Linköping University Post Print

Improved Feature Detection over Large Force Ranges Using History Dependent Transfer Functions

Petter Bivall Persson, Gunnar E. Höst, Matthew D. Cooper,
Lena A. E. Tibell and Anders Ynnerman

N.B.: When citing this work, cite the original article.

©2009 IEEE. Personal use of this material is permitted. However, permission to reprint/republish this material for advertising or promotional purposes or for creating new collective works for resale or redistribution to servers or lists, or to reuse any copyrighted component of this work in other works must be obtained from the IEEE.

Petter Bivall Persson, Gunnar E. Höst, Matthew D. Cooper, Lena A. E. Tibell and Anders Ynnerman, Improved Feature Detection over Large Force Ranges Using History Dependent Transfer Functions, 2009, Third Joint Eurohaptics Conference and Symposium on Haptic Interfaces for Virtual Environments and Teleoperator Systems, WorldHaptics 2009, 476-481.
<http://dx.doi.org/10.1109/WHC.2009.4810843>

Postprint available at: Linköping University Electronic Press
<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-45355>

Improved Feature Detection over Large Force Ranges Using History Dependent Transfer Functions

Petter Bivall Persson*

Department of Science and Technology

Matthew D. Cooper‡

Department of Science and Technology

Gunnar E. Höst†

Department of Science and Technology

Lena A.E. Tibell§

Department of Clinical and Experimental Medicine

Anders Ynnerman¶

Department of Science and Technology

Linköping University, Sweden

ABSTRACT

In this paper we present a history dependent transfer function (HDTF) as a possible approach to enable improved haptic feature detection in high dynamic range (HDR) volume data. The HDTF is a multi-dimensional transfer function that uses the recent force history as a selection criterion to switch between transfer functions, thereby adapting to the explored force range.

The HDTF has been evaluated using artificial test data and in a realistic application example, with the HDTF applied to haptic protein-ligand docking. Biochemistry experts performed docking tests, and expressed that the HDTF delivers the expected feedback across a large force magnitude range, conveying both weak attractive and strong repulsive protein-ligand interaction forces. Feature detection tests have been performed with positive results, indicating that the HDTF improves the ability of feature detection in HDR volume data as compared to a static transfer function covering the same range.

Index Terms: H.5.1 [Information Interfaces and Presentation]: Multimedia Information Systems—Artificial, augmented, and virtual realities; H.5.2 [Information Interfaces and Presentation]: User Interfaces—Haptic I/O; I.3.7 [Computer Graphics]: Three-Dimensional Graphics and Realism—Virtual reality; J.3 [Life and Medical Sciences]: Biology and Genetics; K.3.1 [Computers and Education]: Computer Uses in Education—Computer-assisted instruction (CAI)

1 INTRODUCTION

Proteins bind to small molecules (called ligands) through a multitude of intermolecular forces in a docking process, a phenomenon that lends itself well to haptic perceptualization. For a molecular understanding of life, proteins and their capacity for molecular recognition are critical. Essentially all chemical processes in the cell are catalyzed by proteins known as enzymes, and other types of proteins carry out other functions, such as the detection of foreign substances by antibodies. The application of haptics to protein-ligand docking is a growing field, with promising applications in education and research [5, 19, 20, 23, 11, 4, 21].

The force acting on the ligand during docking is determined by its local environment in the protein's force field. The magnitudes of these forces generally span a wide range, from relatively weak

attractive forces when the ligand approaches an optimal distance to the protein surface, to strong repulsive forces from the interpenetration of the atoms' electron clouds when the ligand is moved too close to the surface. The high dynamic range (HDR) property of the forces constitutes a key challenge in the design of the haptic feedback system. The energetic potentials around the protein are often represented in volumetric potential grid maps from which the forces are calculated.

The forces derived from volumetric datasets are usually mapped to the output force range of the haptic device through a transfer function (TF). It has been pointed out in several studies that a satisfactory mapping is not trivial to achieve [15, 8, 13]. In particular, achieving full feature detection capacity across the entire range of forces is a challenge, an issue also noted in previous work [12, 4, 25, 6, 21]. It seems that more research on TF design is required, as suggested by [15]: "*The state-of-the-art in haptics research does not provide general guidelines on how to design haptic transfer functions that can aid the user of a data perceptualization system to perform a task well.*"

In this study, we present and evaluate a possible solution to the HDR-related problems encountered in haptic perceptualization of HDR volumetric data. Using a History Dependent Transfer Function (HDTF), which is a multi-dimensional TF that adapts the force output based on the recent history of encountered forces, the possibility of feature detection over large force ranges is increased. In the case of an ordinary static TF, it is possible to optimize the TF for sensitivity in a limited range of forces, but this will be accompanied by a corresponding loss of resolution in some other region. Our results indicate that the HDTF approach overcomes this limitation, potentially making it more suitable for haptic interaction with HDR volumetric data.

The main contributions of this study are the application of a multi-dimensional transfer function, the HDTF, to the field of haptics, and the demonstration of this concept's potential for improved feature detection in HDR data. Thereby, this study is a contribution to the search for transfer function designs that aid data perceptualization.

2 HAPTICS AND HIGH DYNAMIC RANGE DATA

Some types of volume data contain very high differences between their lowest and highest values, that is, they have a very high dynamic range. If the data's interesting features are known beforehand to be within a very limited part of the total range, then a normal transfer function adapted to that range is probably sufficient. Otherwise it might be impossible to design a single static TF that allows feature discrimination across the entire range. We here bring up issues regarding haptic HDR perceptualization that, to our knowledge, have not been discussed in previous research.

One such issue is to make the entire HDR accessible through the available force output range of the haptic device. Most likely, con-

*e-mail: petbi@itn.liu.se

†e-mail: gunho@ifm.liu.se

‡e-mail: matco@itn.liu.se

§e-mail: lenti@ike.liu.se

¶e-mail: andyn@itn.liu.se

veying the HDR is constrained by the maximum force output of the device. Also, the limitations of human perception need consideration. Even if the haptic device can deliver forces with high resolution, it is not certain that humans are able to perceive the differences through the sense of touch. Research on just noticeable differences (JND) in force has shown that a difference between forces of 10%-14% is required for distinction [1, 16]. Those studies were, however, based on forces felt in succession, and not continuous probing as is common with haptic volume rendering (HVR). Still, it is an indication of the limitations of haptic perception.

3 RELATED WORK

Protein-ligand docking through a virtual and haptic environment is a previously explored concept. The most well known example is probably the GROPE project, started at UNC Chapel Hill as early as the 1960's [5]. The GROPE project used volumetric grid maps to calculate the protein-ligand interaction force, and several subsequent systems have implemented similar techniques to enable haptic exploration of molecular data [19, 20, 23, 11, 4, 21]. Application of potential grid maps for docking has been validated through their use with automated docking systems in which a global energy minimization procedure is run, searching for the configuration that gives the ligand the lowest potential. AutoDock [7, 18, 17] is an example of an automated docking system, and it also produces the potential grid maps read by the Chemical Force Feedback (CFF) system, a haptic docking system presented in our previous research [4]. The CFF system was evaluated in the setting of a university course on biomolecular interactions and was found to influence how the students reasoned about the way molecules interact. In CFF, a static 1D transfer function was implemented to map the molecular force to the output of the haptic device.

Transfer functions have been extensively studied within graphical direct volume rendering (DVR). The basic functionality of the TFs is to decide coloration and transparency for different voxels, based on their data values. Different approaches have been developed also for multi-dimensional TFs in graphical DVR, using the TFs to enhance features in the data [9, 10].

In HVR, also called haptic DVR, transfer functions have become a common way to haptically perceptualize features in volumetric data. Two early examples using this approach are [2, 3]. To date, force TFs have been one-dimensional ($\mathbb{R} \rightarrow \mathbb{R}$), although they are sometimes combined to generate the final force output [8, 14, 13]. For example, one transfer function can control strength and another friction before the TFs' outputs are combined in accordance with a chosen force feedback model.

The study presented in [15] is one of the rare publications where the impact of different transfer functions on HVR is examined. In the study, which is based around a molecular docking example, two TFs are tested, one giving a hard surface experience on molecular contact, and one conveying a softer contact. Results did not show a statistical significance in favor of either transfer function. There was, however, a trend towards better accuracy using the soft contact version.

Despite the frequent use of transfer functions for haptic exploration of volumetric data, the design and utility of transfer functions in haptics has received much less attention than in graphical DVR. To our knowledge, there has been no research published in the area of haptic data exploration on either multi-dimensional transfer functions, or anything similar to a history dependent transfer function. Neither have we found publications illuminating the issue of using haptics to examine high dynamic range volume data.

4 METHOD

In our previous work [4] (see section 3), we used a static transfer function with non-linear transfer in the lower region of the force domain and linear transfer above a threshold magnitude of the input

force (see equations 1-3). Through this TF, hereafter referred to as the static square to linear transfer function or the static TF, the weak interactions are amplified while the strong interactions are still kept distinct. In this section we will first describe the square to linear transfer function in detail, followed by a description of the principles behind the history dependent transfer function. The latter parts of this section presents the evaluation-oriented design of test data sets and tasks, and how these were used to compare the feature detection performance of the HDTF against the static TF.

4.1 Static Square to Linear Transfer Function

After extensive testing of different static transfer functions, using qualitative assessments from experts in the biomolecular life sciences, the square to linear model was initially chosen for the CFF protein-ligand docking system [4]. The assessments stated that the transfer function produced acceptable force feedback and was easy to setup.

A suitable force domain must be defined for the static transfer function. In the case of protein-ligand docking the domain maximum (D_{max}) can be estimated either by manual exploration around a likely docking site, or by using the ligand structure for a regular sampling of the volumetric grid. In this work a domain of ($0 \leq x \leq D_{max}$) is used. The transfer function is designed to give a zero output force for a zero input force, a seemingly intuitive mapping considering the close coupling to a physical force phenomena in the docking case. The non-linear part of the TF is defined as:

$$f(x) = y_a - y_a \frac{(x - x_a)^2}{x_a^2} \quad (1)$$

Where y_a is the maximum of f and x_a is where in the domain that maximum occurs. The cutoff between the f -function and the linear part is controlled by the parameter x_b . After testing several different protein-ligand datasets in the static TF development process, it was determined from the experts' assessments that this parameter functions acceptably when set to approximately cover the lower 1%-15% of the domain. The linear part of the TF is defined as:

$$g(x) = \frac{y_b - f(x_b)}{D_{max} - x_b}x + f(x_b) - \frac{y_b - f(x_b)}{D_{max} - x_b} \cdot x_b \quad (2)$$

Where y_b is the g maximum value (at D_{max}). Equations 1 and 2 are combined into the complete static transfer function as:

$$t(x) = \begin{cases} f(x) & \text{for } x < x_b \\ g(x) & \text{for } x \geq x_b \end{cases} \quad (3)$$

The function defined in equation 1 describes a curve and has roots at zero and $2x_a$. By changing the parameters x_a and y_a the function's maximum and the rate of increase are easy to control. For values above x_b the transfer function turns into a linear function as described by equation 2. Normally the parameters x_a and x_b are equal, making the function go linear at the maximum of f , although that is not a requirement. For input values exceeding the domain (D_{max}) of the transfer function, the output value at the maximum of the domain will be used. Since there is no such thing as a negative magnitude of a force vector, the TF has no negative values. In our implementation the following requirements must also be fulfilled:

$$\begin{matrix} x_a \leq x_b & y_a \leq y_b \\ x_a < D_{max} & x_b < D_{max} \end{matrix} \quad (4)$$

4.2 History Dependent Transfer Function

Surveys administered to students in connection with the work presented in [4] indicated that the static square to linear TF performed reasonably, although there were suggestions that it could be improved. Some students expected a stronger guidance in the docking process, and while they claimed to be satisfied with the forces

Figure 1: Principle of the HDTF used in the test cases. Note that the F_{in} - and F_{acc} -axes have been mirrored to avoid visual occlusion.

delivered in the upper parts of the force domain, their comments especially contained criticism on the experience in the lower parts of the domain that cover the weaker intermolecular interactions.

Setting the transfer function to a high sensitivity in the lower domain can, however, cause other problems. One consequence is that as repulsive forces will increase over a shorter distance when the ligand is moved towards the protein surface, the surface will appear to have been moved outwards. Also, because the ligand binding sites are usually located in a pocket on the protein surface, and as the volume accessible for the ligand will be decreased with a higher sensitivity, the binding site might be rendered inaccessible if the passage into the binding site is narrow. A partial closing of the pathway to the binding site is a common phenomenon, for example in the ultra-high affinity binding interaction between the vitamin biotin and the protein streptavidin [22]. The history dependent transfer function was developed to improve the total force experience without constraining the utility of the system.

An HDTF can adapt to the currently explored part of the force domain. Thereby an HDTF has the ability to benefit from using more of the haptic device's force output range to represent the range of the data in the local environment of the probe. An alternative approach could be to perform a sampling around the probe, and adjust the transfer function settings based on some criteria applied from the sampling results. The development of this alternative solution and a possible comparative study will be left for future work.

The HDTF produces a force output magnitude (F_{out}) based on the current input force magnitude (F_{in}) and the input force history (F_{acc}). This means that the transfer function is two-dimensional, producing an $\mathbb{R}^2 \rightarrow \mathbb{R}$ mapping where one dimension is input force derived from the data, and the other is the value of accumulated input force magnitudes over a set time window, see figure 1.

On HDTF initialization a set number of 1D transfer functions are generated and distributed evenly along the F_{acc} axis, connecting a single transfer function to a segment on the F_{acc} domain. At run-time, the TF corresponding to the current accumulated force will be selected from the HDTF lookup table and set as active to deliver the adapted force output. Switching between TFs was set to occur with an interval matching the accumulation time window. Applying transfer function switching at high rates, for example at the approximate 1000Hz of the haptic loop, introduces a risk of instability in the force feedback. These instabilities could arise if there are dramatic changes in output force as a result of switching between two TFs with widely different settings. Accumulation time windows in the order of 1-3 seconds have been successfully used in prelimi-

Figure 2: Examples of a static TF (red line) and two possible transfer functions in an HDTF (green dashed and blue dotted lines), here showing overlap in the lower region of the domain.

Figure 3: Left: Illustration of the artificial test potential fields (see table 1). The blocks show the DISC field and the plane shows the GRAD field's structure, with potential increases represented by the colour gradient. Right: Screenshot from the docking application showing the AAL protein coloured by its secondary structure and a stick model of the ligand molecule in front of the docking site.

nary tests, and a window of 1.5 seconds was chosen for the tests presented in this paper (see section 4.3).

Since the evaluation presented in the present work (see section 4.4) related to the application area of protein-ligand docking, an adaptation of the previously developed and tested static TF was chosen for the HDTF example. This HDTF uses progressively larger fractions of the total F_{in} -domain, so that TFs that are active for low accumulated forces are set to cover a part of the lower domain while still using the full range of the HDTF's force output, see figure 1. For a large F_{acc} , the transfer functions cover a larger part of the total domain, and the threshold x_a, x_b (see equation 3) is adjusted accordingly, resulting in a TF that enables differentiation between features in higher parts of the domain, nevertheless benefiting somewhat from the non-linear part of the TF if moving too rapidly into an area of weaker forces.

Following the manner of the static TF, input values exceeding the domain (D_{max}) of the active transfer function produces the output of the current D_{max} . If using the mapping of higher output forces for higher inputs, this means that when a TF adapted to weak input forces is used, atom surfaces (high potential gradients) are still experienced as hard.

The transfer functions shown in figure 2 indicate how the HDTF

Table 1: Data for the test potential fields.

	Main block	Sub-block	Factor
High potential block	75000	56250	0.75
Low potential block	0.05	0.0625	1.25
Increase step	0.1	0.7	7
AAL potential ranges, lowest and highest	0-106218 0-329997	(Hydrogen) (Electrostatic)	

may improve feature detection and require less TF parameter adjustments. The example presented here is based on the static transfer function described in section 4.1, albeit the concepts could be applicable to other cases of static transfer functions. Examining figure 2, the red solid line illustrates a normal static transfer function and the green dashed line and the blue dotted line illustrate two different transfer functions of the HDTF in this example. While the static transfer function might enable a user to distinguish features in the lower parts of the domain, and also when F_{in} differs enough between samples in the higher parts of the domain, it does not perform as well as the HDTF once the static TF enters its linear segment. It can be seen that for two close F_{in} in the part of the domain where the static TF is linear and all the TFs overlap, the difference in force output is greater in both HDTF cases, thereby making features in the data easier to perceive. The level of difference required for feature detection when working with continuous exploration of volumetric data will be left for future work, although the work on JND might provide an indication (see section 2). Using an HDTF with transfer functions partially overlapping in the domain makes it more likely to have a well adapted TF active. Although TF setup is still an important part of the process, with the HDTF the system might become less dependent on manual fine tuning of the transfer function to ensure that sought features can be found.

4.3 Test System for Evaluation of the HDTF

To establish if the HDTF can deliver the predicted level of functionality in improved feature detection, an experimental test system was developed. In this system, test subjects interact with potential field volumes containing structural features consisting of distinct variations in an otherwise homogeneous field. The external boundaries of each structure have the shape of a block, and each block contains two internal boundaries, see figure 3. Two volumes were used, differing in the number of blocks and in the specific nature of the structure-defining potential field variations.

In one type of field, later referred to as DISC, structural boundaries were constructed strictly by introducing discontinuities in the potential fields. Each structure was made by positioning a large block of positive potential in a surrounding field with zero potential, and an internal structure was similarly created by changing the potential field value in a corner of the large block to a different value, thereby introducing two additional discontinuities in the block. Two such large blocks with different potential values were positioned in the volumetric grid. One block contained potential values resulting in a very low force, and the other block yielded a large force magnitude.

In the other field type, later referred to as GRAD, the structural boundaries consisted of both discontinuities and changes between different gradients in the potential field. A single large block was positioned in the volume, also bounded on all sides by discontinuities in the potential. The potentials inside the block increased along the Z-direction, giving a constant F_{in} . Internal structure was created by introducing a greater potential increase, forming a corner sub-block, see the plane in figure 3. Table 1 contains a summary of the potentials used in the test fields.

Table 2: Summary of transfer function parameters.

	Static TF	HDTF
Total data points	5 M	5 M
Total D_{max}	20000	20000
Threshold (x_a, x_b)	0.04	5% of the current domain
Output at threshold	1.5 N	1.5 N, for each TF
Output at D_{max}	3.0 N	3.0 N, for each TF
Accumulation time		1.5 s
Number of TFs		50000

Since part of the background to the development of the HDTF lies in its use within interactive virtual molecular docking, the potential field values in the test system were chosen to yield F_{in} magnitudes within a realistic range in relation to a typical protein-ligand docking task, in this case docking of L-fucose (a carbohydrate molecule) to a lectin protein from the fungus *Aleuria aurantia* (AAL) [24]. The range of the AAL potentials presented in table 1 are significantly higher than those in the test fields because some grid points are very close to the center of atoms in the protein. However, the highest parts of these potentials are not relevant for the docking case as they represent almost complete overlap of atoms. Instead, the potential range for the test cases was determined by extensive manual probing during a docking to AAL and should thereby provide a reasonable comparison to a real docking case.

Since a previously identified issue was the exploration in the lower parts of the potential range, it was decided that the static transfer function should be very steep and have a high resolution. Thus, the static TF was given conditions that should allow for detection of features in the low potentials, see table 2.

The high number of data points in the transfer function is needed to get a reasonable density in the part of the static TF that transfer the fine-grained weak forces, while still covering such a large force domain. This is especially apparent in the non-linear segment, otherwise the number of samples in that region would be inadequate, even though values are interpolated on transfer. A consequence of the high number of samples in this example is a large number of redundant data points in the linear part of the transfer function, where a linear interpolation would suffice.

The test system is less complex than real docking cases. A single point probe is used to interact with potential fields of low complexity. This can be compared to protein-ligand docking, where the force experienced is determined by the sum of the forces on each atom in the ligand (commonly containing 5-20 atoms), and the potential fields are highly non-linear. The visual scene in the test system is also simplified, only containing a cube made up by red lines indicating the potential grid's bounding box, and a short bar representing the point probe. The block structures are not rendered visually. In the docking case, the scene consists of the protein which can be displayed using a set of representational modes, and the ligand visualized using a stick model (see figure 3).

4.4 Evaluation

The HDTF was evaluated using artificial test data and in a realistic application example. For the artificial data, a set of tasks were designed to test whether subjects could detect features in the data, both in the low and in the high range of force magnitudes and using both the static TF and the HDTF. A detailed set of instructions was used to make the experience as similar as possible between test subjects, and the tests were supervised to ensure that the subjects followed the test instructions.

The subjects were instructed to use the CFF system, in a semi-immersive desktop workbench with stereo graphics and a SensAble Technologies PHANTOM Desktop haptic device, to locate an ob-

ject in the potential field volume and examine its shape and size. Then they were instructed to slowly move the probe through the object from the back of the block towards themselves, and to report if they could detect any internal structures. This procedure was repeated on both the right and the left half of the block, and they decided themselves which side to start with. Thus the subjects moved the probe across a block in the volume that contained an internal boundary in one half, and no internal boundary in the other half. In the case of the potential field that contained two blocks (DISC), they were instructed to repeat the procedure for the second block.

Combining the two types of potential field volumes and the two types of TFs (the static transfer function will be referred to as STF) yields four different test conditions: DISC/HDTF, DISC/STF, GRAD/HDTF, and GRAD/STF. Because the order of the conditions might introduce biases in the form of learning effects, haptic after effects and fatigue, the sequence of test conditions was varied between subjects. A reduced set of the $4! = 24$ possible permutations was used, consisting of 16 task sequences in which the field type was changed between the first and the second task. For example, if the first test involved the DISC potential field, then the second test involved the GRAD potential field. Thus, each test subject experienced at least two switches in potential field type over the four tasks. This was done to minimize potential order effects for a limited number of test subjects (less than 24).

Data on the subjects' performance on the tasks described above were collected using an observation approach. In the instructions for the tasks, the subjects were asked to make verbal responses to the monitoring researcher. Specifically, they were asked to indicate if they could detect any internal structure in the blocks, and the responses were recorded manually by the researcher. The time required to complete each task was also recorded, but the subjects were informed of the fact that there were no time limitations. After collecting the data, the response for each block was coded as a successful feature detection if the internal structure was correctly detected, or unsuccessful if detection failed. If a subject reported an internal structure in both halves of the block, the response was coded as successful if indicating a more distinct structure in the part of the block corresponding to the true position of the internal structure, otherwise it was coded as unsuccessful.

A survey was performed to gather additional data about the subjects and their experiences in performing the tasks. Background information was collected about each subject's age, sex and previous experience using haptic devices. Further queries concerned difficulties in performing the tasks, understanding the instructions, if there were technical problems with the haptic device or the visual display, and the subjects' overall attitudes to using the system.

The test tasks with the artificial data were performed by 16 volunteering subjects recruited from various sources. A majority were employees of the Department of Science and Technology at Linköping University, but some external test subjects were also involved. There were 4 females and 12 males, and the age span was between 25 and 58, with a mean age of 33. The subjects varied a lot with respect to their experience level of using haptics, ranging from those trying haptics for the first time to experts with several years of experience. A heterogeneous test group, containing subjects of different ages and experience levels, could be beneficial as the HDTF potentially has a wide variety of application areas and end users.

As a realistic application test of the HDTF, a protein-ligand docking task was performed by three additional subjects, all biochemistry experts from Linköping University. They were asked to dock an L-fucose ligand to a binding site on a lectin protein (AAL, see section 4.3) [24]. An informal interview was conducted during the task to probe the users for their experience of the docking application, giving a qualitative insight into the potential value of the HDTF for protein-ligand docking tasks.

5 RESULTS

In general, the test subjects considered the test experience to be positive, and there were very few technical problems or difficulties in performing the tasks. In the cases where problems were reported, some related to minor problems with stereo vision, and others concerned slight vibrations at the boundaries of the blocks in the test tasks. This kind of instability at higher forces is a well known artifact in non-proxy based volume haptics, and all subjects were still able to complete all tasks. The time taken to complete the tasks varied among test subjects, between 8 and 29 minutes, with a mean value of 14 minutes. Most likely, the subjects performed the tasks in a comfortable tempo and did not experience a time pressure, as indicated by the large variation in time.

For the DISC/HDTF condition, feature detection was achieved by all subjects. Similarly, in the DISC/STF condition, feature detection was accomplished by all subjects in the high range of force magnitude, and by a majority (13/16) in the low range of force magnitude. In the GRAD/STF condition, only two subjects reported feature detection. Interestingly, these subjects falsely found features in both parts of the block. These two cases were the only false positive responses encountered. As one subject reported a stronger feature in the correct part, using the coding scheme (see section 4.4) this detection was coded as successful and the other subject's as unsuccessful. By contrast, all 16 subjects correctly detected the feature in the GRAD/HDTF condition.

The expert panel contributed information about the performance of the HDTF in a real, complex docking situation. They found the docking task to be a positive experience, and did not report any negative effects of the HDTF. The relatively weak attractive forces were readily detected, and in general their experience of the force feedback compared well with their expectations. One aspect of the system was reported to deviate from their expectations, in that it does not provide a feature that facilitates the final adjustments of the ligand's orientation to obtain a perfect docking. This was due to the lack of torque feedback, a feature which is implemented in the application but requires a six degrees of freedom haptic device. It was noted that, when the ligand was pushed against the wall of the protein for some time, the HDTF adapted as predicted and allowed a temporary interpenetration of the atoms in the ligand and the protein surface, accompanied by a corresponding temporary decrease in sensitivity towards the weak attractive forces.

6 CONCLUSIONS AND FUTURE WORK

In this paper we have presented the principles of a History Dependent Transfer Function for haptic volume rendering and demonstrated its application to high dynamic range data in the area of haptic protein-ligand docking. Feature detection tests have been performed with positive results, indicating that the HDTF improves the ability of feature detection in the volume data as compared to a static transfer function covering the same range.

The HDTF also performed well in a realistic haptic docking, and allowed both examination of weak attractive forces and movement through high-force trajectories. The latter feature means that a wide range of protein-ligand binding systems with partially closed binding sites have been made available for potential use in haptic docking systems with rigid protein models, without sacrificing sensitivity in the low force range.

Some subjects were unable to detect the low force feature in the DISC/STF condition, while all subjects managed this in the DISC/HDTF condition. This is likely an effect of the HDTF's adaptability, giving a slightly higher sensitivity in this range with the current parameter settings. Using the GRAD field, the success rate in feature detection was clearly in favor of the HDTF. This indicates that when using the HDTF a higher sensitivity can be achieved in the low as well as in the intermediate range of force magnitudes. If adapted to enhance differences in the high range, the

HDTF seems likely to reach the same results in that part of the force domain. Thus, an HDTF is efficient over a larger dynamic range compared with a static transfer function, allowing the opposing requirements of high sensitivity in widely differing force magnitude ranges to be accommodated in one force feedback system.

Moving rapidly between areas giving low F_{in} and areas with high F_{in} will result in an intermediate F_{acc} , thereby activating a TF that may not be optimal (or appropriate) for transfer of the current F_{in} . Also, discontinuities in the force feedback might be perceived if switching occurs between two widely different TFs. However, no effects arising from these potential drawbacks of the HDTF have been noted by the test subjects. This seems to indicate that if presented with proper instructions, making the user aware of this effect, and with human fine-grain searches naturally being carried out slowly, the force accumulation principle works well.

Although the example described in the present work is focused around a case using a specific static transfer function and its subsequent use in a history dependent transfer function, the application of the HDTF model is general and can be used to switch between arbitrary transfer functions based on any numerically based switching criteria. For example, an HDTF can be designed using identically shaped TFs, thereby retaining the same slope as TFs adapted for different regions of the F_{in} domain are activated.

There is a lack of published research about multi-dimensional transfer functions in volume haptics, a research area with growth potential considering the amount of publications about TFs in graphical volume rendering. Being speculative, one reason for this difference can be that graphical volume rendering has grown dramatically and matured as a research field, whereas research on haptic exploration of volumetric data still has a long way to go.

Further research concerning transfer functions and HVR is needed if connections between feature detection, limitations in human perception and haptic equipment are to be fully understood. For example, the force ranges optimal for human feature detection could be investigated to establish if there are benefits in mapping data to certain output ranges of the haptic devices. The two false feature detections reported could be a result of influence on force perception from factors other than the actual force fed through the device. Also, further development and comparisons of multi-dimensional and adaptive transfer functions could contribute to the HVR field as it has to the progress of the graphical DVR field.

ACKNOWLEDGEMENTS

This work was funded by the Swedish Research Council, grant number 2003-4275.

REFERENCES

- [1] S. Allin, Y. Matsuoka, and R. Klatzky. Measuring just noticeable differences for haptic force feedback: Implications for rehabilitation. In *Proceedings of the 10th symposium on haptic interfaces for virtual environments & teleoperator systems (HAPTICS02)*, 2002.
- [2] R. S. Avila and L. M. Sobierajski. A haptic interaction method for volume visualization. In *Proceedings of the 7th conference on Visualization '96*, pages 197–204. IEEE Computer Society Press, 1996.
- [3] W. A. Aviles and J. F. Ranta. Haptic interaction with geoscientific data. In *Proceedings of the Fourth PHANTOM Users Group Workshop*, November 1999.
- [4] P. Bivall Persson, M. D. Cooper, L. A. Tibell, S. Ainsworth, A. Ynnerman, and B.-H. Jonsson. Designing and evaluating a haptic system for biomolecular education. In *Proceedings of IEEE Virtual Reality 2007*, pages 171–178, Charlotte, NC, USA, March 2007. IEEE.
- [5] F. P. Brooks Jr., M. Ouh-Young, J. J. Batter, and P. J. Kilpatrick. Project GROPE - haptic displays for scientific visualization. In *SIGGRAPH '90: Proceedings of the 17th annual conference on Computer graphics and interactive techniques*, pages 177–185, New York, NY, USA, 1990. ACM Press.

- [6] B. Daunay, A. Micaelli, and S. Rgnier. 6 dof haptic feedback for molecular docking using wave variables. In *2007 IEEE International Conference on Robotics and Automation*, pages 840–845, April 2007.
- [7] D. S. Goodsell and A. J. Olson. Automated docking of substrates to proteins by simulated annealing. *Proteins: Structure, Function, and Genetics*, 8(3):195–202, 1990.
- [8] M. Ikits, J. D. Brederson, C. D. Hansen, and C. R. Johnson. A constraint-based technique for haptic volume exploration. In *IEEE Visualization 2003 (VIS 2003)*, pages 263–269, October 2003.
- [9] J. Kniss, G. Kindlmann, and C. Hansen. Multidimensional transfer functions for interactive volume rendering. *IEEE Transactions on Visualization and Computer Graphics*, 8(3):270–285, July-Sept 2002.
- [10] J. Kniss, S. Premoze, M. Ikits, A. Lefohn, C. Hansen, and E. Praun. Gaussian transfer functions for multi-field volume visualization. In *Proceedings of the 14th IEEE Visualization Conference (VIS'03)*, pages 497–504, 2003.
- [11] S. K. Lai-Yuen and Y.-S. Lee. Computer-aided molecular design (camd) with force-torque feedback. In *Ninth International Conference on Computer Aided Design and Computer Graphics*, pages 199–204, Los Alamitos, CA, USA, December 2005. IEEE Computer Society.
- [12] Y.-G. Lee and K. W. Lyons. Smoothing haptic interaction using molecular force calculations. *Computer-Aided Design*, 36(1):75–90, January 2004.
- [13] K. Lundin, M. Cooper, A. Persson, D. Evestedt, and A. Ynnerman. Enabling design and interactive selection of haptic modes. *Virtual Reality*, 11(1):1–13, March 2007.
- [14] K. Lundin, C. Lundström, M. Cooper, and A. Ynnerman. Enabling haptic interaction with volumetric mri data through knowledge-based tissue separation. In *Proceedings of the International Workshop on Volume Graphics 2006*, pages 75–78, 2006.
- [15] R. Maciejewski, C. Seungmoon, D. S. Ebert, and H. Z. Tan. Multi-modal perceptualization of volumetric data and its application to molecular docking. In *Proceedings of the 2005 World Haptics Conference (WHC05)*, pages 511–514, Pisa, Italy, March 2005.
- [16] Y. Matsuoka, S. J. Allin, and R. L. Klatzky. The tolerance for visual feedback distortions in a virtual environment. *Physiology & Behavior*, 77:651–655, 2002.
- [17] G. M. Morris, D. S. Goodsell, R. S. Halliday, R. Huey, W. E. Hart, R. K. Belew, and A. J. Olson. Automated docking using a lamarckian genetic algorithm and an empirical binding free energy function. *Journal of Computational Chemistry*, 19(14):1639–1662, 1998.
- [18] G. M. Morris, D. S. Goodsell, R. Huey, and A. J. Olson. Distributed automated docking of flexible ligands to proteins: Parallel applications of autodock 2.4. *Journal of Computer-Aided Molecular Design*, 10(10):293–304, 1996.
- [19] M. Ouh-young, M. Pique, J. Hughes, N. Srinivasan, and F. P. Brooks Jr. Using a manipulator for force display in molecular docking. In *Proceedings of IEEE Robotics and Automation Conference 3*, pages 1824–1829, Philadelphia, USA, April 1988.
- [20] G. Sankaranarayanan, S. Weghorst, M. Sanner, A. Gillet, and A. Olson. Role of haptics in teaching structural molecular biology. In *Proceedings of the 11th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems (IEEE HAPTICS'03)*, pages 363–366, Los Angeles, CA, USA, March 2003.
- [21] E. Subasi and C. Basdogan. A new haptic interaction and visualization approach for rigid molecular docking in virtual environments. *Presence: Teleoperators and Virtual Environments*, 17(1):73–90, 2008.
- [22] P. C. Weber, D. H. Ohlendorf, J. J. Wendoloski, and F. R. Salemme. Structural origins of high-affinity biotin binding to streptavidin. *Science*, 243:85–88, 1989.
- [23] S. Weghorst. Augmented tangible molecular models. In *IWSM'03-'04: The Fourth International Workshop on Spatial Media and the Sixth International Conference on Humans and Computers*, Aizu-Wakamatsu, Fukushima-ken and Tokyo, Japan, August 2003.
- [24] M. Wimmerova, E. Mitchell, J.-F. Sanchez, C. Gautier, and A. Imbert. Crystal structure of fungal lectin. *The Journal of Biological Chemistry*, 278:27059–27067, 2003.
- [25] A. M. Wollacott and K. M. Merz Jr. Haptic applications for molecular structure manipulation. *Journal of Molecular Graphics and Modelling*, 25(6):801–805, March 2007.