6D haptic feedback for molecular docking

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1. Introduction

Drugs are made of small molecules (ligands) which interact with proteins in order to inactivate them through a specific pocket (binding site or active site). Efficiency of a drug molecule is measured by its ability to find a specific position and orientation inside a protein. The computational process of searching for a ligand that is able to fit the binding site of a protein is called molecular docking. The docking configuration should satisfy some constraints based on geometry, electrostatic, and chemical reactions between the ligand and the protein's atoms. The conformation (atoms' positions) of the ligand in the binding site has the lower potential energy. Therefore the energy surface generated by the atoms' force field has to be explored. All of these simulations are fully automated and can take, in the worst case, up to one month [1]. The only information provided by the softwares used are a visual return of the conformation of the molecules and a value of the energy brought into play. Because of the relatively low success rates of the docking for fully automated algorithms, adding a human operator appears as a novel solution.

Interactive haptic feedback for molecular docking can give additional information on the behavior of the forces present inside the receptor. The operator would then be able to feel the repulsive or the attractive areas and define a better geometry of the ligand. It supposes a real time simulation.

2. Minimization and molecular docking

A molecule is made of a collection of atoms vibrating around their equilibrium position. Because simulations are long, classic mechanics is often preferred to Schrödinger theory to model atomic interactions. These are modeled as springs because one can consider that an atom will not move far away from its equilibrium position. Stiffness, initial conditions (positions), initial torsions and all the other constants (l, r, ω, θ, ε, A, B, k_θ, k_l , V_i …) are described in a force field which depends on the nature of the molecule. The one called MMFF94 [2],[3], is the most appropriate for small molecules. The dimension of each term is energy and the total energy of the molecule is equivalent to their sum. This force field (simplified) is described below.

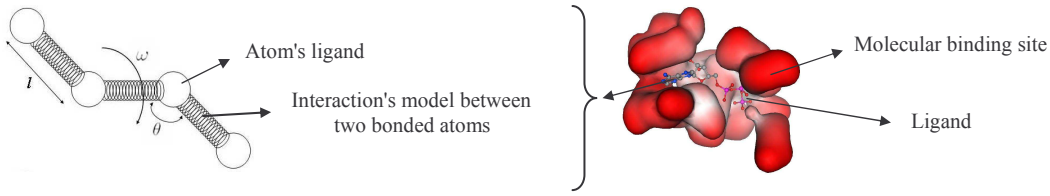

Fig.1: Description of atomic interactions in a molecular force field

Total potential energy: $E_{\text{Molecule}} = E_{\text{B}}(l) + E_{\text{V}}(\theta) + E_{\text{T}}(\omega) + E_{\text{VdW}}(r) + E_{\text{E}}(r)$ (1)

Where all terms are defined as:

Binding energy: $E_B(l) = \sum \frac{k_l}{2}(l - l_0)^2$ (2)

Valence energy: $E_V(\theta) = \sum \frac{k_\theta}{2}(\theta - \theta_0)^2$ (3)

Torsion energy: $E_T(\omega) = \sum \left(\frac{V_1}{2}(1 + \cos\omega) + \frac{V_2}{2}(1 - \cos 2\omega) + \frac{V_3}{2}(1 + \cos 3\omega) \right)$ (4)

Van der Waals energy: $E_{vdw}(r) = \sum \sum_{\text{non-bonded atoms}} \left(\frac{A}{r^{12}} - \frac{B}{r^6} \right)$ (5)

Electrostatic energy: $E_E(r) = \sum \sum_{\text{non-bonded atoms}} \left(\frac{q_1 q_2}{4\pi\varepsilon_0 \varepsilon r} \right)$ (6)

Van der Waals and electrostatic energies are calculated between non-bonded atoms with a distance *r*. These take the most computational time. The position of all the atoms in the system is controlled by this force field. When an atom has moved away from its equilibrium position, the unique way to find the real behavior of the molecule is to minimize the force field described above. As soon as an atom moves away from its equilibrium position, the energy of the molecule is modified. The minimization of the energy consists then in finding the position of all the atoms which generate a conformation of lowest energy. One has to take into account the energy between all the atoms in both the ligand and the molecule. Note that this force field is non-linear and has more than four terms to describe an interaction between two atoms. Consequently, to minimize a molecule's total energy is very expensive in computational time and some approximations are necessary for a real time minimization.

3. Haptic rendering

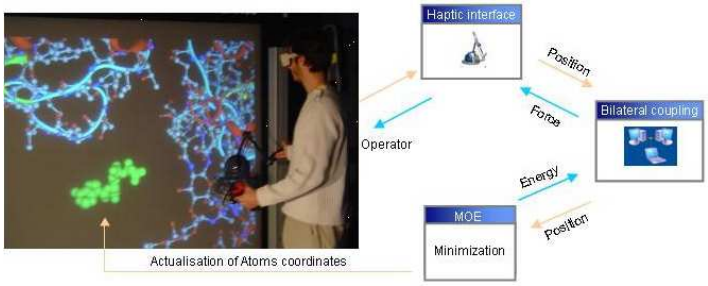

Fig.2: Principle of a molecular docking with haptic feedback

Our approach consists in using a preexistent simulator for the conformational computation of the ligand and the protein. We decided to use MOE: Molecular Operating Environment, a well known and widely used software for pharmacophore elucidations. In order to obtain new positions of the atoms of both the molecule and the ligand, a minimization of the force field described below is performed.

The first interesting problem is to convert the calculated energy into a force sent to the haptic interface. The admittance control (more stable and passive) implies that the haptic position is sent to the ligand which is moved consequently in the active site. The energy is then modified and MOE searches the ligand's conformation of the lower external energy for this new position. In response, MOE sends an energy converted, after derivation, into a force corresponding to the new position. This force can be felt by the interface.

In order to interpret the response, a metaphor, which can help us understand what kind of forces act on the ligand, has to be found. Also, the command has to consider the time delay necessary to complete the conformational search of the ligand by MOE. Considering that one process of minimization takes around 300 milliseconds, and depends on the size of the system and the height of the energy barrier, we can consider two cases of simulations: firstly, we use MOE with small molecules and we have to find a command which integrates computational time delay implying a study of the stability of the system. One possibility to overcome the stability problem is to train the operator, this one knowing that it possibly has a certain response time. Secondly, we can determine the best path to dock the ligand. The result of the minimization can then be prerecorded for this path in position and orientation. This simulation supposes having a grid model of the space, and at each point of this grid, prerecording the result of the minimization of the ligand around his equilibrium position. After this step, we can play again and have a real time feeling of the forces acting around the ligand. These simulations will be done on the MOE platform.

4. Conclusion and future work

Time simulation has to be considerably decreased to integrate human decisions in the conformational search process. A robotic representation of the molecule (as poly-articulated chains) can perhaps solve this problem. Haptic commands will integrate time delay and have to overcome the problem of micro forces feeling that have to be represented in our Macro world. Impedance and admittance control will be tested and compared.

5. References

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