A Mobile Game for Crowdsourced Molecular Docking Pathways

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ABSTRACT

Mobile gaming has become a popular pastime in recent years making it a viable avenue for crowdsourcing data collection with scientific games. We present one such application of scientific games on mobile devices by adapting an existing molecular docking game with a user interface suitable for this platform. In this initial study, players explore the state space of molecular interactions, and data is collected to be used in molecular motion planning. The results were compared to states collected from an automated Gaussian sampler commonly used in motion planning. Players were able to contribute states that could aid planners in finding molecular motion pathways with energies lower than the automated sampler. However, there remain challenges to the players' ability to reach states in difficult areas due to the lack of molecular flexibility and guidance towards exploration over simply finding the lowest energy state.

CCS CONCEPTS

• **Human-centered computing** → **Mobile devices**; **Handheld game consoles**; • **Applied computing** → *Bioinformatics*.

KEYWORDS

mobile gaming, molecular docking, motion planning

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1 INTRODUCTION

Mobile games have become prevalent as a consequence of the rising popularity of touch screen mobile devices. As of this date, it is estimated that 65% of American adults play video games, and smartphones are the most common platform [Association 2019]. Due to their pervasiveness, mobile games are ideal platforms for collecting crowdsourced data. Games that benefit from crowdsourcing are typically gamified scientific simulations that incorporate this data into solutions for specific, complex problems [Cooper et al. 2010; Khatib et al. 2011]. While the use of crowdsourced resources to help solve a science problem is not new [Anderson et al. 2002], gamification of scientific simulation on mobile platforms shows great promise to reach a wider audience, thus enabling a larger database of crowdsourced data.

One such complex scientific simulation that can be gamified is *molecular docking*. Molecular docking software packages have been developed to simulate biomolecular binding experiments [Moustakas et al. 2006; Trott and Olson 2010; Verdonk et al. 2003]. Small molecules (ligands) can trigger a multitude of biological processes when they bind to receptor proteins on a cell membrane. Examples of such processes include allergic reactions, neurotransmission, smell, and taste. Understanding which ligands will bind to certain receptors, discovering the final configuration of the ligand-receptor complex, and determining ligand pathways for binding are still open problems in molecular biology and drug discovery.

Figure 1: *Left:* User playing our mobile molecular docking game, *DockAnywhere*, on an Android phone. Biomolecules displayed are a receptor protein and a ligand. Players move the ligand to find its bound position on the receptor. *Right:* Ligand position data generated by all players are combined and plotted around the protein receptor. This data is used to find low energy docking pathways.

In this paper we introduce *DockAnywhere*, a mobile molecular docking game which allows players to explore interactions between 3D models of the ligand and receptor to find docked configurations (Figure 1, *Left*). As players translate and rotate the ligand freely around a stationary receptor to try to dock the molecules, they also generate data that is later used to determine ligand binding pathways via motion planning (Figure 1, *Right*). *DockAnywhere* is adapted from the desktop molecular docking game described

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in [Adamson et al. 2014]. With a gamified, interactive molecular docking platform we can utilize human intuition to perform global explorations of the state space of the molecules. In each environment, players are presented with a set of unbound ligand-receptor pairs. Visual and vibrational feedback along with a score based on the interaction energy guide the player's search to a docked state. Since the docked state represents the global energy minimum, players are encouraged to find low potential energy states.

The adaptation of a desktop game that is played typically with a force-based haptic device or vibration-enabled game controller to a touch screen mobile platform requires a major redesign of the input controls. Controlling 6 degrees of freedom (DOF) motions of the ligand (translation and rotation) is inherently challenging on a 2D touch screen. We overcome this problem with a simple and intuitive set of touch screen gestures that still enable multidimensional exploration of the ligand and receptor state space. Additionally, we implemented an undo button to allow the player more freedom to explore without the fear of losing their progress. To our knowledge, *DockAnywhere* is the first mobile molecular docking game that implements molecular motion in 3D and uses interaction energy as a visual (score) and tactile (vibration) guide to inform players.

Individual player data is collected and grouped to determine binding pathways with motion planning. Because our data analysis benefits from large datasets of low energy states near the docking site on the receptor, the main goal of *DockAnywhere* is not only to progress through levels, but to explore environments thoroughly to improve scores by finding lower interaction energies. Since people turn to their mobile devices for entertainment during short periods of downtime in contrast with longer sessions for desktop games [Grüter et al. 2014], its important to design a game that allows a seamless return to previous exploration. To address this, we implemented new features (displaying the best ligand state, restoring the game state) that support short periods of play.

We report a pilot study performed with a *proof-of-concept* version of *DockAnywhere*. The main objectives of this study are: (1) feasibility assessment of 3D docking on a mobile device, by testing whether the 2D touch interface allows players to explore the 6 DOF state space; (2) test of player ability to find low potential energy states; and (3) evaluation of ligand pathways constructed from the collected data using motion planning algorithms. This initial analysis will set the stage for future user studies and large scale distribution of *DockAnywhere*.

2 RELATED WORK

Molecular docking is an active field of research, and finding novel strategies for simulating molecular binding events is constantly in demand. There are many challenges involved with simulating the interaction of biomolecules, mainly due to the large number of DOF involved in binding events [Grinter and Zou 2014]. These require molecular docking to be performed with reduced complexity, at the cost of losing detailed biochemical information. To reduce complexity, the molecular system can be represented as coarse-grained models with limited flexibility or as rigid bodies. Then, a search algorithm finds states and scores them by computing their energy, as is done in AutoDock Vina [Trott and Olson 2010], DOCK [Moustakas et al. 2006] and GOLD [Verdonk et al. 2003]. Potentially docked states can also be found by incrementally constructing feasible conformations of the ligand [Kramer et al. 1999], or by volumetric analysis of the molecules [Chen and Honig 2010]. Molecular docking prediction can be seen as a search for bound states that satisfy potential energy constraints in a high dimensional space.

Interactive molecular docking tools have used human input with haptic feedback, allowing the operator to feel interaction energies between molecules [Bayazit et al. 2001; Bolopion et al. 2009; Hou and Sourina 2011]. Along with haptics, users can also be immersed in 3D visual feedback [Cakici et al. 2009]. Interactive molecular docking has applied high end graphics hardware for realtime receptor flexibility [Matthews et al. 2019] and can be *gamified* as was done with UDOCK [Levieux et al. 2014]. In molecular docking games, players use visual information (such as cavities in the surface of the protein) and haptic feedback to search for a docked configuration [Bayazit et al. 2001; Bolopion et al. 2009; Hou and Sourina 2011; Levieux et al. 2014]. Since automated docking over this large area would be computationally intractable, relying on human intuition to explore this space methodically is more practical. BioBlox2D is an educational mobile molecular docking game designed for playability [Sternberg et al. 2019]. Molecules are docked in 2D, and users are guided by geometry and by connecting opposite charges that are highlighted by the game. Our game takes molecular docking prediction away from expensive specialized hardware and towards a wider audience with ubiquitous use of mobile devices.

One way to express molecular motion at a coarse-grained level is through state transition *roadmaps*. Our approach in this study is based on the Probabilistic Roadmap method (PRM) originally applied in robotics [Al-Bluwi et al. 2012; Amato et al. 1998]. Edges in a roadmap represent feasible motion transitions between molecular conformations (roadmap nodes). Roadmap methods combined with human operator input have been applied to molecular docking [Adamson et al. 2014; Bayazit et al. 2001]. Earlier work has adapted PRM to protein folding by considering the molecule as if it were a robot with articulate linkages [Amato and Song 2002].

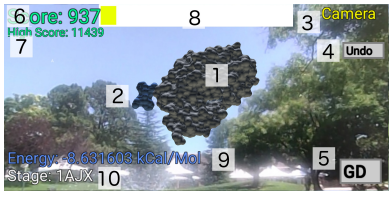


Figure 2: *DockAnywhere* user interface. Elements of the display include: (1) Receptor, (2) Ligand, (3) Control indicator of ligand or camera, (4) Undo button, (5) Gradient Descent button, (6) Score, (7) High Score, (8) Score bar, (9) Current potential energy in kcal/mol, (10) Current environment.

Adapting an interactive molecular docking game for mobile devices requires not only the optimization of energy calculations, but needs to consider the situations and motivations of a mobile game playing audience. Previous research into molecular docking as an interactive puzzle game considered crowdsourcing, but not necessarily using mobile gaming as a vehicle [Adamson et al. 2014]. Gamification uses gameplay elements to encourage players to perform tasks they wouldn't otherwise be motivated to do [Darejeh

and Salim 2016]. For a mobile docking game, it is important to encourage continued play. Players can be motivated with attractive, easy to use interfaces [Merikivi et al. 2017], acknowledging contributions with virtual points or badges [Goh et al. 2017], and encouraging regular playing with daily rewards [Taylor et al. 2019].

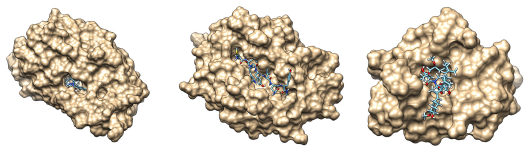
3 *DOCKANYWHERE*

DockAnywhere is an interactive molecular docking mobile game in which players perform 3D global searches for low energy ligand states. The player's goal is to try docking the ligand by exploring the region around the receptor. During gameplay, ligand states are saved and later used for generation of docking pathways with motion planning. *DockAnywhere* was developed for the Android mobile platform. A screenshot of *DockAnywhere* is shown in Figure 2.

In the initial menu, the player can choose from three environments to play, each corresponding to a different molecular model of ligand-receptor pairs (Figure 3). Once an environment is chosen in the *new game* screen, the player finds the 3D structures of receptor and ligand separated by about 42Å against a pond background.

3.1 Molecular Docking Methods

3.1.1 Molecular Models. The 3 ligand and receptor 3D structures were obtained from the RCSB Protein Data Bank, and are: HIV-1 Protease (PDB ID: 1AJX) [Bäckbro et al. 1997] with 3128 atoms (receptor) and 74 atoms (ligand), Human Major Histocompatibility Complex (MHC-Tel1P, PDB ID: 3H9S) [Borbulevych et al. 2009] with 2863 atoms (receptor) and 164 atoms (ligand), and Human FK506 Binding Protein (FKBP-FK506, PDB ID: 1FKF) [Van Duyne et al. 1991] with 1663 atoms (receptor) and 126 (ligand) (see Figure 3). All models are initially docked in their native state. Each model is loaded into the analysis software UCSF Chimera [Pettersen et al. 2004], where we add hydrogen atoms to the models. Then we save the ligand and receptor as separate structures, rendered in different colors as 3D isosurfaces at full resolution.



(a) 1AJX (b) 3H9S (c) 1FKF

Figure 3: Three molecular models of ligand-receptor complexes obtained from X-ray crystallography used in this study (not shown in scale). Receptors are shown as an isosurface in tan, and ligands are depicted as ball-and-stick models in blue. All ligands are shown in their bound, native state.

3.1.2 Energy Calculations. The 3D conformations of the receptor and the ligand are held rigid throughout game play. For this reason, intramolecule atomic interactions are disregarded and only intermolecular (receptor-ligand) interactions are computed. This simplification allows energy to be calculated in real time. The intermolecular potential energy U is shown in Equation 1. It is the sum of electrostatic (first term in the right side of Equation 1) and van der Waals interactions (second term in the right side of Equation 1) between all atoms in the ligand and the receptor.

$$U = \sum_{i}^{R} \sum_{j}^{L} \left\{ C \frac{q_i q_j}{r_{ij}} + \sqrt{\epsilon_i \epsilon_j} \left[\left(\frac{\rho_i + \rho_j}{r_{ij}} \right)^{12} - 2 \left(\frac{\rho_i + \rho_j}{r_{ij}} \right)^{6} \right] \right\} \quad (1)$$

Here the double sum is over all atoms i, j of the receptor R and ligand L. C is the electrostatic constant, $q_{i(j)}$ is the atomic charge of atom i or j, r_{ij} is the distance between atoms i and j, $\epsilon_{i(j)}$ is the van der Waals well depth parameter and $\rho_{i(j)}$ is the van der Waals radius parameter. All parameters are from the Amber99 force field [Duan et al. 2003]. Ligand parameters for AHA1 (1AJX) and FK5 (1FKF) were obtained from Antechamber [Wang et al. 2006].

3.1.3 Atomic Collisions. Atomic collisions (as opposed to chemical bond formation) do not occur in actual molecular binding events at normal conditions. In Equation 1, as atoms overlap, the distance r_{ij} between atoms tends to zero and the value of U tends to infinity. Therefore, we assume that very high values of U imply that the molecules are in collision. We regard all states with interaction energies greater than 10,000 kcal/mol to be collision states.

3.1.4 Gradient Descent. Gradient descent allows fine-grained exploration of local minima, and is also used for vibrational feedback. The gradient of Equation 1 gives a force that is applied at the ligand's geometric center to translate it towards lower energies. To rotate the ligand during gradiate descent, we compute the torque as the cross product between each ligand's atom distance from the ligand's center and the intermolecular force between the ligand atom and each receptor atom (similar to [Hou and Sourina 2011]).

3.2 Game Mechanics and User Interface

3.2.1 Game Controls. The receptor is fixed in space. To manipulate the camera and the ligand in 3D space, players perform gestures on the 2D touch screen. The same gestures are used to manipulate the camera and the ligand (see Table 1). The player can switch between controlling the camera or the ligand by double tapping the screen. The object under the player's control (camera or ligand) is indicated by onscreen text (3 in Figure 2). Because of the 2D interface and this particular control design, the camera needs to be manipulated to control all 6 DOF of the ligand. This interface allows the player to move and orient the ligand into any state.

Players can tap the undo button (4 in Figure 2) to go back one *gesture* (from the time they put their finger on the screen to the time they take it off). This is useful when the player makes an unintended movement while trying to optimize fit for a higher score and loses their place. Players can also toggle a gradient descent method on or off (5 in Figure 2) to continuously descend into local minima (see 3.1.4), allowing for fine adjustments. They are also able to manipulate the ligand while it is descending.

3.2.2 Indicating Player Progress. The potential energy and score displays (9 and 6 in Figure 2 respectively) give players feedback about the potential energy of the current ligand state. The score is a positive integer based directly on the potential energy function (Equation 1). States with a positive potential energy result in a score of 0. As the potential energy decreases, the score increases. A score

Table 1: Description of the different gestures that are used to control the ligand and the camera in *DockAnywhere*.

Gesture	Ligand	Camera
One finger drag (rotate)	Rotates the ligand along an axis perpendicular to the drag vector. It appears to the player that they grabbed an edge of the ligand and dragged it to rotate the ligand.	Rotates the camera's focus around the camera's position, along an axis perpendicular to the drag vector. It appears to the player that they can "drag" the world to rotate the camera.
Two finger drag (translate)	Ligand is translated in the direction of the finger's motion	Camera is panned in the direction of the finger's motion
Pinch (scale)	The ligand is pulled toward or away from the camera along the camera's *look vector* (the vector from the camera's location to its focus point.)	The camera is zoomed in and out. Implemented as a pan along the camera's *look vector*

bar (8 in Figure 2) indicates how close the player is to finding a new high score (7 in Figure 2) with pop-up numbers appearing when they do. This way, players are motivated as they would be in a conventional game towards finding lower potential energy states.

Because haptic feedback was such a large component of the desktop version [Adamson et al. 2014], vibration feedback is implemented in *DockAnywhere* as well. This allows the player to feel changes in the interaction energy which can guide their play. Devices running API 26 or higher scale the magnitude of the vibration according to the magnitude of the current force vector (see 3.1.4). Older API versions don't support variable magnitudes, so the device instead vibrates when moving toward higher potential states.

3.2.3 Mobile Device Performance. To achieve realtime performance on mobile devices, energy calculations and gradient descent are calculated in separate threads, synchronized with the main thread responsible for rendering visual output and processing user input. This allows the frame rate to remain high regardless of the molecular system. On a Samsung Galaxy S6 phone (3GB RAM, Exynos 7420 Octa, 2.1 1.5GHz), a single energy calculation takes 46ms for environment 1AJX, 90ms for environment 3H9S, and 33ms for 1FKF.

3.2.4 Saving and Restoring Gameplay. *DockAnywhere* implements two features to help players resume where they left off. The game's *most recent state* is saved to external storage so that the game can be resumed later. The ligand's current location and orientation, as well as the camera's are saved to unique files for each molecular model. Then, if *DockAnywhere* is closed and opened later, the game is resumed by restoring the ligand and camera locations (and orientations) from these files. The game also saves the ligand's *best state* (lowest potential energy) from all play sessions. If a best state has been saved from previous gameplay and the game is resumed, this best state is displayed as a translucent ligand in the lowest energy location. Then the player can decide whether to continue exploring that area and try to improve their best score, or, if they feel they have explored that area thoroughly, to explore elsewhere.

3.3 Data Collection and Analysis

3.3.1 Player-Generated Data. *DockAnywhere* records ligand states as the player moves the ligand. The translation and rotation of the ligand, the current potential energy (see 3.1), and a time stamp are included in each state, saved as a line in a .csv file on the device's external storage. A new file is created for each play session. To conserve space on the mobile device, only states which meet the following conditions are saved: (1) 10ms must have passed since the last state was saved; (2) the state must be different from the previous state; and (3) the state must not be a collision state (see 3.1.3). The player is allowed to collide the molecules because collision states can be very close to low energy states in the high-dimensional, rugged energy landscape of the system. These low energy states would be inaccessible if molecular collisions were not permitted.

3.3.2 Roadmaps. Collected ligand states are used to predict molecular motion pathways with a roadmap method. In the roadmap, edges represent state transitions that are weighted and queried to produce possible motion paths, an approach similar to PRM [Amato et al. 1998; Bayazit et al. 2001]. In our roadmap construction, we create edges to connect different ligand states. States are connected within an edge length limit based on the root mean square distance (RMSD) metric. The RMSD between two ligand states measures how far atoms in the ligand move from one state to another.

To find low energy paths in the roadmap, our edges are weighted with a function of the potential energy difference between the two states that they connect. Once a roadmap is constructed, it can be reused to perform any number of motion planning queries from one state to another. In this work, queries are performed with a shortest weighted path algorithm, and the edge weight between connected states i, j as a function of energy difference, $W_{ij}(\Delta E)$, is:

$$W_{ij}(\Delta E) = \begin{cases} 1/\ln(-\Delta E), & \text{if } \Delta E \leq -2 \text{ kcal/mol} \\ c_1 \Delta E + c_2, & \text{if } \Delta E > -2 \text{ kcal/mol} \end{cases} \quad (2)$$

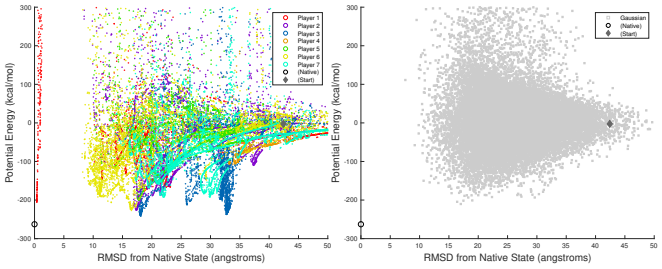
In Equation 2, the constants are $c_1 = 0.1858$ and $c_2 = 1.8142$, and $\Delta E = E_j - E_i$ is the energy difference between the final (j) and initial (i) states connected by an edge. This expression for the edge weight function guarantees that all $W_{ij}(\Delta E) > 0$, which is a necessary condition for performing shortest weighted path searches.

3.3.3 Gaussian Sampler. To compare the player data against an automated sampling method, a Gaussian sampler was used to find an equal amount of states to that collected from players, as was done in the desktop version [Adamson et al. 2014]. Gaussian distributed states of the ligand are generated with a mean centered around the native state (for each environment) and a standard deviation of 10.0Å translational, 180° rotational. We compute the interaction energies for these states, keeping only those under 10,000 kcal/mol until the number of automated states matches the amount collected

from players. Depending on the environment, this could take up to three hours (as was the case with 3H9S). More details about computation times are available in the Supplemental Materials. A roadmap is also constructed from Gaussian samples according to 3.3.2. Note that using the native state as the mean for the Gaussian distribution provides this sampler with a distinct advantage, biasing it towards the lowest known potential energy state.

4 RESULTS AND DISCUSSION

A pilot study demonstrating the capabilities of *DockAnywhere* was conducted with 7 players as they attempted to find the lowest potential energy states in the 3 molecular environments (Figure 3). Players could play at any time and choose any of the three molecular environments, playing them in no particular order. These guidelines were provided to mimic a typical mobile game play environment. The controls were explained verbally and on the initial menu screen. Players had the option to resume their game or start over when beginning a new play session in any environment.



(a) Players **(b) Gaussian**

Figure 4: Comparison between player generated data and automated Gaussian sampler in environment 3H9S. (a) Each individual player is given a color to illustrate specific regions they have explored. (b) The Gaussian sampler was well-informed by having its mean around the native state.

33,795 states were collected from players in environment 1AJX, 38,850 in 1FKF and 29,431 in 3H9S. The players were not shown the exact native state and only the two players familiar with the molecular environments approached the native state closer than 1.0Å RMSD. All players were able to find low potential energy states, even those with as few as 570 states recorded. These low potential energy minima were found in various places by different players, illustrated as valleys at the bottom of Figure 4a.

States found with the Gaussian sampler are shown in Figure 4b. While the players acted based on potential energy feedback (score and vibration) attracting them to specific areas, the Gaussian sampler only had one focal point (native state). These different exploration patterns can be seen in Figures 4a, 4b. If the goal of each player is to increase their score, they will be rewarded for finding each minima. Some environments may have a high energy barrier to navigate, such as the region close to the native state in 3H9S (RMSD $\in$ [1,9]Å) where it was difficult for both the players and the sampler to find feasible states (below 10,000 kcal/mol).

Coarse-grained ligand pathways can be found by performing motion planning queries on roadmaps. The roadmaps were constructed using the method described in 3.3.2 with an edge length limit of 10.0Å RMSD. We found that roadmaps built from player submitted states had a higher connectivity due to focused clusters of states in discovered minima or lines of states drawn out as players moved the ligand (examples of both seen in Figures 4a and 1, *Right*). More detailed player data, roadmap construction data, and scatter plots of ligand states for the 1FKF and 1AJX environments are available in the Supplemental Information.

Once the roadmaps were constructed, a shortest weighted path query was performed from the game start state to the native state (about 42Å away in each environment). The resulting paths are shown in Figure 5. Players could find lower potential energy states that are useful in finding a low total weight path, even if that player did not reach the native state, as was the case with Player 7 in environment 1FKF (cyan dots in the middle of Figure 5b). However, this path assumes that each transition is energetically feasible, which might not be the case for our chosen limit of 10Å. Reducing this limit would require more dense sets of states and the ability to reach the more difficult areas of state space.

5 CONCLUSION

We presented a pilot study showcasing the capabilities of *DockAnywhere*, an adaptation of [Adamson et al. 2014] for crowdsourcing molecular docking on mobile devices. This system uses a multithreaded approach to bring responsive all-atom potential energy feedback to a future mobile gaming audience. Here we explored whether existing mobile docking interfaces could be adapted to a 2D touch system that allows players to find ligand states that could assist motion planning algorithms. We found that the ligand control scheme and interface design allows players to sample low energy states in a few concentrated areas whereas a Gaussian sampler would search in a wider, less dense area. We also found it is possible for players to find states that contribute to smoother ligand motion paths than those collected from a Gaussian sampler.

Limitations on the players' ability to explore the state space in *DockAnywhere* must be addressed before deployment to a wider audience. Some areas of the state space were difficult to reach (the unexplored low RMSD region seen in Figure 4) because we use rigid body models. For this reason, future studies will address molecular flexibility. In addition, we want to continue iterating on the control scheme developed here to improve its usability. We will also include gamification elements and performance metrics to encourage players to explore widely, since the current scoring system only rewards optimizing states against energy minima. Even though it isn't feasible to have a global maximum to compare scores, a leaderboard might inform players about their overall performance, possibly motivating them to continue efforts. In summary, our findings motivate a crowdsource scale deployment of *DockAnywhere*, and for additional gamification. Our future work will help us progress toward the goal of releasing *DockAnywhere* to the public.

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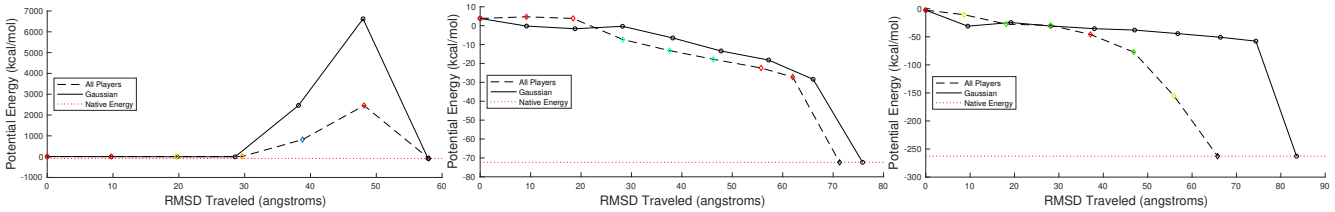

(a) Environment 1AJX (b) Environment 1FKF (c) Environment 3H9S

Figure 5: Queries performed from the game start state to the native state using roadmaps constructed from player data (dashed lines) and automated Gaussian sampler (solid lines). The native state energy is indicated by the dotted red line. The x axis represents the total distance traveled in RMSD (measured from the previous state). The diamonds are colored according to the player that contributed the state used in the path.

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