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Accessible haptic technology for drug design applications

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Abstract Structure-based drug design is a creative process that displays several features that make it closer to human reasoning than to machine automation. However, very often the user intervention is limited to the preparation of the input and analysis of the output of a computer simulation. In some cases, allowing human intervention directly in the process could improve the quality of the results by applying the researcher intuition directly into the simulation. Haptic technology has been previously explored as a useful method to interact with a chemical system. However, the need of expensive hardware and the lack of accessible software have limited the use of this technology to date. Here we are reporting the implementation of a haptic-based molecular mechanics environment aimed for interactive drug design and ligand optimization, using an easily accessible software/hardware combination.

Keywords De novo · Drug design · Haptic · Lead optimization · ZODIAC

Introduction

In the last decade, the availability of faster and cheaper computers has dramatically accelerated the development of computer-aided drug design software and applications. Large and free databases such as ZINC [1] can now be tested in a virtual screening simulation processed by a desktop machine in a few days. Continuous improvement in user interface design has simplified user interaction to a few mouse clicks; the development of many modeling software packages is often oriented toward limiting the human intervention, considered to be the bottleneck of the process. The user carries out preparation of the input and analysis of the output, leaving the rest of the discovery process to the computer. Indeed, the use of these methodologies has led to many successes [2, 3], however, it could be argued that in some cases an interactive and informed direct human intervention in a computer simulation could significantly improve the results obtained.

Of the five senses we use to probe our environment, so far only sight has been extensively exploited in molecular modeling. We here describe an interactive methodology where the combined use of sight and touch is used to facilitate a computer-aided drug design simulation.

Haptic technology has already been applied in a number of different fields. Haptics have been taken up by the media-related industries, e.g., for their use as a virtual sculpting tool; an artist can model with (and feel) a virtual clay model, particularly useful with rapid prototyping [4]. Medical training has shown particular promise, such as training interventional radiologists to guide needles – haptic feedback is essential for a computer simulation to be of use [5]. Haptics is essential to simulate conditions that could not be directly sensed, such as feeling the forces involved when molecules repel or attract each other [6].

The application of haptic technology to molecular modeling is not new and has been explored previously in different academic and industrially funded projects [7–10]. However, the need of relatively expensive devices and the limited public availability of the software programs capable of supporting the use of haptics in molecular modeling have

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considerably limited the use of this technology in a research environment. With this in mind our efforts have been directed to the development of a simple and affordable system, easily accessible by virtually any researcher interested in this field.

Methods

In previously developed software packages like the Chemical Force Feedback [11] system and HAMStER [12] the force feedback was successfully applied to different chemical systems. However, these systems relied on the use of pre-calculated potential grids and, as pointed out by Wollacott, this would limit the use of the haptic on large biological systems like proteins [12]. In our project, we moved from the above experiences and focused our research on the design of software that could have a concrete use in a de novo drug design simulation, thus capable of handling protein/ligand interactions in real time. In our scenario, the haptic pointer is linked to the position of the mass center of the ligand, while the protein atoms are kept fixed in their coordinates. While the user moves the ligand to probe the protein's surface, the total force on the ligand is computed and applied to the haptic device. To obtain this result, we have avoided the use of pre-calculated force grids, choosing a more demanding but also more precise approach consisting in the continuous recalculation of the force from the forcefield equations. Furthermore, we did not construct any specific haptic objects (via a haptic developer kit). Every virtual object in the scene (atoms and bonds) has a visual representation (spheres and lines or sticks) but not a haptic one. This avoids the use of unnecessary collision detection algorithms, which are generally slow and unnecessary to our calculations.

The haptic feedback is calculated directly from the molecular mechanics forcefield functions. In particular, the steepness of the van der Waals function makes the steric repulsion virtually behave as rigid body clash, making the collision detection superfluous.

Merck Molecular Force Field 94 (MMFF94) [13–17] was implemented to drive the haptic simulation, as it is one of the most frequently used force fields for ligand-protein interactions in molecular mechanics. The center of mass of the fragment atoms is linked to the haptic pointer position, and is therefore directly controlled by the user, while the other degrees of freedom of the fragment are controlled by a minimization algorithm (steepest descent). We implemented two different models of ligand flexibility. In the first one the ligand is considered rigid, and its interaction energy is continuously minimized as the user moves it by acting on its orientation. This allows us to neglect all inner energy contribution (bond stretchings, dihedral torsions etc) and is particularly suited for a fragment-based approach. The second model is a fully flexible one, and each atom of the ligand is free to move toward an energy minimum.

Given that a haptic interface needs to be updated around 1,000 Hz [6], we make use of multiple asynchronous threads to enable such a very high refresh of the haptic device working with a slower (>30 Hz) graphics interface. The haptic thread runs faster than the molecular mechanics thread by asynchronously making use of the latest available information from the simulation, resulting in a smooth interaction. A desktop computer [18] is thus able to simulate a system with a receptor of 5537 atoms and a flexible ligand of 16 atoms with over 200 updates per second for the force field calculations and over 1000 updates per second for the haptic feedback.

The haptic-driven minimization routine was implemented in ZODIAC [19], a cross-platform modeling software available under the GPL license. ZODIAC is built on the OpenBabel library [20], which allows access to over 80 chemical formats in input and output, and QT4, which provides GUIs for Linux, MacOS/X and Microsoft Windows. The implementation in ZODIAC allows us to access other useful features of this software in the haptic simulation such as 3D visualization via polarizing glasses, coloring individual atoms of the ligand based on their interaction energy, identifying favored/disfavored interactions with the receptor and it is also possible to visualize the formation and the breaking of hydrogen bonds between the protein and the ligand. It should be stressed that all these features work in real time during the haptic simulation, adding to the force feedback also a visual feedback that dramatically increases the user experience.

The use in ZODIAC of multiple asynchronous threads has produced a very usable, interactive system whilst making use of low-end haptic devices. This has removed the requirement for complex interfacing between the haptic and the simulation, such as wave variables as reported by [10].

As haptic device, we have initially implemented the Novint FALCON [21], currently the most affordable device on the market. As consequence for the affordability, this instrument allows only 3 DoF (3 degrees-of-freedom), thus rotation of the examined fragment cannot be performed directly. This somehow restricts the freedom the researcher has in placing the fragments and the user has to rely on the minimization process to support the correct placement in a putative active site. However, support for several other common haptic devices, which allow a 6DoF interaction, including the PHANTOM devices [22], is currently under development. This will give ZODIAC enough flexibility to be used by different researcher with the different devices available to them.

Results

As a proof of concept, we have tested ZODIAC usability on the colchicine binding site of tubulin, an important biological target on which we have worked extensively in the last few years [23–26].

Many colchicine analogues, and colchicine itself, present a trimethoxyphenyl moiety, which establishes a key interaction for biological activity with a specific sub-pocket of the binding site. In our research we have seen that the correct placement of this group in the active site is required to fully understand the binding of novel designed inhibitors and to assess their potential activity before being synthesized. Therefore, we decided to test the ability of the haptic software to place the trimethoxyphenyl group in the correct pocket.

Figure 1 shows the results of our simulation, where it can be seen that the aromatic ring placed by ZODIAC is virtually overlapping with the corresponding ring of the co-crystallized DAMA-colchicine. We then build a substituted indole ring (another group very often present in tubulin binding agents) [26] and we use the haptic driven placement of the heterocycle, leaving the trimethoxyphenyl ring in the binding site as previously calculated. The results are shown in Fig. 2, noting that the position of the indole ring is compatible with the docking results obtained and the arylthioindeoles inhibitors previously reported [24]. In a drug design project, at this stage of the simulation it would be possible to connect the two fragments directly, using the researcher's intuition and chemistry knowledge, possibly followed by another haptic driven placement to optimize the pose of the novel structure, or maybe using other automated algorithms such as the LINK algorithm of LigBuilder [27] or molecular docking simulations.

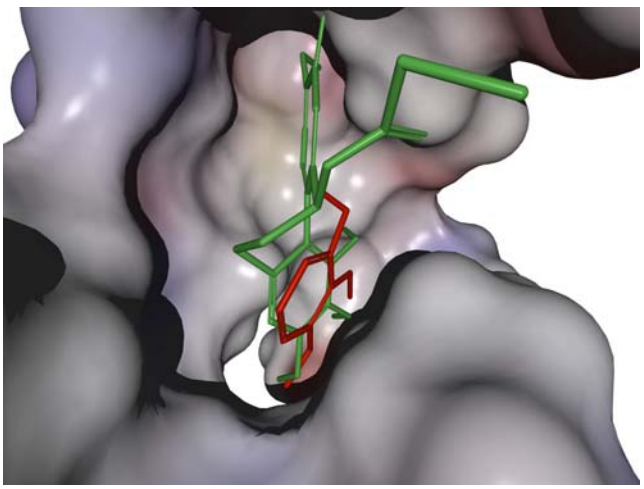

Fig. 1 Overlapping of DAMA-Colchicine (green) and the trimethoxyphenyl ring (red) placed with ZODIAC

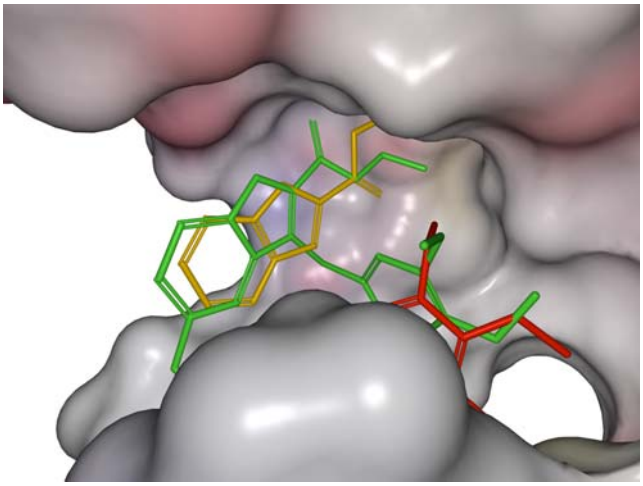

Fig. 2 Overlapping of an arylthioindole inhibitor (green) with the indole-2-methylcarboxylate (yellow)

Discussion

We believe that the haptic driven methodology would be extremely useful in the placement of small fragments/ligands in target binding sites, especially in large ones, leading to an extensive exploration of a binding pocket. It is fair to say that the usefulness of this technology in docking full size ligands in a target protein is questionable, considering the speed and accuracy of modern docking algorithms in handling structures with several degrees of freedom. However, we think that the haptic technology would be particularly useful in de novo drug design [28, 29]. This approach can be described as the process of producing novel molecular structures with desired pharmacological properties, using the structural information of the biological target. The software generally builds a structure by combining a set of fragments or single atoms, evaluating the interaction with the biological target and keeping the best scored structures. In de novo drug design, the quality of the final structures generated by the computer depends not only on the size of the fragment library used to build them, but also on the method of placement of these fragments in the desired pocket. A large fragment library would explore the chemical space efficiently, but it would very likely generate a high number of structures that are not synthetically feasible. Computer applications generally have difficulty in handling pattern recognition problems such as assessing the synthetic accessibility of compounds, applying chemical knowledge to ligand-target binding, and suggesting possible modifications to a lead structure. Human reasoning and intuition still outperform computers in many such applications. No matter how well de novo drug design software is itself designed, an average medicinal chemist would probably address this problem more efficiently than a computer. The chemist would select the fragments to be attached to the growing structure using the chemistry knowledge that a computer does not yet

possess. Ideally, to exploit human competence at its full it would be necessary to provide the user with an interface that could give the ability to interact in real-time with the computer, adding the user knowledge and intuition directly into the ongoing simulation. ZODIAC allows this level of interaction through the building of the desired fragment and the haptic driven placement into the target site.

Furthermore, thanks to the affordability and the usability of this system, ZODIAC could also be suitable in a teaching environment, where students could have a better understanding of the nature of the forces involved in protein/ligand interactions through haptic feedback.

Conclusions

Considering the level of user interaction, it is possible to imagine the potential impact that the haptic technology could have on drug design, not only on de novo approaches, but also on lead optimization and other aspects of computer-aided drug discovery. This methodology would allow the researcher to interactively use the information obtained from the real-time multi-sensory feedback in the design and optimization of novel potential drugs. More importantly, considering the affordability of the computer hardware, the haptic device used and the implementation of the haptic approach in a user friendly, freely available software package [30], this makes this technology easily accessible to the average medicinal chemist and usable for research or teaching purposes.

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