Molecular Simulation via Lyapunov Principle and NURBS Curves

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ABSTRACT. A Lyapunov principle to explore the Computer-aided drug design (CADD) is proposed. Based on NCBI’97 reports, the most significant challenge is the docking procedure. In this work, Lyapunov stability theorem is used to decrease the number of binding sites and to enhance the docking performance. These novel techniques are significantly based on the concept of minimum energy and optimal geometry search strategies to ensure the stability of protein – ligand interactions. This study also applies the Lyapunov stability theorem to discuss the molecular orbit adjustment of molecular dynamics equations when the equilibrium point moves away from the initial state with zero input in molecule infinite time t. From the viewpoint of the minimum energy, we have used the Non-Uniform Rational B-Splines (NURBS) curves to accelerate the molecular docking system by the short route. Furthermore, the folding of various proteins is discussed. The force field is also analyzed. Finally, simulation results are given to show the feasibility and effectiveness of this study.

Keywords: Lyapunov, NURBS, Drug Docking, CADD
1. Introduction. The most important application of molecular docking is virtual screening for drug discovery and improvement. Molecular docking explores how two or more molecular structures interact, and is like solving a 3-dimensional puzzle. In molecular docking, this work endeavored to predict the structures of the intermolecular complex formed between two or more molecules. Molecular docking is a nonlinear dynamics chaos system; the indirect and direct Lyapunov theorems were used to find the optimal solution with low cost and to accelerate the docking by using Lyapunov approach. The docking problem involves many degrees of freedom. One molecule has six degrees of translational and rotational freedom relative to the other, as well as the conformational degrees of freedom of each molecule [3].

Four different optimal geometry search strategies are introduced for locating the binding sites of the minimum energy in the receptor structure. Then, the following results were obtained: the Monte Carlo Algorithm is randomly calculated and has the lowest precise ratio; the Simulated Annealing Algorithm is randomly calculated and liable to local minimum error; the Genetic Algorithm performs better than the above two, but its selection is still random and the result of performances is not high efficient when the docking system is in running various compound and ligand. In this work, the Lyapunov stability theorem is employed to reduce the number of binding sites to enhance the docking performance, and the NURBS knot and weight are modified to cut down the docking time. The schemes are mainly based on the application of minimum energy and optimal approaches to ensure the stability of protein – ligand interaction. The following sections will be elaborated. [6] [7].

2. Brief of Lyapunov Stability Theorem. The minimum energy and Lyapunov theory of dynamical systems are the most helpful general theory for investigating the stability of nonlinear systems. The behavior of the orbits of a dynamic system is significantly affected by the location and the nature of the constant and the periodic solution, call equilibrium point and cycles. This chapter discusses the stability theory, minimum energy and Lyapunov’s direct/indirect method; also give some examples of applications in every method.

First, the equilibrium point is defined:
Assume that the point \( p \) in \( S \) is such that \( f(p)=0 \), then \( p \) denotes an equilibrium point for the autonomous system

\[
\dot{x} = f(x)
\]

where \( \dot{\cdot} \) denotes the differentiation with respect to time.

Notably, if \( p \) represents an equilibrium point, then \( x=p \), for all \( t \), denotes a constant solution. A constant state (initial state) solution of dynamics equation is normally
described as stable state, indicating that the system is perturbed by inside or outside, the result is a deviated constant state solution and the eigenvalue is changed. Finally, the system automatically returns the constant state solution and lies in a stable state for a long time, or at least the system does not deviate the state very far. Conversely, a constant state (initial state) solution of dynamic equations is unstable meaning that in perturbation motion, the system solution orbit continues to deviate from the initial state.

Finally, the system does not return. In the Lyapunov stability theorem, first the stability concept of differential equation is described.

\[
\frac{dX_i}{dt} = f_i(X_1, X_2, \ldots, X_n) \quad (i = 1, 2, \ldots, n)
\]  

(2)

Suppose that in the initial condition \(X_i(t_0) = X_i^0\), equation (2) has a solution \(X_i(t)\).

When the initial condition yields a small perturbation motion \(\eta_i\), then the initial condition becomes \(X_i'(t_0) = X_i^0 + \eta_i\), equation (2) has a new result \(X_i(t, \{\eta_i\})\). The stability definition follows:

The solution \(X_i(t)\) of system equation (2) is stable if for each positive \(\varepsilon > 0\) a positive number \(\delta > 0\) exists such that the condition \(|\eta_i| \leq \delta\) is satisfied, for all \(t \geq t_0\) invariably:

\[
|X_i(t, \{\eta_i\}) - X_i(t)| < \varepsilon \quad (i = 1, 2, \ldots, n)
\]

(3)

Conversely, the system is unstable under when this condition is not correspondence.

If \(X_i(t)\) is stable and the following is satisfied:

\[
\lim_{t \to \infty} |X_i(t, \{\eta_i\}) - X_i(t)| = 0 \quad (i = 1, 2, \ldots, n)
\]

(4)

Than the function \(X_i(t)\) is termed “Asymptotic Stability” or “Lyapunov Stability”.

The above definition of system stability can also be described simply: If the initial condition is \(X(t_0) = X_0\), then the solution of system is \(X(t)\). When the initial condition is a finite change \((\delta)\), the solution of the system equation is still sited in the finite field \((\varepsilon)\) with the solution \(X(t)\) of original initial condition, meaning that \(X(t)\) is stable. When the initial condition indicates a finite change, the solution of the system near \(X(t)\) and the solution comes back to \(X_0\) after a long time, then \(X(t)\) is asymptotically stable [4].
Let $x = 0$ represent an equilibrium point of a nonlinear system, as in equation (1). Let $V : \mathbb{R}^n \to \mathbb{R}$ denote a continuously differentiable function such that:

\[ V(0) = 0 \quad \text{and} \quad V(x) > 0 \quad \forall x \neq 0, \quad (5) \]

\[ ||x|| \to \infty \quad \Rightarrow \quad V(x) \to \infty \quad (6) \]

If $\dot{V}(x) \leq 0$ for $\forall x \neq 0$, then $x = 0$ is **globally asymptotically stable**.

The classical theory of mechanics reveals that a vibratory system is stable if its total energy is continually decreasing until an equilibrium state is reached. The second Lyapunov method is based on a generalization of the following rule: if a system has an asymptotically stable equilibrium state, then its stored energy displaced within a domain of attraction decays with increasing time until it finally achieves its minimum value at the equilibrium state. For purely mathematical systems, however, no simple means exists of defining an “energy function”. Lyapunov introduced the Lyapunov function, which is a fictitious energy function. This concept is more general and more widely applicable than that of energy. Any scalar function which adheres to the hypotheses of Lyapunov’s stability theorems can serve as a Lyapunov function [1].
Fig.2: Global stability occurs in an energy minimum when the molecular dynamics system free energy is continually falling until an equilibrium state is reached (\(v\) denotes potential energy and \(x,y\) denote an 2D plane) [2] [9].

3. Computer Simulation of Minimum Energy Experiments (C\(_2\)H\(_2\)X\(_2\)). This experiment employs C\(_2\)H\(_2\)X\(_2\) receptor for minimum energy experiment for which it obey the instruction of qualitative analysis. The experimental steps are given below:

(1). Indicate distance matrices elements of molecular structure.

(2). Employ AMBER force field simulation to figure out each element.

(3). Exhibit every element of distance matrices, various force for their contribution ratios, free energy, and eigenvalue in each sampling time.

(4). Analyze every variation of items, and compare error ratio with the standard values by nuclear magnetic resonance (NMR) spectroscopy with X-ray approach.

(5). Finally, drawn relation chartings for discussing and surveys.

Initialize the molecular structure of the C\(_2\)H\(_2\)X\(_2\) compound:

![Diagram of C\(_2\)H\(_2\)X\(_2\) molecule]

The Table1 (a) and Table1 (b) show the minimum energy experiment with C\(_2\)H\(_2\)X\(_2\) compound.

Table 1 (a). Minimum energy simulation example with C\(_2\)H\(_2\)X\(_2\) compound

<table>
<thead>
<tr>
<th>Sampling Time (ps)</th>
<th>Energy (kcal/mol)</th>
<th>Distance Matrices (by Lappalainen’s theorem)</th>
<th>(\Delta G_{\text{min}})</th>
<th>Various Force for their Contribution Ratios (kcal/mol)</th>
<th>RMSD (Å)</th>
</tr>
</thead>
</table>
| 0.63 s            | 3.65              | \[
\begin{bmatrix}
-1.3 & 1.3 & 1 \\
-1.2 & -0.6 & 1 \\
2 & 1 & -3.1 \\
\end{bmatrix}
\] | -2.906 | 13.18 37.5 537.3 2.096 0.578 12.1 17 3.36 34.1 2.866 0.790 | 1.09   |
Table 1 (b). Minimum energy simulation example with C₂H₂X₂ compound

| Molecular Graphs | Folding Graphs | | |
|------------------|----------------|------------------|
| Sampling Time Point | 9.32 s | 15.73 s | 38.82 s |
| 

<table>
<thead>
<tr>
<th>Force Field</th>
<th>Energies (kcal/mol)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray Free Energy</td>
<td>1.05</td>
<td>0.74</td>
</tr>
<tr>
<td>Computer Simulation Free Energy (kcal/mol)</td>
<td>1.3</td>
<td>1.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distance Matrices (By Laplace’s theorem)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S: stretching B: bending T: torsion V: van der Waals H: Hydrophobic E: electrostatic O: other stray forces (Include Ionic Bond and Hydrogen)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>From Table 1(a) and Table 1(b), it is found that during the process of docking for the C₂H₂X₂ compound the longer the sampling time, the lower the free energy. That is to say, it will get more stable. In addition, It is clear that the primary contributor is Hydrophobic with Van Der Waals.</td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion of the Result.

(1). A force field is defined for each molecule a unique potential energy surface (PES). Each point on the PES represents a molecular conformation characterized by its structure and energy.
Minimization Definitions:

Given a function:

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

(7)

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

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

(8)

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

\[ v(x) = v(x_k) + (x - x_k)v'(x_k) + (x - x_k)^2v''(x_k)/2 + \ldots \]  

(9)

Gradient (first derivatives) vector:

\[ \mathbf{v}'(x_k) = g_k = \left( \begin{array}{c} \frac{\partial v}{\partial x_1} \\ \frac{\partial v}{\partial x_2} \\ \vdots \\ \frac{\partial v}{\partial x_N} \end{array} \right) \]  

(10)

Hessian (second derivatives) matrix:

\[ \mathbf{v}''(x_k) = \left( \begin{array}{ccc} \frac{\partial^2 v}{\partial x_1^2} & \frac{\partial^2 v}{\partial x_1 \partial x_2} & \frac{\partial^2 v}{\partial x_1 \partial x_N} \\ \frac{\partial^2 v}{\partial x_1 \partial x_2} & \frac{\partial^2 v}{\partial x_2^2} & \frac{\partial^2 v}{\partial x_2 \partial x_N} \\ \frac{\partial^2 v}{\partial x_1 \partial x_N} & \frac{\partial^2 v}{\partial x_2 \partial x_N} & \frac{\partial^2 v}{\partial x_N^2} \end{array} \right) \]  

(11)

Most minimization method can only go downhill and so locate the closest (downhill sense) minimum. No minimization method can guarantee the location of the global energy minimum. Having found out these local minimum energy points at various
folding state, we employ Lyapunov stability theorem to improve the molecular docking cost.

(2). Eigenvalue $\lambda_{\text{max}}$ represents the slop of energy curves. By way of energy surface and energy convergence routes, we can look for the shortest route and curtail the molecular docking.

![Initial Point](image1)

Fig.4: Two local minima (M) and a reaction path (in red) connecting them are shown. The blue line represented the shortest route via $\lambda_{\text{max}}$ decision from the initial point.

(3). Refer to equation (1), (2), (3), (4), and (5), are can calculate the various force field and its contributions for molecular docking via AMBER tool.

(4). To analyze the initial and complete molecular folding process, the contributions of Van Der Waals have the maximum difference. Because of the distance between each atom, the changes of non-bonded energy are very obvious.

![Figure 5](image2)

Fig.5: The contribution of various force fields in C$_2$H$_2$X$_2$ folding via AMBER.

(5). Finding out the C$_2$H$_2$X$_2$ receptor active binding sites and pocketing the ligand into
the cave via measuring around hydrophobic and Van der Waals interactive force.

Fig.6: \( \text{C}_2\text{H}_2\text{X}_2 \) receptor active binding sites are shown and the ligand pocketed into the cave.

5. Application of Non-Uniform Rational B-Splines Curves (NURBS) [12]. In 1975, Versprille proposed the Non-Uniform Rational B-Splines (NURBS). This shape modeling is a representation for the geometric design of a generalized Riesenfeld’s B-splines. NURBS quickly gained popularity and were incorporated into several commercial modeling systems primarily because they have many attractive properties. The NURBS offer a unified mathematical formulation for representing not only free-form curves and surfaces, but also standard analytic shapes such as conics, quadrics, and surfaces of revolution. NURBS are very flexible and powerful because of their large number of control variables (or degrees of freedom) which comprise control points, non-unity weights, and non-uniform knot sequence. In essence, through the manipulation of control points, weights, and/or knots, users can design a vast variety of shapes using NURBS. A wide array of techniques for NURBS has been developed for a geometric design. To ameliorate the geometric design with NURBS, researchers have been widely employing the energy optimization technique in shape modeling, geometric design, and interactive graphics. A NURBS curve generalizes the B-spline curve. Let us consider the way of introducing homogeneous coordinates to a B-spline curve and derive the NURBS definition:

Given \( n+1 \) control points \( \mathbf{P}_0, \mathbf{P}_1, \ldots, \mathbf{P}_n \) and knot vector \( U = \{ u_0, u_1, \ldots, u_m \} \) of \( m+1 \) knots, the B-spline curve of degree \( p \) defined by these parameters is the following:

\[
\mathbf{C}(u) = \sum_{i=0}^{n} N_{i,p}(u) \mathbf{P}_i
\]  

(12)
Let control point $P_i$ be rewritten as a column vector with four components with the fourth one being 1:

$$P_i = \begin{bmatrix} x_i \\ y_i \\ z_i \\ 1 \end{bmatrix}$$

(13)

We can treat this $P_i$ as a homogeneous coordinate. Since multiplying the coordinates of a point (in homogeneous form) with a non-zero number does not change its position, let us multiply the coordinates of $P_i$ with a weight $w_i$ to obtain a new form in homogeneous coordinates:

$$P_i^w = \begin{bmatrix} w_i x_i \\ w_i y_i \\ w_i z_i \\ w_i \end{bmatrix}$$

(14)

Note that $P_i^w$ and $P_i$ represent the same point in homogeneous coordinate.

This is the NURBS curve of degree $p$ defined by control points $P_0, P_1, ..., P_n$, knot vector $U = \{ u_0, u_1, ..., u_m \}$, and weights $w_0, w_1, ..., w_n$. Note that since weight $w_i$ is associated with control point $P_i$ as its fourth component, the number of weights and the number of control points must agree.

5.1 Knot Insertion. Let us take a look at an example.

Table 2. Suppose we have 9 knots

<table>
<thead>
<tr>
<th>$u_0$</th>
<th>$u_1$</th>
<th>$u_2$</th>
<th>$u_3$</th>
<th>$u_4$</th>
<th>$u_5$</th>
<th>$u_6$</th>
<th>$u_7$</th>
<th>$u_8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

and a NURBS curve of degree 3 defined by the following 5 control points in the $xy$-plane:

Table 3. A NURBS curve of degree 3 defined by the following 5 control points in the $xy$-plane:

<table>
<thead>
<tr>
<th></th>
<th>$x$</th>
<th>$y$</th>
<th>$w$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_0$</td>
<td>-70</td>
<td>-76</td>
<td>1</td>
</tr>
<tr>
<td>$P_1$</td>
<td>-70</td>
<td>75</td>
<td>0.5</td>
</tr>
<tr>
<td>$P_2$</td>
<td>74</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>$P_3$</td>
<td>74</td>
<td>-77</td>
<td>5</td>
</tr>
<tr>
<td>$P_4$</td>
<td>-40</td>
<td>-76</td>
<td>1</td>
</tr>
</tbody>
</table>

The following shows the NURBS curve:
Let us insert a new knot $t = 0.4$. Since $t$ is in knot span $[u_3, u_4]$ and the degree of the NURBS curve is 3, the affected control points are $P_3, P_2, P_1$ and $P_0$. Since this is a NURBS curve, we shall use homogeneous coordinates by multiplying all control points with their corresponding weights. Call these new control points $P^w_i$:

Table 4. These new control points $P^w_i$ by multiplying all control points with their corresponding weights.

<table>
<thead>
<tr>
<th>$P^w_0$</th>
<th>$x$</th>
<th>$y$</th>
<th>$w$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-70</td>
<td>-76</td>
<td>1</td>
</tr>
<tr>
<td>$P^w_1$</td>
<td>-35</td>
<td>37.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$P^w_2$</td>
<td>296</td>
<td>300</td>
<td>4</td>
</tr>
<tr>
<td>$P^w_3$</td>
<td>370</td>
<td>-385</td>
<td>5</td>
</tr>
</tbody>
</table>

Note that since $P_4$ is not affected, it is not computed in the above table. Then, we shall compute $a_3, a_2$ and $a_1$ as follows:

\[
\begin{align*}
a_3 &= \frac{t - u_3}{u_0 - u_3} = \frac{0.4 - 0}{1 - 0} = 0.4 \\
a_2 &= \frac{t - u_2}{u_3 - u_2} = \frac{0.4 - 0}{1 - 0} = 0.4 \\
a_1 &= \frac{t - u_1}{u_4 - u_1} = \frac{0.4 - 0}{0.5 - 0} = 0.8
\end{align*}
\]  

(15)

The new control points $Q^w_3, Q^w_2$ and $Q^w_1$ are:

\[
\begin{align*}
Q^w_3 &= (1 - a_3)P^w_2 + a_3 P^w_3 = (325.6, 26.4, 4.4) \\
Q^w_2 &= (1 - a_2)P^w_2 + a_2 P^w_3 = (97.4, 142.5, 1.9) \\
Q^w_1 &= (1 - a_1)P^w_0 + a_1 P^w_1 = (-42, 14.8, 0.6)
\end{align*}
\]  

(16)

Projecting these control points back to 2D by dividing the first two components with the third (the weight), we have:

\[
\begin{align*}
\text{new } P_3 &= (74, 5.9) \quad \text{with weight 4.4} \\
\text{new } P_2 &= (51.3, 75) \quad \text{with weight 1.9} \\
\text{new } P_1 &= (-70, 24.6) \quad \text{with weight 0.6}
\end{align*}
\]  

(17)

The following is the resulting NURBS curve with three new control points:
5.2 Modification of Weights. Since NURBS curves are defined by a set of control points, a knot vector, a degree and a set of weights, we have one more parameter for shape modification (i.e., the weights). Therefore, increasing and decreasing the value of \( w_i \) will increase and decrease the value of \( R_{i,p}(u) \), respectively. More precisely, increasing the value of \( w_i \) will pull the curve toward control point \( P_i \). In fact, all affected points on the curve will also be pulled in the direction to \( P_i \). When \( w_i \) approaches infinity, the curve will pass through control point \( P_i \). On the other hand, decreasing the value of \( w_i \) will push the curve away from control point \( P_i \).

5.3 Modifying the curve to become a straight pattern

Fig.8: (a) weight \( 9 = 1 \)  
Fig9: (b) weight \( 9 = 20 \)  

Fig.10: (a) A initial NURBS curve  
Fig11: (b) After modifying the control points
Fig.12: Shorten reaction route in docking process.

Table 5. Three optimal methods for docking in practices

<table>
<thead>
<tr>
<th>Optimal Algorithms</th>
<th>number of binding sites</th>
<th>Docking time</th>
<th>Average interaction energy for ligand (Kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monte Carlo</td>
<td>453</td>
<td>4.53 hr</td>
<td>−115</td>
</tr>
<tr>
<td>Genetic Algorithms</td>
<td>371</td>
<td>3.25 hr</td>
<td>−96.3</td>
</tr>
<tr>
<td>This method</td>
<td>342</td>
<td>3.05 hr</td>
<td>−89.0</td>
</tr>
</tbody>
</table>

According to the Computer Simulation of Minimum Energy Experiments (C₂H₂X₂), we employ NURBS knot insertion is employed and weights are modified to accelerate the reaction time of the molecular docking and protein folding about 20%.

6. Using the Lyapunov to delete some points with local minimum energy [11]. The drug docking using DOCK software and improvement in reducing the number of binding sites by Lyapunov λ and the global energy minimum. DOCK explores ways in which two molecules, such as a drug and an enzyme or protein receptor, might fit together. Compounds which dock to each other well, like pieces of a three-dimensional jigsaw puzzle, have the potential to bind. Why must small molecules which may bind to a target macromolecule be identified? A compound which binds to a biological macromolecule may impede its function, and thus acts as a drug. The DOCK current version is 4.5. The program DOCK postulates binding orientations, given the frameworks of ligand and receptor molecules. The structure of a molecule that is important in physiology or disease is often employed to find other molecules to bind it and modulate usually inhibit its function. Normally, a large database of commercially available compounds is searched
with DOCK, with each compound regarded as a possible "ligand" against the structure of a target protein, which is considered 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 according to these best orientations. The output comprises a large number of candidate ligands in the binding orientations regarded as most favorable by DOCK. Human users must then look through the molecules and identify those which are worth pursuing in the real world. DOCK was devised by Kuntz and coworkers, who have created and developed the method over the last few years. The DOCK system is adopted to complete a docking task in this investigation, which is described in detail as follows. Initially, the ras.pdb file was configured to act as receptor (the structure of the receptor, H-ras), and the gto.pdb file was set to act as ligand (the ligand GTO bound to H-ras in the original PDB file, for comparison with docked molecules). The DOCK program was run for about 4–5 hours, after which the docking procedure was undertaken. 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 (a file containing commands that configure the viewing context) into our working directory. In following steps, ViewDock was applied to help choose from the output of DOCK. The receptor is C$_2$H$_4$OX$_3$ with 10 atoms and the ligand is indirubin by Sybyl mol2 format \[8\] \[9\].

![Fig13](image)

**Fig13:** The experimental result for various local minimum and global minimum points.

This study uses a Lyapunov theorem to improve the search for minimum energy point and accelerate drug docking. Form the minimum energy theorem the compound will be convergent and existence in practice. The final drug candidate can achieve a complete folding and docking at the acceptor with global minimum energy point. Furthermore, this Lyapunov approach can delete some local minimum point so as to reach the global
minimum points in order to decrease the docking time[13].

7. Conclusions. In this presentation, Lyapunov stability theorem has been used to enhance the docking performance, and the energy minimum theorem has also been employed to improve the molecular simulation, protein folding, molecular force field and NURBS curves trimming. The NURBS knot and weight are modified to cut down the docking time. The scheme is a novel technique based on the concept of the minimum energy and optimization approaches to ensure the stability of protein – ligand interaction. The computer simulation result shows the feasibility and effectiveness of this study.

Acknowledgments. The authors wish to thank the financial support of the National Science Council of the Republic of China under Contract NSC 94-2213-E-008-031.

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