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When Binding Poses Refuse to Remain Still: A Conformational-Ensemble Theory of Drug–Target Recognition across Dynamic Energy Landscapes

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ABSTRACT

Drug–target recognition is often represented by a preferred binding pose and a scalar estimate of binding favorability. These representations are valuable for structural interpretation, but they become pharmacologically incomplete when affinity, selectivity, efficacy, or residence time depends on alternative molecular states, hidden intermediates, transition barriers, allosteric coupling, or condition-dependent population shifts. This article proposes Conformational-Ensemble Drug–Target Recognition theory (CE-DTR), an original conceptual synthesis that represents recognition through five linked layers: baseline molecular ensembles, joint ligand–target compatibility, ligand-conditioned population redistribution, transition pathways, and observable mapping with explicit validation gates. Static poses are treated as informative members of broader ensembles rather than sufficient mechanistic explanations. Conformational selection, ligand-induced change, and mixed recognition are interpreted as pathway-weighted behaviors that may coexist within one energy landscape. The theory separates state occupancy from transition kinetics and distinguishes affinity, selectivity, efficacy, and residence time as related but non-equivalent consequences of ensemble behavior. It generates testable propositions concerning static-pose insufficiency, ligand-driven redistribution, mixed recognition, ensemble-weighted affinity, kinetic bottlenecks, differential selectivity, functional-state coupling, and convergent validation. Computational evaluation requires defensible state definitions, adequate sampling, uncertainty analysis, independent replicas, and comparison with alternative representations. Experimental evaluation requires structural, kinetic, and functional evidence without assuming that agreement at one scale establishes pharmacological performance at another. CE-DTR is proposed as a theory-building framework, not a validated predictive model, clinical recommendation, or universally applicable decision standard.

Key words: *Molecular dynamics, Conformational ensemble, Energy landscape, Drug–target recognition, Conformational selection, Induced fit*

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INTRODUCTION

A bound ligand is commonly communicated through a compelling structural image: one target conformation, one ligand conformation, and one interaction geometry. Such structures remain indispensable, yet they describe molecular organization under particular conditions rather than the full motions, state transitions, solvent rearrangements, and alternative configurations through which recognition occurs. Molecular dynamics provides

a means of representing time-dependent motion and state interconversion beyond a single coordinate set, although its conclusions remain conditional on the physical model and accessible timescale [1].

Trajectory generation alone does not produce a mechanistic ensemble. Markov state models and related kinetic representations can organize configurations into metastable states, estimate transition probabilities, and identify characteristic timescales [2]. This separation of occupancy from interconversion is essential because similar endpoint structures may arise through different pathways or barriers.

Drug–target binding is therefore both thermodynamic and kinetic. Binding free energy concerns the relative statistical weights of bound and unbound ensembles, whereas association and dissociation depend on pathways, barriers, diffusion, and intermediate states [3]. CE-DTR is proposed to organize these dimensions without claiming that an ensemble model is always superior. Its purpose is to state what must be represented, what may be inferred, and what requires independent validation.

Why static binding poses provide an incomplete pharmacological explanation

A binding pose can reveal steric complementarity, hydrogen bonds, hydrophobic packing, and candidate interaction determinants. It may nevertheless omit encounter complexes, quasi-bound configurations, metastable intermediates, water rearrangements, and exit routes. Dynamic-undocking studies show that quasi-bound states may contain recognition and dissociation information absent from the final complex [4]. The limitation is therefore explanatory compression: one configuration is asked to represent a distributed, time-dependent process.

Receptor-state choice can also change the resulting interaction hypothesis. Docking against multiple receptor conformations can produce different poses, contacts, or rankings from those generated with a single structure [5]. This does not establish improved therapeutic prediction; it shows that structural conclusions are conditional on the conformations represented and the scoring assumptions used.

The limitation is greater for allostery. Regulation may arise through changes in correlated motions, state populations, or communication pathways without a dramatic structural switch. Dynamic accounts of allostery therefore emphasize redistribution across coupled conformational states [6]. A static structure may identify where a ligand binds but not how binding changes distant functional-state probabilities. CE-DTR consequently treats a pose as structurally informative but potentially mechanistically insufficient when a decision-relevant observable depends materially on alternative states, population changes, intermediates, kinetic barriers, or allosteric coupling.

Conformational ensembles, energy landscapes, and population redistribution

A conformational ensemble is a condition-dependent probability distribution over molecular configurations represented at a specified resolution. Fine-grained microstates may be grouped into macrostates or metastable basins with shared structural or kinetic properties. Enhanced sampling is often required when relevant transitions cross barriers beyond conventional trajectory timescales [7]. Enhanced sampling, however, does not prove that the chosen coordinates, force field, reweighting procedure, or state partition is correct.

An energy landscape represents relative stability and barriers along selected coordinates. Potential energy, free energy, occupancy, and transition rate are related but non-identical. Useful reaction coordinates should preserve information relevant to both thermodynamics and kinetics rather than merely separating visually distinct structures [8]. Any low-dimensional landscape is therefore a conditional model, not a uniquely complete representation of molecular behavior.

Population redistribution is a change in state probabilities after ligand binding or another perturbation. Learned kinetic models may help identify slow processes and metastable organization [9], but inferred states remain dependent on features, model structure, temporal resolution, and sampling. CE-DTR therefore combines occupancy with connectivity: occupancy describes where probability resides, whereas connectivity describes which transitions occur, how rapidly they occur, and where bottlenecks constrain movement.

Proposed conformational-ensemble theory of drug–target recognition

CE-DTR reframes recognition as a condition-dependent distribution over joint ligand–target states rather than solely as formation of one preferred pose. Bioactive-conformation resources already show that receptor structures relevant to drug discovery can be organized as ensembles [10]. CE-DTR extends this premise into five proposed layers: baseline target and ligand ensembles; compatible encounter and bound states; ligand-conditioned redistribution; transition pathways, barriers, and intermediates; and observable mapping with validation gates.

States may be defined through physical coordinates, learned representations, experimental restraints, or hybrids. Machine learning may assist dimensionality reduction and dynamical modeling, but learned outputs require

physical constraints and external validation [11]. **Figure 1** contrasts the explanatory compression of a static-pose model with the state-distribution and pathway structure proposed by CE-DTR.

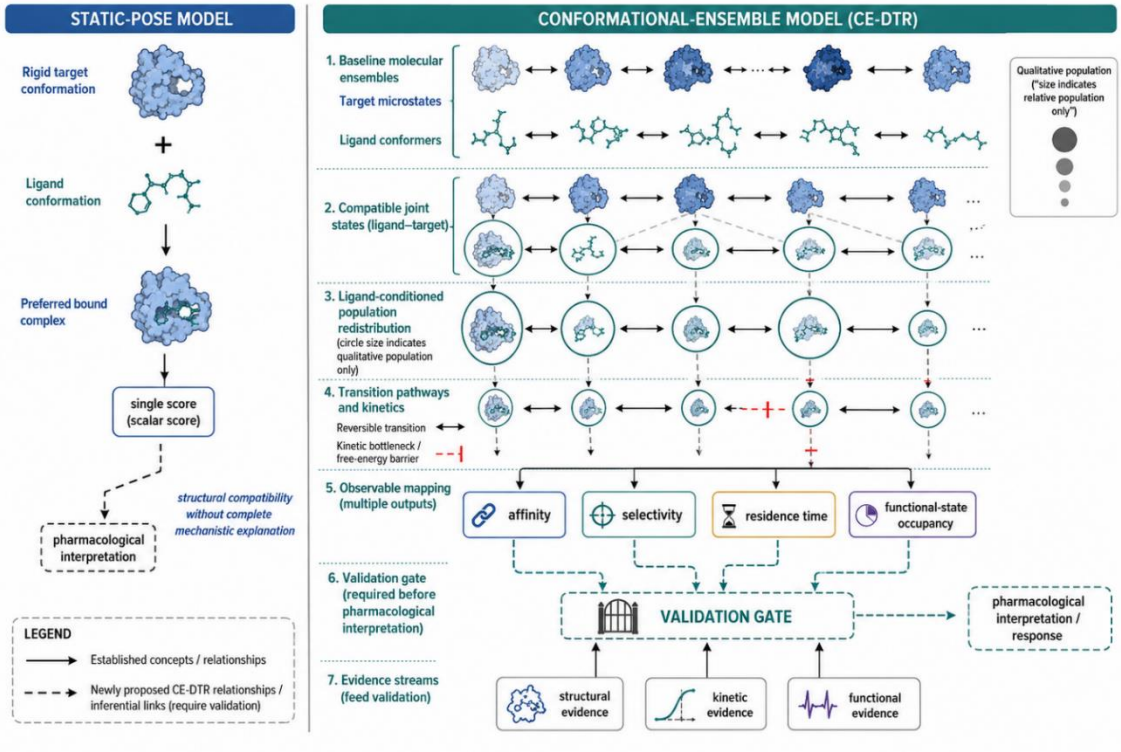

Figure 1. Static-Pose versus Conformational-Ensemble Models of Drug–Target Recognition

The left side represents one target conformation, one ligand conformation, one preferred complex, and a scalar score followed by an unsupported inferential leap toward pharmacological interpretation. The right side represents the proposed CE-DTR account: baseline ensembles, compatible joint states, ligand-conditioned redistribution, transition pathways, observable mappings, and a validation gate. Established concepts are distinguished from newly proposed relationships. Node sizes and arrows are qualitative and do not represent measured occupancies, rates, effects, or validated thresholds. The figure is an original conceptual synthesis and not a validated predictive model.

Collective variables and state partitions are therefore testable modeling choices, not neutral descriptions. Data-driven collective variables can organize trajectories into candidate metastable basins [12], but adequacy depends on whether the representation preserves distinctions required for the intended observable. The theory's components and intended uses are summarized in **Table 1**.

Table 1. Definitions, components, relationships, and intended uses in When Binding Poses Refuse to Remain Still.

Element	Operational definition and relationship	Intended use	Evidence/status boundary
Static binding pose	One experimentally observed or computationally proposed complex; potentially one member of a larger ensemble.	Identify structural compatibility and candidate contacts.	Quasi-bound states may add pathway information [4]. A pose is not rejected, but its sufficiency is conditional.
Molecular state	A configuration represented at a chosen structural and environmental resolution.	Define analyzable units for occupancy and transition models.	State decomposition is conditional on sampling and features [2].
Conformational ensemble	A condition-dependent distribution over represented states.	Describe heterogeneity and baseline probabilities.	Established concept; not an arbitrary snapshot collection [7].
Energy landscape	A coordinate-dependent representation of relative stability and barriers.	Interpret basins, pathways, and bottlenecks.	No low-dimensional landscape is assumed uniquely true [8].

Ligand-conditioned redistribution	A change in state probabilities after encounter or binding.	Compare baseline and ligand-conditioned ensembles.	**Proposed CE-DTR core construct**, supported conceptually by dynamic allostery [6].
Transition network	Connectivity, rates, and bottlenecks among states.	Separate population from kinetic accessibility.	Established kinetic construct [2].
Recognition mechanism	Pathway-weighted selection, ligand-induced change, or mixed behavior.	Avoid mutually exclusive endpoint labels.	**Proposed classification** requiring time-resolved or kinetic evidence.
Observable-mapping layer	Explicit connection from populations and transitions to measurable outcomes.	Separate affinity, kinetics, selectivity, and function.	**Proposed CE-DTR layer**; thermodynamics and kinetics remain distinct [3].
Validation gate	Checks of representation, sampling, uncertainty, reproducibility, and experimental agreement.	Limit claims to the level directly tested.	**Proposed decision rule**; no universal threshold is asserted.

Note: Established concepts are distinguished from original CE-DTR constructs. The table does not imply comparative performance, clinical utility, or regulatory readiness.

Ligand-induced selection, conformational selection, and mixed recognition mechanisms

Conformational selection and induced fit are often treated as alternatives. Under selection, a ligand preferentially binds a compatible state already present before association; under induced change, encounter is followed by structural adjustment. Molecular dynamics–Markov analyses show that selection-like and induced-fit behavior can coexist within one binding process [13]. Their apparent contribution may depend on temporal resolution, chosen coordinates, and which intermediates are observable.

Conformational selection is most strongly supported when a ligand-compatible state is detected before binding and is preferentially captured or stabilized. Structural and biophysical analysis of the first Tudor domain of PHF20L1 provides a system-specific example [14]. Subsequent relaxation may still occur, so evidence for selection does not exclude post-binding change.

Human cytochrome P450 systems likewise show that recognition may be dominated by conformational-selection modes [15]. CE-DTR therefore proposes pathway-weighted recognition rather than exclusive labels. A bound–unbound structural difference does not prove induced fit, because the bound-like state may have been rare and unresolved before binding. Conversely, detecting a compatible unbound state does not prove that most binding flux passes through it. Mechanism requires evidence about timing, populations, pathways, or kinetics.

Linking ensemble occupancy to affinity, selectivity, efficacy, and residence time

Affinity is an equilibrium property determined by the relative statistical weights of bound and unbound ensembles. A score assigned to one pose is not equivalent to binding free energy. Rigorous free-energy calculations require adequate configurational sampling, controlled thermodynamic cycles, and uncertainty analysis [16]. Within CE-DTR, omitted states are acceptable only when they do not materially alter the intended estimate.

Residence time concerns dissociation kinetics and may depend on intermediate states, solvent exchange, protein rearrangement, and exit barriers [17]. It can vary independently of equilibrium affinity and is not universally preferable when longer. Accelerated dissociation simulations can identify candidate exit routes and relative residence behavior [18], but their interpretation remains conditional on perturbation strength, starting-state distribution, pathway reproducibility, and comparison with measured kinetics.

Selectivity may arise because homologous targets possess different baseline ensembles, ligand-compatible states, or redistribution costs. Efficacy requires an additional mapping from molecular states to functional-state occupancy and then to cellular response. A useful pharmacological explanation must therefore treat populations, equilibrium free energies, and transition kinetics as coupled but non-interchangeable quantities [2, 16, 17]. Predicted redistribution alone does not establish efficacy, therapeutic benefit, or safety.

Testable propositions and computational evaluation criteria

CE-DTR requires propositions that can fail. Predicted dissociation pathways or rates should be evaluated against discriminating kinetic observations rather than accepted because they appear chemically plausible [19]. Ensemble-derived claims must also include uncertainty and sensitivity analyses because apparently stable trajectories may conceal inadequate exploration or underestimated variance [20]. Independent replicas are needed to reveal stochastic variability and reduce false mechanistic conclusions [21].

Computational support therefore requires evaluated kinetic predictions, quantified uncertainty, and independent replicas rather than one apparently stable trajectory [19–21]. The principal propositions and failure conditions are consolidated in **Table 2**.

Table 2. Testable propositions, evidence requirements, and validation criteria for When Binding Poses Refuse to Remain Still.

Proposed proposition	Computational evaluation	Experimental evidence	Failure condition and boundary
P1. Static-pose insufficiency is conditional.	Compare static and ensemble representations under matched assumptions.	Structural heterogeneity or kinetic evidence discriminating states.	One state explains relevant observations within uncertainty; complexity alone is not beneficial [4].
P2. Ligands redistribute target populations.	Estimate baseline and ligand-conditioned populations with sensitivity analysis.	Orthogonal population-sensitive measurements.	Redistribution is absent, unstable, or model-dependent; redistribution alone does not establish function [6].
P3. Recognition can be mixed.	Permit competing selection-like and induced-change pathways.	Time-resolved or kinetically discriminating evidence.	One mechanism explains all observations without unresolved alternatives [13].
P4. Affinity is ensemble-weighted.	Test state-aware free-energy estimates with uncertainty.	Equilibrium binding measurements under matched conditions.	Additional states do not improve explanatory adequacy [16].
P5. Residence time depends on bottlenecks.	Compare exit pathways, barriers, and replica sensitivity.	Direct association and dissociation measurements.	Predicted pathway or rate ordering fails external testing [17].
P6. Selectivity may reflect differential redistribution.	Compare related targets under harmonized models and sampling.	Cross-target affinity and kinetic measurements.	Predicted ensemble differences do not correspond to discriminating observations [5].
P7. Efficacy requires functional-state coupling.	Map molecular states to a defined functional observable.	Functional assays and perturbation evidence.	Redistribution occurs without the predicted functional consequence [6].
P8. Mechanistic validity requires convergent evidence.	Test alternative models, replicas, uncertainty, and prospective predictions.	Independent structural, kinetic, and functional evidence.	Support depends on one assay, one model, or post hoc state definitions [19].

Note: These propositions and decision rules are proposed components of CE-DTR. No universal cutoff, replica number, validation score, or decision-readiness threshold is asserted.

Experimental validation through structural, kinetic, and functional evidence

Structural ensembles should be tested against heterogeneous experimental observations through explicit forward models. Ensemble determination integrates experimental restraints, physical models, and uncertainty, but different experiments report different averages, timescales, or local features [22]. Agreement with one averaged observable cannot identify a unique ensemble.

Simulation and experiment should constrain one another rather than operate as substitutes [23]. Simulations may interpret underdetermined measurements, whereas experiments may reject, reweight, or refine simulated states. The theory's multiscale claims and the distinct evidence required at each inferential transition are shown in **Figure 2**.

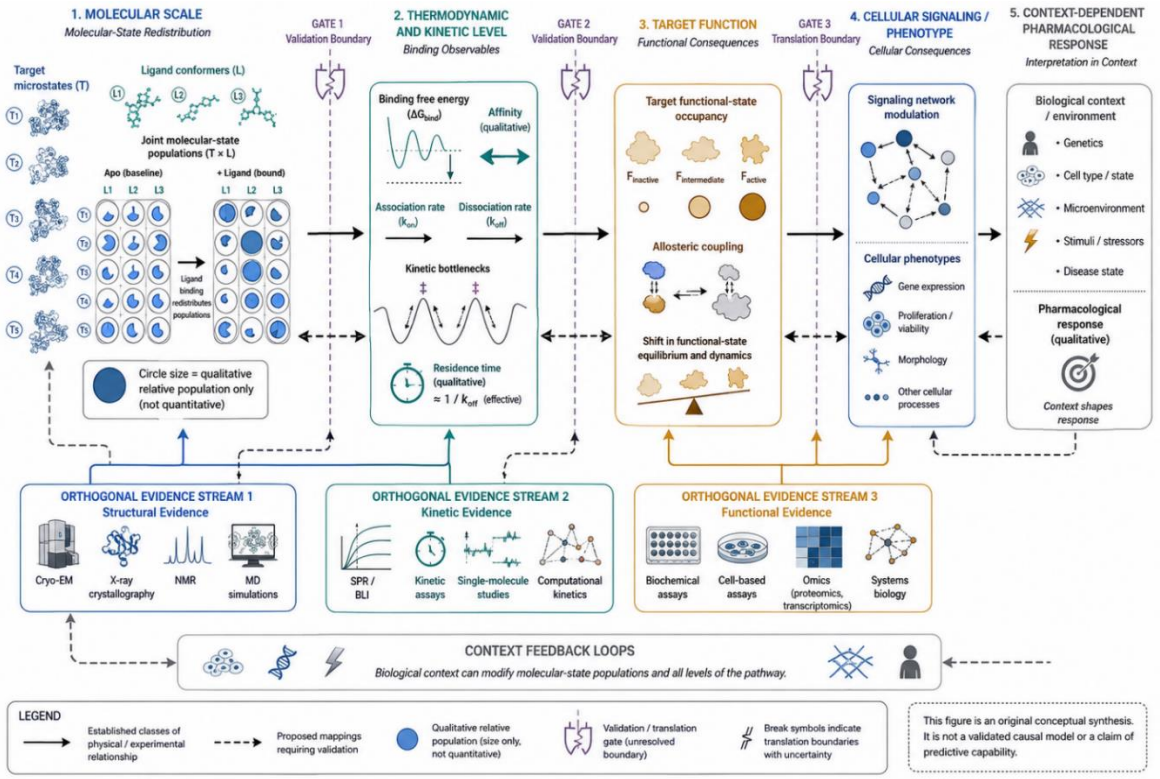

Figure 2. Multiscale Pathway from Molecular-State Redistribution to Pharmacological Response

The figure presents the proposed sequence through which ligand-conditioned molecular-state redistribution may relate to binding thermodynamics and kinetics, target functional-state occupancy, cellular consequences, and context-dependent pharmacological response. Structural, kinetic, and functional evidence interrogate different portions of this sequence and are not interchangeable. Solid relationships denote established classes of physical or experimental connection; dashed relationships and gates identify mappings requiring system-specific validation. The figure is an original conceptual synthesis, not a validated causal model, clinical recommendation, or guarantee of translation.

Ligand-conditioned heterogeneity should be tested directly where possible. Structural evidence shows that binding can remodel side-chain conformational heterogeneity rather than merely stabilize one rigid configuration [24]. Such observations test redistribution but do not independently validate transition pathways or functional mappings. Mechanistic validation therefore requires ensemble inference, simulation–experiment integration, and direct evidence of ligand-conditioned heterogeneity [22–24]. Structural, kinetic, and functional agreement are complementary; none alone validates the complete multiscale interpretation.

Limitations and boundary conditions

Force-field error can distort state ordering, barrier heights, and population estimates. Work addressing both folded and disordered protein states illustrates the difficulty of achieving transferability across conformational regimes [25]. Increased sampling cannot correct a systematically inaccurate physical model, and ligand, solvent, protonation, ion, membrane, or cofactor parameters may introduce additional error.

Reproducibility also requires transparent reporting of initial conditions, force fields, biasing protocols, collective variables, parameters, reweighting, and analysis. Community guidance for enhanced simulation emphasizes such transparency [26]. Reproducibility enables scrutiny but does not guarantee validity: independent investigators may reproduce the same biased result.

Binding-kinetics methods differ in assumptions, approximations, accessible timescales, and suitable outputs [27]. No method should be ranked universally. CE-DTR should not support decision interpretation when relevant states cannot be defensibly defined, sampled, reproduced, or linked to measurable observables. It is also unnecessary when a simpler model explains the intended observable within uncertainty and survives prospective testing.

Research agenda for ensemble-aware drug design

Learned and coarse-grained force fields may extend accessible scales, but they must preserve recognition-relevant ligand orientations, hydration states, side-chain rearrangements, allosteric communication, and bottlenecks. Learned coarse-grained force fields illustrate this opportunity and its transferability requirements [28]. Faster simulation is an enabling property, not evidence of mechanistic adequacy.

Future workflows must also diagnose poor collective variables. Enhanced sampling with suboptimal variables shows that apparent convergence speed and landscape accuracy can diverge [29]. Robust workflows should compare alternative coordinates, inspect hidden slow modes, and test whether conclusions persist across representations.

Finally, prospective programs should integrate structural, kinetic, allosteric, and functional measurements. AI-augmented, multilevel studies of HSP90 inhibitors illustrate how such evidence can be assembled around binding kinetics and allosteric mechanisms [30]. This provides a validation pattern, not validation of CE-DTR. Progress should be judged through prospective, externally replicated tests across target classes and ligand chemotypes.

CONCLUSION

Drug–target recognition cannot always be explained by a binding pose that remains conceptually still while molecules and environments fluctuate. Static structures remain indispensable, but their explanatory scope is limited when relevant outcomes depend on alternative states, redistribution, pathways, barriers, or allosteric coupling.

CE-DTR is proposed to organize these determinants through baseline ensembles, compatible joint states, ligand-conditioned redistribution, transition pathways, and observable-specific validation. It treats conformational selection, ligand-induced change, and mixed recognition as pathway-weighted behaviors and separates affinity, selectivity, efficacy, and residence time. The theory does not require an elaborate ensemble for every system and does not claim validated prediction. Its central requirement is proportional explanation: additional states and pathways should be introduced only when needed and should remain open to falsification through replicated computation and convergent structural, kinetic, and functional evidence.

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