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Molecular Docking With Haptic Guidance and Path Planning

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Abstract

Molecular docking drives many important biological processes including immune system recognition and cellular signaling. Molecular docking occurs when molecules interact and form complexes. Predicting how specific molecules dock with each other using computational methods has several applications including understanding diseases and virtual drug design. The goal of molecular docking prediction is to find the lowest energy ligand states. The lower the energy state, the more probable the state is docked and biologically feasible. Existing automated computational methods can be time intensive, especially when using direct molecular dynamic simulation.

One way to reduce this computational cost is to use more coarse-grained models that approximate molecular docking. Coarse-grained molecular docking prediction is generally performed first by sampling ligand states using a rigid body model or a partial flexibility model to reduce computation, then by screening the states. The ligand states are screened using a scoring function, usually a potential energy function for interactions between the atoms in each molecule. Ligand state search algorithms still have a significant computational cost if a large portion of the state space is to be explored. Instead of an automated ligand state search method, a human operator can explore the state space instead. Haptic force feedback devices providing guidance based off the energy function can aid the human operator.

Haptic-guidance has been used for immersive semi-automatic and manual molecular docking on a single operator scale. A large amount of ligand state space can be explored with many human operators in a crowdsourced effort. Players in an interactive crowdsourced protein folding puzzle game have aided in finding protein folding prediction solutions, but without haptic feedback. Interactive crowdsourced methods for molecular docking prediction is not well-explored, although non-interactive crowdsourced systems such as Folding@home can be adapted for molecular docking.

This thesis presents a molecular docking game that produces low potential energy ligand states and motion paths with crowdsource scale potential. In an exploratory user study, participants were assigned four different types of devices with varying levels of haptic guidance to search for a potentially docked ligand state. The results demonstrate some effect on the type of device and haptic guidance seen in the study. However, differences are minimal thus potentially enabling the use of commonly available input devices in a crowdsourced setting.

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Chapter 1

Introduction

A greater understanding of life-threatening allergic reactions, diseases and immune system responses can be achieved through studying molecular docking. Many biological processes rely on molecular docking, a process that occurs when two molecules bind together to form complexes. Molecular docking is a complex problem that is not always easily predictable in simulations. To predict if a given receptor-ligand pair will bind to form a complex, a low energy state between the molecules must be found. The location where the ligand binds to the receptor is known as the active binding site. Some receptors could have multiple binding sites for a particular ligand. Existing methods of direct molecular simulation can predict molecular docking, but are computationally expensive [1].

As an alternative, coarse-grained simulations of molecules are more efficient in predicting molecular docking, but can still be computationally expensive [2]. Coarse-grained molecular docking is typically performed using an automated ligand state search function and evaluated by the potential energy between the molecules [3]. Other methods adapt algorithms that were originally developed for robotics, such as the Probabilistic Roadmap Method (PRM) [4, 5]. States are sampled and connected

with edges based on finding feasible transitions between the states using potential energy functions.

Instead of an automated search algorithm, ligand states could also be found by a human operator with a haptic device for force feedback from the potential energy between the ligand and receptor. The roadmap method has been combined with haptic guided user input to aid molecular docking prediction [6]. Haptic guidance has been included in interactive molecular docking simulations [7, 8, 9], but not for a crowdsourced application. A crowdsourced application would utilize data from thousands of participants. Crowdsourcing such a system could produce a massive volume of potentially docked ligand states to be gathered which could provide more accurate results in both single docked ligand states and ligand motion paths around the receptor. This thesis introduces a molecular docking puzzle game "DockIt" that has been adapted to various input devices and can be extended onto a crowdsourced platform.

In our previously published study, the feasibility of DockIt to produce low potential energy ligand states was evaluated in comparison to an existing automated ligand state sampler [10]. DockIt has achieved runtime performance on commodity hardware combined with the Novint Falcon haptic device [11] to produce potentially docked ligand states. The sets of ligand states can also be constructed into a roadmap to find energetically feasible ligand motion paths. The simulation was expanded to support more common input devices such as the XBOX PC controller with vibration haptic feedback [12]. A game interface and simple integer score were also introduced to provide additional visual feedback. A small user study was performed on the game interface with four devices to evaluate the performance of molecular docking and user experience [13]. User feedback was also collected to determine possible improvements to the game interface for future versions of DockIt.

The contributions of this thesis are as follows:

- A haptic guided molecular docking game was explored with a proof-of-concept game [10, 12] and user feedback was analyzed.
  - Haptic guided molecular docking was adapted to multiple devices of varying degrees-of-freedom to support a wider potential audiance.
  - An exploratory human subject study was completed to evaluate four different devices for molecular docking [13].
  - Game elements were applied to an interactive molecular docking system.
- User recorded data has been combined into a roadmap for collaborative ligand motion path prediction [10, 12].
  - Roadmaps were constructed incrementally to support online incorporation of new user data.
  - Ligand motion paths from queries were shown to improve when additional users explore the space near the query.
- Evaluated the necessity of using expensive six degree-of-freedom haptic solutions for molecular docking [13].
  - Users found less expensive devices more familiar.
  - All device types were used to produce low potential energy ligand states.

Chapter 2

Related Work

2.1 Human Interaction with Haptic Feedback

A system implementing haptic feedback to guide a human operator will be affected by their perceptions and interaction, therefore the docking game's performance can be altered based on participant reactions and behavior. Previous participant studies exploring the effectiveness of various haptic devices have found that higher cost haptic devices do not always offer performance gains. An example is demonstrated in the study providing non-visual hints to blind operators for finding web page elements [14].

The physical setup can affect a participant's perception of virtual objects and illusions must be avoided. For example, preventing illusions are important in situations where organ tissue softness must be accurately felt by the operator as demonstrated in [15] between alignment of the haptic device and visual display of the objects. The physical setup of devices in this thesis were instead chosen according to user comfort in pilot studies.

Another potential issue that could impact human operator performance for hap-

tic devices is degree-of-freedom asymmetry in sensor/force feedback, but previous studies have found no significant effect between asymmetry and performance efficiency [16]. For the asymmetry between force with torque and force without torque devices, no significant reduction in performance should occur if the task is simple [17].

Haptic and visual feedback can both depend on each other for reducing biases in size or softness perception when either visual depth cues or haptic feedback was missing [18]. Combining visual feedback with haptics can also reduce errors in asymmetry between axes in hand degrees-of-freedom, despite varying the specific function of haptic feedback [19]. Haptic feedback can also improve operator training, but only for specific kinds of complex tasks [20]. DockIt was tested in a small participant study to gather user feedback and evaluate docking performance in the presence of combined visual and haptic feedback.

2.2 Motion Planning with Haptic Feedback

Originally applied in robotics, Probabilistic Roadmaps (PRMs) attempt to build approximate models of state space. In this model, a state of a robot is a configuration (e.g., degrees-of-freedom which often includes position and orientation). A roadmap is constructed with a set of robot states and edges representing possible transitions between states. First, states are probabilistically sampled while states in collision are discarded as invalid states. Second, an attempt is made to find a valid path from each state to nearby states using a local planner. A local planner moves the robot between two states and results in a valid local path if the movement was collision free. An edge is created between two states if the local planner succeeds for those states. Finally, the edges and states together form a roadmap of state space. Queries can be performed on the resulting roadmap to produce a series of motions through this state space.

The ligand motion planning approach in this study is similar to the probabilistic roadmap method (PRM) of motion planning in 3D environments [4], but the ligand state samples are sampled by human operators and not with probabilistic methods. Edges in such a roadmap represent energetically feasible transitions of the ligand from one state to another. Partial haptic guidance has been combined with PRMs and applied to molecular docking [6]. Ideas from robotic motion planning have been incorporated into predicting protein folding and molecular docking [21, 22]. An early approach adapted motion planning for articulate linkage robots to a protein folding prediction problem [23, 5]. Haptic devices have been used to allow an operator to provide hints to an existing motion planner in both robotics and a molecular docking context [24, 25, 26].

2.3 Molecular Docking

Molecular dynamics simulations are computationally expensive, so more coarse-grained model approaches can be used to reduce this cost to reach optimal ligand states with less time. Ligand states can be sampled and scored based on their biological feasibility to potentially be docked states [27, 28]. These states are typically scored using the potential energy between the molecules [29, 30]. Some of these potential energy scoring functions contain components for modeling hydrogen bonds and other interactions, while the docking game only calculates intermolecular potential energy with electrostatic and Lennard Jones potentials.

Automated docking tools can use rigid body molecular models or ligands with partial flexibility to provide more accurate results efficiently [2, 3]. Side chain flexibility can also be included in automated docking [31]. Rigid bodies consider the entire complex of atoms as a single object to be translated or oriented, while partial flexibility may add articulated degrees of freedom to this rigid body to increase

the capability of finding more potentially docked ligand states at a small computational cost. Automated docking can employ various ligand search methods from simulated annealing to genetic algorithms [32, 33], including Lamarckian genetic algorithms [34]. Flexibility of the ligand can be considered through incrementally constructing the protein to produce ligand states [35, 36]. Other approaches include volumetric analysis of the models to predict ligand-receptor interaction [37]. The docking game simulation currently uses a rigid body model for both the receptor and ligand for realtime performance consideration.

2.4 Molecular Docking with Haptic Feedback

A variety of different interactive molecular simulations with haptic feedback have been explored. These simulations have been be performed on specialized hardware in immersive environments, typically with 6-degree-of-freedom haptic input and output devices [38, 39, 40, 41, 8] which enable the user to move the ligand in a 3D space. A variation on 3D interactive molecular simulations can replace the ligand with a water molecule and allow an operator to explore solvent accessible spaces on a receptor [9]. Molecular simulations can also provide feedback on potential energy as the user modifies molecular structures [8]. The previously mentioned studies use either the PHANToM Omni or PHANToM Premium devices while this study considers cheaper, more available alternatives and their impact on the simulation.

2.5 Crowdsourcing Molecular Problems

One form of crowdsourcing is done when volunteers can directly donate computing time to solve problems, involving no interactivity or required knowledge of the problem [42]. This study is concerned with an interactive type of crowdsourcing where

participants' actions are directly involved in solving the problem. In order to leverage human insight, the problem must be converted into a puzzle for participants to interact with and solve, which has been applied with FoldIt [43] to solve difficult protein folding tasks [44] and to aid in the development of new protein folding prediction algorithms [45]. Local collaboration on molecular docking has been explored [46] but not with haptics or on a crowdsourcing scale. The concept of crowdsourcing molecular docking has been mentioned in [47] but not investigated. Before such an effort can be made, the effects of haptic feedback and the interface should be tested for both effectiveness in producing potentially docked ligand states and feasibility of implementation.

Chapter 3

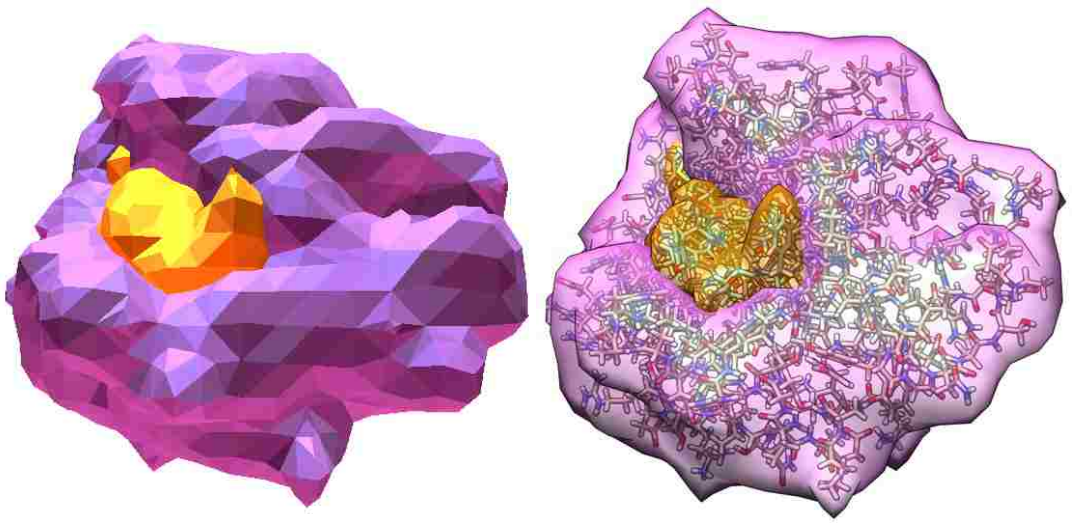
Molecular Model

This thesis uses a rigid body molecular model approximation to achieve real-time performance required for an interactive game. Adapting existing flexible models to improve their performance to this level is considered for future work. Three environments were used in this thesis, two were based on structural data taken from the Protein Database [48, 49], and one was artificially created using abstract point charges for practice purposes.

3.1 Representation of Protein Structure and Isosurfaces

In our simulation the receptor and ligand are represented as rigid bodies with static atoms. This rigid body representation reduces complexity for runtime performance, but prevents the docking game from finding docked ligand states that require flexibility. The receptor is fixed in place while the ligand is free for the user to move. The underlying set of atoms (Figure 3.1b) are used for the potential energy approx-

imation, but the molecules are only shown to the user as isosurfaces (Figure 3.1a). Drawing only the isosurface representation decreases the time spent drawing the scene and shows characteristics of the molecules (e.g. cavities). The colors chosen for the molecules are used to visually differentiate them. The isosurface models were generated from PDB structure files using Chimera with a resolution setting of 2 for the ligand and 3 for the receptor [50]. The ligand atoms translate and rotate as a rigid body when the user moves the ligand. The missing hydrogen atoms in each model (due to the nature of X-Ray Crystallography) were inserted using Chimera [50] and its built-in Add H tool.



(a) Isosurface (b) All Atoms

Figure 3.1: Example (a-b) Ligand (orange) with receptor (purple). The docking site can be seen as a cavity in the receptor's isosurface.

3.2 Energy Approximation Function

The intermolecular potential energy U_{inter} (3.1) between receptor R and ligand L is calculated as the sum of all pairwise electrostatic U_{es} (3.2) and Lennard-Jones

U_{vdw} (3.3) atomic interactions of receptor atoms i and ligand atoms j:

$$U_{\text{inter}}(R, L) = \sum_{i}^{R} \sum_{j}^{L} U_{\text{es}}(i, j) + U_{\text{vdw}}(i, j), \tag{3.1}$$

$$U_{\text{es}}(i, j) = C \frac{q_i q_j}{r_{ij}}, \tag{3.2}$$

$$U_{\text{vdw}}(i, j) = \sqrt{\epsilon_i \epsilon_j} \left[\left(\frac{\rho_i + \rho_j}{r_{ij}} \right)^{12} - 2 \left(\frac{\rho_i + \rho_j}{r_{ij}} \right)^{6} \right]. \tag{3.3}$$

In the above equations, r_{ij} is interatomic distance and C the electrostatic constant. The current implementation uses values for partial charges q_i, Lennard-Jones well depths ϵ_i, and Lennard-Jones minimal distances $\rho_i = 2^{\frac{1}{6}} \sigma_i$ from the AMBER 94 force field [29].

The intermolecular potential energy is used directly to rank potential ligand-receptor interactions. Because the rigid body assumption is used for both molecules, intramolecular interactions are not calculated, therefore the total energy is $E = U_{inter}$. The force approximation used for feedback is calculated from the gradient of the potential approximation. For torque, the cross product between each ligand atom's displacement vector (from the center of mass) and the force from the interaction between the ligand atom and each receptor atom can be used, similar to [38]. However, torque and force may not be handled at the same time if the particular device is not a 6-degree-of-freedom haptic feedback device. For devices that only support 3-degree-of-freedom input or less, the operator can hold one button down for translation movement and force feedback, or a different button for angular movement and torque feedback. Users are encouraged to manipulate the ligand to discover local and global potential minima. These calculations are done using an all-atom cloud model between ligand and receptor (see Figure 3.1b).

3.3 Limitations

This rigid body all atom model is an approximation used to achieve runtime performance, but it can't model all potential bound ligand states. Some bound states require the ligand or the receptor to be flexible, and additional terms of the energy function (such as hydrogen bonding) are not modeled. The lack of explicit solvent modeling (water molecules) often seen in molecular dynamics will also impact the results. DockIt does not use a free energy approximation function like some other docking tools, such as AutoDock VINA [3] which can contain implicit solvation.

3.4 Environments

Three environments were used in this study. Each environment consists of associated point charges that guide to possible docking solutions. The first environment was designed to be the least difficult with the next two environments selected in order of increasing difficulty.

3.4.1 Cube

The Cube environment was artificially created as a cube of point charges with four round depressions made, one on each side excluding top and bottom (see Figure 3.2a). Spheres of positive charge were arranged in a cube, each 1.813 angstroms away from one another. The sphere also contains positive charges so the two objects repel one another, even from a distance. In one of the depressions, the point charges at the surface were replaced with artificial negative charges which will attract the sphere as it comes near. This results in a simple potential energy field where only one solution is possible, and the attractive force is easy to locate as the sphere moves closer to the

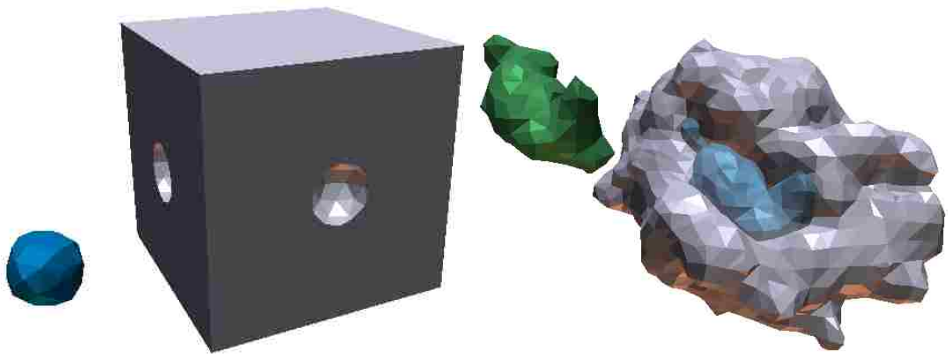
correct depression. This environment has the goal depression initially facing away from the camera. This ensures the player must know how to move the object and rotate the camera to dock the sphere in the correct depression.

3.4.2 3H9S

The 3H9S environment uses the human class I MHC receptor bound to Tel1p peptide with the known bound state shown in Figure 3.2b as translucent blue. This molecular model was taken from the Protein Database (PDB ID 3H9S) [48]. MHC is a part of the human immune system involved in antigen presentation. Ligands that can bind to this molecule can be presented to the immune system for recognition. The known bound state of the ligand can be seen as a cavity in the center of the receptor.

3.4.3 1AJX

The 1AJX environment involves the interaction between HIV1 protease receptor and a given inhibitor ligand. If HIV1's function of cutting peptides into HIV virion is obstructed, the disease itself cannot reproduce. These models were taken from the Protein Database (PDB ID 1AJX) [49].



(a) Cube (b) 3H9S

(c) 1AJX

Figure 3.2: Visual appearence of the molecular docking environments inside the simulation.

Chapter 4

Methods

DockIt allows users to manipulate ligand molecules in an interactive environment that combines haptic and visual feedback. There were four different types of input used in this thesis with varying levels of haptic feedback. Ligand states are recorded as each user plays DockIt. Roadmaps are constructed from these ligand states.

4.1 Force Feedback

Docked ligand states are scored using energy functions, therefore, the force feedback should reflect the potential energy function as closely as possible. The user would then be enabled to sense optimal energy values in addition to visual isosurface feedback and explore an otherwise imperceptable environment. The potential energy approximation is highly sensitive to the position of the atoms when the ligand is near the receptor due to the nature of the Lennard-Jones potential. Because of these large differences between low and high energy approximation values, a logarithmic scaling function (4.1) is used to bring the values into a smaller range for force-feedback (Figure 4.1):

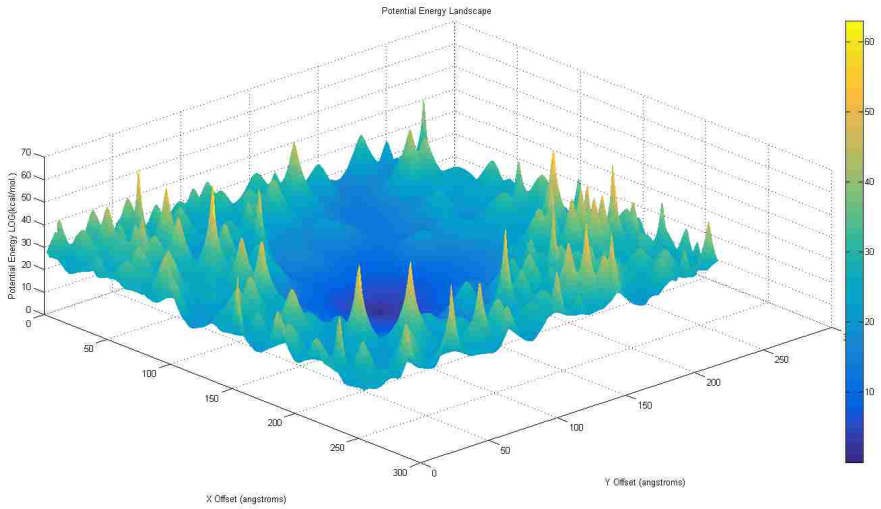


Figure 4.1: Scaled potential energy approximation near the native, bound state of HIV1 protease receptor and the inhibitor ligand. The lowest energy points are in dark blue.

$$E_s(E) = \begin{cases} \ln(E), & \text{if } E \geq 1 \\ -\ln(2-E), & \text{if } E < 1 \end{cases}, \tag{4.1}$$

where E is the original energy value and E_s is the rescaled energy value. To prevent sudden device tremors and confusion with force-feedback, the feedback vector is time-smoothed according to:

$$\vec{v_t} = S(\vec{v_i} - \vec{v}_{t0}), \tag{4.2}$$

$\vec{v}_t$ is the new force-feedback direction, $\vec{v}_i$ is the eventual target feedback direction, and $\vec{v}_{t0}$ is the current force-feedback direction. S is an adjustable factor that increases or decreases the speed at which $\vec{v}_t$ reaches $\vec{v}_i$. This proportional time delay applied to each frame of the program maintains the need for quick changes in feedback for

extreme energy differences, as well as smooths out the peaks in the scaled energy approximation. Higher values of S "tighten" the force-feedback with $S = 1$ resulting in no time delay. A value of $S = \frac{1}{2}$ was used in the study, chosen to balance stability with responsiveness in pilot studies. "Tighter" values result in less delay but can cause the force feedback device to vibrate with a period determined by the speed of the potential energy calculations as the new force feedback vectors are suddenly updated. After scaling and proportional time delay, the resulting vector is passed to the haptic device for output.

The XBOX PC game controller used in this thesis has a single motor for vibro-tactile feedback which lacks high degree-of-freedom haptics. The motor is a scalar output and the force feedback was adapted by using the magnitude of force as the vibration feedback strength. This magnitude is normalized from the maximum haptic force feedback strength set to the maximum vibration of the controller (as allowed by the DirectInput library) and the frequency cannot be changed. This enables the user to feel the atomic forces through the strength of the vibration.

The Novint Falcon and the PHANToM are capable of strong force feedback in order to simulate hard impassable objects such as walls. The potential energy field mentioned here was designed to be felt, but remain passable. The final output force may be scaled by a uniform factor to adjust for each device and user preference, but this setting is subjective. For this study, the maximum force was scaled to 1.5 newtons for all participants of the Novint Falcon and PHANToM to make those devices easier to keep under control while still being noticable. This maximum force is known to be within the range of human sensitivity [19].

Figure 4.2: Photographs of the four devices used in the study.

4.2 Devices

Four devices were used in this thesis (pictured in Figure 4.2). In the prototype study, the Novint Falcon with three degree-of-freedom force feedback is contrasted with the XBOX PC controller with single motor vibration feedback. All four devices were assigned arbitrarily to the participants in the user study, 5 per device. Each participant was assigned only one out of four devices, each with varying levels of haptic feedback. Due to price fluctuations and confidentiality, only approximate prices are shown.

- **Mouse**: A standard computer mouse with keyboard with 2DOF position input. Users receive no haptic feedback. (Between 10 and 20 USD)

- **XBOX**: A Microsoft XBOX 360 PC Controller with 2DOF position input and vibration haptic feedback. (Tens of USD)

- **Novint Falcon**: The Novint Falcon with 3DOF position input and 3DOF haptic feedback [11]. (Hundreds of USD)

- **PHANToM**: The PHANToM Premium 6DOF 1.5 prototype. Also has 6DOF haptic feedback (position and torque). (Tens of thousands of USD)

4.3 Game Mechanics

The input schemes vary for each device, but the user has a basic set of actions they may take, listed in Figure 4.4. The ligand itself may be translated or rotated around the receptor. An orbital style camera points at the receptor and can be rotated or zoomed in and out. A gradient descent method is provided to help the users optimize the current ligand state. The gradient of the potential energy function U_{inter} (3.1) is calculated between the atoms of the ligand and receptor. The ligand will translate and rotate according to this gradient. For rotation, a torque is calculated using the sum of the cross product between the gradient and the displacement vector, similar to [7].

The game interface and display is shown in Figure 4.3. A bar at the top filled as the user moved the ligand closer to a new lowest potential energy state. Both the lowest potential energy state and the potential energy of the current state are shown as a simple integer score directly based off the potential energy. If the user finds a new lower potential energy state of the ligand, green numbers rise out of the ligand on the screen to also indicate progress.

4.4 Roadmap Construction

The Probabilistic Roadmap (PRM) method involes the sampling of states and connecting between transitions of states. The user takes the place of a probabilistic sampling method as ligand states are recorded directly when they play DockIt. A new ligand state is recorded when the user brings the ligand at least 0.1 angstroms in scaled Euclidean distance away from the last recorded state. This distance can be larger if the user moves the ligand fast enough (the duration of a frame is variable) that the ligand state is further than 0.1 angstroms in the next frame.

An edge between two ligand states (c_1, c_2) is weighted by a function of the difference between the maximum potential energy among interpolated ligand states between the start and end ligand state, $c_1 = s_0, s_1, ..., s_n = c_2$, and the initial potential energy $E(c_1)$. When interpolating, the step size is chosen such that the distance between each sampled point along the edge is no greater than a maximum scaled Euclidean distance, R (0.5 angstroms for this thesis). The edge weight, W_{c_1,c_2}, is the difference in energy, ΔE, is $max(E(s_0), ..., E(s_n)) - E(c_1)$. If the two states are already within R Euclidean distance, interpolation is not necessary and the potential energy difference between the destination and start ligand states is used for the edge weight.

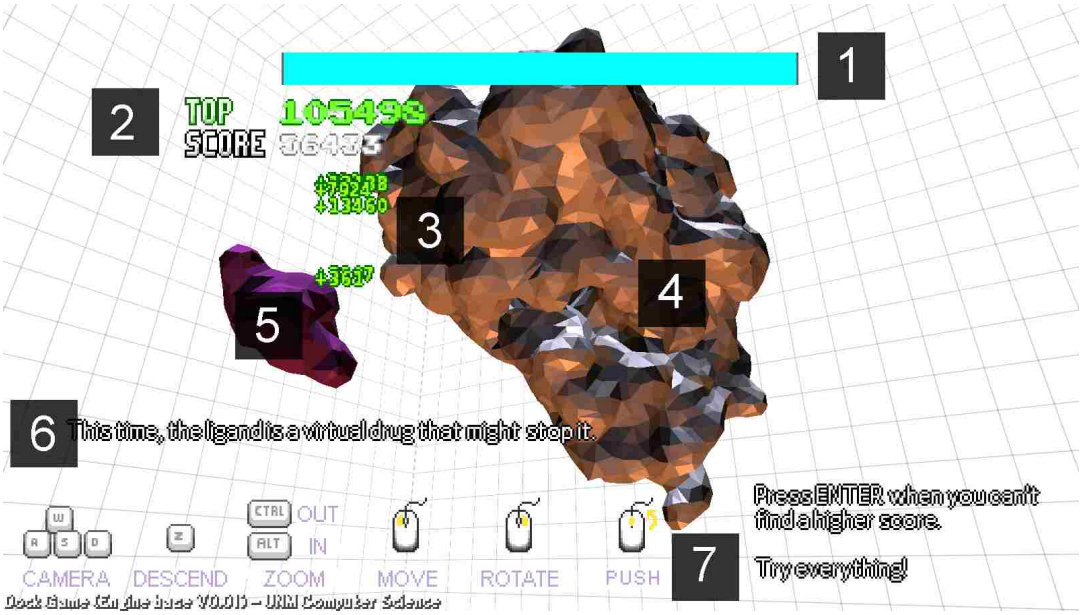
Edges of decreasing potential energy are given a weight of 0, otherwise the weight reflects an energetic traversal cost. This is needed to identify shortest paths using Dijkstra's algorithm. Edges are calculated for every pair of ligand states in both directions. New edges are built to existing roadmaps by appending them with new user sets using the incremental roadmap generation method [51]. This incremental construction reflects the online sequential nature of incoming user sampled ligand state data.

Sets of connected ligand states may be isolated from one another in components.

To connect these components, a K-closest edges component connection method is used. The K shortest edges in Euclidean distance between each components are found and the same edge weight method described above is used. Edges are not created if they are longer than 10 angstroms in scaled Euclidean distance to save computation time. Incremental roadmap construction [51] allows new data to be incorporated into the roadmap which aids a crowdsourced scale implementation.

4.5 Roadmap Query

Queries can be performed on roadmaps between a starting ligand state and an ending ligand state to produce motion paths. First, the starting ligand state is connected to the closest K ligand states in Euclidean distance. The edges are added to the roadmap and weighted using the method in Section 4.4. The same is then done for the ending ligand state. Dijkstra's shortest weighted path algorithm is performed from the start ligand state to produce the resulting motion path. Particularly relevant queries include the path taken by the ligand to the docked state, or alternatively, the possible docked state identified by users.



- **1**: Progress bar
- **2**: Top score and current score display
- **3**: Pop up numbers indicating a higher score was achieved
- **4**: The receptor
- **5**: The ligand
- **6**: Instructions (this text is read audibly along with these subtitles)
- **7**: Hints showing the available controls at all times

Figure 4.3: The game display screen with a list of interface elements.

- **Grab**: The user can hold the left mouse button, the A button on the XBOX controller, the swirl button on the Novint Falcon, or the button on the PHANToM handle while moving to translate the ligand.
- **Rotate**: The user can hold the right mouse button, the B button on the XBOX controller, or the right cross button on the Novint Falcon. With the PHANToM, the ligand is always translated and rotated with the device handle simultaneously.
- **Push**: Because the XBOX controller and mouse lack 3 dimensional input, the mouse wheel can be spun or the directional pad on the XBOX controller used to push and pull the ligand at and away from the camera view.
- **Pan**: The camera can be rotated about the Y axis using A or D on the keyboard, or the right joystick on the XBOX controller.
- **Tilt**: The camera can be rotated about the X axis using W or S on the keyboard, or the right joystick on the XBOX controller.
- **Descend**: The ligand can be moved in the direction of the gradient of potential energy by holding Z on the keyboard, or the right trigger on the XBOX controller.
- **Zoom**: The camera can be zoomed in and out using the left CTRL and ALT keys on the keyboard. The further zoomed in the user is, the slower and more accurate the ligand can be moved.

Figure 4.4: Actions users of DockIt can take.

Chapter 5

Prototype Results

To examine the performance and capabilities in a proof-of-concept, an initial prototype study [12] with six play tests and two devices was completed. Despite the native state being hidden, low potential energy states and ligand motion paths near the native state were found for both the Novint Falcon and XBOX PC controller. DockIt is capable of displaying the isosurfaces and calculating the potential energy in real-time simultaneously.

5.1 Performance

Table 5.1: Runtime Performance With 3H9S Receptor Isosurface Model Polygon Count.

Resolution (Chimera setting)	Polygons in Isosurfaces	Time per Frame (ms)
-	0 (No Drawing)	18
3	3160	21
2	7840	23
1	60184	51

Runtimes for the interactive system were recorded to quantify the computational time for both visual rendering and potential energy calculation. The isosurface models are rendered with polygons in the visual display which are efficient for a GPU to display, while rendering the 3027 atom spheres used in the model would be less efficient. Various settings for model resolution when producing isosurface representations were tested, seen in Table 5.1. The first entry (No Drawing) represents the amount of computation time spent on the system overhead. The model resolution can be chosen based on the target machine hosting the simulation, and on user preference.

The molecular simulation performs potential energy calculation in real time on commodity hardware. Each potential energy calculation takes about 86 ms for the 3H9S environment with MHC, and about 44 ms for the final 1AJX environment with HIV1 protease. For realtime performance, single precision floating point numbers were used. When double precision floating point numbers are used, the realtime performance is poor with a calculation time of 137 ms for the 3H9S environment and 67 ms for the 1AJX environment. In order to preserve the visual display frame rate regardless of the actual molecular model being used, the visual display and energy calculations are done in separate threads. Force feedback is rendered based on the last calculated values for the gradient of the potential energy from the thread calculating this energy. These runtimes were achieved using 61.4MB of memory on a commodity laptop equipped with an AMD A6-5200 APU chipset containing a 4-core CPU at a 4GHz clock rate and a Radeon HD 4800 GPU.

5.2 Ligand Docking

Initial test data from members of the research team, each producing 1000 ligand states were recorded to evaluate DockIt's ability to find low potential energy states.

Table 5.2: Lowest RMSD from native state found for each initial user run.

Type	(User,Run)	Lowest RMSD (Angstroms)
Novint Falcon	(1,1)	0.128
	(1,2)	4.143
	(2,1)	0.143
	(2,2)	0.126
	(3,1)	0.079
	(3,2)	0.075
XBOX PC Controller	(4,1)	0.100
	(4,2)	0.106
	(5,1)	0.088
	(5,2)	0.077
	(6,1)	0.157
	(6,2)	0.068

These ligand states were collected in the 3H9S environment (Section 3.4.2 Figure 3.2b).

The states collected from these runs are shown in Figure 5.1 as dots. Each state is plotted by its RMSD to the known native state and energy calculation. The first three runs were collected from a Novint Falcon haptic device (Figure 5.1a) while the second three used the XBOX game controller (Figure 5.1b). From the distinct colors from Figure 5.1, it can be seen that each user explored the receptor in different ways. The figures show sampled ligand states near the native state. There are particular locations where users would focus exploration, such as User 3 (blue) between 2 and 4 angstroms RMSD and the cluster generated by several users near the native ligand state (Figure 5.1a). Also, the area around the native ligand state was densely explored despite users not explicitly being told of the native ligand state location.

The lowest RMSD from the known native state found amongst the sampled ligand states in each set are similar between the two devices, shown in Table 5.2. Low RMSD

ligand states were found with both the Novint Falcon and XBOX game controller (0.075 angstroms and 0.068 angstroms, respectively). This shows that in this initial study, users were able to find ligand states extremly close to the experimentally determined bound state with only haptic and visual guidance.

5.3 Roadmap Construction

Table 5.3: Roadmaps from haptic-guided ligand states and Gaussian distributed ligand states.

Data type	Cumulative Sets (User,Run)	Ligand States Count	Edge Count
Force-Feedback Device	(1,1)	1000	12516
	(1,1),(2,1)	2000	25246
	(1,1),(2,1),(1,2)	3000	37424
	(1,1),(2,1),(1,2),(3,1)	4000	50240
	(1,1),(2,1),(1,2),(3,1),(2,2)	5000	63126
	(1,1),(2,1),(1,2),(3,1),(2,2),(3,2)	6000	75750
Game Controller	(4,1)	1000	1998
	(4,1),(5,1)	2000	15926
	(4,1),(5,1),(4,2)	3000	29498
	(4,1),(5,1),(4,2),(6,1)	4000	44086
	(4,1),(5,1),(4,2),(6,1),(5,2)	5000	59892
	(4,1),(5,1),(4,2),(6,1),(5,2),(6,2)	6000	75326
Gaussian	-	6000	88758

To evaluate the ability to produce ligand motion paths, the initial test ligand states were constructed into a roadmap. Roadmaps were built incrementally with each subsequent user adding to the existing roadmap. To find candidates for constructing edges, a K-closest connection method was used to connect the ligand states (with $K = 10$ for this roadmap), then a K-pair component connection method was used to connect isolated components (with $K = 10$). Edges are constructed according to the weights described in Section 4.4. After the first 1000 ligand states were

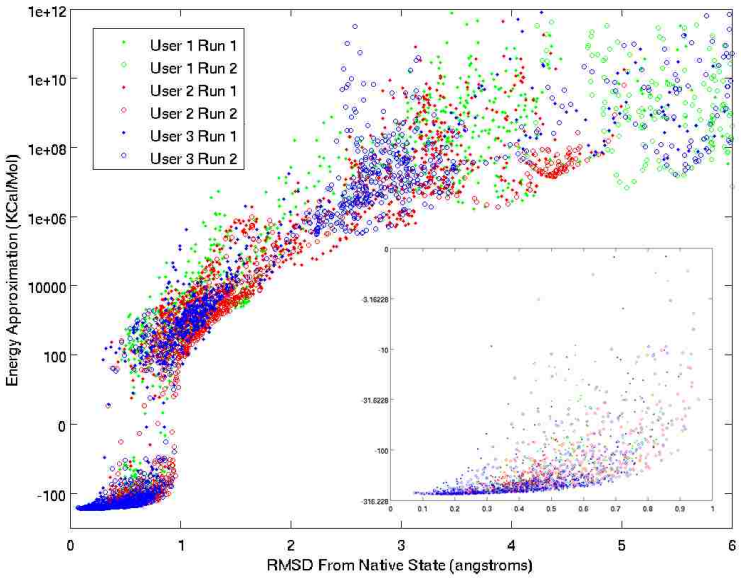
built into a roadmap, each succeessive set was added and edges were added between the old and new ligand states. Using this technique allows a large amount of collected data to be combined, thereby promoting crowdsourcing.

As a comparison to an automated ligand state sampler, a Gaussian sampler was used. This sampler is biased to the previously known native state. 6000 sampled ligand states were generated with a mean centered around the native state, 5 angstroms in translational deviation, and 5 angstroms in rotational deviation. In total, 88,758 weighted edges were created.

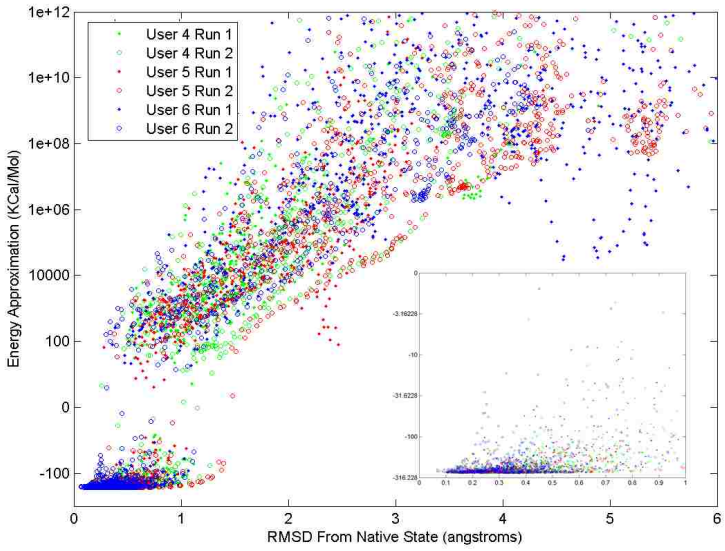
5.4 Motion Path

For the initial proof-of-concept, a query was performed between the known native state and a start ligand state about 5.02 angstroms RMSD from the native state in the 3H9S environment (Section 3.4.2 Figure 3.2b). As user sets were combined into larger roadmaps, the resulting query path became smoother with less peaks or energy barriers to overcome as seen in Figure 5.2. The query path results from the Novint Falcon device data in Figure 5.2a are similar to the results from the XBOX controller data in Figure 5.2b. The path resulting from 6 user sets, shown in blue, also has the least potential energy as it approaches the native ligand state.

The query from the Gaussian roadmap, displayed in black, contains less pronounced energy peaks. However, recall that the Gaussian ligand states were generated with a mean centered around the known native ligand state while the game players did not know the precise native ligand state and had only the force feedback to guide them. Because of this, the Gaussian sampler can't be applied to ligands and receptors where there is no known docked, native ligand state.

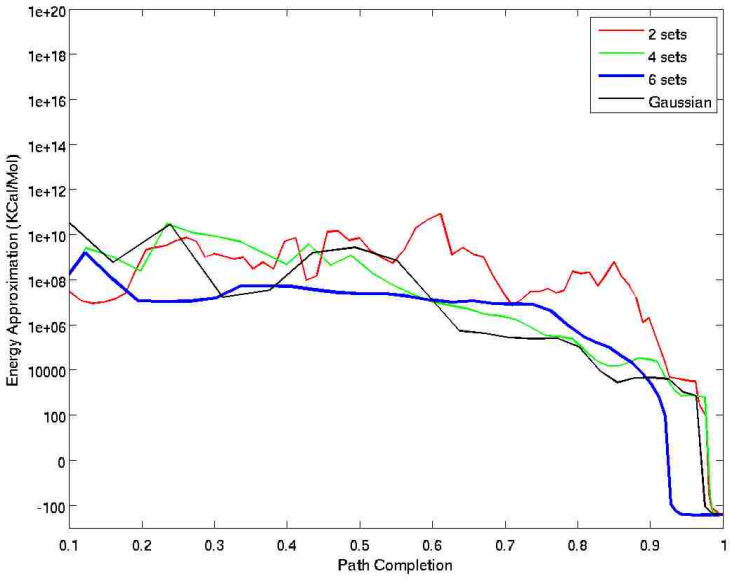


(a) Force Feedback Device

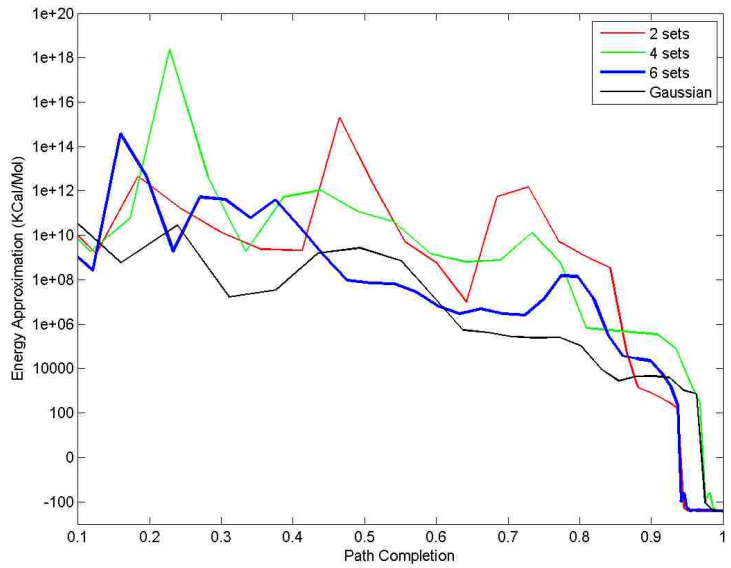


(b) Game Controller

Figure 5.1: Initial potential energies (logarithmic scale) and RMSD for ligand states collected with force feedback device (a) and game controller (b).



(a) Force Feedback Device



(b) Game Controller

Figure 5.2: (a-b) Potential energy (logarithmic scale) from the query to the docked ligand state for constructed roadmaps.

Chapter 6

User Study Results

An exploratory human subjects study [13] (under submission) on the feedback and performance of users with four different input devices was performed after the prototype study. Three goals were examined in this study. First, if cheaper and more commonly availiable input devices could produce results that do not differ significantly from expensive haptic devices, e.g. a six degree-of-freedom device. Second, if haptic feedback was necessary at all for molecular docking and finally, if general players without a background in molecular docking could find results. Participants completed the Cube and 3H9S environments as training with the 3H9S native state shown in translucent blue. The 1AJX environment was used as the trial environment with hidden native state.

6.1 User Study Protocol and Demographics

The study protocol, recruitment, and compensation was aproved by the university's Institutional Review Board (IRB ref. 22714). Participants were invited using e-mails posted to mailing lists and flyers posted around The University of New Mexico

(UNM). Interested applicants filled out an online survey to sign up for the study. The interested applicants were contacted to schedule their participation time inside the Department of Computer Science building. Before each session began, the accepted applicants were provided the IRB consent form to review and sign. Each play session lasted between 30 minutes to an hour. Participants were given a gift card upon completion of the study.

Twenty participants completed the play session out of 47 possible applicants. Those remaining interested applicants did not follow up after the online survey to schedule a session time. Users were aged from 18 to 66, with an average age of 30.2 years. A majority of the participants were male (65%) with an even split (10/10) of users with and without a technical background (in biological or computational sciences).

After the participation consent form was reviewed and signed, the participant was requested to take part in a session of DockIt. Users were given the following tasks:

- **Training Task**: docking in Cube environment (Section 3.4.1, Figure 3.2a)
- **Molecule Task 1**: docking in 3H9S environment (with binding site shown, Section 3.4.2, Figure 3.2b)
- **Molecule Task 2**: docking in 1AJX environment (Section 3.4.3, Figure 3.2c)
- **Post-Game**: post-participation feedback survey

For each play test, the user was presented with written and audible instructions combined with prompts displayed on the screen as shown in Section 4.3, Figure 4.3. A copy of the control information matching the current device is shown at the bottom left. During the training stages, a progress bar is shown above the ligand object. The play test session starts on the Cube environment (Section 3.4.1, Figure 3.2a) designed

to introduce the controls to the participant. Next, the 3H9S enviornment introduces real molecules (Section 3.4.2, Figure 3.2b) and demonstrates the need to pass the ligand through higher potential energies to reach a new lower potential energy minima for the ligand. These training environments ensure every participant is given the same experience and chance to find low potential energy states for the model of HIV protease used in the trial, as well as providing a practice ground to understand the game controls with simple docking tasks. Once the user has completed the training environments, they move on to the 1AJX environment (Section 3.4.3, Figure 3.2c).

6.2 Behavior

Participants had to first complete the training environments to help understand how to play DockIt (Section 3.4.1 Figure 3.2a and Section 3.4.2 Figure 3.2b) before attempting the last trial environment (Section 3.4.3 Figure 3.2c). The time each participant spent during training is listed in Table 6.1. The users assigned to the mouse for the input device took considerably less time completing the training environment for 3H9S than the other users (2.47 minutes on average vs. 13.72, 22.82, and 19.44 minutes on average). This might be due to the familiarity of a keyboard and mouse as input devices. There is also no haptic feedback guidance and the user may place the objects anywhere without the object resisting or moving without user input according to force.

The average amount of time specific input actions were taken are shown in Table 6.2 (see Figure 4.4 for the list of action names and functions). When attempting to dock the ligand in the trial environment, participants generally favored translating the ligand over rotating it (with the exception of the PHANToM device where translation and rotation are simultaneous). Participants using the mouse or XBOX controller were given the ability to push and pull the ligand away and toward them-

Table 6.1: Time Spent in Training Environments by Participants

Device	User	Cube (min.)	3H9S (min.)	1AJX (min.)	Total (min.)
Mouse	M1	2.66	3.78	3.81	10.25
	M2	14.01	2.56	4.28	20.88
	M3	6.29	1.42	6.73	14.43
	M4	3.79	0.52	4.45	8.76
	M5	4.49	4.06	2.56	11.10
	Avg.	*6.25*	*2.47*	*4.37*	*13.09*
Novint	N1	8.46	0.75	3.09	12.29
	N2	2.86	2.80	3.10	8.76
	N3	6.09	25.85	6.89	38.83
	N4	15.21	32.99	4.98	53.18
	N5	5.00	6.22	1.77	12.99
	Avg.	*7.52*	*13.72*	*3.97*	*25.21*
PHANToM	P1	2.57	29.01	17.31	48.49
	P2	3.16	9.21	5.66	18.04
	P3	4.38	24.23	18.57	47.18
	P4	3.30	40.30	9.53	53.13
	P5	2.35	11.34	3.30	16.98
	Avg.	*3.15*	*22.82*	*10.87*	*36.84*
XBOX	X1	3.02	22.03	5.16	30.22
	X2	4.43	37.68	5.41	47.52
	X3	2.14	0.51	1.92	4.57
	X4	2.73	0.77	9.87	13.38
	X5	4.74	36.20	20.92	61.86
	Avg.	*3.41*	*19.44*	*8.66*	*31.51*

selves to overcome the dimensional limitation of the input.

Users were given access to a gradient descent function to optimize a good score further. For the XBOX controller, all functions were mapped onto the device along with this descent function (on the right trigger). This places the descent function on the device itself instead of on the keyboard which could account for the higher usage. The same can be seen for the camera controls where participants using the XBOX controller manipulated the camera more often.

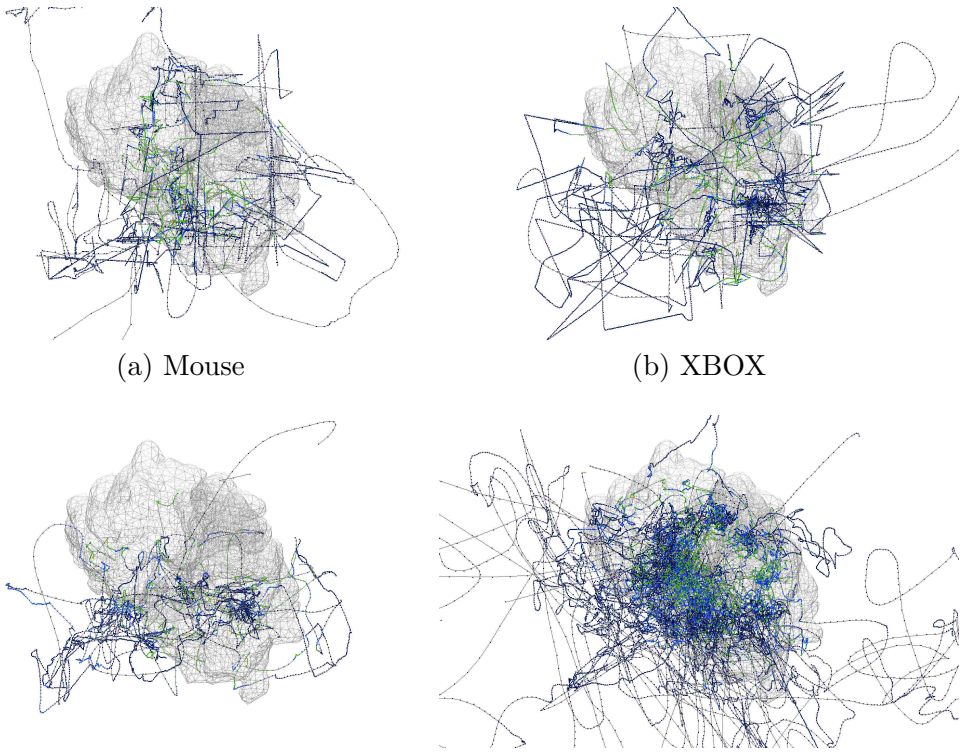
Table 6.2: Average Input Usage of the Devices by Total Percent of Play Time in 1AJX Environment

Device	Grab	Rotate	Push	Pan	Tilt	Zoom	Auto Descend
Mouse	36.3%	11.7%	12.5%	13.4%	7.7%	0.0%	0.0%
Novint	21.8%	9.4%	-	10.5%	5.5%	0.6%	17.6%
PHANToM	34.0%	-	-	10.4%	6.7%	2.1%	11.0%
XBOX	18.8%	17.2%	9.0%	26.5%	19.0%	0.0%	21.4%

Figure 6.1 shows the trajectories explored by all participants for each device, with colors representing different energy values. While the different types of movements are not quantified, the mouse and XBOX controller allow for straight paths while the Novint Falcon and PHANToM encourage more organic exploration with their wider range of motion. The PHANToM has such a wide range of motion that participants were often not near the molecule, moving erratically through open space.

6.3 Ligand Docking

Table 6.3 shows collected ligand states in the 1AJX environment, the time each participant took, the lowest potential energy found, and the lowest RMSD found. The closest RMSD to the known native state was not shown to the participant in any way as this would be unknown when finding new ligand-receptor docking interactions. Participants using any of the devices were able to find low potential energy ligand states. Users assigned to the mouse and keyboard didn't reach a close RMSD from the native state in comparison to the other three devices (5.649 angstroms VS. 0.711, 1.878, and 2.494 angstroms). Because no user exceeded the time limit alotted for participation nor was any time limit mentioned or shown to them on screen, the times reflect the actual time the user was willing to spend in their docking state search attempt.



(a) Mouse (b) XBOX

(c) Novint (d) PHANToM

Figure 6.1: User movement in the 1AJX environment, 5 participants per device.

6.4 Roadmap Construction

All the data collected from the 1AJX environment (Section 3.4.3 Figure 3.2c) was constructed into a roadmap to aid in ligand motion path prediction. When each set of new ligand states were added, new edges were connected between them using the method described in Section 4.4. Ligand states within 0.5 angstroms (computed by Euclidean distance) are connected. At the end of this step, isolated connected components are possible, indicating some ligand states are not "reachable" from others. These components are connected using the K-closest edge component connection method from Section 4.4. The amount of connected components are recorded in the 4th column of Table 6.4. 20 sets were added in iterative roadmap

Table 6.3: Docking Performance in Environment 1AJX (Best values in bold)

Device	User	States	Time (min.)	Lowest Energy (kCal./Mol.)	Lowest RMSD (Angstroms)
Mouse	M1	2458	3.81	-11201.14	7.716
	M2	1267	4.28	-10306.92	**5.649**
	M3	**4568**	6.73	-11165.17	6.509
	M4	3144	4.45	**-11391.06**	6.694
	M5	2463	**2.56**	-10598.89	11.408
Novint	N1	828	3.09	-11153.45	**0.711**
	N2	1540	3.10	-11429.83	14.923
	N3	**5881**	6.89	**-12224.38**	9.246
	N4	944	4.98	-9116.20	14.684
	N5	512	**1.77**	-8915.64	13.255
PHANToM	P1	**18941**	17.31	**-12253.31**	5.581
	P2	3868	5.66	-11087.31	8.147
	P3	14652	18.57	-11940.61	7.144
	P4	7719	9.53	-11919.45	10.554
	P5	2446	**3.30**	-10608.76	**1.878**
XBOX	X1	4926	5.16	**-12368.97**	**2.494**
	X2	4061	5.41	-11760.15	9.276
	X3	1816	**1.92**	-10901.79	6.949
	X4	6858	9.87	-11582.36	12.465
	X5	**12743**	20.92	-12331.62	12.725

construction until a well-connected 7.4 million edge roadmap was made.

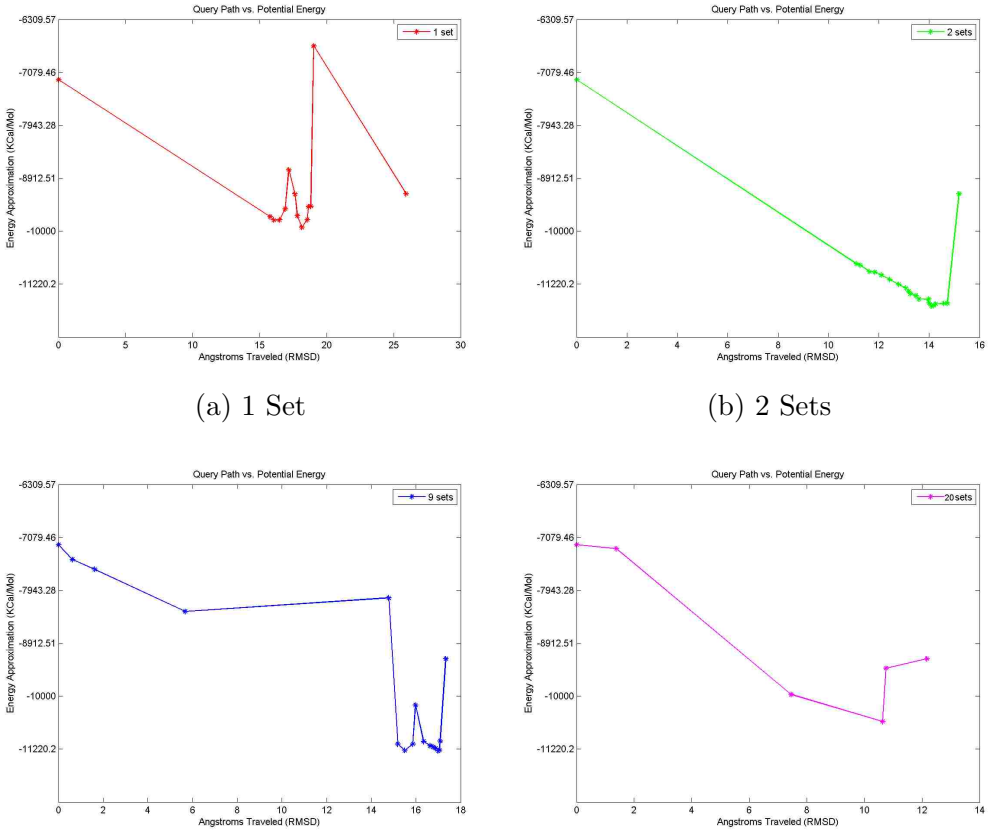
6.5 Motion Path

A query in environment 1AJX from a higher potential energy ligand state to a lower energy state about 12 angstroms RMSD in length was performed on each of the 20 roadmaps shown in the previous Table 6.4. In order for the potential energy path to improve, new ligand state ligand states must be added near the query for the result to be affected. The goal and start state were connected to each roadmaps prior to the query using the method in Section 4.5 with $K = 80$.

Table 6.4: Participant Data Roadmap Construction

Sets	Ligand States	Edges	Components
1	828	6692	46
2	5754	1153684	43
3	8212	1310695	116
4	9752	1371326	87
5	13813	1615716	15
6	32754	3633764	4493
7	36622	3805046	770
8	37889	3830386	28
9	43770	4291175	1520
10	45586	4313797	7
11	60238	4638002	274
12	67957	4922746	1774
13	72525	5051472	284
14	73469	5063288	6
15	80327	6370444	35
16	83471	6495372	488
17	83983	6523175	49
18	96726	7186672	1053
19	99189	7276610	455
20	101635	7414950	419

The potential energy vs. RMSD traveled in a path is shown for the query using increasing numbers of combined user data sets (1 set, 2 sets, 9 sets and 20 sets) in Figure 6.2. Each tick mark on the graph represents a single ligand state along the resulting path from the roadmap query. Initially, there is one great barrier and one small barrier the ligand overcomes on the way to the goal state (red) with a total edge weight along the path of 427.5 billion kCal./Mol. When a data set is added, the potential energy barrier occurs near the end of the path (green) with a total edge weight along the path of 108.8 thousand kCal./Mol. The total edge weight decreases to 3344.57 kCal./Mol. when 9 user sets are combined, and then to 1348.96 kCal./Mol. with all 20 sets. There isn't any improvement adding more data sets after 12 user sets were combined and this path contains only a single smaller barrier



(a) 1 Set

(b) 2 Sets

(c) 9 Sets

(d) 20 Sets

Figure 6.2: Potential energy over 4 ligand query result paths with varying combined user sets with decreasing energy barriers as sets are combined.

at the end, making this the most energetically feasible path. Initially, there is one massive barrier and one small barrier the ligand overcomes on the way to the goal state (red). When a data set is added, the potential energy barrier occurs near the end of the path (green). There isn't any improvement adding more data sets after 12 user sets were combined and this path contains only a single smaller barrier at the end, making this the most energetically feasible path. Because the improvement of the path requires that the users explore states between the start and goal state, it is possible for some queries to show no improvement.

6.6 Feedback

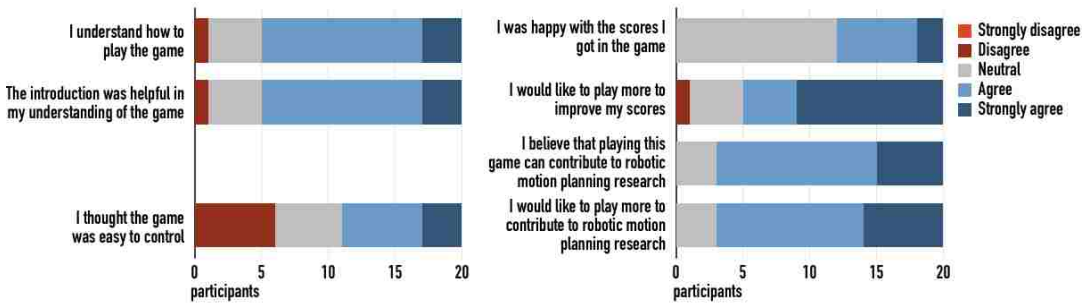


Figure 6.3: Likert Responses to Questions Asked in the Feedback Survey.

Feedback surveys were completed at the end of each participation (see Appendix A). Users were asked about their feelings to various statements (on a 5-point Likert scale) with results shown in Figure 6.3. The survey included questions about the participant's perceive understanding of the game interface, the goal of docking, the ease of control, and the participant's interest in playing future versions of the game.

6.6.1 User Understanding

Participants believed they understood the game with 15 of 20 reporting agreement or strong agreement, with only one participant stating he did not understand how to play. 5 out of 20 participants were unsure about the molecular representation and how the collision bar reports information. 3 out of 20 participants did not fully understand the controls; M5 said "Little confused on how to gauge optimal fit" and X1 said "I did not understand that I was supposed to just force the ligand into place." 3 out of 20 participants didn't grasp the purpose of the game including N2 who said "Not all too sure what I'm supposed to be taking away from this."

Each environment contained instructions spoken through the audio with an on-screen text subtitled version. 15 out of 20 participants found this introduction help-

ful, including the one participant who didn't understand how to play. Some participants wanted more out of the introduction, with participant M5 and N4 asking for a video demonstration. N4 asked for the video demonstration with the written response "video play of how the pieces are placed and include video of content around the situation of puzzle for instance a video demonstration of the purpose of proteins in real life." Participants N5, P1, P2, P4, X3 requested more explanation of the controls in the feedback survey.

Participants were also quizzed on the interface in the feedback survey where they match labels onto the on-screen interface. 15 out of 20 participants matched all interface objects correctly with the remaining 5 confusing the ligand for the receptor. The ligand and the receptor are both shown as different colored polygon isosurfaces without on-screen labels which may have led to this confusion.

6.6.2 Ease of Control

It is important to consider the ease of control and the willingness of participants to play DockIt, otherwise it will be less effective at collecting data if crowdsourced. All participants on the mouse and XBOX controller responded with neutral or positive statements on their ability to control the game. Participants using the Novint Falcon haptic device gave mixed responses (2 disagree, 2 agree, 1 strongly agree) and no participant agreed that the PHANToM device was easy to control. For the willingness to continue, 15 participants responded that they would like to continue playing to achieve a higher score and 17 participants responded that they wanted to contribute to molecular docking research.

Participants using the mouse and keyboard felt the controls were simple, given practice. M1 wrote "The controls are definitely functional, but they require a fair bit of practice to get used to," M2 also wrote "It took practice for me to get the feel

of it," M4 wrote "Was easy once I practiced a bit!" But M3 and M5 still found the controls somewhat awkward, with M5 responding, "Rotation was a little awkward" and suggested we "[add] handles you can select and rotate." Participants with the XBOX controller found the controls simple, but three participants (X1, X2, and X5) all felt the rotation was difficult. X1 wrote "The controls were on the screen and were clear, I just get a little confused when rotating."

Participants with the Novint and PHANToM had more trouble. P1 responded with "[I was] unfamiliar with the control device. It was hard to really get the ligand to move/rotate the way I wanted. Maybe there could be a button to rotate about both axes." P4 also found the rotation difficult. P2 found the PHANToM to be unresponsive, and P5 had trouble zooming. N5 didn't like having to push keyboard buttons while holding the Novint, N1 described using the Novint as having a "slight learning curve." N4 said "Too many controlling functions," but also added "but then again I am not an avid gamer," This difficulty could be from the unfamiliarity of the more advanced Novint and PHANToM haptic devices.

6.6.3 Future Versions of the Game

When asking participants if they would play future versions of the game, there will always be a bias where participants will say what they expect us to want. The participants were also aware we had developed DockIt. These feedback results are reported with this in consideration.

Only 8 participants were satisfied with their score, however, 15 participants said they "would like to play more to improve their scores," with only one participant (N5) stating he would not. When asked if they believed the game contributed to molecular docking research, 17 participants agreed and 17 participants said they would play more to contribute to this work. M1 wrote "I love microbiology and video gmaes,

so I would love to continue playing games like this." M2 said "It's fun" and M4 said we would "need many more levels." Not all participants were as enthusiastic. When several of the Novint and PHANToM users were asked if they would continue, responses were cautious and focused on the difficulties of control. P4 wrote "At the end I felt very frustrated when I couldn't get a small change to happpen." N4 was more optimistic about the controls improving with practice, responding "I would like to play more to get used to the controls."

When asked if they would play a future version of the game, no participant selected "No," with 11 participants answering "Yes, I would give it a try." The remaining 9 answered "Yes, I am eager to try solving all the puzzles for high scores." When we asked what device they would want to use at home, 18 of the 20 participants said they would, but would rather use a keyboard and mouse without haptic feedback.

Finally, we asked if the participants would play a mobile version of the game on a smart phone or tablet. 16 participants would play the game if it was implemented on iOS or Android devices (12 and 4 respectively). Only two would not play on mobile devices, and of these two, one said he did not have a phone and the other wrote "I think it would be a difficult game to play on a touch screen device but I would still try it."

6.7 Discussion and Future Work

6.7.1 Docking Performance

Low potential energy states were found with haptic feedback providing a slight improvement with little difference between haptic devices. Despite the common usage of expensive 6 degree-of-freedom haptic devices in prior research, such devices are not necessary for finding potentially docked ligand states in DockIt. Participants

using a keyboard and mouse with no haptic feedback were still able to contribute, however, their exploration space was smaller with the lowest potential energies found higher than with other devices.

Among the haptic devices, no significant differences in the performance of the docking results were recorded despite the large differences in degrees-of-freedom of their feedback. Even the simple vibrotactile feedback from the XBOX PC controller provided some guidance, although users have also reported a familiarity with this device so a further exploration into the contribution from each should be made. Variations in time spent, user exploration, degrees-of-freedom and the cost of the device were present but did not appear to change the performance. This may be a task which could be enhanced with any sort of haptic feedback regardless of method. Therefore, cheaper haptic devices should be used in future studies of DockIt, perhaps even using the vibrotactile feedback present in mobile phones.

6.7.2 User Performance

The runtime performances described in the results were attained on a laptop with commodity hardware, although performance on a mobile device such as a smart phone or tablet has not been evaluated yet. DockIt and users produced low potential energy ligand states in no more than 21 minutes, with indiviual runs averaging much shorter across all devices (from 3.97 minutes to 10.87 minutes). Despite only one user finding a low RMSD of 0.711 angstroms, one user finding a close candidate state would be enough as the data collected is combined and included in constructed roadmaps. More exploration from users would be helpful in ligand-recptor interactions that have more than one docking site, and adding feedback to encourage exploration could improve this.

6.7.3 User Experience

A positive reception was recorded in the feedback survey to the enjoyment or willingness to continue playing the game across all devices. However, the participants had some difficulty with the controls. A longer, easier to understand introduction and tutorial would improve the user experience, perhaps one with a video demonstration of DockIt being played to provide an example.

Changing the camera from a manual system to an automatic one would also improve the experience. The zoom function can adjust the sensitivity when moving the ligand, but it was rarely utilized in actual participant play. An automatic camera system would also have to predict when the user desires more or less fine-grained control.

Finding a method to automate the gradient descent function should also improve performance and user experience. In the current version of DockIt, once the operator reaches a desired location they must hold down the button to engage the descent function to optimize the score. It is possible to hold down and activate the descent function while translating or rotating the ligand and to see the ligand react to changes in potential energy as it is moved. It should be explored if this automatic descent could provide a visual cue representing what would normally be felt through haptic feedback.

Despite the difficult controls and partial lack of understanding, they enjoyed the experience and said they would play more. They prefered the familiar controls of the keyboard and mouse, and most said they would play on a mobile device. The participants did not spend much time in the trial, so the game format would work well on a mobile device. It should be investigated if the added amount of players and docking sessions can overcome this performance reduction.

Chapter 7

Conclusion

This is the first work that investigates molecular docking by combining haptics and multiple users' results to find molecular docking pathways. First, from the preliminary test, the Novint Falcon restricted the space explored, but both the Novint Falcon and the XBOX controller allowed the users to identify potentially docked ligand states. Smooth ligand trajectories were also found in this test from both devices. Docking results from the second in-depth user study resulted in low potential energy ligand states being found within 21 minutes in a new ligand-receptor pair regardless of user enjoyment, control, and time spent in the trial environment. Any haptic feedback seemed to improve results slightly, with participants on the more advanced haptic devices reporting difficulty controlling them. A better control scheme could be implemented to improve this. A much larger participant sample set would be needed to determine the efficiency and performance of DockIt for molecular docking in general. A version of the molecular docking with an improved visual interface and more common input devices, including mobile devices could be used in successful crowdsourcing of molecular docking.

Appendices

Appendix A

Feedback Response Survey

For many of the following statements, indicate how strongly you agree or disagree.

1. I understand how to play the game

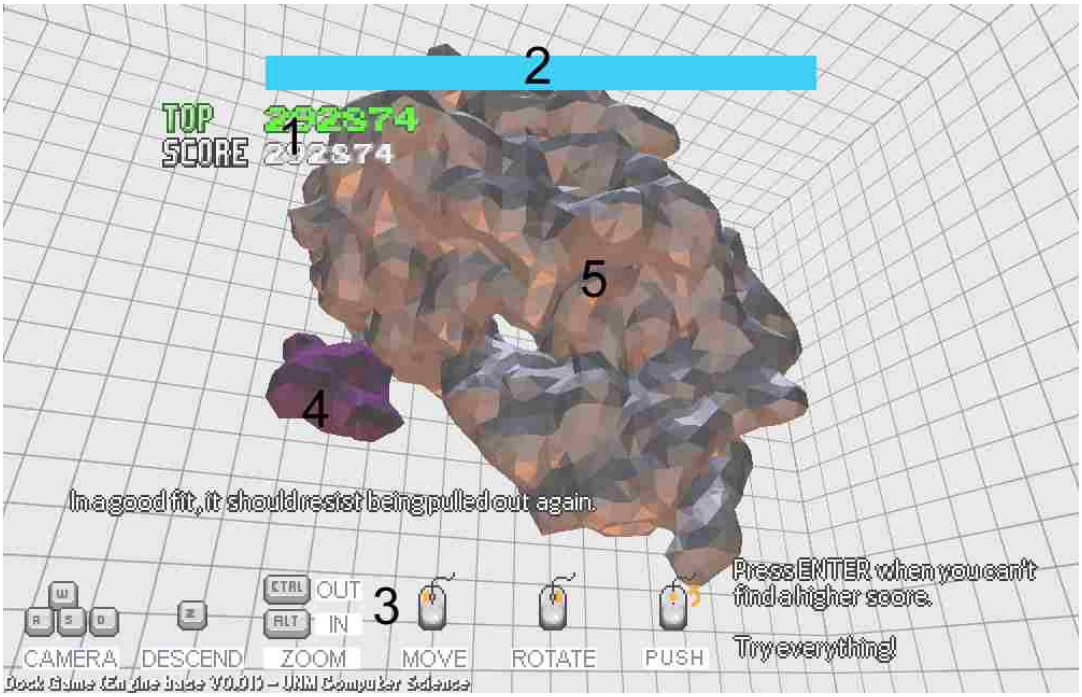
☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

2. The introduction was helpful in my understanding of the game

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

3. What would you change in the introduction for it to be more helpful?

4. Match the following component names to the numbers in the screenshot



- ☐ **Ligand**
- ☐ **Collision Bar**
- ☐ **Score**
- ☐ **Control Info**
- ☐ **Receptor**

5. What parts of the game (if any) did you not understand? Explain?

6. It was easy to tell the receptor and ligand apart

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

7. I thought the game was easy to control

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

8. Explain why the game was or wasnt easy to control...

9. I was happy with the scores I got in the game

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

10. I would like to play more to improve my scores

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

11. I believe that playing this game can contribute to immune system research

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

12. I would like to play more to contribute to immune system research

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

13. Do you have other thoughts on why you would or wouldnt like to play more?

14. Knowing the goal of the game is to solve molecular docking puzzles which could be used for immune system research, would you play a final version?

☐ No, I wouldn't be interested

☐ Yes, I would give it a try

☐ Yes, I am eager to try solving all the puzzles for high scores

15. Would you try the game at home using a game controller, or mouse and keyboard?

☐ No, I wouldn't be interested

☐ No, I don't think this would be fun without the special haptic controller

☐ Yes, I would play even though I wouldn't have the haptic controller

☐ Other:

16. Would you try the game if it were available for mobile devices such as tablets and phones (Android, iOS)?

☐ No, I would not try even if it were available for mobile devices

☐ Yes (Neither), I would still play even if it were not available for mobile devices

☐ Yes (Android), I would play the game if it were available for Android

☐ Yes (iOS), I would play the game if it were available for iOS

☐ Other:

17. Do you have any other feedback, suggestions, criticisms, or other

information you'd like to give us about the game, the controller, or anything else that will help our research

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