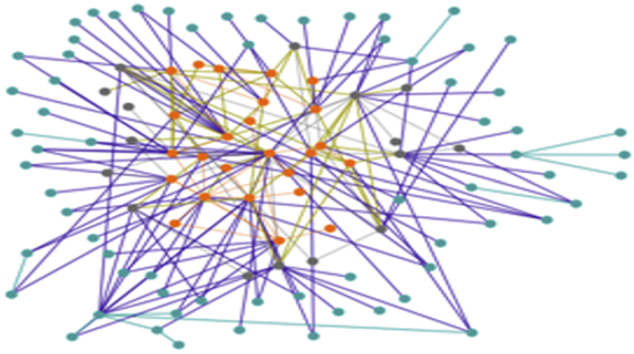


FIG. 3. Network unimolecular reactions covered by user test 3. Orange denotes node or edge found in the Kinbot mechanism, and gray denotes a node or edge found in the Fitzpatrick mechanism, but not in Kinbot. Gold, purple, and cyan edges all signify reactions that are not found in the literature and denote whether zero, one, or both, respectively, of the connected nodes are found by either Kinbot or Fitzpatrick.

literature. To analyze whether any of these reactions might compete with the know reactions in the literature, we took the reactions or edges marked in gold, purple, or cyan in Fig. 3 and attempted to locate a true transition state for the reaction by performing a saddle point optimization on the maximum of the spline path using the PM6 method in Scine Sparrow.[53] Then, we attempted to refine these PM6 saddle points with geometry optimizations at the M062x/6-311++G(d,p) method in Gaussian.[55] These calculations were done in an automated pipeline, but for two particular classes of reactions, the PM6 saddle point did not optimize to a corresponding saddle point at the M062x level of theory.

One class of reaction for which this behavior was observed was that of hydroxyl radical migration from one carbon to another. A PM6 saddle point for this type of reaction is shown in the left panel of Fig. 4. These hydroxyl migration reactions are not observed in either of the literature and typically provide a shortcut between two known nodes for which a connecting edge has not previously been identified. Another class of reaction that was observed frequently in the user tests but for which saddle points cannot be found at higher levels of theory is that of molecular hydrogen dissociation, where one hydrogen atom dissociates and takes another with it. A PM6 saddle point for this type of reaction is shown in the right panel of Fig. 4. Manual attempts to find the majority of these saddle points have also been unsuccessful at the M062x and B3LYP levels of theory with varying basis sets indicating that if such saddle points exist, they exhibit very different structures to the PM6 transition state structures. Interestingly, observations of the users performing some of these reactions showed instances of roaming type behavior[56–58] (although non-dissociative in the case of the OH migrations) as seen in videos of the supplementary material, and this raises the question of whether some of these reactions actually exhibit dynamical bottlenecks rather than the traditional transition state in the statistical sense.

The remaining reactions for which an M062x saddle point could not be found involved potentially barrierless dissociations or cases where a user had performed two reactions rapidly in a pseudo-concerted manner and the saddle point optimization returned the saddle point for one of the two sequential reactions, which was already found in the literature. In the latter case, it was sometimes observed that the energy redistribution following the initial reaction directly precipitates the second reaction, and this again raises the question of whether some of the dynamical behavior observed might be applicable to the high temperatures of a combustion engine.[59]

The new saddle points that were found were further refined by coupled-cluster singles doubles and perturbative triples [CCSD(T)]/cc-pVTZ single point calculations in Gaussian.[60] Saddle points with zero-point corrected energies less than 50 kcal mol^{-1} above OH and propyne are listed in Table I. These reactions are too high in energy to be presented in the Kinbot study, and given the relatively small system size and the unusually comprehensive nature of the Kinbot search, it is possible that all the important low energy pathways have already been discovered. However, users have found reactions that were not found in the Fitzpatrick study, demonstrating that our crowd sourced reaction finding approach is quite capable of finding reactions that may have been missed by previous "by-hand" transition state searches (Table I).

B. User test 3 vs ChemDyME

The ChemDyME[61] code has previously been used to automatically map the OH + propyne reaction network, and like the user tests presented here, it has been shown to capture the known channels well. For the current work, our main interest in using ChemDyME is that it utilizes molecular dynamics to identify chemical reactions (coupled with the TSCDS algorithm used here). We can also run ChemDyME using the same PM6 level of theory from Scine Sparrow.[53] The main difference then between the user generated iMD-VR results in the current work and those from ChemDyME

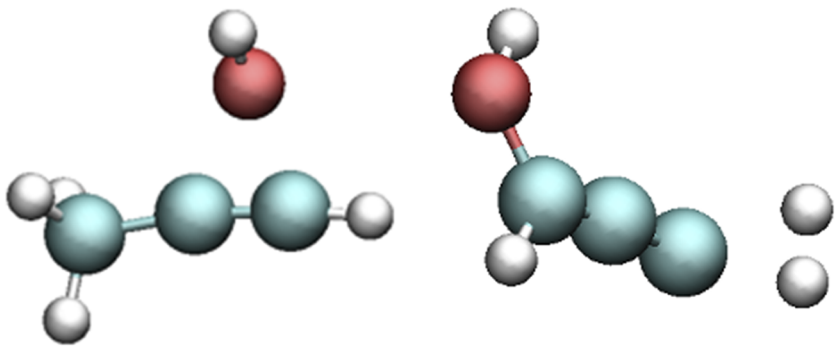
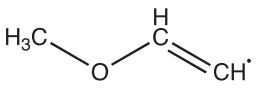
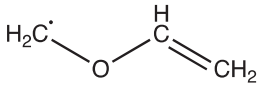
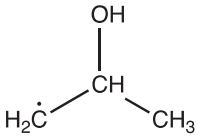
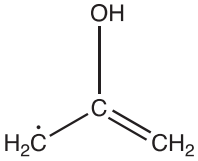
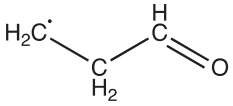
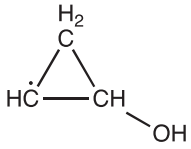
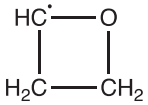
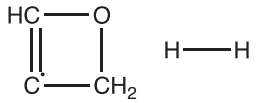
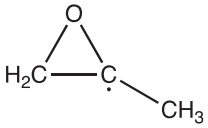
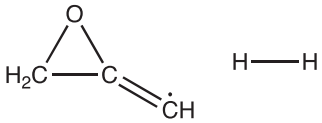
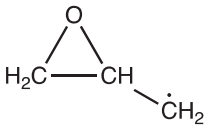
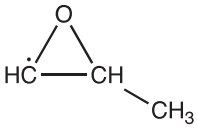
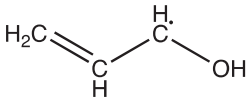
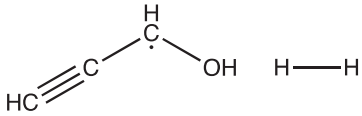
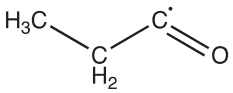
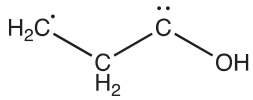


FIG. 4. Two example saddle points only found with the PM6 level of theory. They correspond to the OH transfer from one carbon to another (left) and H_2 loss (right).

TABLE I. New saddle points discovered from the analysis of the user test results.

Reactant	Product	CCSD(T)/cc-pVTZ energy relative to OH + propyne (kcal mol^{-1})
		20.52
		31.05
		35.29
		36.19
		37.27
		42.06
		42.08
		46.36

is that in the current case, the molecular dynamics trajectories are biased by humans, whereas in the ChemDyME case, an approach called "Boxed Molecular Dynamics in Energy" (BXDE)[62] is used. Since it has already been demonstrated independently that both methods capture the important chemistry, here, we instead wish to focus on the differing dynamical behavior between algorithmically biased MD and human biased MD. The input for the ChemDyME simulations is given in Sec. S4 of the supplementary material.

One way to visualize the space covered by an MD trajectory is through using dimensionality reduction techniques to extract the salient features that change over the course of the trajectory. Recent work by Hare *et al.*[63] presented the PathReducer code for exactly this type of analysis.

Briefly, PathReducer generates a set of new principal coordinates, each comprising a linear combination of interatomic distances within the system, in a manner designed to capture the maximum amount of structural variance with the fewest coordinates. The general form of these new principal coordinates, is shown in the following equation:

$$PC = \sum_{i,j,i\neq j}^{N} C_{ij} d_{ij}, \tag{3}$$

where N is the number of atoms in the system, C_{ij} are the scalar coefficients, d_{ij} is the interatomic distance between the atoms *I* and j, and indices *I* and *j* run over the atoms of the system. To visualize the space covered by both the user studies and the ChemDyME run, we combined the trajectory frames from each and used the PathReducer code to capture as much of the variance in the chemical structure as possible using three degrees of freedom. This approach maps the Cartesian coordinates of each frame in the trajectory onto the three principal coordinates, allowing visualization of what would otherwise be a high dimensional dataset.

Figure 5 shows the points from both the user test trajectories and the ChemDyME trajectories mapped onto this PC space, and it is immediately apparent that the coverage of the user tests

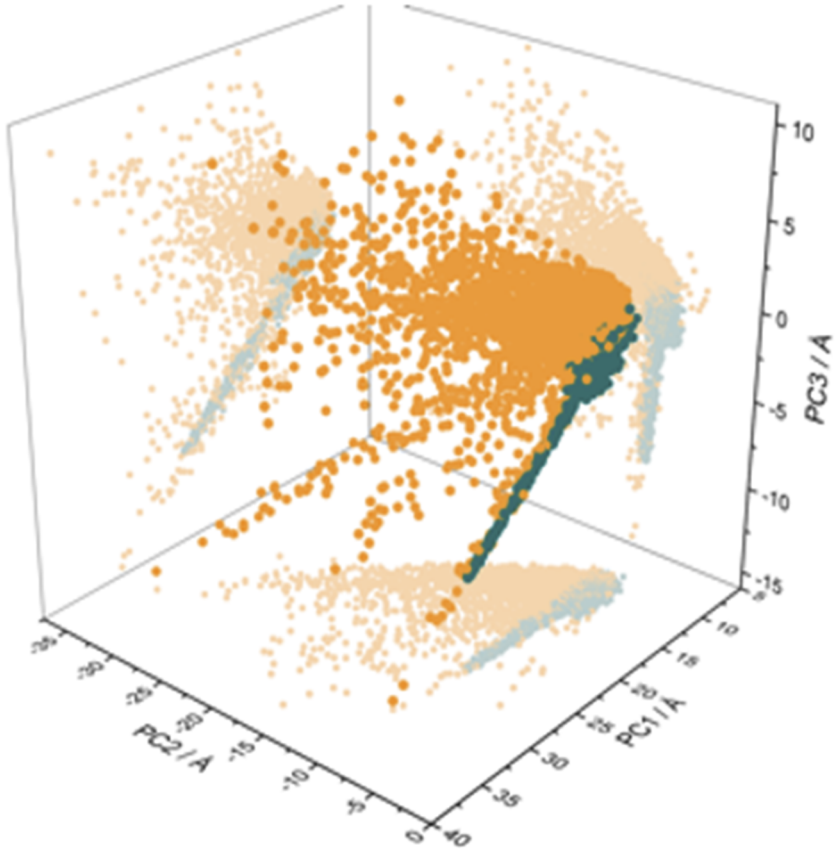


FIG. 5. Reduced dimensional space for trajectory frames from both user study 3 and a ChemDyME run. Cyan represents the points from ChemDyME, and orange represents the points from the user test.

in terms of changes in molecular geometry is much larger than in the ChemDyME case. In the user tests, "players" often discovered dissociation pathways and there were frequently two or more molecular fragments in the system at a given time. Conversely, for the ChemDyME trajectories, once the initial OH + propyne association has occurred, the chemistry sampled is predominantly unimolecular and any dissociative events are terminated not long after the bond breaking event occurs. The large space covered by the user test reflects the large internuclear separations that occur with molecular fragmentation, and the "tendrils" reaching out into different regions of PC space correspond to different dissociative chains discovered by different users.

The amount of chemical space coverage from the user test studies can be framed as a difference in scope between the user tests and the literature and ChemDyME studies. Although the Kinbot and ChemDyME explorations are formally studying the C_3H_5O atomic space, in reality, the search is confined to those areas of space, which are energetically or kinetically viable, starting from the OH + propyne (and OH + allene in the Kinbot case) moieties. In this regard, they are comprehensively sampling a valley in the full C_3H_5O space bounded by regions of high potential energy. In the case of the user tests, "players" were able to input sufficient energy to escape this OH + propyne valley and explore other valleys corresponding to alternate C_3H_5O chemistries. Thus, while the reaction game may miss some of the low energy OH + propyne

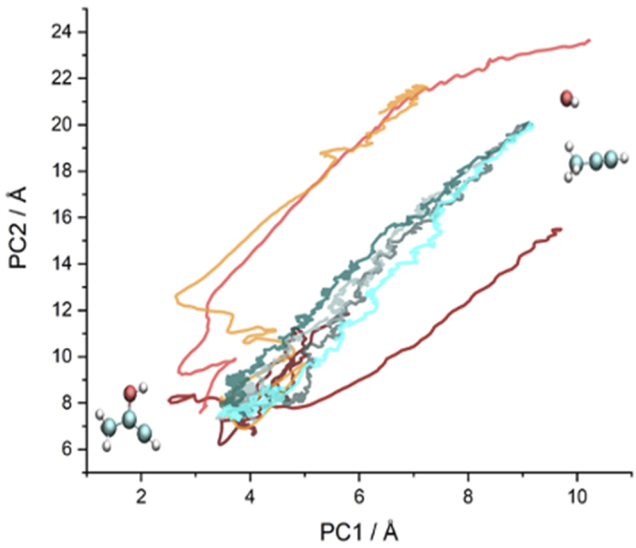


FIG. 6. Reduced dimension trajectories for the bimolecular association reaction P to W11. The reactant and product geometries are shown near their corresponding regions of PC space. Trajectories on the blue/green spectrum are from ChemDyME, and trajectories on the Red/Orange spectrum are from user test 3.

reactions, as a tool for exploring wider chemical space, it has many advantages.

Given the observations in Fig. 5, it is perhaps more informative to compare ChemDyME and the user tests for specific reactions. We have chosen two reactions: a bimolecular association (P to W11 in Kinbot nomenclature) and a unimolecular hydrogen transfer (W11 to W10 in Kinbot nomenclature). For each reaction, corresponding trajectories were taken from ChemDyME and the user studies and PathReducer was used to perform a dimensionality reduction. For the dimensionality reduction, only the heavy atoms and the H of the OH moiety were considered since the other hydrogens do not participate in either reaction.

Starting with the bimolecular association, a total of eight trajectories were combined, four from the user tests and four from ChemDyME, and PathReducer was used to generate two PCs capturing 0.99 of the structural variance of the fully dimensional trajectories. Figure 6 maps the eight different reactive trajectories onto the PC space. One thing to note in regard to Fig. 6 is the fact that all ChemDyME trajectories start from the same orientation and intermolecular distance of the OH and propyne fragments, while the user test trajectories exhibit a variety of starting coordinates due to the random way in which the two fragments are spawned in the user tests. This accounts for the variation in starting position in the user test trajectories.

An investigation of the terms of the linear combination of interatomic distances for PC1 and PC2 (Tables S3 and S4) of the supplementary material shows that PC1 is dominated by distances between the O and H atoms of the OH radical and the CH_3 group of the propyne, whereas PC2 has large contributions from interatomic distances between the O and H atoms of the OH and terminal H's on both ends of the propyne. This means that changes in PC1 are almost exclusively related to the intermolecular distance between OH and propyne, whereas PC2 is more sensitive to the angle of the OH moiety relative to the carbon chain in the propyne.

Considering Fig. 6, the ChemDyME trajectories show gradual changes in PC2 across the course of the reaction representative of a relatively straight association path with little need to reorient the two moieties. On the other hand, the user test trajectories show a rapid (smooth lines with little sign of oscillations from molecular vibrations) reduction in the intermolecular distance between fragments followed by some fine tuning of the approach angle, signified by the changes in the PC2 coordinate at lower values of PC1. This observation is supported by observing the length of the user and

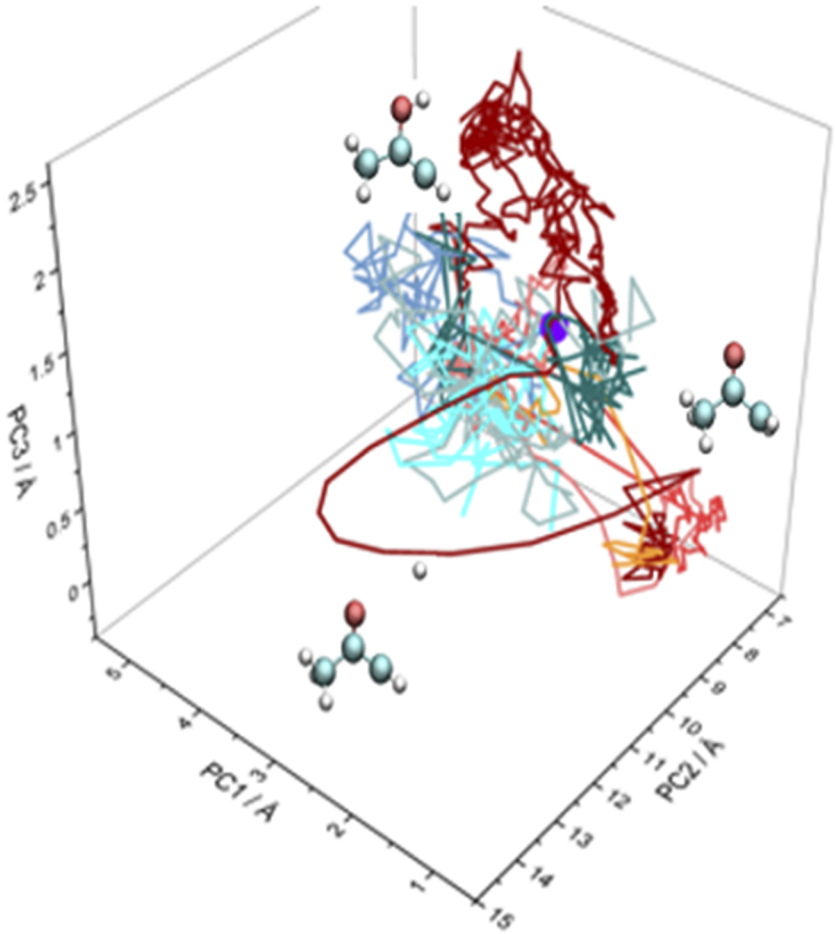


FIG. 7. Reduced dimension trajectories for the hydrogen reaction W11 to W10. The reactant and product geometries are shown near their corresponding regions of PC space. Trajectories on the blue/green spectrum are from ChemDyME, and trajectories on the red/orange spectrum are from user test 3.

ChemDyME bimolecular trajectories. The ChemDyME trajectories take an average of 2570 ± 300 (at the 2σ level) femtoseconds to react whereas the user test trajectories take an average of 1340 ± 730 fs, indicating that users in VR were able to perform the bimolecular reaction more quickly.

Turning to the isomerization reaction, a total of eight trajectories were used (four from the user tests and four from ChemDyME). For ease of visualization, the stable reactant and product geometries were added to either end of each reaction path such that all trajectories started and ended at the same point. In this case, three PCs were obtained from pathReducer, which together capture 0.84 of the total variance of the fully dimensional trajectories. These trajectories are shown in Fig. 7, and the structure of the saddle point for this reaction is projected onto PC space (marked by a purple circle).

The first thing to consider is the red trajectory from the user tests. In this trajectory, the user almost fully dissociates the hydroxyl hydrogen before reattaching it to the correct carbon in an almost "roaming" like manner. This trajectory follows a very different path to the others, and PC2 primarily differentiates this trajectory from the others. The other trajectories are more closely clustered around the saddled point structure marked in purple, although the user test trajectories stretch further from this structure at lower values of PC1 and PC3. In this case, the reaction time for the user test trajectory is more than three times larger than all the other trajectories with the user taking 3700 fs to perform the reaction. Discounting this trajectory, the average reaction time for the user tests and the ChemDyME trajectories agree well with values of 840 ± 520 and 820 ± 90, respectively.

Figures 6 and 7 combined show some interesting differences between the human-guided behavior and computer biased MD. In the bimolecular case in particular, the bias in the ChemDyME trajectories is shown to be more "gentle" with oscillatory behavior being observed along the trajectories as the molecule vibrates naturally on the way toward reaction. Conversely, in the human biased trajectories, the points at which a force is applied are often very visible in the reduced dimensional trajectories, signified by a very rapid change in PC coordinates in a short number of time frames. This behavior was shown to be particularly efficient at rapidly drawing separate fragments together before fine tuning the association path. This could motivate the use of mixed time step trajectories for association reactions where large MD time steps are used at large internuclear separations and the time step is reduced as the moieties approach.

V. CONCLUSIONS

In this work, we leverage the interactive molecular dynamics approach in the Narupa software to design a new crowd sourcing platform to gather data from players in VR from which we explore chemical networks. There are two strands to this work. First, we demonstrate that analyzed data from "players" in VR capture the important parts of a known benchmark network. Second, we compare the human biased molecular dynamics from these user tests with algorithmically biased MD and find key distinctions between the two strategies employed, particularly in the case of bimolecular reaction.

Considering the first of these strands, after refinement of the reaction game over three separate sets of user tests, we demonstrate that the final set of user tests is extremely comprehensive in its sampling of a well-studied combustion system, finding all "apart from four" of the known reactions. In addition, data from the user tests reveal many new higher energy pathways, which do not appear in either of the two benchmark studies we have chosen to compare against. While these new pathways may have been found and discounted by the automated, Kinbot, study, they are not explored in the Fitzpatrick study, which includes reactions with barriers in a similar energy range. It is also worth noting that being based on molecular dynamics, the user studies are capable of observing dynamical behavior that approaches based on saddle point searches might miss. These three findings suggest that the reaction game presented here is a valuable addition to the array of existing mechanism generation approaches. Given the small system and the comprehensive nature of the Kinbot study, it is likely that all of the lowest energy pathways have already been found, precluding the user studies from finding new reactions in this energy range. However, the data gathered by users demonstrate a particularly extensive exploration of chemical space, and this coupled with the relative central processing unit (CPU) efficiency of user biased dynamics (as discussed below) gives us hope that this approach will scale well to larger and less well understood systems.

Turning to the second strand, we have compared the raw, user generated molecular trajectory data with reactive trajectories from automated calculations in the ChemDyME code. By visualizing the raw trajectory data in a reduced dimensional space, we observe that the user tests explore a much larger area of chemical space than the ChemDyME calculations particularly with respect to molecular fragmentation. Considering a specific bimolecular reaction from the C3H5O system, we observe very distinct strategies employed by the differing algorithmic and human biases to the MD. In the user case, it is observed that the two molecular fragments were pulled together rapidly in contrast to the more gentle, oscillatory association observed in the algorithmic case. This observation is supported by the fact that the human biased trajectories reacted significantly faster than those from ChemDyME.

In summary, this work demonstrates that an iMD-VR based reaction game is an effective tool for mechanism discovery that both captures known chemistry and has the capability of discovering novel reactions. We also highlight key strategic differences between the iMD-VR approach and a popular algorithmically accelerated MD approach. It is hoped that more data will allow these differences to be examined further in the future. One limitation of this approach is that running these experiments at home requires (a) a computer that is powerful enough to run molecular dynamics and VR simultaneously and (b) expertise in setting up and running molecular dynamics within a Python environment. Understandably, this could create a barrier to entry for the typical end-user. In the future, we aim to address this with cloud-hosting of simulations; in practice, users need to only open the Narupa iMD app and connect to an IP address, greatly streamlining the process of starting and running an IMD-VR simulation. The 18 users in the final set of tests only spent a cumulative 4.5 h in VR, and with the increasing home ownership of VR capable hardware, it is hoped that rolling out this reaction game framework to the cloud could gather substantially more user participation.

Alongside this cloud based roll out, there are many further refinements to be made to the UI elements to make the game as engaging as possible. In particular, improvements in the real-time analysis of reaction pathways would both improve the scoring mechanism and allow players to visualize the reaction network that they have created. With ongoing UI development and the distributed nature of the Narupa cloud-based infrastructure, we hope in the future to leverage the large community of citizen scientists in order to roll out this reaction finding the framework described here as a more complete reaction finding tool.

SUPPLEMENTARY MATERIAL

See the supplementary material for the tutorial video shown to all participants of the user tests, two videos showing examples of possible dynamical behavior in the user test trajectories, xyz files with all user generated trajectory data, a document with more detailed information on the initial user test results and the dimensionality reduction calculations.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available within the article and its supplementary material.

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