

Development of a Gesture-Based Molecular Visualization Tool Based on Virtual Reality for Molecular Docking

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Molecular modeling for drug discovery includes analyses of three-dimensional structures of molecules. One-dimensional character strings of molecular structures are translated into three-dimensional structures of molecules. This three-dimensional molecular structure is the principal basis of docking simulations for the structure-based drug design.¹⁻³ Researchers fit together such three-dimensional structures in terms of their shapes, features, and thermodynamic stabilities. The promise of molecular docking is that the structure of the receptor will provide a template for the discovery of novel ligands, dissimilar to those previously known.⁴ There have been many researches and tools for molecular modeling. Most of them focus on visualizing structures of molecules in three-dimensions with two-dimensional space. Molecular modeling procedures require scientists to examine and manipulate three-dimensional models of molecules. 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. RasMol,⁵ VMD,⁶ Qmol⁷ and GRASP⁸ are representative molecular modeling tools and they visualize three-dimensional structures of molecules. RasMol is a simple and useful program representing for the visualization of proteins three-dimensional structures and the scripting capabilities have enabled programmers to add this package to the web interface. Qmol is also widely used, because it provides fast and easy ways on examining three-dimensional structures of molecules. VMD supports stereoscopic views so that users can utilize polarized glasses or HMD (Head-Mounted Display) in order to examine three-dimensional structures of molecules. GRASP provides fast and powerful surface rendering for biomolecules. However, all of them do not provide functions of manipulating true three-dimensional structures with real-time operations. Even the highly costed commercial programs⁹ for molecular modeling provided by Accelrys or Tripos just support three-dimensional graphics with a front view and a side view. Though researchers could examine the front and the side views, it is not very intuitive

to have deeper information for docking procedures from these visualized models. Recent development of computational capacity such as parallel or GRID computing makes the molecular simulations be an easy and intuitive tool for researchers in view of virtual reality.¹⁰ The combination of the virtual experiment with sensorial perceptions of the user (human virtual reality, HVR) and the simulated interaction between atoms and molecules (molecular virtual reality, MVR) has been realized for the effective molecular simulations.¹¹ In this paper, a novel molecular visualization tool based on virtual reality (MVVR) system was developed in order to perform an effective molecular docking, where human intuition with three-dimensional interface can directly involved in the searching procedure for optimized molecular docking state.

This system was designed to allow a large stereoscopic display and encourages researchers to 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. 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. Researchers can examine, magnify, translate, rotate, combine and split the molecular models in more natural and convenient ways using gestures. They are used in molecule building procedures, and docking procedures. It is expected that users would feel more natural and comfortable with the hand and the arm gestures than with a mouse and a keyboard.

Overview. MVVR (Molecular Visualization based on Virtual Reality) consists of five components (Figure 1A): File Manager, Operation Manager, Rendering Engine, Computing Engine and Sensor Manager. Information of molecules is stored in PDB files. *File Manager* reads data from PDB (Protein Data Base) files and exercises parsing the data. *Operation Manager* arranges the parsed data in order to compute potential energy equations extracted by various sources such as CHARMM,¹² Amber¹³ or AutoDock.¹⁴ The results can be arranged to be properly displayed by *Rendering Engine*. *Sensor Manager* handles input signals

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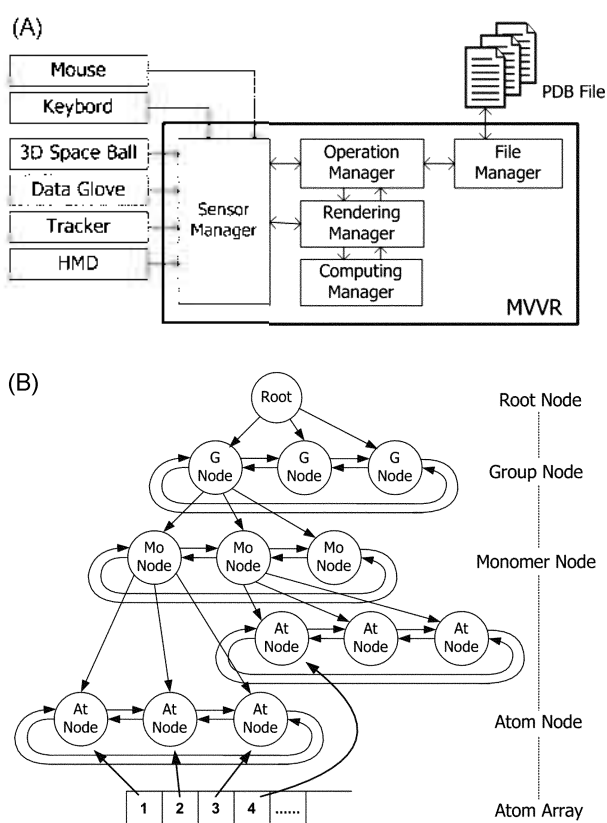


Figure 1. System overview (A) and data structures (B) for molecular modeling. MVVR consists of File Manager, Operation Manager, Rendering Engine, Computing Engine and Sensor Manager. Information of molecules is stored in PDB files. The data structure of four node lists (*Root*, *Group*, *Monomer*, and *Atom* Node List) is based on scene graph.

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 Cube¹⁵ are implemented. *Computing Engine* computes potential energy equations supported by various force fields which are essential in the molecular simulations.

Data structures. Besides visualization, MVVR supports various functions such as docking procedures for ligands and receptors through non-bonding energy calculations equipped with multiple loading environments. Figure 2A shows a docking procedure by loading multiple molecules. A manipulation for the amino acid is supported in terms of extraction and assembling (Figure 2B). This operation was could be realized by fast rendering algorithm and real-time computation of potential energy equations in MVVR. Since the docking and the assembling/disassembling operations change structures and status of molecular models, MVVR needs a new data structure to support such changes in a real-time scale. The design concept of the data structure is based on scene graph. As shown in Figure 1B, four node lists are defined: *Root*, *Group*, *Monomer*, 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,

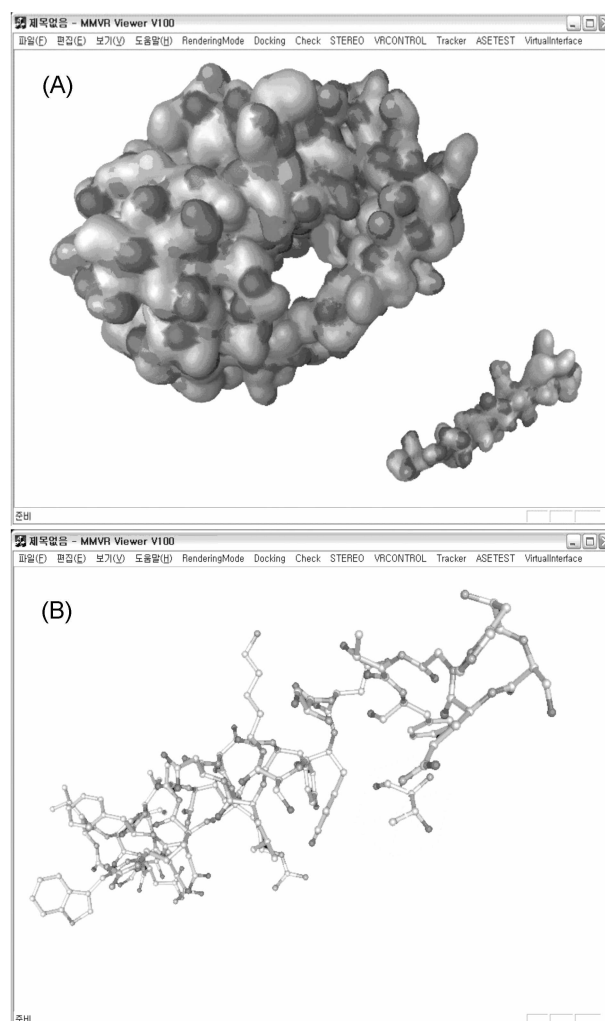


Figure 2. Procedures of (A) docking and (B) molecule building using MVVR. MVVR provides the users with three-dimensional views of molecules so that they can directly combine a receptor and a ligand without examining two dimensional data such as a front view and a side view.

time for navigating the node lists might delay response time of MVVR. Therefore in, *Atom Array* is introduced. The response time could be reduced because nodes can be directly accessed with atomic coordinate values of atoms without traversing the node lists. The visualization for the any other bio-molecules such as protein, nucleic acid, carbohydrate as well as small organic molecule is possible if they were saved as a standard PDB file format.

A stereoscopic display device for multiple viewers. MVVR has a large (72 inch) display device and generates stereoscopic views. The stereoscopic display helps scientists in examining three-dimensional structures of molecular models (Figure 3). A conventional two-dimensional monitor cannot provide them with useful 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

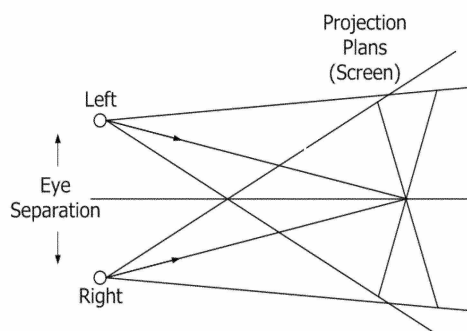
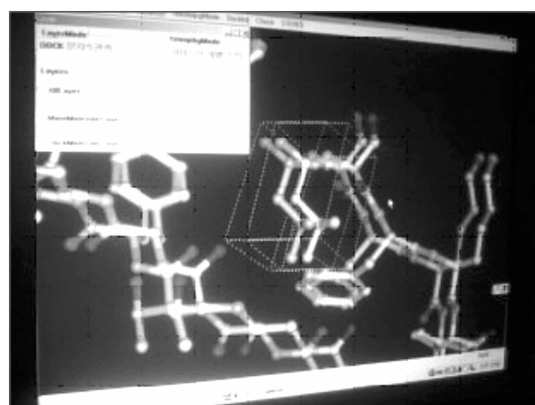


Figure 3. Stereoscopic display and projection. Stereo pairs create a "virtual" three-dimensional image. binocular disparity and convergence cues are correct but accommodation cues are inconsistent because each eye is looking at a flat image.

users at the same time.

Molecular manipulating procedures. During molecular manipulation, users examine three-dimensional structures of a receptor and a ligand in order to search the possible binding sites. MVVR 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, and a distance table, etc. The researchers use their hands and arms in order to give commands to MVVR. They can exercise hand gestures and arm gestures. These gestures are one of the following modes: system mode, observation mode and docking mode. In the system mode, users can issue two commands: "start" and "end" of an operation. They 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 4A. Whenever an operation is initiated, the "start" command must be issued. The "end" command means opening both hands as shown in Figure 4B. We used 5DT's Data Glove as a tool of expressing gestures and Polhemus 3DSpace Tracker as a motion tracking device (Figure 4C). 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. Docking mode consists of

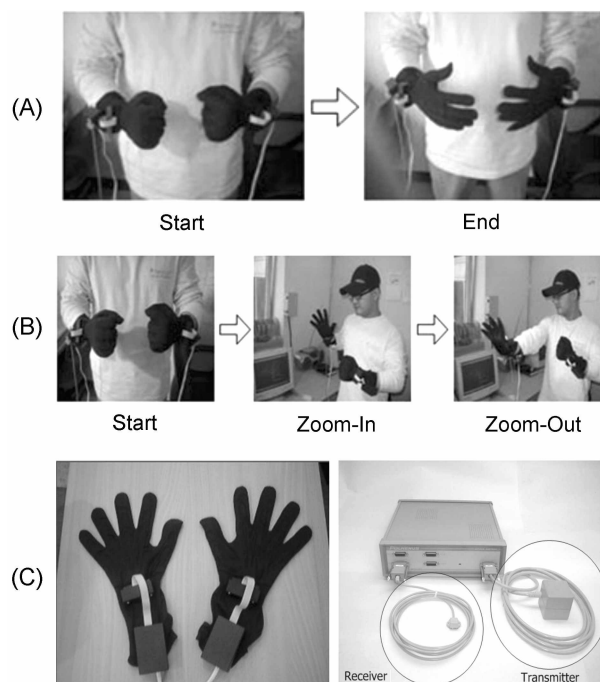


Figure 4. Examples of (A) modeling gestures, (B) data glove, and (C) motion tracking devices. The data glove features advanced fiber-optic flex sensors to generate finger-bend data. The tracker is VR equipment for the position measuring requirements of applications and VR environments. Tracker accurately computes the position and orientation of a small receiver as it moves through space.

Table 1. The definition for the action set in the MVVR

Symbol	Action	Symbol	Action
S	Start	RFO	Right Finger Open
E	End	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
RARM	Right Arm Right Move	LFIS	Left Finger in Separate
RALM	Right Arm Left Move	RFOA	Right Finger out Separate

three layers which are complex, receptor and ligand layers. The manipulation for the individual layer is possible in a natural way. Each layer can be selected by just clicking the equivalent one of the three icons. Users can pick the ligand using a forefinger, and then drag it to the active site of the receptor. In these sets of actions for the molecular docking, MVVR computes interaction energy between the ligand and the receptor in a real-time scale. Figure 5 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" causes a transition from a state to another.

We suggested a possible solution for the constraints of present molecular visualization tools. A conventional two-

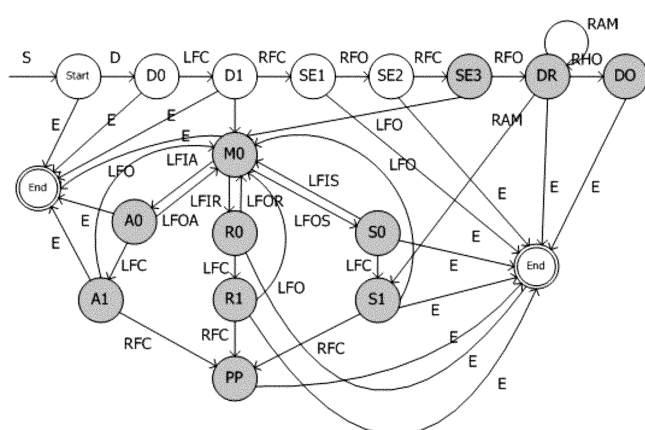


Figure 5. State transition diagram for docking. Each node represents a state of the docking procedure. Each action like "S", "E", and "LFC" causes a transition from a state to another.

dimensional monitor was 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 gesture set of researchers are used in molecule building procedures, and docking procedures. We developed new data structures for fast rendering and efficient computations of potential energy functions. The potential energies of molecular docking between the HIV protease as a receptor and the ligands were successfully calculated based on MVVR implemented with CHARMM parameters. Table 2 presents interaction energy values between the receptor and fifteen ligands obtained from the calculation by InsightII (Accelrys Inc. San Diego, USA) or MVVR. The results calculated by MVVR gave interaction energies very similar to those obtained by the InsightII program. We also checked the reliability of the

Table 2. Comparisons of interaction energy (kcal/mol) and RMSD (Å) values from the manual docking using InsightII and MVVR

PDB code	InsightII				MVVR			
	ΔE_{vibr}	ΔE_{elec}	ΔE_{total}	RMSD	ΔE_{vibr}	ΔE_{elec}	ΔE_{total}	RMSD
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	-16.25	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
1HFE	-1.24	-0.23	-1.47	0.39	-1.89	-0.65	-2.54	0.98
1HFF	-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
1UPJ	-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

molecular docking results. RMSD (Root Mean Squared Deviation) values of the docked structures between simulated ones and reference crystal ones were investigated as the index for the reliability. The average RMSD value was 0.99 Å for the InsightII calculation and 1.18 Å for the MVVR calculation, respectively. Therefore, the results of docking procedures using these two tools would not be significantly different. These results for the interaction energy and RMSD comparison by MVVR suggest the potential possibility of this new methodology in molecular modeling field.

In the future, we would like to remove data gloves and motion tracking devices. We probably use computer vision technologies to replace data gloves. It would be more economical way of viewing and manipulating three-dimensional structures of molecular models. The potential performance of MVVR as a novel molecular visualization program will be increased when it combines with Monte Carlo or Grid docking simulations in the future. Implementation of the Monte Carlo docking simulations with energy minimization¹⁶⁻¹⁸ to the MVVR system is now in progress.

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