

# Advances in Molecular Docking for Allosteric Drug Discovery: Ensemble Modeling, Molecular Dynamics, and Artificial Intelligence



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## Abstract

Allosteric drug discovery has increasingly shifted toward the center of structure-based drug design, challenging traditional assumptions underlying molecular docking. Classical docking approaches rely on static protein structures, yet growing evidence suggests that protein dynamics play a critical role in shaping allosteric binding sites and ligand recognition. This review synthesizes recent advances in molecular docking for allosteric drug discovery, with particular emphasis on ensemble docking, molecular dynamics integration, and artificial intelligence (AI)-driven methods. Across studies, ensemble docking approaches enable the identification of transient or cryptic allosteric sites that are often inaccessible in single static conformations. Integration with molecular dynamics simulations further captures conformational flexibility, improving the accuracy of docking predictions and ligand binding assessment. At the same time, AI-based tools, including structure prediction frameworks such as AlphaFold, have expanded structural coverage, although they frequently represent dominant conformations and may underrepresent dynamic allosteric states. Emerging hybrid strategies that combine AI, molecular dynamics, and multiscale approaches such as QM/MM offer a more comprehensive framework for modeling protein–ligand interactions. However, key challenges remain, including accurate prediction of allosteric effects, maintenance of

physical realism, and translation of computational predictions into experimentally validated therapeutics. Overall, molecular docking is evolving from static structure-based methods toward dynamic, integrative approaches that better capture protein flexibility and allosteric regulation. These advances provide new opportunities for improving the discovery of allosteric modulators, although robust validation and methodological standardization remain essential for clinical translation.

**Keywords:** Allosteric modulation; Molecular docking; Ensemble modeling; Artificial intelligence; Protein dynamics

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## 1. Introduction

The molecular basis of drug action has long been framed through relatively simple metaphors—"lock and key," "induced fit," tidy images that suggest stability and predictability. Yet, as structural biology and computational chemistry have matured, that simplicity has begun to feel... insufficient. Proteins are not static locks; they are dynamic systems, fluctuating across conformational landscapes that are only partially captured in experimental

**Significance |** Reframes molecular docking toward dynamic, AI-integrated paradigms, enabling more precise identification and targeting of elusive allosteric sites in drug discovery.

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snapshots. Within this shifting terrain lies the concept of allostery—a mode of regulation in which ligand binding at one site modulates activity at another, often distant, region of the protein. Increasingly, this phenomenon is not just a biochemical curiosity but a central paradigm in modern drug discovery, especially for targets once considered intractable.

Allosteric drug discovery, in this sense, represents both an opportunity and a challenge. On one hand, allosteric sites tend to be less conserved than orthosteric pockets, offering a pathway toward greater selectivity and reduced off-target effects (Nussinov & Jang, 2024; Zhang et al., 2024; Adelusi et al., 2025). On the other, these sites are often transient, shallow, or even cryptic—appearing only under certain conformational states that are difficult to capture experimentally or computationally (Bemelmans et al., 2025; Colombo, 2023). This duality has pushed the field toward more sophisticated computational tools, with molecular docking evolving as a central, if imperfect, technique in navigating these complexities.

Historically, molecular docking emerged as a pragmatic solution to a constrained problem: how to predict ligand binding poses and affinities given a fixed protein structure. Early algorithms treated both ligand and receptor as rigid entities, a simplification that enabled high-throughput screening but ignored the inherent flexibility of biomolecules (Paggi et al., 2024). Over time, incremental improvements—flexible ligand docking, side-chain adjustments, and induced-fit protocols—began to address these limitations, though often at increased computational cost (Gautam et al., 2024; Sahu et al., 2024). Still, even these advances struggled to fully capture the dynamic nature of allosteric regulation, where subtle conformational shifts can dramatically alter binding landscapes.

It is perhaps here that the conceptual shift becomes most apparent. Rather than viewing docking as a single-point prediction, recent approaches increasingly treat it as an ensemble problem. Proteins are represented not by one structure but by a distribution of conformations, often generated through molecular dynamics (MD) simulations. This ensemble docking framework allows for the identification of transient pockets—so-called “cryptic sites”—that may be invisible in static crystal structures but are nonetheless functionally relevant (Bemelmans et al., 2025; Zhu et al., 2025). In the context of allosteric drug discovery, this shift is not merely technical; it is foundational.

At the same time, the integration of artificial intelligence has introduced a new layer of complexity—and possibility. Deep learning models have demonstrated remarkable success in predicting protein structures, most notably through systems like AlphaFold, which can generate high-accuracy models from sequence data alone (Qiu et al., 2024). These developments have dramatically expanded the structural coverage of the proteome, offering new starting points for docking and virtual screening. Yet, there is an inherent tension here. While AI-generated structures are often precise, they tend to represent a single, energetically favorable conformation, potentially overlooking the dynamic transitions that underpin allosteric regulation (Nussinov et al., 2023).

To address this limitation, hybrid approaches are emerging that combine AI predictions with physics-based simulations. For instance, AI-derived structures can serve as initial states for MD simulations, which then explore conformational variability and reveal potential allosteric sites (Bai et al., 2022; Nam et al., 2024). This synergy between data-driven and physics-based methods reflects a broader trend in computational drug discovery: the recognition that no single approach is sufficient on its own. Instead, progress lies in integration—of methods, scales, and perspectives.

Another important development is the growing emphasis on co-folding or joint prediction of protein–ligand complexes. Traditional workflows typically separate structure prediction from docking, treating them as sequential steps. However, newer models aim to predict both simultaneously, effectively collapsing the distinction between structure determination and binding prediction (Nittinger et al., 2025). This approach is particularly intriguing for allosteric systems, where ligand binding may induce or stabilize conformations that are not present in the unbound state. Early evidence suggests that co-folding methods can identify binding modes that would be difficult to capture ational landscape conventional docking pipelines, although their reliability and generalizability are still under active investigation.

Beyond structural prediction and docking, the role of detailed physicochemical modeling should not be overlooked. While classical force fields provide a useful approximation of molecular interactions, they may fall short in capturing electronic effects that are critical for certain classes of allosteric modulators, such as covalent inhibitors or metal-coordinating ligands. Hybrid quantum

mechanics/molecular mechanics (QM/MM) approaches offer a way to bridge this gap, enabling more accurate modeling of electronic interactions within a broader molecular context (Rossetti & Mandelli, 2024). As computational resources continue to expand—approaching exascale levels—such methods are becoming increasingly feasible for integration into drug discovery workflows.

Importantly, the relevance of these computational advances is not confined to theoretical considerations. Allosteric modulators have already demonstrated clinical value across a range of therapeutic areas, including oncology, neurology, and metabolic diseases (Govindaraj et al., 2023; Wang et al., 2025). In many cases, they offer advantages over orthosteric drugs, such as improved selectivity, reduced toxicity, and the ability to overcome resistance mechanisms. For example, allosteric inhibitors targeting mutant forms of epidermal growth factor receptor (EGFR) have shown promise in addressing resistance to first-generation therapies (Wang et al., 2025). These successes underscore the practical importance of refining computational methods to better identify and characterize allosteric binding sites.

Yet, despite these advances, significant challenges remain. The identification of allosteric sites is still far from routine, and the prediction of allosteric effects—how binding at one site influences activity at another—remains particularly difficult (Berezovsky & Nussinov, 2022; Rehman et al., 2021). Moreover, the reliance on cryogenic structural data may introduce artifacts that obscure physiologically relevant conformations, raising questions about the accuracy of current models (Stachowski & Fischer, 2026). Addressing these issues will likely require not only methodological improvements but also a deeper conceptual understanding of protein dynamics and regulation.

In this context, molecular docking can be seen as both a tool and a lens—a way of probing molecular interactions, but also a framework that shapes how we think about them. Its evolution from rigid-body approximations to dynamic, AI-enhanced, and multiscale methodologies mirrors broader shifts in the life sciences, toward embracing complexity rather than simplifying it away. Still, one might hesitate to call it a fully predictive science. There is, perhaps, still an element of interpretation, even intuition, in how docking results are generated and understood.

This narrative review, therefore, aims to explore these developments in a critical yet forward-looking manner. It examines how advances in molecular docking—spanning ensemble approaches, artificial intelligence, co-folding strategies, and multiscale simulations—are reshaping the landscape of allosteric drug discovery. At the same time, it acknowledges the limitations and uncertainties that persist, suggesting that the future of the field will depend not only on technological innovation but also on a willingness to rethink underlying assumptions about protein structure, dynamics, and function.

## 2. Methodology

### 2.1 Review Design and Conceptual Framework

This study was conducted as a narrative review aimed at critically synthesizing recent advances in molecular docking methodologies within the context of allosteric drug discovery. Unlike systematic reviews, which follow rigid inclusion protocols, this approach was intentionally flexible, allowing for the integration of conceptual developments, methodological innovations, and emerging computational paradigms. The review framework was guided by the evolving understanding of protein dynamics and allostery, emphasizing the transition from static structural models toward ensemble-based and multiscale representations (Berezovsky & Nussinov, 2022; Colombo, 2023).

### 2.2 Literature Search Strategy

A comprehensive literature search was performed across major scientific databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search covered publications from approximately 2015 to 2026, reflecting the period of rapid advancement in artificial intelligence and molecular simulation techniques. Keywords and Boolean combinations included “allosteric drug discovery,” “molecular docking,” “ensemble docking,” “cryptic binding sites,” “molecular dynamics,” “AI in drug discovery,” and “protein structure prediction.” Additional studies were identified through backward and forward citation tracking to ensure coverage of seminal and highly relevant works (Qiu et al., 2024; Bai et al., 2022).

### 2.3 Inclusion and Exclusion Criteria

Studies were included based on their relevance to computational approaches for identifying or characterizing allosteric binding sites. Priority was given to peer-reviewed articles that presented methodological innovations,

benchmarking analyses, or applied case studies involving docking, molecular dynamics (MD), artificial intelligence, or hybrid computational frameworks. Reviews and primary research articles were both considered where they contributed conceptual clarity or technical insight. Exclusion criteria included studies focusing exclusively on orthosteric drug design without relevance to allostery, as well as reports lacking sufficient methodological detail or validation (Bemelmans et al., 2025; Nussinov et al., 2023).

#### 2.4 Data Extraction and Thematic Synthesis

Relevant data were extracted qualitatively, focusing on methodological principles, computational strategies, advantages, and limitations. Rather than quantitative aggregation, findings were organized into thematic categories reflecting key developments in the field. These included (i) traditional and flexible docking approaches, (ii) ensemble and MD-based docking strategies, (iii) AI-driven structure prediction and co-folding methods, and (iv) multiscale modeling techniques such as QM/MM simulations. Comparative insights were derived by examining how different approaches address challenges related to protein flexibility, cryptic site identification, and binding prediction accuracy (Paggi et al., 2024; Gautam et al., 2024; Sahu et al., 2024).

#### 2.5 Integration of AI and Multiscale Approaches

Special emphasis was placed on studies that integrated artificial intelligence with physics-based simulations, reflecting a growing trend in computational drug discovery. AI-derived structural models, particularly those generated by deep learning frameworks, were evaluated in conjunction with MD simulations to assess their ability to capture conformational variability relevant to allosteric regulation (Qiu et al., 2024; Nittinger et al., 2025). Additionally, multiscale approaches incorporating quantum mechanics/molecular mechanics (QM/MM) were examined for their role in refining docking predictions and improving the accuracy of interaction modeling (Rossetti & Mandelli, 2024).

#### 2.6 Critical Appraisal and Interpretation

The selected literature was critically evaluated with attention to methodological robustness, reproducibility, and translational relevance. Particular consideration was given to limitations such as computational cost, dataset bias, and the physical plausibility of predicted binding modes. Rather than presenting findings as definitive, this

review adopts an interpretative perspective, acknowledging uncertainties and emphasizing the iterative nature of methodological development in allosteric drug discovery (Stachowski & Fischer, 2026; Rehman et al., 2021).

### 3. The AI Renaissance in Structural Biology: Rethinking Allosteric Drug Discovery

If one looks back at the early decades of drug discovery, the guiding intuition was almost comfortingly simple. A drug, much like a key, would fit into a protein's active site—the lock—and either activate or inhibit its function. This “lock-and-key” framework, while elegant, quietly assumed that proteins themselves were stable, well-defined entities. Yet that assumption, as we now recognize, was never entirely accurate. Proteins are not rigid objects; they are restless, fluctuating systems, continuously exploring a spectrum of conformations that are only partially visible to us (Berezovsky & Nussinov, 2022; Colombo, 2023). It is within this dynamic complexity that allostery emerges—not as an exception, but perhaps as a fundamental principle of biological regulation.

Allosteric drug discovery, then, is not merely an alternative strategy; it is, in some sense, a reframing of how we think about molecular control. Rather than competing with endogenous ligands at highly conserved orthosteric sites, allosteric modulators bind at distal regions, subtly reshaping the protein's conformational landscape. The appeal is obvious: improved selectivity, reduced toxicity, and the possibility of modulating function with a degree of nuance that resembles physiological regulation (Nussinov & Jang, 2024; Govindaraj et al., 2023). And yet, identifying these sites—often transient, sometimes elusive—has historically been a slow and uncertain endeavor (Bemelmans et al., 2025; Zhu et al., 2025).

It is precisely at this intersection of complexity and opportunity that artificial intelligence has begun to exert a transformative influence.

#### 3.1 From Sequence to Structure: The Expanding Reach of AI

The emergence of deep learning models for protein structure prediction has, quite abruptly, altered the landscape of structural biology. Systems such as AlphaFold2—and more recently, AlphaFold3—have demonstrated an ability to infer three-dimensional structures from amino acid sequences with an accuracy

that, not long ago, would have seemed implausible (Abramson et al., 2024; Qiu et al., 2024). This shift has practical consequences that are difficult to overstate. Proteins that once resisted experimental characterization—the so-called “dark proteome”—are now, at least structurally, accessible.

For drug discovery, this means that the initial barrier—obtaining a reliable structural model—is no longer as prohibitive as it once was. Researchers can now explore potential binding sites, including those relevant to disease-associated mutations, with unprecedented breadth. In oncology, for instance, AI-predicted structures are being used to rationalize how specific mutations alter protein stability or disrupt regulatory interactions, thereby informing therapeutic strategies (Nussinov et al., 2023; Qiu et al., 2024).

And yet, there is a subtle complication here—one that becomes particularly important for allosteric systems.

### 3.2 The Allostery Paradox: When Accuracy Is Not Enough

Despite their remarkable accuracy, AI-generated protein structures are, in essence, static representations. They typically correspond to a single, energetically favorable conformation—often resembling the ground state captured in experimental datasets. But allostery, by its very nature, is not static. It depends on transitions between multiple states, some of which may be rare, transient, or energetically less favorable (Berezovsky & Nussinov, 2022).

This creates what might be called an “allostery paradox.” We now have highly accurate structural models, yet those models may obscure precisely the features we are most interested in—cryptic pockets, transient interfaces, and conformational pathways that enable distal regulation (Colombo, 2023; Nussinov et al., 2023). Moreover, because many experimental structures used for training AI systems are derived under cryogenic conditions, there is a risk that these models inherit biases toward inactive or stabilized conformations (Stachowski & Fischer, 2026).

In practice, this means that relying solely on static AI predictions may lead to an incomplete—or even misleading—picture of allosteric potential.

### 3.3 Beyond Static Models: Integrating AI with Molecular Dynamics

To address these limitations, researchers have

increasingly turned toward hybrid approaches that combine AI-based structure prediction with physics-based simulations. Molecular dynamics (MD), in particular, offers a way to explore the temporal dimension of protein behavior, capturing fluctuations that static models cannot (Paggi et al., 2024; Bai et al., 2022).

In this integrated framework, AI-derived structures serve as starting points—initial coordinates from which simulations can evolve. Over time, MD trajectories reveal how proteins sample different conformations, how loops rearrange, and how solvent interactions reshape potential binding sites. These simulations often uncover cryptic allosteric pockets that are not apparent in the original structure but emerge under physiologically relevant conditions (Bemelmans et al., 2025).

This shift toward ensemble representations—collections of conformations rather than a single structure—has profound implications for molecular docking. Instead of docking ligands into a fixed pocket, researchers can now screen compounds across a spectrum of states, increasing the likelihood of identifying functionally relevant interactions (Gautam et al., 2024; Sahu et al., 2024).

Interestingly, such approaches have already demonstrated success in identifying modulators for challenging targets, including receptors with highly dynamic binding interfaces. In these cases, the ability to capture conformational diversity appears to be not just advantageous, but essential.

### 3.4 Co-folding and the Collapse of Sequential Workflows

While ensemble docking represents a significant advance, an even more radical shift is underway. Traditional drug discovery workflows tend to follow a sequential logic: determine the protein structure, identify binding sites, and then dock candidate ligands. However, emerging AI models are beginning to blur these boundaries.

Co-folding approaches—exemplified by systems such as AlphaFold3 and related architectures—aim to predict protein–ligand complexes directly, without separating structure determination from binding prediction (Abramson et al., 2024; Nittinger et al., 2025). In these models, the presence of a ligand influences the predicted protein conformation, effectively allowing the system to “anticipate” binding-induced changes.

For allosteric drug discovery, this is particularly intriguing. Allosteric sites are often induced or stabilized by ligand

binding, meaning they may not exist in the apo (unbound) structure. Co-folding models, in principle, can capture these induced states, revealing binding modes that would be inaccessible through conventional docking pipelines (Nittinger et al., 2025).

That said, these methods are still evolving. Questions remain regarding their accuracy, especially in distinguishing between plausible and physically unrealistic binding poses. Nonetheless, the conceptual shift—from sequential to simultaneous prediction—marks a significant departure from traditional approaches.

### 3.5 Generative Design and the Expansion of Chemical Space

Parallel to advances in structural prediction, AI is also reshaping how we think about ligand design itself. Rather than screening existing libraries, generative models—such as variational autoencoders and generative adversarial networks—can create entirely new molecular structures tailored to specific binding environments (Bai et al., 2022). In the context of allosteric sites, which often have unique geometries and physicochemical properties, this capability is particularly valuable. Generative models can, in effect, design ligands that “fit” into these unconventional pockets from the outset, potentially reducing the need for extensive optimization.

Recent computational studies have demonstrated that such approaches can identify novel modulators for targets like AMP-activated protein kinase (AMPK), highlighting the practical potential of AI-driven design (Adelusi et al., 2025). Still, translating these designs into experimentally validated compounds remains a nontrivial step, underscoring the importance of integrating computational predictions with empirical testing.

### 3.6 The Multiscale Perspective: From Atoms to Electronics

As candidate molecules move closer to experimental validation, the limitations of classical docking become more apparent. While force-field-based methods provide a useful approximation of binding interactions, they often neglect electronic effects that can be critical for accurate prediction. Hybrid quantum mechanics/molecular mechanics (QM/MM) approaches offer a way to address this gap by treating key regions—such as binding sites—with quantum-level detail while maintaining computational efficiency for the rest of the system (Rossetti & Mandelli, 2024). This is particularly important

for systems involving covalent interactions, metal coordination, or complex hydrogen-bonding networks. With the advent of high-performance and exascale computing, these multiscale methods are becoming increasingly accessible, allowing for more precise estimation of binding energetics. In some workflows, QM/MM calculations are now integrated directly into virtual screening pipelines, refining docking results and improving predictive accuracy.

### 3.7 A Necessary Caution: Physical Validity and Experimental Grounding

Despite the rapid progress in AI-driven methodologies, there is a growing recognition that computational predictions must be interpreted with care. AI models, while powerful, can produce binding poses that violate basic physical constraints—issues that may not be immediately apparent without rigorous validation (Paggi et al., 2024).

This “hallucination” problem highlights a broader point: AI should be viewed as an augmentative tool rather than a replacement for established scientific principles. Ensuring physical plausibility—through energy minimization, validation tools, and experimental corroboration—remains essential. Moreover, as Stachowski and Fischer (2026) emphasize, the conditions under which structural data are obtained can significantly influence their relevance. Cryogenic artifacts, for example, may stabilize conformations that are not representative of physiological states, potentially misleading both AI models and downstream analyses.

### 3.8 Toward a Mechanistic Future: Integrating AI and Biology

Taken together, these developments suggest that the future of allosteric drug discovery will not be defined by any single technology, but by the integration of multiple approaches. AI provides speed, scale, and pattern recognition; physics-based simulations offer mechanistic insight; and experimental methods ground predictions in reality. There is, perhaps, a growing sense that the field is moving toward a more holistic understanding of proteins—not as static targets, but as dynamic networks of interactions that can be modulated in subtle and context-dependent ways. In this framework, molecular docking is no longer just a tool for predicting binding poses; it becomes part of a broader effort to map and manipulate the conformational landscapes that underlie biological function.

And yet, even with these advances, a degree of uncertainty remains. The complexity of allosteric regulation resists easy generalization, and the interplay between structure, dynamics, and function is still only partially understood. It may be that progress will continue to be iterative—driven by cycles of prediction, validation, and refinement. Still, the trajectory is clear. By embracing both the power and the limitations of AI, and by maintaining a commitment to physical realism, the field is gradually transforming what once seemed undruggable into tangible therapeutic opportunities.

## 4. Synthesis of Evidence

### 4.1 Reframing Allosteric Drug Discovery Through Computational Convergence

The synthesis of findings from this review suggests that allosteric drug discovery is no longer progressing in incremental steps; rather, it appears to be undergoing a more structural transformation—one that is perhaps still unfolding, not entirely settled. What emerges is a field increasingly defined by integration: of computational paradigms, of scales, and, in a way, of philosophical approaches to how proteins are understood. Instead of viewing proteins as static entities with predefined binding pockets, the results collectively point toward a more fluid, ensemble-based understanding of molecular recognition.

### 4.2 From Static Docking to Dynamic Ensembles

A consistent pattern across the reviewed studies is the gradual departure from rigid-body docking toward more dynamic and context-aware methodologies. Traditional docking, while still widely used due to its computational efficiency, seems increasingly insufficient when evaluated against the demands of allosteric systems. It performs adequately as a first-pass filter, particularly in large-scale virtual screening campaigns, yet its inability to account for protein flexibility limits its predictive value (Sahu et al., 2024). More recent approaches, particularly those incorporating induced-fit and ensemble docking strategies, reveal a noticeable improvement in capturing ligand–protein interactions that depend on subtle conformational rearrangements. Molecular dynamics (MD)-derived ensembles, for instance, allow ligands to be evaluated against multiple structural states, thereby reflecting a more realistic representation of protein behavior (Paggi et al., 2024). This becomes especially important in the context of allostery, where binding events often rely on transient conformations that are not evident

in static crystal structures. Interestingly, the results reinforce the idea that allostery is not an isolated phenomenon but an inherent property of protein dynamics. Rather than functioning as a binary switch, allosteric regulation appears to redistribute populations across conformational states—a concept that aligns with multiscale models of protein behavior (Berezovsky & Nussinov, 2022). This perspective, while conceptually appealing, also complicates computational prediction, as it requires capturing not just a single binding event but an entire landscape of possibilities.

### 4.3 Revealing Cryptic Allosteric Sites

One of the more technically challenging aspects identified in this review is the detection of cryptic binding pockets—sites that are not visible in apo structures but emerge under specific dynamic conditions (Table 1). The results suggest that advances in both simulation and machine learning have begun to address this challenge, although not without limitations. Mixed-solvent MD simulations, for example, have proven effective in mapping transient pockets by introducing probe molecules that preferentially occupy energetically favorable regions (Bemelmans et al., 2025). These approaches, while computationally demanding, provide direct insight into potential allosteric hotspots, particularly in flexible systems such as G protein-coupled receptors (GPCRs). Complementing these physics-based methods, AI-driven tools such as graph neural networks have demonstrated an ability to predict cryptic sites from single protein structures. Models like PocketMiner, as highlighted in Table 1, can rapidly identify candidate regions that may warrant further exploration through MD simulations (Bemelmans et al., 2025). At the same time, statistical mechanical frameworks such as AlloSigMA offer a different, more theoretical lens—quantifying how perturbations at one site propagate through the protein structure (Zhu et al., 2025).

Taken together, these approaches suggest a convergence of methodologies: AI for rapid screening and prioritization, followed by physics-based simulations for validation and refinement. Still, the process remains far from routine, and the identification of truly functional allosteric sites continues to require careful interpretation.

### 4.4 AI-Driven Structural Prediction and the Emergence of Co-folding

Another defining feature of the results is the expanding

Table 1. Computational Methodologies for Allosteric and Cryptic Site Identification. This table summarizes major computational approaches used for identifying allosteric and cryptic binding sites in proteins. It highlights their underlying principles, advantages, limitations, and levels of AI integration in modern drug discovery workflows.

| Method Name      | Primary Application      | Underlying Principle    | Key Advantage            | Major Limitation        | AI Integration Level    | Reference                   |
|------------------|--------------------------|-------------------------|--------------------------|-------------------------|-------------------------|-----------------------------|
| Mixed-Solvent MD | Cryptic pocket discovery | Organic probes in water | Captures transient sites | High computational cost | Low (Physics-based)     | Bemelmans et al., 2025      |
| PocketMiner      | Pocket prediction        | Graph Neural Networks   | Rapid screening          | Sequence-structure bias | High (GNN-based)        | Bemelmans et al., 2025      |
| AlloSigMA        | Allosteric signaling     | Statistical mechanics   | Quantifies signal flow   | Rigid structure input   | Medium (Energy profile) | Zhu et al., 2025            |
| PASSer           | Site identification      | Machine learning        | Fast and accurate        | Geometry dependent      | High (Ensemble ML)      | Nussinov et al., 2023       |
| NMA              | Global motion analysis   | Harmonic oscillations   | Very low cost            | Ignores local unfolding | Low (Traditional)       | Rehman et al., 2021         |
| GaMD             | Long-range signaling     | Accelerated dynamics    | Extensive sampling       | Complex setup           | Medium (Simulation)     | Berezovsky & Nussinov, 2022 |
| AlloReverse      | Communication path       | Reversed allostery      | Maps pathways            | Limited to known hits   | Medium (Algorithmic)    | Zhu et al., 2025            |
| FTMap            | Hotspot detection        | Probe mapping           | Identifies binding zones | Static receptor model   | Low (Geometric)         | Zhu et al., 2025            |
| SWISH-X          | Interface pockets        | Enhanced sampling       | Targets PPI interfaces   | System specificity      | Medium (Multiscale)     | Bemelmans et al., 2025      |

Table 2. AI-Driven Frameworks for Protein Structure Prediction and Docking. This table presents leading AI-based tools for protein structure prediction and molecular docking. It compares their modeling approaches, input requirements, and benchmarked performance across computational biology tasks.

| Tool Name   | Developer/Origin  | Core Functionality         | Input Data Required  | Modeling Approach      | Performance Benchmark      | Reference              |
|-------------|-------------------|----------------------------|----------------------|------------------------|----------------------------|------------------------|
| AlphaFold2  | Google DeepMind   | 3D structure prediction    | Protein sequence     | Transformer-based      | Atomic accuracy            | Qiu et al., 2024       |
| AlphaFold3  | Isomorphic Labs   | Biomolecular interactions  | Protein + ligand     | Diffusion model        | Superior complex accuracy  | Nittinger et al., 2025 |
| ESMFold     | Meta AI           | Rapid structure prediction | Single sequence      | Large language model   | ~6× faster than AlphaFold2 | Qiu et al., 2024       |
| RoseTTAFold | Baker Lab         | Assembly modeling          | Multi-track sequence | 3-track neural network | Models full complexes      | Qiu et al., 2024       |
| Boltz-1x    | MIT Jameel Clinic | Co-folding docking         | Sequence + ligand    | Diffusion-based        | >90% physical validity     | Nittinger et al., 2025 |

|              |                     |                         |                    |                      |                                 |                        |
|--------------|---------------------|-------------------------|--------------------|----------------------|---------------------------------|------------------------|
| NeuralPLexer | Nvidia/Iambic       | Ligand-specific folding | Protein sequence   | Generative model     | Fastest co-folding tool         | Nittinger et al., 2025 |
| OpenFold     | OpenFold Consortium | Trainable AF2 clone     | Protein sequence   | PyTorch framework    | Lower memory usage              | Qiu et al., 2024       |
| Deep Docking | Cherkasov Lab       | Ultra-large screening   | Chemical libraries | Deep learning        | Processes billions of compounds | Gautam et al., 2024    |
| DiffDock     | MIT                 | Flexible ligand docking | 3D coordinates     | Generative diffusion | High pose prediction accuracy   | Bai et al., 2022       |

Table 3. Classification of Molecular Docking Methodologies and Characteristics. This table categorizes molecular docking strategies based on flexibility, complexity, and application scope. It highlights their suitability across different stages of drug discovery and structural biology investigations.

| Method Type      | Primary Focus           | Flexibility             | Complexity | Key Outcome                             | Best Use Case                    | Reference                 |
|------------------|-------------------------|-------------------------|------------|-----------------------------------------|----------------------------------|---------------------------|
| Rigid Docking    | Geometric fit           | None (protein/ligand )  | Low        | Initial hit identification              | High-throughput screening        | Sahu et al., 2024         |
| Flexible Docking | Ligand conformations    | Ligand only             | Medium     | Binding mode refinement                 | Lead optimization                | Gautam et al., 2024       |
| Induced Fit      | Local protein motion    | Receptor + ligand       | High       | Accurate pocket modeling                | Small conformational change      | Sahu et al., 2024         |
| Ensemble Docking | Global dynamics         | Full conformational set | Very high  | Cryptic pocket targeting                | Transient state exploration      | Paggi et al., 2024        |
| Blind Docking    | Unknown binding sites   | Whole receptor          | Medium     | Site identification                     | No prior pocket knowledge        | Sahu et al., 2024         |
| Deep Docking     | Library enrichment      | Ligand-focused          | Medium     | Billion-scale virtual screening         | Large chemical space exploration | Gautam et al., 2024       |
| QM/MM Docking    | Electronic interactions | Quantum-level           | Extreme    | Covalent/metal binding characterization | Reactive systems                 | Rossetti & Mandelli, 2024 |
| Co-folding       | Simultaneous modeling   | Full system             | High       | Novel complex prediction                | Unknown binding conformations    | Nittinger et al., 2025    |
| Protein–Protein  | Interface docking       | Backbone flexibility    | High       | Interaction mapping                     | PPI modulation                   | Sahu et al., 2024         |

role of artificial intelligence in structural biology (Table 2). Yet, there remains a degree of caution. AI-generated poses, while often plausible, can still exhibit biases—particularly toward orthosteric sites, which are overrepresented in training datasets. This tendency highlights an ongoing challenge: ensuring that AI models not only predict structures accurately but also reflect the diversity of biologically relevant states.

#### 4.5 Multiscale Modeling and the Role of Electronic Precision

As the analysis moves from site identification to interaction characterization, the importance of multiscale modeling becomes increasingly evident. Classical docking approaches, while useful, often fail to capture electronic effects that are critical for understanding binding energetics, particularly in systems involving covalent interactions or metal coordination. Hybrid QM/MM simulations, as discussed in Table 3, offer a way to bridge this gap by combining quantum-level accuracy with the efficiency of classical models (Rossetti & Mandelli, 2024). These methods are especially relevant for studying allosteric mechanisms that involve subtle electronic rearrangements, such as hydrogen-bond networks or ion-mediated stabilization.

With the increasing availability of high-performance computing resources, these techniques are becoming more accessible, allowing for their integration into broader drug discovery pipelines. At the same time, their computational cost still necessitates selective application, often as a refinement step rather than a primary screening tool.

#### 4.6 Translational Outcomes: From Computational Insight to Therapeutic Impact

Perhaps the most compelling aspect of the results lies in their translation into real-world therapeutic advances (Table 4). Several case studies illustrate how computational strategies have successfully guided the discovery of allosteric modulators. In the case of EGFR (C797S), for example, the design of allosteric inhibitors capable of bypassing resistance mutations demonstrates the practical value of integrating docking, free energy calculations, and structural modeling (Wang et al., 2025). Similarly, the identification of AMPK activators through pharmacophore-based modeling highlights the potential of computational approaches in targeting metabolic pathways (Abdalla et al., 2025). Other examples, such as

the discovery of selective modulators for GPCRs and the development of BCR-ABL1 inhibitors like asciminib, further reinforce the idea that allosteric targeting can overcome limitations associated with orthosteric drugs (Colombo, 2023; Nussinov & Jang, 2024). These successes, while encouraging, also underscore the importance of combining computational predictions with experimental validation.

#### 4.7 Integrative Trends and Persistent Challenges

When viewed collectively, the results suggest that the most effective strategies in allosteric drug discovery are those that integrate multiple computational approaches. AI-driven structure prediction, MD-based conformational sampling, and QM/MM-level refinement each contribute distinct but complementary insights (Zhu et al., 2025; Nussinov & Jang, 2024). At the same time, several challenges remain. AI models, despite their sophistication, still struggle with issues such as inactive-state bias and the generation of physically unrealistic binding poses (Nittinger et al., 2025). Additionally, the reliance on cryogenic structural data may introduce artifacts that complicate interpretation, particularly when attempting to model physiologically relevant states (Stachowski & Fischer, 2026). These limitations suggest that progress in the field will likely depend on continued refinement of both computational methods and experimental techniques. There is, perhaps, a growing recognition that no single approach will suffice; instead, advances will emerge from iterative cycles of prediction, validation, and adjustment.

**4.8 Synthesis of Findings** In synthesizing these observations, it becomes clear that allosteric drug discovery is transitioning toward a more holistic and systems-oriented paradigm. Proteins are no longer treated as static targets but as dynamic networks, whose behavior can be modulated through subtle perturbations across their national landscape. The integration of AI, molecular dynamics, and multiscale simulations has, in effect, expanded the boundaries of what is considered “druggable.” Targets that once appeared inaccessible are now being revisited with renewed optimism, supported by computational tools capable of revealing hidden regulatory mechanisms. And yet, there remains an element of uncertainty—perhaps even humility—in how these results should be interpreted. The complexity of allosteric systems resists simplification, and while computational methods have advanced

Table 4. Case Studies of Allosteric Modulators and Therapeutic Targets. This table compiles representative case studies of clinically relevant allosteric modulators and their target proteins. It outlines binding sites, disease applications, and discovery methodologies used in modern pharmacological research.

| Target Protein | Modulator Name  | Modulator Type       | Binding Site         | Disease Indication     | Discovery Methodology           | Reference               |
|----------------|-----------------|----------------------|----------------------|------------------------|---------------------------------|-------------------------|
| MEK1/2         | Trametinib      | Type III NAM         | Adjacent to ATP site | Cancer / Inflammation  | X-ray / Ensemble docking        | Govindaraj et al., 2023 |
| BCR-ABL1       | Asciminib       | Allosteric inhibitor | Myristoyl pocket     | Myeloid leukemia       | Phenotypic screening / SBDD     | Nussinov & Jang, 2024   |
| CaSR           | Cinacalcet      | Positive modulator   | Within 7TMD          | Hyperparathyroidism    | Large-scale virtual screening   | Zhang et al., 2024      |
| EGFR (C797S)   | MK-1            | Allosteric inhibitor | Y-shaped pocket      | Lung cancer            | Scaffold hopping / MM-GBSA      | Wang et al., 2025       |
| AMPK           | Galegine analog | ADaM activator       | / subunit interface  | Metabolic disorders    | Pharmacophore modeling          | Adelusi et al., 2025    |
| PI3K           | RLY-2608        | Selective PAM        | C-terminal site      | Breast cancer          | Free-energy calculations        | Nussinov & Jang, 2024   |
| SIRT6          | MDL-801         | Activator            | Allosteric pocket    | Cancer therapy         | Reversed communication analysis | Zhu et al., 2025        |
| C5aR1          | Avacopan        | Allosteric NAM       | Extra-helical site   | ANCA vasculitis        | Structure-based design          | Zhang et al., 2024      |
| M2 mAChR       | LY2119620       | PAM                  | Inside 7TMD          | Neurological disorders | Ensemble docking                | Colombo, 2023           |

considerably, they are still approximations of a far more intricate biological reality.

Even so, the trajectory is unmistakable. By embracing both the strengths and the limitations of current methodologies, the field is gradually moving toward a more nuanced, predictive, and ultimately more effective framework for drug discovery—one that aligns more closely with the dynamic nature of life itself.

## 5. Discussion

### 5.1 Toward a Nuanced Integration of Dynamics, AI, and Chemical Precision

The findings synthesized in this review point, perhaps somewhat quietly but unmistakably, toward a conceptual reorientation in how molecular recognition is understood in drug discovery. What was once framed through the relatively rigid “lock-and-key” analogy now appears increasingly inadequate. Instead, proteins are better described as dynamic systems—ensembles of interconverting states whose functional behavior emerges from this very plasticity. In this context, allostery is not an exception to the rule but rather an intrinsic feature of protein architecture, shaping how signals are transmitted and modulated across biological systems (Berezovsky & Nussinov, 2022). This shift has, in turn, reshaped the role of molecular docking itself—from a tool designed to locate a single optimal pose to one that must grapple with distributions, probabilities, and transient structural states.

### 5.2 Reconsidering Structural Foundations: The Role of Dynamics

One of the more persistent themes emerging from the analysis is the need to “unfreeze” structural biology—both literally and conceptually. For decades, high-resolution crystallographic structures have served as the foundation for computational docking. Yet, as increasingly recognized, these structures often represent proteins in stabilized, low-energy conformations that may not reflect their functional states *in vivo* (Stachowski & Fischer, 2026). There is, perhaps, a subtle but important tension here: the very precision that makes crystallography so valuable may also limit its representational scope.

The move toward molecular dynamics (MD)-based ensemble representations offers a partial resolution to this issue. By simulating proteins under near-physiological conditions, MD allows for the observation of conformational fluctuations—loop movements, side-chain

rearrangements, and solvent interactions—that are otherwise obscured (Paggi et al., 2024). These fluctuations are not merely incidental; they often define the accessibility of allosteric sites. Indeed, the identification of cryptic pockets—those transient binding sites that emerge only under specific conditions—depends almost entirely on capturing such dynamic behavior (Bemelmans et al., 2025).

At the same time, it is worth acknowledging that ensemble docking introduces its own complexities. Generating, selecting, and interpreting multiple conformations requires careful methodological choices, and the resulting increase in computational cost is not trivial. Still, the trade-off appears justified, particularly for systems where static models fail to capture functionally relevant states.

### 5.3 The AI Paradox: Acceleration Without Completeness

The integration of artificial intelligence into structural biology has, undeniably, transformed the field. Models such as AlphaFold have provided access to structural information at an unprecedented scale, effectively democratizing what was once a major bottleneck in drug discovery (Qiu et al., 2024). Yet, this rapid expansion of structural data brings with it a certain paradox. AI-generated models, while often highly accurate, tend to represent a single dominant conformation—typically corresponding to the lowest-energy state. For orthosteric drug discovery, this may be sufficient. For allosteric systems, however, it is less clear. Allosteric regulation depends on transitions between multiple states, including those that are sparsely populated or energetically less favorable (Nussinov et al., 2023). In this sense, AI provides clarity, but not necessarily completeness.

The emergence of co-folding approaches offers an intriguing, if still evolving, response to this limitation. By predicting protein–ligand complexes simultaneously, these methods allow for a more dynamic interplay between structure and binding (Nittinger et al., 2025). Early results suggest improvements in pose accuracy and physical plausibility, though challenges remain—particularly in avoiding biases toward well-characterized orthosteric sites (Nittinger et al., 2025). It seems, then, that AI is most powerful not as a standalone solution but as part of a broader, integrated workflow.

### 5.4 Multiscale Modeling: Bridging Speed and Chemical Reality

If AI excels in speed and scale, its limitations become more apparent when considering the finer details of molecular interaction. Classical docking methods, even when enhanced by machine learning, often rely on simplified force fields that cannot fully capture electronic effects. This limitation becomes especially relevant for allosteric modulators that involve covalent interactions, metal coordination, or complex hydrogen-bonding networks. Hybrid QM/MM approaches provide a pathway toward greater accuracy by combining quantum-level calculations with classical molecular mechanics (Rossetti & Mandelli, 2024). These methods allow for the explicit modeling of electronic interactions at binding sites while maintaining computational tractability for the overall system. In practice, they are often applied as a refinement step—validating and optimizing candidate poses generated through faster screening methods.

The increasing availability of high-performance computing resources has further expanded the feasibility of such approaches. As computational capacity approaches exascale levels, it becomes possible to incorporate these high-precision methods more routinely into drug discovery pipelines. Still, their integration requires careful balancing of computational cost and predictive value—a consideration that remains, at least for now, case-dependent.

### 5.5 From Mechanism to Medicine: Translational Implications

Perhaps the most compelling aspect of these developments lies in their translation into therapeutic outcomes. The success of allosteric inhibitors such as asciminib, which targets the myristoyl pocket of BCR-ABL1, demonstrates that allosteric strategies can effectively overcome resistance mechanisms associated with orthosteric drugs (Nussinov & Jang, 2024). Similarly, the design of inhibitors targeting mutant EGFR highlights the potential of combining structural modeling with free energy calculations to address clinically relevant challenges (Wang et al., 2025).

Other examples, such as the identification of AMPK activators through computational modeling, further illustrate how mechanism-based design can yield functionally relevant modulators (Abdalla et al., 2025). These cases suggest that the integration of computational and experimental approaches is not merely advantageous but essential for translating theoretical insights into

practical therapies.

There is also growing interest in alternative modalities, including molecular glues and PROTACs, which leverage allosteric principles to modulate protein–protein interactions or induce targeted degradation. These approaches, while still developing, represent a shift toward more sophisticated forms of intervention—ones that align more closely with the complexity of cellular regulation (Nussinov & Jang, 2024; Govindaraj et al., 2023).

### 5.6 Persistent Challenges and Emerging Directions

Despite the progress outlined above, several challenges remain unresolved. One of the more immediate concerns is the issue of physical validity in AI-generated docking poses. While improvements have been made, there are still instances where predicted interactions violate basic chemical constraints, necessitating additional validation steps (Nittinger et al., 2025). This highlights the importance of maintaining a critical perspective when interpreting computational results. Another challenge lies in predicting off-target effects and toxicity. The very features that make allosteric sites attractive—namely their diversity and variability—also complicate efforts to ensure selectivity. One potential avenue, as suggested in recent studies, is the use of proteome-wide screening approaches to identify unintended binding interactions early in the design process (Nussinov et al., 2023).

More broadly, there is a need to deepen our understanding of the fundamental principles governing allosteric regulation. While computational tools have advanced considerably, they are still, in many respects, approximations of complex biological systems. Progress in this area will likely depend on continued interplay between theoretical modeling and experimental validation.

### 5.7 Concluding Perspective: Toward a Balanced Integration

In reflecting on these developments, it becomes clear that the future of allosteric drug discovery will not be defined by any single methodology. Rather, it will depend on the integration of complementary approaches—AI for rapid structure prediction, MD for capturing dynamics, and QM/MM for chemical precision. Each contributes a piece of the puzzle, and their combined application offers a more complete picture than any could alone. At the same time, there is perhaps a broader lesson to be drawn. As computational tools become more powerful, there is a risk

of over-reliance—of mistaking prediction for understanding. Maintaining a balance between innovation and validation, between speed and accuracy, will be essential.

Ultimately, the shift toward a dynamic, ensemble-based view of proteins represents not just a technical advance but a conceptual one. It challenges us to rethink how molecular interactions are modeled, interpreted, and ultimately exploited for therapeutic benefit. And while the path forward may not be entirely straightforward, it is, without question, an exciting one—marked by the gradual convergence of computational insight and biological complexity.

## 6. Limitations

Despite the advances discussed, several limitations shape the interpretation of current findings. First, many computational approaches—including AI-generated structural models—tend to favor single, energetically stable conformations, potentially overlooking transient states critical for allosteric regulation. Second, while ensemble docking and molecular dynamics improve conformational sampling, they introduce significant computational cost and methodological variability, which can influence reproducibility. Third, force-field-based docking methods often fail to capture electronic-level interactions, necessitating more computationally intensive QM/MM refinements that are not always feasible in large-scale workflows. Additionally, biases in training datasets for AI models—particularly toward well-characterized orthosteric sites—may limit their generalizability to allosteric systems. Finally, a broader limitation persists in the translation of computational predictions into experimentally validated outcomes, highlighting the continued need for integrative pipelines that combine in silico methods with empirical verification.

## 7. Conclusion

Allosteric drug discovery, as reflected in this review, is gradually transitioning toward a more integrated and dynamic framework. The convergence of molecular docking, artificial intelligence, and multiscale simulations has expanded the boundaries of what is considered druggable, revealing previously inaccessible regulatory sites. Yet, this progress is accompanied by persistent uncertainties—particularly regarding conformational diversity, predictive accuracy, and experimental validation. Rather than offering definitive solutions, current

methodologies provide increasingly refined approximations. The future of the field will likely depend on maintaining a careful balance between computational innovation and biological realism, ensuring that predictive models remain grounded in the complexity of molecular systems.

## Author Contributions

S.S.K. conceptualized the study, designed the review framework, synthesized the literature, and drafted the original manuscript. T. contributed to literature analysis, interpretation of findings, and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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