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Supplementary Materials for

Sampling molecular conformations and dynamics in a multiuser virtual reality framework

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The PDF file includes:

Other Supplementary Material for this manuscript includes the following:
(available at advances.sciencemag.org/cgi/content/full/4/6/eaat2731/DC1)

- movie S1 (.mp4 format). Sampling molecular conformational dynamics in VR (www.vimeo.com/244670465).
- movie S2 (.mp4 format). Interactively sampling dynamical pathways of benzylpenicillin binding to β-lactamase (www.vimeo.com/235894288).

section S1. Launching a cloud-hosted iMD session

Binaries for each platform (Windows desktop, Windows with SteamVR, Mac OS X, and Android) are available at https://isci.itch.io/nsb-imd

To run a task on a particular piece of interaction hardware, simply download the appropriate version of the application for your device and launch. Note that Android users may need to edit their security settings to allow installation of apps from external sources. Windows and Mac users will similarly need to ensure that their OS security permission enable them to run the app. Once the app is launched, follow the in-app buttons to select from one of the available servers which will host the simulations, then choose a molecular task to try. The following devices and operating systems are supported:

- Desktop/laptops running Windows XP SP2 or higher; or Mac OS X 10.9 or higher;
- Android touchscreen devices running Android OS 4.1 or later; with either an ARMv7 CPU with NEON support or Atom CPU, and OpenGL ES 2.0 or later.
- For the VR version of the app, a desktop running Windows 10 with a VR-capable GPU, as well as an HTC Vive headset and controllers.

Note that iOS is not currently supported. We have tested the application on a variety of machines, including Windows 10 desktops; Macbook Pro laptops running OS X High Sierra; Samsung Galaxy phones (S5, S6, S7) and tablets (S3); and Google Pixel, Pixel XL and Nexus 5 phones. Any issues or bugs found when using supported devices should be reported by leaving a comment on the itch.io website.

The latency of cloud-mounted interactive simulations depends on network speeds and wifi performance. Note that the experience using the application will vary according to one's distance from the server. For best results, we recommend choosing your simulation server to be hosted on the Oracle data center (Frankfurt, Germany; Phoenix, Arizona; Ashburn, Virginia) nearest to your physical location. Round trip measurements of the average latency (± standard deviation) for transmitting data from our lab in Bristol to each of the three Oracle data centers were as follows: 48.7 ± 9.5 ms for Bristol to Frankfurt; 118.7 ± 11.5 ms for Bristol to Ashburn; and 182.1 ± 18.3 ms for Bristol to Phoenix. For each round trip measurement, we investigated performance when interaction and visualization clients were connected via wifi (the Bristol eduroam network), and also via an ethernet cable. The results are shown in fig S1. The latencies measured on wifi were statistically indistinguishable from those measured on an ethernet connection. Outside the confines of the lab, we noticed that we obtained acceptable latencies even on 4G mobile networks.

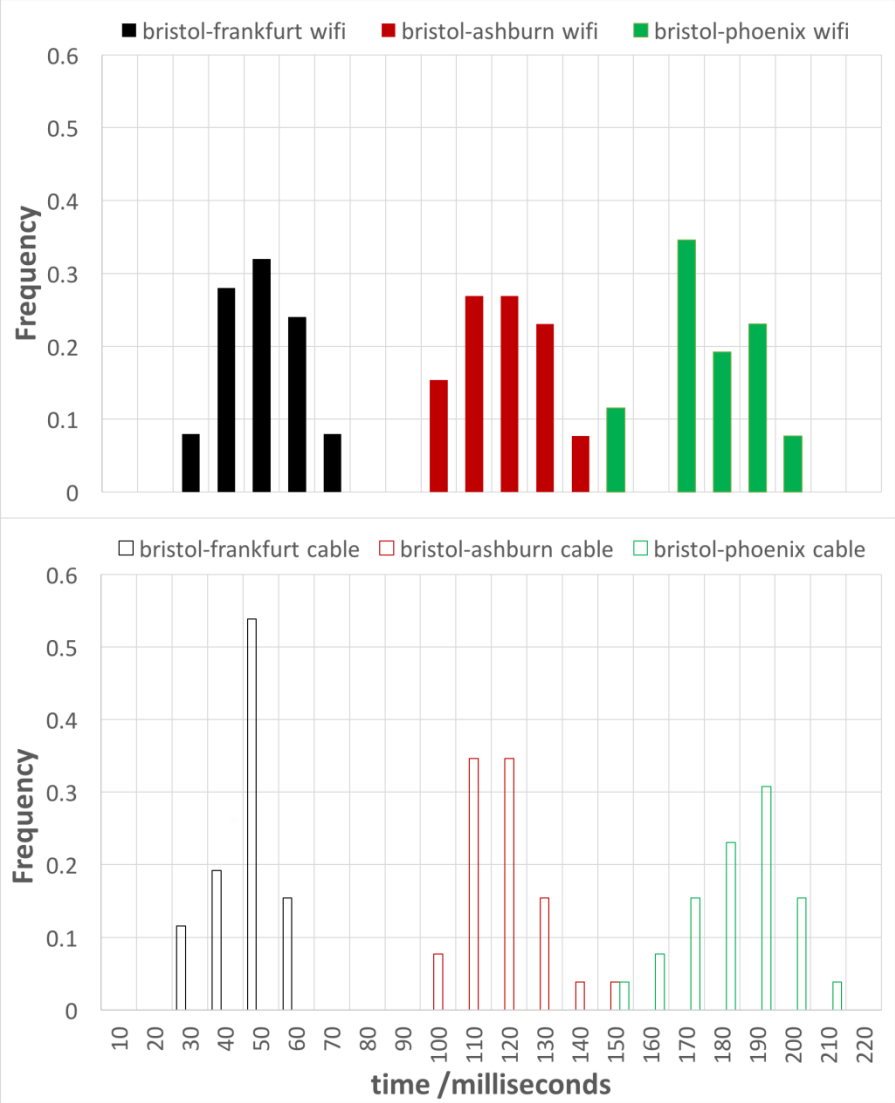

fig. S1. Distribution of round-trip latencies, measured from Bristol to each of the cloud data centers. The top panel shows measurements where the interaction/visualization client is connected via wifi, and the bottom panel shows measurements where the connection was via ethernet cable.

As described above, the simulation servers utilized during our user studies were hosted on machines operating on a local network. The reason for this is that, at the time this work was carried out, Oracle's Frankfurt-based European cloud resources which give the best latencies from Bristol (as shown in fig S1) were not yet available. The cloud-mounted simulation engine offers the most straightforward way for interested readers to test our framework, and also eliminates a host of issues which could arise from hardware and OS incompatibilities. Those readers who are unable to achieve reasonable latency on the available cloud servers but who wish to test out the framework described herein should contact the corresponding author.

section S2. User study data

table S1. Self-reported familiarity with the VR and tablet platforms on a Likert scale for user study one (*n* = 32), user study two (*n* = 12), and user study three (*n* = 32), where 1 represents having no experience and 5 represents being very experienced. Mouse familiarity was assumed to be high.

	Prior Experience with	1	2	3	4	5
User study 1	Virtual Reality	20 (62.5%)	8 (25.0%)	3 (9.38%)	1 (3.13%)	0
	Tablet Computers	1 (3.13%)	5 (15.6%)	9 (28.1%)	10 (31.2%)	7 (21.9%)
User study 2	Virtual Reality	7 (58.3%)	4 (33.3%)	0	1 (8.3%)	0
	Tablet Computers	1 (8.3%)	0	6 (50%)	2 (16.7%)	3 (25%)
User study 3	Virtual Reality	20 (62.5%)	7 (21.875%)	3 (9.375%)	0	2 (6.25%)
	Tablet Computers	1 (3.125%)	3 (9.375%)	10 (31.25%)	12 (37.5%)	6 (18.75%)

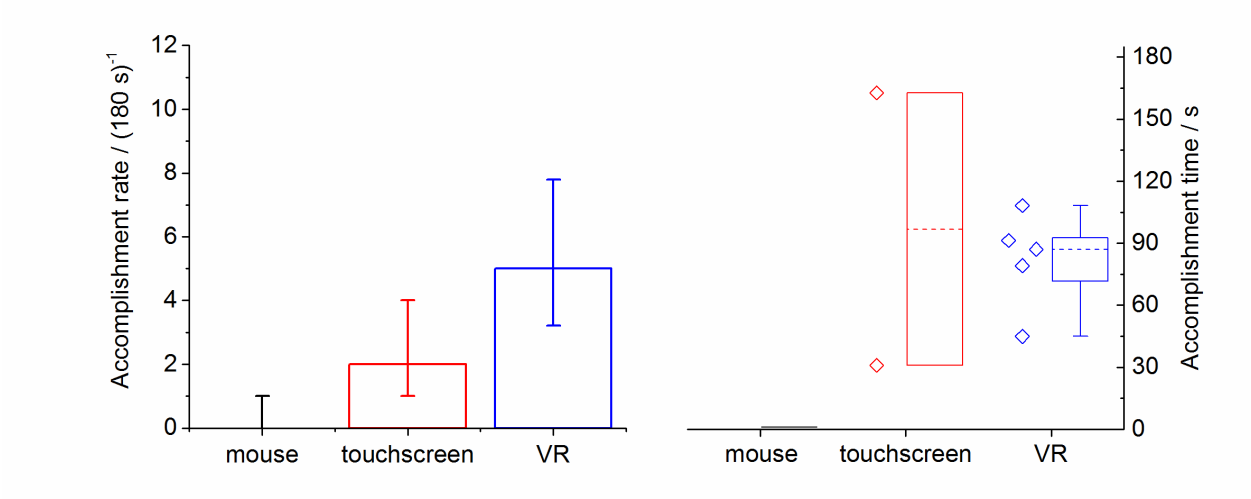

fig. S2. User study results. Left-hand panel shows user accomplishment rates for the knot tying task in the second user study (n = 12), with Poisson errors bars. Right hand panel shows the corresponding distribution of task accomplishment times, along with box-and-whisker plots, where whiskers span the data range, box limits indicate the standard error of the distribution, solid lines show the mean, and dotted lines show the median.

section S3. Platform design

Supplementary video 1 and Supplementary video 2 give a good indication of how interaction in VR works, along with the controls which participants can access in order to accomplish the tasks outlined in the main text. We briefly outline those controls in what follows.

Virtual Reality: The simplest way for a user to change the perspective or angle from which they view a real-time molecular simulation is to walk around the molecule, exactly as they might do with a physical model. Alternatively, he/she has the option to rotate the 3d camera view by holding down the two 'grip' buttons on each side of the HTC vive controller (illustrated as purple rectangles in fig S3a), and then carrying out the 3d rotation which he/she wishes to achieve. Scaling the size of the simulation render is achieved by holding down the two grip buttons, and moving the controllers either toward each other (zooming out from the simulated molecules) or away from each other (zooming in on the simulated molecules), gesture which is intended to mimic the popular 'pinch-to-zoom' gesture that is popular on mobile platforms. To accomplish tasks, users pulled the triggers of their wireless controllers (shown in fig S3a) to 'grab' specific atoms within the simulation, which they can then manipulate as they like. The small purple sphere (situated at the end of the long axis of the controllers in fig S3a and S3b) indicates the center of the Gaussian defined in Eq (4) of the main text. Embedding the sphere into a particular atom and pulling the trigger results in a force being exerted on that particular atom, during which time there is a change in color of all the atoms except those on which a force is being exerted. A menu button, shown in fig S3b, is accessible by pressing the orange controller button. ↺ resets a particular simulation to its initial conditions, ⏸ pauses the simulation, ⏭ advances the simulation one step at a time, and ⏵ resumes the simulation at the standard propagation rate of 30 Hz. Additional menu options allow users to change the molecular renderer; however, these options were disabled during the user studies, in order to ensure that the renderers utilized on each platform were in fact identical.

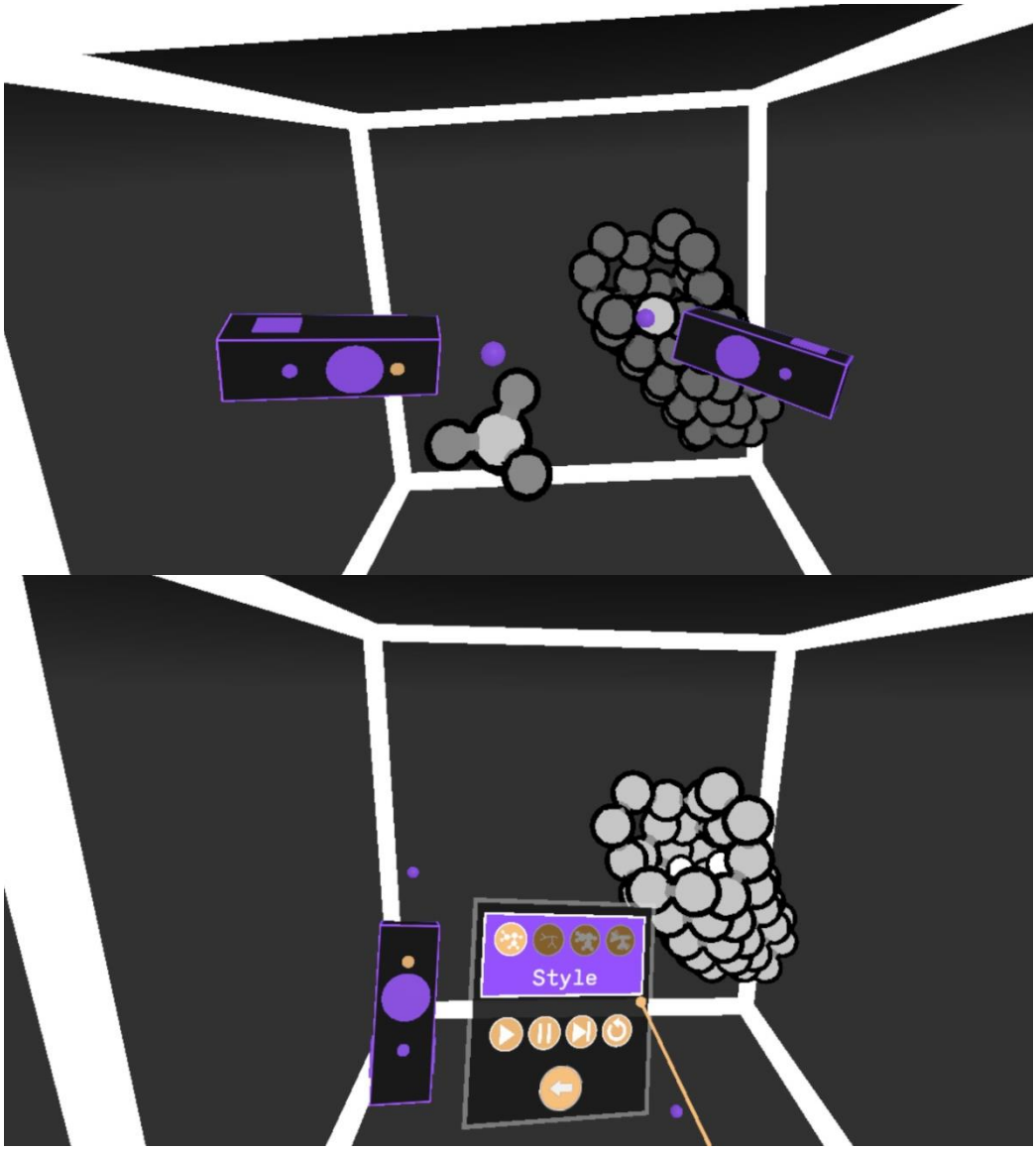

fig. S3. Screenshots of a user's view from within VR carrying out the nanotube task. The top panel (**A**) shows the user's controllers, along with the menu button, grip buttons, and positioning sphere. The bottom panel (**B**) shows the menu available when a user presses the menu button.

Screen & Mouse: When using a mouse to accomplish simulation tasks, the user is obviously unable to navigate the molecular simulation by walking around. Changing the camera view is therefore the only reorientation strategy. To change the rotation angles which define the camera's perspective with respect to the simulation box (see fig S4a), we used the same strategy common to a number of molecular simulation/visualization tools, where the rotation angles of the camera in the vertical and horizontal directions can be changed by simply clicking the mouse, moving it across the screen, and then releasing once the desired rotational perspective has been achieved. To achieve such rotations, the user must ensure that the initial click is not located on an atom; in cases where the initial click occurs on an atom, then that particular atom is selected and 'grabbed', an interaction which persists until the user releases

the mouse button. As an indicator that a user is ‘grabbing’ an atom, all atoms change color except for the atom being manipulated; once the atom is released, its color changes back to the default (this choice of visual feedback ensured consistency with both the VR and touchscreen interfaces, for which the design rationale is discussed below). As a result of the 2d limitations of the hardware, the user ‘grabs’ that atom measured to be nearest to the mouse icon in the 2d plane of the screen. Because atoms which are closer to the user are bigger, they are therefore easier to ‘grab’. Once an atom is ‘grabbed’ it can only be moved in the 2d perspective of the camera; 3d motions must be built up from successive 2d motions followed by repositioning of the camera. To scale the size of the simulation render, we again used a strategy which is common to other molecular simulation/visualization programs, in which the user controls the zoom level via the mouse scroll wheel, with up/down scrolling motions allowing participants to zoom in/out. fig S4b shows a user’s view having undertaken a rotation, and a then subsequently zoomed in. The left hand panel of figs S4a and S4b show the location of the ↺, ⏸, ⏭, and ▶ icons, each of which has identical functionality to the VR version of the app.

Touchscreen: The touchscreen interface looks identical to the screen/mouse platform interface in fig S4a and S4b. The only differences are in how interaction and navigation are carried out: (1) the user changes the camera orientation by moving a single finger across the touchscreen surface, ensuring that their initial contact position does not overlap with an atom; (2) zooming in an out is accomplished by the now ubiquitous ‘pinch-to-zoom’ gesture which is commonplace on mobile devices and touchscreen apps; (3) the user ‘grabs’ an atom by simply placing his/her finger on top of the atom that he/she wishes to manipulate. To indicate that a user is ‘grabbing’ an atom – i.e., exerting a force on a particular atom, he/she sees all atoms change color except for the atom which is being manipulated; once the atom is released, all colors change back to the default. This form of visual feedback we found to be particularly effective as a solution to the fact that the atom a user is trying to manipulate is often hidden under his/her finger (i.e., we required a form of visual feedback which could be easily perceived despite a finger obstructing the target).

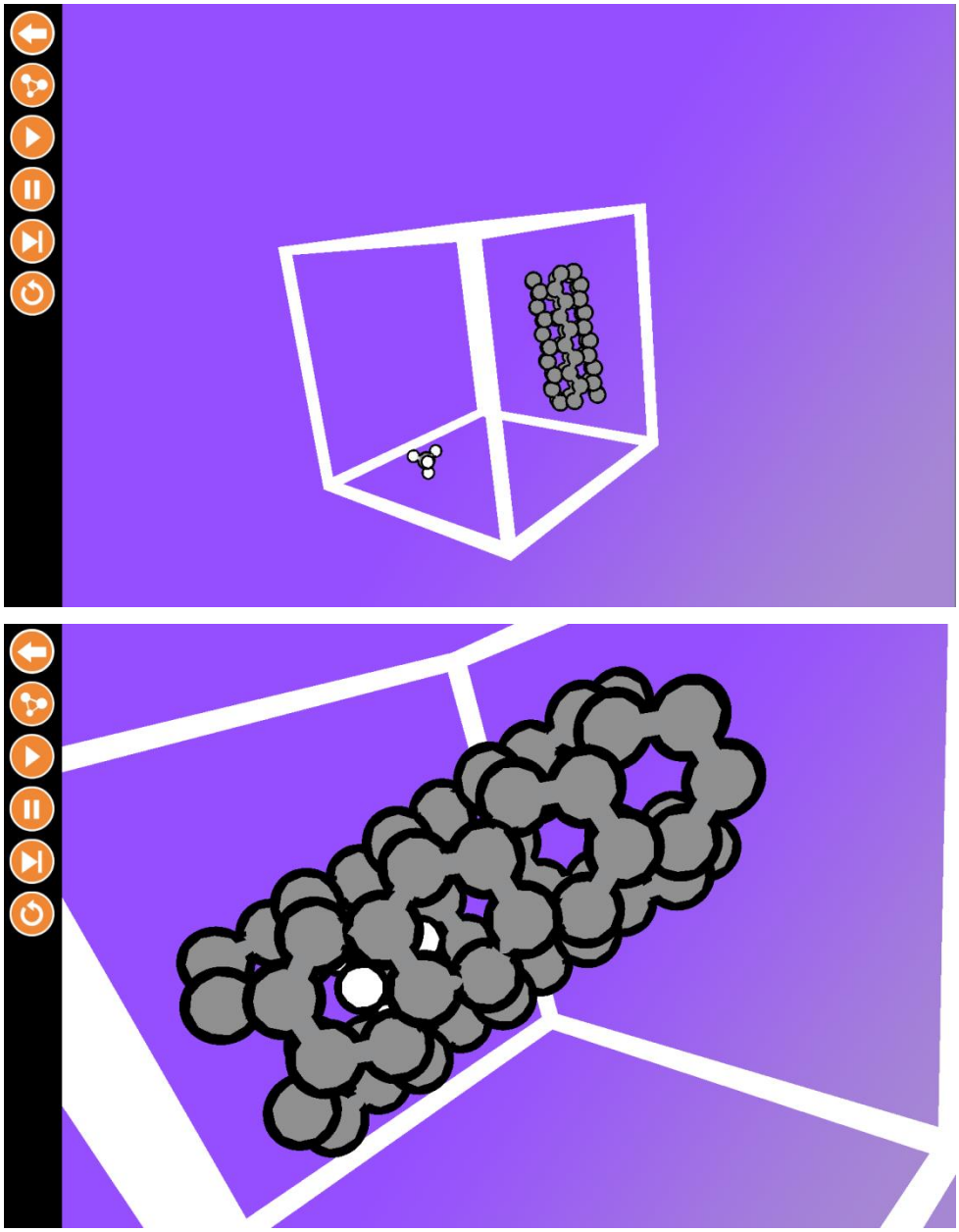

fig. S4. User's view of the molecular manipulation application when using either a mouse or touchscreen. Top panel (**A**) and bottom panel (**B**) shows the view from two different camera orientations and zoom levels.

section S4. Qualitative analysis of participants' subjective feedback

Interactively chaperoning molecular processes requires some degree of spatial reasoning: guiding chemical processes requires users to move, rotate and align molecules in 3D space. In order to gain a deeper understanding of the relationship between platform and spatial reasoning, participants were either given a questionnaire or interview after attempting tasks. Specifically, the 32 participants who completed the nanotube/methane and helicene tasks were given a questionnaire to complete. The 12 participants who completed the knot task were interviewed in groups of two or three in order to facilitate discussion and elicit more feedback. The task completion rates for first and third user tests can be found in the main text. Completion rates for the second user test can be found in fig S2 within this SI. Regardless of session, all participants were asked to state their favorite platform to use. We used a thematic analysis to analyse this data following a grounded approach (see the 'Materials and Methods' section of the main text) , which enabled us to build themes up as we went through the interview transcripts. One researcher iteratively identified codes and common themes that emerged across the transcripts, resulting in 15 initial code categories that focused on the usability and experience of undertaking the experimental tasks. These formed the list of first order themes, which were then refined into the following three main high level themes: 1) *impact of depth perception*, 2) *control over perspectives*, and 3) *two-handed gesture control and sense of agency.*

4.1 Impact of depth perception

Overwhelmingly, VR was selected as the preferred platform (41 out of 44 total participants). Commenting on the positive or negative features of VR, participants felt that it gave a distinct advantage to depth perception, making the 3D shape of molecules easily comprehendible: *"I would say that the VR is probably the best platform because both the tablet and the computer can't really get to the three-dimensional control but VR you can" (P2 – session 5) (N=6).* When asked to rate the importance of depth perception to task completion, all responses indicated it was important to some degree, by far the most positive response. VR also had a second advantage with regards to depth perception. As the user is immersed in a fully-3D space, they can easily make movements into and out of the plane of their screen. When limited to the flat screen however – as is the case with the mouse and touchscreen platforms – participants found pinpointing 3D space more difficult. In particular, the two dimensional view caused difficulty for the knot task; participants needed to successfully circle one end of the protein string around the other and pull it through the resulting loop: *"because the [Screen and Mouse & Touchscreen platforms] are on flat screen it was hard for me to figure out what was actually*

where in terms of relative like when you try to tie a knot one bit over the other but back under but getting it to do that was quite hard whereas in VR it was easier to see where things were." (P1 – session 1) (N=10).

1.2 Control over perspectives

With the three-dimensional 17-ALA molecule rendered on a 2d screen, users found themselves changing 2d camera orientation in order to inspect whether the initial loop shape was appropriate for tying the knot. At this point, participants forfeited some degree of control over the molecule in order to adjust the camera; in several cases, the real-time molecular dynamics simulation led to a loss of molecular shape during the time that the user was adjusting the 2d camera view: *"I had to try and rotate the entire thing if I wanted to pull something in a new direction and by the time I had rotated it that thing had already shaken into a different conformation" (P3, session 2) (N=4).* For the platforms where the molecules were rendered onto a flat screen, participants found it harder to see the overall shape of a molecule: *"[in VR] you could walk round the thing you were doing, whereas I found with the tablet as soon as you pulled, as soon as you were able to get the chain into its extended conformation as well as trying to get it ready to knot, you still had to somehow turn [it] round and doing that with a mouse or your finger was really difficult" (P1 – session 4) (N=5).* This attitude is corroborated by the questionnaire responses undertaken by the participants who completed the nanotube and helicene tasks. Participants were asked to rate the importance to task completion of depth perception, two-handed control, and orientating around the virtual space. Figure S5 provides a summary of these results.

fig. S5. Number of participants (*y* axis) self-reporting their attitudes on the importance of depth perception, navigating the virtual space, and controlling molecules with two hands. Responses were given on a Likert scale between 1 and 5 (x axis), where 1 represents no importance and 5 represents high importance.

In VR, not only can the camera and molecules be easily controlled simultaneously, users can also freely make molecular manipulations in any dimension, allowing a significantly higher degree of control: *"I think that because I felt much closer to the actual molecule I could see it better because you really could look at it from more angles and get much closer to it as if it was right there and so it was more like dealing with the physical thing" (P2 – session 2) (N=5).* As an additional consideration, the touchscreen camera and molecule were both controlled with the same action of dragging their finger against the screen, meaning that some participants would unintentionally rotate the camera at points where they may have intended to grab a molecule (and vice versa): *"it was pretty fiddly with the tablet to use two fingers." (P3 – session 2) (N=4).* In VR, camera view is controlled by head position, and the molecules are separately controlled by hand gestures, which removes input ambiguity.

4.3 Two-handed gesture control and sense of agency

VR, as a co-located from of 3d interaction, directly maps user movements to in-world gestures, meaning that actions (e.g., tying a knot, or threading a methane molecule through a nanotube) were more intuitive. Participants expressed a sense of agency over the VR simulations owing to the fact that 'real-world' physical gestures can be directly utilized for VR molecular interactions. For example, the physical gesture required to tie a virtual molecular knot is essentially identical to that of tying a

physical knot: *"The actual knot-tying action was quite natural" (P2 – session 1); "the chain a lot easier to manipulate in the VR than I did either with the tablet or the mouse just because you had two paddles" (P1 – session 4) (N=6).* For the two other platforms, this is not the case: participants are forced to translate what are familiar physical gestures (e.g., tying a knot) into a secondary set of gestures adapted to the limitations of the platform. In many cases, these secondary gestures are far less intuitive, especially when attempting to accomplish complicated 3d tasks: *"[it felt] like tying a knot in the real world whereas this [Touchscreen] and that [Screen & Mouse] I felt much further away and everything felt more fiddly" (P2 – session 2) (N=10).*