Innovation of Visualized Interactive Tools for Learning Molecular Simulation Curriculum

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ABSTRACT: The goal of molecular simulation stability is to predict the detailed structure and physical properties of molecules in bioengineer’s experiment curriculum. This work succeeds in citing minimum energy and some computer graphics technologies to support this theme. Molecular structure is that given the uncountable number of possible conformations for a protein, how we can determine the lowest energy structure. In this article the authors employed the previous researches-WebDeGrator and some existing molecular graphics tools to simulate various protein folding, ligand acceptor interaction, and molecular visualization. For this reason, bioengineer experimental curriculum will be visualization and interactive among learning members. Finally, Simpson’s Taxonomy and pre- and post-test examinations are applied to System Evaluation, and molecular simulation and minimum energy will be discussed. © 2009 Wiley Periodicals, Inc. Comput Appl Eng Educ; Published online in Wiley InterScience (www.interscience.wiley.com); DOI 10.1002/cae.20226

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INTRODUCTION

Computers graphics is a vital technology in modern medicinal chemistry and is also important in molecular structure and properties prediction. Rapid advances in computer hardware and software imply that many operations, which were once the preserve of the expert can now be carried out on ordinary laboratory computers by users with little specialist expertise in the molecular or quantum mechanics involved [1]. The early 1990s saw significant optimism that
computer-aided drug design (CADD) would revolutionize the development of drugs. Although drug design is an extremely complicated process and still not completely understood [2], computer graphics technology can now construct vector models of chemical structures and manipulate them in real-time, offering the ability to interactively investigate computer models of ligand structures and their binding interactions with a receptor. Furthermore, silicon screening of compound databases is currently among the most popular chemoinformatics applications in pharmaceutical research [3].

In addition to improving molecular simulation technology in learning, this investigation employed computer modeling to accomplish molecular structure and properties prediction in WebDeGrator [4]. The computer modeling system applied herein was based on previous computer graphics and virtual reality searches [4—6]. This study discusses the folding of protein, DNA, amino acids, protein, SARS, and viruses in the 3D molecular visualization interactive system. These themes are helpful in researching and establishing novel valuable modern bioinformatics curriculum.

**VISUALIZE PROTEINS STRUCTURES BY WEBDEGRATOR 3D ENVIRONMENT**

A molecular graphics visualization tool is necessary to view the structures that are encoded by these atomic coordinate files (which have the extension .pdb), and to manipulate the images to view the molecules from various perspectives. Without an appropriate tool, the PDB file is read as a text file listing each atom and its numerical coordinates in 3D space [7].

To visualize the molecule directly when the link to a PDB files is activated, two configuration changes are necessary on the computer system:

- The server sending the file must be set up to inform the browser that the file is a pdb file, a chemical MIME type.
- The browser must have a molecular graphics visualization tool that can recognize that MIME type (in this case, a pdb file) as either a helper application or a plug-in.

Proteins are a class of macromolecules, which play a significant role in biological processes. A 3D structure of protein is valuable to researchers for designing experiments to study the functions of proteins. To visualize a protein whose structure has been obtained experimentally, several tools such as Roger Sayle’s RasMol and MDL’s Chime have been developed [8]. Most protein structures are solved experimentally. This process is boring and time-consuming. Homology modeling is becoming a more accessible and easier method for detecting a protein’s 3D structure. The users construct a homology model of their protein based upon its sequence similarity to a protein whose structure has already been found experimentally. Building an approximate model of a protein can provide a starting point for experimental design. Presently, the most popular free software programs are SwissPdb Viewer and DINAMO. SwissPdb Viewer, which is closely linked to an automated protein modeling server Swiss-Model, provides a user friendly interface to analyze several proteins simultaneously [9]. DINAMO provides interactive protein alignment and comparative modeling, and runs as either a web-based applet in conjunction with the Internet browser plug-in Chime, or as a standalone application using RasMol as molecular graphic display [10].

Visualization and virtual reality are novel tools in computer science for computational modeling with typical applications in computer-aided design and computer-aided engineering. Previous published investigations have employed the WebDeGrator system to establish molecular computer modeling for the docking process [11—13]. This study demonstrates examples in protein folding kinetics and drug docking computations. In this study, the application of WebDeGrator for bioinformatics education, particularly for 3D structural analysis of biomolecular system, is discussed. Surface- and volume-based visualization provide three-dimensional theories of biomolecular structures. Virtual reality offers a channel to reach-into the molecular space in an immersive and interactive environment (Fig. 1).

**MINIMUM ENERGY FOR PROTEIN FOLDING STRUCTURE**

The major stabilizing forces of protein structures are hydrophobic and electrostatic forces. While consensus exists on the hydrophobic contributions, the roles of electrostatic interactions in protein stability are uncertain. Significant progress has been made in modeling electrostatic effects (Fig. 2).

Molecular dynamics emerged as one of the first simulation methods from the pioneering applications to the dynamics of liquids by Alder and Wainwright and by Rahman in the late 1950’s and in the early 1960’s. According to statistical mechanics, physical quantities are represented by averages over microscopic states of the docking system. Generally,
the intention of protein folding is to find the best appropriate stability state for existing when the free energy with thermodynamics and molecular mechanics arrived at the lowest point. In nature, protein folding have finished automatically in very short time and become a dynamic stability. Unfortunately, some protein cannot afford to find the energy minimum point for existing stable state. In many experiments, the best final state of protein folding is that it has the lowest free energy and already reached the key point. Some diseases cause of protein folding is incomplete and error. In the other reasons, some compounds are not suitable due to their folding are also error or incomplete. Therefore, this study will discuss that how to find out the energy lowest point via compute simulation force field, and furthermore utility some examples for students in learning bioengineer experiment simulation courses.

This investigation applies AMBER force field simulation for finding out the statistical mechanics of molecular in the experiment simulation courses. A protein molecular has very important feature by its atom type. Therefore, this studies use the Ullman’s algorithm to solve the molecular system for drug docking. Each element represents one atom or unit protein the interaction relationship in the docking system. These elements are produced from the scoring function with various force field simulation and thermodynamics.

MINIMIZATION DEFINITIONS

Given a function:

\[ f = f(x_1, x_2, x_3, \ldots, x_N) \]  

(1)

Find values for the variables for which \( f \) is a minimum:

\[ \frac{\partial f}{\partial x_i} = 0, \quad \frac{\partial^2 f}{\partial x_i^2} > 0 \]  

(2)
For an N-atoms system expand the energy around $x_k$:

$$v(x) = \frac{v(x_k) + (x - x_k)v'(x_k) + (x - x_k)^2 v''(x_k)}{2} + \ldots$$

(3)

Gradient (first derivatives) vector:

$$v'(x_k) = g_k = \left( \frac{\partial v}{\partial x_1}, \frac{\partial v}{\partial x_2}, \ldots, \frac{\partial v}{\partial x_N} \right)$$

(4)

Hessian (second derivatives) matrix:

$$v''(x_k) = \begin{bmatrix}
\frac{\partial^2 v}{\partial x_1^2} & \frac{\partial^2 v}{\partial x_1 \partial x_2} & \ldots & \frac{\partial^2 v}{\partial x_1 \partial x_N} \\
\frac{\partial^2 v}{\partial x_2 \partial x_1} & \frac{\partial^2 v}{\partial x_2^2} & \ldots & \frac{\partial^2 v}{\partial x_2 \partial x_N} \\
\ldots & \ldots & \ldots & \ldots \\
\frac{\partial^2 v}{\partial x_N \partial x_1} & \frac{\partial^2 v}{\partial x_N \partial x_2} & \ldots & \frac{\partial^2 v}{\partial x_N^2}
\end{bmatrix}$$

(5)

Most minimization method can only go downhill and so locate the closest minimum. No minimization method can guarantee the location of the global energy minimum. According to my previous researches, I employed Lyapunov stability theorem to improve the molecular docking cost. [14–17]

### 3D MOLECULAR VISUALIZATION

INTERACTIVE—ASPIRIN, HIV PROTEASE: SARS TARGET I TGEV 3CL-PRO

The following three interactive demonstrations illustrate how 3D molecular visualization methods can be used in drug design. To view them, users must download the Chime plug-in, which allows the user to visualize the chemical structure within the web browser.

In Figure 3a, the box on the left depicts a three-dimensional representation of an Aspirin molecule. This representation is a conventional ball-and-stick model where the balls indicate atoms, connected by sticks for bonds. It approximates the positioning and connectivity of the real atoms in three dimensions. The atoms are colored by atom type: Carbon atoms are gray, and Oxygen atoms are red. Nitrogen atoms (not present in this molecule) are colored blue. Figure 3b depicts the electrostatic potential using color coding (Red-White-Blue). Blue coloring signifies positive charge, whereas red and white coloring denotes negative charge and neutral charge. The electrostatic surface shows that the negative charge in this molecule is centered on the Oxygen molecules.

Figure 4a illustrates a ball-and-stick model of the HIV Protease protein with docked inhibitor. Since proteins are formed of “strings” of building-block molecules known as amino acids, they are sometimes easier to view using a simplified ribbon rendering. Figure 4b depicts how drugs fit into the protein, using a “volume rendering” of the protein. Volume rendering can be performed using a molecular surface.

Scientists at CDC and other laboratories have identified a previously unrecognized coronavirus in patients with SARS. While the new coronavirus remains the leading hypothesis for the cause of SARS, other viruses are still considered as potential causes. Coronaviruses are a group of viruses with a halo or crown-like (corona) appearance when viewed under a microscope. These viruses are a frequent cause of mild to moderate upper-respiratory illness in...
Coronaviruses can survive in the environment for up to 3 h. SARS is a respiratory illness that has recently been reported in Asia, North America, and Europe. Three-dimensional structures are more resistant to alteration than the primary “sequence”, and hence “SARS Target 1” is expected to have the same functionality and active site across all strains, and allow the selection of compounds with broad activity against all coronavirus strains [11] (Fig. 5).

EXPERIMENT 1: PROTEIN SERIES

Proteomic analysis can be divided into three main components: expression proteomics, bioinformatics analysis, and functional proteomics. While the most important part of proteomic analysis is the functional study, expression proteomics may be a necessary initial step. To date, most proteomic studies have compared protein expression in normal and disease states in cells and tissues. Expression proteomics alone, however, does not provide any functional or physiological significance. Functional proteomics and other functional studies become important after candidates or hypotheses have been determined from initial expression studies. Figure 6 summarizes this typical proteomic method [5].

Typical processes in expression proteomics are protein extraction and separation; protein identification, and bioinformatics-based analyses. Protein extraction isolates the proteins from tissues. Protein separation can be performed either by 2-DE or by LC
approaches. The proteins are then detected using various MS methods. Bioinformatics-based analyses are employed to obtain protein information to guide further functional proteomic studies. The final step in proteomic study is to create a new hypothesis from both expression and functional proteomic data. The novel hypothesis is then examined by various approaches.

Figure 7 shows a flowchart of the system architecture for protein structure prediction. Beginning at the top block diagram, three sequence samples of bamboo shoot (Native, 15 cm out of the Ground and 30 cm out of the Ground) were received from National Taiwan University, Biotechnology department in summer biotechnology experiment courses in 2005. The three samples were analyzed via BLAST and SAS bioinformatics websites. A similar sequence was searched using PDB search to discern whether the sequence was homologous. Then, protein fold recognition or Comparative modeling was performed. Finally, the 3D structure of bamboo shoot protein was predicted. Figure 8a,b shows the 1 DE SDS–PAGE and 2-DE SDS–PAGE result. Results of this experiment, in which got three different series were obtained in every stage (Table 1).

Table 2 presents the characteristics of the protein series as determined using the ProtParam tool
Extinction coefficients:

(1) Native.

Conditions:

(a) 6.0 M guanidium hydrochloride.
(b) 0.02 M phosphate buffer.
(c) pH 6.5.

Extinction coefficients are in units of $\text{M}^{-1} \text{cm}^{-1}$ (Table 3).

(2) Ground (10 and 30 cm).

As no Trp, Tyr, or Cys were discovered in the zone considered, the protein should not be visible by UV spectrophotometry.

Finally, the bamboo shoot 3D structure was visualized by serial bioinformatics methods on the web-based browser. Figure 9a–c illustrates this visualization of results of this experiment.

Because of the fast personal medical rise, personal protein analysis technology is very important for contrasting between normal samples and diseased or treated samples. If two different 2D gel electrophoresis are analyzed and an unusual protein is identified, the protein may indicate a disease source. According to the protein characterization analysis, the 3D structure was obtained and the protein folding was searched. Setting as target receptor, some ligand docking was performed on this target from compound libraries for drug design and discovery (Fig. 10).

### EXPERIMENT 2: TWO PARTICLES INTERACTIVE BY FORCE FIELD SIMULATION

The equivalent first-order molecular motion system is:

$$x' = y, \quad y' = -\left(\frac{k}{m}\right)x$$  \hspace{1cm} (6)

### Table 1 Results of This Experiment

| Stage          | Protein series | PI  | MW     | Formula                      |
|----------------|----------------|-----|--------|------------------------------|
| Native         | LNYPAFQA       | 5.52| 923.04 | $C_{44}H_{62}N_{16}O_{12}$   |
| Ground (10 cm) | DNENENN        | 3.57| 847.75 | $C_{30}H_{42}N_{13}O_{18}$   |
| Ground (30 cm) | SGAGTGN        | 5.24| 562.5  | $C_{20}H_{34}N_{8}O_{11}$    |

### Table 2 Characteristics of Protein Series

| Item           | Stage               | Negative charged | Positive charged | Instability index | Aliphatic index | Grand average of hydropathicity |
|----------------|---------------------|------------------|------------------|-------------------|----------------|-------------------------------|
| Native         | 0                   | 0                | 0                | 48.25 (unstable)  | 73.75          | 0.037                         |
| Ground (10 cm) | 3                   | 0                | 0                | 8.57 (stable)     | 0              | -3.5                          |
| Ground (30 cm) | 0                   | 0                | 0                | -39.94 (stable)   | 14.29          | -0.629                        |
whose general solution is given by
\[ x = A \cos \left( \frac{k}{m} t + \phi \right), \]
\[ y = -A \sqrt{\frac{k}{m}} \sin \left( \frac{k}{m} t + \phi \right) \tag{7} \]
where \( A \) and \( \phi \) represent constants. Suppose that \( k/m = 4 \), then the orbits defined by the ellipses form as:
\[ x^2 + \frac{y^2}{4} = A^2 \tag{8} \]
whose minimal distance from the origin is \( |A| \) and maximal distance is \( 2|A| \). Significantly if \( 0 < A_1 < A_2 \), the ellipse defined by \( A_2 \) encloses the ellipse defined by \( A_1 \). Thus, if the \( \varepsilon \) in the stability definition is interpreted as \( 2|A| \), and if \( \delta = \varepsilon/2 \), then clearly if \( (x^2(t) + y^2(t))^{1/2} < \delta \), then \( (x^2(t) + y^2(t))^{1/2} < \varepsilon \), for all \( t > 0 \), and the molecular system (11) for the Hooke’s law spring is stable at the origin (Fig. 11).
EXPERIMENT 3: PROTEIN FOLDING FOR SEARCHING THE MINIMUM ENERGY LOCATION

See Figure 12.

EXPERIMENT 4: COMPUTER ANIMATION SIMULATION AND RMSD ANALYSIS OF AUREUS STAPHYLOCOCCAL PROTEIN FOLDING:

The RMSD is Root-mean-square Deviation. An RMSD value less than 0.9 Å is acceptable [15]. As the van der Waals force is the most influential factor in $\lambda_{\text{max}}$, and the among various molecular distance affects the van der Waals force, this investigation applied the Lyapunov minimum energy equation to determine that $\lambda_{\text{max}}$ is smaller than $\varepsilon$, where $\varepsilon \in \mathbb{R}$ represents the convergence value of the distance. When $\varepsilon$ is less than RMSD, the molecular system has the more close global minimum energy conformation and the molecular system is stable (Fig. 13).

Aureus Staphylococcal Protein A, immunoglobulin-binding domain B (Fig. 14).

Most approaches for comparing structures employ superposition and dynamic programming. Superposition can be utilized to identify and score equivalences, by measuring how closely the equivalent pairs can come together. The structures can be considered to be on top of each other so that the equivalent elements from the two structures lie as close as possible. If the geometry of the structures is not changed in this process, the configuration is referred to rigid-body superposition. The score is then a function of the distances between the elements of each equivalent pair. The root of the mean of the squares of the distances is applied, and is termed the root-mean-square deviation (RMSD). Low RMSD values are most suitable, and below about 0.9 Å the structure is stable [10,16].

\[
\text{RMSD}(E) = \min_T \sqrt{\frac{1}{\sum_{i=1}^{r} w_i} \sum_{j=1}^{r} w_i(Tx_i - \beta_j)^2} \tag{9}
\]

Let $(\alpha_1, \beta_1), \ldots, (\alpha_r, \beta_r)$ represent the coordinate sets of the equivalent elements of the equivalence

Figure 11 This molecular system is stable but not asymptotically stable [14]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 12 (a,b) Protein folding indicated by the JAVA program and the EMC tool to simulate the protein third structure. (The video film was made using Wincam 2000). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 13 Discriminate various molecular by each ball with difference color. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
E (\(\alpha_i\) from A and \(\beta_i\) from B structure, where the A structure is unfolded and the B structure is folding, for three dimensions a coordinate set consisting of three values.) A transformation \(T\) was discovered for A which minimizes the coordinate RMSD, where \(w_i\) denote weights corresponding to each pair \((\alpha_i, \beta_i)\) and often set to 1. In this investigation, these measures were experimentally shown to have a close to linear relation, and the RMSD approached 0.76 Å (Table 4).

Table 1 Computer animation simulation and RMSD analysis of Aureus Staphylococcal protein folding [8,10,14].

| Protein folding analysis | RMSD (Å) | Free energy (kcal/mol) |
|--------------------------|----------|------------------------|
|                          | 6.3      | 1.75                   |
|                          | 3.7      | 1.26                   |
|                          | 1.4      | 0.93                   |
|                          | 0.86     | 0.74                   |
|                          | 0.72     | 0.32                   |

EXPERIMENT 5: EXHIBITING DNA AND 20 AMINO ACIDS IN WEB-BASED BROWSER

See Figures 15 and 16.

CURRICULUM EVALUATION AND DISCUSSIONS

A system evaluation is conducted to evaluate system performance. Related results are employed to revise the learning process to in turn improve the system performance. Therefore, Simpson’s Taxonomy (Simpson, 1967) and pre- and post-test examinations are applied to System Evaluation. Biology correlative Students at National Chin-Yi University of Technology, Taiwan who were enrolled in Bioinformatics and information team participate in completes the test. \((N = 20)\) Examination questions are classified according to Simpson’s seven classes. Simpson provided a psychomotor taxonomy to develop behavioral objectives, which is suitable for use learning process evaluation that is based on constructivism. Simpson’s Taxonomy in the following:

Table 4 Computer Animation Simulation and RMSD Analysis of Aureus Staphylococcal Protein Folding [8,10,14]

Figure 14 Protein folding depicted by computer animation simulation. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 15 Example of dA-dT and dG-dC base pair as found within DNA double helix[7]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
5. Complex overt response: Behavior is skilled, and involves complex movement patterns, which are quick, accurate and coordinated—resolution of uncertainty and automatic performance.

6. Adaptation: Modification of movement patterns to fit special requirements or to achieve a problem situation.

7. Origination: Creation of new movement patterns to match a particular situation or problem. Learning outcomes emphasize creativity, which is based upon highly developed skills.

Compare the pre- and post-test examinations, 10 questions, each of which asks the student to assess his or her level of knowledge level. The class’s level understanding ranges from 0 to 10.

Figure 17 demonstrates the examination results and lists some generalized conclusion:

1. After students used WebDeGrator, the system gained lower standard deviation and variation values in the post-test scores analysis. The standard deviation value and the variation value decreased by 74.1% and 93.6%, respectively. This reveals that WebDeGrator promotes every student’s learning outcome potential.

2. After students use WebDeGrator, the post-test score ascertained that WebDeGrator system could aid in learning biology courses (Compare the rings of the pre- and post-test radar chart).

3. After using WebDeGrator, originality, adaptation, and complex overt response are promoted obviously.

4. WebDeGrator applies constructivism and VR technology to learning, which increases student’s biologics capabilities, particularly origination.

Figure 16 (a,b) The 20 amino acids shown in the webpage for molecular visualization [18]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 17 Course evaluation charts. Comparison of the pre- and post-test examinations results. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
5. WebDeGrator reduces the gap between origination and perception capabilities.
6. Due to Simpson’s Taxonomy, the move from perception to origination is a gradual process.

Therefore, although students construct knowledge and experiences repeatedly, they will be more proficient in the lower layers, such as perception, set, guided response, and mechanism. The result will encourage student’s origination and influence them to construct more appropriate knowledge and experience.

Table 5 shows that students assess their own understanding of the course topics as low (14.20/10 = 1.4) before the course and as very good (73.21/10 = 7.3) by the end of the course. A dependent t-test shows that the average gain score for the students who took both pre- and post-test is statistically significant with $P < 0.001$. Compared with quiz and exam scores, this was a fair assessment. Therefore, students did gain a good understanding of the subjects.

Reactions from students were also very positive. Here are some typical comments from an attitudinal survey:

The protein folding programs were very nice and helpful.
Run-time simulation assignments let us have much creativity.
The assistant helped understanding immensely.

CONCLUSIONS

Visualization technologies were employed to promote the research on structure biology:

(1) The folding of various proteins was studied, and the force field application was computed, applying a novel technology in exhibiting the protein structure with describes their function.
(2) The function genomic was searched for personal medicine and drug design.
(3) The computer modeling technologies were enhanced, and the reliable and precise ratio in drug docking reinforced.

This investigation seeks to improve molecular computer simulation technology. Furthermore, many examples for molecular visualization and protein folding in practice have been exhibited. The final goal of this research is to progress computer modeling technologies and reinforces the reliable and precise ratio in bioinformatics. We believe that this investigation succeeds in integrating biology, information technology (IT), system engineering, and chemistry into modern bioinformatics curriculum. Important research will continue in the future.

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