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Article

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A virtual environment for studying the docking interactions of rigid biomolecules with haptics

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Abstract

Haptic technology facilitates user interaction with the virtual world via the sense of touch. In molecular docking, haptics enables the user to sense the interaction forces during the docking process. Here we describe a haptics-assisted interactive software tool, called Haptimol_RD, for the study of docking interactions. By utilising GPU-accelerated proximity querying methods very large systems can now be studied. Methods for force scaling, multipoint collision response and haptic navigation are described that address force stability issues that are particular to the interactive docking of large systems. Thus Haptimol_RD expands, for the first time, the use of interactive biomolecular haptics to the study of protein-protein interactions. Unlike existing approaches, Haptimol_RD is designed to run on relatively inexpensive consumer-level hardware and is freely available to the community.

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Introduction

The term *haptics* comes from the Greek word "Haptesthai" which means "to touch". Haptic technology enables the user to interact with, and manipulate a virtual environment through the sense of touch. Tactile (e.g., object texture) and kinesthetic (e.g., force sensation) information from the virtual world are transmitted back to the user via the device, allowing one to feel the physical properties of virtual objects and interact with the virtual world. In general, haptic feedback enhances the realism of a virtual simulation while improving the user experience.

Over the years, haptics has gained acceptance from the research community and has been applied in areas such as medicine (e.g. surgical simulation, rehabilitation of patients with neurological disorders), art (3D painting, morphing and sculpting), mechanical design (path planning and assembly sequencing, virtual prototyping), and scientific visualization (geophysical data analysis, molecular manipulation). In biomolecular science haptic technology has been incorporated in various academic and industrial projects. In particular, haptics has assisted users to study interactively the problem of molecular docking,[? ? ?] investigate the importance of haptic technology in e-learning and education,[? ? ? ?] intervene in molecular dynamics simulations,[? ?] explore interactively the solvent accessible surface (ISAS) of a protein,[?] deform an elastic network model of a biomolecule by applying forces to individual atoms,[?] to explore molecular propensity for reaction,[?] and interact with properties related to molecular quantum dynamics (wave-packet dynamics) and potential energy surfaces.[?]

In molecular docking, haptics provides the user with a natural and intuitive way to model and sense the intermolecular interactions of docking. It allows the user to feel interaction forces and gain a better awareness of the docking process. Haptics-assisted interactive docking systems provide a visuohaptic representation of the molecular world, while enabling the user to interact with the virtual molecules, and perform a knowledge-guided search and selection of the final binding pose. They offer an immersive virtual

learning environment for the study of molecular docking, and a test bed for exploring new ideas and hypotheses[?] (e.g. whether electrostatic steering is involved in the process). Although they are not able to search a large number of docking pairs as in automated docking,[????] they do allow the user to focus the search and to potentially improve the result based on their knowledge and expertise.[??] For example, in virtual screening they can assist experts to improve upon or reject the high-scoring docking conformations identified by automated methods.[??] Unlike automated docking in which implicit solvent force fields and molecular flexibility are sometimes included, most of the existing interactive docking applications are limited to rigid-molecule models with interaction forces calculated as sums of pairwise distance-dependent interactions. The fundamental reason for this is the demanding refresh rate of 500Hz to 1 kHz which is required due to the sensitivity of the human haptic system.[???] Failure to meet this rate can result in vibrations and force discontinuities that can limit the practical use of such a system. Because of this demanding refresh-rate requirement interactive haptics-assisted docking applications employ various approximations and computational-cost-reduction techniques (e.g. precomputed force-grids, model van der Waals interactions only). Nonetheless, it has been shown that such interactive docking systems can assist Molecular Dynamics (MD) engines to obtain correct binding results quicker,[?] and improve the users' (experts or students of structural biology) understanding of the process of molecular binding.[??]

The field of haptics-assisted docking was pioneered by Brooks et.al with the GROPE project.[?] His group demonstrated the potential benefits of haptics in the field of molecular docking by enabling experienced biochemists to accelerate a rigid docking process by a factor of two. Subsequent improvements to that solution were proposed by Lee and Lyons,[?] Wollacott and Merz Jr,[?] Subasi and Basdogan,[?] and Sourina et.al[?] and were related to a) the acceleration and accuracy of the force calculations, b) haptic stability during the rendering of the Lennard-Jones interactions (i.e. the hard-surface problem), c) the haptic navigation of large surfaces, and d) the real-time repositioning of the haptic interface

point (HIP). These applications were designed to facilitate the study of rigid protein-drug and small protein-protein docking (comprising a couple of hundreds of atoms), while rendering back to the user 3dof (degrees of freedom) or 6dof force cues attributed to the intermolecular van der Waals (van der Waals) and/or electrostatic interactions, i.e. 3dof renders force, 6dof renders force and torque. Taking a different approach, Lai-Yuen and Lee[?] attempted to model ligand flexibility in their interactive docking system for computer-aided molecular design and assembly. Their system could deform drug-sized, ligand molecules while rendering in real-time forces and torques on a 5dof custom-built haptic device. However, the system rendered van der Waals forces only and allowed the ligand to deform only when in contact with the rigid receptor. Recently, Anthopoulos et.al[?] attempted to address protein-ligand flexibility to some degree, while evaluating the induced-fit effect during 3dof protein-drug docking. Even though they employed GPU-parallel-processing in order to accelerate the underlying computations, their approach could not satisfy the refresh rate requirements of the haptic device since it ran at only 33Hz. Other studies took a less direct approach to haptics-assisted docking and built a hybrid system, combining haptic technology with an automated probabilistic motion planning system,[?] a molecular-fitting and visualization engine,[?] an automated docking system,[?] or a MD simulation engine.[?] In these approaches the haptic device was used primarily as a means to help the system to overcome known intrinsic issues (e.g. narrow passage in probabilistic motion, trapping in MD simulations), and guide it eventually into obtaining better docking results. Protein-ligand flexibility with 6dof rendering was addressed only by Daunay and Regnier,[?] but again their hybrid system could not achieve the required haptic refresh rates, and relied on wave theory to bridge the rate disparities between haptic rendering and simulation engine responses. As it stands, molecular flexibility and the modelling of the respective interactions have not been addressed adequately, and rigid docking therefore still remains the popular modelling approach. Furthermore, the size of molecules supported, and software availability for the community are other important

issues that remain unaddressed.

Currently, despite all this research effort, there are very few interactive haptics-assisted docking applications freely available to the molecular docking community. The majority of the existing applications are either proprietary/inaccessible, and/or utilize expensive 6dof or proprietary haptic devices (except the work of Zonta et.al[7] which was designed to facilitate computer-aided drug design simulations). To the best of our knowledge, none of the existing approaches can accommodate the study of large protein-protein docking, which limits further the scope and usefulness of such applications for the molecular docking community. We believe that these are the main reasons why the adoption rate of this technology by the community has been slow.

Our main contributions to the field address many of the aforementioned issues. Specifically, we introduce and make available to the community an interactive haptics-assisted docking application, Haptimol_RD, that can facilitate, at haptic refresh rates, the study of the binding interactions between very large, rigid biomolecules (comprising several hundreds of thousands of atoms each). The application is designed to run on consumer level hardware. It utilizes a relatively inexpensive 3dof haptic device (3DOF Geomagic Touch, formerly known as the Phantom Omni), and can be applied to protein-drug and protein-protein docking. Additional contributions include the design and development of a) a force scaling method that allows the user to study/experience a specific range of intermolecular forces during the simulation, b) a multipoint (distributed) collision response technique capable of providing stable forces at molecular collision, prohibiting extensive atom overlapping, and c) a haptic navigation technique that can facilitate docking simulations of large proteins.

Figure 1 shows the Haptimol_RD software being used to dock BPTI to Trypsin. The user controls the position and orientation of BPTI using the haptic device, and feels the interaction forces on the device during an interactive exploration of Trypsin's structure. Haptimol_RD is freely available to the community and can be downloaded from

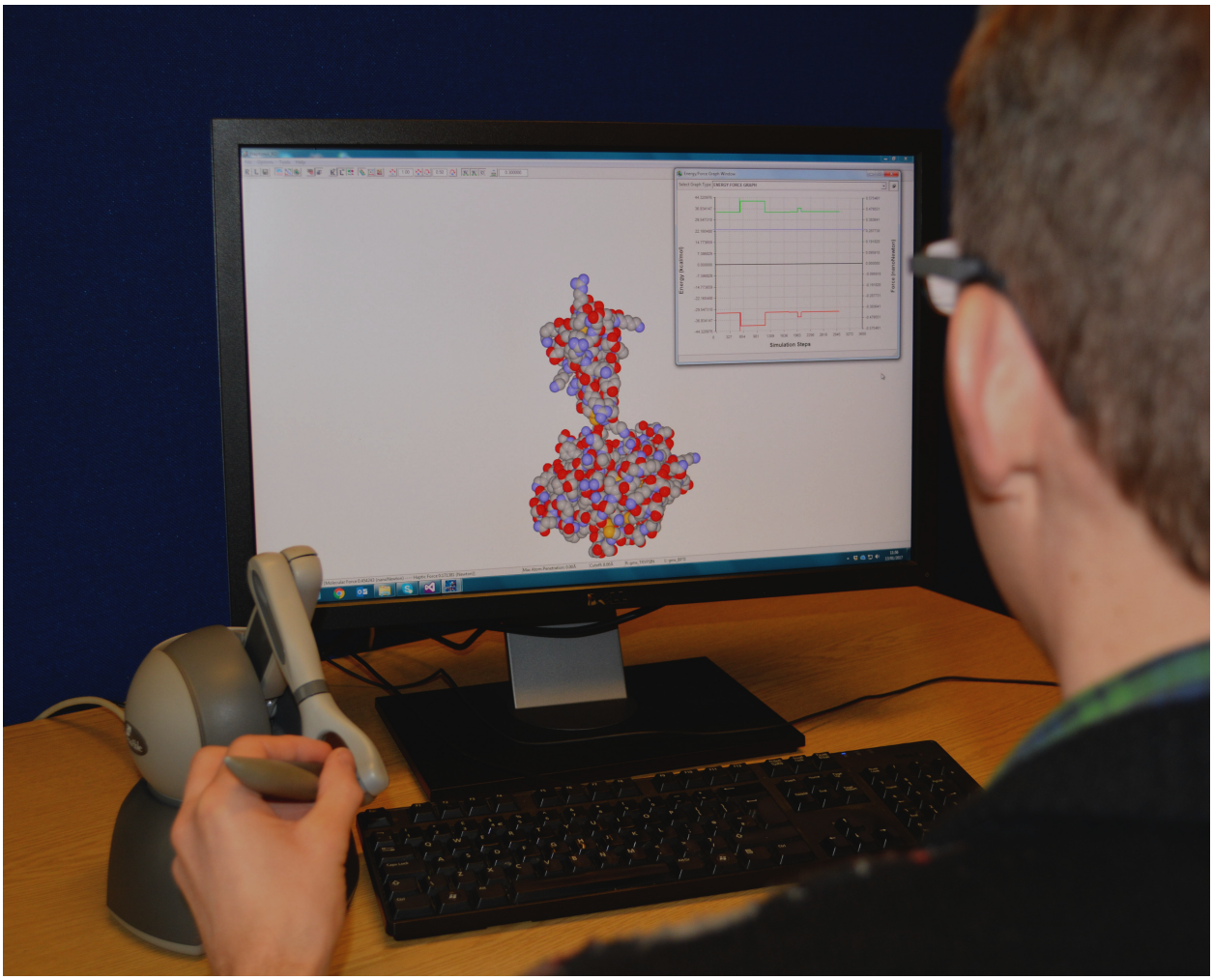


Figure 1: Haptimol_RD and the 3DOF Geomagic Touch haptic device during an interactive rigid docking simulation with proteins BPTI and Trypsin. The user controls the position and orientation of BPTI using the haptic device, and feels the interaction forces on the device during an interactive exploration of Trypsin's structure.

http://www.haptimol.co.uk.

Methods

Force Model

If the molecules are treated as rigid then the nonbonded interactions can be assumed as the only ones acting. As with existing haptic-based rigid docking systems, Haptimol_RD models the van der Waals and electrostatic nonbonded interactions only, using the 12-6 Lennard-Jones (LJ) potential for the van der Waals, and Coulomb's law for the electrostatics. All force computations are performed in real time (no precomputed force-grids are used) either on the CPU or the GPU, depending on the hardware specifications.

To achieve force responses at haptic refresh rates, Haptimol_RD relies on two proximity-querying-based force calculation approaches (the first optimized for the CPU the second for the GPU), discussed in Iakovou et.al.[??] Both approaches employ spatial decomposition structures to decrease the computational cost of these calculations. Specifically, they compute the force on the set of atom pairs within a given cut-off distance by utilising either a regular grid or an octree. Haptimol_RD uses an octree approach on the CPU if the computing architecture lacks GPU processing capability. Otherwise, it typically uses a regular grid on the GPU where our algorithm maintains a high level of occupancy and minimizes execution divergence. The approach can achieve force updates in less than 2ms for molecular structures comprising hundreds of thousands of atoms each.[?] The values for the force parameters are taken from the Gromos54a7[?] force field, as specified and implemented in Gromacs version 4.6.2.[?] Other force fields can be used as long as they are in the Gromacs topology format. We use the Gromacs tool, pdb2gmx, as follows:

```
pdb2gmx -f xxxx.pdb -o gmx_xxxx.pdb -p gmx_xxxx.top
        -ff gromos54a7 -ignh -water none -merge all
```

where xxxx is the molecule's pdb code. pdb2gmx processes the pdb file, adds the necessary hydrogens in the molecular structure, and returns the actual Gromos54a7 force field topology file (*.top) containing the nonbonded parameters (information about this tool

can be found in the Gromacs manual[?]). Other force fields supported by Gromacs, such as AMBER, will become available in future releases. Parameters for molecules that are not already available can be determined using servers such as PRODRG[?] or ATB.[?]

Since all force calculations are performed in real time, Haptimol_RD enables the independent handling of the electrostatic and van der Waals forces in a manner similar to the one reported in Lee and Lyons.[?] This allows the user to switch on/off dynamically the electrostatic and van der Waals forces, as well as, the repulsive and attractive parts of the van der Waals force. This option allows the user to assess which type of interaction is dominant during binding.

Force Scaling

A haptic device has a finite force-rendering range (0-3.3 Newtons for the Geomagic Touch), whereas the intermolecular forces can take a very large range of values. As such the mapping between the forces acting at the molecular level and the forces rendered to the user at the physical level must take into account these range differences. Failure to do so could hinder drastically the user's perception of the interaction forces. For example one could feel the van der Waals forces at close range but not be able to feel the weaker electrostatic forces at long range. To address this issue Haptimol_RD allows the user to select in real time amongst three different scaling methods, each of which is capable of altering the magnitude of the interaction force felt by the user during the simulation. The first method is a fixed scaling method, similar to the one proposed by Wollacott and Merz.[?] In fixed scaling mode, the molecular force in nanoNewtons (nN) is scaled by 10^9 to give the force in Newtons (N) applied to the haptic device. If the magnitude of the interaction force is greater than 3nN then the force on the haptic device is capped at 3N. The second method is a new intuitive method we propose, which scales the total interaction force by mapping it linearly to a user defined min-max range of force magnitudes. The min-max method enables the user to experience/focus on a specific range of intermolecular forces

during the simulation. As such, it can help the user perceive certain force ranges on the haptic device (e.g. weak VDW repulsive/long range electrostatic), which would have been otherwise undetectable. When applied, all interaction forces greater than max are mapped to a haptic force of 3N and all forces less than min are capped to a haptic force of 0N. Unlike fixed scaling, the magnitude of the interaction force rendered on the haptic device depends on the range. Specifically in min-max scaling mode, $\mathbf{f}$ is mapped to a user-defined scaling range using Equation 1, and the result is rendered on the haptic device. Equation 1 returns the force rendered on the device $\mathbf{f_h}$ which is given by,

$$\mathbf{f_h} = \begin{cases} \mathbf{0}, & \text{if } f \leq f^{min} \\ \left(f_h^{max}\right)\hat{\mathbf{f}}, & \text{if } f \geq f^{max} \\ \left(\frac{(f-f^{min})f_h^{max}}{f^{max}-f^{min}}\right)\hat{\mathbf{f}}, & \text{if } f^{min} \leq f \leq f^{max} \end{cases} \quad (1)$$

where $\hat{\mathbf{f}}$ is the unit vector in the direction of $\mathbf{f}$, f^{max} and f^{min} are the upper and lower limits of the user defined range of interaction force magnitudes in nanoNewtons, f is the magnitude of $\mathbf{f}$, and f_h^{max} is the magnitude of the maximum force exerted by the haptic device (3N in our case).

The third method is the variable gain scaling method proposed by Bolopion et.al.[?] Their method amplifies small amplitude forces using a series of arctangent functions. In all scaling methods, the maximum force rendered on the haptic device is limited to 3N. Moreover, for the Geomagic Touch the user cannot perceive haptic forces less than or equal to 0.26N because they are masked by the back-drive friction of the haptic device.

Haptic Stability and Multi-point Collision Response

In an interactive haptics-assisted docking application, attaining haptic-refresh rates and an appropriate scaling factor is crucial but does not guarantee force stability. For those

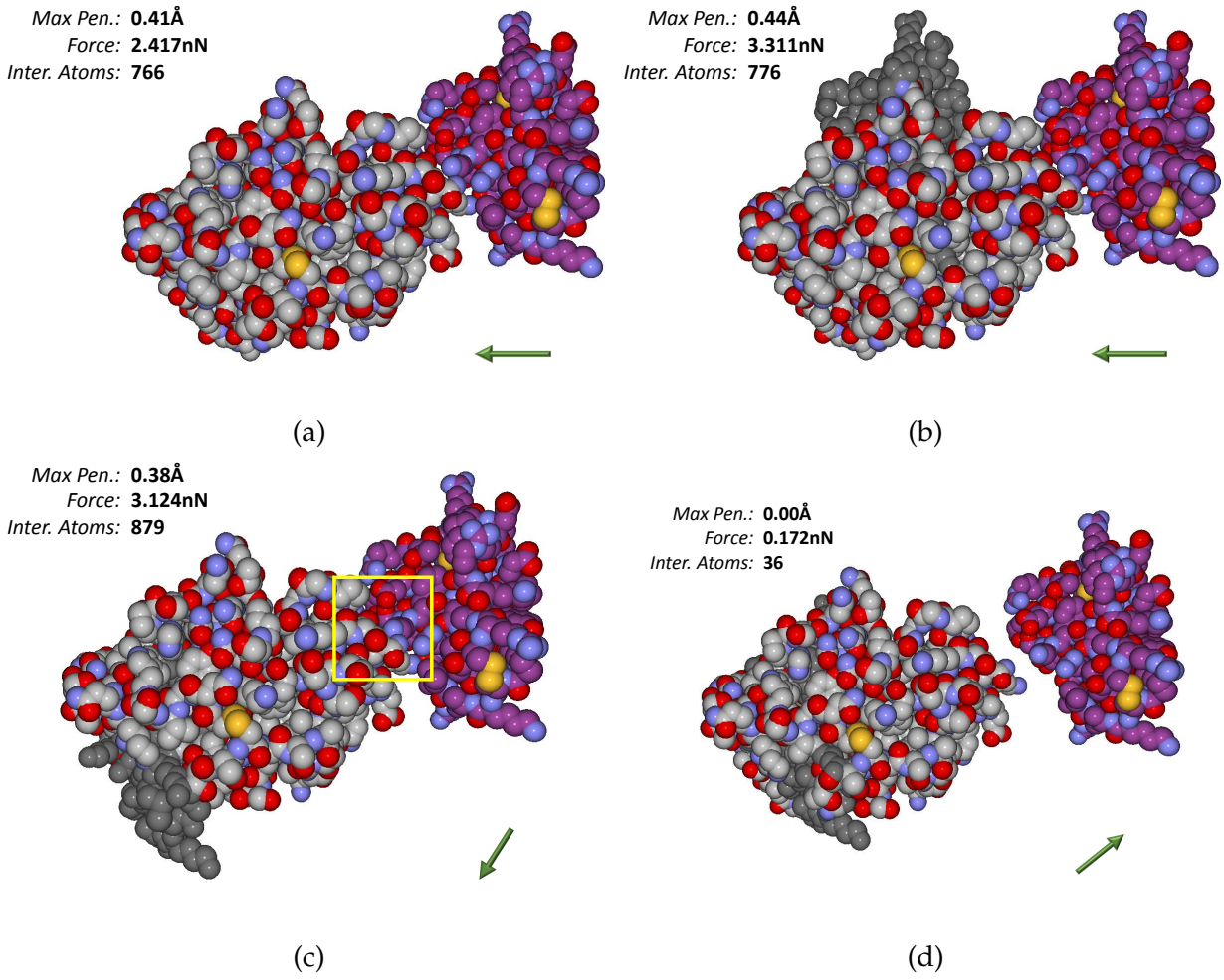


Figure 2: Applying the multipoint, force-based collision response method during a docking simulation. The figure shows the ligand in two positions, one centred at the virtual cursor (shown with all atoms in dark grey) and the other is restricted due to collisions (carbon atoms are shown in purple). The green arrow at the bottom of each picture depicts the relative displacement of the HIP. During collision the virtual cursor can be displaced without constraints, unlike the ligand shown in purple which must remain at its last valid (i.e. collision free) position. Collision occurs when the interaction force is greater than 3nN. (a) The ligand moves towards the negative x axis without causing a collision. (b) The molecules are in collision while the user keeps pushing the virtual cursor (grey molecule) down the negative x axis. (c) The user moves the virtual cursor diagonally (along the negative x,y axes), the algorithm allows slight ligand movement and then sets the molecules in a collision state. (d) Relative HIP movement towards the positive x,y axes, results in a collision free movement for the ligand so it moves in this direction. The following information are also included for each snapshot: *Max Pen.*-the maximum atom-overlap distance in Ångstroms; *Force*-the interaction force in nano Newtons; *Inter. Atoms*-number of interacting atom pairs.

applications that model the van der Waals interactions using the Lennard-Jones potential, instabilities arise when the two molecules are in very close proximity causing device vibrations and jittering. The more the atoms interpenetrate the more erratic the forces become in both magnitude and direction, causing the haptic stylus to move uncontrollably. We address atomic interpenetration by implementing an intuitive force-based multi-point collision response method which prevents atom overlapping. The method allows the application to update the interaction force and the ligand position only if the computed force satisfies certain criteria (Figure 2). Otherwise, the application keeps the ligand at its last valid position, and renders on the haptic device the last valid force. Unlike other approaches,[??] the method does not rely on penetration depths and uniform grids/distance maps in order to resolve ligand movement during collision, and as such it is free of any spatial constraints. Instead, ligand movement is resolved using the concept of relative movement as discussed in the next section (see also Figure 3). Algorithm 1 outlines this method.

The main idea of Algorithm 1 is that ligand-position updates should occur only if the magnitude of the force on the ligand is less than a specified threshold. Through empirical study we found that an appropriate threshold was 3nN, which allowed us, in all of our test cases, to constrain atom penetration at depths no deeper than 0.5A, based on the van der Waals radii. Since the van der Waals repulsive interactions dwarf all other interactions during atom overlapping (especially when there are multiple atom overlaps), the method guarantees that atom interpenetration is kept at acceptable levels. In addition, the method enables the user to experience the sliding of the ligand over the receptor, as the former moves over the latter during a multipoint collision event. In that case the user will sense the interaction force whilst being able to slide the ligand over the surface of the receptor. This sliding effect is important in haptics-assisted docking because it enables the user to explore structural complementarity between the molecules, like a 3D jigsaw puzzle. Force damping, based on the device's current velocity, is also applied as a means to further

Algorithm 1 Force-based Collision Response

Require: p_{curr}, current HIP possition
Require: p_{last}, last HIP possition
Ensure: f_{curr}, the force rendered on the haptic device
1: $m_{tmp}^{Cursor} \leftarrow$ GetTmpRelativeCursorMovement(p_{curr}, p_{last})
2: $T_{tmp} \leftarrow$ GetTmpTransformationMatrix(m_{tmp}^{Cursor})
3: $p_{tmp}^{L} \leftarrow$ UpdateTmpLigandPosition(T_{tmp})
4: $f_{tmp} \leftarrow$ ComputeTmpForce(p_{tmp}^{L})
5: // check/set the force/position updating flags
6: **if** $f_{last} > 3nN$ **then**
7: $flag_f \leftarrow$ true
8: **else**
9: $flag_f \leftarrow$ false
10: **end if**
11: **if** $f_{tmp} \leq 3nN$ OR ($flag_f$ is true AND $f_{tmp} \leq f_{last}$) **then**
12: update $\leftarrow$ true
13: **else**
14: update $\leftarrow$ false
15: **end if**
16: **if** update is false **then**
17: set all positions back to their last valid values
18: $f_{curr} \leftarrow f_{last}$
19: **else**
20: // set all temporary positions as current
21: $p_{last} \leftarrow p_{curr}$
22: $m_{curr}^{Cursor} \leftarrow m_{tmp}^{Cursor}$
23: $T_{curr} \leftarrow T_{tmp}$
24: $p_{curr}^{L} \leftarrow p_{tmp}^{L}$
25: $f_{curr} \leftarrow f_{tmp}$)
26: **end if**

reduce device jittering during penetration (necessary when the docking involves large proteins). Unlike the most popular approach in the field (proposed by Lee and Lyons[?] and improved upon Wallcot and Merz[?]), our method does not have to alter the force profile of the docking simulation (i.e. add spring-based forces) in order to achieve haptic stability.

Haptic Navigation

The haptic navigation of very large and geometrically complex structures is not a trivial task as the mapping between the size of the haptic workspace (HW) and the size of the biomolecule needs to be appropriately defined to enable the perception of the changes in the molecular force. A straightforward solution follows from our previous work ,[?] where we scale the virtual world such that the larger of the two molecules loaded fits within the HW. The HW is a cuboid defining the reachable area of the haptic stylus and the Virtual Haptic Workspace (VHW) is a scaled version of the HW within the virtual world. The Haptic Interface Point (HIP) is the tip of the haptic stylus and the virtual cursor is the HIP's virtual representation in the virtual world. The user navigates within the virtual world by controlling the location of the VHW using the haptic device.

This movable VHW allows the ligand to explore and interact with receptors of arbitrary size (while keeping the receptor fixed in space), and enables the collision response method discussed earlier to resolve efficiently intermolecular collisions at multiple points. Real-time rotation (using an Arc ball rotation method) of the receptor, ligand, or both (i.e. global rotation of the scene) is provided to ensure that all parts of the receptor/ligand structures are viewable and accessible to the user. The method allows for position and rate control displacements. We define an inner box to be a scaled down version (approx. 80% of the dimensions) of the HW. When the HIP remains within the inner box, position control displacements occur and rate control displacements occur when the HIP is outside of the inner box (See Figure 3). During rate control, the displacement vector updates the

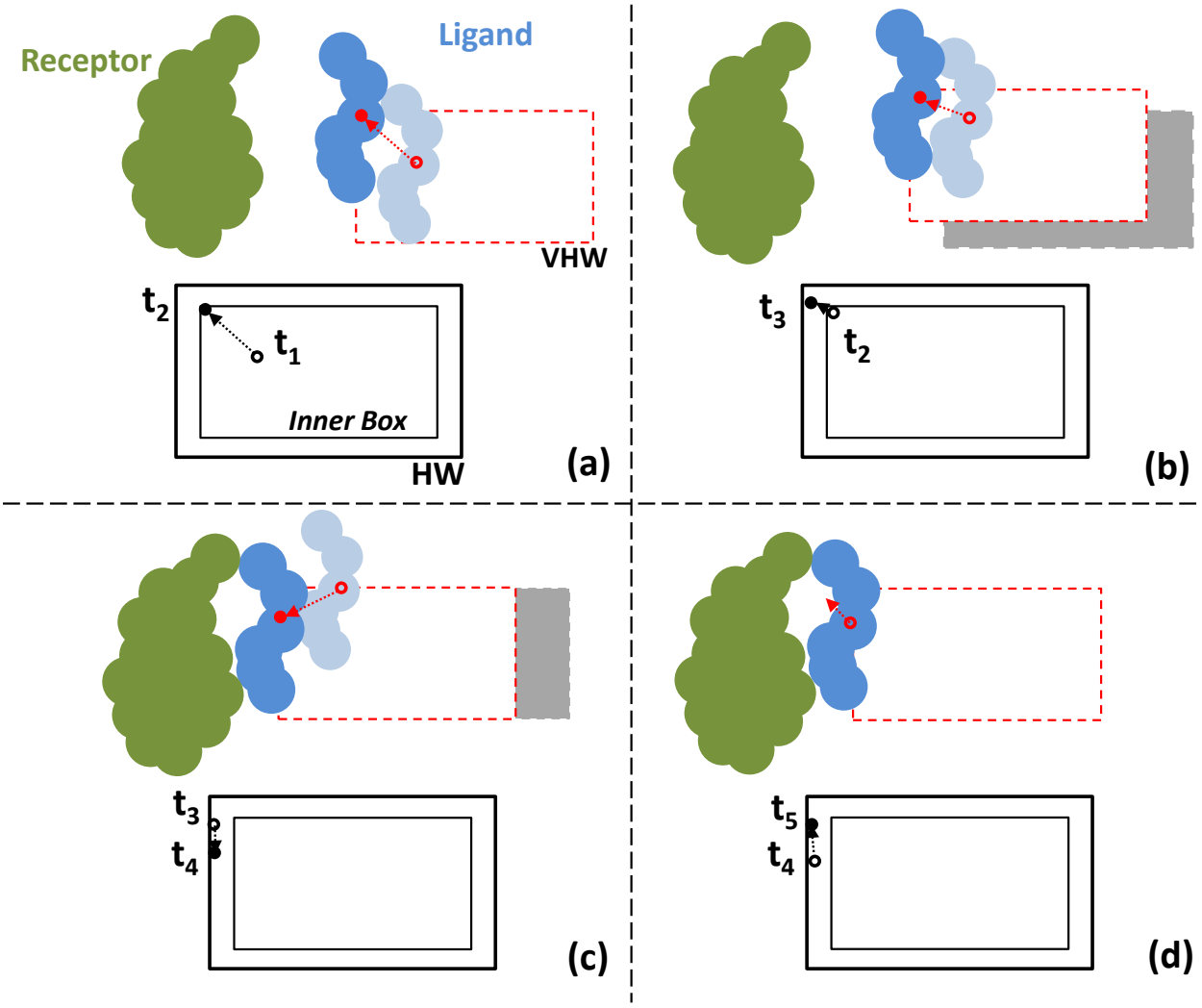


Figure 3: A 2D conceptual illustration of the Virtual Haptic Workspace (VHW) implemented in Haptimol_RD. The HIP, representing the tip of the haptic stylus, moves within the Haptic Workspace (HW) controlling the displacement of the ligand in the VHW. The black and red arrows give the direction of the HIP and the corresponding virtual cursor displacements, respectively. The light blue structure, and the grey box display the previous positions of the ligand and VHW. All displacements are sampled at consecutive haptic frames from t_1 up to t_5. (a) The HIP moves within the inner box of the HW finishing its movement just on the edge of the inner box. This causes position control displacement of the ligand within the VHW. The displacement matches the movement vector of the HIP between t_1 and t_2. (b) The HIP moves outside the HW's inner box causing rate displacements of the ligand and VHW together. (c) The HIP moves from t_3 to t_4 within the HW causing rate displacement of the ligand on the horizontal axis and position control of the ligand in the vertical axis. The ligand moves according to the displacement vector shown in red. After this movement the ligand has just come into contact with the receptor. (d) HIP movement from t_4 to t_5 would cause the ligand to move in the direction indicated by the red arrow. However, this movement cannot occur due to collision.

coordinates of both the virtual object (ligand) attached to the cursor and the VHW. The VHW coordinates are also updated when the user applies a global rotation to the scene. It is possible for the HIP to move without updating the position of the cursor. This occurs when the molecules collide with each other (Figure 3f). Under molecular collision, the HIP will update the cursor only if the given displacement moves the cursor/object to a valid (i.e. collision free) position (see Section on Haptic Stability and Multi-point Collision Response). As such the method decouples virtual object movement from HIP movement completely, unlike the virtual coupling approach which connects (constrains) the HIP and virtual object with a spring.[?] This decoupling is the main advantage of this method since it allows unconstrained object/VHW movement(i.e. unconstrained by the spatial resolution of the HW) within the visual world, and enables the efficient handling of intermolecular collisions during a docking simulation. By keeping the receptor fixed in space and moving only the ligand, the method differentiates itself (in addition to the VHW) from those of Subaci and Basdogan,[?] and Stocks et.al,[?] both of which apply rate and position control displacements to the receptor and ligand molecules respectively. Since it feels natural to place a key into a steady lock rather than a movable one, the author's finds this type of haptic navigation to be more intuitive than the previous ones for molecular docking. Nonetheless, Haptimol_RD has also implemented the other mode of receptor/ligand movement, for the user accustomed to that type of navigation.

Implementation

Haptimol_RD (Figure 1) is developed using the Visual C++ programming language, the Windows Standard Development Kit (win SDK), and the OpenGL and OpenCL libraries. The win SDK and the OpenGL library were used for developing the Graphical User Interface, and for rendering/visualizing the 3D molecular structures respectively. The OpenCL library was used for programming the GPU to compute the interaction forces

and it was chosen in order to maximize the portability of Haptimol_RD to different GPU architectures. Finally, the interface with the Geomagic Touch haptic device was implemented using the OpenHaptics toolkit from Geomagic.

Haptimol_RD provides two modes of molecular visualization. The first mode renders the molecule using a space-filling model, whereas the second uses a Cα backbone model. The user is allowed to select the two modes interchangeably at runtime. Haptic rendering of the interaction force is provided in either mode, with the force being computed, however, based on all interatomic interactions within the cut-off distance (regardless of the mode). In addition to the visuohaptic feedback, the application offers additional visual cues that can provide further assistance to the user during the docking simulation. These cues include a real-time graph of the interaction energy and the magnitude of the force. This information can be used qualitatively by the user to identify potential local energy minima/barriers, and score/evaluate the respective conformations. With a residue colouring feature the user can colour-code different parts of the molecule (e.g. potential active sites), and use these codes to identify these parts readily during the docking simulation (reducing the search space). In addition to colouring the user can also "ghostify" residues in order to remove their contribution to the total interaction force. Residue selection, colouring and "ghostifying" is implemented in a manner similar to PyMol,[?] and can be applied to both receptor and ligand molecules (Figure 4). A file-save feature allows the user to store the coordinates of potential docking conformations in different PDB files. Using this feature the user can export various docking poses, throughout the simulation, which can then be imported into other applications for further analysis. In addition to a haptics-assisted navigation, Haptimol_RD allows the user to conduct the docking simulation using a keyboard and a mouse. This allows users who do not have access to a haptic device to use the application in their studies. The lack of force feedback however, would have a negative impact on the usefulness of the application.

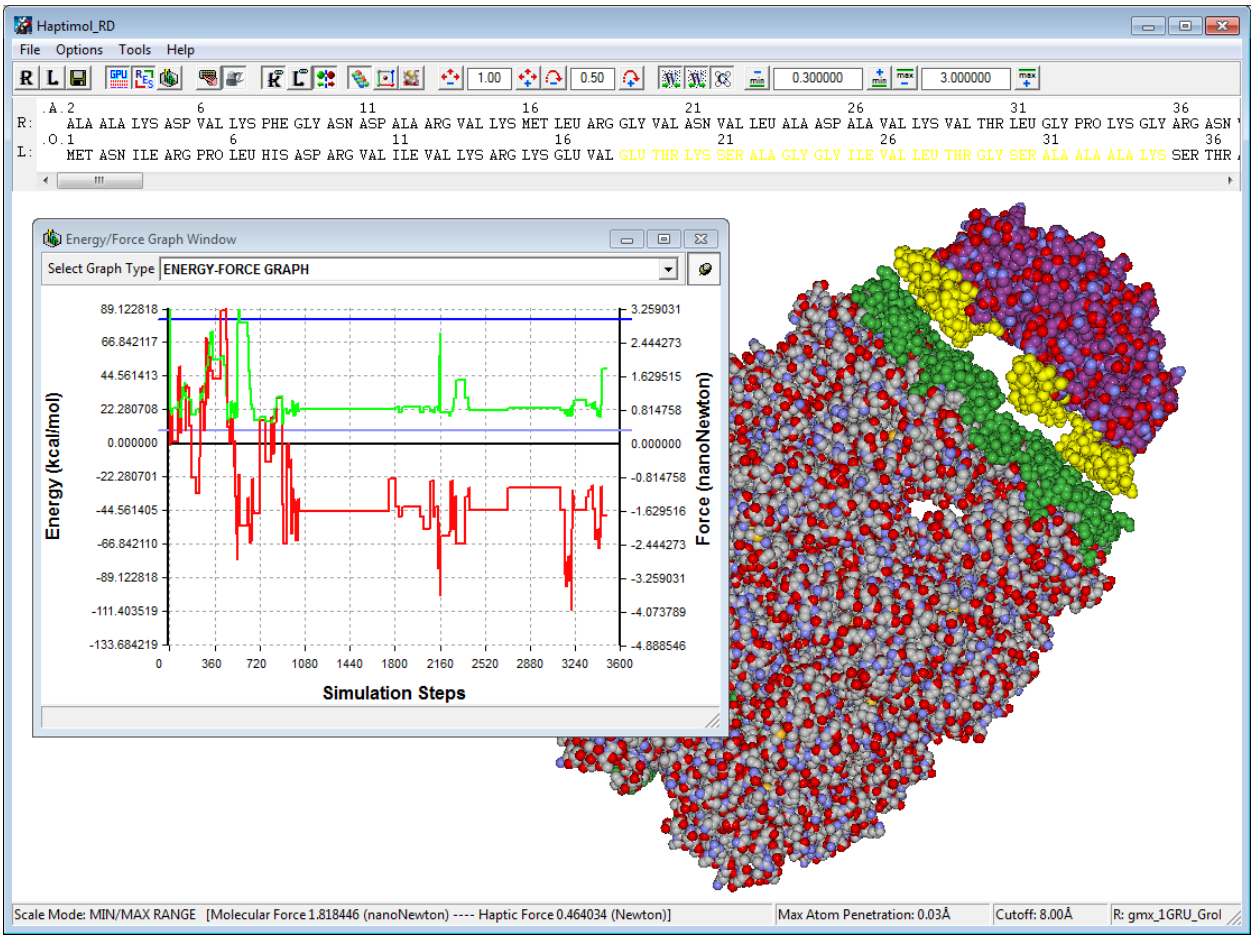


Figure 4: The Graphical User Interface of Haptimol_RD. The GroES interacts with its receptor GroEL, PDB code:1GRU. The interaction energy (red line) and force (green line) are displayed in real-time in the Energy/Force Graph Window. The dark and light blue lines within the same window depict the user-defined max and min limits of the force scaling range, respectively. The user can adjust this range during the simulation in real-time, and as such affect the profile of the forces rendered on the haptic device. Using the residue selection/colouring control (the scrollable area above the Energy/Force Graph Window) the residues with interacting atoms of GroEL and GroES are coloured in green and yellow, respectively. The user utilizes this information in order to focus the haptic simulation in this regi on only, and thus reduce the search space of docking conformations substantially.

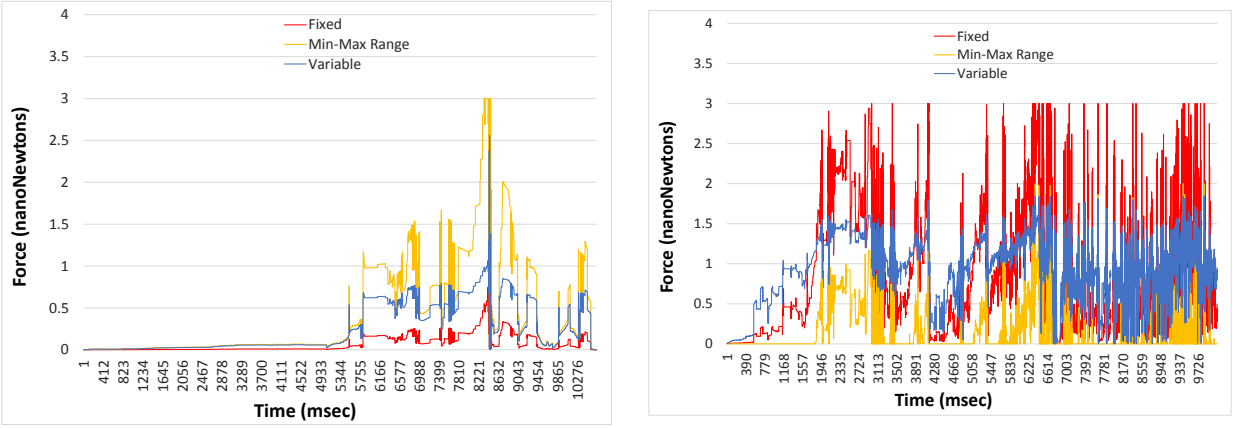
Results and Discussion

We have conducted a series of experiments using Haptimol_RD in order to: a) evaluate the force profile obtained by the min-max range force scaling method during the rigid docking of large proteins, b) to study and gain insights of the docking process with an emphasis given to the forces (type of interactions) felt near the docking site, and c) discover how the "ghostify" option of Haptimol_RD can facilitate the rigid docking of proteins that undergo conformational changes during binding. All simulations were conducted on a 2.93 GHz Intel Core i7 PC with 8 GB of RAM and on an NVIDIA GTX580 GPU with 1.5 GB RAM. The PC ran under a 64 bit version of Windows 7 and as a haptic device we utilized the 3DOF Geomagic Touch, formerly known as the Phantom Omni from SensAble Technologies.

Force Scaling

In Figure 5 we show the profiles of the interaction forces obtained after scaling for the three different force scaling methods implemented in Haptimol_RD. The experiment shows the interaction forces between GroES and GroEL and highlights the benefits of the min-max range method in two specific cases. Figure 5(a) illustrates the forces when investigating long-range interactions when the structures are relatively far apart. Here we set the min-max range equal to 0-0.5nN. With the min-max range we are able to expand the force range to give the user more perceptible differences in force magnitude than the previous two methods which should aid the user in understanding the differences in force magnitudes during interaction. In Figure 5(b) we compare the force profiles when studying complementarity close to the docking site. Here we set the min-max range to 1-6nN which scales down the short-range repulsive van der Waals interactions. In this case the min-max range force profile benefits most significantly over the fixed approach which tends to oscillate between zero and the maximum force of 3nN too rapidly to be

useful when attempting to perceive small variations in relatively large forces occurring when the structures are in close proximity.

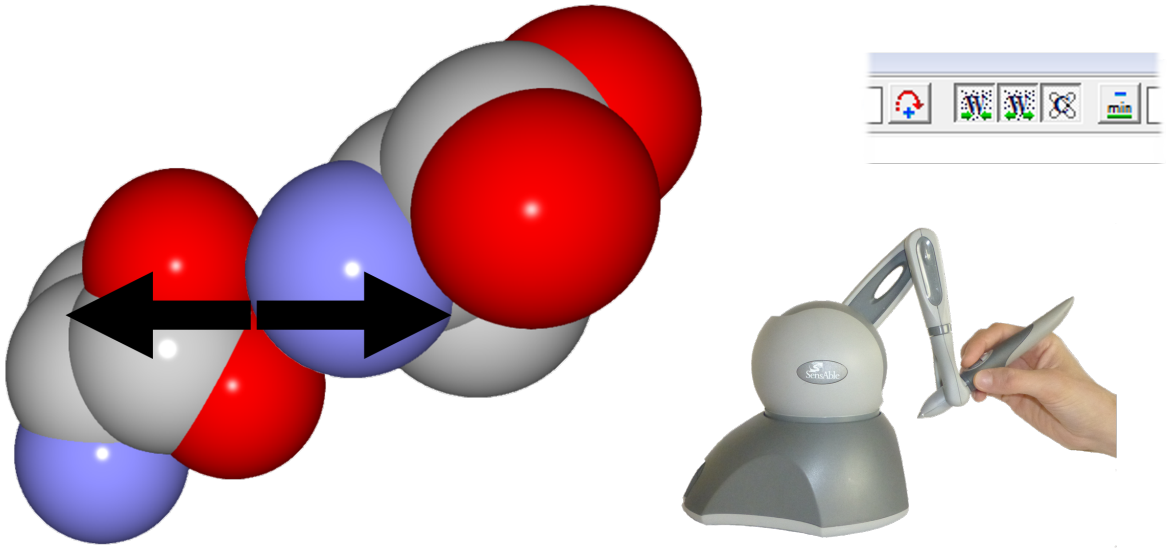


(a) (b)

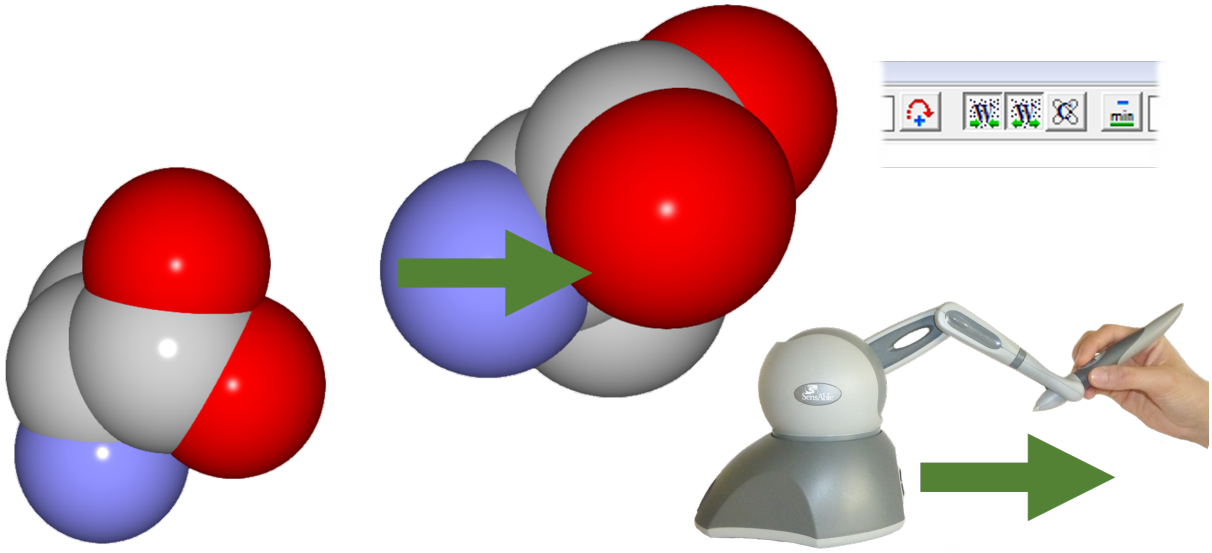
Figure 5: Graphing the interaction forces obtained after scaling, during two different rigid docking simulations of protein *GroES* and the receptor protein *GroEL*. Each simulation lasted for approximately 10 seconds and the force was scaled using the fixed, min-max range and variable gain methods. (a) The min-max range was set equal to 0-0.5nN in order to scale up (focus the study on) the long-range interactions when the molecules are farther apart. (b) The min-max range was set equal to 1-6nN in order to scale down the magnitude of the short-range, repulsive van der Waals interactions, and study structural complementarity close to the docking site.

Switching different force components on and off

When using Haptimol_RD the user may switch the electrostatic component of the force as well as the repulsive and attractive parts of the van der Waals force on or off. This enables the user to explore the contribution of each component. A dramatic demonstration appropriate for teaching purposes is illustrated in Figure 6. Here two alanines are held together by bifurcated hydrogen bonds between the amide group of the ligand-alanine (the one under control of the haptic device) and the carboxylic group of the receptor-alanine. Gently pulling on the haptic device in a direction to extend these bonds is clearly resisted by a restoring force. That this is due to the attractive electrostatic interaction can be verified by switching off the electrostatic term whilst applying the same gentle pulling force. Upon



(a)



(b)

Figure 6: Initially both the electrostatic and van der Waals forces are being calculated during the interaction of two alanines. In (a) the force applied to extend the bond via the haptic device is resisted by an opposing force due to the hydrogen bonds. The black arrows show the two opposing forces. The top-right of the figure shows a portion of the interface with the attractive van der Waals, repulsive van der Waals and the Coulombic forces all being calculated. In (b) the user has turned off the electrostatic force (indicated by the raised up coulombic button in the top-right) and the ligand and haptic stylus move freely as indicated by the green arrows.

pressing the button to switch off the electrostatic interaction the restoring force suddenly disappears and the ligand-alanine moves away freely from the receptor-alanine.

Sucking effect

One interesting application of this rigid docking tool is to see if molecules from structures solved in the docked conformation can be brought from an undocked conformation back to the true docked conformation. The ability of Haptimol_RD to handle large molecules means that this can be tested on multimeric proteins. Here we present the examples of Bovine Pancreatic Trypsin Inhibitor (BPTI) and Trypsin and the two subunits in the homodimer Aspartate Rasemase. In these experiments a PDB file for each of the two subunits was created from the PDB file of the complex and the coordinates of the subunit assigned as the ligand were changed such that the ligand and receptor were well separated in space. The purpose of the experiment is to see if it is energetically possible to bring the two molecules into the correct pose, not to see if one can find the correct pose without guidance. Therefore we were aided, if necessary, by the knowledge of the correct pose, e.g. by having a molecular graphics window open showing the complex whilst performing docking.

Figure 7(a) and 7(c) show the result of docking BPTI and Trypsin and Figure 7(b) and 7(d) show the result of the docking of the two subunits of Aspartate Rasemase. The RMSD trajectories (Root Mean Square Deviation between the ligand in its position during the interactive docking session and it position in the complex) in Figure 7(c) and 7(d) show that the true pose could be achieved in both cases. The energy trajectories show that as the correct pose is achieved there is a sudden drop. This drop in interaction energy is accompanied by a strong force on the haptic device that gives the impression that the ligand is being sucked into the correct pose with the receptor. A previous study of this effect[?] indicated that whether the correct pose can be achieved with rigid body docking is related to the nature of the interface. Some interfaces are simple and suggest

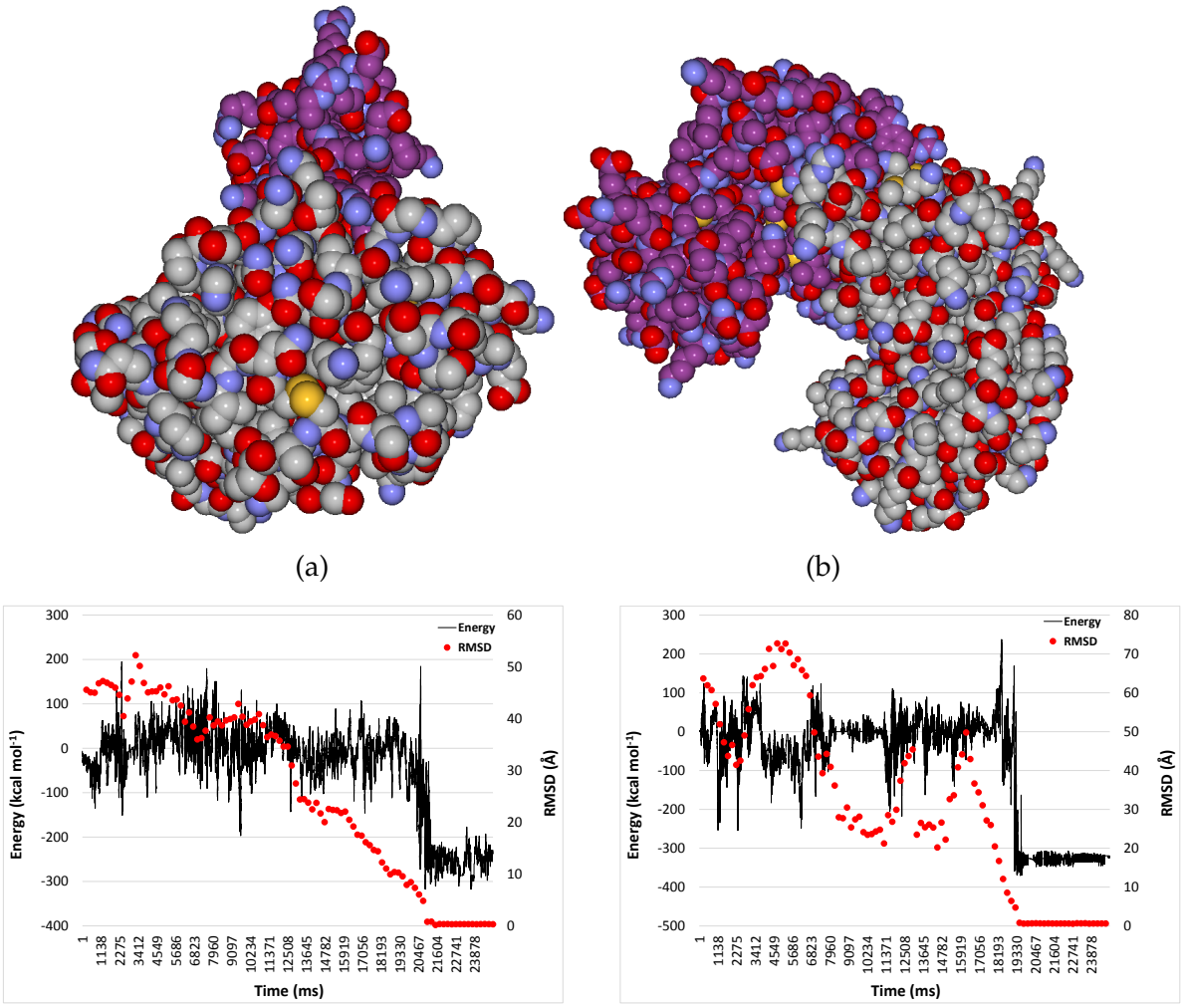
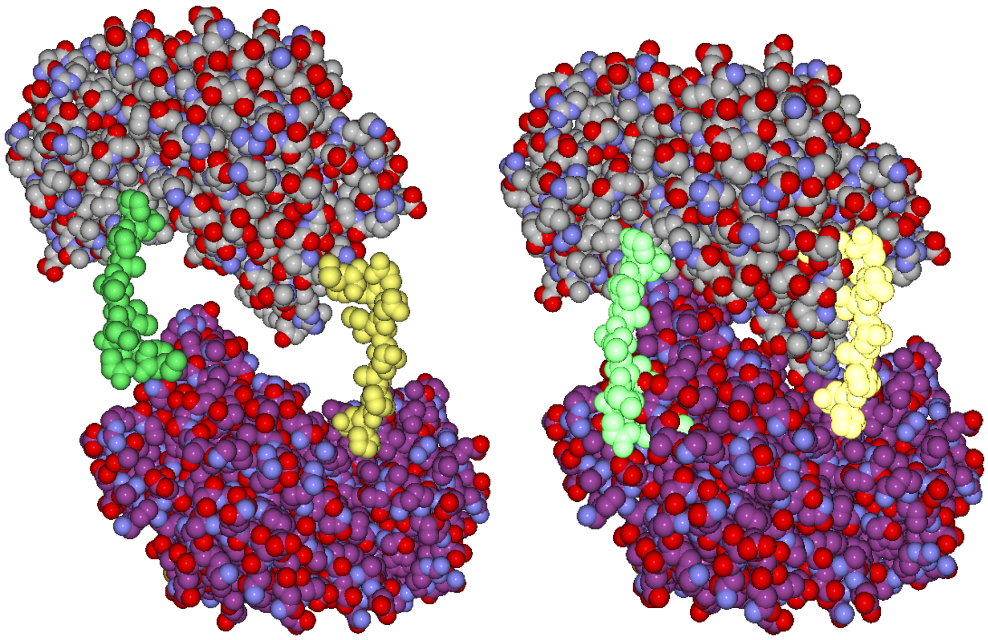


Figure 7: Juxtaposing the final docking conformation and energy/RMSD graph obtained during an interactive docking simulation of protein *BPTI* (purple) and receptor protein *Trypsin* (3OTJ), as well as, of the two subunits of the homodimeric protein *Aspartate Racemase* (1JFL). (a, b) Visualization of the final docking conformation obtained by Haptimol_RD for these complexes respectively, i.e. BPTI-Trypsin and Aspartate Racemase. (c, d) The trajectories of the interaction energy (black lines) and the backbone RMSD between the ligand position during docking and the ligand position in the experimental structure (red dots), for the same complexes.



(a) (b)

Figure 8: Testing the residue ”ghostify” option of Haptimol_RD. (a) Chain A and chain B of the homodimer Aspartate Aminotransferase (1AHE) in closest docking conformation using Haptimol_RD. The N-terminal regions (i.e. green colour for the receptor, yellow colour for the ligand) prevent the two subunits from achieving the correct docking pose. (b) The new closest docking conformation obtained for chain A and chain B of Aspartate Aminotransferase after ”ghostifying” the repsective N-terminal regions, i.e. coloured in lighter green and yellow colours.

that the molecules are already folded before complex formation, whereas others have an interwinding interface indicating considerable intrasubunit conformational change occurs upon complex formation.? For the former successful rigid docking may be possible, whereas for the latter rigid docking should not be possible.

The sucking effect, felt with several examples, appears to be due to the fact that in X-ray refinement the same force-fields are being used and as such an energy minimum at the correct pose is also a minimum of the target function for X-ray refinement.

Ghostifying

Consider a complex with an interwinding interface, i.e. with regions that would apparently have to change conformation in order for the molecules to dock. It would be useful to be able to test which regions are playing a part in preventing successful docking. The ghostifying feature allows one to do this as illustrated with Aspartate Aminotransferase in Figure 8. In this homodimer the N-terminal residues 1-13 are in an extended conformation and have extensive contacts with the other subunit. Attempts to rigidly dock the subunits using Haptimol_RD fail. Figure 8(a) shows the closest achievable docking pose indicating that these N-terminal regions would need to move out of the way for the correct docking pose to be achieved. This is confirmed as ghostifying these regions allows the subunits to come into a near-docked pose as seen in Figure 8(b), although there is apparently another region that prevents the true docked pose from being achieved.

Conclusion

A new haptics-assisted tool for rigid biomolecular docking, Haptimol_RD, has been developed. As has been recognised previously there are some unique problems that face developers of such tools. A major one, is the requirement for the force refresh rate to be greater than 500Hz in order to avoid jittering on the haptic device and force discontinuities.

Previous applications have used force-grids in order to achieve this, but using cut-off-based methods for the non-bonded interactions means Haptimol_RD is able to calculate forces in real-time. Obviously the larger the system the more difficult it becomes to achieve the required force refresh rate but the advanced spatial decomposition methods tailored for GPU parallel processing implemented in Haptimol_RD, mean that it is able to perform with systems as large as GroES docking onto GroEL. Even for computers without a GPU, the octree-based spatial decomposition querying method running on a CPU enables it to dock molecules comprising several thousand atoms using a standard desktop computer.

A further challenge is the problem of force scaling and maintaining sensitivity over a large range of intermolecular forces when the device itself is sensitive over a very narrow range. Previous researchers have addressed this problem and one of the solutions, the variable gain scaling method,[?] has been implemented in Haptimol_RD. We have also implemented a fixed scaling method and a min-max scaling method which uses a user-defined minimum and maximum for the molecular force which is linearly mapped onto the minimum and maximum force range of the haptic device. With this scaling one could, for example, feel changes in a weak electrostatic force when the molecules are apart, but by adjusting the range, feel comparatively large changes in the van der Waals forces when the molecules are in close proximity.

At close proximity the van der Waals interactions give rise to a complex and rapidly changing force field that can cause a strong vibration of the haptic device. In order to overcome this we have implemented a force-based multi-point collision response method which prevents further updates on force and position as long as the intermolecular force remains above an empirically derived threshold (3nN). This drastically reduces the vibration on the haptic device and prevents the occurrence of overlapping molecules.

Interactive docking tools allow an expert user to guide the docking process. In contrast to automated docking tools they can inform the user about the docking process, e.g. whether electrostatic steering is involved in bringing the two molecules together. Our

implementation enables the user to switch different types of interactions on or off and to remove forces arising from selected residues during the docking process. This can inform the user about which forces are dominating and to determine their source. This kind of exploration and testing of ideas is not suited to automated docking. The tool developed here could be used subsequent to automated docking in order to review results, perhaps rejecting some or refining others. Interactive docking tools are particularly useful when the user already has some knowledge of the system as in structure-based drug design. Automated methods are necessary to screen a large number of compounds but the software developed here could be used once a small number of leads have been identified in order to visualize the possible docking conformations, feel the underlying interaction forces and improve upon or reject these conformations based on knowledge, experience and expertise.

Haptimol_RD could also be used as a highly engaging and informative tool for teaching students about the nature of molecular interactions and biomolecular function. Experience with existing biomolecular haptics software[????] has demonstrated that interactive docking systems are excellent tools for helping students understand the process of molecular binding.

Haptimol_RD enables the study of large systems such as when two proteins interact. Thus it expands, for the first time, the use of interactive biomolecular haptics beyond the confines of studying small molecule-protein interactions to the study of protein-protein interactions.

As with all current interactive docking tools the two molecules are held rigid, but our main contribution here is in developing a tool that does not involve the use of a pre-computed force grid but calculates interaction forces in real-time. In principle, this means that protein flexibility can be incorporated into the system provided one has a method to calculate the conformational response of the molecules to changes in interaction forces within the update time constraint.

Software Download

A version Haptimol_RD can be downloaded from the following location

http://www.haptimol.com/haptimolrd/rdinstaller.zip

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