Stable six degrees of freedom haptic feedback for flexible ligand–protein docking

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ARTICLE INFO

ABSTRACT

This paper presents a new method for haptic feedback in molecular docking simulations as applied to the design of new drugs. These simulations, typically used by the pharmaceutical industry, for example Sanofi-Aventis, are based on the description of atomic energies to estimate the interactions between a ligand and a protein. The main drawback is that forces and torques cannot be calculated using a simple derivation. Moreover, when considering flexible ligand–protein docking, it is essential to take into account the delay in the molecular simulator's response, as it may lead to an unstable bilateral control scheme. The proposed method allows for stable haptic feedback using wave variables. For the operator to feel the molecular interactions, this method builds a local energy model based on the interatomic interactions and on the haptic device's displacement. The interaction wrench can be obtained using an analytic derivation of the energy model. Consequently, the teleoperation system is software independent, and can be extended to any bio-application, provided that it is energy based. Additionally, it ensures stable six degrees of freedom manipulation, therefore allowing comprehensive and stable haptic feedback.

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1. Introduction

Computational docking studies have become compulsory for the study of molecular structures and interactions in the field of drug design. The software used only returns visual information about the energy involved, and the attractive or repulsive areas. This visualization can be used to design an empirical three-dimensional structure of a ligand with an optimum binding site fit. However, it is not satisfying because of the need for detailed knowledge of attractive or repulsive areas, and the long computational time required to estimate the best candidates. Given the relatively poor success of automatic docking algorithms, including a human operator in the loop would appear to be a solution. This operator can act directly on the molecular dynamic process by moving the ligand through a desired position or act on-line on the optimization parameters. Adding haptic feedback to increase the docking interactivity [1] and understanding of the binding site will speed up such simulations [2] or provide a better knowledge of the binding forces [3]. In this case, the operator is able to feel the repulsive or the attractive areas, and define the best ligand geometry. The design becomes interactive and each modification of the geometry can be tested on-line to verify the accuracy of the design. One major drawback of molecular simulations is the long computational time needed to calculate the

protein conformations. This is mainly due to the high number of degrees of freedom, and may lead to haptic instability. Energy-based methods used by pharmaceutical engineers are preferable for determining a reliable solution for the conformation of both the ligand and the protein. In order to simulate their behavior, minimization of the energy during the ligand teleoperation is performed, making the conformation of both the ligand and the protein evolve. The goal is to determine the potential minimum at each step of the ligand teleoperation to ensure a stable conformation, close to nature. Moreover, during their research, pharmaceutical engineers use several force fields, each being specific to a molecular property.

Given that several force fields (depending on the proteins' properties) need to be minimized, that energetic interactions need to be described, that drug design has to be built on-line (the operator can add atoms and directly feel the modification of the ligand's affinity), and that the computing time for conformational changes is high, we have developed a method making it possible to feel the forces during molecular docking using any molecular simulator based on a force field minimization process.

The aim of our work is not to optimize the molecular simulators but to design a teleoperation platform composed of a haptic device, its controller and a particular control scheme that takes into consideration the simulator's specific characteristics. Our approach, specifically focused on molecular design tasks, makes the control scheme independent of the force field and software used, and of the simulation computation time. It ensures stable force feedback for general applications with an energy-based description. This strong property makes the teleoperation platform

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useful for other applications, such as feeling the interaction forces of a molecule through a transmembrane channel.

The control scheme is passive, to ensure that the haptic device is stable with regard to delayed responses. To be software and force field independent, the correspondence between interaction energies and the interaction forces is based on a predetermined local energy model, the analytical derivation of which provides the interaction forces. The application of this model can be extended to any biology-based software provided that the interactions between the components are described using energy. The teleoperation platform is then reusable for any energy-based application without the need to modify the relevant software.

This article is structured as follows. Our work based on the available literature is briefly outlined in the second section. The third section describes a simple force/position bilateral coupling to list the various problems to be overcome. We then propose a stable method for the control scheme for such a simulation, and show how the forces can conveniently be felt. In the last section, the energy involved is converted into forces and torques using an adaptive method providing analytical solutions for the wrench to be felt. The results discussed are taken from an experimental validation.

2. Review of the literature on the purpose of molecular docking

Over the past decade, a lot of research has been undertaken in the field of molecular docking using a haptic device. Mostly, it only considers optimization of molecular simulators, using, for example, robotics optimization methods [4,5] or a path-planning approach [6], and does not optimize the communication (or control scheme) between the simulation task and the haptic device (including the macro-feeling of the micro-forces). Moreover, it usually only considers force feedback regarding the translations (three degrees of freedom) and not the rotations (three more degrees of freedom). Furthermore, researchers design haptic feedback for their own software, and so their systems are not software independent.

The literature proposes many methods allowing force feedback for molecule steering or molecular docking. Stone [7] studied the haptic feedback of an ion through a gramicidin channel. He used molecular dynamic simulations to perform the calculation of the forces to be felt. The relation between the micro-forces and the human environment is only due to displacement and force factors. When considering ligand–protein docking, as the computational time increased too much, some approximations were made to ensure real-time computation needed for interactivity. [8] only considered a low number of atoms to be simulated and only considered the electrostatic forces. They developed a system to explore the surface of a protein molecule to search for sites where the manipulated probe is attracted. The docking is then only considered between a globular probe and the binding site of a protein. Rigid docking, only implying force calculation and not conformational change calculation, is often the case [9,10]. It leads to a decrease in the computational time to ensure the haptic device's stability. The forces can be precalculated using three-dimensional grids to speed up the simulations, as in [11,12]. Finally, haptic feedback of only three degrees of freedom is mostly used as in [13,14]. All these publications report that the forces vary suddenly, have high amplitudes, and that the force coefficient responsible for the macro-feeling of the micro-forces is difficult to calculate. A low force coefficient will result in amplifying only some strong interaction forces. On the other hand, a high force coefficient will result in a larger range of forces being felt, and may lead to feeling undesired force variations. During the docking manipulation, if many ligand atoms are in contact with the receptor, the force calculated will be infinite. The force factor

level then directly influences the force feeling and also the task's stability.

From this research that only considers rigid molecular docking based on three degrees of freedom haptic feedback, some conclusions can be highlighted. The first is the usefulness of including haptic feedback in molecular docking processes, thereby allowing the molecular energy to be explored and the binding site to be found [15,10]. Adding visual information to haptic feedback allows experienced biochemists to find the right ligand for which the shape fits a determined binding site [16], allows some students to understand the binding process in terms of the forces involved [3], and allows ordinary users to find the true binding pocket and then to align the ligand inside the binding cavity [10]. The second conclusion concerns the spatial limitation of the ligand's manipulation around the receptor, because of the precalculated grid forces. The force profile shows sudden variations between attractive and repulsive forces leading to the haptic device's instability. The last conclusion concerns the force factor, which has to be precisely calculated insofar as the ligand–protein contacts are concerned.

There is little research that considers haptic-based molecular docking with six degrees of freedom. Lai-Yen [17,18] studied flexible ligand docking in a rigid receptor. The torques are only calculated at the ligand–receptor contact. In order to accelerate the simulation, all the forces and the torques were determined using a three-dimensional grid and were only based on an analytical derivation of the van der Waals interaction energy.

This approach does not lead to realistic docking. First, the torques are only determined at the ligand–receptor collision, thus avoiding the torque feeling around the binding site, or when the ligand and the receptor are not in contact. Second, as the approximation does not take into account electrostatic energy, it is questionable because of its influence on the protein's conformational change.

Until now, molecular docking simulations using a haptic interface have been simplified; on the one hand, there are molecular simulations for which the equations and energy influence are simplified, and on the other hand, the simplification is with regard to the bilateral control scheme. Most of the research is based on haptic feedback with three degrees of freedom including a basic control scheme. Thus, some specific studies, such as the manipulation of a protein inside a transmembrane channel, that require torques to study the channel deformations, cannot be performed. Moreover, the forces are obtained by means of a simple derivation of a specific force field, resulting in the teleoperation system being highly dependent on the simulation methods.

Taking pharmaceutical engineers' needs as the starting point, we developed a method enabling the forces and the torques to be felt during six degrees of freedom molecular docking, using any molecular simulator based on a force field minimization process and without the need for particular molecular simulation knowledge. The minimized interaction energy between the ligand and the protein is approximated locally with an energy equation containing the terms to be evaluated. The haptic device then interacts with the new model, itself updated as soon as a new energy is calculated, allowing the haptic interaction to be in real time, even if the molecular simulation is not. The main contribution of the paper is the independence of the haptic system (the control scheme and the conversion of the energy into tridimensional forces and torques) from the molecular simulators, even if they are not in real time.

3. Haptic specification and force/position coupling

The aim of this article is to provide six degrees of freedom haptic feedback for a flexible ligand–protein docking (they can
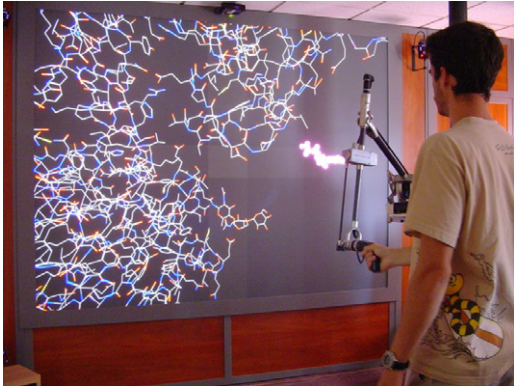
Fig. 1. Manipulation scene. The ligand has to be moved through the protein to the binding site. The protein will search for a stable conformation during docking.

both change their conformation during the manipulation). The molecular behavior is simulated using a force field chosen from the existing force fields that are well suited for the properties to be simulated. This is done using software called *Molecular Operating Environment* (http://www.chemcomp.com/), designed for pharmaceutical engineers. The flexibility of both the ligand and the protein is obtained by minimizing the force field during teleoperation of the ligand inside the binding site. The six degrees of freedom haptic device used is called *Virtuose*, from Haption company (http://www.haption.com).

A force/position control scheme is described in Fig. 2. It is a graphical representation of Fig. 1. The haptic device's positions and orientations are sent to the simulation. The position of each atom in the ligand is modified accordingly, as in Eq. (1) (the ligand is virtually coupled to the manipulation system and manipulated through the rotation ($\mathbf{K}_R$) and the displacement ($\mathbf{K}_D$) factors). The teleoperation factors are linear to avoid a non-linearity addition (specific non-linear scaling factors would be more appropriate in order to resolve the damping problem encountered in the haptic feedback and may be included in future work). The displacement of the ligand is a composition of the haptic device's displacement and the minimization result. The energy between the ligand and the binding site is evaluated, converted into forces and torques and sent to the *Virtuose* device. While evaluating the energy, the positions of the atoms of both the protein and the ligand are once again modified by the result of the minimization process. The global evolution of the position of the ligand atoms is then described by Eq. (1), while the binding site's evolution (and also the rest of the protein's evolution) is modified by the minimization process Eq. (2).

$$\mathbf{H}_L = \begin{bmatrix} \mathbf{R}_L & \mathbf{X}_L \\ \mathbf{0} & 1 \end{bmatrix} \tag{1}$$

where $\begin{cases} \mathbf{X}_L = \mathbf{K}_D\,\mathbf{X}_H\,\mathbf{X}_E^L \\ \mathbf{R}_L = \mathbf{K}_R\,\mathbf{R}_H\,\mathbf{R}_E^L \end{cases}$

$$\mathbf{H}_{BS} = \mathbf{H}_E^{BS} \tag{2}$$

where $\mathbf{H}_L$ and $\mathbf{H}_{BS}$ represent the positions and orientations of the ligand and the binding site (here *binding site* refers to what is defined as flexible: it can be only the binding site or the whole protein in this article) in the simulation, $\mathbf{K}_D$ is the displacement factor, $\mathbf{K}_R$ is the rotation factor (set to the identity matrix), $\mathbf{X}_H$ and $\mathbf{R}_H$ are the position and orientation of the *Virtuose* device, and $\{\mathbf{X}, \mathbf{R}\}_E^L$ and $\mathbf{H}_E^{BS}$ are respectively the position and the rotation, representing the conformational modification induced by the energy, 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* device

at the rate of 1 kHz to provide good haptic feedback [19]. Both the ligand and the protein are flexible; they change into stable conformations when the ligand is moved.

3.1. Nano/macro coefficients

The first problem to overcome is the conversion of the displacement in the simulation's nanoscale (Å) to the operator's macroscale (haptic displacement) and then to feel in the macro world the micro-forces acting on the ligand. Two coefficients were introduced [20]. The first, $\mathbf{K}_D$ (three components), responsible for the macro to nano scaling, is determined as (in Eqs. (3)–(5), we exemplify by showing only the *x*-direction):

$$K_D(x) = x_L / x_H \tag{3}$$

where x_H and x_L are respectively the position of the haptic interface (macro displacement) and the ligand (nano displacement). The second coefficient is $\mathbf{K}_W$ (six components), a micro to macro scaling force factor. $\mathbf{K}_W$ is determined as in Eq. (4):

$$K_W = \frac{W_H^{\max}}{W_S^{\max}} \tag{4}$$

where the maximum force/torque admissible on the *Virtuose* device ($W_H^{\max}$) is 5 N and the maximum force/torque of the simulation ($W_S^{\max}$) is predetermined using a molecular dynamic simulation between the ligand and the protein for the stable configuration. Note that the other components of $\mathbf{K}_W$ are obtained using the same equation. The simulation's maximum force/torque can be increased, but will be less precise, or, on the contrary, decreased by the user.

The force field describing the protein's behavior uses the inter-action energies (E). Consequently, a derivation of this interaction energy in the three space directions is made (as a first approximation) to obtain the interaction wrench ($\mathbf{W}$ for which the dimension is [6×1]) sent back to the user:

$$W_k^{\text{Simulation}} = \frac{E_k - E_{k-1}}{x_k^{\text{nano}} - x_{k-1}^{\text{nano}}} \tag{5}$$

where k is the iteration number and x^{nano} is the position (and also the 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 set to the previous calculated force/torque.

4. Passive control of a docking simulation

4.1. Wave transformation

Wave variables are a derivation of well-defined scattering parameters. Niemeyer [21] 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 of sending the information by the haptic device, its transformation in the wave domain, its interpretation by the simulator and its feedback, becomes stable and robust whatever the delay. This is only for constant time delays. To ensure there are no variations in the delay, a stack containing the data sent by the simulation provides the data to the wave variables at a given rate.

During the communication, there is no loss of data. The data provided by the master is identical when it arrives at the slave. So, in the wave domain, including a delay τ (and considering Fig. 3), the equations governing the transmission are

$$\mathbf{U}_{\text{Slave}}(t) = \mathbf{U}_{\text{Master}}(t - \tau)$$
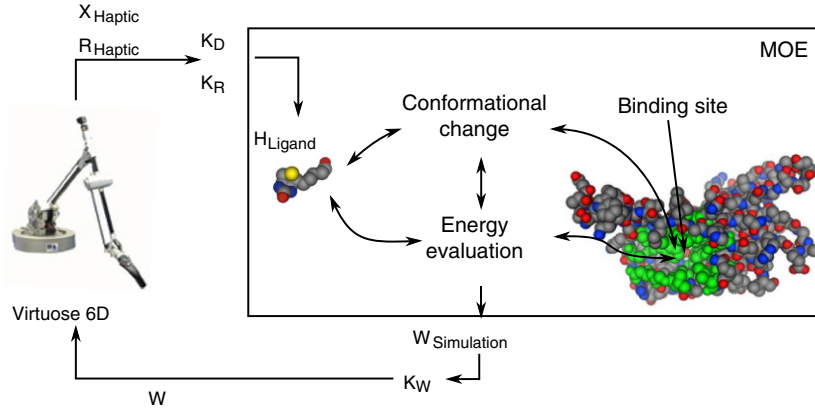$$\mathbf{V}_{\text{Master}}(t) = \mathbf{V}_{\text{Slave}}(t - \tau).$$

Fig. 2. Force/position coupling of a six degrees of freedom haptic device (called *Virtuose*, from Haption, http://www.haption.com, *Virtuose-6D35-45*) with a docking simulation. The homogeneous matrix H_{Haptic} is sent to the simulation and a wrench W is sent back.
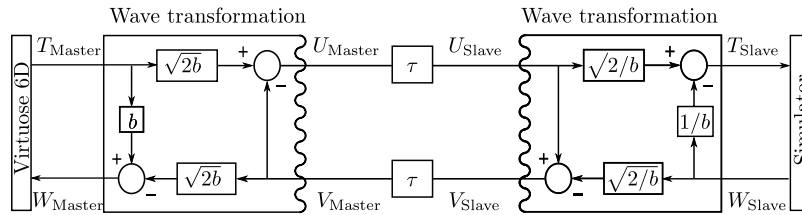

Fig. 3. Wave transformation **U** (transmitted wave) and **V** (reflected wave) of information (velocity **T** and wrench **W**) from master to slave in a time-delayed τ transmission. b is a stiffness factor.

In order to interpret the data provided by the wave variables, it is necessary to successively encode and decode the wave using two bijective expressions, Eqs. (6) and (7), for encoding, which implies Eqs. (8) and (9) are to be decoded.

$$\mathbf{U}_{\text{Master}}(t) = (b\mathbf{T}_{\text{Master}}(t) + \mathbf{W}_{\text{Master}}(t)) / \sqrt{2b} \tag{6}$$

$$\mathbf{V}_{\text{Slave}}(t) = (b\mathbf{T}_{\text{Slave}}(t) - \mathbf{W}_{\text{Slave}}(t)) / \sqrt{2b} \tag{7}$$

$$\mathbf{T}_{\text{Slave}}(t) = \sqrt{2/b}\mathbf{U}_{\text{Slave}}(t) - 1/b\mathbf{W}_{\text{Slave}}(t) \tag{8}$$

$$\mathbf{W}_{\text{Master}}(t) = b\mathbf{T}_{\text{Master}}(t) - \sqrt{2b}\mathbf{V}_{\text{Master}}(t) \tag{9}$$

where the wave impedance b is an *arbitrary constant* that determines the *stiffness* of the transmission; **T**, **W**, **U** and **V** are respectively the velocity, the wrench and the forward and backward waves. Their dimension is $[6 \times 1]$.

4.2. Application to a docking simulation

The proposed approach described below is based on the time delay not being between the two wave transformations but occurring 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. While the simulation is running, the last calculated force is repeated through the device at 1 kHz and updated as soon as the simulation updates the force. Thereafter the force update depends on the simulation rate. This leads to an asynchronous manipulation. The visualization of the ligand and the molecule's position and orientation are updated as soon as the molecular simulator receives a value; that is to say, at the rate of 1 KHz. The forces and the torques are updated and sent back after the wrench calculation, while the minimization process changes the protein's conformation (Fig. 4).

The haptic device's velocity is encoded into a wave, sent to the simulation and then decoded. 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 continues (Fig. 4).

The velocity integration is as follows:

$$[\mathbf{T}] = \dot{\mathbf{H}}_{\text{Haptic}}\mathbf{H}_{\text{Haptic}}^{-1} \tag{10}$$

where $[\mathbf{T}]$ is the velocity skew symmetrical matrix determined from $\mathbf{T}_{\text{Slave}}$. The discretization of Eq. (10) leads to Eq. (11):

$$\begin{aligned}
\mathbf{H}_{k+1} &= t[\mathbf{T}]\mathbf{H}_k + \mathbf{H}_k \\
&= (\mathbf{I} + t[\mathbf{T}])\mathbf{H}_k \\
&= e^{(t[\mathbf{T}])}\mathbf{H}_k
\end{aligned} \tag{11}$$

where k is the iteration number and **I** the identity $[4 \times 4]$ matrix. $\mathbf{H}_{k+1}$ modifies the position and orientation of the ligand as in Eq. (1).

Fig. 5 shows the haptic device's response to the simulation forces. F_{Slave_x} is saturated at 5 N in order to protect the haptic device. As the forces start suddenly to vary with a large amplitude, the waves act as a damper and the response does not have the same variations. The control is inherently stable; the users only determine the wave's stability coefficient b. To set b, the ligand (set as rigid) is put into contact with the protein (set as rigid). The coefficient b is chosen until the forces sent back reflect an infinite stiffness such as the haptic rendering of an object's contact on a wall (stiff contact). Then, the maximum value of b is known and both the ligand and the protein are set as flexible for the manipulation. Then, if a lower coefficient is chosen, the contact will be felt as a soft contact. That is to say, the high repulsive forces will be felt as low repulsive forces leading to the haptic device's stability (in the sense that it is not oscillating between repulsive areas) but not to feeling the real force profile. The main advantage of this method is that the forces sent back by the simulator are not as filtered as in a virtual damping system [22], thereby enabling the micro-forces to be easily felt.

Compared with force/position control, which is unstable (Fig. 6), this method in which waves are used as a filter for the high force dynamic (due to a loss of transparency and viscosity), and
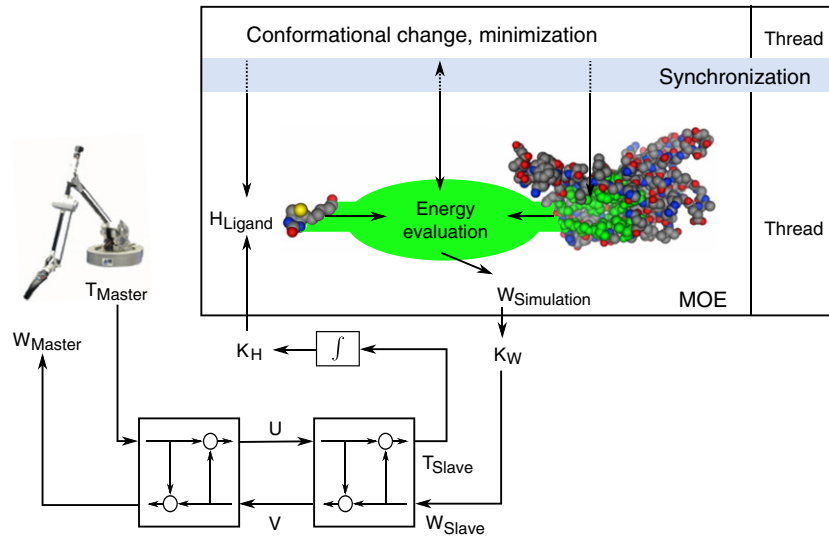
Fig. 4. Description of the molecular docking simulator. $\mathbf{T}_{\text{Slave}}$ and $\mathbf{W}_{\text{Slave}}$ are successively decoded from wave variables and encoded to wave variables (Fig. 3).
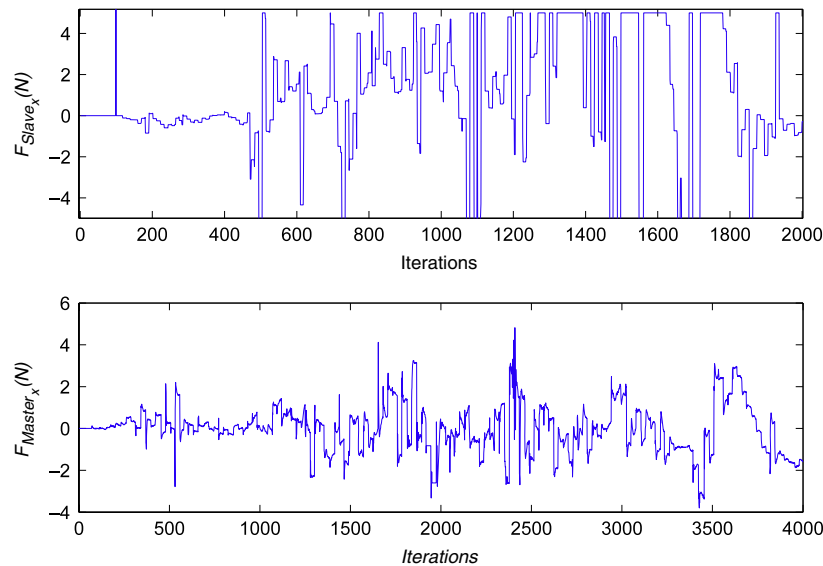
Fig. 5. Force feedback of the simulator, before wave transformation ($\mathbf{W}_{\text{Master}} = \mathbf{K}_W \mathbf{W}_{\text{Simulation}}$), and after having decoded the wave (on the x axis). $K_W = 5 \times 10^7$, $K_D = 1 \times 10^{-9}$. The time scaling is different between the first and the second graphic due to different update frequencies.

as a time-delayed stabilization method, could be a solution to the problem of molecular docking. By introducing viscosity through coefficient b and integrating a 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 will be difficult to understand because of the loss of transparency. A suitable adjustment of coefficient b will result in playing on the communication transparency. A high coefficient will lead to feeling the contacts with a high stiffness, making the profile of the forces difficult to understand, while a low coefficient will lead to feeling the ligand protein forces as soft contacts. This property makes control useful for applications where the force amplitudes are high and the time-delayed response is considerable.

5. From an energy description of a force field to force feeling

5.1. Introduction

As described in Section 3.1, the forces and torques calculated from the interaction energy are a spatial derivation from the haptic
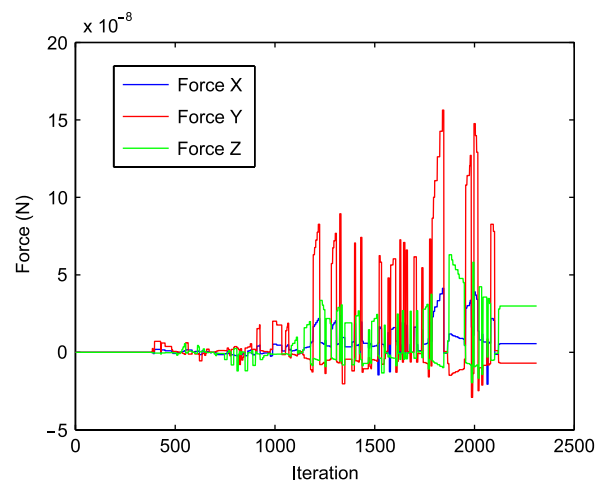

Fig. 6. Force profile around the minimized ligand position along the x, y and z axes using the simple derivation method.

device's position. Deriving the energy relative to the variation of the position or the angle variation of the haptic device is not a good way of obtaining the interaction wrench. The results are not the exact wrench of the interaction efforts because of numerical divergences. The force profile obtained using this method is shown in Fig. 6. This force profile cannot be clearly interpreted by the user. In other words, the user cannot determine the affinity difference of two ligands for the same binding site. The need for a smooth and correct force profile means a different method must be adopted. Given that energies depending on specific directions cannot be calculated from classical molecular simulators, we decided to calculate an energy field in which each term provides an analytical solution for the relevant forces and torques. First, an energy model is predetermined. Its parameters have to be estimated to ensure convergence between the model and the molecule energy field. Second, the wrench interaction is determined using a derivation of this analytical model. These two points are discussed below.

5.2. Energy modelization of the interaction

To build an energy model depending on the parameters to be identified, from which the derivation has no singularity, appears to be a solution for easily converting the energy provided by the minimization process into a wrench. The predetermined energy model is compared to the interaction energy to ensure its convergence. At the equilibrium position, the energy field has no wide variations for a specific protein conformation, ensuring good convergence for the model. Energy barriers are filtered out due to the latency of the model's convergence. If they do occur, they are no longer felt by the user.

The principle of our method is to approach the energy calculated by the minimization process ($E^{measure}$) using a potential ($\widehat{E}(\mathbf{p}, \mathbf{R}, \theta)$) containing terms, each of which depending on the parameters to be estimated, here represented by θ. The potential gradient at each ligand position $\mathbf{p}$ and orientation $\mathbf{R}$ is equal to the interaction forces and torques ($\mathbf{W}(\mathbf{p}, \mathbf{R})$):

$$\forall (\mathbf{p}, \mathbf{R}) \nabla_{(\mathbf{p}, \mathbf{R})} \widehat{E}(\mathbf{p}, \mathbf{R}, \theta) = \mathbf{W}(\mathbf{p}, \mathbf{R}).$$

This new potential has to be compared to the interaction energy using a root mean square method to determine its parameters at each ligand position and orientation.

As shown in Fig. 7, the interaction energy field looks like a polynomial function (quadratic function). The shape of the function to be estimated must approximate the polynomial function in order to ensure the algorithm's convergence. Let us consider the function described in Eq. (12) as a potential to be evaluated. Let i be the current object frame and e the equilibrium frame. Then

$$\widehat{E}_i(\mathbf{p}, \mathbf{R}, k_t, \mathbf{p}_e, g_0, \mathbf{R}_e) = \frac{1}{2} k_t \|^i\mathbf{p} - {}^i\mathbf{p}_e\|^2 - g_0 tr({}^i\mathbf{R}^T\mathbf{R}_e) + c \quad (12)$$

where $\mathbf{p}$ is the position of the ligand's center of mass (haptic device position), $\mathbf{R}$ the haptic device rotation, and k_t and g_0 are arbitrarily set as spring constants, which should be chosen as a diagonal matrix in order to provide different gains according to the displacement direction (translations (Fig. 7b) and rotations (Fig. 7a) have different values, according to the displacement axes). $\mathbf{p}_e$ and $\mathbf{R}_e$ are the equilibrium position and orientation of the estimated potential, and c is a positive constant to be estimated (it is set to zero initially). The function has two terms (considering a null constant); their derivation is used to find the forces and the torques, respectively. The estimated potential parameters are found by solving the problem described below:

$$\min_{\theta} \sum \|E^{measure} - \widehat{E}(\mathbf{p}, \mathbf{R}, \theta)\|^2 = \varepsilon^2 \to 0 \quad (13)$$

where θ represents the parameter set $(k_t, \mathbf{p}_e, g_0, \mathbf{R}_e)$, $E^{measure}$ the interaction energy provided by the minimization process, $\widehat{E}(\mathbf{p}, \mathbf{R}, \theta)$ the estimated energy calculated from Eq. (12) and ε the quadratic error between the estimation and the measure. Considering that $\widehat{E}(\mathbf{p}, \mathbf{R}, \theta)$ does not depend linearly on its parameters, Eq. (13) has to be linearized:

$$E_{i+1}^{measure}(\mathbf{p}, \mathbf{R}) = \widehat{E}_{i+1}(\mathbf{p}, \mathbf{R}, \theta) + \frac{\partial E_{i+1}(\mathbf{p}, \mathbf{R}, \theta)}{\partial \theta} \delta\theta \quad (14)$$

where i represents the step number. The measured potential can then be expanded in order to evaluate the estimated gradient of the potential with regard to its parameter set θ.

$$E_{i+1} = \widehat{E}_{i+1} + \frac{1}{2} \|^{i+1}\mathbf{p} - {}^{i+1}\mathbf{p}_e\|^2 \delta k_t - k_t ({}^{i+1}\mathbf{p} - {}^{i+1}\mathbf{p}_e)^T \delta\mathbf{p}_e$$
$$- tr\left({}^{i+1}\mathbf{R}^T\mathbf{R}_e\right) \delta g_0 + 2g_0 \left[as \left({}^{i+1}\mathbf{R}^T\mathbf{R}_e\right)^{VT}\right] \delta\theta_e$$

where $as \left({}^{i+1}\mathbf{R}^T\mathbf{R}_e\right)^V$ is the antisymmetric part of the equilibrium rotation matrix, written as a vector. The predicted gradient is then written as

$$\nabla_\theta \widehat{E}_{i+1} = \left[+\frac{1}{2} \|^{i+1}\mathbf{p} - {}^{i+1}\mathbf{p}_e\|^2, -k_t ({}^{i+1}\mathbf{p} - {}^{i+1}\mathbf{p}_e)^T, \right.$$
$$\left. - tr \left({}^{i+1}\mathbf{R}^T\mathbf{R}_e\right), +2g_0 \left[as \left({}^{i+1}\mathbf{R}^T\mathbf{R}_e\right)^{VT}\right] \right]. \quad (15)$$

Eq. (14) can then be rewritten, taking into consideration Eq. (15):

$$\begin{bmatrix} \nabla_\theta \widehat{E}(i, p(i), \theta(i-1)) \\ \nabla_\theta \widehat{E}(i-1, p(i-1), \theta(i-2)) \\ \vdots \\ \nabla_\theta \widehat{E}(i-m, p(i-m), \theta(i-m-1)) \end{bmatrix} \begin{bmatrix} \delta k_t \\ \delta \mathbf{p}_e \\ \delta g_0 \\ \delta \mathbf{R}_e \end{bmatrix}$$
$$= \begin{bmatrix} E^m(i, p(i)) - \widehat{E}(i, p(i), \theta(i-1)) \\ E^m(i-1, p(i-1)) - \widehat{E}(i-1, p(i-1), \theta(k-2)) \\ \vdots \\ E^m(i-m, p(i-m)) - \widehat{E}(i-m, p(i-m), \theta(i-m-1)) \end{bmatrix}. \quad (16)$$

Each parameter can be updated from Eqs. (16) and (17), using a recursive or not, weighted or not, root mean square method.

$$\theta(i+1) = \theta(i) + \delta\theta. \quad (17)$$

That is to say,

$$\begin{cases} k_t(i+1) = k_t(i) + \delta k_t \\ p_e(i+1) = p_e(i) + \delta p_e \\ g_0(i+1) = g_0(i) + \delta g_0 \\ R_e(i+1) = R_e(i) exp^{[\delta\mathbf{R}_e]}. \end{cases} \quad (18)$$

The larger the size of the matrix of the predicted gradient, the more precise the estimation of the parameters will be. However, the calculation time needed for the inversion of the matrix will also be greater. The size of the matrix will then have to be a compromise between the short computational time needed for real-time haptic feedback and the precision of the model. These approximations will depend on the computer used.

5.2.1. Limits

This last algorithm step Eq. (18) provides updated values for the approximated energy to be obtained. This estimation should provide a close representation of the energy field provided that the shape of the estimator is not too remote from the measured field. The algorithm also depends on the initial conditions and on the excitation type. For initial conditions that are very remote from the solution, the algorithm will take a long time to converge.
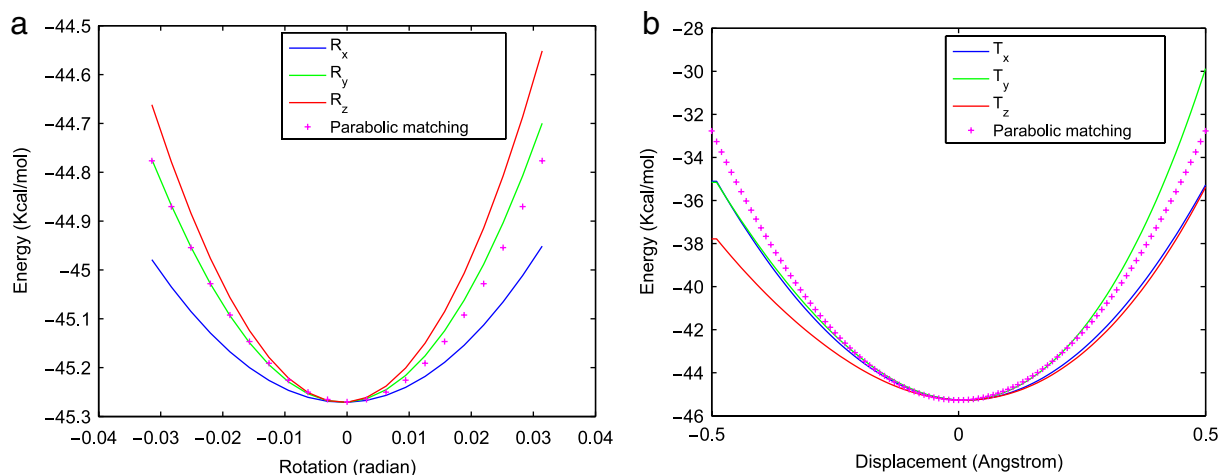
Fig. 7. Energy field evaluation between the ligand (biotin) in the minimized streptavidin complex. (a) Rotation of the ligand around its equilibrium position. (b) Translation of the ligand around its equilibrium position. A comparison with a quadratic function is made, validating the choice of quadratic terms for the predicted energy.

An estimation of the solution could be a good way of ensuring the convergence, knowing that the forces are calculated from the estimation. This implies ensuring the convergence at each time step. The estimated gradient matrix shape is important, as updated parameters are provided by its inverse. A guarantee of its existence is that there are no linear combinations of the lines. In other words, if the ligand is fixed (the haptic device is consequently fixed), the matrix will be singular. During the ligand's manipulation, if such a case appears, the ligand has to be moved around its current position to prevent the estimated gradient from being uninvertible. This is automatically done (in background mode, without any visualization of the motion so that the user can not see the little displacement variations) when the ligand is fixed to prevent altering the user's perception. The imposed motion (little translations and rotations around the ligand's center of mass) prevents the divergence of the energy model by keeping the parameters of the energy model constant or almost constant. Then, the calculated force is almost constant, or the variations in the force are unperceivable.

5.2.2. Application

In order to feel the docking forces, the force field first has to be approximated. The operator will then interact with the approximated model, which is updated at each time step.

Fig. 9 is the graphical representation of the simulation for which the results are shown in Fig. 8. The interaction energy has to be approximated using a polynomial function. Graphically, the interaction surface can be represented by the yellow sphere and the orientation of the half sphere. Then, the forces felt correspond to the distance between the real haptic device's position and the yellow sphere, and the torques correspond to the orientation difference between the haptic device's rotation and the half sphere (in an approximate way). For each ligand manipulation, all the parameters of the model are updated to obtain the potential minimum position and its orientation, knowing that forces and torques are obtained for these parameters.

5.3. Calculation of the interaction's wrench

Once the interaction energy is predicted, its gradient is used to calculate the forces. The new gradient is obtained not from the parameters but from the haptic device's position and orientation. Unlike the direct derivation (Section 5), the forces obtained are defined whatever the haptic device's displacement. The wrench is

calculated at the protein's center of mass, and is as follows:

$$\mathbf{W} = \left[k_t (\mathbf{p} - \mathbf{p}_e), 2g_0 \left(as(\mathbf{R}^{\mathrm{T}} \mathbf{R}_e)^{VT} \right) \right]$$

Fig. 10 shows the forces and torques obtained during a ligand manipulation inside the binding site using the wave variable coupling. The ligand is turned around its equilibrium position, resulting in the torques being felt. Fig. 10a represents the profile of the forces obtained from the derivation of the real energy. The forces' amplitude seem very high. This result has to be compared to Fig. 10b. In fact, this last graph plots the forces we obtained after having approximated the energy. It is clear that, because of the small variation in the parameter set, the force profile looks smoother, and is therefore haptically comprehensive. The torques are shown in Fig. 10c.

Interestingly, unlike the results obtained with direct energy derivation, the results here show that the forces inside the active site seem to vary very little. The forces inside the active site are well depicted and do not seem to have the same profile as those obtained from a derivation of the real energy. The results are also due to the control scheme's stability with regard to the delayed response and the chosen communication transparency (dictated by the choice of b). This makes it possible to establish a parallel between the micro world and the macro world. Additionally, these results make it possible to perform further research on the issue of force factor, in contrast to the first method, in which the forces are unstable.

6. Conclusions, discussion and future work

6.1. Conclusions and discussion

In this paper, a flexible molecular docking simulation with six degrees of freedom haptic feedback is presented. Starting from initial observations – a simulation based on the energy, long computation time for haptic manipulations, and high force amplitudes – we have implemented a new method for stable manipulations, which is based on wave variables that guarantee stability in time-delayed manipulation. This makes it possible for the operator to interpret the micro-forces. Moreover, the interaction energy provided by the minimization process is approximated using an energy model containing the parameters to be evaluated, and allowing the forces and torques to be obtained. The important point is that it ensures stable manipulation whatever the molecular simulator. With the use of a coefficient, the operator can opt either for smooth haptic feedback, reflecting
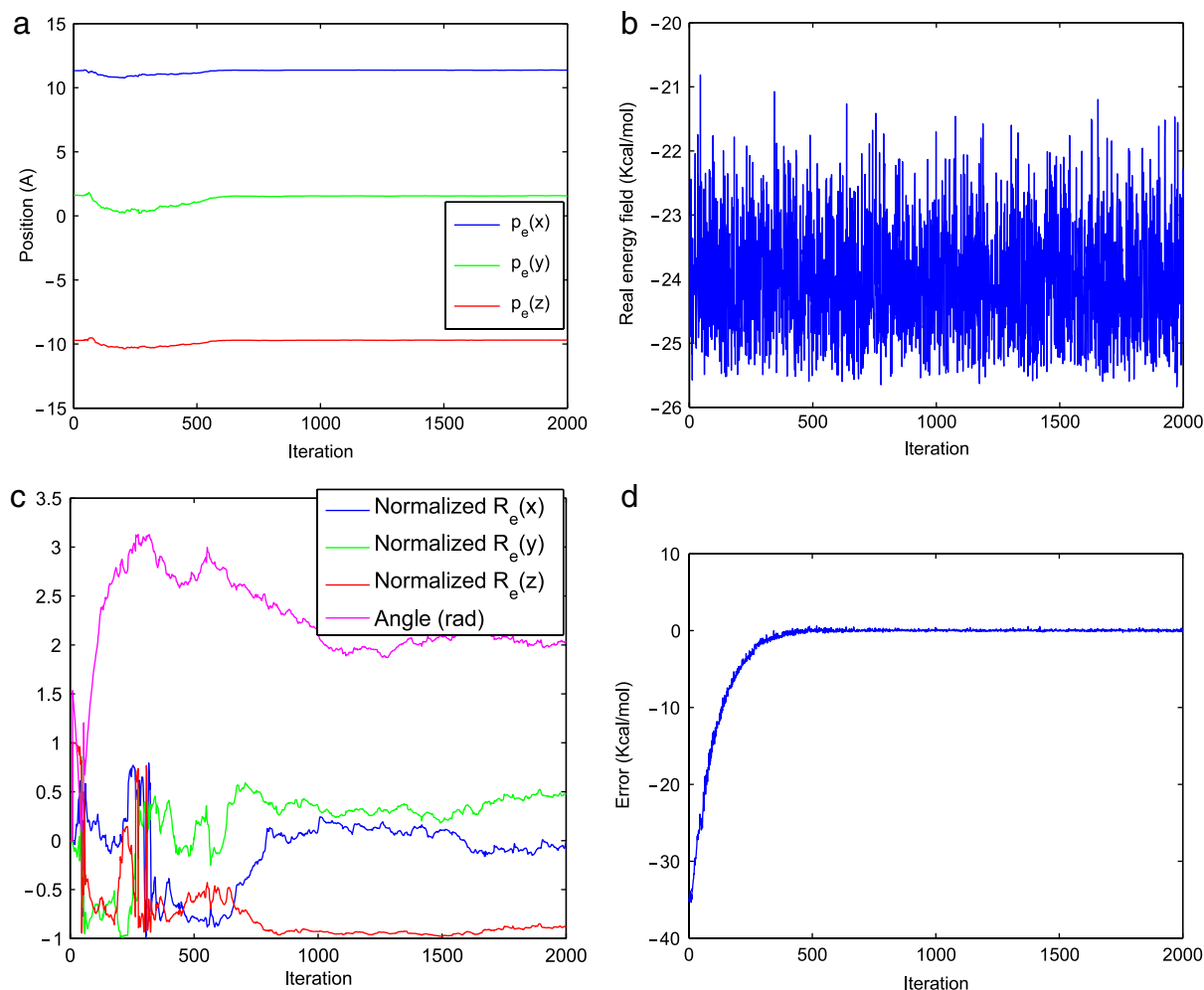
Fig. 8. Approximation of the force field in a minimized streptavidin complex. (a) Position of the potential minimum, (b) Measured interaction energy, (c) Orientation of the potential minimum, (d) Estimation error.
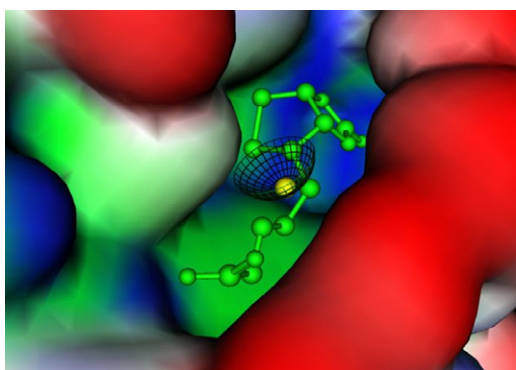

Fig. 9. Graphical interpretation of Fig. 8. The yellow sphere represents the predicted interaction potential minimum (obtained from Fig. 8) itself represented by the colored surfaces. The potential orientation is determined by the orientation of the half sphere (obtained from Fig. 8). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a rough interaction energy trend, or for the real energy profile, which is not necessarily the best solution for designing new drugs (because of the excessively high number of variations).

However, some limitations can be put in place. First, the control scheme uses fixed force/position scaling factors. If the protein model is scaled to fit into the workspace of the haptic device, it will be too small to explore. If the protein molecule is very large, then it is possible to explore only some of it. Then, the control is dedicated to a predetermined task: precise docking and precise feeling or protein surface exploration implying large displacements. Second, the communication delays and the coefficient b of the wave variables introduce inertia and viscosity. Even if b is determined to obtain stiff or soft contact (depending on the user desired perception), in both cases, the transparency of the control is affected by the delays. In the case of a low coefficient b, the macro-feeling of the micro-forces is felt in an ambient viscosity, whereas a high value of b will lead to feeling stiff contacts and all the sudden variations of the profile of the forces. Finally, the energy-based formulation, while powerful for control independence regarding the software used and suitable for obtaining forces and torques of the interaction without any knowledge of the force field used, suffers from its definition (suitable for local energy estimation) and from the optimization method used (time computation). An improvement could be to find a general non-local shape for the estimation, which does not need to be optimized at each time step. This will lead to decreasing the computational time.

6.2. Future work

The interaction energy profile is determined around the ligand's position. This could be a time-consuming method because several parameter estimations have to be made in order to provide very precisely estimated energy. An optimized interpolation method would be preferable. Moreover, it should be possible to optimize the shape of the estimated energy given that a quadratic form only fits the real energy locally. It should also be possible to use non-local approximations to find a cubic form. Automatic
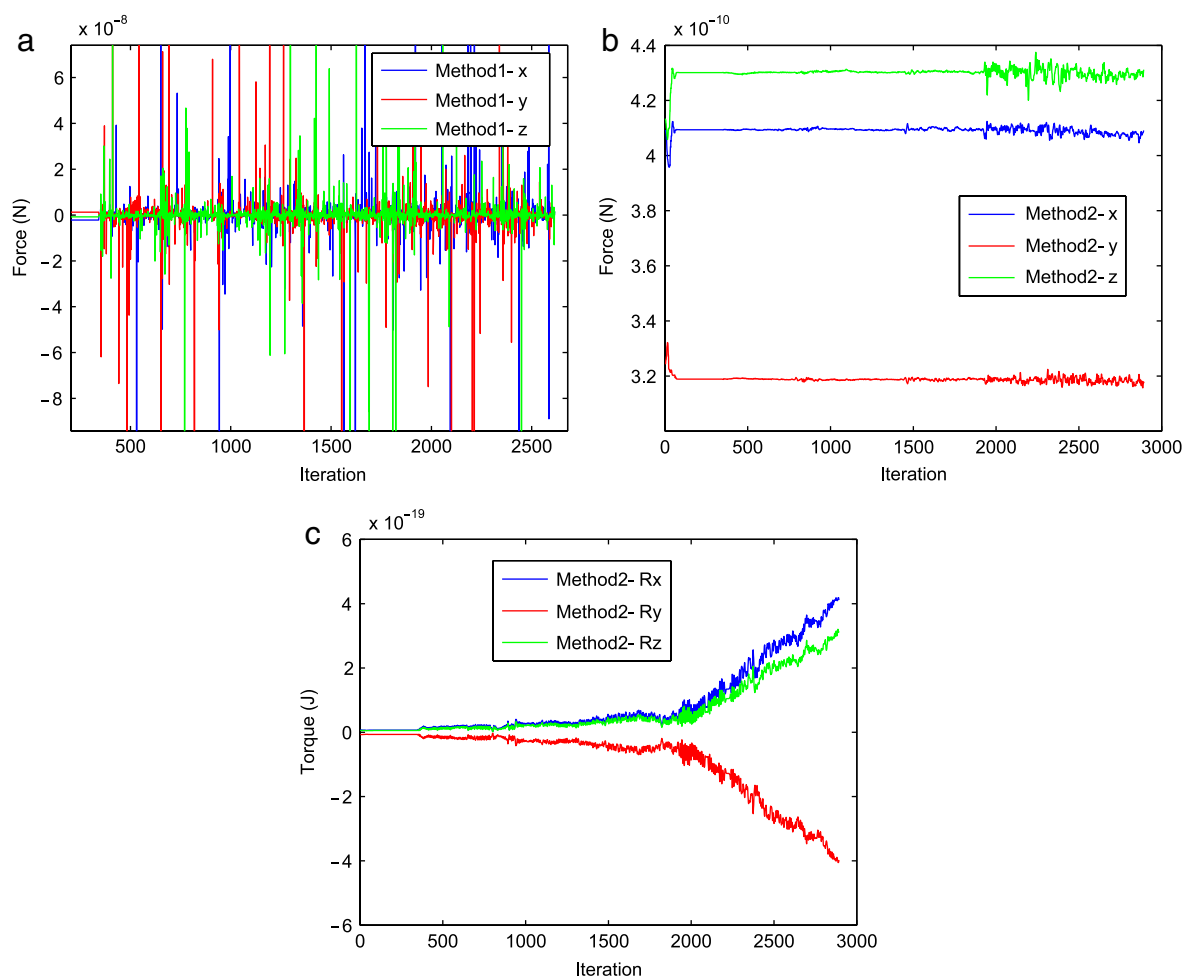
Fig. 10. Forces and torques during the ligand's manipulation inside the active site. (a) Forces calculated considering the derivation of the real energy, (b) Forces obtained after having approximated the energy field, (c) Torques calculated after having approximated the energy field.

adaptive factors have to be included. Then, inside the protein, little displacements would be preferred, whereas outside the protein, larger displacements would be possible. For this scheme, a strong relation between the scaling factors has to be maintained for the control's stability. Another study would involve switching control schemes for precise manipulation or rapid manipulation. Switching between velocity control for large displacements and position control for precise manipulation combined with adaptive factors should be a way of solving the problem. Also, a set of manipulation tasks has to be performed to improve the bilateral control scheme and its transparency modification.

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