International Journal of Innovative
Computing, Information and Control
Volume 8, Number 6, June 2012

 ISSN 1349-4198
pp. 4319–4332

EMPLOYING REDUCED ORDER APPROACH FOR COMPUTING PROTEIN FOLDING VIA LANGEVIN EQUATION AND LYAPUNOV THEOREM

Wen-Tsai Sung[1,*] and Hung-Yuan Chung[2]

[1]Department of Electrical Engineering
National Chin-Yi University of Technology
No. 57, Sec. 2, Zhongshan Rd., Taiping Dist., Taichung 41170, Taiwan
*Corresponding author: songchen@ncut.edu.tw

[2]Department of Electrical Engineering
National Central University
No. 300, Jhongda Rd., Jhongli City, Taoyuan County 32001, Taiwan

Received March 2011; revised September 2011

Abstract. *Molecular structure computation involves an NP-complete algorithm. The order of the distance matrix is especially important, and reduced order processing is attempted to accelerate the folding computation. In my previous researches, the Ullman algorithm and the scoring function with force field simulation are used to reduce the dimensionality of the determinant and evaluate some important parameters for molecular docking acceleration. Additionally, the emergence of brand-new molecular structure processing is expected, and in particular, a simpler and more effective computation model can be established. This paper succeeds in using the Langevin Equation and Laplace's theorem for reducing molecular order, and employing Lyapunov theorem to delete some points that have local minimum energy for accelerating the calculation of protein folding.*
Keywords: Drug docking, Minimum energy, Protein folding, Molecular visualization

1. **Introduction.** Folding proteins are nanomachines before proteins can undertake their biochemical function; they assemble themselves, which is known as "folding". The process of protein folding, while essential to virtually all of biology, remains a mystery. Furthermore, when proteins do not fold correctly (i.e., "misfol"), serious effects can arise, including many well-known diseases, such as Alzheimer's, Mad Cow (BSE), CJD, ALS, and Parkinson's disease [1].

In order to perform protein function (e.g., enzymes or antibodies), proteins must take on a particular shape that assemble themselves before they do their work. One of the study goals is to simulate protein folding in order to understand how proteins fold so quickly and reliably, and to comprehend how to make synthetic polymers with these properties and find out the binding activity sites. Some diseases such as Alzheimer's disease, cystic fibrosis, BSE (Mad Cow disease), an inherited form of emphysema, and even many cancers are believed to result from protein misfolding [2]. Proteins misfolding can clump together that can often gather in the brain which is thought to lead to the symptoms of Mad Cow or Alzheimer's diseases.

Not only do proteins self-assemble fold but they do so surprisingly rapidly, sometimes in only a millionth of a second. While this time is very fast on a person's timescale, it is remarkably long for computers to simulate. In fact, a computer takes about a day to simulate a nanosecond (1/1,000,000,000 of a second). Unfortunately, proteins fold on a timescale of tens of microseconds (10,000 nanoseconds). Thus, a computer would take

10,000 CPU days to simulate folding; i.e., 30 CPU years, this is a long time to wait for one result [3]. Although the computer hardware is to change with each passing day, the computation loading is still heavy and wastes a lot of time. The better solution is that we employed reduced order approach to enhance the protein folding simulation. The reduced order approaches include Lyapunov rule, Langevin Equation, molecular force field simulation, and Laplace's theorem surfaces. Protein folding is receptor structure measure for pro-docking. In the following, we would like to discuss protein folding simulation and docking related content.

A promising solution to this challenge is to employ the Lyapunov function on the docking that observes the binding site points. Through the direct Lyapunov method, the global minimum energy site is extracted from various binding sites. This approach is quite reasonable in a drug molecule in which the molecule's motion is derived from the applied energy and control theory. An alternative means is to solve the eigenvalue λ of the drug docking dynamic system and determine whether λ is less than the convergence value ε from the initial state to an infinitely long time. If the docking system conforms to this condition, then the system is stable. If the convergence rate of the eigenvalue λ is directly proportional to the Lyapunov exponential function, then the docking system is Lyapunov asymptotically stable. This scheme is termed the "indirect Lyapunov method" [4].

2. **Reduced Matrix Order via Laplace's Theorem.** Laplace's theorem provides a convenient way of calculating determinants using a computer. Equation (1) is Laplace's formula:

$$\det(A) = \sum_{j=1}^{n} A_{i,j} C_{i,j} \tag{1}$$

where $C_{i,j}$ denotes the matrix cofactors; $C_{i,j}$ is $(-1)^{i+j}$ times the determinant of the matrix that is obtained from A by removing the ith row and the jth column.

Example 2.1. *Find the determinant of the following distance matrix (C_3H_2);*

$$\begin{bmatrix} 1 & -3.2 & 1.5 & 1.2 & 0 \\ 3.2 & 1 & 5.4 & 0 & 0 \\ 1.8 & 6.3 & 1 & 2 & 2.3 \\ 0.1 & 0.2 & 0 & 1 & 9 \\ 0 & 0 & 0 & 0.3 & 1 \end{bmatrix} \tag{2}$$

The following distance matrix is obtained by computation according to Laplace's theorem, with two iterations;

$$\begin{bmatrix} 1 & -2.1 & -0.8 \\ 0 & 1 & 2.4 \\ 3 & 0 & 1 \end{bmatrix} \tag{3}$$

When molecular system has many eigenvalue, all but the maximal eigenvalue are ignored, to preserve the original molecular mechanical characteristics. Equations (2) and (3) have similar molecular mechanical features because Equation (3) retains the maximal eigenvalue. Figure 1 shows the computed complex matrix.

The paper, "A new algorithm for designing a compensator for a high-order system is using a reduced model" in Automatica journal, proposed the "reduced model" to perform high-order matrix computation. A second-order model of the system is derived by retaining one unstable and one stable eigenvalue, 0.3 and -2, respectively, and by matching the first two moments. Therefore, the original matrix becomes the new second-order model. Table 1 indicated the original matrix and reduced order model.

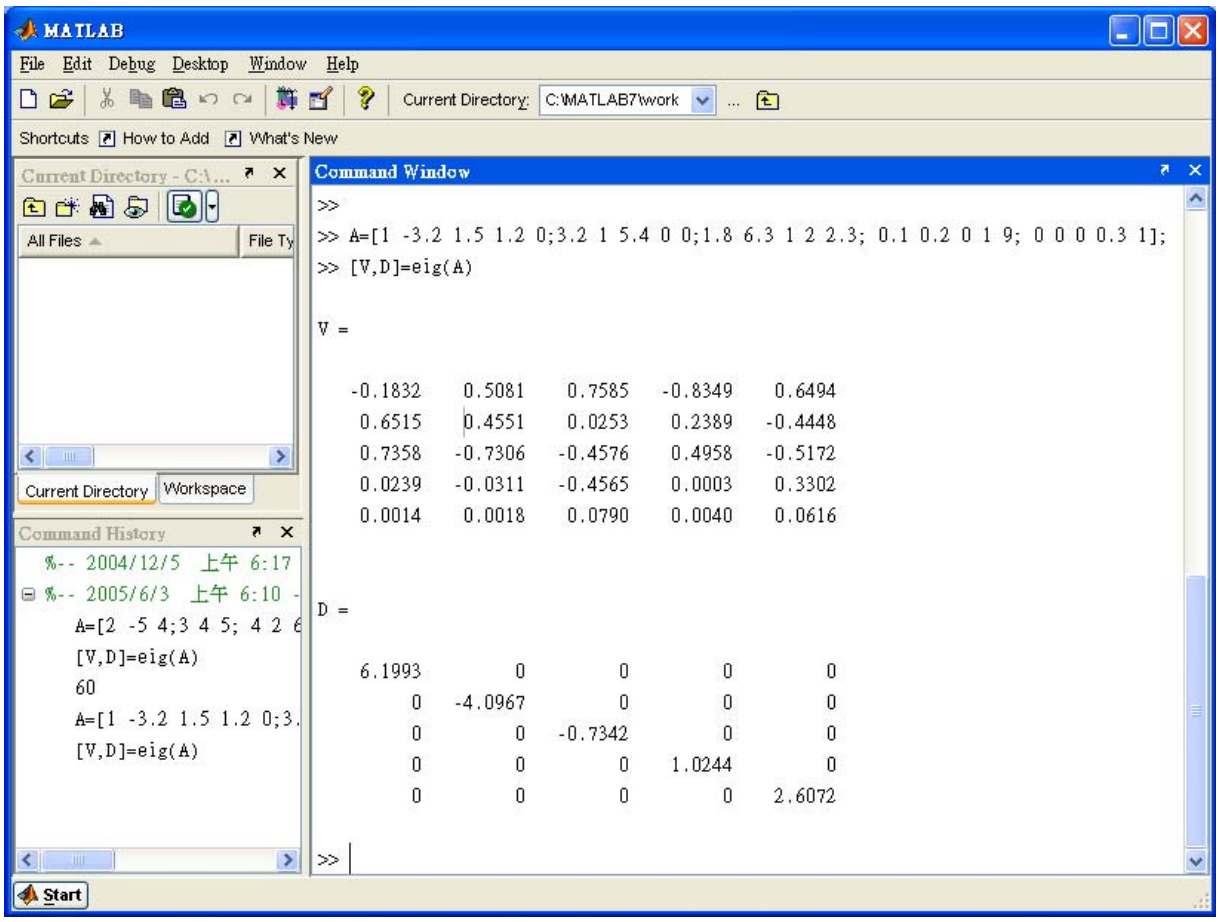


FIGURE 1. Computed the complex matrix

TABLE 1. The original matrix and reduced order model

original matrix	second-order model
$\begin{bmatrix} 0.3 & -1 & 6 & -2 \\ 0 & -2 & 2 & 0 \\ 0 & 0 & -3 & 1 \\ 0 & 0 & 0 & -4 \end{bmatrix}$	$\begin{bmatrix} 0.3 & 0 \\ 0 & -2 \end{bmatrix}$

3. **Langevin Equation.** The Langevin equation is a popular model for macromolecular simulations, because it is computationally less demanding than ordinary Newtonian molecular dynamics. This investigation is an analytical comparative study of the stability of several molecules for the molecular docking system using the Langevin equation. In the Molecular Physics Journal of the University of Illinois on 20 July 2003 Vol.101 No.14, pp.2149-2156, the author Wang referred to the Langevin equation and analyzed the macromolecular simulations [5]; other related literature includes the followings; scheme of van Gunsteren and Berendsen (vGB82) (1982) [6], the Brooks–Brünger–Karplus (BBK) scheme [7], and a 'Langevin impulse' (LÎ) integrator [8]. The Langevin equation under

consideration is given by

$$\begin{aligned} dx &= vdt, \\ dv &= M^{-1}F(x)dt - rvdt + (2rk_BT)^{1/2}M^{-1/2}dW(t) \end{aligned} \tag{4}$$

where x is the displacement vector; v is the velocity vector; t is the time; M is a diagonal matrix of masses; $F(x)$ is the collective force vector; r is the friction coefficient; k_B is the Boltzmann constant; T is the temperature, and $W(t)$ is a collection of independent standard Wiener processes [9].

This work applies the modified equation to analyze the Lyapunov λ convergence in the numerical solution to a molecular harmonic force field model problem. This procedure is based on the work of Wang et al. A modified equation, which is solved exactly by the molecular force field calculation used to solve the original equation, is proposed. The modified equation resembles the original Langevin equation, but with different values of parameters and an extra term. This study focuses on molecular docking stability associated with the Lyapunov. The modified equation used herein takes the form,

$$\frac{d}{dt}\begin{bmatrix} x \\ v \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\tilde{\omega}^{-2} & -\tilde{\gamma} \end{bmatrix}\begin{bmatrix} x \\ v \end{bmatrix} + \begin{bmatrix} \alpha \\ \tilde{\gamma} \\ \beta \end{bmatrix}\left(\frac{2\tilde{\gamma}k_BT}{M}\right)^{1/2}\frac{dW(t)}{dt} \tag{5}$$

where $W(t)$ is a standard Wiener process [10]; $\tilde{\omega}$ and $\tilde{\gamma}$ are the modified frequency and friction coefficient, and α and β are dimensionless parameters.

Robert, in the "Stability of Planar Nonlinear System" section in the book, "Differential Equation: a modeling perspective", this content (p.499), compared the stability characteristics and orbital portraits of a nonlinear system with the linear approximation at the origin [11]. Equation (5) is a linearized equation to ignore the nonlinear parts. The modified equation is,

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + O\begin{bmatrix} x^{1/2} \\ x^{1/2} \end{bmatrix} \tag{6}$$

where (x_1, x_2) is a reference state; O represents a nonlinear part; matrix A and a parameter represent the molecular motion and are determined by various chemical patterns. The nonlinear item in Equation (6) is ignored and the following linearized equation obtained;

$$X' = AX(t) \tag{7}$$

This equation is a common molecular simulation Langevin equation for computer calculation in a 2D environment.

4. **Determined Molecular Motion by Variable.** The molecular modeling software used to present the molecule using computer graphics, requires that the structure of the molecule be provided in the form of a sketch on the screen. It is normally provided using a mouse or other pointing device. This section discusses examples of ways in which a chemist's drawing of a molecule may be transformed into a series of numbers.

Each atom of the molecule is typically assigned an ordinal number, from 1 to N, where N is the total number of atoms in a molecule. Most modeling systems do not impose a particular system for numbering atoms, so the numbers of the atoms generally do not follows the strict rules of the IUPAC convention [12]. However, most modeling systems require that atoms of a given residue be numbered consecutively, as stated on the PDB web-site.

Each of the atoms that make up the molecule is normally assigned a type, which identifies it chemically. This type is usually an integral number or a mnemonic symbol,

such as "21" or *"Csp3"*. The type reflects not only an element but also a particular arrangement of bonds formed by the atom, as well as its formal charge. The atom type may also depend on its neighbors in the molecule. For instance, the amine, ammonium, imine, amidic, pyridinic, pyrrolic and other nitrogens are considered to be of different types in most molecular modeling systems. No universal table of atom types is yet available because different approaches may require different levels of detail in specifying types of atoms. Similarly, bonds are assigned types single, double, aromatic, hydrogen and others. As well as real chemical atoms and bonds, most systems have dummy atoms or dummy bonds also commonly called virtual. This study can be used to help mark important features of the molecule, to orient two molecules relative to each another, or to impose some geometric constraints on real atoms and bonds in the molecule.

The relative position of atoms must be known to completely specify molecular objects to the computer. This information comprises two parts – the specification of bonds and the specification of geometry spatial relationship between atoms. Millions of molecules are known, and surprisingly, no accepted standard for representing molecular structure exists.

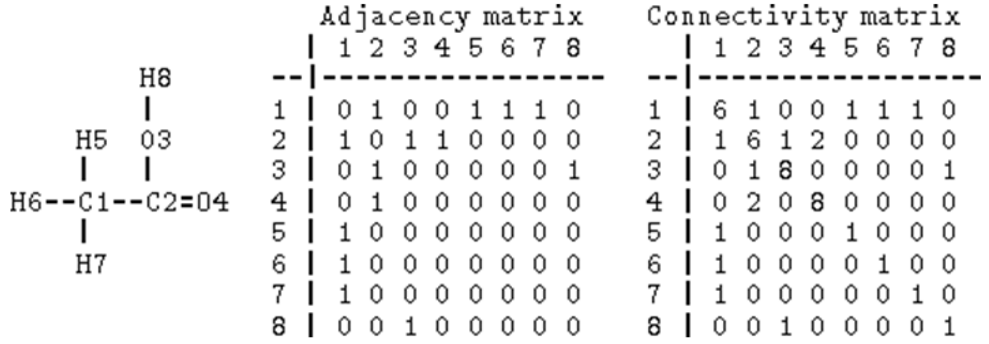


FIGURE 2. Adjacency and connectivity matrices for acetic acid

Rows and columns correspond to the numbering of the atoms presented on the left of the figure. Off-diagonal elements of both matrices represent the order of the bonds between the atoms. The diagonal elements of the connectivity matrix represent the atomic number.

Bonds can be specified as a list of bonded atom pairs with accompanying bond types or as an adjacency matrix or attachment list. Figure 2 depicts an example adjacency matrix. It is a square matrix in which the numbers of columns and rows equal the number of atoms in the molecule. Positions that correspond to bonded atoms are marked "1" (or sometimes by bond type), and all other entries are zero. A variant of the adjacency matrix, called the connectivity matrix, differs from the former in that it includes the atomic number on the diagonal, and for each bond the actual bond order "1 for single bond, 2 for double, 1.5 for conjugated, and so on" is used.

$3N$ values must be entered (X, Y and Z) for each atom to specify fully the molecular geometry in Cartesian coordinates for a molecule that contains N atoms. The $3N$ coordinates specify not only the intramolecular distances and angles but also the orientation of the molecule in space. Internal coordinates specify only intramolecular distances and angles, and the spatial orientation of the molecule is typically assumed. The most popular way to specify molecular geometry using internal coordinates is to use the Z-matrix convention (Figure 3). Each line of the Z-matrix, with the exception of the first three, has the following format.

The first column of the Z-matrix corresponds to the atomic number. The next columns represent the numbers of atoms and internal coordinates (Rx – distance, Ax – valence

angle, Tx – torsional angle). For instance, a C_2 molecule (C_1-C_2) will produce various patterns, as determined by molecular force field tools analysis. The coefficient 1 is a weighting value; –1 denotes repulsion, and zero represents an inactive relationship. The weighting is related to two neighborhood atoms distance. A equation of order two is obtained by reduced-order approaches to yield matrix A.

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} 0 & -1 \\ 1 & -1 \end{bmatrix},$$

where $a_{11} = 0$ represents atom 1, which is self-non-active; $a_{12} = -1$ is the weighting of the bond between atom 1 and atom 2. These definitions are described using the Gaussian force field tool.

```
#P RHF/6-31G* OPT SCF=DIRECT TEST

Acetic acid, 6-31G* geometry optimization

0 1
    6
    8    1 R2                                        H3
    1    2 R3      1 A3                              |
    6    1 R4      2 A4      3 T4                 H5  O2
    1    4 R5      1 A5      2 T5                 |   |
    1    4 R6      1 A6      2 T6              H6-C4--C1==O8
    1    4 R7      1 A7      2 T7                 |
    8    1 R8      2 A8      3 T8                 H7

R2 =   1.332561
R3 =   0.948824
R4 =   1.502662
R5 =   1.083886
R6 =   1.083790
R7 =   1.079334
R8 =   1.189311
A3 =    108.454
A4 =    112.009
A5 =    109.421
A6 =    109.403
A7 =    109.499
A8 =    122.246
T4 =   -180.010
T5 =     58.989
T6 =    -58.934
T7 =   -179.996
T8 =      0.029

                Corresponding cartesian coordinates
 Atom No.          X             Y             Z
    1          0.000000      0.000000      0.000000
    2          0.000000      0.000000      1.332561
    3          0.900034      0.000000      1.632904
    4         -1.393154     -0.000255     -0.563127
    5         -1.924808      0.875760     -0.209925
    6         -1.924489     -0.875974     -0.209007
    7         -1.345884     -0.000322     -1.641426
    8          1.005877     -0.000512     -0.634565
```

FIGURE 3. Data for Gaussian 90 program in the form of a Z-matrix

5. H_2O Potential Energy Calculation.

$$E = K_{OH}(b - b^0_{OH})^2 + (b' - b^0_{OH})^2 + K_{HOH}(\theta - \theta^0_{HOH})^2 \tag{8}$$

where K_{OH}, b^0_{OH}, K_{HOH} and θ^0_{HOH} are the parameters of the force field; b is the current length of one of the O-H bonds; b' is the length of the other O-H bond and θ is the H-O-H angle. The other non-bonding forces are weak and can be neglected. In the following steps, Finally, p is confirmed to be positive-definite, and the stability is verified:

$$p_{11} > 0, \quad p_{22} > 0, \quad p_{11}p_{22} - p_{12}^2 = 1.25 > 0 \tag{9}$$

$$\lambda(A) = -\frac{1}{2} \pm j\frac{\sqrt{3}}{2} \tag{10}$$

The molecular motion system is **asymptotically stable** at the origin.

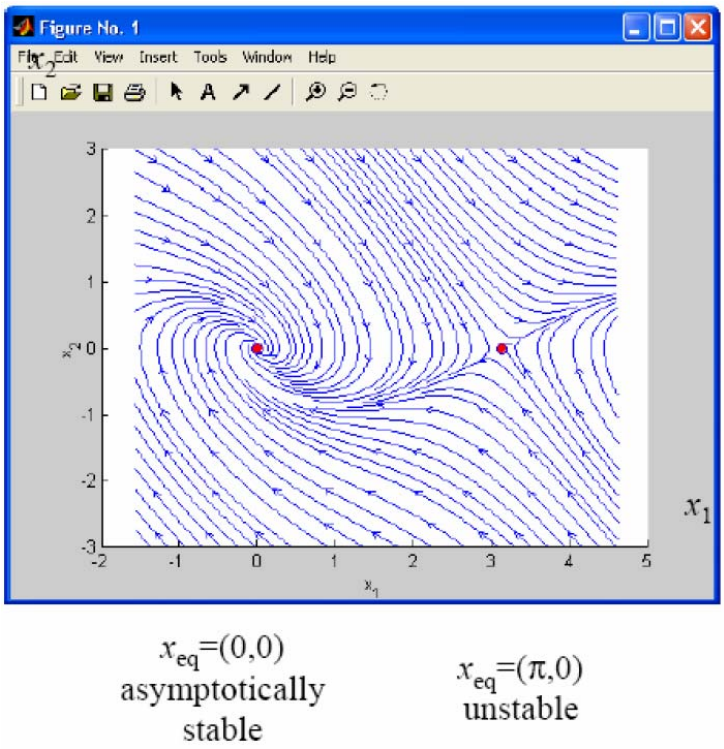


FIGURE 4. Two molecules interact with each other in the Matlab simulation according to the Langevin equation using the force field by Gaussian tools

6. **Using the Lyapunov Theorem to Delete Some Points That Have Local Minimum Energy.** Recent developments in molecular biology and structural biology mean that many pharmacologically important receptor proteins have been cloned and expressed, and some of their structures have been resolved. This investigation employed a molecular mechanics based force field to model the interactions between ligands and proteins in software. The software, developed as DOCK and HEX, searches a protein database for potential targets of a particular small chemical based on the 3D geographical and chemical complement of the protein and the compound. Further improvements are being undertaken to make it a very comprehensive drug virtual screening process [13]. Using graphical and numerical simulation of the binding of a biological key molecule to a receptor, CADD enables semi-quantitative prediction of the activity of potential drug molecules. New drugs can be tailor-made for a specific receptor without animal testing; substances with little or no pharmacological activity are unambiguously discovered and eliminated from the evaluation process before preclinical *in vivo* tests become necessary.

Drug docking was conducted using DOCK software and the number of binding sites reduced using the Lyapunov λ and the global energy minimum. DOCK explores ways in which two molecules, such as a drug and an enzyme or a protein receptor, might fit together. Compounds that dock with each other well, like pieces of a three-dimensional jigsaw puzzle, have the potential to bind. Why must small molecules that may bind to a target macromolecule be identified? A compound that binds to a biological macromolecule may impede its function, and thus act as a drug. The current version of DOCK is 4.5. The program DOCK postulates binding orientations, given the frameworks of the ligand and receptor molecules. The structure of a molecule that is important in physiology or disease is frequently considered to identify other molecules that can bind to it and modulate – typically inhibit – its function. A large database of commercially available compounds

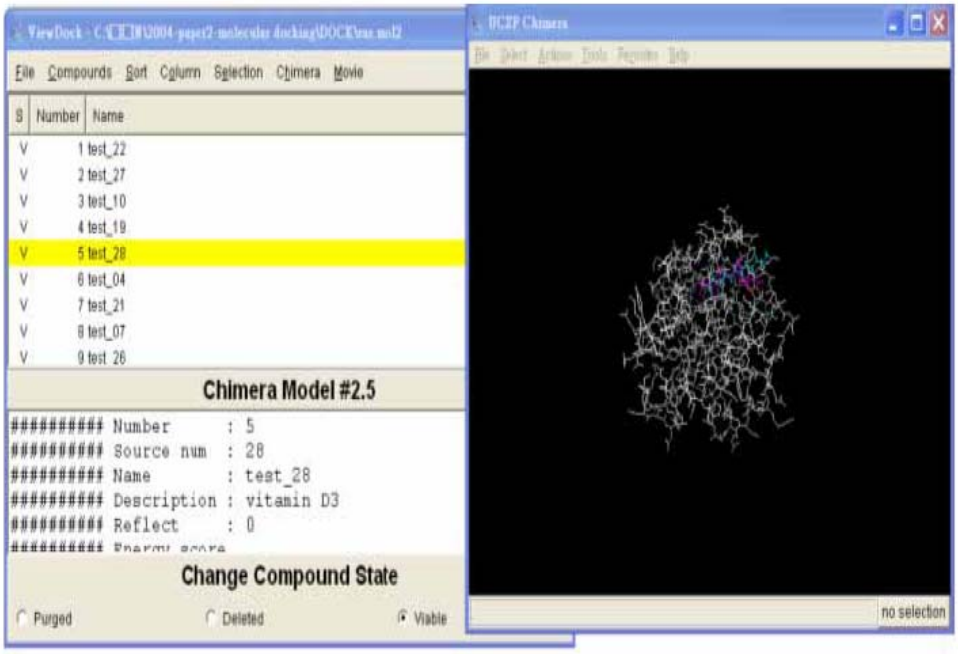


FIGURE 5. Number of factors improved in this docking (in 25 binding sites)

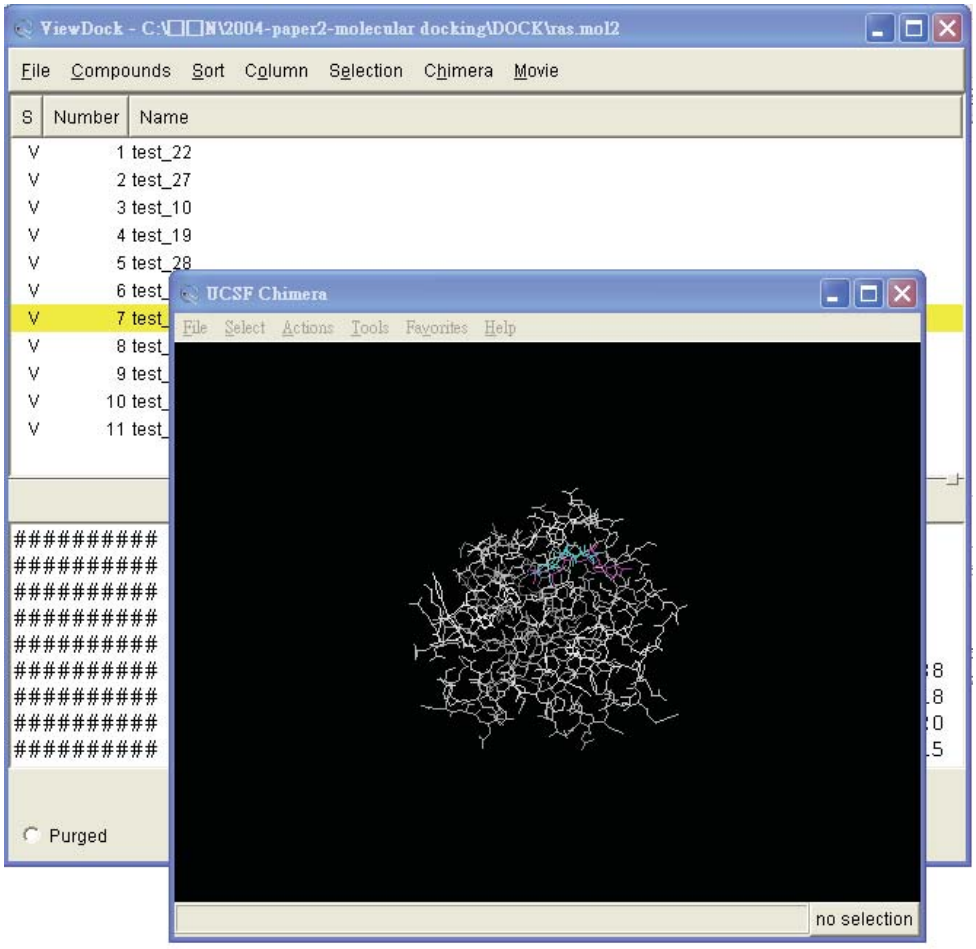


FIGURE 6. Lyapunov λ and globe energy minimum were considered to reduce the number of binding sites and accelerate docking

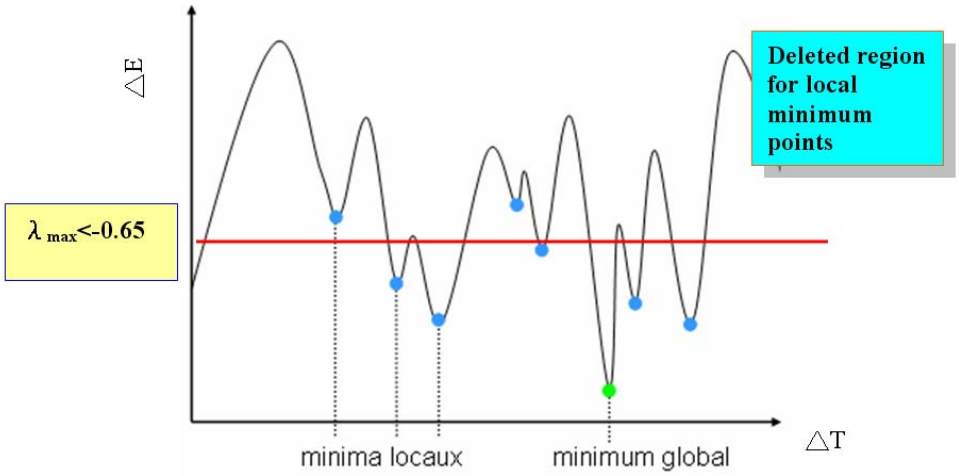
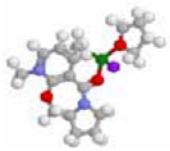
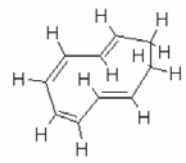
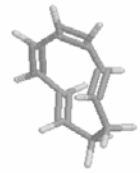
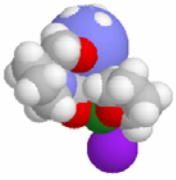


FIGURE 7. Various local minimum and global minimum points for example

TABLE 2. Some simulation results obtained using AMBER in the experiments herein

PDB/ Ligand	Various Structure and Patten	Simulated Product
1ydr/GTO		stretch = 14.734 angle = 19.834 stretch bend = -0.058 dihedral = 27.585 improp torsion= 0.315 van der Waals= 16.633 electrostatics= -3.313 hydrogen bond= -0.529 The Mechanics energy of the final structure is **75.20** kcal/mol.
la30/MID		stretch = 0.490 angle = 1.353 stretch bend = 0.044 dihedral = 8.366 improp torsion= 0.254 van der Waals = 6.036 electrostatics= 0.133 hydrogen bond = 0.000 The energy of the final structure is **16.6773 kcal/mol.**
3fh1_fv/CLT		stretch = 0.497 angle = 5.453 stretch bend = 0.076 dihedral = 8.415 improp torsion= 0.292 van der Waals = 6.406 electrostatics= 0.146 hydrogen bond = 0.000 The energy of the final structure is **21.2843 kcal/mol.**
2ptc/BEN		stretch = 14.962 angle = 20.117 stretch bend = 0.023 dihedral = 25.369 improp torsion = 0.307 van der Waals = 16.707 electrostatics = -3.453 hydrogen bond = 0.000 The Mechanics energy of the final structure is **74.03** kcal/mol.

is usually searched with DOCK, with each compound regarded as a possible "ligand" against the structure of a target protein, which is regarded as the "receptor". Simple scoring methods are utilized to determine the most favorable binding modes of a given molecule, and then to rank the molecules by these best orientations. The output consists of a large number of candidate ligands in the binding orientations that are regarded as most favorable by DOCK. Human users must then look through the molecules and identify those that are worth pursuing in the real world. DOCK was devised by Kuntz et al. who created and developed the scheme over the last few years. In this study, the DOCK system was adopted to complete a docking task, which is described in detail as

follows. Initially, the ras.pdb file was configured to act as a receptor (whose structure was H-ras), and the gto.pdb file was set to act as a ligand (the GTO bound to H-ras in the original PDB file, for comparison with docked molecules). The DOCK program was run for approximately 4-5 hours, after which the docking procedure was performed. The DOCK program created the ras.mol2 in Mol2 format (the docked molecules output by DOCK 4, in Mol2 format), and a setup.com file (which contains commands that configure the viewing context) in the working directory. In the following steps, ViewDock was used to help choose from the outputs of DOCK. Figure 5 displays the experimental results concerning the completing of this task before molecular docking is improved. Figure 6 shows that Lyapunov λ and the globe energy minimum were employed to reduce the number of binding sites and accelerate docking [14,15]. Table 2 indicated some simulation results obtained using AMBER in the experiments herein.

7. **Langevin Equation and Lyapunov for Minimum Energy Experiments.** Langevin Equation and Lyapunov theory represents a landmark in the stability of dynamical systems and differential equations, which has profoundly impacted both significant mathematical results and important applications. This theory is based on an investigation of the energy of molecular system. In our molecular dynamics system, energy is first motivated using simple models from mechanics, and is then developed as a mathematical quantity and employed to determine the qualitative characteristics of equilibrium solutions including stability type and basins of attraction. The rate of change of energy is manipulated via feedback control to force certain equilibria to have the desired qualitative properties. Feedback design methods of back-stepping and adaptation are examined [16]. Energy plays a critical role in the qualitative investigation of the dynamic behavior of nonlinear systems. Mechanical systems and molecular docking system have naturally defined energy. Local minima of energy functions provide stable equilibrium solutions of differential equations. Energy can be exploited through external control and particularly feedback control. The dissertation investigates approaches for manipulating rates of change of energy to identify the stability properties, and the development of other theories based on molecular docking system.

According to Langevin Equation and Lyapunov theory, only differences in energy between two or more conformations have meaning. The MM energy equation along with the parameters necessary to describe the behavior of different atoms and bonds is termed a force-field. Some force-fields include additional energy terms that describe other deformations. Some force-fields account for coupling between bending and stretching in adjacent bonds in order to improve the accuracy of the mechanical model. This investigation employs $\lambda_{\max}$ to express the influence factor of molecular docking. The parameter $\lambda_{\max}$ represents the energy's phase trajectory including various energies, such as the covalent and non-bonded force. These forces are significant in the molecular stability. In the drug docking system, each molecule to produces various forces to reach the stable conformation by protein folding. When the molecular conformation is stable, the site energy is the lowest [16]. Table 4 depicts $\lambda_{\max}$ values including various forces and their contribution ratios in this investigation.

Considering *hydrogen bonding*, *hydrophobic interaction loss*, *deformation entropy loss* and *metal-bonding* upon protein-ligand binding process. Significantly, Table 4 depicts that the proportion of the van der Waals force and **Hydrophobic** is about 80%-90% in the $\lambda_{\max}$ factor, that is, the most significant $\lambda_{\max}$ is the van der Waals force. The stability determinant of the van der Waals force is the "distance" between molecules. The following sections, describe the relationship between $\lambda_{\max}$ and distance.

TABLE 3. Various receptor and ligand character and visualization from PDB

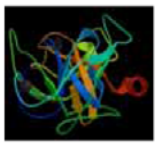
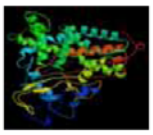
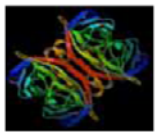
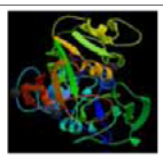
Receptor	Ligand	Formula	Complex	Visualization
3PTB Hydrolase (serine Proteinase)	CA BEN	Ca^{2+} $C_7 H_8 N_2$	Synthetic construct	
2CPP Oxidoreductase (oxygenase)	HEM CAM	$C_{34} H_{32} N_4 O_4 Fe$ $C_{10} H_{16} O$	Synthetic construct	
1STP STREPTAVIDIN COMPLEX WITH BIOTIN	BTN	$C_{10} H_{16} N_2 O_3 S$	Biotin Binding Protein	
4DFR Oxido Reductase	MTX CL CA	$C_{20} H_{22} N_8 O_5$ Cl^- Ca^{2+}	Escherichia coli b	

TABLE 4. Various forces in $\lambda_{\max}$ and their energy contribution ratios in this investigation (Kcal/mol) [17].

Factor / PDB code	Stretching	Bending	Torsion	**van der Waals**	Hydrophobic	electrostatic	Other	global minimum energy
3PTB	**-3.2**	**-5.3**	**-4.5**	**-73.2**	**-24**	**-0.5**	**-0.92**	**-68.25**
2CPP	-4.5	-4.5	-2.3	-67.5	-57	-1.6	-1.26	-91.47
1STP	-5.3	-6.2	-4.1	-51.8	-36	-2.3	-1.18	-83.36
4DFR	-1.9	-5.1	-3.2	-81.6	-58	-1.7	-1.62	-123.1

8. **Lyapunov λ and System Stability with RMSD Experiment.** Assume that a system has N molecules and the position of one molecule in the system is r^N at time t. The free energy function is given by:

$$r(t) = f\left[r^N(0), p^N(0); t\right] \tag{11}$$

If the perturbation motion initial condition (as if motion energy) increases by a small quantity ε, then the system can obtain a different value in time t:

$$r'(t) = f\left[r^N(0), p^N(0) + \varepsilon; t\right] \tag{12}$$

$$\Delta r(t) = r(t) - r'(t) \tag{13}$$

Eventually, $\Delta r(t)$ and ε are in direct proportion, but the linear relevant coefficient is presented an exponent dissipative. i.e.,

$$|\Delta r(t)| \sim \varepsilon \exp(\lambda t) \tag{14}$$

If $0 < t < t_{\max}$ facing the $|\Delta r(t)|$ keep a constraint limited $\Delta_{\max}$; from Equation (14), then this term can be constructed:

$$\varepsilon \sim \Delta_{\max} \exp(-\lambda t_{\max}) \tag{15}$$

The initial condition can form the accepted error in following $t_{\max}$ that presented a exponent descent. For proof that the result is accurate, two similar experimental effects are presented. The difference between the first case and the second case is that the 10000 times the direction velocity steps of a molecule is modified by $+10^{-10}$ and -10^{-10} seconds, respectively. The RMSD value of all molecules is given by:

$$\sum_{i=1}^{N} |r_i(t) - r_i'(t)|^2 \tag{16}$$

The Lyapunov λ was employed to determine that t and RMSD are positively correlated in the Lennard-Jones system model in Figure 8.

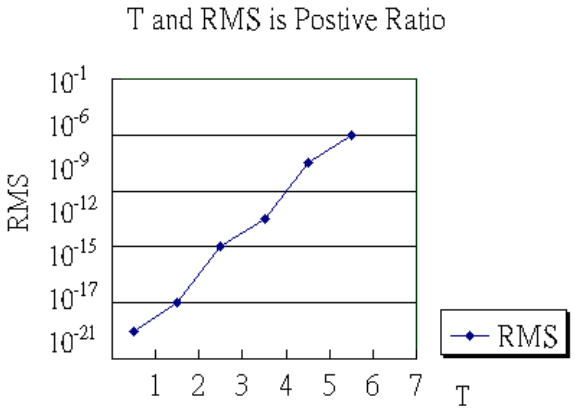


FIGURE 8. Lyapunov λ demonstrates that t and RMSD are positively correlated in the Lennard-Jones system model

9. **Conclusions.** This investigation improves computer simulation in protein folding. It presents some examples of protein folding and the practical minimization of energy. The effect of molecular motion system by reduces order was calculated for protein folding, and the feedback viewed and corrected, to accelerate the computing task. This study demonstrates examples in protein folding kinetics and reduces order computations, and successfully applies the Lyapunov function and Langevin Equation to help determine the system stability. This work integrates various research fields to find advanced and novel solutions to problems in bioinformatics. The combination of biology, information, system, and chemistry will be a powerful molecular computing strategy. Bioinformatics has advanced across various research fields, combining biology, information, system and chemistry, and will become powerful in future.

Acknowledgment. This research was supported by the National Science Council of Taiwan under grant NSC 99-2622-E-167-004-CC3 and NSC 99-2221-E-426-008-. The authors would like to thank the National Chin-Yi University of Technology, Taiwan for financially supporting this research.

REFERENCES

[1] M. G. B. Drew, G. R. H. Wilden, W. J. Spillane, R. M. Walsh, C. A. Ryder and J. M. Simmie, Quantitative structure-activity relationship studies of sulfamates RNHSO3Na: Distinction between sweet, sweet-bitter, and bitter molecules, *J. Agric. Food Chem.*, vol.46, pp.3016-3026, 1998.

[2] M. G. Albuquerque, A. J. Hopfinger, E. J. Barriero and R. B. Alencastro, Four dimensional quantitative structure-activity relationship analysis of a series of interphenylene 7-oxabicycloheptane oxazole thromboxane A2 receptor antagonists, *Journal of Chemical Information and Computer Sciences*, vol.38, pp.925-938, 1998.

[3] Y. Tominaga, Novel 3-D descriptors using excluded volume 2: Application to drug classification, *Journal of Chemical Information and Computer Sciences*, vol.38, pp.1157-1160, 1998.

[4] C.-C. Tsai, S.-C. Ou, C.-Y. Chung, W.-T. Sung, C.-C. Chien and D.-Y. Su, Predict protein structure and similar function via 3D visualization tools-case study of bamboo shoot, *International Proteomics Conference*, Taipei, Taiwan, 2004.

[5] W.-T. Sung, J.-H. Chen, M.-H. Wang and Y.-C. Hsu, Remote medical care system design based on RFID and zigbee technology via wireless sensors network, *International Journal of Innovative Computing, Information and Control*, vol.6, no.11, pp.5203-5220, 2010.

[6] S.-C. Ou, C.-Y. Chung, W.-T. Sung, C.-C. Tsai, C.-C. Chien and D.-Y. Su, Virtual screening and computer-aided drug design in molecular docking via lyapunov function, *WSEAS Trans. on Biology and Biomedicine*, vol.01, no.4, pp.384-390, 2004.

[7] J. R. Ullman, An algorithm for subgraph isomorphism, *J. Assoc. Comput. Mach.*, vol.23, no.1, pp.31-42, 1976.

[8] S.-J. Hsiao, W.-T. Sung and S.-C. Ou, Web-based search system of pattern recognition for the pattern of industrial component by an innovative technology, *Computer in Industry Journal*, vol.53, no.2, pp.179-192, 2004.

[9] W.-T. Sung and S.-C. Ou, Using virtual reality technologies for manufacturing applications, *International Journal of Computer Applications in Technology*, vol.17, no.4, pp.213-219, 2003.

[10] J.-M. Yang and C.-Y. Kao, Flexible ligand docking using a robust evolutionary algorithm, *J. Comput. Chem.*, vol.21, pp.988-998, 2000.

[11] E. D. H. Wolpert and W. G. Macready, No free lunch theorems for optimization, *IEEE Trans. on Evolutionary Computation*, vol.1, pp.67-82, 1997.

[12] W.-T. Sung and S.-C. Ou, Integrating network, CAD and VR into the design and development of web-based computer graphics learning materials, *Journal of Computer Science*, vol.14, no.2, pp.47-63, 2001.

[13] E. C. Meng, B. K. Shoichet and I. D. Kuntz, Automated docking with grid-based energy evaluation, *J. Comput. Chem.*, vol.13, pp.505-524, 1998.

[14] A. Vedani, M. Dobler and P. Zbinden, Quasi-atomistic receptor surface models: A bridge between 3-D QSAR and receptor modeling, *Journal of the American Chemical Society*, vol.120, pp.4471-4477, 1998.

[15] D. Levine, M. Facello, P. Hallstrom, G. Reeder, B. Walenz and F. Stevens, STALK: An interactive system for virtual molecular docking, *IEEE Comput. Sci. Eng.*, vol.4, pp.55-65, 1997.

[16] R. J. Davy and I. A. Hiskens, Lyapunov functions for multi-machine power systems with dynamic loads, *IEEE Trans. on Circuits and Systems*, vol.23, no.4, pp.167-173, 1994.

[17] W.-T. Sung and Y.-F. Liu, Energy minimum theorem based on AGA, Lyapunov and Force Field for CADD Techniques, *Computers in Biology and Medicine*, vol.40, no.2, pp.215-222, 2010.

[18] W.-T. Sung and Y.-C. Hsu, Designing an industrial real-time measurement and monitoring system based on embedded system and ZigBee, *Expert Systems with Applications*, vol.38, no.4, pp.4522-4529, 2011.

[19] Z. B. Musa and J. Watada, A particle filter approach for multi-camera tracking systems in a large view space, *International Journal of Innovative Computing, Information and Control*, vol.6, no.6, pp.2827-2836, 2010.

[20] V. Kalashnikov, F. Camacho and R. A. N. Kalashnykova, Comparison of algorithms for solving a bi-level toll setting problem, *International Journal of Innovative Computing, Information and Control*, vol.6, no.8, pp.3529-3550, 2010.

[21] K. Yoshida and Y. Nishizawa, Bifurcation analysis of noise-induced synchronization, *International Journal of Innovative Computing, Information and Control*, vol.5, no.9, pp.2809-2818, 2009.

[22] H. Nakano, A. Utani, A. Miyauchi and H. Yamamoto, Chaos synchronization-based data transmission scheme in multiple sink wireless sensor networks, *International Journal of Innovative Computing, Information and Control*, vol.7, no.4, pp.1983-1994, 2011.

[23] W.-T. Sung, H.-Y. Chung, Y.-C. Hsu and K.-Y. Chen, A light wind speed measurement system design to strengthen wireless sensor network functions, *International Journal of Innovative Computing, Information and Control*, vol.7, no.2, pp.859-868, 2011.