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Determination of locked interfaces in biomolecular complexes using Haptimol_RD

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Interactive haptics-assisted docking provides a virtual environment for the study of molecular complex formation. It enables the user to interact with the virtual molecules, experience the interaction forces via their sense of touch, and gain insights about the docking process itself. Here we use a recently developed haptics software tool, Haptimol_RD, for the rigid docking of protein subunits to form complexes. Dimers, both homo and hetero, are loaded into the software with their subunits separated in space for the purpose of assessing whether they can be brought back into the correct docking pose via rigid-body movements. Four dimers were classified into two types: two with an interwinding subunit interface and two with a non-interwinding subunit interface. It was found that the two with an interwinding interface could not be docked whereas the two with the non-interwinding interface could be. For the two that could be docked a "sucking" effect could be felt on the haptic device when the correct binding pose was approached which is associated with a minimum in the interaction energy. It is clear that for those that could not be docked, the conformation of one or both of the subunits must change upon docking. This leads to the steric-based concept of a locked or non-locked interface. Non-locked interfaces have shapes that allow the subunits to come together or come apart without the necessity of intra-subunit conformational change, whereas locked interfaces require a conformational change within one or both subunits for them to be able to come apart.

Key words: haptic feedback, force feedback, protein docking, protein-protein interactions, interwinding interface

The study of protein-ligand interactions has been and still is an exciting research topic, with important applications in drug design and protein-protein recognition. In nature, molecules interact and bind with other molecules to form complex structures that control various regulatory and metabolic processes of the living cell. In pharmacology for example, drug behaviour (i.e. the therapeutic action and side effects of a drug) depends closely on where and how the drug binds to a given protein [1]. Cellular signalling, gene regulation, and immunity are other examples of biological function that is controlled by these interactions [2]. For several decades researchers have been trying to study and replicate these interactions *in silico*, using various computational models and methods, often referred as to molecular docking.

Generally speaking, molecular docking describes those methods that attempt to orientate and bind a ligand to the active site of a protein by exploring an enormous number of

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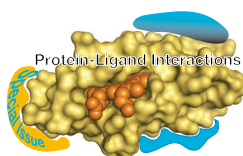
◄ *Significance* ►

Recently we have developed a software tool, Haptimol_RD, which allows the user to control a ligand molecule via a haptic device and feel its interactions with a receptor molecule. Here we have used Haptimol_RD on two types of dimers, those with an interwinding subunit interface and those without a non-interwinding subunit interface. The results show that for the interwinding dimers one or both the subunits much change conformation upon complex formation whereas for the non-interwinding dimers this is not necessary. This leads to a new concept relating to steric interactions between subunits; that of a "locked" interface.

potential binding conformations and selecting the most probable one. To achieve this, automated docking [3–5] approaches utilize efficient search strategies and scoring functions in order to explore the protein/ligand conformational space, evaluate potential binding poses, and score/select the most favourable of those poses. Their execution relies only on computing power, and they can search for and provide probable binding conformations for a large number of protein-ligand targets, e.g. for the virtual screening of drugs [6]. Even though automated methods are the most popular in the field, they often produce incorrect results [7]. Moreover by design, they do not allow human intervention in the docking process, and as such cannot benefit from human knowledge, and expertise. Interactive docking addresses these issues by allowing rational human thought, intuition and experience to execute the pose sampling and selection process. In interactive docking, the user is able to see and move the virtual molecules in real time, and perform a knowledge-guided search and selection of the final binding pose. Interactive docking systems often combine 3D molecular visualization with haptic technology as a means to enhance user experience with the sense of touch. Haptics-assisted docking systems provide an immersive virtual docking environment where the user can interact with the molecules, sense the interaction forces, and utilize this visuohaptic feedback to identify and select the right binding conformation [8,9]. They are also useful learning tools for the study of protein-ligand interactions during docking, and research tools for forming and investigating new ideas and hypotheses pertinent to complex formation (e.g. the effects of a mutation) [10]. Unlike automated approaches, haptics-assisted approaches cannot facilitate the docking of a large number of different protein-ligand targets within a session, due to their interactive nature. However, they allow the user to intervene cognitively in the docking process, and as such can assist experts to improve upon the docking conformation produced by their automated counterparts [9–11].

The benefits of haptic technology in molecular docking were first studied by Brooks *et al.* with the GROPE III project [12]. Their system utilized a modified Argonne E-3 Remote Manipulator (ARM) for ligand movement and force feedback display, and managed to accelerate the docking of small rigid molecules by a factor of two. Subsequent works investigated the benefits of haptics in computer-aided drug design [13], in rational drug design [14], in computer-aided molecular design [15], for the study of protein-drug and protein-protein interactions [9,16,17], and in e-learning and education [18–21]. These studies indicated that haptics-assisted docking can help users' (experts or students of structural biology) learn about the process of molecular binding, and experts to improve upon docking conformations that have not been (or could not be) verified experimentally. In addition to docking, haptic technology has also been used for exploring the solvent accessible surface (ISAS) of a biomolecule [22], deforming protein structure using an elastic network model [23], and for steering molecular dynamics simulations [24].

The majority of existing haptics-assisted docking systems treat the molecules as rigid and account only for the van der Waals and electrostatic interactions, unlike the automated docking systems which often model molecular flexibility to some extent. These limitations stem from the fact that modern haptic technology necessitates force refresh rates of 500 to 1000 Hz for high fidelity smooth and stable force feedback [25–27]. When this rate is not met, the user experiences device jittering and force discontinuities that limit the usefulness of such a system. To address this strict time constraint therefore, existing interactive docking systems rely on various model simplifications (e.g. model rigidity and nonbonded interactions only), and processing-time-acceleration techniques (e.g. precomputed force-grids) [8,9,14,15,28–30]. They also limit the size of molecules they can support to small biomolecules [11]. This is true also for the few interactive systems that have attempted to model molecular flexibility, but failed to satisfy the 2ms time constraint of haptics [31,32]. As it stands, none of the existing interactive docking systems can facilitate the docking of large biomolecules, and as such they cannot help scientists study and gain insights into the mechanisms of protein-protein interactions.

We have recently developed a system for interactive haptics-based rigid molecular docking that is able to handle large biomolecules. Our purpose here is to report on the rigid docking of proteins and ascertain whether there is anything we can learn about the process of docking when the proteins are able to undergo conformational change. It is clear that when two molecules associate there will be to a greater or lesser extent some degree of conformational change. Indeed in some cases, this conformational change can be dramatic as exemplified by examples of structures solved in the presence and absence of their binding partner, e.g. epidermal growth factor and epidermal growth factor receptor. It is clear that in such cases the rigid docking of the proteins in the free state will not result in a favourable binding pose. What though would we learn if we were to try to rigidly dock proteins each in the conformation of the bound state? One unknown is whether the correct binding pose can actually be achieved through rigid docking alone. If it cannot then it shows that conformational change must occur in the process of binding. If, however, the correct binding pose can be achieved, it would imply that conformational change need not occur although it certainly does not preclude the possibility that it has. The main aim of the research presented here, then, is to test whether the correct binding pose can be achieved with rigid docking using selected examples, and if it cannot to conclude that conformational change must have occurred in one or both of the proteins during the binding process. The examples we have selected come from a dataset created by Yura and Hayward [33]. This set of bound state proteins, both homo-oligomers and hetero-oligomers, were

classified as having interwinding or flat-against-flat inter-faces using a measure termed the Surroundedness Factor, *SF*. *SF* is 0 for a perfectly flat interface but rises to values greater than 2.0 for interwinding interfaces. Our selected examples are from those classified as flat-against-flat and interwinding.

Methods

Haptimol_RD

Haptimol_RD is an interactive application that can facilitate the haptics-assisted docking of large rigid biomolecules (Fig. 1). It is designed to run on consumer level hardware, (i.e. there is no need for specialized/proprietary hardware), and utilize a relatively inexpensive haptic device, i.e. 3DOF Geomagic Touch. The application is written in Visual C++, and uses the OpenGL library for 3D graphics rendering. It can compute the nonbonded interaction forces, in real time, either on the CPU or the GPU, using the cut-off-based force calculation methods proposed by Iakovou *et al.* [34,35]. Both methods compute the forces using the set of inter-atomic interactions within a given cut-off distance, and utilize efficient proximity querying algorithms (optimized for CPU and GPU execution) in order to identify this set. Force computations on the GPU are executed using OpenCL. During a docking simulation, the user can switch on/off the electrostatic and VDW forces in order to investigate their effects. Haptimol_RD renders a molecular structure using space-filling and the C_α-backbone models, and depicts a force by an arrow. At any point and time during the simulation, the user can save a given conformation in a PDB file and use it for further investigation. Using Haptimol_RD, we attempted to rigidly dock subunits of heterodimer and homo-dimer proteins solved in the complexed state.

Force Model

The interactions included were van der Waal (VDW) and electrostatic. The VDW was modelled using the 12-6 Lennard-Jones (LJ) potential, and the electrostatic using Coulomb's law. The non-bonded LJ and Coulombic parameters were obtained from the Gromos54a7 [36] force field using the pdb2gmx tool provided by Gromacs version 4.6.2 [37]. All energy/force computations were performed on the GPU using a cut-off distance of 8 Å. To render the resultant
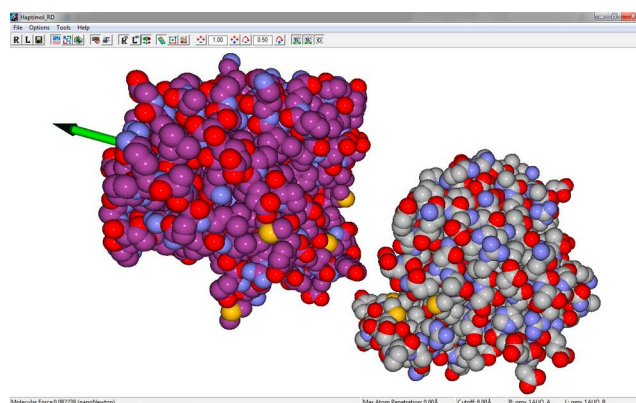
Figure 1 Ligand (purple) interacts with receptor within Haptimol_RD. The green arrow indicates that the user is sensing weak repulsive forces on the haptic device.

interaction forces on the haptic device, the values were converted from kJ mol^{-1} nm^{-1} to Newtons and then scaled by a constant factor. Similarly to Iakovou *et al.*, we converted the initial force to Newtons by dividing by 6.02329×10^{11} (since 1N is equivalent to 6.02329×10^{11} kJ mol^{-1} nm$^{-1)}$, and then scale it by 10^9 to obtain a good range of haptic forces.

Homodimers and Heterodimers Investigated

In this study we attempt to dock rigidly the subunits of known homodimer and heterodimer proteins. Four known dimer proteins were selected for this purpose; namely, the two heterodimer proteins *Nitrile Hydratase* and *C-Phycocyanin*, and the two homodimer proteins *Aspartate Aminotransferase* and *Aspartate Racemase* as defined in the PDB files 1AHJ, 1I7Y, 1AHE, and 1JFL, respectively (Table 1). The proteins were selected from the Yura and Hayward [33] dataset based on their *SF* values. Yura and Hayward utilized this dataset in order to study the interwinding nature of protein-protein interfaces, and discovered that subunits with *SF* < 1.25 do not have interwinding interfaces, whereas subunits with *SF* > 2.0 have interfaces that interwind extensively. The protein-protein interface in the former case is classified as *flat-against-flat*, whereas the interface in the latter case is classified as *interwinding*. For those subunits with a flat-against-flat interface, we expect to be able to dock them rigidly, since no major structural deformations are

Table 1   The two heterodimer and homodimer proteins used in the interactive rigid docking experiments studied here

Name	PDB Code	Type	# of Residues in Subunit A	# of Residues in Subunit B	SF
Nitrile Hydratase	1AHJ	Heterodimer	198	212	2.11
C-Phycocyanin	1I7Y	Heterodimer	162	172	0.87
Aspartate Aminotransferase	1AHE	Homodimer	396	396	2.84
Aspartate Racemase	1JFL	Homodimer	228	228	0.78

The subunits of dimers with an SF value less than 1.25 are expected to interface rigidly, whereas the subunits of dimers with an SF value greater than 2.0 are expected to undergo substantial conformational change during docking.
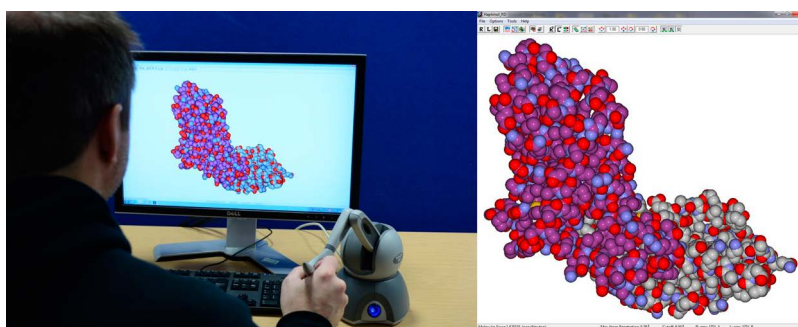
Figure 2 Left: The docking of chain A (grey carbon atoms) and B (purple carbon atoms) of homodimer protein *Aspartate Racemase* (1JFL) using Haptimol_RD and the 3DOF Geomagic Touch haptic device. Using the haptic device the user guides, orientates and docks chain B to chain A, while sensing the interaction forces on the haptic device. Right: A close-up view of the same docking simulation.

anticipated during docking. By contrast, rigid docking is not expected to work for those subunits with an interwinding interface, since they would be expected to undergo substantial conformational changes upon binding.

Results

Using Haptimol_RD and the dimers of Table 1, we executed interactive docking simulations in an attempt to dock rigidly the subunits forming those dimers. The purpose of these simulations was threefold: (a) to examine whether or not it is possible to obtain the correct binding conformation using an interactive haptics-assisted rigid-docking application, b) to relate rigid-docking success or otherwise to structure-related indicators such as the *SF* value, and c) to devise a test that could easily identify which molecules have to undergo conformational changes during docking. All interactive docking simulations were executed on a 2.93 GHz Intel Core i7 PC running under a 64 bit version of Windows 7 with an NVIDIA GTX580 GPU. The PC was equipped with 8 GB RAM, the GPU with 1.5 GB RAM, and we utilized the 3DOF Geomagic Touch haptic device, formerly known as the Phantom Omni from SensAble Technologies (Fig. 2).

To obtain the receptor and ligand molecules for each simulation, we used the initial PDB file, and separated the two subunits described within into different PDB files, thus producing eight new PDB files in total. For the purpose of these simulations we assigned subunit A as the receptor, and subunit B as the ligand. To add the necessary hydrogen atoms and obtain the values for the nonbonded terms of the Gromos54a7 force field (and the respective topology files), we used Gromacs' *pdb2gmx* tool 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 (see Gromacs manual [37] for more information). We also deleted all heterogen atom coordinates (e.g. water) listed within the receptor and

ligand PDBs prior to invoking pdb2gmx. In these simulations the ligand was attached virtually to the haptic device, whereas the receptor was set fixed in space. Using the 3D structure of the original complex as a visual guide, we moved the ligand around the receptor with the haptic device, explored the receptor's surface, sensed the interaction forces, and attempted to guide the ligand back to its binding pose (Fig. 2). We executed each simulation for several minutes, in order to experiment with different docking conformations, and investigate visually (i.e. by displaying the energy) and haptically the respective energy and force landscapes. We also recorded the energy value at each haptic frame. Figure 3 shows the energy trajectories and backbone RMSD trajectories between the ligand position during interactive docking and the ligand position in the experimental structure when both receptor structures are superposed. As can be seen for *C-Phycocyanin* (Fig. 3(a)) and *Aspartate Racemase* (Fig. 3(b)) docking succeeded in reproducing the experimentally determined pose, whereas for *Aspartate Aminotransferase* (Fig. 3(c)) and *Nitrile Hydratase* (Fig. 3(d)) the experimental pose could not be achieved.

Our results reveal two interesting points. The first is the existence of a "sucking effect" on the haptic device as we approached the correct binding pose that coincided with the sudden drop in energy. In order to confirm this we performed a further four independent docking experiments on *C-Phycocyanin* and *Aspartate Racemase*. The results are shown in Figure 4 and in each experiment the sucking effect was felt on the haptic device as the correct binding pose was achieved and the energy dropped. The other finding is that in some cases the true binding pose can be achieved using rigid docking whilst for others it cannot, and that this relates to the nature of the interface as classified by its *SF* value, i.e. flat-against-flat or interwinding. For example, in aspartate aminotransferase the N-terminal regions prevent docking (see Fig. 5). It is probable that these regions are flexible for the two subunits to be able to bind.
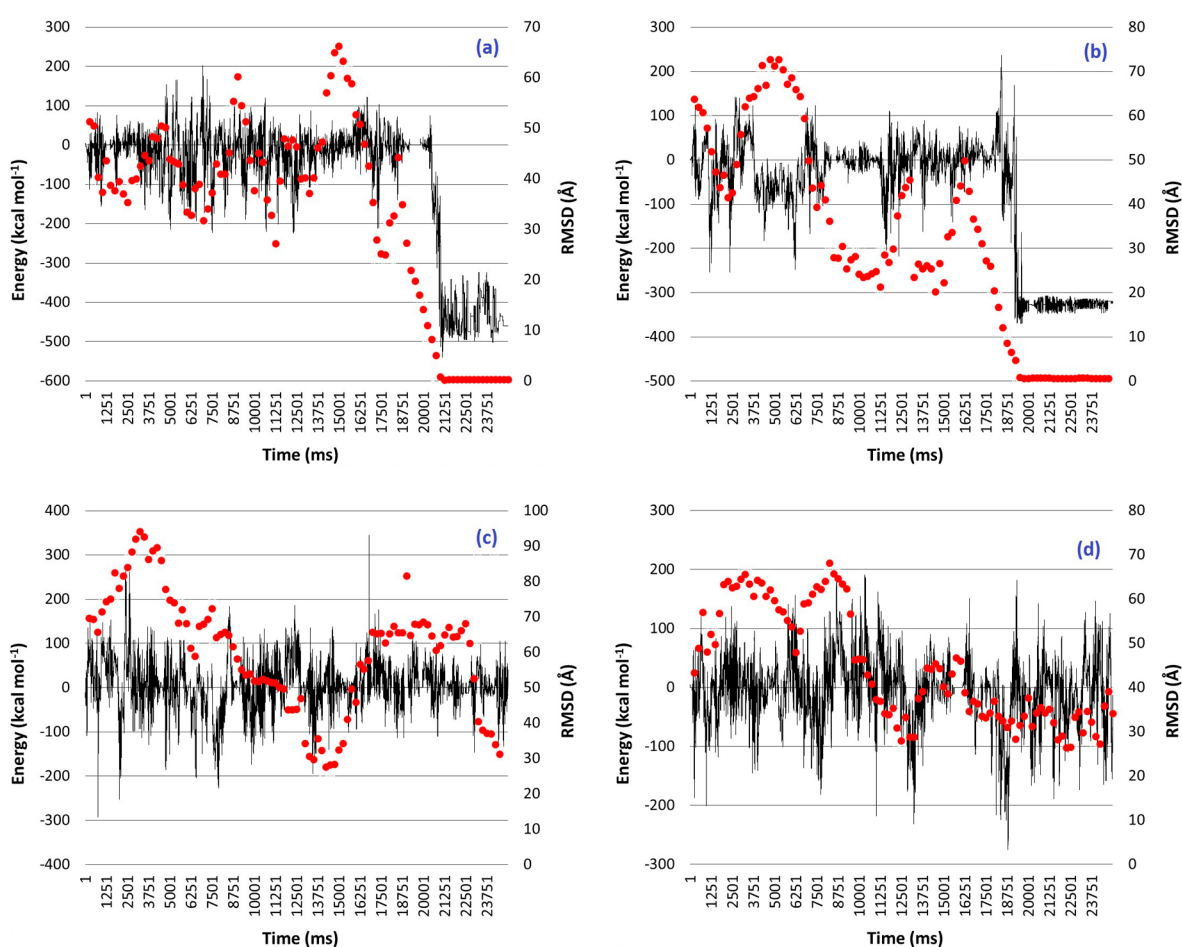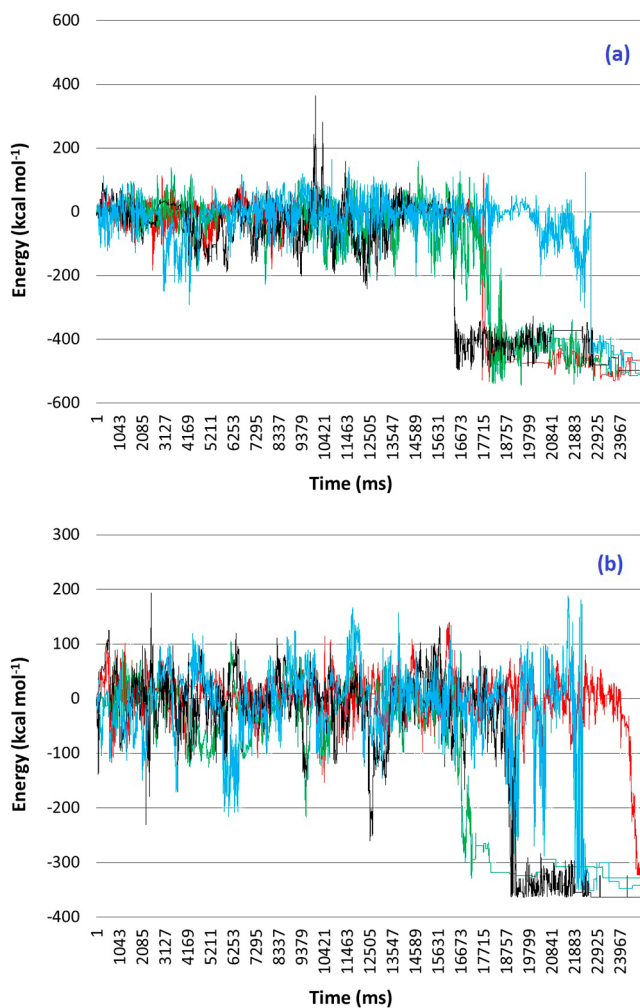
Figure 3   Trajectories of the interaction energy (black lines) and the backbone RMSD between the ligand position during docking and the ligand position in the experimental structure (red dots) obtained during the interactive docking of: (a) the α and β subunits of the heterodimeric protein *C-Phycocyanin* (1I7Y); (b) the two subunits of the homodimeric protein *Aspartate Racemase* (1JFL); (c) the two subunits of the homodimeric protein *Aspartate Aminotransferase* (1AHE); (d) the α and β subunits of the heterodimeric protein *Nitrile Hydratase* (1AHJ). We were able to dock the subunits in (a) and (b), but not in (c) and (d).
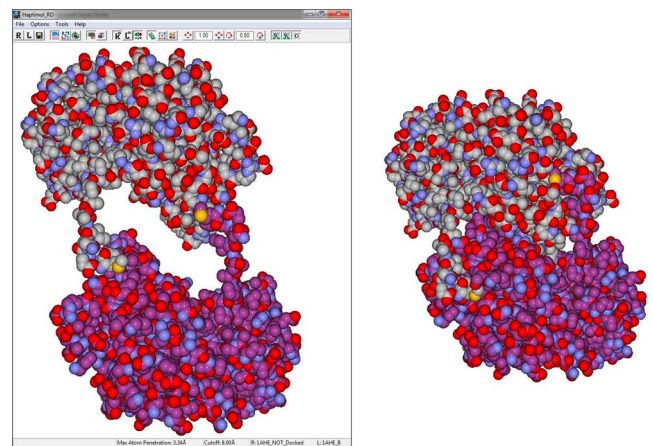
Discussion and Conclusion

Haptics assisted docking software allows the user to learn about the docking process and the interactions involved. Although there is a long history of the use of haptics in biomolecular docking, until now these methods have been applied to the docking of small molecules or a small molecule to a protein as in drug development applications. Advanced spatial decomposition methods, particularly in conjunction with the parallel processing capabilities of the modern GPU, has enabled the development of Haptimol_RD, a software tool for the docking of large biomolecules. Here, using Haptimol_RD, we have, for the first time, been able to study the interaction of two large protein subunits as they come together to form a larger complex. Haptimol_RD does not model protein flexibility and this study is therefore necessarily restricted to rigid docking. As rigid docking would not be expected to be able to dock molecules that have been solved separately in the free state, this study has been limited to the docking of molecular structures solved in the bound state. X-ray refinement methods use force-fields that are also used in Molecular Dynamics simulations such as the Gromos54a7 force-field used here for the non-bonded interactions between the two subunits. Although in X-ray refinement the "energy" contains terms which include structure-factors from the X-ray experiment, given the overwhelming contribution of the Lennard-Jones repulsive terms when atoms overlap, it is perhaps not surprising to find that the docked structure is at an energy minimum when the experimental terms are omitted. This explains the "sucking effect" felt on the haptic device, which pulls the ligand into the correct pose when one gets close to the experimentally determined conformation (<5 Å RMSD) and is not felt for incorrect binding poses. Our results using complexes that have interwinding and non-interwinding interfaces suggest that conformational change must occur upon binding for those with an interwinding interface as determined by its *SF* value. Conversely, those tested with a non-interwinding interface

Figure 4 Trajectories of the interaction energies obtained during four independent (shown in black, red, blue and green) docking experiments on: (a) the α and β subunits of the heterodimeric protein *C-Phycocyanin* (1I7Y); (b) the two subunits of the homodimeric protein *Aspartate Racemase* (1JFL). The graphs display only the last 25 seconds from each simulation for clarity purposes. The experimental docking pose could be achieved for each of the trials and attainment of the experimental docking pose was associated with a dramatic drop in the interaction energy. This drop in energy coincided with the sucking effect felt on the haptic device.

Figure 5 Left: Chain A and chain B of the homodimer *Aspartate Aminotransferase* (1AHE) in closest docking conformation using Haptimol_RD. The N-terminal regions prevent the two subunits from achieving the correct docking pose. Right: The X-ray structure of the homodimer.

could be docked correctly suggesting that conformational change need not occur upon binding. It is clear that one could generalise these results beyond interwinding and non-interwinding interfaces to a new concept, namely locked and non-locked interfaces. A non-locked interface is one where no change in internal conformation is necessary to bring the subunits into their correct pose or to take them apart. By contrast a locked interface is one where the two subunits cannot be brought into the correct binding pose or be taken apart without a change in internal conformation of at least one of them. For a truly interwinding interface this conformational change may involve a folding type process but one

can imagine other kinds of interfaces where the two subunits are locked, e.g. where a domain movement has enclosed part or all of the other subunit. It could also involve only inter-locking side chains although further investigations will need to be carried out to confirm this. This locked and non-locked concept relates to steric interactions and not to softer inter-actions such as electrostatic interactions. It relates therefore to the shape of the interface.

Although rigid docking has obvious limitations we have shown here that it can be used to reveal features of protein complexes that would be difficult to determine by other means.

A video showing the docking of *C-Phycocyanin* is avail-able through the following link: http://www.haptimol.co.uk/movies/iakovouetal.mp4.

Haptimol_RD will be released before the end of 2016.

Author Contribution

SH and SL conceived the experiment, GI carried out the simulations and all authors contributed to writing the manu-script.

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Conflict of Interest

There is no conflict of interest related to this work.

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