# Molecular Virtual Reality System with Force Feedback Device

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## Abstract

We designed a novel concept of computer aided drug design system using virtual reality technologies, in particular the tactile sense technology, and developed a prototype. The most characteristic function of the system is enabling its user to "touch" and sense the electrostatic potential field of a protein molecule. The user can scan surface of a protein using a globular probe, which is given an electrostatic charge, controlled by a force feedback device. The electrostatic force between the protein and the probe is calculated in real time, and immediately fed back into the force feedback device. The user can easily search interactively for positions where the probe is strongly attracted to the force field. Such positions can be regarded as candidate sites where small chemical groups corresponding to the probe, functional parts of lead compounds, can bind to the target protein. Certain limitations remain, for example, only ten protein atoms can be used to generate the electrostatic field. Furthermore, the system can use only an globular probe, rather than drug molecules or small chemical groups. These limitations are due to our computer resources being insufficient. However, our prototype system has the potential to serve as a new application method as well as being applicable to conventional VR technologies, especially to force feedback technologies.

**Key words**: Force Feedback, Virtual Reality, Drug Design, PHANToM, Electrostatic Potential

## 1. Introduction

We developed a new drug design strategy utilizing virtual reality (VR) technologies, focusing especially on tactile sense technology. Then, we designed a molecular VR system for drug design according to this strategy, and developed a prototype. The prototype enables users to tactually sense electrostatic force fields surrounding proteins using a force feedback device. Users can scan protein molecules with various probes, which represent chemical groups and small molecules capable of becoming parts of drug molecules. Our concept and method are anticipated to be useful for designing new drugs in the post genome age.

Genome studies have advanced greatly over the past decade[1, 2)]. Many genes related to various diseases have been elucidated. Because each gene encodes the design for a protein, if the sequence of a gene governing a certain disease is decoded, it becomes possible to predict and analyze the molecular structure of the protein encoded by the gene[3)]. If the protein structure is determined, it may be possible to design new compounds, candidates for new drugs, which can specifically bind the protein[4)]. This is one of the important strategies of drug design based on genome science. Realization of this scenario would be feasible if the advanced computer science and engineering now available are applied creatively. Many drug design support systems have been developed for use in universities and pharmaceutical companies[5,6,7)].

However, such tools are not easy to use. In particular, these tools are not suitable for interactively manipulating molecules. Moreover, their functions are insufficient to express interactions between a drug molecule and a protein. Therefore, it is difficult to reflect the insights and experiences of the drug designer into new drug designs employing these conventional tools.

We speculated that these problems could be solved using VR technologies, because VR is suitable for achieving excellent user interfaces. The incorporation of VR into molecular science has only just begun. Several types of software for displaying 3D models of bio-molecules have been developed. Most of them are implemented using VRLM (Virtual Reality Modeling Language)[8,9,10]. However, drug design support using force feedback technology is still in its infancy. In this study, we attempted to use force feedback technology for molecular design, and succeeded in developing a prototype for a unique drug design system. We consider force feedback technology have enormous potential for improving the methodology of drug design.

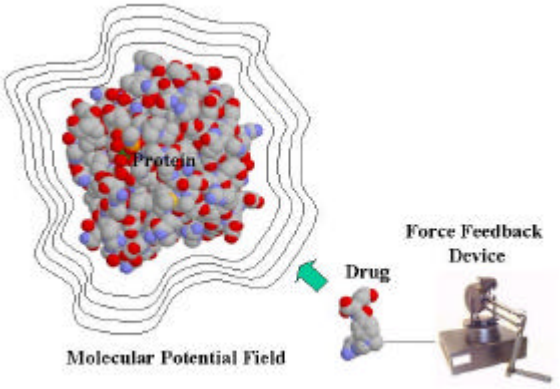


Fig. 1 Basic concept behind applying the force feedback technology to drug designing

## 2. The New Concept of The New Drug Design Method

The targets of drugs are protein molecules. Proteins are the only products of genes. These proteins have peculiar structures and functions necessary for maintaining life. A drug molecule binds only with a specific site of a specific protein, which is called the "target protein", and obstructs the function or changes the structure of the protein. The medicinal effect is the result.

Drug molecules approach the specific binding sites of target proteins guided by physical-chemical potential fields surrounding the proteins. The most important potentials are the electrostatic potential, the van der Waals potential, and the hydrogen bond potential. The van der Waals and hydrogen bond potentials, which operate only over short distances, work mainly to assure the final binding of drugs and proteins. In contrast, the electrostatic potential is thought to play major roll in attracting drug molecules to nearby the binding sites, because it can work over relatively long distances. Several experiments and simulations support this hypothesis [11,12].

The strength and sign of the electrostatic force produce drug molecule changes by altering molecular structure, the distance to the protein, and both posture and direction. Therefore, it is difficult to visually express the general electrostatic force potential commonly affecting all drugs.

However, it is feasible to make the electrostatic potential field available for tactile sensation using force feedback technology. Figure 1 illustrates this concept.

## 3. Potential Force Field

The molecular potential field surrounding a protein consists of electrostatic, van der Waals, and hydrogen bond potentials. The total potential energy between a drug molecule and a protein can be expressed by the following formula (1) [13,14,15].

$$E = \sum_{v=1}^{V} \sum_{w=1}^{W} (E_{lj}(v,w) + E_{el}(v,w) + E_{hb}(v,w)) \quad (1)$$

In the formula, V and W are the numbers of atoms in the drug and the protein, respectively. $E_{lj}$, $E_{el}$, and $E_{hb}$ are the van der Waals potential energy, electrostatic potential energy, and hydrogen bond potential energy between the v'th atom of the drug and the w'th atom of the protein, which are given by formula (2) to (4)

$$E_{lj}(v,w) = \frac{A}{d_{vw}^{12}} - \frac{B}{d_{vw}^{6}} \quad (2)$$

$$E_{el}(v,w) = \frac{p_v q_w}{K\varepsilon}\left(\frac{1}{d_{vw}} + \frac{(\xi+\varepsilon)/(\xi+\varepsilon)}{\sqrt{d_{vw}^{2} + 4 s_p s_q}}\right) \quad (3)$$

$$E_{hb}(v,w) = \left(\frac{C}{d_{vw}^{6}} - \frac{D}{d_{vw}^{4}}\right)\cos^{k}\theta\cos^{2}\psi \quad (4)$$

In these formulas, $d_{vw}$ is the distance between the v'th and the w'th atoms; $p_v$ and $q_w$ are the electrostatic charges of the atoms;. $K$ is the combination of a geometrical factor and natural constants; $\varepsilon$ is the dielectric constant of the protein surface; $e$ is the dielectric constant of the solvent; $s_p$ is the depth of the m'th atom of the drug molecule on the protein surface; $s_q$ is the depth of the n'th atom of the protein molecule on its surface; dmn is the distance between the m'th atom of the drug molecule and the n'th atom of the protein molecule.

The forces of each potential exerted on the v'th atom by the protein are given by formulas (5) to (7) as summations of differentiations by the distance $d_{vw}$ of these formulas.

$$F_{lj}(v) = \sum_{w=1}^{W} \left( -12\frac{A}{d_{vw}^{13}} - 6\frac{B}{d_{vw}^{7}} \right) \quad (5)$$

$$F_{el}(v) = \sum_{w=1}^{W} \left[ \frac{pq}{K\xi} \left[ \frac{1}{d_{vw}^{2}} - \frac{d_{vw}(\xi - \varepsilon)/(\xi - \varepsilon)}{(d_{vw}^{2} + 4s_p s_q)^{3/2}} \right] \right] \quad (6)$$

$$F_{hb}(v) = \sum_{w=1}^{W} \left[ \left[ 6\frac{C}{d_{vw}^{7}} - 4\frac{D}{d_{vw}^{5}} \right] \cos^{k}\theta \cos^{2}\psi \right] \quad (7)$$

The total force exerted on the drug is given by formula (8).

$$F_{Total} = \sum_{v=1}^{V} (F_{lj}(v) + F_{el}(v) + F_{hb}(v)) \quad (8)$$

Our ultimate goals are to calculate and interactively feedback the $F_{Total}$ to a force feedback device in real time. However, achieving these goals simultaneously appears to be very difficult. Therefore, we designed and implemented the simple prototype described below.

## 4. System Concept, Requirements, and Design of the Prototype

We designed and developed a prototype system by which the variations in the electrostatic force can be felt while scanning the surface of the protein with the drug molecule as a probe. The following are the system concepts for our prototype system.

(a) A protein molecule and a drug molecule are placed in a VR space. The molecules are displayed as 3-dimensional computer graphics.

(b) The drug molecule is moved and its posture controlled by using a force feedback device.

(c) The drug molecule is used as a probe, and with this probe, the user can scan the surface electrostatic potential field of the protein. Atoms of the molecules are assigned sizes based on their Van der Waals radii, and these are restricted to avoid adherence to each other.

(d) The electrostatic force, which the probe receives from the potential, is calculated and fed back to the force feedback device in real time.

The requirements for the prototype system are as follows.

Computers: A graphic workstation (OCTAINE MX1) and a Windows NT PC(MMX Pentium II).

Force Feedback Device: PHANToM™ Desktop

Force Feedback: Output 0 to 1.5 N(Newton). 1au (atomic unit) = 1N.

Force Potential: generated using a maximum of 10 protein atoms.

Molecular Graphics: Space filling model[16], Connolly model[17,18].

Probe: Spherical. The user can set the charge and the radius. Position is input by PHANToM™.

Manipulation of protein: Rotation by X-Y-Z axis.

A graphic workstation is used to provide a graphical user interface and display a VR space. A Windows NT personal computer (PC) is used to control the PHANToM™. Initially, we planned to draw real time molecular graphics using the same PC, but this was difficult because the CPU power was insufficient. Therefore, we divided the software between two computers. The position of the probe is input by the PHANToM™ interactively. The PC immediately calculates the electrostatic force working on the probe and then feeds this information back to the PHANToM™. The force exerted on the probe is fed back to the PHANToM™ according to a linear relationship based on 1AU(atomic unit) = 1N(Newton). However, we limited the maximum output of the PHANToM™ to 1.5N, to avoid breakdowns.

It is necessary to calculate the electrostatic force on the probe using all atoms of the protein, but we had to limit the number of atoms to 10 to calculate the power in real time. As mentioned above, the probe is a spherical object, and an arbitrary radius and charge can be assigned to it. Posture control of the probe was not attempted at this time.

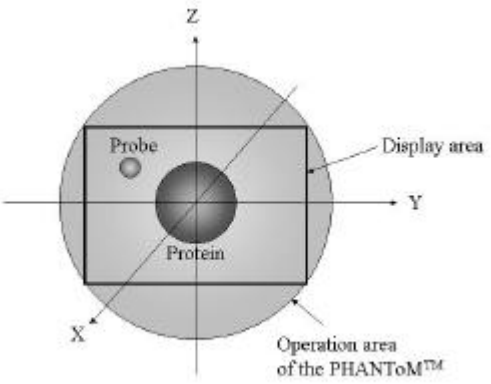


Fig. 2. VR space coordinates

We coordinated the VR space as shown in Figure 2. We defined the centers of the PHANToM™ and the protein

so as to be corresponding to the center of the VR space. The radius of the VR space was defined as being equal to the operation radius of the PHANToM™. To facilitate scanning, the protein should be rotatable to the X-Y-Z axis of the VR space.

The prototype system was designed as shown in Figure 3. The PC and the workstation are linked by a TCP/IP LAN, which inter-exchanges the data on the coordination of the probe and the protein.

The workstation software provides a graphical user interface, which consists of functions for drawing and rotating a protein molecule, transmitting data to the PC, and drawing and moving the probe in the VR space according to the coordinate data transmitted from the PC. It also provides the user interface needed to change the properties of the probe. Several kinds of probes can be registered, and the user can select and change them interactively. Protein 3D data can be obtained from the Brookheaven Protein Data Bank over the Internet ([On-line]. Available: http://www.rcsb.org/pdb/). The user selects ten atoms to calculate the electrostatic force. The MOPAC, among the most popular software for computational chemistry, is used to calculate the charges of the selected atoms.

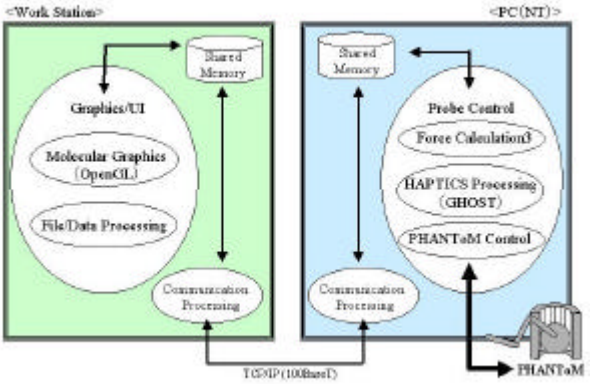


Fig.3 System design of the prototype

The properties of the probe, the protein structure data, and information on the rotation of the protein and the 10 atoms selected by the user are stored in shared memory and sent to the PC. On the PC, the electrostatic force is calculated and fed back to the PHANToM™. The PC also calculates the coordinates of the probe in the VR space according to the movements of the PHANToM™, and sends the results to the workstation.

## 5. Implementation and Results

Figure 4 shows the user interface of the workstation software. The graphical user interface was implemented using Open GL, and the internal processing functions were implemented using C++ programming language. The left half of the user interface shows the VR space, in which a protein is displayed in it. Prominently displayed points are the atoms selected to generate the force field. Several control buttons are also implemented in this area. All of the buttons are implemented in VR, and they can be selected by using the PHANTOM™. The right half shows system status and the communication situation with the PC.

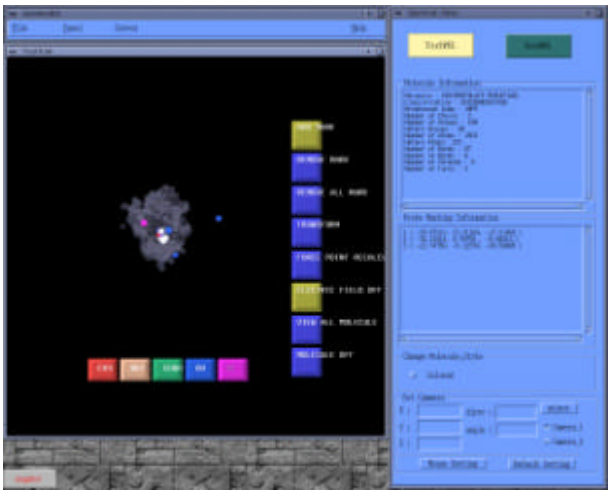

Fig. 4 User interface of the workstation software

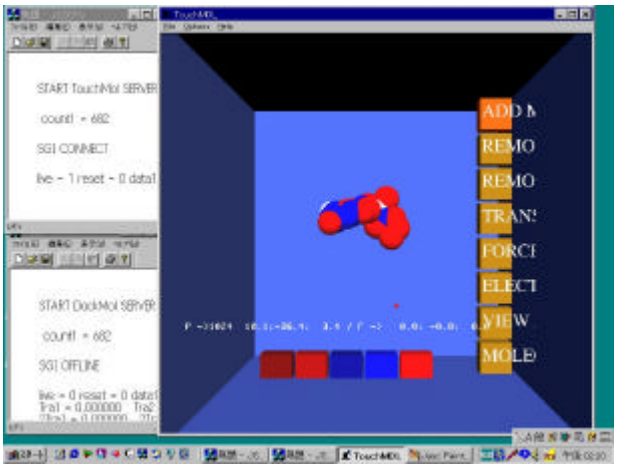


Fig.6 User interface of the PC software

The PC software was implemented using Visual C++ and the GHOST, the control function library for the PHANToM™. Figure 5 shows the user interface of the PC software. It has two windows, one is for displaying the same VR space as that of the workstation, and another is to monitor the communication status. The quality of the molecular graphics is much lower than that of the workstation, such that the VR space of the PC is mainly for debugging. However, it may be possible to generate and display high quality molecular graphics on the PC when its CPU power is greatly improved. The workstation will become unnecessary, and the system

design will be simpler.

We carried out various tests to confirm the system to be correctly implemented. For example, a virtual atom with a radius of 1Å (approximately equal to that of an oxygen atom) was given a charge -1 and placed in the VR space. We then scanned it using a probe with a radius of 0.5Å (approximately equal to that of a hydrogen atom) and a charge of +1. The probe was thereby confirmed to be strongly attracted to the virtual atom. The electrostatic force was in inverse proportion to the second power of the distance. It was also felt that the attractive force increased rapidly as the probe approached a virtual atom, and that the force was rapidly attenuated as the probe was moved away. We also increased the number of virtual atoms and repeated the tests, ultimately concluding that the system had been implemented correctly.

Next, we evaluated the system employing actual protein data. We used several enzymes which are known to be targets of anti-cancer drugs. For example, dihydrofolate reductase, one of the most important enzymes for cancer chemotherapy, was prepared. The binding sites of these drugs have been identified. From atoms that form the binding site, ten atoms on the exposed surface of the protein were selected, and the force field was generated. The charges of these atoms were calculated by MOPAC. We scanned the force field using the PHANToM™ (Figure 6), and succeeded in "feeling" the complex structure of the electrostatic force field. Because the probe was subjected to attractive and repulsive forces from the ten atoms simultaneously, the direction and the strength of the force changed even when the probe was moved only slightly. Moreover, it was possible to "feel" situations in which the probe was not able to easily escape local minimal points when captured by such points. It was confirmed that the force changed when the radius and charge of the probe were changed. These results confirmed the ability to scan and "feel" the electrostatic potential field of a protein using tactile sense technologies.

Fig. 6 Illustration of the scanning of a molecule using the PHANToM™

## 6. Discussion

We developed a new drug design concept based on force feedback VR technology, and implemented a prototype system which enables users to "feel" the electrostatic potential field surrounding a protein molecule. The prototype still has several limitations. It cannot account for all electrostatic interactions between the protein and the probe, but we believe that our system, with certain improvements, will be useful for molecular design in the future.

To improve the system sufficiently to allow practical use, we must overcome several technological hurdles. First, it is necessary to improve the computer power by 10 to 100 fold. Our prototype can use only 10 atoms to generate the electrostatic field, but the drug binding site of a protein is usually composed of several hundred atoms. Network parallel processing may be an effective means of to increasing the calculation power by tens of folds.

At this time, we used only the electrostatic potential. However, several other potentials including van der Waals potential and hydrogen bond potential are more important than the electrostatic potential in the final stage of creating chemical bonds between a drug and a protein. It is necessary to consider these potentials in searching for probe binding sites more accurately. To achieve this, far greater computer resources may be necessary.

It is also necessary to improve the probe. Herein, the probe was globular and had a single charge. However, our goal is to use a drug molecule as the probe. A drug molecule generally consists of 10 to 100 atoms, which have individual charges and various other chemical properties. Additionally, drug molecules have their unique shapes and structures. Therefore, it will necessary to use the posture control if drugs are to serve as probes. We plan to introduce the control theory of a robot arm into our system. We believe network parallel computing may also be needed to achieve all of the calculations in real time.

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