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Molecular Binding in a Visuohaptic Environment: An Enhanced Approach in STEM Learning

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Abstract

Learning science, technology, engineering, and mathematics (STEM) can be dull in the absence of adequate incentives; students may lose interest in STEM subjects during their high school education. This could result in a decline in enrollment in STEM fields in postsecondary education and employment as well. However, learning can be reinforced in a multimodal environment. For example, a haptic virtual environment (VE) that incorporates both vision and touch can provide better affordance in learning. This multimodal VE may help students to better understand the underlying concepts of molecular formation while pursuing chemistry and related subjects at the secondary level. Visuohaptics may work as an incentive in learning complex molecular structures and become a source of edutainment and extra motivation for students. Thus, a multimodal VE enhances attentiveness and interest among students in pursuing STEM fields in secondary and postsecondary education.

CCS Concepts

• Computing methodologies → Molecular simulation; Scientific visualization; Interactive simulation; • Human-centered computing → Visualization systems and tools; HCI design and evaluation methods;

1. Introduction

Computer-aided design systems allow a real-time interactive visualization and manipulation of molecules [STW09]. Molecular modeling is an inseparable part of drug design and drug discovery. In recent years, haptic VEs have become popular in research works besides the visualization techniques. There has been growing interest in using haptic interfaces to facilitate the exploration and analysis of molecular docking. However, not much research incorporates multiple senses into educational tools to enhance secondary and postsecondary learning of related subjects. Hence, it is imperative to develop educational tools and assistive technologies so that students can better understand scientific and mathematical concepts of postsecondary STEM subjects.

In STEM subjects such as chemistry, biochemistry, and more, a visuohaptic interface can be added to provide effective tools to enhance the molecular binding process and make it more intuitive in learning. Visualization techniques help users to better understand the interaction between the molecules generally represented as the receptor and ligand molecules. A ligand molecule joins a receptor molecule to form a compound molecule that can be explored and analyzed better in visuohaptic multimodal systems. Students understand and analyze the underlying configuration of molecules better as they model, touch, and grab molecules in a VE. In haptic-based molecular docking systems, the user can manipulate molecules and feel the intermolecular force directly. This hands-on practice on molecular binding in a multimodal environment makes students less dependent on memorization. Being able to actively interact with molecular systems is particularly empowering, and works as an edutainment tool for extra motivation. This immersive environment of a visuohaptic system can potentially enhance attention to learning. This is in contrast to the existing passive learning approaches delivered via text books, lectures, or visual feedback-only demonstrations.

The goal of this project is for high school students to experience molecular docking simulation by interacting with atoms; then, develop and experience different molecules in a visuohaptic VE. Learning in this way can help students assimilate STEM materials in an immersive and engaging environment. Molecular docking applications have been developed that focus on visualization. However, a visuohaptic VE enhances and enriches the experience to explore the energy or force feedback behind molecular docking applications.

Additionally, an immersive VE that incorporates haptic feedback can create a positive impact on students who have started learning science and technology at secondary educational levels. This can help reduce decline in interest in STEM fields at a pre-university age, too. In order to increase student participation in secondary and post-secondary STEM education, a multimodal learning environment can ensure increased learning experiences [IHL17].

This initial research proposes an interactive and multimodal molecular docking system for computer-aided design and assembly. Currently, there are very few interactive haptics-assisted

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molecular docking applications available to students at secondary and post-secondary levels. The art of gradually developing complex molecules by docking simple molecules and simulating the environment can be a source of inspiration and delight.

This pilot research aims to create an effective approach for preparing a diverse, globally competitive STEM workforce and a STEM-literate citizenry. It emphasizes research on secondary and postsecondary STEM learning, cognition, and development of instructional approaches, technologies, and materials in both formal and informal STEM settings. In this paper, a multimodal VE is used to develop a software application that enhances and strengthens learning by providing access to different modalities.

2. Background

Most molecular docking applications are mainly focused on drug discovery research([MZMC11], [DM17]). Scientific visualization becomes more predictable and perceptible with haptic or touch feedback as the virtual world can better replicate the real environment ([BOYBK90], [OYB90]). In particular, a visuohaptic VE has assisted users to experiment and intervene with molecular docking so that correct binding results can be obtained [NMT02, SGS01]. Research on docking simulations of drugs into large protein structures has been carried out in a visuohaptic VE. Haptic navigation techniques can facilitate docking simulations of large protein structures. This includes orientations of drug and protein molecules, molecular propensity determination, adjustment of bonds for the lowest potential energy of the docked combination, and so on.

Parallel computing and genetic algorithms have been developed for optimum docking configuration [LFH*97]. Interactive molecular docking methods investigated molecular dynamics and studied binding properties of biomolecules and their response to mechanical forces in a haptic-enhanced VE [SGS01]. An interactive design for molecular docking and assembly was proposed by Lai-Yuen et al. [LYL06] considering rigid receptors and flexible ligand molecules. The application provided force-torque feedback to the users for computer-aided molecular design (CAMD). However, this research seemed to be in its exploratory stage and lacks adequate examples of this application in molecular binding.

Using a visuohaptic interface, scientists grab, translate, and rotate ligand and receptor molecules, and directly manipulate them [CBZ*06]. Sourina et al. investigated haptic technology in a collaborative e-learning and online education setting [HSK]. Molecular simulation engines provide time-dependent atomic positions, velocities, and system energies according to biophysical models [NDGB08]. An elastic network model of biomolecules lets users apply force to atoms to investigate the flexibility of the molecules [SLH11].

'Molecular Tetris' helps users to explore the binding between a protein receptor and a ligand [ABM*14]. Haptic touch devices enable users to feel the interactions of two molecules as they move the ligand into an appropriate binding site on the receptor. Users are encouraged to manipulate the ligand to discover local and global potential minima. Most molecular binding approaches are about receptor-ligand bindings by identifying low potential energy configurations.

Recently, Tantillo et al. [TSS*19] carried out research on protein-ligand complexes, optimizing geometries of potential drugs with quantum chemistry and automated docking, and so on for undergraduate students' learning enhancement. This involved a number of steps, i.e., a series of laboratory experiments and introduction to software for molecular docking as well. However, haptic or multimodal environment has not been explored in their research.

This research mainly focuses on exploring molecular binding in a visuohaptic system to enhance the understanding of molecular data structures in a secondary classroom environment. A multimodal VE can be an incentive to students as theys cannot use their intuition and every day experience to grasp certain concepts; a combination of visual and tactile experience has the potential to accelerate understanding and assimilate concepts related to intermolecular interaction [STW09]. Multimodal VEs prove to be more flexible and scalable by offering unlimited sets of educational opportunities. Future research include deployment of the tool in classroom settings to measure how students' performance gain can be achieved with haptic augmentation.

3. Design Principles and the Proposed Approach

Research findings demonstrate that an interactive visual environment becomes more immersive as users touch and feel the virtual objects. Hence, a visuohaptic VE has been implemented for molecular docking. In computational chemistry literature, it is common to represent the receptor molecule as a stationary molecule and the ligands as moving dynamic molecules. It is also a common practice to display the receptor larger in size than the ligand. This molecular configuration is demonstrated in Figure 1.

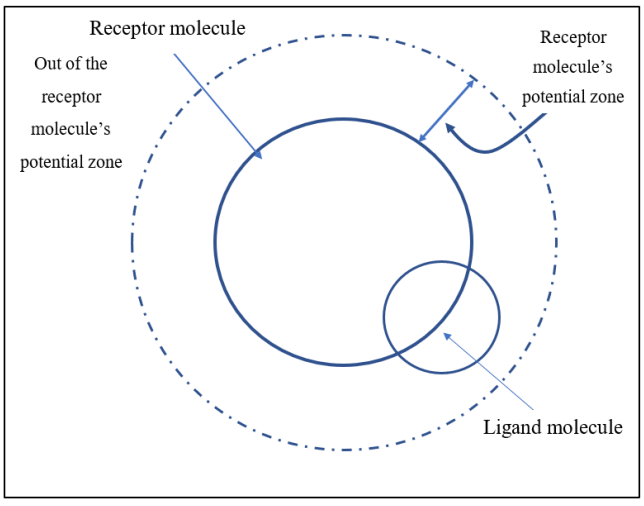

Figure 1: *The receptor (center) and the ligand molecule after binding has taken place.*

A potential energy field is created surrounding the receptor molecule within a certain radius around its center. The intermolecular attraction force between the ligand and receptor molecule is

zero when the ligand resides outside the energy field of the receptor. As the ligand atom/molecule moves inside the energy zone of the receptor, a quick intersection test between the ligand and receptor is calculated which eventually determines the interactive force between the ligand and the receptor. During binding, the ligand enters into the potential field created by the receptor's atoms, and the system searches for a stable low potential configuration before the ligand joins the receptor. This has been demonstrated in Figure 1; the ligand molecule joins the receptor molecule and remains centered at the receptor's boundary.

In order to simulate the ligand binding process, we need to have an interactive model between the ligand and receptor molecules. Haptic technology provides interactivity through forces transmitted by haptic devices. This makes it possible to feel and manipulate atoms and molecules, and transform molecular interactions into touch-enhanced sensory experiences during a virtual experiment [STW09]. As the ligand molecule enters into the potential energy zone of the receptor molecule, an interaction force is calculated at each movement of the molecules; the user feels the resulting attraction force between them through the haptic device. A number of ligands join a receptor molecule in a visuo-haptic VE and in each case, users feel the force.

Thus, VR devices offer interactive modalities, especially the haptic modality, allowing a user to dynamically control a biomolecular process and thus gain understanding of its intrinsic properties [SGS01, NDGB08]. In our simulation, the receptor and ligand are represented as rigid bodies. A haptic-enhanced interactive molecular docking process helps to study the dynamic assembly and interaction of two rigid molecules, by applying global modifications to the atomic positions. During molecular binding, the receptor remains fixed in place while the ligand is free for the user to move around the virtual workspace. A free ligand is represented by a haptic cursor which the user can freely move in the VE by moving the handle of the haptic device. As the ligand joins the receptor, a compound molecule is formed; this can be explored and analyzed in a visuohaptic system. The user can feel the newly formed complex molecule and touch, grab, translate, or rotate it in the VE to better analyze the molecular structure.

As the program starts, the receptor molecule represented by a sphere is seen at the center of the window; the user can feel it with a haptic device represented by a haptic cursor (a small red cone) in the VE (Figure 2a). This is described as the undocking mode in the application. In this mode, the haptic cursor freely moves around in the scene. Next, the user enters into the docking mode and the cursor turns into a smaller sphere (the ligand molecule) as shown in Figure 2b. In the docking mode, as the ligand (represented by the smaller sphere) enters the potential zone of the receptor, it gets attracted to the receptor. Next, a copy of the smaller sphere is created and attached to the larger sphere, i.e., the receptor molecule. The two are then considered a single molecule. This has been demonstrated in Figure 2c. Later, the user switches to the undocking mode and the haptic cursor returns back to its previous state, i.e., a small red cone. This lets the user touch and feel the newly formed compound molecule in detail. Figures 2c-e depict this scenario. This process can be repeated as many times as the user likes to create different molecules.

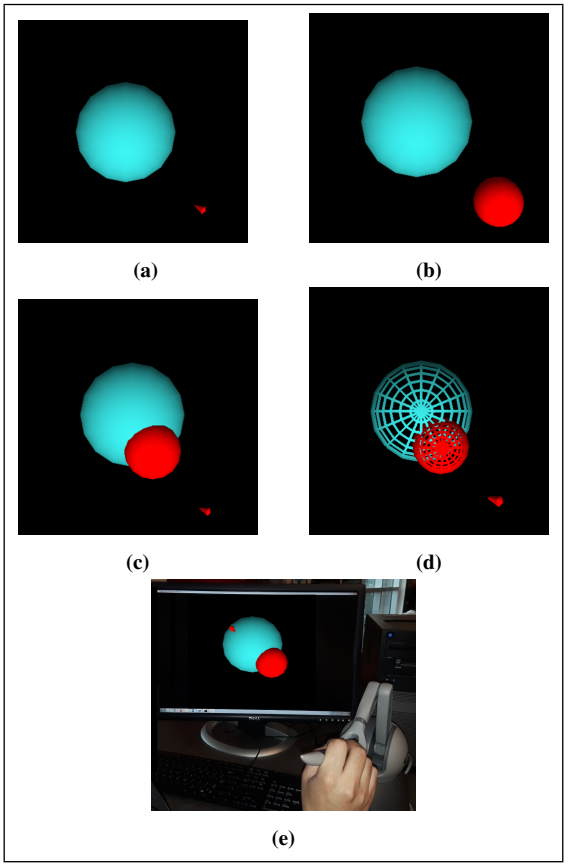

Figure 2: *Different steps of the molecular binding process: (a) the receptor molecule (in the middle) and the haptic cursor (represented by a red cone); (b) in the docking mode, the cursor turns into the ligand molecule shown as a red sphere; (c) the ligand is bound to the receptor and the system returns to the undocking mode; (d) a wireframe representation of (c), (e) in the undocking mode, a compound molecule is being explored with a 'Touch' haptic device (www.3dsystems.com).*

In the docking mode, as the cursor is being pulled out of the energy zone of the receptor, the user feels a restraining force until the cursor leaves the energy zone. When the user returns to the undocking mode, the cursor can freely move in the VE to feel and explore the molecules. Figure 3 demonstrates the formation of a water molecule with oxygen as the receptor molecule and hydrogen atoms as the ligands.

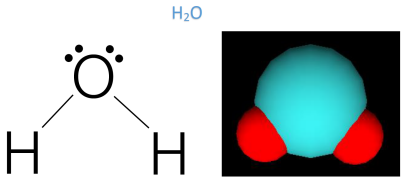

Figure 3: *(Left) The chemical structure of a water molecule, (right) a water molecule formed using the visuohaptic VE system.*

4. Implementation and Results

The application software has been developed using 3D Systems' OpenHaptics software in C/ C++ programming language. For the haptic interface, a 'Touch' haptic device manufactured by 3D Systems has been used (www.3dsystems.com). Both HLAPI and HDAPI platforms of OpenHaptics have been used for haptic feedback. The program mainly uses the HLAPI provided by OpenHaptics. OpenHaptics' HDAPI interface has been used to generate force feedback from the haptic device. As the ligand molecule enters into the potential energy-zone of the receptor as detailed in the previous section, an attraction force towards the receptor is generated and users should feel this force. This requires sending force to the haptic device, which is accomplished with call back functions at the device level provided by the HDAPI platform. In the docking mode, the attraction force or energy around the receptor is calculated from the center of the receptor to the center of the ligand. As the ligand enters into the energy-zone, an imaginary line joining the center of the receptor and the center of the ligand is drawn. Next, a force is calculated towards the center of the receptor that reaches an equilibrium state as the ligand becomes a part of the receptor. The ligand remains attached to the receptor with its center at the boundary of the receptor.

In the field of chemistry, this program has been used to create rough models of different molecules: a single larger atom to demonstrate the receptor and smaller atoms representing ligands. Figure 4 displays some examples of such molecules as modeled with the program. Note that the positions of the molecules are all approximated. Figure 4a demonstrates the formation of an ammonia molecule created from nitrogen and hydrogen atoms. Here, the receptor molecule is the nitrogen molecule represented by a large sphere at the center with hydrogen atoms as ligands drawn as smaller spheres around the receptor molecule. Similarly, sulfur tetrafluoride and sulfur hexafluoride molecules have been formed from sulfur and fluoride molecules with sulfur as the receptor molecule and fluoride as the ligand molecules. Figure 4b and Figure 4c show a sulfur tetrafluoride molecule and a sulfur hexafluoride molecule, respectively, with their chemical configurations.

The basic molecular docking algorithm with one receptor molecule and several ligands was extended. Figure 5 demonstrates how carbon and hydrogen molecules were docked to form ethane and propane molecules. Ethane has two receptor molecules and 6 ligands whereas propane is composed of 3 receptors and 8 ligands. The chemical configurations of both molecules are shown to the right of their molecular structures.

5. Evaluation

This research work was carried out as part of a directed study by a Computer Science undergraduate student with Chemistry as the second major. As the project is still in an ongoing stage, formal evaluation is yet to be carried out. However, after the pilot version as detailed above was developed, an informal evaluation was carried out by participants comprising students from the Computer Science department and a faculty member. All participants' levels of immersion and engagement were observed as they explored the molecular docking application in a multimodal visuo-haptic environment. A chart comprising configurations of different molecular

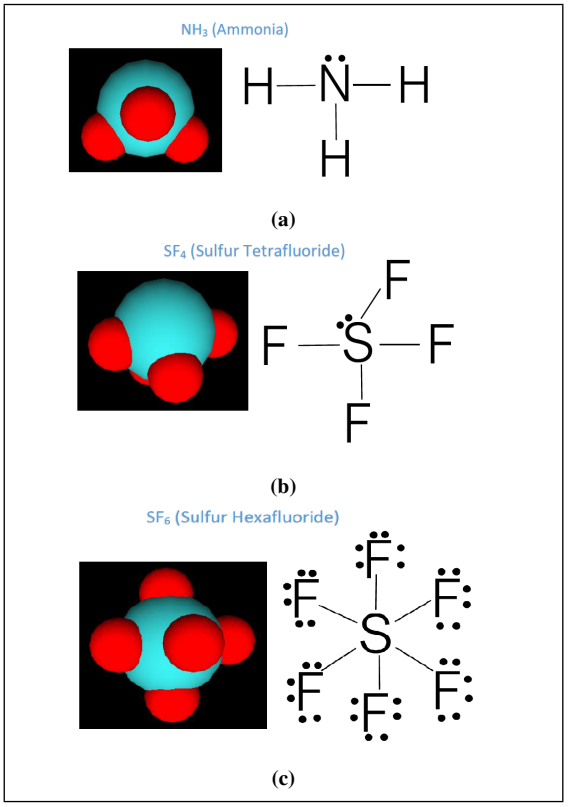

Figure 4: *A few compound molecules have been created with the proposed molecular binding tool; the right side demonstrates the chemical configurations of the compund molecules. (a) an ammonia molecule, (b) a sulfur tetrafluoride molecule, and (c) a sulfur hexafluoride molecule.*

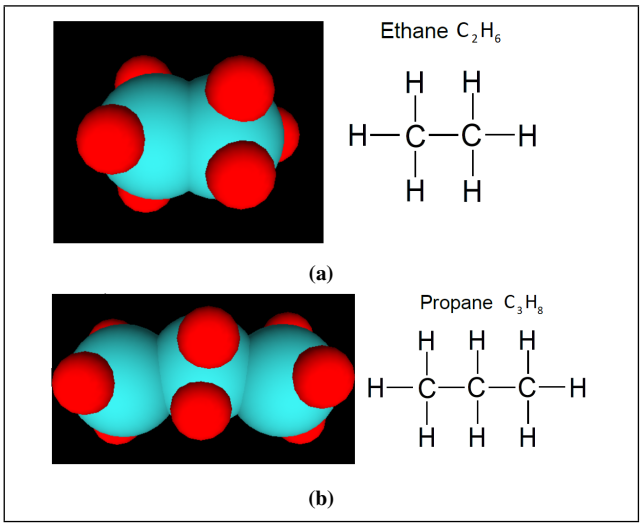

Figure 5: *Some compound molecules with more than one receptors developed with the proposed molecular binding tool: (a) an ethane molecule and (b) a propane molecule.*

structures was provided to each participant before they started to explore the application. Participants started with building simple molecular structures like water and ammonia molecules. Then, they gradually worked towards complex molecular structures such as sulfur tetrafluoride, sulfur hexafluoride, ethane, and propane. Participants demonstrated noticeable excitement and interest as they completed binding operations for different molecules. The force feedback they received via the haptic device, used in this application as molecules were bonded, enhanced their overall learning experience. The informal evaluation demonstrated an inherent preference to explore molecular docking operations in a multimodal VE. After completing each docking application, participants grabbed the newly formed molecules with the help of a haptic device and explored the structural details with great interest and care.

6. Conclusion and Future Works

This program is currently rather primitive, but will be improved by making some adjustments. While implementing molecular docking, proper bond angles and molecular geometry will be calculated by the program. So, as molecules bind together, the user would not have to approximate the molecular configurations by sight. Next, variable force will be implemented depending on the exact molecule or bonds that are being modeled so that optimum potential energy can be determined during docking operations. The user will be able to create different sizes of spheres to model molecules with different types of atoms.

At EWU, faculty actively coordinate and participate in after school youth programs that provide college access materials to K-12 youth while helping them prepare and plan for their future. This provides faculty opportunities to share educational materials with students from different socioeconomic and historically underrepresented regions of the state. Students seem to be enthusiastic about software applications and research projects, especially those related to haptic-enhanced technologies.

The software will be demonstrated at local high schools for the learning enhancement of chemistry and related STEM subjects. A small efficacy study will be carried out to assess the learning outcome by monitoring student participation, engagement, and proficiency in the subject matter.

Additionally, learning can be reinforced in a multimodal environment. A mixture of speech and touch-based output could eventually provide a powerful platform for supporting the processing of visual information in a semantic-aware environment to the blind and visually impaired (VI). A multimodal VE can be an immense source of inspiration and engagement to those who are deaf or hard of hearing (HoH) as touch would make the learning environment more immersive. This research on STEM education in a multimodal environment works towards a diverse, globally competitive STEM-literate citizenry and diverse workforce.

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