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6 DOF haptic feedback for molecular docking using wave variables

Bruno Daunay, Alain Micaelli
Commissariat à l'Energie Atomique (CEA)
LIST / DTSI
92265 Fontenay Aux Roses, France
bruno.daunay@cea.fr,
alain.micaelli@cea.fr

Stéphane Régnier
Laboratoire de Robotique de Paris
CNRS - UPMC
BP 61, 92265 Fontenay Aux Roses, France
regnier@robot.jussieu.fr,

***Abstract*— This paper presents a new method for a six degrees of freedom haptic feedback in molecular docking simulations in virtual reality. The proposed method allows real-time haptic interaction even in the case of classical molecular simulation which implies notoriously long computation time. These simulations are classically used by the pharmaceutical industry (Sanofi-Aventis) and are based on the energetic description of atoms to estimate the interaction between a ligand and a protein. The haptic control scheme uses wave variables for a stable and robust teleoperation, and a transcription of the calculated energy into forces and torques for the manipulation of a flexible ligand around the binding site of a flexible molecule. This method can then be used with any energetic force field using a minimization process, thus avoiding the fastidious optimization of molecular simulation programs.**

I. 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). The computational process of searching for a ligand that is able to fit the binding site of a protein is called molecular docking. The conformation of the ligand in the binding site has the lower potential energy. The only informations provided by the used softwares during the simulation, are a visual return of the conformation of the molecules and the value of the involved energy. Because of the relatively low success rates of the docking for fully automated algorithms, including a human operator in the loop appears as a solution [1].

Interactive haptic feedback for molecular docking can give additional information on the behaviour of the forces present inside the receptor. The operator would then be able to feel the repulsive or the attractive areas and define the best geometry of the ligand. Note that this scenario can only function in the case of a real-time simulation.

The method we use for describing proteins is called empirical. All the molecular interactions are approximated by the Newtonian theory, therefore this method allows to simulate big proteins in an acceptable computational time. In order to simulate their behaviour, several methods are used and differ according to their applications.

The method we use is based on the minimization of the force field during the ligand manipulation. The goal is to reach the potential minimum but independently of time (to the contrary of the molecular dynamic simulation techniques).

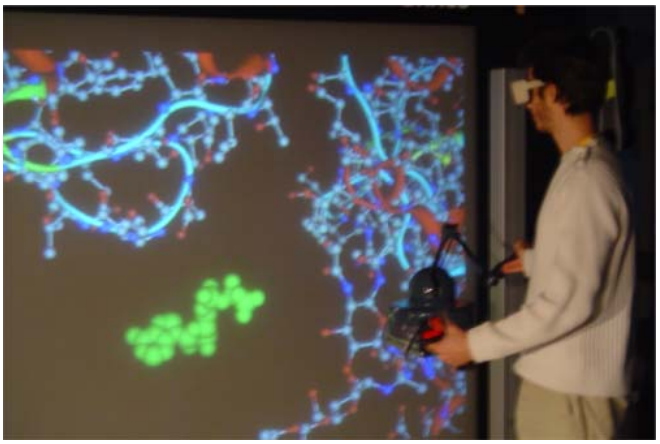


Fig. 1. Manipulation scene. The ligand (green molecule) has to be moved through the protein to the binding site. The protein will search for a stable conformation during the docking.

The aim of our work is not to optimize the molecular simulators (as proposed in some other works [2], [3]) but to conceive a method that takes into consideration their specificities. Indeed, the pharmaceutical engineers use softwares which are not real-time but which describe the interatomic interactions very precisely. Moreover, during their research, they use several force fields, each one being specific to a molecular property. Knowing that several force fields need to be minimized, that energetic interactions need to be described, and that the computing time for conformational changes is important, we developed a method allowing to feel the forces during a molecular docking using any molecular simulator based on a force field minimization process.

This article is structured as follows: the first paragraph describes the force field and the simulation we use in order to evaluate both the interaction energy between the ligand and the protein and the conformational change of these two molecules. The second paragraph describes a simple force/position bilateral coupling in order to specify the different problems to overcome. Then we propose a stable method for the control scheme of such a simulation and show how the forces can conveniently be felt in order to make the operator "feel" the binding site's force field.

II. Force field model and Simulation method

A. Force field

There are many different force field models that can be used to simulate proteins and other organic molecules as AMBER [4], [5], CHARMM [6], MM3 [7], MM4 [8] and MMFF94 [9]. If each force field is normally developed for a particular type of molecule, they rather well adapt to different structures in atomic types. The one we use and which is described below is called MMFF94. It is more suitable for small molecules, as ligands, but it is also applicable for big proteins. The interactions between the ligand and the binding site of the protein should then be well defined to a pharmaceutical point of view.

The model described above is typically expressed as summations of several potential energy components. A general equation of total energy, such as (1), includes terms for bond stretching (E_{Bond}), angle bending (E_{Angle}), torsion ($E_{Torsion}$), and non-bonded interactions such as electrostatic (E_{Elec}) and Van der Waals energies (E_{VdW}).

$$E_{Total} = E_{Bond} + E_{Angle} + E_{Torsion} + E_{Elec} + E_{VdW} \quad (1)$$

Bond stretching and angle bending energies allow a flexible geometry. The simplest approach, based on the fact that most bonds are near the minimum of their energy, employs a quadratic term to model bond stretching and angle bending energies, as in (2) and (3).

$$E_{Bond} = \sum k_{Bond}/2(l - l_0)^2 \quad (2)$$

$$E_{Angle} = \sum k_{Angle}/2(\theta - \theta_0)^2 \quad (3)$$

Where k_{Bond} and k_{Angle} (stiffness of the bond and the angle) are experimentally obtained. l, l_0 and θ, θ_0 are respectively actual and ideal bond lengths and actual and ideal bond angles. In fact, these energy terms are more complicated. For bond energies, cubic terms are introduced as angle energies [10].

The torsion energy expression is represented by a Fourier series expansion which, as shown in (4), includes three terms.

$$E_{Torsion} = 1/2 \sum [\, V_1 (1 + \cos\phi) + V_2 (1 - \cos 2\phi) + V_3 (1 + \cos 3\phi) \,] \quad (4)$$

Where V_1, V_2 and V_3 are torsional barriers specified for the pair of atoms around which the torsion occurs. ϕ is the torsion angle (the rotation angle around the bond between the second and third atom in any serially connected four atoms).

Vand der Waals interactions are described with the "Buffered 14-7" form [11]. The form of the potential is shown in (5). Van der Waals interactions are included whenever atoms i and j belong to separate domains or are separated by three or more chemical bonds. R_{ij} corresponds to the distance between atom i and atom j.

$$E_{VdW_{ij}} = \varepsilon_{ij} \left(\frac{1.07 R^*_{ij}}{R_{ij} + 0.07 R^*_{ij}} \right)^7 \left(\frac{1.12 R^{*\,7}_{ij}}{R^7_{ij} + 0.12 R^{*\,7}_{ij}} - 2 \right)^7 \quad (5)$$

This form is used with an expression that relates the minimum energy separation R^*_{ii} (which can be assimilated close to the Van der Waals radius of atom i) to the atomic polarizability α_i (6), with specially formulated combination rules (7, 8), and with the potential depth ε_{ij} describing the minimum energy for a given atomic pair i and j.

$$R^*_{ii} = A_i \alpha_i^{1/4} \quad (6)$$

Where A_i is an experimentally defined constant.

$$R^*_{ij} = 1/2(R^*_{ii} + R^*_{jj})(1 + 0.2(1 - \exp(-12\gamma^2_{ij}))) \quad (7)$$

$$\gamma_{ij} = (R^*_{ii} - R^*_{jj})/(R^*_{ii} + R^*_{jj}) \quad (8)$$

Van der Waals and electrostatic energies influences are limited to 8 ÅOne can consider that passed this distance, the long range energies influence is neglectable for the conformational changes of the molecule.

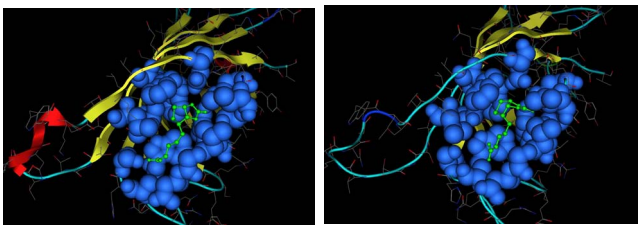
MMFF94 uses the buffered coulombic form as electrostatic interaction. As for Van der Waals energy, interactions are calculated when atoms i and j are separated by three or more chemical bonds.

$$E_{Elec_{ij}} = 332.0716 q_i q_j / \left(D(R_{ij} + \delta)^2 \right) \quad (9)$$

Where q_i and q_j are partial atomic charges of atoms i and j, R_{ij} is the internuclear separation. $\delta = 0.05$ Å is the electrostatic buffering constant and D the dielectric one.

B. Simulation

Energy minimization consists in finding a set of atomic coordinates that corresponds to a local minimum of the molecular energy function (it appears clearly that the simulation should take a long time to reach the global minimum). This is done by applying large scale non-linear optimization techniques to calculate a conformation (near the starting geometry) for which the forces on the atoms are zero (Fig. 2).



(a) (b)

Fig. 2. Minimization of biotin (ligand - green) in the streptavidin complex (binding site - blue). (a) Before minimization : E_{Total} = 2864.07 Kcal/mol, E_{Ligand} = 70.73 Kcal/mol. (b) After minimization : E_{Total} = 919.74 Kcal/mol, E_{Ligand} = 35.00 Kcal/mol.

The optimization algorithm has the following structure. Let x_k denote the vector of atomic coordinates at step k of the procedure and let E be the energy function. Then,

1. Test for convergence. If the convergence criteria are satisfied (see below), then x_k is returned.

2. Compute the search direction. Compute a non-zero vector p_k called the search direction. This is done with the

Steepest Descent method ($p_k = -gradE(x_k)$), continued by the Conjugate Gradient method after a few iterations and finished by a Truncated Newton method.

3. Compute the step size. Compute a non-zero scalar a_k, called the step size, for which $E(x_k + a_k p_k) < E(x_k)$.

4. Set $x_{k+1} = x_k$ and $k = k+1$ and go to step 1.

The step size in step 3 is computed by using a safeguarded bicubic interpolation search along the search direction. In step 1, the optimization is done when any of the following three conditions are satisfied:

1. Root mean square gradient test: $|gradE(x_k)| < A\sqrt{n}$, where A is a predefined constant and n is the number of unfixed atoms.

2. Iteration limit test: $k > K$, where K is a predefined upper limit on the maximum number of iterations.

3. Progress tests: The following three conditions are simultaneously satisfied:

$$E(x_{k-1}) - E(x_k) < C(1 + |E(x_k)|) \tag{10}$$

$$|x_{k-1} - x_k| < C^{1/2}(1 + |x_k|) \tag{11}$$

$$|gradE(x_k)| \leq C^{1/3}(1 + |E(x_k)|) \tag{12}$$

In these conditions, C is a predefined constant indicating the number of significant figures in E that are required (the function test).

Because the calculation takes a certain amount of time (typically less than 0.5 seconds for a system composed of 200 atoms), the forces feeling of this transformation could not be satisfying. In fact, one can consider that a comprehensive haptic feedback needs a force feedback at the rate of 1 KHz. Considering that a pharmaceutical engineer wants to use different force fields to obtain the best docking conformation, rather than optimize a force field, we decided to use the response delay in the control law using the wave variables.

III. Haptic's specification and Force/Position coupling

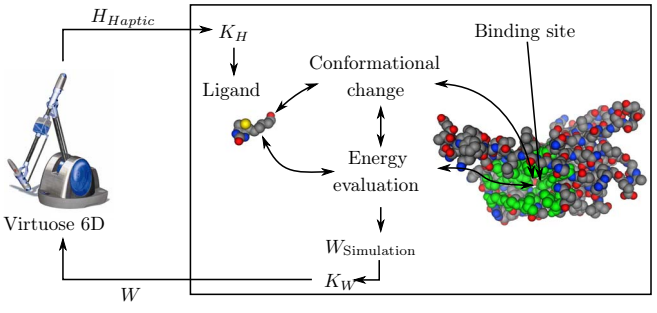


Fig. 3. Force/position coupling of a 6 DOF haptic device (*Virtuose from Haption Society*) with a docking simulation. The homogeneous matrix H_{Haptic} is sent to the simulation and a wrench W is sent back.

A force/position control law is described on Fig. 3. Positions and orientations of the haptic device are sent to the simulation. Each position of each ligand's atom is modified consequently as in (13) (the ligand is clamped to the manipulation system). Then, the energy between the ligand and the binding site of the protein is evaluated, converted into forces and torques and sent to the *Virtuose*. During the energy evaluation, the protein and the ligand atoms' positions are once again modified by the minimization process's result. The global evolution of the ligand atoms' position is then described by (13), while the binding site evolution is only modified by the minimization process (14). Only the binding site and the ligand are flexible (to limit computation time).

$$H_{\text{Ligand}} = \underbrace{\begin{bmatrix} I & K_D \\ 0 & 1 \end{bmatrix}}_{K_H} H_{\text{Haptic}} H_{\text{Force field}}^{\textit{Ligand atoms}} \tag{13}$$

$$H_{\text{Binding site}} = H_{\text{Force field}}^{\textit{Binding site atoms}} \tag{14}$$

Where H_{Ligand} and $H_{\text{Binding site}}$ represent the positions and orientations of the ligand and the binding site in the simulation, K_D is the displacement factor, H_{Haptic} is the position and orientation of the *Virtuose*, $H_{\text{Force field}}^{\textit{Ligand atoms}}$ and $H_{\text{Force field}}^{\textit{Binding site atoms}}$ are respectively the homogeneous matrix, representing the position variation induced by the force field, applied to the ligand and the binding site.

The wrench, reflecting the interatomic interactions between the ligand and the binding site, has to be sent to the *Virtuose* at the rate of one 1 KHz, to provide a good haptic feedback. Both the ligand and the protein are flexible, they change their conformation to a stable one while the ligand is moved.

A. Nano/Macro coefficients

The first problem to overcome is to convert a displacement in the simulation's nanoscale (Å) to a macro one in the operator's scale (haptic displacement) and then to feel in the macro world the micro forces acting on the ligand. Two coefficients were introduced. The first, K_D (displacement factor), responsible for the macro to nano scaling, is determined as

$$K_D = x_{\text{Ligand}}^{\textit{Nano displacement}} \;/\; x_{\text{Haptic}}^{\textit{Macro displacement}}, \tag{15}$$

where x_{Haptic} and x_{Ligand} are the position and the orientation of the haptic interface and the ligand, and the second, K_W (force factor) a micro to macro scaling factor. K_W is determined as in (16)

$$K_W = \frac{\text{Maximal force/torque admissible on Virtuose}}{\text{Maximal force/torque of the simulation}} \tag{16}$$

where the maximal force/torque admissible on *Virtuose* is 5 N and the maximal force/torque of the simulation is a user determined constant depending on the required precision.

B. Energy

As described in paragraph II, the force field describing the protein's behaviour uses the interaction energies. Consequently, a derivation of this interaction energy in the three space directions is made as a first approximation (highly approximative formulation of the forces starting from the energy, only allowing us, at first, to understand the profile

of the forces during a docking. The effort is corrected in the displacement direction):

$$W_k^{\text{Simulation}} = \frac{E_k - E_{k-1}}{x_k^{nano} - x_{k-1}^{nano}} \quad (17)$$

where k is the iteration number and x^{nano} the position and orientation of the interface in the nano world. A singularity will appear if the interface displacement between step k and $k+1$ is nil. Then, the force/torque sent to the interface is arbitrarily set to the previous one.

C. Results

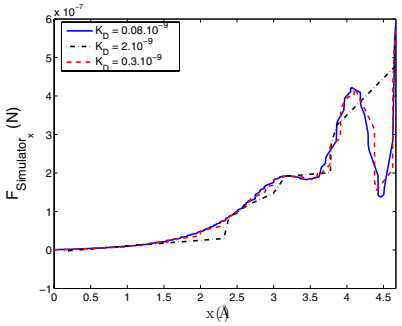


Fig. 4. Experimental results showing the influence of K_D on the forces' stability (on the x axis for the Van der Waals and electrostatic forces) during a docking of a biotin into a streptavidin complex.

Fig. 4 shows the forces (on the x axis) obtained during a ligand displacement ($\approx$ 5 Å on the x axis) in its binding site starting from its equilibrium position, with a displacement factor successively equal to 8.10^{-11}, 3.10^{-10} and 2.10^{-9}. A small displacement factor will lead to a force which can be easily interpreted because of its stability. The Van der Waals instabilities and the electrostatics forces can be then precisely depicted. But a high one will lead to forces with higher dynamic. In the first case, we can precisely feel the interaction forces but a docking is not possible (in the macro world, 1 meter corresponds to 0.08 Å). In the second case, the docking is possible (1 meter corresponds to 2 Å), but the simulation is unstable and the feeling unsatisfying.

The influence of K_W can be shown on Fig. 4. K_W makes the correspondence between the maximal force/torque admissible on the *Virtuose* and a desired maximal force/torque on the simulation ($K_{W\text{Max simulation}}$). If $K_{W\text{Max simulation}} = 1.10^7$, all the forces grater than $F = 5.10^{-7}$ N will be felt like a barrier. But all the forces smaller than this one will be felt according to this ratio. This coefficient has to be chosen according to the desired precision.

Fig. 5 shows the necessary computation time to evaluate the interaction energy. With many approximations (on the energy's influence and on the protein's behaviour), to evaluate the interaction energy between the biotin ligand and its complex could take from 7.10^{-3} s to 10.10^{-3} s. This leads to a real instability in the control law and implies that a good feeling of the forces is impossible.

The last paragraph presents some solutions to overcome the problem of time delayed manipulation which is not passive [13]. The aim is to obtain a stable control of the simulation, and to have a better feeling of the forces taking into account the high dynamic range shown above.

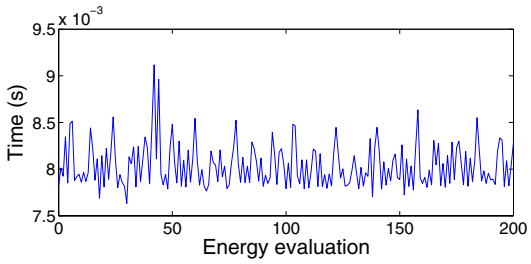


Fig. 5. Computation time for the energy evaluation between a ligand composed of 30 atoms (biotin) and a binding site composed of 250 atoms (streptavidin) during a docking.

IV. Passive control of a docking simulation

A. Wave transformation

Wave variables are a derivation of the well defined scattering parameters. Niemeyer [12] demonstrates that time delay is a passive element of a control chain if it is considered in the wave domain. If all components of the transmission are passive, as well as the haptic device and the simulation, then the entire process consisting in sending the information by the haptic device, its transformation in the wave domain, its interpretation by the simulator and its feedback, become stable and robust whatever the delay is.

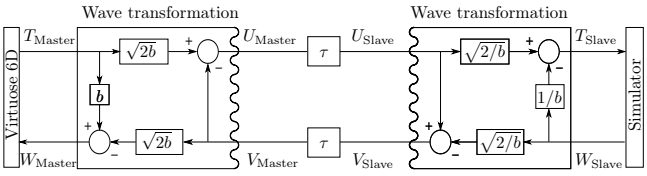


Fig. 6. Wave transformation (U and V) of informations (velocity and wrench) from master to slave in a time-delayed τ transmission. b is a stiffness factor.

In the wave domain, including a delay τ (and considering Fig.6), the equations governing the transmission are:

$$U_{Slave}(t) = U_{Master}(t-\tau) \quad (18)$$
$$V_{Master}(t) = V_{Slave}(t-\tau) \quad (19)$$

In order to interpret the informations provided by the wave variables, it is necessary to successively encode and decode the wave. This is done by two bijective expressions, (20) and (21) for encoding which implies (22) and (23) to decode.

$$U_{Master}(t) = \left(bT_{Master}(t) + W_{Master}(t)\right)/\sqrt{2b} \quad (20)$$
$$V_{Slave}(t) = \left(bT_{Slave}(t) - W_{Slave}(t)\right)/\sqrt{2b} \quad (21)$$
$$T_{Slave}(t) = \sqrt{2/b}U_{Slave}(t) - 1/bW_{Slave}(t) \quad (22)$$
$$W_{Master}(t) = bT_{Master}(t) - \sqrt{2b}V_{Master}(t) \quad (23)$$

Where the wave impedance b is an arbitrary constant which determines the stiffness of the transmission, T, F, U and V are respectively the velocity and force, the forward and backward waves.

B. Application

The proposed approach, described below, is based on that the time delay is not between the two wave transformations but occurs only after having decoded the wave. The forward wave U is sent at the rate of the haptic device, 1 kHz. The simulator sends a response at the rate of 400 Hz. V is refreshed as soon as the simulator can compute a force.

1) Damping and wave variables: The molecular simulator described on Fig. 3 needs a position at its entry port. This position is applied to the ligand via a displacement factor. But the wave variables are expressed from the master's velocity. Our first approach was to send the master's position to the simulation and use the wave variables as a back carrier information wave (Fig. 7).

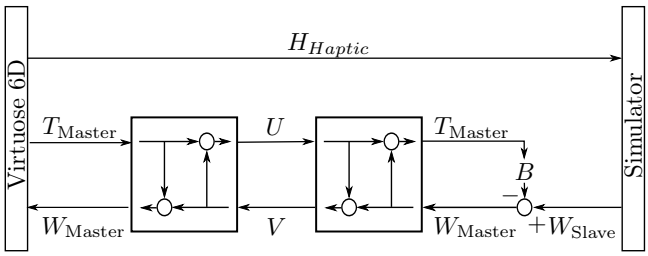


Fig. 7. Wave based control of molecular docking simulation. B is a user defined damping constant.

This wave is then considered as a damper (as it depends on the coefficient B, which is a user defined constant, and also on b) responsible for the dynamic attenuation of the forces send by the simulator (24).

$$W_{Master} = W_{Slave} - BT_{Master} \tag{24}$$

Considering an admittance local loop, the two waves U and V had to be expressed as in (25) and (26).

$$U = (bT_{Master} - W_{Master})/(\sqrt{2b}) \tag{25}$$

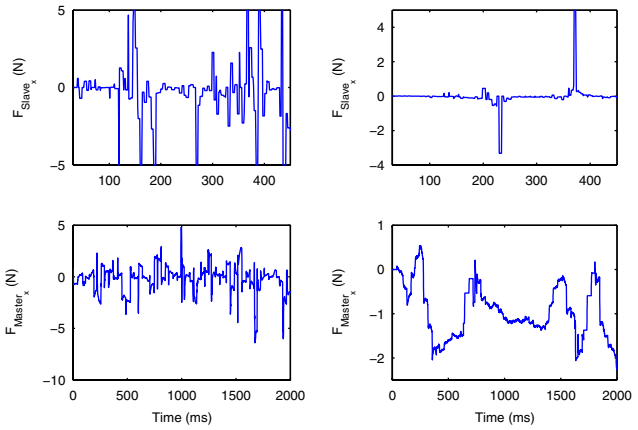
$$V = U + \sqrt{2/b}W_{Master} \tag{26}$$

These two expressions lead to the expression of the velocity (27) and the backward wave (28).

$$T_{Master} = \frac{1}{b+B}\left[\sqrt{2b}U + W_{Slave}\right] \tag{27}$$

$$V = \left(1 - \frac{2B}{b+B}\right)U + \left(\sqrt{\frac{2}{b}} - \sqrt{\frac{2}{b}}\frac{B}{b+B}\right)W_{Slave} \tag{28}$$

Two coefficients had to be chosen: the first one, b, determining the stiffness of the control loop and the waves' stability, and the second, B, responsible for the internal damping of the high forces' amplitude acting during the docking. There is an other meaning of the damping factor B. Indeed, the simulation is not passive as it would create energy. This coefficient could then dissipate it in order to make the control stable. An infinite value for B will dissipate all the energy ($V = -U$), the haptic device is blocked (all the incoming energy is sent back).



(a) $B = 0, K_D = 2.10^{-9}, K_W = 5.10^7$ (b) $B = 50, K_D = 2.10^{-9}, K_W = 5.10^7$

Fig. 8. Influence of coefficient B on the simulation's stability.

Fig. 8(a) shows the haptic device's response with $B = 0$. The energy is not dissipated and the only damping existing in the control is b (mainly responsible for the wave variables stabilisation). The docking is stable and possible but the intermolecular forces could not be conveniently interpreted. If $B = 50$ (Fig. 8(b)), the docking is possible and stable but all the forces are filtered because of the viscosity induced.

To compare with the force/position control which is clearly unstable, this method, consisting in using the waves as a damper filtering the high forces' dynamic, also as a time-delayed stabilisation method, could be a solution to the problem of molecular docking. By introducing viscosity and integrating time delayed simulator response in the control loop, the control becomes stable.

However, even if the control is stable, the macro feeling of the micro forces should be difficult to understand because of the damping factor B. A new approach, allowing to have a better transparency in the bilateral control, is described below.

2) Wave variables control loop: For this control scheme, a modification of the simulator is needed. The haptic device sends a velocity to the simulator after having encoded it to a wave and decoded it. However, the simulation needs position data to manipulate the ligand. Integrating a velocity into a position will create a drift, the haptic device has to be regularly repositioned while the simulation is continuing (Fig. 9).

The velocity integration is done as follows:

$$[T] = \dot{H}_{Haptic}H_{Haptic}^{-1} \tag{29}$$

where $[T]$ is the velocity skew symmetric matrix determined from T_{Slave}. The discretisation of (29) leads to (32)

$$H_{k+1} = t[T]H_k + H_k \tag{30}$$

$$= (I + t[T])H_k \tag{31}$$

$$= e^{(t[T])}H_k \tag{32}$$

where k is the iteration number and I the identity $[4 \times 4]$

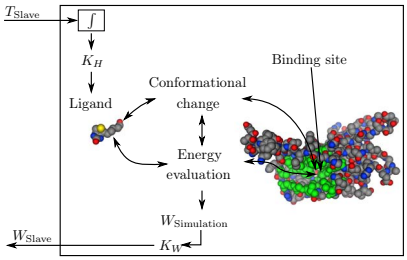


Fig. 9. Description of the molecular docking simulator. T_{Slave} and W_{Salve} are successively decoded from wave variables and encoded to wave variables (Fig. 6)

matrix. H_{k+1} modify the position and orientation of the ligand as in (13).

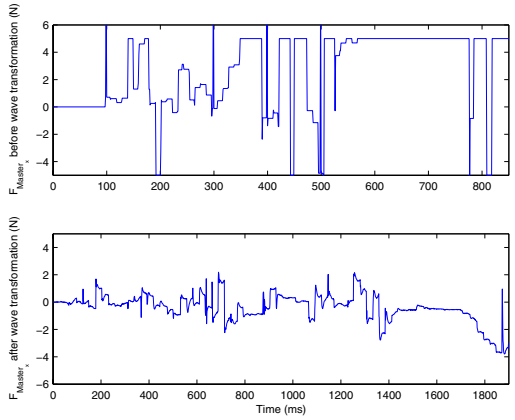


Fig. 10. Force feedback of the simulator, before wave transformation ($W_{Master} = K_W W_{Simulation}$), and after having decoded the wave. $K_W = 5.10^7$, $K_D = 1.10^{-9}$.

Fig. 10 shows the haptic device's response regarding the simulation forces. F_{Slave_x} is saturated at 5 N in order to protect the haptic device. As the forces become unstable, the waves act as a damper and the response is not as unstable as the excitation is. The control is inherently stable, the users only determine the wave's stability coefficient b. The main advantage of this method is that the forces sent back by the simulator are not as filtered as the previous method, making possible a good feeling of the micro forces.

V. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

In this paper, a molecular docking simulation, with six degrees of freedom haptic feedback, is presented. Starting from initial observations - simulation based on the energy, long computation time for haptic manipulations, high forces' amplitudes - we have implemented two new methods for stable manipulations. They are both based on wave variables because it guarantees the stability in time delayed manipulation. The first one allows to overcome the problem of the high forces' dynamic dissipating the energy in a virtual damper, but the feeling of the forces is not quite satisfying. The second one, based on the real wave variables allows to obtain a stable simulation, making possible the interpretation of the micro forces by the operator.

B. Future Works

The high forces' amplitude problem, due to large displacement factors, deserves a particular attention. As a first approach, we only derivated the energy provided by the simulator but some singularities appeared. A solution could be to consider a quadratic potential $E = 1/2kp^2 - g\mathrm{tr}(R)$ - where E is the potential, k and g are two positive constants and p and R are respectively the position and the orientation of the ligand. To find the forces and the torques means searching for the constants k and g in order to approach the real potential energy by the new quadratic one. The results have to be more stable than a simple derivation. The macro feeling of micro forces is not conveniently solved. A simple force factor K_W is not the best approach, because of the high dynamic range of these forces. A variable force factor could be an interesting solution. Far from the binding site, a small force factor could be applied in order not to feel the high forces' amplitude. In the binding site, near the equilibrium position, a small force factor could be set therefore refining the ligand's position. The goal of this method is to provide a fully integrative and semi-autonomous program usable for *Sanofi-Aventis*, in order to accelerate the design of new drugs and make it more reliable.

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