Learning Molecular Interaction Concepts through Haptic Protein Visualization

Petter Bivall Persson*
Department of Science and Technology, Linköping University, Sweden

Abstract

The use of haptics is growing in the area of science education. Haptics appears to convey information to students in a manner that influences their learning and ways of thinking. This document outlines examples of how haptics has been employed in science education contexts and gives a more detailed description of an education oriented evaluation of a haptic protein-ligand docking system.

In molecular life science, students need to grasp several complex concepts to understand molecular interactions. Research on how haptics influences students' learning show strong positive affective responses and, in the protein-ligand docking case, that reasoning with respect to molecular processes is altered. However, since many implications of using haptics in education are still unknown, more research is needed.

CR Categories: 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; K3.1 [Computer Uses in Education]: Computer-assisted instruction— [H.3.4]: Systems and Software—Performance evaluation (efficiency and effectiveness)

Keywords: haptics, molecular visualization, science education research, protein-ligand docking

1 Introduction

Molecular bioscience employs the widespread use of visual representations that range from sketches to advanced computer graphics (CG). There is a need to convey abstract knowledge and to conceptualize complex three-dimensional relationships within and between molecules. However, recent research suggests that students have great difficulty understanding these concepts, despite the use of visualizations aimed at making concepts more comprehensible [Wu et al. 2001].

To investigate the challenges and possibilities of utilizing haptics in life science, we have developed a haptic protein-ligand docking application called Chemical Force Feedback (CFF), which allows the user to manipulate the ligand (a small molecule) and feel its interactions with the protein in the docking process.

The CFF system was developed and evaluated in a collaborative and inter-disciplinary research effort, involving the author, Anders Ynnerman (Prof.) and Matthew D. Cooper (Senior Lecturer) at the Department of Science and Technology, Lena Tibell (Associate Prof.) at the Department of Clinical and Experimental Medicine, Bengt-Harald Jonsson (Prof.) and Gunnar Höst (PhD) at the Department of Physics, Chemistry and Biology, all of the above working at Linköping University, and Shaaron Ainsworth (Associate Prof.) in the School of Psychology at the University of Nottingham.

The next sections include a general description of haptic protein-ligand docking and briefly overviewing examples showing how haptics has been employed within science education. This is followed by a more detailed description of the education oriented evaluation of the CFF system and its results.

2 Haptic Protein-Ligand Docking

In 1967 the GROPE project [Brooks Jr. et al. 1990; Ouh-young et al. 1988] started their research on using haptic feedback to convey molecular interaction forces. The project evolved to include protein-ligand docking in its third version, GROPE III. Since then, several haptic protein-ligand docking systems have been developed and presented in research publications, for example [Sankaranarayanan et al. 2003; Weghorst 2003; Lee and Lyons 2004; Lai-Yuen and Lee 2005; Bivall Persson et al. 2007; Wollacott and Merz Jr. 2007; Daunay et al. 2007; Subasi and Basdogan 2008]. However, most studies do not discuss the explicit use of haptics in educational settings and extensive evaluations are very rare.

In protein-ligand docking the user, or an automated docking simulation, searches for the configuration of the ligand that place it in a global energy minimum. This is a difficult minimization problem with $6 + n$ degrees of freedom, 6 for position and orientation and n for the number or rotational bonds in the ligand. Basically, the energy can be calculated by pairwise atom-atom interactions, but the high number of atoms in most proteins makes that approach unfeasible in haptic systems as they require high update rates (approximately 1kHz). The most common approach used to achieve the required update rate is to use static potential grid maps that represent the potential field of the protein as volumetric data. Forces acting on the atoms in the ligand can be derived from the gradient of the potential field, making computational speed constrained by the number of atoms in the ligand alone. There have been attempts to include dynamic models of proteins, most of which struggle with computational speed that limits the number of atoms that can be used in the molecules. However, as models for molecular dynamics and processor speeds continue to improve, the docking systems will move toward full real-time simulations.

3 Haptics in Science Education Contexts

Novel technology can provide possibilities for new approaches in teaching and learning. Biology and chemistry education has embraced visualization technology as it is expected to aid the understanding of molecular structure and interaction. However, there is still a lot of work to be done to investigate which types of representations best convey information about molecular life science, and in determining the conditions for beneficial use of haptic and visual applications in education. Research regarding the use of haptics in educational settings seems to conclude that force feedback can ease the understanding of a variety of complex processes, especially when dealing with concepts that include elements of forces we handle in our everyday life, or when the mapping between the studied phenomenon and force is intuitive [Křenek et al. 1999]. Also, Druyan [Druyan 1997] has shown that and the ability to use kinaesthetics may help in grasping concepts concerning physical phenomena. A review of the research done to investigate the efficacy of haptics in education is presented in [Minogue and Jones 2006] and in the remainder of this section there will be a short presentation of examples where haptics has been used in education.

Reiner [Reiner 1999] investigated students' understanding and development of force concepts during interaction with a system that provided 2D visual and tactile feedback, allowing learners to feel different force fields. Results of the study suggested that the hap-

---

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

tic feedback induced learners to construct representations of forces that were closely related to the representations of formal physics.

Jones et al. [Jones et al. 2003; Jones et al. 2006] investigated how the use of haptics influences students' interpretation of viruses at the nanoscale. Their research showed that haptics influences learners' construction of concepts and their level of engagement. Students exposed to haptics used more affective terms, expressing that they were more interested in the subject and that they felt like they could participate more fully in the experience. These affective responses can be very important in learning contexts.

Another example where haptics appears to aid the understanding of a complex concept is presented in [Harvey and Gingold 2000], where an electron density function (an $R^3 \rightarrow R$ function) is used as basis for the generated force feedback. It is stated that the electron density function is hard for students to grasp, and that images do not suffice, often leading to misconceptions because a representation of the function requires four dimensions. Haptics is found to ease understanding and avoid oversimplifications by translating the fourth dimension to force.

In [Sankaranarayanan et al. 2003; Weghorst 2003] an application of augmented reality is presented, mixing a physical molecular model with CG. The system described consists of three major parts: augmented reality (AR), a voice command interface and force feedback. Haptics appears to provide a natural and intuitive method for representing the interaction between molecules, voice commands enables more focus on the model and less on the computer interface, and the combination of a physical model and CG through augmented reality is an attempt to take advantage of the best of two worlds, the physical and the virtual.

Tests with a few cases are presented, for example a physical model of the HIV protease augmented with CG generated inhibitors, and a physical protein model combined with visualization of its potential field. A lesson plan was created to evaluate the usefulness of the model in teaching, and an assessment was performed with a biology class. The assessment shows the model to be engaging and instructive and the AR model is received by both scientists and students as being very intuitive. However, a more developed lesson plan is required for it to be more effective.

4 A Haptic Docking System Evaluated In situ

In [Bivall Persson et al. 2007] we presented an evaluation of the CFF haptic docking system. We used a combined quantitative and qualitative assessment in an *in situ* learning situation, placing focus on the quality of learning and understanding of the molecular interactions. The aim was to evaluate the CFF system's features, its interface and usability, but specifically to explore the impact of haptics on students' performance and learning, investigating what the haptic modality adds to a visual 3D protein structure representation in this context.

The study was performed with life science and engineering students enrolled in a course at Linköping University, called *Biomolecular interactions*. The course deals with the interactions between proteins and ligands, factors determining structure recognition and the dynamics of molecular exchange. To understand these processes the students have to grasp several concepts of varying complexity, for example molecular structure, affinity, specificity, energy levels, binding, molecular dynamics and transition state. Students carried out computer based lab exercises using the CFF haptic environment. The labs were a compulsory part of the course, although participation in the research was voluntary.

4.1 Test Design

A partial cross-over test design was employed, partly because of the limited number of students (13 females and 10 males). The subjects were divided into two groups, *0/H* and *H/0*, according to gender and score on an initial domain knowledge test, aiming at an even distribution with respect to gender and achievement levels. The group names include a condition coding where *0* denotes no haptics and *H* indicate active haptic feedback.

In two lab tasks the students were required to attempt to find the best docking to the enzyme *human carbonic anhydrase II*, using ligands that produced different force binding strengths to the enzyme. Both groups performed the labs with the CFF system but the *H/0* group performed the first task (*Task IS*) with force feedback enabled, whereas it was disabled for the *0/H* group. For the second task (*Task TS*) the condition between the groups was reversed. Both groups were probed according to the following time-line:

1. Background survey
2. Pre-test Task IS
3. Lab exercise IS
4. Post-test Task TS
5. Items 2-4 repeated for Task TS
6. Experience survey
7. Interview with a subset of students

Pre- and post-tests were designed to enable a measure of the cognitive gain from the use of the haptic representation. Additionally, written answers to the lab tasks were available for qualitative analysis, and a subset of the students were chosen (based on achievement levels) for semi-structured clinical interviews [Ginsburg 1997; Kvale 1996]. Interviews were centred on cognitive understanding, affective factors and opinions, as well as on meaning making and the use of the haptic representation while solving a docking problem.

To ensure a reliable assessment of responses to lab tasks as well as to pre- and post-tests, two teachers/scientists individually marked the students' answers. The equally assessed responses covered more than 95% of the total, indicating a strong reliability consistency. Reasoning in the task responses and interviews was analyzed using analytical induction, a process involving repeated readings of the responses and interview transcripts, focusing on key terms of the subject.

The students' docking performance was scored by comparison with automated docking results (as calculated by AutoDock [Goodsell and Olson 1990; Morris et al. 1996; Morris et al. 1998]) using a Root-Mean-Square error (RMS, expressed in Ångström), a common technique used to compare alignment of molecules.

4.2 Results of the Study

Survey data showed that the affective responses to the docking experience was clearly positive and that students found the haptic feedback to be helpful. Interviewed students also expressed that the haptic system aided their understanding by allowing them to connect different parts of their knowledge in a more coherent way.

By comparing scores on the students' pre- and post-tests it was found that the students learned from their experience with the CFF system. However, the scores did not reveal a significant difference between the conditions (*H/0, 0/H*). Reasoning, on the other hand, was influenced by the condition as students using haptics showed more reasoning regarding forces and dynamics.

5 Conclusion

Based on the low number of cases where haptics has been applied in science education, it can be argued that there is a lack of empirical evaluations performed in educational settings, a conclusion also reached in [Minogue and Jones 2006].

The examples presented in section 3 provide an indication for how haptics can be beneficial in learning situations. Our study also shows that the implications go somewhat beyond mere speed gains and positive affective responses and induce new ways of reasoning. Nevertheless, the use of haptics in education is largely an uncharted territory and further research is required to understand how haptics should be applied to support learning and teaching.

References

BAYAZIT, O. B., SONG, G., AND AMATO, N. M. 2000. Ligand binding with obprm and haptic user input: Enhancing automatic motion planning with virtual touch. Tech. Rep. TR00-025, Department of Computer Science, Texas A&M University, Texas, USA, October.

BIVALL PERSSON, P., COOPER, M. D., TIBELL, L. A., AINSWORTH, S., YNNERMAN, A., AND JONSSON, B.-H. 2007. Designing and evaluating a haptic system for biomolecular education. In *Proceedings of IEEE Virtual Reality 2007*, IEEE, 171–178.

BROOKS JR., F. P., OUH-YOUNG, M., BATTER, J. J., AND KILPATRICK, P. J. 1990. Project GROPE - haptic displays for scientific visualization. In *SIGGRAPH '90: Proceedings of the 17th annual conference on Computer graphics and interactive techniques*, ACM Press, New York, NY, USA, 177–185.

DAUNAY, B., MICAELLI, A., AND RGNIER, S. 2007. 6 DOF haptic feedback for molecular docking using wave variables. In *2007 IEEE International Conference on Robotics and Automation*, 840–845.

DRUYAN, S. 1997. Effect of the kinesthetic conflict on promoting scientific reasoning. *Journal of Research in Science Teaching 34*, 10 (December), 1083–1099.

GINSBURG, H. P. 1997. *Entering the Child's Mind: The Clinical Interview In Psychological Research and Practice*. Cambridge University Press, Cambridge.

GOODSELL, D. S., AND OLSON, A. J. 1990. Automated docking of substrates to proteins by simulated annealing. *Proteins: Structure, Function, and Genetics 8*, 3, 195–202.

HARVEY, E., AND GINGOLD, C. 2000. Haptic representation of the atom. In *Proceedings of the International Conference on Information Visualisation 2000*, 232–235.

JONES, M. G., ANDRE, T., SUPERFINE, R., AND TAYLOR, R. 2003. Learning at the nanoscale: The impact of students' use of remote microscopy on concepts of viruses, scale, and microscopy. *Journal of Research in Science Teaching 40*, 3 (March), 303–322. Haptic feedback, physical paper and clay models.

JONES, M. G., MINOGUE, J., TRETTER, T. R., NEGISHI, A., AND TAYLOR, R. 2006. Haptic augmentation of science instruction: Does touch matter? *Science Education 90*, 1 (January), 111–123.

KVALE, S. 1996. *InterViews: An Introduction to Qualitative Research Interviewing*. Sage Publications, Inc, Thousand Oaks.

KŘENEK, A., ČERNOHORSK, M., AND KABELČ, Z. 1999. Haptic visualization of molecular model. In *WSCG'99 Conference Presentation*, V. Skala, Ed., vol. 1, 133–139.

LAI-YUEN, S. K., AND LEE, Y.-S. 2005. Computer-aided molecular design (camd) with force-torque feedback. In *Ninth International Conference on Computer Aided Design and Computer Graphics*, IEEE Computer Society, Los Alamitos, CA, USA, 199–204.

LEE, Y.-G., AND LYONS, K. W. 2004. Smoothing haptic interaction using molecular force calculations. *Computer-Aided Design 36*, 1 (January), 75–90.

MINOGUE, J., AND JONES, M. G. 2006. Haptics in education: Exploring an untapped sensory modality. *Review of Educational Research 76*, 3, 317–348.

MORRIS, G. M., GOODSELL, D. S., HUEY, R., AND OLSON, A. J. 1996. Distributed automated docking of flexible ligands to proteins: Parallel applications of autodock 2.4. *Journal of Computer-Aided Molecular Design 10*, 10, 293–304.

MORRIS, G. M., GOODSELL, D. S., HALLIDAY, R. S., HUEY, R., HART, W. E., BELEW, R. K., AND OLSON, A. J. 1998. Automated docking using a lamarckian genetic algorithm and an empirical binding free energy function. *Journal of Computational Chemistry 19*, 14, 1639–1662.

NAGATA, H., MIZUSHIMA, H., AND TANAKA, H. 2002. Concept and prototype of protein-ligand docking simulator with force feedback technology. *Bioinformatics 18*, 1, 140–146.

OUH-YOUNG, M., PIQUE, M., HUGHES, J., SRINIVASAN, N., AND BROOKS JR, F. P. 1988. Using a manipulator for force display in molecular docking. In *Proceedings of IEEE Robotics and Automation Conference 3*, 1824–1829.

REINER, M. 1999. Conceptual construction of fields through tactile interface. *Interactive Learning Environments 7*, 1 (April), 31–55.

SANKARANARAYANAN, G., WEGHORST, S., SANNER, M., GILLET, A., AND OLSON, A. 2003. 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)*, 363–366.

SUBASI, E., AND BASDOGAN, C. 2008. A new haptic interaction and visualization approach for rigid molecular docking in virtual environments. *Presence: Teleoperators and Virtual Environments 17*, 1, 73–90.

WEGHORST, S. 2003. Augmented tangible molecular models. In *IWSM'03-'04: The Fourth International Workshop on Spatial Media and the Sixth International Conference on Humans and Computers*.

WOLLACOTT, A. M., AND MERZ JR., K. M. 2007. Haptic applications for molecular structure manipulation. *Journal of Molecular Graphics and Modelling 25*, 6 (March), 801–805.

WU, H.-K., KRAJCIK, J. S., AND SOLOWAY, E. 2001. Promoting understanding of chemical representations: Students' use of a visualization tool in the classroom. *Journal of Research in Science Teaching 38*, 7 (September), 821–842.