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Haptic applications for molecular structure manipulation

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Abstract

We describe the application of haptic technology to enhance the information available in chemical systems, specifically related to computational drug design. These methods are designed to build upon the visual information presented by molecular viewers and add the sensation of touch, or force feedback. The addition of sensory input can aid in the analysis of molecular structures and the understanding of intermolecular interactions by delivering chemically relevant forces to the end user.

Keywords: Haptic; Drug design; Force feedback

1. Introduction

Computational methods for drug discovery are inherently focused on the study of intermolecular interactions. A myriad of forces exist between a drug molecule and its target, which determine both the mode and affinity of binding. While both entropic and enthalpic effects are important for binding, rational drug design primarily focuses on the enthalpic contributions. In attempting to produce viable lead targets, the number of enthalpically favorable interactions is maximized while minimizing those that are unfavorable. Providing a tool for medicinal chemists and molecular modelers to easily investigate important enthalpic interactions and manipulate drug molecules in real-time would be an essential asset to drug discovery groups.

Allowing greater interaction between modelers and the working environment enables users to utilize one of their greatest assets—human intuition. Current methods in drug discovery focus on using either raw computational power or rational thought, so introducing novel means to merge the two could prove more successful. Even with the development of newer algorithms to aid in drug design, algorithms cannot account for every nuance in a problem as complex as drug design. Rational drug design is primarily a pattern recognition problem, which is an area where humans often excel, while algorithms have traditionally had difficulty in encapsulating such concepts.

Being able to ''feel'' molecular interactions and subsequently optimize drug molecules to improve these interactions can be an invaluable tool for molecular modelers. Haptic devices are instruments that can provide the sensation of touch to an end user [1]. Through the use of force feedback, haptic devices are able to direct a user to place ligand molecules in favorable positions and orientations, facilitating rational drug design.

We have developed a program, haptic application for molecular structure and energy refinement (HAMStER), that is designed to aid in the drug discovery process. The novel aspect of the program lies in the combination of tactile and visual feedback combined with standard energy analyses. By providing a more information-rich environment for scientists to work with, the goal of HAMStER is to enhance a user's ability to understand the interactions between a drug and its target.

2. Discussion

The enthalpic contribution to molecular binding is composed primarily of the Coulombic and van der Waals attractions between two molecules. Providing ways to visualize these interactions is not easily implemented. One can visualize

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the effects of forces or query the magnitude of forces, but it is much more informative to ''feel'' a force as opposed to only ''seeing'' it. As such, haptic devices have previously been applied to the study of intermolecular interactions [2–7], with varying degrees of success. This work has focused on implementing a general environment for rational drug design to be used with a PHANToM haptic device [8], developed by Sensable Technologies.

2.1. Haptic scene rendering

For our haptics scenes, each atom of interest was represented as a haptic object. In this implementation, only atoms of the ligand molecules were rendered as haptic objects, where a haptic object is described as a hard sphere that is ''touchable'' with the pointer of the PHANToM device (the haptic pointer). These haptic objects appear to the user as an impenetrable sphere. In contrast, visual objects are merely graphical representations of the atom that do not provide the illusion of touch.

The application of haptics to the study of molecular interactions remains a particularly challenging problem. One obstacle is the computational expense associated with the rendering of large, complex scenes. The recommended frequency for haptic updates in an application is 1 kHz. During each cycle, the scene manager must check every haptic object on screen to see whether contact is being made, and if so an appropriate resultant force must be calculated to represent the sensation of shape. On our development machine, only approximately 100 haptic objects could be realistically rendered before the system became too unresponsive. This limit did not account for the calculation and rendering of intermolecular forces, so the number of haptic objects was generally kept to below 50 for general use.

Since haptic devices must be updated at a frequency of at least 1 kHz, all force calculations must also be completed 1000 times per second in addition to other computational expenses such as graphics rendering. This affects the choice of scenes that can be rendered as well as the complexity of the force calculations.

In the application of intermolecular forces between a ligand (referred to as the ''probe'') and a protein (referred to as the ''target''), the internal energy of each molecule can be ignored and only the interactions between the two considered. This assumes a rigid docking approach where the conformation of the ligand cannot change in response to the target system. Any user manipulation that changes the conformation of the ligand such as torsional rotation about bonds, therefore, would require that the internal energy be recalculated. For most applications, rigid bond lengths and angles can be assumed which simplifies calculations.

By ignoring the internal energy of each system, intermolecular forces can be described by the van der Waals and Coulombic forces between two molecules. Since it is the intermolecular forces, and not the energy, that is rendered by the haptic device, the derivative of each potential energy function with respect to the Cartesian coordinates must be calculated. Again, this affects the choice of scoring potential that can be modeled with HAMStER as the functions should be differentiable (although forces for non-differentiable functions could be calculated using numerical approaches).

Since molecular mechanics-based potentials are pairwise additive, the functions lend themselves well to force calculations. Energy function evaluations scale linearly with the number of atoms in the ligand; explicitly, calculating the interaction between targets and probes in real-time at a frequency of 1 kHz is not feasible for all but the smallest systems.

2.2. Grid approximations

Intermolecular forces were modeled using a grid-based approach instead of calculating forces real-time. This approach allows for large haptic systems to be rendered on a single desktop. The grid-based method differs in that all forces are pre-computed and then as probe atoms move through the grid the appropriate forces are accessed from memory. The choice of grid size is important as the storage requirements scale as N^3, where N is the number of grid points for each dimension of the grid. In addition to the memory storage and access requirements, placing forces on grid points creates a coarse force profile. This effect can be seen in Fig. 1A where the van der Waals force between two interacting oxygen atoms is displayed using both a continuous function and a grid-based function with a grid spacing of 0.5 Å. While more costly interpolating schemes could be applied to the problem, in the interest of speed, only a tri-linear interpolation was performed.

Pre-computing forces using a grid-based approach also affects the type of calculations that can be modeled. Grid-based approaches by their very nature are coarse-based. Therefore, in order to streamline the computation of intermolecular forces, the van der Waals interactions between atoms were reduced to only two atom types—hydrogen atoms and heavy atoms. The atomic radii of heavy atoms defined in many molecular mechanics parameter sets, such as AMBER [9], do not deviate significantly and so can be modeled by using an average radius. The errors in van der Waals forces using this reduced atom type set are acceptable given the coarseness and limitations of a grid-based approach.

A separate force grid was computed and stored for each component of the energy function; van der Waals and Coulombic. Storing forces in this manner allowed for individual terms of the potential energy function to be turned on and off or scaled in real-time. While this increases the amount of time and memory access for calculations, it provided the necessary flexibility to allow users to scale and switch between potentials easily.

In the modeling of intermolecular forces with haptic devices, it was difficult to represent the relative scales of the forces involved. The van der Waals potential is very steep, with the magnitude of repulsive forces dwarfing the attractive forces. While the PHANToM device can produce forces up to 6.5 N, continuous rendering of forces over 1.5 N led to system

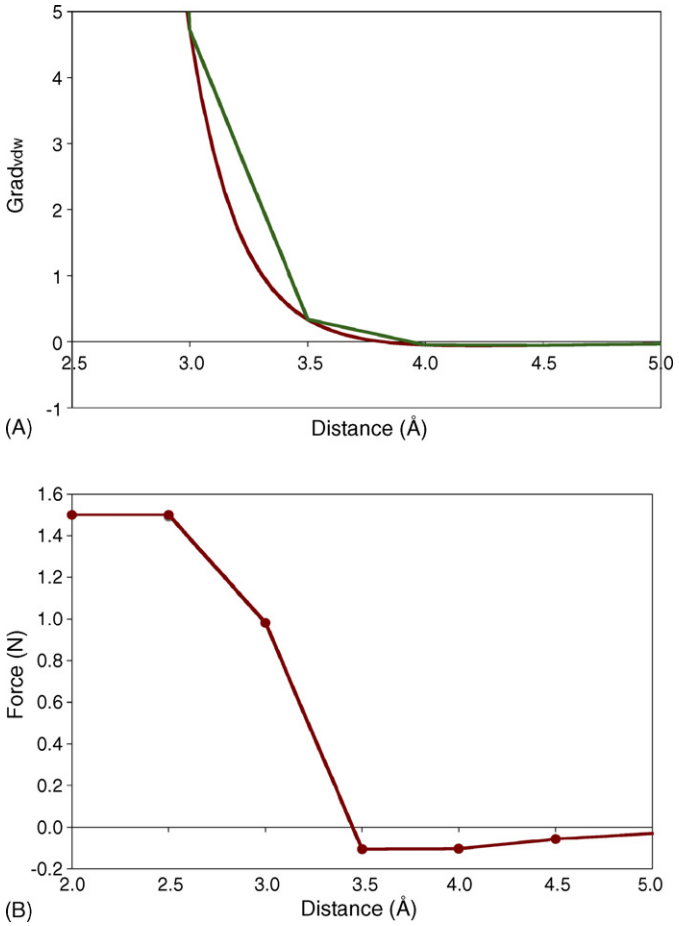

Fig. 1. Van der Waals interactions between two oxygen atoms using the Lennard–Jones potential with AMBER parm94 parameters. (A) Continuous function (red) and grid-based function using linear interpolation and a grid spacing of 0.5 Å (green) and (B) haptic representation of the van der Waals force between two atoms, scaled and capped at a maximum force of 1.5 N.

instability. Using the van der Waals potential as an example, if repulsive gradients are represented as 1.5 N in magnitude with the PHANToM device, then the attractive portions of the potential would have to be scaled very low, on the order of 0.05 N or less. Using the PHANToM desktop, a resultant force of 0.05 N was barely noticeable; usually, 0.3 N was the minimum force that was significant to most users. To prevent instability in force rendering, repulsive gradients were cutoff at a maximal value of 1.5 N and other forces were then scaled accordingly. The altered van der Waals potential can be seen in Fig. 1B for two oxygen atoms interacting with each other. This functional form appeared to provide the best compromise in the rendering of repulsive and attractive forces. It should be noted that while the attractive force between two atoms was represented as a force of 0.1 N, the van der Waals potential is additive, and so larger attractive forces are generated and felt.

For intermolecular interactions, forces were computed at all grid points throughout the grid. In order to provide smooth forces between grid points, a tri-linear interpolation scheme was applied. To improve memory access, grids were only placed near points of interest, such as the active site of a protein. This scheme is illustrated in cartoon form in Fig. 2.

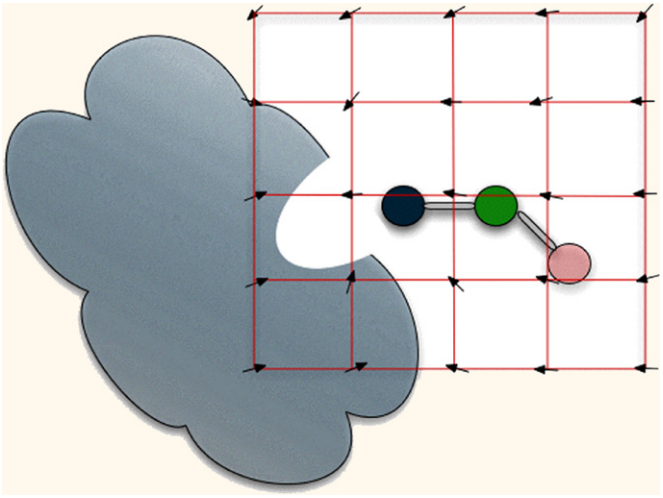

Fig. 2. Schematic diagram of the placement of grids near protein active sites.

2.3. Application to 18-crown-6

In order to demonstrate the capabilities of HAMStER, the interaction of a potassium ion with the 18-crown-6 ether was chosen as a model system. Crown ethers are used in phase-transfer catalysts, where the oxygen atoms have been shown to bind with various ionic species. The 18-crown-6 ether is symmetrical, and contains a negatively charged core, or crown. For this study, a potassium ion was chosen as the probe molecule and the 18-crown-6 ether was designated as the target.

A 25 × 25 × 25 grid was created and centered about the 18-crown-6 system using a grid size of 0.5 Å. This is shown in Fig. 3, although the number of grid points drawn has been reduced for clarity purposes. Van der Waals and Coulombic forces were then calculated for each grid point using parameters

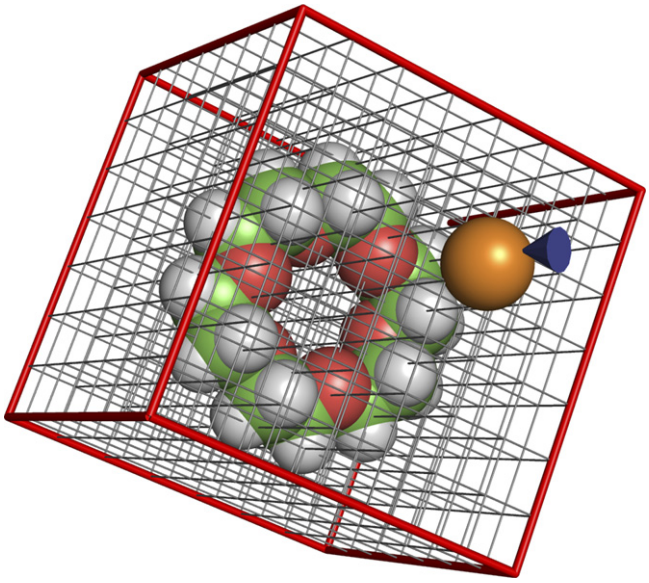

Fig. 3. Haptic scene rendering of 18-crown-6 interacting with a potassium ion. The haptic pointer (blue cone) is used to ‘‘pick up’’ the potassium ion (orange) and move it through the force grid surrounding the target molecule.

from the AMBER parm94 [10] set. All forces were scaled so that the maximum resultant force exerted by the PHANToM device did not exceed 1.5 N.

This system illustrated some of the strengths and weaknesses of the HAMStER approach. Picking up the potassium ion and moving it in space around the crown ether, one could feel the van der Waals interactions and the repulsive forces, which gave the impression that the atoms of 18-crown-6 were solid. Both attractive and repulsive Coulombic forces could be felt as well, with the forces becoming more attractive towards the negatively charged groups. When moving the potassium ion through the center of the crown ether, it was relatively easy to pass through the core. Fig. 4 shows the movement of the potassium ion through the center of the crown ether and the forces that were rendered by the PHANToM device. As can be seen, the force at the center of the crown ether was rendered as 0 N, with only a small repulsive barrier to prevent the ion from passing through the core.

2.4. Applicability to larger systems

One of the more severe problems with using larger systems occurred when docking small molecules into a protein active site. Active sites and general binding sites in proteins are frequently irregular in shape, leading to large repulsive forces whose directionality in space is also highly irregular. When moving molecules around the active site, forces were rendered in a "jerky" manner making precise manipulation difficult. Various compensatory methods were used to reduce this effect, such as adding viscosity or drag effects to the forces. While this dampened the force effects somewhat, movement through grids still resulted in rough force transitions at grid interfaces. The van der Waals potential is exponential in nature, so linear interpolations perform poorly at estimating the force at a given position in space, making the forces feel discontinuous.

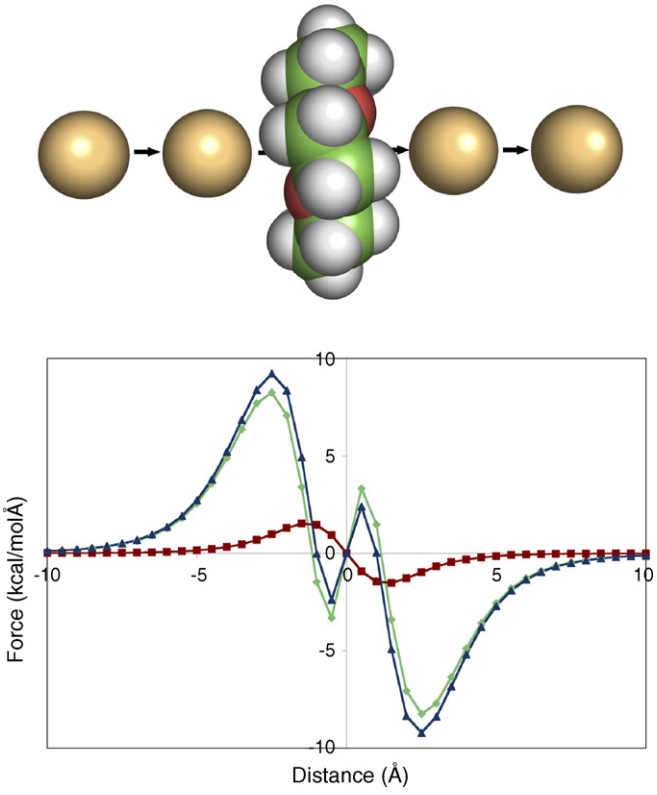

Fig. 4. Interaction profile of the potassium ion moving along the *Z*-axis relative to the 18-crown-6 target. The overall force rendered (blue curve) can be decomposed into the van der Waals component (green) and the Coulombic component (red).

3. Conclusions

The use of haptic devices for molecular modeling can provide useful sensory information about the forces acting between systems. The addition of touch technology aids in the examination of intermolecular interactions, especially since current approaches are hindered by the use of two-dimensional input devices. While the use of haptic devices may be beneficial, the major obstacle lies in the implementation of such devices to maximize their utility without interfering with the user's workflow.

As prices of haptic devices drop, and the speed of computer hardware increases, it should become easier to routinely incorporate haptic applications into molecular modeling applications. The challenge remains to create such an application that will be useful, not just for teaching or demonstration purposes, but also for industrial use in areas such as drug discovery.

4. Materials and methods

HAMStER was written in C++, using Qt (Trolltech) as its GUI front end. The General Haptic Open Software Toolkit (GHOST) developed by Sensable Technologies (Sensable Technologies, Boston, MA) was used to interface with the PHANToM haptic device, also developed by Sensable Technologies. When interacting with three-dimensional molecules on-screen it provides greater control over molecular manipulation than a mouse, which is the standard input device for current three-dimensional molecular viewers. A mouse allows a user to move only in two-dimensional planes while the PHANToM device allows objects to be both easily moved and manipulated in three-dimensional space. Additionally, the PHANToM device uses servomotors to provide force-feedback to the user, relaying forces in three-dimensions. The PHANToM can provide up to 6.4 N of force along the major Cartesian axes.

The HAMStER environment also combines useful visual cues to supplement the tactile feedback. These visual cues can provide instantaneous qualitative information about the molecular interactions. One such cue is the "heating effect" that is implemented in HAMStER. Individual atoms are colored based on the force they experience, ranging from blue (no force) to bright red (large force). In this way, a user can identify the parts of a molecule that are interacting and the relative magnitude of the interaction simply from the color changes on the atoms. This information can be used to identify atoms or groups of atoms that may be contributing favorably or unfavorably to binding.

In order to render real-time interactions between molecules, several cost-cutting measures were implemented. First, in order to be able to display large proteins onscreen, these proteins were not displayed as haptic objects, but rather were treated as graphics objects only. The ligand molecule was the only system treated as a haptic object. While adding tactile stimulation for touching the probe molecule is not important for the investigation of molecular forces, the probe was treated as a haptic object for easier integration into the haptic scene that allowed resultant forces to be rendered. Since most uses of the HAMStER would focus on smaller probe molecules, they could be treated as haptic objects without causing the system to become unresponsive.

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