

Transition-State-Guided Strategies in Natural Product-Based Drug Design

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For over a century, natural products have played a pivotal role in modern medicine, serving as sources of essential drugs for the treatment of infectious, oncological, metabolic, and neurological disorders. These compounds have evolved in plants, microbes, and animals to interact specifically with biological targets, resulting in complex structures and diverse chemical features that confer biological relevance.¹ One notable example is the recent approval of eribulin mesylate, a synthetic derivative of the marine natural product halichondrin B, which has shown efficacy in treating metastatic breast cancer.² Nevertheless, developing effective drugs from natural products remains a slow and challenging process, primarily because biological systems are inherently complex and dynamic, and these complexities are not fully addressed by conventional screening methods.³

In the past three decades, molecular simulation has become essential for elucidating molecular behavior at the atomic scale. Molecular dynamics simulations enable the observation of proteins, nucleic acids, and ligands over time, capturing critical fluctuations, conformational changes, binding events, and reactions that are fundamental to biological function. Unlike static models, which only provide a snapshot in time, molecular dynamics reveals the temporal evolution of molecular interactions, highlighting dynamic phenomena that static models miss. It is now widely accepted that processes such as enzyme catalysis, ligand recognition, and allosteric regulation are intrinsically dynamic and cannot be fully understood through static structural analysis alone.⁴ Despite significant advances in molecular dynamics methodologies, broader adoption in biological and pharmaceutical research is hindered by challenges in simulation setup, software heterogeneity, and the lack of standardized, reproducible computational environments.

To overcome these obstacles, researchers developed the Biomolecular Reaction and Interaction Dynamics Global Environment (BRIDGE)^{5,6}, an open simulation platform built on the Galaxy framework. BRIDGE

integrates genomics, bioinformatics, and molecular simulation within a unified system. It provides web-based tools for configuring, executing, and analyzing molecular dynamics simulations, along with advanced capabilities for interpreting simulation outcomes.

Although classical molecular dynamics is valuable for investigating binding events and conformational changes, numerous biological processes also involve chemical reactions that form or break covalent bonds. Accurate modeling of these reactions requires hybrid quantum mechanics/molecular mechanics (QM/MM) approaches, in which the reactive region is treated quantum-mechanically, and the remainder of the system is modeled classically. In contrast, purely quantum mechanical (QM) methods offer higher accuracy by treating the entire system quantum-mechanically, but they are often computationally infeasible for large biological systems due to intensive resource requirements. Therefore, QM/MM provides a practical balance between accuracy and tractability. QM/MM has become a standard methodology for elucidating enzyme function, enabling the calculation of reaction energy profiles, transition states, and the roles of specific amino acid residues. A recently developed method, the Free Energies from Additive Reaction Coordinate Forces (FEARCF) method, has provided a detailed framework for decomposing reaction energies and elucidating the factors underlying catalytic efficiency.^{7,8}

The FEARCF method enables researchers to characterize reaction pathways from QM/MM simulations by projecting forces onto the reaction coordinate. This approach quantifies the contributions of specific interactions, electrostatic effects, and protein dynamics to the stabilization or destabilization of the transition state. Such insights extend beyond simple estimates of energy barriers by elucidating their magnitudes and underlying causes, as well as by identifying strategies to modulate them. This concept aligns with Linus Pauling's transition-state hypothesis in enzymology and drug design, which posits that enzymes achieve catalytic efficiency by binding the

transition state more tightly than the substrate, thereby reducing the activation energy and accelerating the reaction.^{9, 10} As a result, the design of molecules that mimic the transition state can produce highly potent enzyme inhibitors.

One primary approach is to design transition-state analogues at the atomic level. Once the geometry, charge distribution, and key interactions of a transition state are defined, researchers can synthesize molecules that closely replicate these features. This approach has yielded some of the most potent enzyme inhibitors to date. However, such analogues are often highly complex, strained, or contain unusual functional groups, rendering their synthesis and large-scale production challenging. As the structural fidelity to the true transition state increases, synthetic difficulty also rises, necessitating a balance between molecular accuracy and practical manufacturability. To identify transition-state mimics in existing chemical collections, particularly among natural products, evolution has created a wide variety of molecules, and traditional medicine has often found active compounds even when their exact effects were unknown. By screening natural product databases with templates based on transition-state shape and charge, researchers can find molecules that resemble the key configuration of a target enzyme. This method avoids many problems of designing new molecules from scratch and combines practical experience with detailed scientific understanding to help discover new, mechanism-based drugs.¹¹

This strategy is most effective when supported by computational platforms that integrate molecular databases, simulation tools, reaction modeling, and statistical analysis within a unified workflow. Open platforms such as BRIDGE are well-suited to this purpose, as they integrate simulation engines, analytical tools, and reaction modules into reproducible workflows. This configuration enables transition-state calculations, molecular docking, molecular dynamics, and energy analyses within workflows that can be shared and refined by the scientific community. Consequently, open computational systems are transforming molecular simulation into a more scalable and collaborative discipline.

Natural products are well-suited to this computational approach. Their complex structures and

diverse features often make them more similar to enzyme transition states than simple synthetic molecules. By using transition states from QM/MM simulations as search templates, researchers can find natural molecules that might mimic the key conformations of certain enzymes. After identifying these candidates, scientists can use docking and molecular dynamics simulations to assess binding affinity, complex stability, and how protein motion affects binding.

The integration of natural product chemistry, transition-state theory, and open molecular simulation represents a significant advancement in drug discovery. Rather than relying on empirical screening, this approach utilizes mechanistically informed templates based on the functional characteristics of target enzymes. Transparent, reproducible workflows supplant ambiguous procedures, directly linking biological data to detailed molecular insights. Natural products are increasingly recognized as components of an extensive, evolutionarily shaped chemical library accessible to modern computational chemistry, rather than as isolated curiosities. To bridge the gap between computational predictions and real-world applications, experimental follow-up is crucial. This involves validating computational predictions through targeted *in vitro* and *in vivo* experiments to ensure that predicted interactions are observed in biological systems. Such experimental validation enhances the reliability of computational models, thereby reinforcing their role in the full research pipeline.

As chemistry enters an era defined by data-driven, simulation-guided discovery, the integration of biodiversity, quantum mechanics, and open computational infrastructure is becoming increasingly essential. Platforms such as BRIDGE exemplify the potential to unify genomic data, protein structures, molecular dynamics, and reaction chemistry within a single framework. Innovations such as FEARCF further facilitate quantitative analysis of the most complex aspects of enzyme catalysis, particularly transition states. Collectively, these advances are reshaping chemists' and biologists' perspectives on molecules, mechanisms, and therapeutics, thereby supporting the shift from natural molecular diversity to rational, transition-state-guided drug discovery to address urgent health challenges.

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