FEELING MOLECULAR FORCES:

TACTILE FEEDBACK TO ENHANCE DRUG DESIGN

A Senior Honors Thesis

By

JOCYLIN AMBER WILLIAMS

Submitted to the Office of Honors Programs
& Academic Scholarships
Texas A&M University
In partial fulfillment of the requirements of the

UNIVERSITY UNDERGRADUATE
RESEARCH FELLOWS

April 2000

Group: Computer Science

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ABSTRACT

FEELING MOLECULAR FORCES:

TACTILE FEEDBACK TO ENHANCE DRUG DESIGN. (April 2000)

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Molecular modeling is a vital component for structure-based drug design. Currently implemented technology combines data and graphics to give the user visual capabilities to assist in discovering possible binding arrangements. Visual modeling has become a tremendous help to scientists in reducing the amount of time needed to create new inhibitory compounds. However, the visual medium used for modeling lacks the ability to convey the forces between the molecules to the user. Potentially, tactile feedback can provide this missing information. SensAble Devices has developed a device capable of producing force feedback to a user-defined environment called the PHANToM, The PHANToM is a 6 dimensional (3 translational and 3 rotational) haptic device that can return force and torque to the user through a hand held stylus.

The system configuration for molecular modeling consists of integrating the haptic device with a high-end PC running Windows NT and developing

code to model the intermolecular forces. The programming language used was C with some C^{++} constructs and the OpenGL graphics library for the graphics implementation. The optimized code running with the system has proven capable of calculating and relaying tactile feedback between a 100-atom active site of a protein and a small 15-atom inhibitor in real time (ca. 1 millisecond).

Trials are now underway on the system to evaluate accuracy and explore other forms of useful output. Once this is accomplished, modeling will be done on an active site and an untested inhibitor to evaluate novel binding modes.

To Stan, who revived my curiosity.

ACKNOWLEDGEMENTS

I would like to thank the Undergraduate University Fellows Program for the opportunity to participate in the program. I also want to thank Dr. Stanley Swanson, Prof. Edgar Meyer, Osman Burchen Bayazit and Prof. Nancy Amato for their helpful suggestions and support.

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INTRODUCTION

Computer graphics methods are a key component of the spectacular success of structure-based drug design. They make it possible to visualize molecular structures and interactions in three-dimensions. Despite all their strengths, these methods still only utilize the visual capabilities of the investigator. A case can be made that as other human senses are utilized in the design process, the chance for conceiving, docking, and evaluating a novel compound (for example a drug, inhibitor, or ligand) is substantially increased [1-4].

The idea of integrating instant tactile feedback of molecular interactions into molecular modeling has intrigued scientists since the mid 1980's [5], but technological limits in hardware speed, equipment size and graphic resolution have prevented practical tools from being developed [6]. Cutting edge technology lends itself to realizing the virtual dream by integrating a novel input/output device, the PHANToM, (refer to Figure 1) with a top of the line PC running Windows NT.

The purpose of the project is to set up the haptic/PC system to relay real time tactile feedback of the intermolecular forces between a protein and substrate to the user. The initial goals of the project consist of developing C code to calculate the intermolecular forces, integrating the hardware and software, and modelling known binding configurations with the system. The

This thesis follows the style and format of Journal of Computer-Aided Molecular Design.

ultimate goal is to facilitate modeling an active site of a protein and docking an untested inhibitor to explore novel binding possibilities.

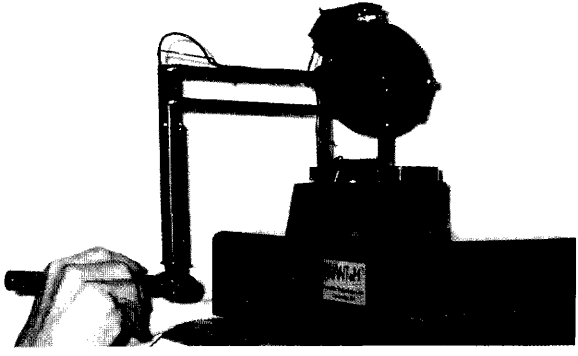

Figure 1. The PhANToM Haptic Device. The PHANToM haptic device provides tactile feedback with 6 degrees of freedom. It provides the force feedback to the user by a stylus attached to three torque motors. The stylus position is associated with a cursor on the screen, which can be set to represent an object under investigation. The cursor then interacts with a user-defined environment that returns the force interactions to the PHANToM.

METHODS

The combination of hardware was chosen because of accessibility, proven effectiveness and the availability of experts who are familiar with the systems. The PHANToM haptic device (by SensAble Devices, Inc., Cambridge, MA) is made available for the project by Professor Nancy Amato in the Department of Computer Science at Texas A&M University. A version of the device with three degrees of freedom has already proven its usefulness by modeling the atomic force manipulation of nanotubes [7]. Thus, the device is amenable to adaptation to molecular modeling. The choice of PC, a 550 MHz Pentium III Xeon HP Kayak running Windows NT, was based on its compatibility with the haptic device, high-resolution graphics capabilities and on its operating speed.

A subroutine calculates the non-bonded Lennard-Jones 6-12 potential (van der Waals forces) and electrostatic interactions (Coulombic forces). Assumptions for the calculations are dictated by the need for real-time speed [8]. The interatomic forces can be calculated based on three- dimensional coordinates from X-ray crystallographic determinations. The parameters used for AMBER (Assisted Model Building with Energy Refinement) were chosen for the calculations because the data are widely accepted and easily accessible [9].

To reduce the complexity of the modeling system, the active site of the protein is treated as a rigid body instead of a dynamic one. The site is also

stationary in space so the mobile probe can attack from any direction or orientation. A control panel was first used to simulate the haptic control of the probe (refer to Figure 2). With both the haptic input and the control panel the intermolecular forces are calculated after each translational or rotational movement of the probe. The user chooses which forces to calculate and whether the potential energy is to be calculated during the modeling.

The programming code is primarily in C using some C^{++} constructs, the OpenGL graphics library for the graphics interface and sections of the haptic library. To increase the program optimization, approximate molecular parameters are used along with a reduction in the amount of mathematical operations being performed in the force function. Adjusting the data type used in the calculations, and reallocating processor time has also increased optimization. The current calculating speed is less than 1 millisecond for 1500 calculations, which equates to a 100-atom active site and a 15-atom inhibitor.

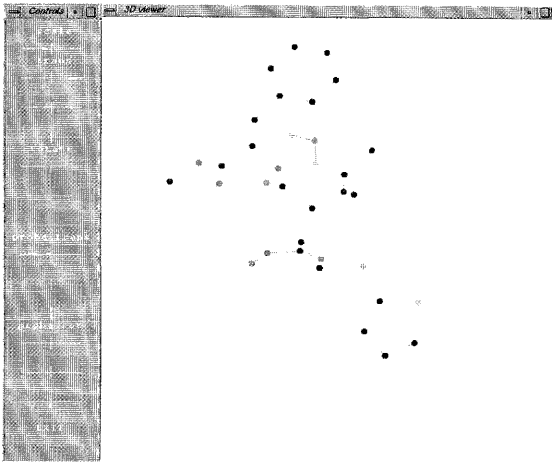

Figure 2. The Control Panel. The control panel is used in the system development to simulate interaction with the haptic device. Each line controls a specific coordinate motion. The graphics are coded in C using the OpenGL graphics library. In this model, the stationary test molecule is Batimastat [10] and the water molecule is the movable probe set as the cursor.

RESULTS

- These items were created in C code
  - A function to calculate the van der Waal and Coulombic forces
  - Functions to set up of molecular parameter dictionaries for the force field calculations based on user input of the protein and substrate files
  - Functions to the Graphics using the OpenGL graphics library
- Optimized the force function to real time speeds of 1 millisecond for a protein active site of 100-atoms and a small inhibitor of 15-atoms
- Interfaced the PHANToM haptic device and PC with the developed code
- Provided the ability to feel the intermolecular forces for user defined model systems

CONCLUSIONS

To our knowledge this is the first application of a haptic device with 6 degrees of freedom to drug binding studies. Major challenges include the integration of hardware and software for the system, the adaptations of atomic interaction parameters, and the exploration of visual and tactile man-machine interactions.

The rest of this semester will be used to evaluate and optimize the system based on information from the model trial of Batimastat and Hemoragic Toxin D [10]. This summer will be spent focusing on the accuracy of the system and testing known binding models. The time will also be used to evaluate the types of output that are useful for experimenters. Hopefully by the end of the summer a number of modeling trials between active sites and drug derivatives will have been evaluated.

Future work on the system includes evaluation of the intermolecular force model being used, extending the system to incorporate three-dimensional visualization for the graphics, and the possible addition of sound to add another sensual dimension to the modeling. Once the system has been optimized it is hoped that it will be used for real world applications.

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VITA

Jocylin Amber Williams was born in 1977 and spent her childhood traversing the globe as an U.S. Air Force military brat. She received her high school diploma from M. B. Lamar High School in Houston, Texas along with an International Baccalaureate Diploma. She is currently a senior biochemistry major at Texas A&M University and will graduate as a University Fellow with University Honors, and biochemistry honors in August 2000.

Honors include recognition as a finalist for a Fulbright Grant to Spain, Sigma Xi Scientific Research Society, Golden Key National Honor Society and a Senior Merit Award.

For fun she started a ballroom dancing club at A&M, and when she's not dancing can be found folding origami or pruning her bonsai.

Future plans include going to medical school, continued activity as a researcher, and having a family.

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