A Gesture-Based Molecular Modeling System

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Abstract

Molecular modeling is based on analysis of three dimensional structures of molecules. It can be used in developments of new materials, new drugs, and environmental catalyzers. We propose a gesture-based molecular modeling system which visualizes three dimensional models of molecules, presents them using a large stereoscopic display and allows scientists observe and manipulate the molecular models using their gestures of hands and arms. The system consists of a three dimensional stereoscopic display, data gloves, and motion tracking devices. Scientists can examine, magnify, translate, rotate, combine and split the molecular models in more natural and convenient ways using gestures. These operations require real-time simulations to validate corresponding chemical phenomena such as chemical bonding. We developed new data structures and algorithms for the simulations. The proposed system was compared with the most popular molecular modeling tool called Insight II. For the comparison, HIV-1(Human Immunodeficiency Virus) was used as a receptor and fifteen candidate materials were used as ligands. No significant differences were found between Insight II and the proposed system in the results of the simulations. An experiment of measuring performances of the system showed that users of the proposed system improved their performance faster than those of Insight II as they learned and experienced more about the system. Another experiment of testing subjective satisfaction demonstrated that users preferred to use the proposed system

Key words: Interaction Techniques, Gesture-based Interaction, Three Dimensional User Interface, Visualization, Modeling and Simulation, Bioinformatics, Molecular Modeling, Human Factors.

1. Introduction

Molecular modeling includes analyses of three dimensional structures of molecules. One dimensional character strings of molecular structures are translated into three dimensional structures of molecules. Then, scientists examine such three dimensional structures in terms of their shapes, features, and their stability. They perform a docking procedure by which a receptor combines with a ligand at a special position called an active site. The simulation is required because it can computationally prove or disprove if such a chemical operation is possible. The simulation is basically calculating energy minimization equations.

There have been many researches and tools for molecular modeling. Most of them focus on visualizing structures of molecules in three dimensions. Molecular modeling procedures require scientists to examine and manipulate three dimensional models of molecules. During a docking process, the shapes of a receptor and a ligand are visually examined by scientists. Also, many molecular models should be processed. For each case, the distances between the models must be measured. Since three dimensional structures of most molecular models look quite similar, it is very difficult for scientists to differentiate the structures using views projected on conventional two dimensional monitors.

As for their input devices, most tools provide a mouse and a keyboard. However, it is not easy to complete molecular modeling procedures using such devices. Molecular modeling operations, such as translation of models, rotation of models, combination of two molecular models (a receptor and a ligand), etc., require more sophisticated input methods. The operations are essential when we exercise simulations of energy minimization[1] in order to verify the stability of the result of the docking procedure. The operations are required to compute parameters such as the distance between molecular models, the angles of rotations of the models for docking. Therefore, more natural input methods are required. Just a mouse and a keyboard are not sufficient enough.

We propose a molecular modeling system in this paper. The system adopts a large, stereoscopic display device. The stereoscopic views are more realistic and helpful for scientists to understand three dimensional structures of molecules. The system provides data gloves and motion tracking devices rather than a mouse and a keyboard. So, scientists can use their hands and arms in examining and manipulating molecular models. The operations include translation, rotation, zoom-in and out, selection, separation, combination, etc. They are used in assembling and disassembling procedures, and docking procedures. It is expected that scientists would feel more natural and comfortable with the hand and the arm gestures than a mouse and a keyboard. Therefore, the molecular modeling procedure becomes easier and more

productive.

This paper is organized as follows: Session 2 describes related works on tools of molecular modeling. Session 3 deals with visualization of three dimensional models, gesture-based interactions, and simulations based on energy minimization algorithms. Session 4 presents experiments and their results. We summarize the paper and discuss future research directions in Session 5.

2. Related Works

RASMOL[2], VMD[3] and QMOL[4] are molecular modeling tools and they visualize three dimensional structures of molecules. Accelrys commercialized another molecular modeling tool, Insight II[5].

RASMOL and QMOL are widely used, because they provide fast and simple ways of examining three dimensional structures of molecules. But they do not provide functions of manipulating molecular structures with real-time simulations. This implies that we cannot directly use these tools in molecular modeling.

Theoretical Computational Biophysics Group, University of Illinois developed VMD. The software for molecular modeling is bundled with NAMD, SMD, and IMD. VMD offers many functions including visualization of three dimensional molecular models and their animation. It can visualize and analyze large-scale(more than 5,000) molecular structures. VMD also supports stereoscopic[6] views so that scientists can utilize polarized glasses or HMD(Head-Mounted Display) in order to examine three dimensional structures of molecules.

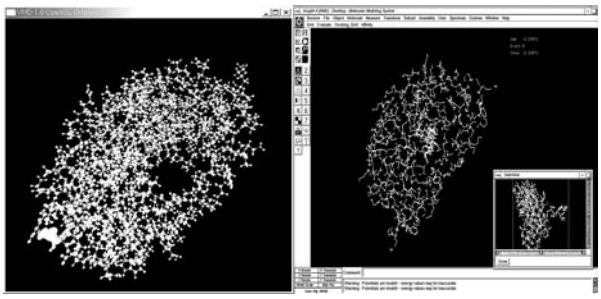

Fig. 1 Sample screens of (a) VMD (b) Insight II

Accelrys developed Insight II, a tool for molecular modeling. It is the most popular tool and used in the fields of biology, new drug design, etc. It is commercially available. Insight II offers various functions of protein structure design, simulation, structure-based drug design, NMR spectroscopy, etc.

Those tools are based on conventional input and output devices such as a two dimensional monitor, a mouse, and a keyboard. For example, Insight II users perform molecular modeling by examining a front view and a side view as shown in Figure 1-(b), because the tool does not provide "real" three dimensional views. It is not easy to find active site, where binding a receptor and ligand can occur, with the two dimensional views of the front and the side. Though scientists could examine the front and the side views, it is not intuitive to have the depth information for docking procedures from the visualized models.

3. System

3.1 Overview

MMVR (Molecular Modeling on based Virtual Reality) consists of five components: File Manager, Operation Manager, Rendering Engine, Computing Engine and Sensor Manager.

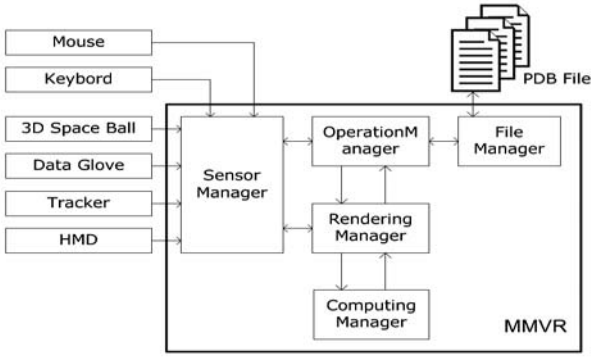

Fig. 2 System Overview

Information of molecules is stored in PDB files. *File Manager* reads data from PDB files and exercises parsing the data. *Operation Manager* arranges the parsed data in order to compute energy equations. The results are arranged to be properly displayed by *Rendering Engine*. *Sensor Manager* handles input signals from sensing devices such as a mouse, a keyboard, data gloves, etc. Rendering Engine visualizes three dimensional models of molecules using graphical libraries like OpenGL. Various rendering algorithms such as Stride, Marching Cube[4][7] are implemented. *Computing Engine* computes energy equations which are essential in the simulation.

3.2 Data Structures

In addition to visualization, MMVR supports various functions such as docking procedures for molecules using multiple loading, non-bonding atoms and amino acids from molecules, bonding molecules based on peptide bonds, etc. Figure 3-(a) shows a docking procedure by multiple loading molecules. An amino acid is extracted and assembled in Figure 2-(b). MMVR supports these operations by rendering molecular models fast and computing energy equations in real time.

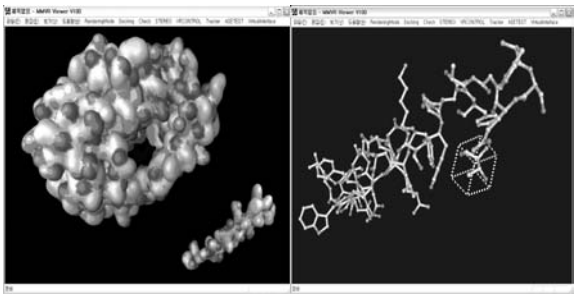

Fig. 3 Procedures of (a) Docking (b)Assembling and Disassembling using MMVR

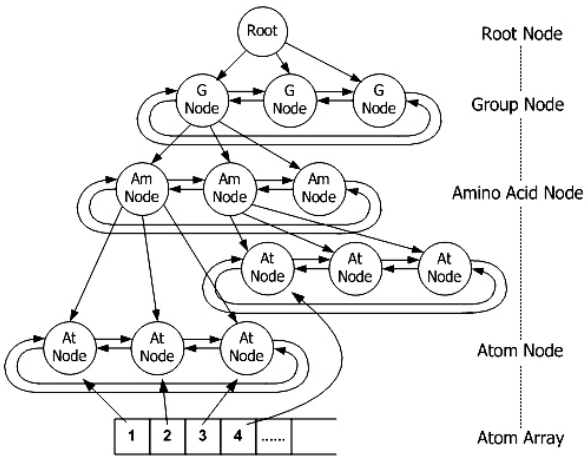

Fig. 4 Data Structure for molecular modeling

Since the docking and the assembling/disassembling operations change structures and status of molecular models, MMVR needs a new data structure to support such changes in real-time. The design concept of the data structure is based on scene graph. As shown in Figure 4, four node lists are defined: Root, Group, Amino Acid, and Atom Node List. An array called Atom Array is also defined in order to reduce rendering time. If the node lists are used during rendering, time for navigating the node lists could become significantly long. It could delay response time of MMVR. Therefore, Atom Array is introduced. The response time could be reduced because nodes can be directly accessed with coordinate values of atoms without traversing the node lists.

3.3 A stereoscopic display device for multiple viewers

MMVR has a large (72 inch) display device and generates stereoscopic views. The stereoscopic display helps scientists in examining three dimensional structures of molecular models. A conventional two dimensional monitor cannot provide them with useful

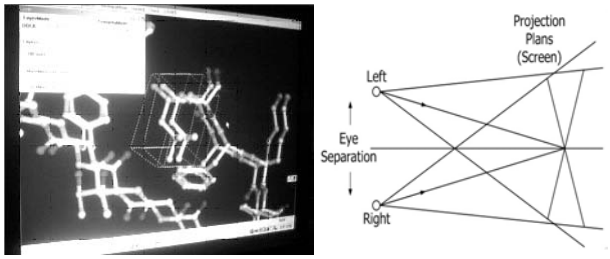

Fig. 5 Data Structure for molecular modeling

views which are realistic enough to perform three dimensional observations and manipulations.

HMD could generate three dimensional views. However, the device is designed for a single user. On the other hand, the large display device could allow participating in molecular modeling procedures for multiple users at the same time.

3.4 Docking Procedures

During docking procedures, scientists examine three dimensional structures of a receptor and a ligand in order to check if they can be chemically combined. MMVR provides the scientists with three dimensional views of molecules so that they can directly combine a receptor and a ligand without examining two dimensional data such as a front view, a side view, a distance table, etc. The scientists use their hands and arms in order to give commands to MMVR. They can exercise hand gestures and arm gestures. The gestures are one of the following modes: system mode, observation mode and docking mode. In the system mode, scientists can issue two commands: “start” and “end” of an operation. The scientists can examine molecular models by performing “translation”, “rotation”, “zoom-in” and “zoom-out” the models in the observation mode. For instance, the “start” command is recognized when a scientists clenches both of his hands as shown in Figure 6-(a). Whenever an operation is initiated, the “start” command must be issued. The “end” command means opening both hands as shown in Figure 6-(b).

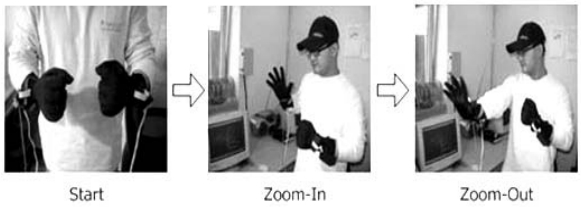

Fig. 7 Gestures of Zoom-In and Zoom-Out

We used 5DT's Data Glove as a tool of expressing gestures and Polhemus' 3DSpace Tracker as a motion tracking device.

Fig. 8 Data Gloves and Motion Tracking Devices

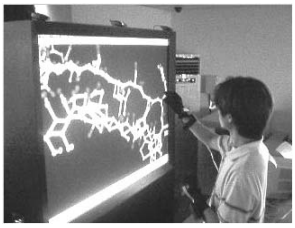

Fig. 9 Molecular modeling using MMVR

A set of actions are defined as presented in Table 1. For example, LHC(Left Hand Clench) is an action of clenching a left hand and RHO(Right Hand Open) is an action of opening a right hand. A series of these actions can form an operation of docking. Figure 10 presents a state transition diagram for operations of docking. Each node represents a state of the docking procedure. Each action like "S", "E", and "LFC" cause a transition from a state to another.

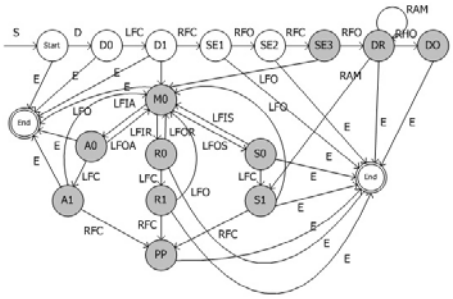

Fig. 10 State transition diagram for Docking

Table 1.

Symbol	Explanation	Symbol	Explanation
S	Start	RFO	Right Finger Open
D	Docking	RFC	Right Finger Clench
LHC	Left Hand Clench	LFO	Left Finger Open
RHC	Right Hand Clench	LFC	Left Finger Clench
RHO	Right Hand Open	RAM	Right Arm Move
RARR	Right Arm Right Rotation	LFIA	Left Finger In All
RALR	Right Arm Left Rotation	LFOA	Left Finger Out All
RAF	Right Arm Forward	LFIR	Left Finger In Remain
RAB	Right Arm Backward	LFOR	Left Finger Out Remain
RALM	Right Arm Left Move	LFIS	Left Finger In Separate
RARM	Right Arm Right Move	RFOS	Right Finger In Separate

3.5 Energy Minimization

When scientists perform the docking procedures by combining a receptor and a ligand, MMVR executes a simulation and checks if such a bonding is chemically possible. In other words, MMVR computes energy minimization equation for the docking. The energy stability computation for docking is defined as a sum of electrostatic energy (E*elec*) and Van der Waals energy(E*vdw*)

$$E_{(total)} = Eelec + Evdw$$

$$E_{elec} = \sum_{excl(i,j)=1} \frac{q_i q_j}{4\pi\varepsilon_o r_{ij}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{E}elec$$

$$E_{vdw} = \sum_{exel(i,j)=1} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) sw\left(r_{ij}^2, r_{on}^2, r_{off}^2\right) \ldots \text{E}vdw$$

ε_o is a constant which is provided by a scientist. Its value ranges from 1Å to 80Å. We set up the value as 1 Å during our experiments. r_{ij} means a distance of each atom in a receptor and a ligand. $q_i q_j$ means a multiplication of electric charge values of each atom.

4. Experiments

We compared MMVR with Insight II which is the most popular tool of molecular modeling. HIV-1 (Human Immunodeficiency Virus [8][9][10] was selected as a receptor. Fifteen materials related to reproduction of HIV-1 were chosen as ligands. First, the values of computing energy equations for binding the fifteen ligands with the receptor were calculated. The comparison would show how different or similar the simulation results of Insight II and MMVR were. The second experiment was designed to compare times for

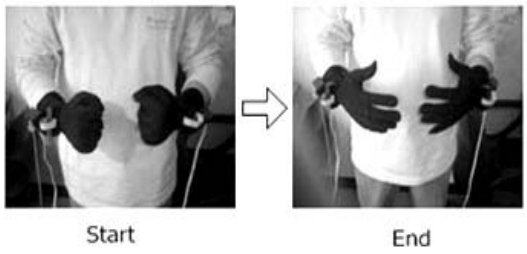

Fig. 6 Gestures of (a) Start and (b) End

exercising docking procedures using the tools. The docking procedures were preformed with Insight II and MMVR and their processing times were measured. These values could be used in evaluating the usability of the tools. Finally, we surveyed degrees of user satisfaction of the tools.

The results from first experiment are listed in Table 2 and graphically presented in Figure 11. Table 2 present

energy values of fifteen ligands using Insight II and MMVR. The results show that there are no significant differences between the values of calculating energy equations using Insight II and those using MMVR. Therefore, the results of docking procedures using the two tools would not be significantly different. Table 2 and Figure 10 show the energy values of docking procedures which aims to combine the HIV-1 receptor with fifteen ligands(expressed in the PDB code).

Table 2. Comparison of values from the simulations using Insight II and MMVR

T = Elec + Vdw

PDB code	Insight II Energy Value				MMVR Energy Value			
	ΔE^{Vdw}	ΔE^{elec}	ΔE^{T}	RMSD (Å)	ΔE^{Vdw}	ΔE^{elec}	ΔE^{T}	RMSD (Å)
1gno	-7.63	-0.32	-7.95	1.02	-9.08	-0.46	-9.54	0.98
1hbv	-14.73	-1.24	-15.97	0.92	-14.21	-1.14	-15.35	0.86
1hps	-16.87	0.74	-16.13	2.41	-14.64	1.10	-13.54	3.15
1hpv	-10.15	-0.93	-11.08	0.36	-10.28	-0.74	-11.02	0.42
1hvj	-11.85	-0.11	-11.96	1.25	-10.85	-0.21	-11.06	1.28
1hvk	-15.25	0.55	-15.70	0.37	-14.21	0.65	-13.56	0.89
1hvl	-15.43	-1.20	-16.63	0.35	-15.35	-0.98	-16.33	0.39
1hvs	-12.31	-0.24	-12.55	1.66	-11.28	-0.34	-11.62	1.93
1hte	-1.24	-0.23	-1.47	0.39	-1.89	-0.65	-2.54	0.98
1htf	-22.61	-2.30	-24.91	0.32	-18.87	-2.15	-21.02	0.94
1htg	-17.46	-1.23	-18.69	0.49	-18.31	-1.24	-19.55	0.44
1pro	-9.95	0.67	-9.28	1.04	-9.70	0.62	-9.08	1.26
1sbg	-11.29	0.08	-11.21	2.01	-12.99	0.13	-12.86	1.36
2upj	-10.80	0.49	-10.31	1.59	-10.87	0.98	-9.89	1.89
4phv	-17.43	-0.98	-18.41	0.67	-15.64	-1.12	-16.76	0.92

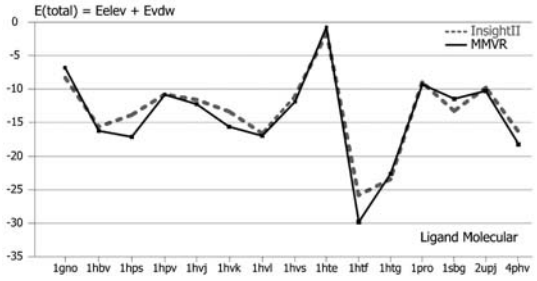

Fig. 11 Energy values of fifteen ligands

In the second experiment, we compared times for completing docking procedures of Insight II and MMVR. The subjects were never exposed to neither Insight II nor MMVR. With ten subjects, we asked to perform docking procedures five times with Insight II and MMVR, respectively. The results are summarized in Table 3. The average times of docking procedures were computed and charted in Figure 12.

Table 3. Comparison of measured times of completing docking procedures with Insight II and MMVR

Subject	Insight II					MMVR				
	1	2	3	4	5	1	2	3	4	5
A	5:36	2:30	2:01	2:32	1:58	15:12	11:20	8:20	3:01	1:38
B	10:33	5:20	3:21	3:12	2:58	12:30	7:20	6:22	3:53	1:28
C	6:58	4:30	2:36	2:20	2:01	5:50	3:16	2:18	2:23	1:35
D	5:33	4:13	3:20	3:13	2:37	12:24	7:30	4:48	2:20	2:36
E	7:20	6:37	5:10	3:24	2:53	10:12	3:30	1:02	1:05	1:50
F	7:48	7:13	4:22	4:01	3:20	7:55	6:30	6:02	1:45	1:38
G	5:48	4:20	3:15	3:20	2:24	10:35	3:22	2:48	3:30	2:56
H	8:12	5:12	4:23	4:40	3:48	10:42	6:18	2:20	2:18	1:54
I	5:32	4:30	3:22	3:07	2:23	10:23	3:48	1:30	2:33	1:49
J	7:32	4:48	3:20	2:28	2:32	12:28	3:20	1:42	1:03	1:12

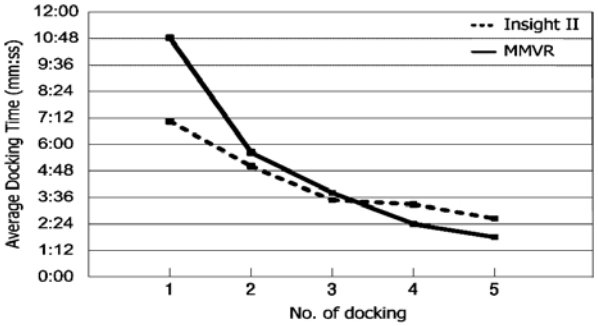

Fig. 12 Comparison of average time for docking procedures as number of dockings increases.

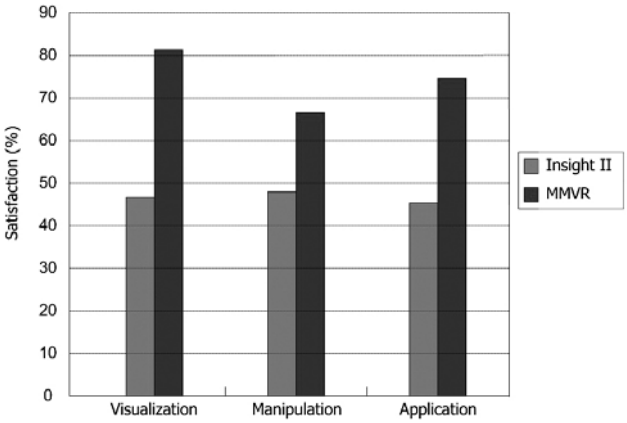

Fig. 13 User satisfaction surveyed in terms of visualization, manipulation and application

Since the subjects never used the tools and learned more about the tools as they experienced the tools, the times required for docking decreased as the number of docking procedures increased. They could exercise docking procedures faster, as they experienced and learned more about the tools. We could find a learning effect. As Figure 12 shows, the subjects did it faster with Insight II in the beginning. However, they did it faster with MMVR in the end. The average docking time of the last trial was reduced to 76% of the first one with MMVR. The results can be interpreted as follows: The subjects were more familiar with a mouse than data gloves.

Therefore, the docking procedure using Insight II showed better performance during the first trial. As the subjects try more docking procedures and learn more

about the gesture-based interaction method, they performed better with data gloves. The learning curve of MMVR was better than that of Insight II.

We surveyed satisfaction of the subjects [11] in terms of usability. We measured degrees of satisfaction in the fields of visualization, manipulation, and new drug design. The subjects mentioned that they were more satisfied by the quality of the visualization in MMVR. The stereoscopic views of molecular models helped the subjects to exercise docking procedures through direct manipulation in MMVR. On the other hand, they had to examine and confirm the status of the docking procedures by viewing the values of energy tables in Insight II. They had to examine a front view and a side view of molecular models at the same time because Insight II does not offer "real" three dimensional views of molecular models.

As for the manipulation method, most subjects preferred to the gesture-based method in the end. Notice, however, that most subjects were more familiar with a mouse than data gloves in the beginning. Therefore, they showed better performance and more preference to a mouse in the beginning. But they changed and became to prefer to data gloves as they experienced more about data gloves. But some people (especially female subjects) showed better performance in docking with a mouse. It is partially because the data gloves were too big for them to manipulate freely.

The subjects expected that MMVR would become more applicable to practical molecular modeling procedures such as new drug design. They expected that the direct manipulation becomes more popular and data gloves and motion tracking technologies could be improved pretty well.

5. Conclusion

We propose a new system which solves constraints of existing molecular modeling tools. A conventional two dimensional monitors were replaced by a stereoscopic display device. This gives not only more realistic views of molecular models but also more accessible views for multiple users. The input method of the proposed system utilized data gloves and motion tracking devices. The gestures of scientists are used in assembling and disassembling procedures, and docking procedures. We developed new data structures for fast rendering and efficient computations of energy minimization.

In the future, we would like to remove data gloves and motion tracking devices. We would use computer vision technologies to replace data gloves. It would be a more economical way of viewing and manipulating three dimensional structures of molecular models.

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