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Interactive fitting augmented by force-feedback and virtual reality

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Abstract

The synthesis of low-resolution electron microscopy data with high-resolution molecular structures has become a common routine in the modeling of biomolecular assemblies. In contrast to algorithmic "black box" solutions, the interactive "fitting by eye" takes advantage of an expert's structural or biochemical knowledge and can be used with very noisy experimental data. In the solution proposed in this paper, we support the expert user in an interactive fitting session by haptic rendering and virtual reality. The quantitative and tactile feedback facilitates and objectifies the otherwise unrestrained modeling. We introduce a highly accurate reduced representation of the gradient of the cross-correlation coefficient that sustains force updates for haptic rendering at sufficiently high refresh rates.

Keywords: Multi-resolution docking; Haptic rendering; Visualization; Vector quantization

1. Introduction

To bridge the resolution gap from individual atoms to the basic functional units in biological cells, electron microscopists combine 3D reconstructions data of large assemblies with high-resolution structures from NMR spectroscopy or X-ray crystallography (Rayment et al., 1993; Schröder et al., 1993; Stewart et al., 1993). The multi-resolution modeling approach has achieved wide acceptance in recent years and has become an active field of computational research (Chacón and Wriggers, 2002; Rossmann, 2000; Volkmann and Hanein, 1999; Wriggers and Birmanns, 2001). Despite these algorithmic advancements it is noteworthy that the manual, interactive docking on the computer screen (Jones, 1978; Jones et al., 1991), aided by the eye of the expert modeler, remains popular among microscopists (Agrawal et al., 1999; Baker and Johnson, 1996; Moores et al., 2000). In interactive modeling, the complexity of the fitting process is handed from the computer to the user. The user's structural and biochemical expertise becomes part of the search strategy, which sometimes compensates for noise artifacts or low resolution of the reconstruction.

Visualization has become a key technique to analyze scientific data acquired by experiment or simulation, so it comes at no surprise that the interactive modeling with the aid of a graphics program remains popular in the modeling field. At least to some practitioners, the interactive rendering of computer generated objects on the computer screen appears to be more intuitive and easier to understand than results generated by a complex program that demands the a priori assignment of search parameters. Also, the development of 3D computer graphics hardware and software in the last decades has significantly contributed to the popularization of 3D visualization. Today, researchers use high-end graphics workstations for their daily work and are capable of visualizing very large datasets interactively.

Despite the attractiveness of the visual docking method among microscopists, it is clear that there are limitations if a physically plausible 3D model is the goal of the fitting. Firstly, the docking by eye is inherently subjective and not fully reproducible. Attempts have been made to minimize this limitation by comparing predictions from several individuals (Sosa et al., 1997). However, the structural evaluation of the resulting fits is cumbersome, and, in the case of ambiguous protein shapes, may give rise to controversial interpretations (Hirose et al., 1999; Kozielski et al., 1998; Sosa et al.,

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1997). Also, researchers may be misled by missing boundaries between the components of assemblies. In the absence of such reference surfaces it is not uncommon that structures are placed "off center" since their centroids in the whole map cannot be estimated by eye.

We propose, therefore, that the visual feedback in an interactive graphics session should be augmented by real-time quantitative feedback technologies to assess multiple alignments by means of a score function. Since we wish to build a quantitative feedback for interactive modeling, a cursory look at existing strategies is useful. The existing programs (reviewed in Wriggers and Chacón, 2001) typically measure the quality of the fit in an exhaustive search over all possible locations and orientations. There are many quality criteria at varying degrees of complexity. The standard cross-correlation

$$C = \int \rho_{\mathrm{em}}(\mathbf{r})\rho_{\mathrm{calc}}(\mathbf{r}, \mathbf{R}, \mathbf{T})d^3\mathbf{r} \tag{1}$$

is perhaps the most basic fitting measure, so it forms a natural starting point for conceptually exploring the proposed feedback. In Eq. (1) the term ρ_{em} denotes the electron microscopy density map. To calculate the correlation between objects at different resolution, the resolution of the molecular structure (Belnap et al., 1999) is lowered, leading to a second volumetric dataset ρ_{calc} at the same resolution as ρ_{em} . $\mathbf{T}$ and $\mathbf{R}$ denote the three translational and three rotational degrees of freedom of the structure.

In this paper we introduce a novel real-time interactive fitting strategy that reduces the search complexity by assisting the user with a correlation-based technique adapted from algorithmic docking programs (Eq. (1)). To support the user in interactive fitting and modeling sessions we employ virtual reality and haptic rendering (force-feedback) methods developed in computer science. The rendered forces and torques guide the modeler to the optimum fit by imitating how a "black box" algorithm would rate the current fitting location and orientation.

2. Methods

In the following we first introduce virtual reality and haptic rendering (force-feedback) as a way to efficiently communicate quantitative information to the user. Unfortunately, forces and torques are expensive to compute and sufficiently high-force update rates using Eq. (1) are unrealistic. Therefore, we reduce the calculation complexity by means of vector quantization to achieve the desired high frequency of force refresh rates.

2.1. Virtual reality and haptic rendering

In the early days of computer graphics and molecular visualization, most of the development effort was spent on the representation of the "virtual," i.e., computer generated objects. Today we are capable of presenting 3D objects in an almost photo-realistic manner. However, the interaction between the user and modeled objects with the aid of a standard 2D display and a 2D mouse is still relatively artificial and unintuitive. Therefore, advanced "virtual reality" (VR) techniques hold much promise to provide intuitive human–computer interaction that brings simulated molecular assemblies to life.

Ideally, a VR system would mimic the way a real object would be experienced. A number of technologies, such as stereoscopic viewing, positional tracking or multi-display immersive projection have come close to provide a realistic experience (for an extensive review see (Burdea and Coiffet, 1994)). In this work we apply VR display methods to the problem of the interactive docking of molecular structures into low-resolution EM density maps. This problem benefits from the enhanced orientational exploration in the virtual space, which facilitates to positioning of 3D objects relative to one another. One of the major features of our VR system is the augmentation of the stereoscopic viewing by haptic rendering.

The word "haptic" is derived from the greek word *haptesthai* which means "to touch". The human body has a haptic sensory system, which enables one to experience the environment by touching objects and to acquire information about surfaces (e.g., their roughness or smoothness) and structural conditions (e.g., their rigidness or softness). Haptic rendering means that an artificial tactual sensation is used to simulate the process of actually touching a real object. Since the 1950s (Stone, 2001) haptic rendering is routinely employed in teleoperation, used for the remote manipulation of unreachable objects (e.g., satellites in the orbit).

Several experimental studies have demonstrated a dramatically improved human performance in terms of speed and precision when supported by force and touch feedback. For example, Hannaford and Wood, 1989, studied the behavior of human operators who were asked to perform simple remote manipulation tasks using a force-reflecting hand controller and a robot manipulator. Different tasks were assigned, e.g., to attach, detach or move two different shaped blocks fixed to a board with Velcro, or to insert a peg into holes with different diameters. Performance parameters that were monitored included the completion time, errors in the alignment, and the force applied to the remote objects. Human operators were separated into two groups. The first group was able to experience the tactual sensations measured by the robot actuator, the other group had only the visual information available. Remarkably, the group that had the haptic information available achieved a far shorter completion time (30% speed up), was able to reduce the applied force by a factor of 7, and reduced the errors by 63% relative to the control group.

Force-feedback was also adapted to interactive computer applications (Ouh-young et al., 1988), and a similar benefit was observed in terms of human performance (Ouh-young et al., 1989; Richard and Coiffet, 1995). Haptic rendering compensates common disadvantages of a pure visual representation, such as the misjudgement of the size of virtual objects (Wu et al., 1999). Together, these studies established that the haptic sensations provide essential information during an interactive task. Since it was our intention "to keep humans in the loop" during the modeling, the benefits of haptic rendering for the 6D docking task appeared worthwhile exploring.

Haptic rendering relies on an unrelated, non-visual sensory system. Therefore it is not possible to substitute the tactual sensation by a visual representation (for example by graphically outputting force and torque vectors). An experimental study (Ouh-young et al., 1988) demonstrated that such an approach leads to different interaction patterns in the human–computer interaction. Subjects in this study were asked to explore a multi-dimensional energy landscape interactively and to find an energy minimum. One group had actual haptic information available whereas the other group could see the force and torque as visual vectors on the computer screen. The group that was able to actually feel the force information was more than twice as fast and was able to detect a mean final energy half as large as that of the control group. The study suggests that the reason for the lower precision of the control group lies in a different search strategy—the control group tried to minimize the translational force vector first and then the torque vector, but was unable to minimize both simultaneously as was done by the subjects that employed haptic rendering.

Similar to the special output devices that are required to stimulate the visual and auditory systems (display and loudspeakers), special devices are required that produce haptic sensations. Most haptic devices dynamically produce a force that gives rise to a kinesthetic sensation. Since the kinesthetic sensation is part of our experience while touching a real object, the brain will associate an appropriately modulated force with the touching of the surface of a virtual object (Burdea, 1996). An example for such a haptic device, based on force output, is the "Phantom" (Massie and Salisbury, 1994), shown in Fig. 1.

The Phantom consists out of a robot-arm-like mechanism with a pencil-like handle. The user moves the handle while the Phantom measures the movements and produces a force (or torque) that is felt at the hand. Among the different commercially available Phantom prototypes (SensAble Technologies) two units are particularly noteworthy, the affordable but very capable "Desktop" device, and the new Phantom "1.5/6DOF" prototype that produces torque- as well as force-feedback for all six rigid-body degrees of freedom. The torque feedback is particularly useful for biomolecular modeling, where the orientational fitting is critical for the proper alignment of structures.

Fig. 1. Haptic device "Phantom 1.5/6DOF" by SensAble Technologies. The translational range of motion and force-feedback is 7.5 in. × 10.5 in. × 15 in., approximating the range of motion of the forearm. Torque feedback is provided through a powered gimbal. The rotational range of motion is 335° in the yaw and roll directions, and 260° in the pitch direction.

The haptic rendering is intended to support the user in the interactive fitting process by providing feedback on the suitability of the current docking location. A suitable quantity for the feedback is the gradient of the correlation coefficient. Using the gradient, one can compute a force that pulls the user's hand "uphill" toward an increasing correlation, i.e., a more suitable fitting location. The force does not only provide an information about the quality of the current fit, but also provides guidance how to improve, which creates a virtual "tactile landscape" in which the user may navigate for local maxima of the correlation. These considerations led us to consider the following force equation:

$$\mathbf{F}(\mathbf{R},\mathbf{T}) = -\nabla(-\mathbf{C}(\mathbf{R},\mathbf{T})) = \nabla\mathbf{C}(\mathbf{R},\mathbf{T}),$$

where $\mathbf{C}(\mathbf{R},\mathbf{T})$ is defined by Eq. (1). Here, the cross-correlation acts as a (negative) potential energy, whose (negative) gradient gives rise to the desired force.

2.2. Vector quantization and reduced fitting criterion

The force output depends on the current position of the user's hand and must be frequently refreshed to incorporate even smallest changes of the location in real-time. In order to achieve a realistic haptic perception, the refresh rate should be at least 500 Hz–1 kHz (Chen and Marcus, 1998; Dow et al., 1999). After implementing the force equation in a straightforward manner we observed that the gradient of the correlation coefficient

cannot be calculated at sufficient frequency. Computation of the standard coefficient from the entire datasets, ρ_{em} and ρ_{calc} , is very expensive.

To simplify the calculation, we adopted *vector quantization*, a widely used compression method in signal processing. Vector quantization is able to replace a complex signal by a small number of so called codebook vectors. The goal of the vector quantization algorithms (Gersho and Gray, 1992; Martinetz et al., 1993) is to find a set of codebook vectors for which the distortion error E is minimal:

$$E = \sum_j m_j \|\mathbf{r}_j - \mathbf{w}_{i(j)}\|^2,$$

where $\mathbf{r}_j$ is the original signal (with a weight m_j associated to it) and $\mathbf{w}_{i(j)}$ is the nearest codebook vector. To avoid getting trapped in local minima of the distortion error, we chose the topology representing network (Martinetz et al., 1993) that performs a stochastic gradient descent on a smooth energy landscape that slowly converges toward the actual distortion error E. The vector quantization is applied here to the probe molecule, replacing it by a number N codebook vectors. This technique was already successfully used in reduced modeling of biophysical data elsewhere, e.g., in rigid-body and flexible docking (Wriggers and Birmanns, 2001). The number of codebook vectors N is selected by the user to balance the accuracy against the speed of the force calculation. In Section 3 we will investigate the influence of the cardinal complexity N on the fitting precision and on the force refresh rate.

Given a set of codebook vectors $\mathbf{w}_i$ we approximate the probe molecule by a sum of Dirac delta functions:

$$\rho_{\text{calc}}(\mathbf{r}, \mathbf{R}, \mathbf{T}) \approx \sum_{i=1}^{N} \delta(\mathbf{r} - \mathbf{w}_i(\mathbf{R}, \mathbf{T})).$$

Introduced into Eq. (1), this reduces the correlation coefficient to

$$C(\mathbf{R}, \mathbf{T}) = \sum_{i=1}^{N} \rho_{\text{em}}(\mathbf{w}_i(\mathbf{R}, \mathbf{T})).$$

With this simplified coefficient one can calculate the force and torque acting on the probe molecule for the haptic rendering. The molecule, which is moved about interactively by the user, is modeled as a rigid-body in a conservative potential defined by the negative cross-correlation. The rigid-body consists of a set of particles, in this case the codebook vectors, which cannot change their positions relative to each other. The potential energy of a single particle is

$$U_i(\mathbf{R}, \mathbf{T}) = -\rho_{em}(\mathbf{w}_i(\mathbf{R}, \mathbf{T})).$$

The potential energy for the entire rigid body is the sum of the potential energies of the constituent particles:

$$U = \sum_{i=1}^{N} U_i = -\sum_{i=1}^{N} \rho_{em}(\mathbf{w}_i(\mathbf{R}, \mathbf{T})),$$

which is by definition the negative simplified correlation coefficient. For the force $\mathbf{F}$ in a conservative potential holds $\mathbf{F} = -\nabla U$. Thus, the force acting on the COM of the rigid body is equal to the gradient of the EM density sampled at the codebook vector positions:

$$\mathbf{F} = \sum_{i=1}^{N} \nabla \rho_{\text{em}}(\mathbf{w}_i(\mathbf{R}, \mathbf{T})). \tag{2}$$

One can compute the total torque $\mathbf{Q}$ acting on the molecule in a similar fashion. Shifting the origin of the coordinate system to the COM, we obtain:

$$\mathbf{Q} = \sum_{i=1}^{N} \mathbf{w}_i(\mathbf{R}, \mathbf{T}) \times \nabla \rho_{\text{em}}(\mathbf{w}_i(\mathbf{R}, \mathbf{T})), \tag{3}$$

where "$\times$" denotes the vector cross-product. The gradient field $\nabla \rho_{\text{em}}$ can be precomputed and is efficiently evaluated in real compute time by tri-linear interpolation.

3. Results

The haptic rendering described above was implemented in our VR-capable fitting and visualization program *SenSitus*. The program is based on the Scientific Visualization Toolkit (SVT), a free C++ class library developed by S.B. at Forschungszentrum Jülich, Germany. For the visualization of atomic structures several drawing modes are implemented, such as van der Waals-spheres, points, lines, and ball-and-stick models. Volumetric data is currently visualized in the form of cross-sections and isosurfaces, calculated by the marching cube (Lorensen and Cline, 1987) algorithm, see Fig. 2.

During the interactive fitting process the user must be able to inspect the structure inside the volume dataset. Transparency of isosurfaces is not easy to achieve in interactive computer graphics. Only inexpensive, local lighting models are used for interactivity. Therefore, all the triangles in a scene would have to be drawn depth sorted to create a correct transparency effect. This expensive sorting, in turn, would prevent interactivity. To avoid this dilemma we use the so-called stipple-mode technique in which only every nth pixel of the isosurface is drawn (typically $n = 2$). If reasonable screen resolutions are used (1024 by 768 or better) this mode closely resembles true transparency.

SenSitus also features an intuitive graphical user interface. Dialogs allow the user to manipulate the visualization of the atomic structures or to make precise changes to the transformation or orientation of the currently selected dataset (see Fig. 2).

In addition to traditional 3D molecular graphics applications, SenSitus is able to drive a VR environment. The implementation is very flexible and can work with arbitrary multi-display VR systems by adjusting a configuration file. The software also supports active and passive stereoscopic glasses, as well as head tracking devices and high-end computer systems with multiple graphics pipelines and CPUs.

3.1. Test of implementation

To validate our force calculation we first created an idealized volumetric map consisting only of a single Gaussian

$$g(r) = e^{-3r^2/2\sigma^2},$$

where $2\sigma = 10$ is the target resolution in Å. We moved a single probe vector $\mathbf{w}$ along the x-axis through the low-resolution map and simultaneously calculated the force according to Eq. (2). The recorded force values can be seen in Fig. 3. Since the force is defined as the gradient of the correlation, the first derivative of $g(x)$,

$$\frac{d}{dx}g = -\frac{3}{25}xe^{-3x^2/50},$$

should equal the observed force.

As one can see in Fig. 3, the recorded force approximates the derivative very well. The small deviations are due to discretization effects, since the density and its gradient are sampled on a lattice.

3.2. Accuracy of the force and torque calculations

We have so far presented a fast way to calculate forces and torques used for haptic rendering based on the standard cross-correlation coefficient. We introduced a simplification of the calculation using vector quantization, which represents a complex data set by a small number of codebook vectors. In this compression scheme one loses information relative to the full molecular structure, so the question arises how the reduction affects the force-calculation.

To analyze this, we created a single molecule density map for which the correct fitting location of the atomic structure is known. To this end, we lowered the resolution of molecular structure (PDB entry 1ATN) to 10 Å. The corresponding probe molecule was placed into this simulated map and shifted from −10 to +10 Å in 0.1 Å increments. Simultaneously, the force was recorded according to Eq. (2). This was done for various numbers N of codebook vectors. What one would expect is a vanishing force at zero displacement.

As one can see in Fig. 4, the force recorded for 10 codebook vectors oscillates at a low level within a relatively wide window from −5 to +5 Å. This is not the desired behavior, since the user does not receive a precise feedback near the optimum fitting location. The loss of information from reducing the atomic structure (5020 atoms) to just 10 vectors is too severe. If one inspects the curve for 20 codebook vectors, the precision increases significantly. The curve now has the expected funnel shape, and the user is directed to a unique fitting location where the force drops to zero. The position of the minimum is not exactly at the origin but at a deviation of 2.6 Å. If one adds more codebook vectors and uses 40 of them to describe the molecule, the force minimum moves closer to the origin (0.15 Å deviation). By adding more codebook vectors, the minimum will remain very close to the origin, within 0.3 Å, but does not converge further (see also the curve for 100 vectors in Fig. 4). This noise is due to the discretization of the density on the lattice (3 Å spacing) that precludes a perfect accuracy of the feedback.

We performed additional tests with more codebook vector sets, inspected the behavior when moving along the y- and z-axes or rotating about x-, y-, and z-axes, and made similar tests with other maps. The results confirmed the observation that a relative small number of codebook vectors is sufficient for sub-voxel accuracy. For example, Fig. 5 shows the rotational accuracy when rotating PDB entry 1CLL. Again, a number of 40 codebook vectors provide a reasonable funnel-shape for the computed torque (Eq. (3)).

As experimental maps often exhibit low resolution we also validated that the codebook vector representation delivers reasonable accuracy in this case. Fig. 6 shows the accuracy of the torque if maps of different resolutions are used. As one can see, the precision remains almost constant while the resolution of the map drops from 10 to 30 Å (deviation of the torque minimum is 1° for 20 and 30 Å, compared to 0° for 10 Å).

3.3. Efficiency and refresh rates

In the previous section we have shown that vector quantization is able to reduce the molecular structure without significant loss of precision in the force or torque calculation. Now the question arises if this reduction will yield a sufficient speed of the force computation to achieve the required refresh rates in the kilohertz range. In the following we list the average observed rates for two computer systems, calculated during a 60 s interactive fitting session. Since the 3D graphics load changes during the session, the CPU load also changes and therefore the rates are not constant. The observed fluctuations in the rates were relatively small (<2%).

Even on a low-end PC (single CPU, Pentium III 1 GHz, 256 MB RAM), whose sole CPU is responsible for force-feedback, rendering of the 3D scene and displaying the graphical user interface, the force recalculation rates were sufficiently high (Table 1). Since the 40

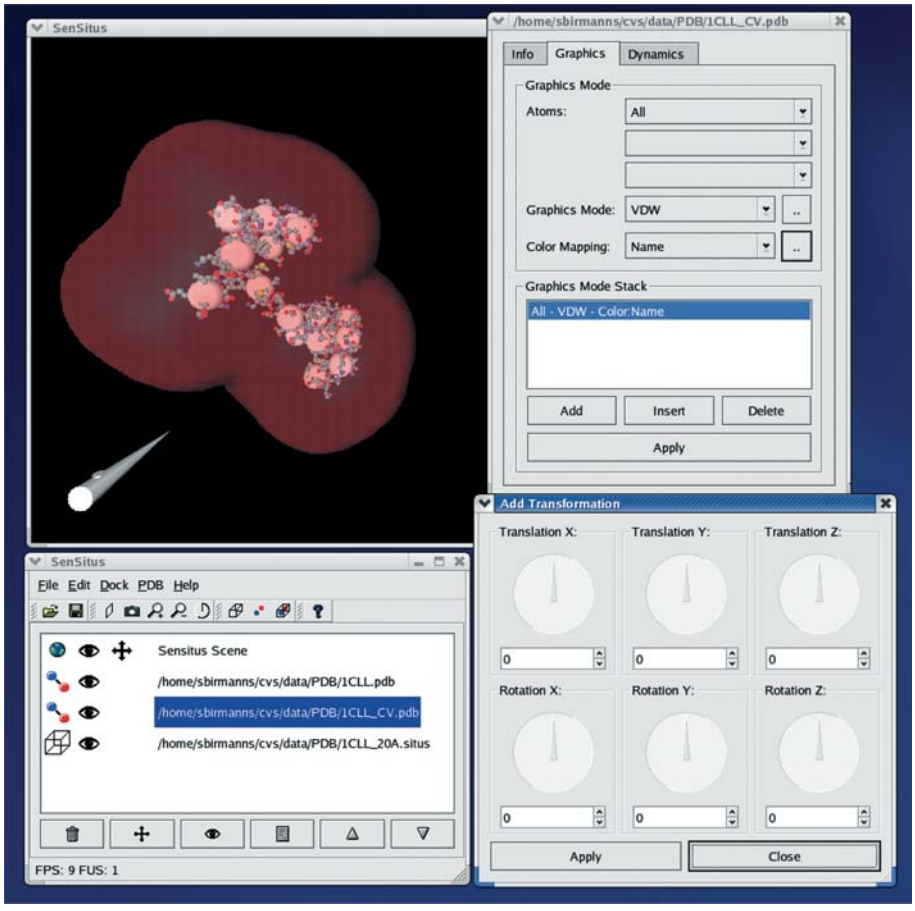


Fig. 2. SenSitus interactive fitting session. Visible are the main 3D graphics window and the central user interface. Also shown are dialog boxes such as the translation and rotation dials or the atomic structure visualization menu.

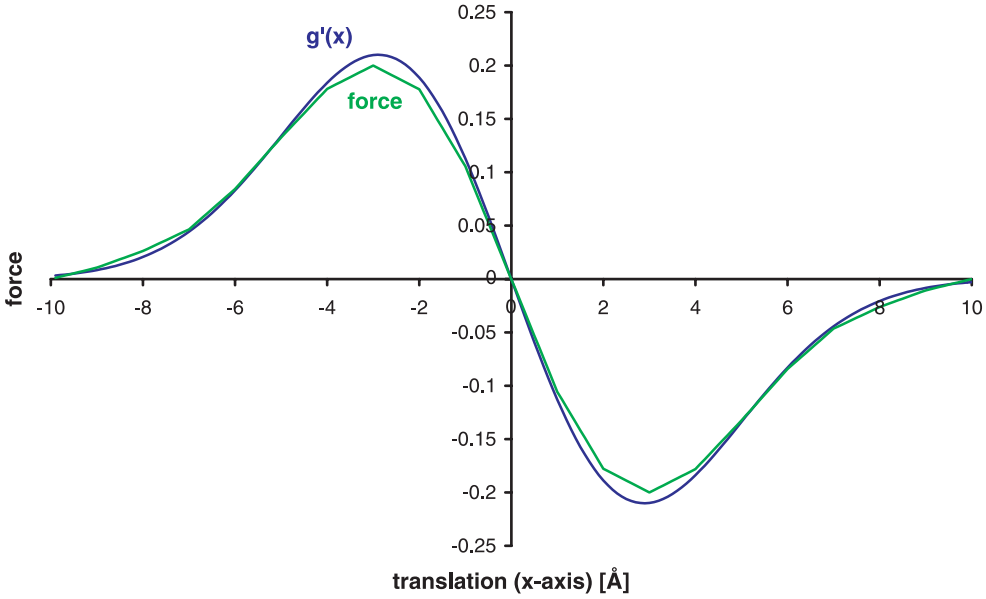
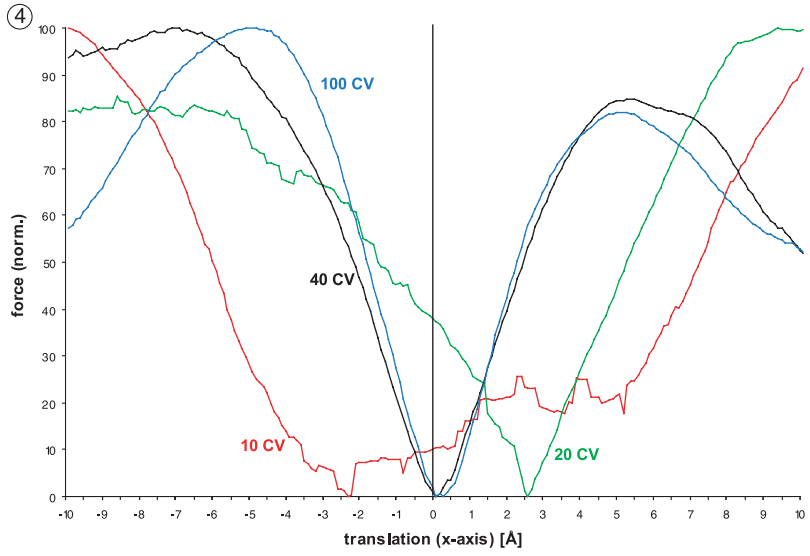


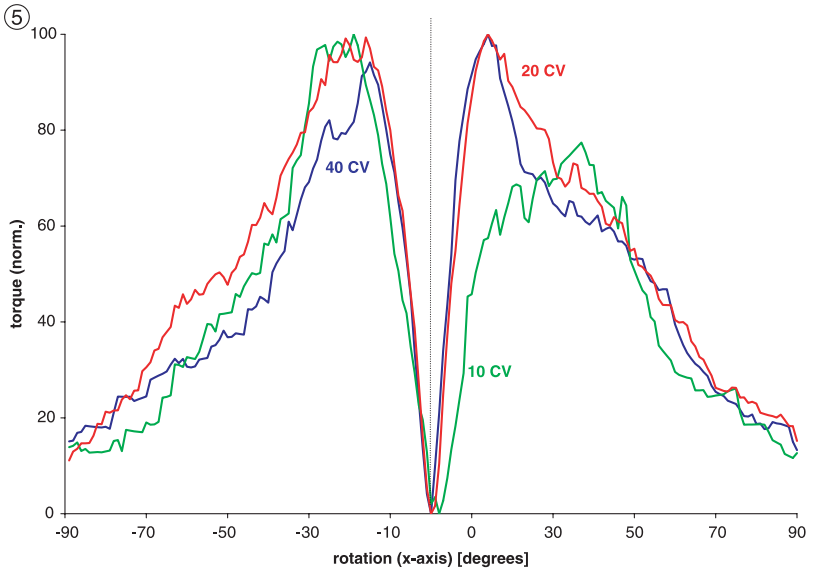
Fig. 3. Recorded force for a probe atom in a single Gaussian test density, and comparison with the analytic solution. See text for details.

Fig. 4. Recorded force for translations of PDB entry 1ATN along the *x*-axis for various numbers of codebook vectors (CV).

Fig. 5. Recorded torque for rotations of PDB entry 1CLL about the *x*-axis for various numbers of codebook vectors (CV).

Fig. 6. Recorded torque for rotations of PDB entry 1CLL about the *x*-axis for volumetric data simulated at various resolution levels.


④
100 CV
40 CV
10 CV
20 CV
force (norm.)
translation (x-axis) [Å]


⑤
20 CV
40 CV
10 CV
torque (norm.)
rotation (x-axis) [degrees]

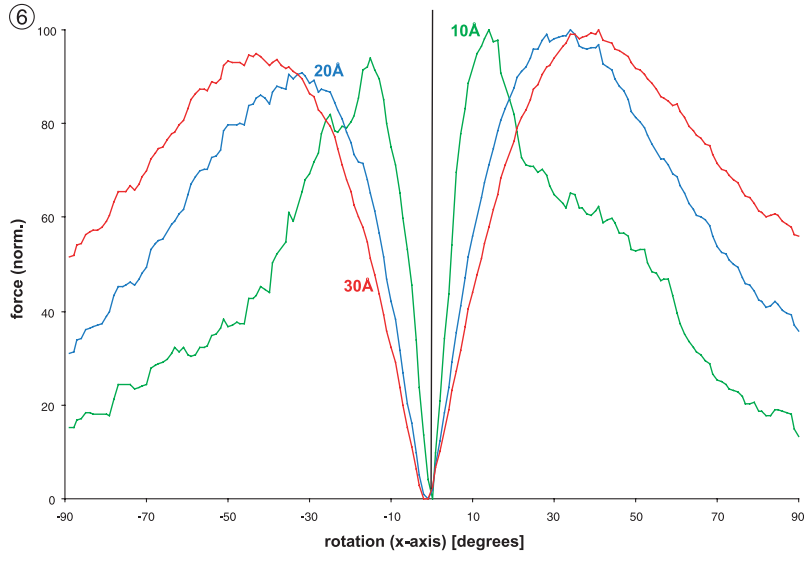

⑥
10Å
20Å
30Å
force (norm.)
rotation (x-axis) [degrees]

Table 1
Force and torque refresh rates observed with PDB entry 1ATN, 1 GHz Pentium III CPU

Number of codebook vectors	Refresh rate (Hz)
10	2530
20	1563
40	954

Table 2
Force and torque refresh rates observed with PDB entry 1ATN, 2×1 GHz AMD Athlon CPU

Number of codebook vectors	Refresh rate (Hz)
10	8542
20	5244
40	2919

codebook vectors yield sufficient accuracy, the interactive fitting process can be supported by haptic rendering even on this low-end platform.

The visualization and the force and torque calculations of SenSitus run in separate parallel threads, so that the program takes advantage of a multiprocessor environment. Therefore, we also performed tests on a dual-CPU workstation (Table 2). As one can see, the refresh rates are well above 1 kHz. Hence, a dual processor PC platform has sufficient compute reserves to deal with an even finer vector quantization or with a more demanding visualization.

3.4. Discussion and conclusions

In this work we introduced a new and innovative way to perform a real-time interactive fitting of atomic structures into low-resolution EM density maps. Supported by virtual reality and haptic rendering, it is more intuitive for users to orient molecules in 3D space and to position the datasets relative to each other. Our software provides feedback in which direction (and orientation) a better fitting location can be found.

We note that the optimum number of codebook vectors in the reduced representation may depend on the molecular shape, the fitting scenario (single molecule or multiple subunits) and on the resolution of the volumetric density map. Although a number 20–40 was sufficient in all our trial runs, a simple algorithmic implementation is possible that detects the optimum number based on the convergence properties of the force or torque minima, or based on the achieved refresh rates.

We originally developed our SenSitus software on a two-display immersive VR system, the *holobench* at Forschungszentrum Jülich in Germany. The active stereo rendering using liquid crystal display (LCD) shutter glasses, emitters, and multiple cathode ray tube (CRT) projectors (for high-frequency optical refresh rates) requires a synchronization of multiple graphics pipelines that is achieved only by high-end computing systems (e.g., Silicon Graphics Onyx). The cost of the computer hardware together with the precision mounting of mirrors, screens, and expensive CRT projectors places this technology well out of financial reach for the average user.

However, there are now modestly priced PC-based solutions available. This new, inexpensive VR technology is based on passive stereo, i.e., the use of polarizing filters and glasses. Instead of CRT projectors, passive stereo uses the ubiquitous LCD projector technology, and no expensive synchronization of the graphics cards is required. We are currently building a passive VR system in Houston that costs little more than a low-end UNIX based graphics workstation. For the future we are seeking also an alternative for the expensive haptic rendering device, which admittedly limits the application of our solution to research labs with sufficient equipment funding. Although an inexpensive Phantom prototype is available from SensAble Technologies, the loss of torque feedback in more affordable devices may compromise the orientational fitting that we deem critical for biomolecular data.

We have demonstrated SenSitus and the Phantom device to audiences at the Biophysical Society Discussions in Asilomar, California (April 2002), and at a Situs (Wriggers and Birmanns, 2001) user workshop in San Diego, California (February 2003). The VR and haptic technology was very well received and did not require a special training. However, a number of users at the live sessions pointed out that interactive fitting is surprisingly challenging even when supported by force and torque feedback. It is possible that this perception is due in part to the relative insensitivity of the cross-correlation to rotational changes. Limitations of the cross-correlation criterion are well documented and we will seek to implement remedies such as filtering (Chacón and Wriggers, 2002) and landmark-based fitting (Wriggers and Chacón, 2001) in future versions of SenSitus. In any event, the calculated forces and torques provide information only in the vicinity of the currently visited part of the six-dimensional fitting landscape. This means that the user is still responsible to explore the global search space before refining it locally.

Computer-aided interactive fitting has been proposed before and is implemented, e.g., in the program "O" (Jones et al., 1991). Typically, the earlier initiatives integrate algorithmic "black box" solutions into the search, e.g., by providing modules that will automatically optimize a found candidate fit. Our strategy presented here is different in the sense that we are guiding the user at all times during the actual interactive modeling process. An integration of the alternative search strategies for the refinement of candidate fits (Wriggers and Birmanns, 2001) is planned for future releases of the SenSitus program.

Source code and executables of SenSitus version 1.0 can be downloaded for various UNIX and PC architectures at http://sensitus.biomachina.org.

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