# Protein Dynamics Comparison Using AlphaFold3 and Molecular Dynamics

## Introduction

Proteins are inherently dynamic, sampling multiple conformations under physiological conditions[nature.com](https://www.nature.com/articles/s41598-024-84066-z#:~:text=static%2C%20the%20folded%20proteins%20are,is%20able%20to%20fluctuate%20between). These intrinsic fluctuations are often crucial for biological function – for example, enabling enzymes to undergo induced-fit rearrangements or allosteric transitions upon ligand binding. In practice, molecular dynamics (MD) simulations have been widely used to capture protein motions, with analyses such as principal component analysis (PCA) or normal mode analysis (NMA) revealing collective motions that underlie function. However, emerging AI methods like AlphaFold2 have so far predicted only static structures[nature.com](https://www.nature.com/articles/s41598-024-84066-z#:~:text=A%20native%20protein%20has%20flexible,a%20stable%20state%20when%20it). Recent work has begun to extend AI predictions toward ensembles: for instance, subsampling multiple sequence alignments (MSAs) in AlphaFold2 can recover alternative conformations and even predict relative state populations[nature.com](https://www.nature.com/articles/s41467-024-46715-9#:~:text=This%20paper%20presents%20an%20innovative,Abl1%20kinase%20and%20the%20granulocyte). Similarly, massively sampling AlphaFold with optimized parallel pipelines (e.g. MassiveFold) has been shown to dramatically increase structural diversity in the predicted models[nature.com](https://www.nature.com/articles/s43588-024-00714-4#:~:text=Massive%20sampling%20in%20AlphaFold%20enables,from%20all%20the%20computing%20nodes). Moreover, using multiple random seeds or clustered MSAs can drive AlphaFold to explore different states of metamorphic proteins; e.g. clustering sequences by similarity allowed AF2 to predict both known conformational states of proteins like KaiB or RfaH with high confidence[nature.com](https://www.nature.com/articles/s41586-023-06832-9#:~:text=We%20demonstrate%20that%20a%20simple,on%20a%20KaiB%20variant%20in). Looking forward, AlphaFold3 – a diffusion-based upgrade to AlphaFold – has demonstrated unprecedented accuracy in modeling complex structures[nature.com](https://www.nature.com/articles/s41586-024-07487-w#:~:text=The%20introduction%20of%20AlphaFold%2021,docking%20tools%2C%20much%20higher%20accuracy), suggesting potential to generate richer conformational ensembles.

Despite these advances, the ability of AF3 to capture functionally relevant dynamics remains unexplored. Here we propose to systematically compare conformational variability from AF3-predicted ensembles to that from explicit MD simulations. We will focus on five key proteins (each <4000 residues) whose function is known to depend on collective motions, as revealed by PCA or NMA in previous studies. By juxtaposing AF3-derived pseudo-trajectories with MD trajectories, we aim to assess whether AI-generated ensembles can reproduce experimentally validated dynamic signatures.

## Methods

**Molecular dynamics simulations (GROMACS/OpenMM):** Proteins will be built from high-quality structures and prepared for MD. Standard protocols will be followed (e.g. as in[journals.plos.org](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002844#:~:text=For%20the%20dynamical%20analyses%2C%20each,was%20calculated%20on%20C%CE%B1%20atoms)). In brief:

1. **System preparation:** Obtain initial structures (from PDB or prior AF predictions); add missing atoms/hydrogens.
2. **Parameterization:** Assign an all-atom force field (e.g. CHARMM36m or AMBER ff) and TIP3P water model.
3. **Solvation and ionization:** Place the protein in a water box with ~1.0 nm padding; add counterions (Na+/Cl–) to neutralize and 0.15 M concentration.
4. **Energy minimization:** Perform steepest-descent minimization of the solvated system.
5. **Equilibration:** Run NVT (constant volume, e.g. 100 ps) and NPT (constant pressure, e.g. 100 ps) equilibration to stabilize temperature and density.
6. **Production:** Run long (e.g. 500 ns or more) unrestrained MD at 300 K using GROMACS. In parallel, a similar protocol will be implemented in OpenMM (GPU-accelerated) to validate results under an independent engine. All trajectories will be saved at regular intervals for analysis.
7. **PCA/NMA analysis:** Align trajectories on the protein backbone and compute the covariance of Cα fluctuations. We will use GROMACS tools (gmx covar / gmx anaeig) or equivalent (as in ref. [journals.plos.org](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002844#:~:text=For%20the%20dynamical%20analyses%2C%20each,was%20calculated%20on%20C%CE%B1%20atoms)) to extract the top principal components. Elastic network models or NMA tools (e.g. ProDy) will also be applied to static structures to identify low-frequency modes.

**AlphaFold3 ensemble generation:** To approximate an AF3-predicted conformational ensemble, we will perform multiple independent AF3 runs for each protein:

* **Multiple predictions:** For each target protein, we will run ~50 AlphaFold3 predictions using varied random seeds (and optionally altered MSA inputs). Different seeds are known to introduce variability in AF2 outcomes, particularly in flexible regions[ebi.ac.uk](https://www.ebi.ac.uk/training/online/courses/alphafold/advanced-modeling-and-applications-of-predicted-protein-structures/customising-alphafold-structure-predictions/#:~:text=AlphaFold2%20uses%20random%20seeds%20to,AlphaFold2%20towards%20a%20correct%20prediction).
* **Ensemble construction:** The top-ranked structure from each run will be collected. All predicted models will be aligned by their backbone atoms. These aligned coordinates will be concatenated in time order to form a pseudo-trajectory. In effect, each AF3 model is treated as one “frame” sampling the conformational space.
* **Ensemble analysis:** The concatenated AF3 conformations will be analyzed analogously to MD: after alignment, we will compute covariance and project onto principal components. This will reveal the extent and nature of structural variability captured by AF3 predictions[ebi.ac.uk](https://www.ebi.ac.uk/training/online/courses/alphafold/advanced-modeling-and-applications-of-predicted-protein-structures/customising-alphafold-structure-predictions/#:~:text=AlphaFold2%20uses%20random%20seeds%20to,AlphaFold2%20towards%20a%20correct%20prediction)[nature.com](https://www.nature.com/articles/s43588-024-00714-4#:~:text=Massive%20sampling%20in%20AlphaFold%20enables,from%20all%20the%20computing%20nodes).

## Results

### Hsp90 (Heat shock protein 90)

Hsp90 is an essential molecular chaperone with complex allosteric regulation. Prior modeling showed that Hsp90’s nucleotide-driven cycle involves inter-domain motions coordinated by conserved regions. MD simulations combined with PCA/network analysis identified a set of evolutionarily conserved residues that act as hubs linking the N-terminal, middle, and C-terminal domains. These regions govern collective motions and allosteric signaling (e.g. ATP binding in the NBD affecting client-binding in the middle domain)[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/22624053/#:~:text=of%20Hsp90%20regulatory%20interactions%20to,standing%20assertion%20that%20allosteric). In fact, a PLOS One study found that a network of conserved residues forms “central regulators of functional dynamics” in Hsp90, mediating principal motions associated with ATP hydrolysis and client interactions[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/22624053/#:~:text=of%20Hsp90%20regulatory%20interactions%20to,standing%20assertion%20that%20allosteric). We select Hsp90 to test whether AF3 can capture similar domain movements. If AF3 ensembles reproduce the same hinge-bending and correlated motions seen in MD (e.g. NTD-CTD anti-correlated motion[dx.plos.org](https://dx.plos.org/10.1371/journal.pone.0037605#:~:text=to%20dissect%20for%20the%20first,and%20biochemical%20studies%20have%20proposed)), this would demonstrate its utility for dynamic predictions.

### Hemoglobin (Hb)

Human hemoglobin A is the prototypical allosteric protein, known for cooperative oxygen binding via a T↔R quaternary transition. MD studies of hemoglobin have directly observed spontaneous T→R transitions; for example, Hub et al. (2010) reported that multi-microsecond simulations starting from deoxy or oxy states sampled both quaternary forms. PCA of these trajectories revealed that the dominant collective motions correspond to the expected 15° α1β1/α1β2 subunit rotation between T and R states[journals.plos.org](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774#:~:text=His,on%20the%20simulation%20results%2C%20we). The simulations also uncovered functional asymmetry: the β subunits contribute more strongly to the transition than α subunits, and each chain’s tertiary populations differ in the ensemble[journals.plos.org](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774#:~:text=projections%2C%20from%20an%20RMSD%20measure%2C,on%20the%20simulation%20results%2C%20we). We include Hb because its allosteric transition is well-characterized by PCA[journals.plos.org](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774#:~:text=His,on%20the%20simulation%20results%2C%20we). In our analysis, we will see if the AF3-generated ensemble similarly captures the T–R motion (e.g. via separation along the principal components) and the cooperative coupling among subunits.

### PDZ3 domain (postsynaptic density protein)

The third PDZ domain of PSD-95 is a classic small allosteric module: ligand binding at one site is long-range coupled to a distal α3 helix. Recent simulations and PCA have revealed how PDZ3’s conformational landscape encodes allosteric regulation. Specifically, MD/PCA studies showed that wild-type PDZ3 samples a binding-competent “closed” state even in the absence of ligand. Perturbing the distal α3 helix (by truncation or mutation) shifts the population away from this state. Covariance analysis identified correlated motions between distant loops (β1–β2 and β2–β3) that connect the α3 helix to the binding groove[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/39076021/#:~:text=extensive%20molecular%20dynamics%20simulations%20corroborated,Covariance). These motions were attenuated when α3 was perturbed, linking dynamics to binding affinity[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/39076021/#:~:text=landscape%20due%20to%20%CE%B13,got%20further%20away%20from%20the). We choose PDZ3 because its function clearly depends on distributed fluctuations, as captured by PCA[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/39076021/#:~:text=extensive%20molecular%20dynamics%20simulations%20corroborated,Covariance). We will test whether AF3 ensembles reproduce the flexibility in the binding pocket and distal loops (for example, seeing a bimodal distribution of open/closed forms) as seen in MD.

### Adenylate kinase (AK)

E. coli adenylate kinase is a small monomeric enzyme that undergoes large domain motions to perform phosphotransfer. Crystal and simulation studies have shown that AK has three domains (core, AMP-binding, and lid), and that the lid and AMP-binding domains exhibit the largest fluctuations in the apo state[www2.chemistry.msu.edu](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf#:~:text=of%20a%20common%20force%20constant,In%20this%20work%2C%20we%20use). Elastic network models confirm that the lid and AMP domains dominate the slowest modes. In high-temperature MD, the principal modes reveal a sequential closing motion: first the lid closes toward the core (resembling the substrate-bound form) and then the AMP-binding domain follows, completing domain closure[www2.chemistry.msu.edu](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf#:~:text=Mode%202%2C%20High%20T,appear%20correlated%20over%20the%20first)[www2.chemistry.msu.edu](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf#:~:text=description%20of%20the%20important%20protein,the%20second%20change%20in%20RMSD). These collective motions have been mapped out by PCA and NMA to elucidate the enzyme’s hinge-bending mechanism. We will analyze AK because its substrate-induced motions are textbook examples of functionally important dynamics. In the AF3 ensemble, we will look for variations in the lid-opening angle and AMP-domain position. Reproducing the MD/PCA-derived path of lid closure would indicate that AF3 is sensitive to the conformational preferences of AK’s domains.

### GroEL (Chaperonin, E. coli)

GroEL is a large oligomeric chaperonin consisting of two stacked heptameric rings. It undergoes cooperative allosteric transitions during the protein-folding cycle (from the T-state to R-state forms upon ATP and GroES binding). Normal mode analysis of GroEL has shown that its global structural changes can be captured by a single dominant mode[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/17557788/#:~:text=favorable%20collective%20motions%20encoded%20in,parametric%20perturbations%20caused%20by%20sequence). In particular, an ENM study found that the largest-amplitude mode encodes the salient inter-ring and intra-ring motions of GroEL: the rings move nearly as rigid bodies (preserving sevenfold symmetry) but with negative cooperativity between rings, matching the experimentally observed R″→TR″ transition[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/17557788/#:~:text=favorable%20collective%20motions%20encoded%20in,parametric%20perturbations%20caused%20by%20sequence). Furthermore, perturbation analysis of this mode identified a network of inter-subunit interface residues that regulate the allosteric signal; these residues form pathways for signal transmission between subunits[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/17557788/#:~:text=favorable%20collective%20motions%20encoded%20in,parametric%20perturbations%20caused%20by%20sequence)[pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/17557788/#:~:text=variations%2C%20which%20validates%20its%20functional,transmitting%20allosteric%20signals%20between%20subunits). We include GroEL as a test of AF3 on a multi-domain assembly. Although AF3 may need to be run on the monomer or single ring, we will examine whether the collection of predicted subunit conformations reflects the key hinge-like motions. If AF3 ensemble retains the dominant collective mode seen in NMA (i.e. an inter-ring twist/bending motion), it would validate the method’s capacity to capture GroEL’s functional dynamics.

**Figure:** Representative structural motions for each protein will be sketched (e.g. hemoglobin T↔R rotation, GroEL inter-ring motion, AK lid closure) to illustrate expected modes of flexibility.

Citations

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[Conformational ensembles for protein structure prediction | Scientific Reports](https://www.nature.com/articles/s41598-024-84066-z" \l ":~:text=static%2C%20the%20folded%20proteins%20are,is%20able%20to%20fluctuate%20between" \t "_blank)

[static, the folded proteins are in constant motion, which is crucial for biological activity. In vitro and cell studies, the free-energy barriers, ΔG+, for folding conformation change is quite small, which is only on the order of ~ 5 kcal/mol3 , 27,9 . So, it is not supervised that a protein has folding flexibility, and its conformation may be changed in various physiological conditions, such as solvent, temperature, ligand and protein interaction, etc. 33. The protein always folds into a structure that is thermodynamically stable under physiological conditions11. It is apparently that protein conformation has flexibility which is able to fluctuate between](https://www.nature.com/articles/s41598-024-84066-z" \l ":~:text=static%2C%20the%20folded%20proteins%20are,is%20able%20to%20fluctuate%20between" \t "_blank)

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[Conformational ensembles for protein structure prediction | Scientific Reports](https://www.nature.com/articles/s41598-024-84066-z" \l ":~:text=A%20native%20protein%20has%20flexible,a%20stable%20state%20when%20it" \t "_blank)

[A native protein has flexible conformations because of lower free-energy barriers between different folding states. Although AlphaFold and other AI machine learning-based methods can predict protein structures in single status with accuracy against 3D structural data from experimental measurements, it has the limitation to obtain multiple conformation structures1 , 25. A native protein structure should be fully represented by an ensemble of multiple conformations in vary degrees3 , 27. Essentially, to overcome the limitation is into the challenge involving the solution for protein folding problem. A protein may take various pathways folding into a stable state when it](https://www.nature.com/articles/s41598-024-84066-z" \l ":~:text=A%20native%20protein%20has%20flexible,a%20stable%20state%20when%20it" \t "_blank)

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[High-throughput prediction of protein conformational distributions with subsampled AlphaFold2 | Nature Communications](https://www.nature.com/articles/s41467-024-46715-9" \l ":~:text=This%20paper%20presents%20an%20innovative,Abl1%20kinase%20and%20the%20granulocyte" \t "_blank)

[This paper presents an innovative approach for predicting the relative populations of protein conformations using AlphaFold 2, an AI-powered method that has revolutionized biology by enabling the accurate prediction of protein structures. While AlphaFold 2 has shown exceptional accuracy and speed, it is designed to predict proteins’ ground state conformations and is limited in its ability to predict conformational landscapes. Here, we demonstrate how AlphaFold 2 can directly predict the relative populations of different protein conformations by subsampling multiple sequence alignments. We tested our method against nuclear magnetic resonance experiments on two proteins with drastically different amounts of available sequence data, Abl1 kinase and the granulocyte-](https://www.nature.com/articles/s41467-024-46715-9" \l ":~:text=This%20paper%20presents%20an%20innovative,Abl1%20kinase%20and%20the%20granulocyte" \t "_blank)

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[MassiveFold: unveiling AlphaFold’s hidden potential with optimized and parallelized massive sampling | Nature Computational Science](https://www.nature.com/articles/s43588-024-00714-4" \l ":~:text=Massive%20sampling%20in%20AlphaFold%20enables,from%20all%20the%20computing%20nodes" \t "_blank)

[Massive sampling in AlphaFold enables access to increased structural diversity. In combination with its efficient confidence ranking, this unlocks elevated modeling capabilities for monomeric structures and foremost for protein assemblies. However, the approach struggles with GPU cost and data storage. Here we introduce MassiveFold, an optimized and customizable version of AlphaFold that runs predictions in parallel, reducing the computing time from several months to hours. MassiveFold is scalable and able to run on anything from a single computer to a large GPU infrastructure, where it can fully benefit from all the computing nodes.](https://www.nature.com/articles/s43588-024-00714-4" \l ":~:text=Massive%20sampling%20in%20AlphaFold%20enables,from%20all%20the%20computing%20nodes" \t "_blank)

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[Predicting multiple conformations via sequence clustering and AlphaFold2 | Nature](https://www.nature.com/articles/s41586-023-06832-9" \l ":~:text=We%20demonstrate%20that%20a%20simple,on%20a%20KaiB%20variant%20in" \t "_blank)

[We demonstrate that a simple MSA subsampling method—clustering sequences by sequence similarity—enables AF2 to predict both states of the metamorphic proteins KaiB, RfaH and MAD2. Importantly, we show that, using our method, AF- Cluster, both states are sampled and scored with high confidence by AF2’s learned predicted local distance difference test (plDDT) measure. We investigated the reason for AF-Cluster’s prediction of multiple states in the KaiB system: by making AF-Cluster predictions for KaiB variants from a curated phylogenetic tree, we found that KaiB variants predicted to fold to one or the other substate were distributed in clusters throughout the phylogenetic tree. We experimentally tested the AF-Cluster predictions on a KaiB variant in](https://www.nature.com/articles/s41586-023-06832-9" \l ":~:text=We%20demonstrate%20that%20a%20simple,on%20a%20KaiB%20variant%20in" \t "_blank)

[[Favicon](https://www.nature.com/articles/s41586-024-07487-w#:~:text=The%20introduction%20of%20AlphaFold%2021,docking%20tools%2C%20much%20higher%20accuracy)nature.com](https://www.nature.com/articles/s41586-024-07487-w" \l ":~:text=The%20introduction%20of%20AlphaFold%2021,docking%20tools%2C%20much%20higher%20accuracy" \t "_blank)

[Accurate structure prediction of biomolecular interactions with AlphaFold 3 | Nature](https://www.nature.com/articles/s41586-024-07487-w" \l ":~:text=The%20introduction%20of%20AlphaFold%2021,docking%20tools%2C%20much%20higher%20accuracy" \t "_blank)

[The introduction of AlphaFold 21 has spurred a revolution in modelling the structure of proteins and their interactions, enabling a huge range of applications in protein modelling and design 51,3 , 53,5 , 55. Here we describe our AlphaFold 3 model with a substantially updated diffusion- based architecture that is capable of predicting the joint structure of complexes including proteins, nucleic acids, small molecules, ions and modified residues. The new AlphaFold model demonstrates substantially improved accuracy over many previous specialized tools: far greater accuracy for protein–ligand interactions compared with state-of-the-art docking tools, much higher accuracy](https://www.nature.com/articles/s41586-024-07487-w" \l ":~:text=The%20introduction%20of%20AlphaFold%2021,docking%20tools%2C%20much%20higher%20accuracy" \t "_blank)

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[Molecular Mechanism of Allosteric Communication in Hsp70 Revealed by Molecular Dynamics Simulations | PLOS Computational Biology](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002844" \l ":~:text=For%20the%20dynamical%20analyses%2C%20each,was%20calculated%20on%20C%CE%B1%20atoms" \t "_blank)

[For the dynamical analyses, each MD trajectory was projected on the first 10 principal components [51] obtained by Essential Dynamics analysis [52] of the original MD run. Gromacs module g\_covar and g\_anaeig were employed to calculate the essential dynamics for each simulation. Each frame of the trajectory was aligned on the Cα atoms of the starting conformation and the covariance matrix was calculated on Cα atoms.](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002844" \l ":~:text=For%20the%20dynamical%20analyses%2C%20each,was%20calculated%20on%20C%CE%B1%20atoms" \t "_blank)

[ebi.ac.uk](https://www.ebi.ac.uk/training/online/courses/alphafold/advanced-modeling-and-applications-of-predicted-protein-structures/customising-alphafold-structure-predictions/" \l ":~:text=AlphaFold2%20uses%20random%20seeds%20to,AlphaFold2%20towards%20a%20correct%20prediction" \t "_blank)

[Customising AlphaFold2 structure predictions | AlphaFold](https://www.ebi.ac.uk/training/online/courses/alphafold/advanced-modeling-and-applications-of-predicted-protein-structures/customising-alphafold-structure-predictions/" \l ":~:text=AlphaFold2%20uses%20random%20seeds%20to,AlphaFold2%20towards%20a%20correct%20prediction" \t "_blank)

[AlphaFold2 uses random seeds to initialise its structure predictions. You can control them by changing the ‘random\_seed’ parameter. In this way, you can sometimes guide AlphaFold2 towards a correct prediction.](https://www.ebi.ac.uk/training/online/courses/alphafold/advanced-modeling-and-applications-of-predicted-protein-structures/customising-alphafold-structure-predictions/" \l ":~:text=AlphaFold2%20uses%20random%20seeds%20to,AlphaFold2%20towards%20a%20correct%20prediction" \t "_blank)

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[Probing molecular mechanisms of the Hsp90 chaperone: biophysical modeling identifies key regulators of functional dynamics - PubMed](https://pubmed.ncbi.nlm.nih.gov/22624053/" \l ":~:text=of%20Hsp90%20regulatory%20interactions%20to,standing%20assertion%20that%20allosteric" \t "_blank)

[of Hsp90 regulatory interactions to systematically investigate functional dynamics of the molecular chaperone. This approach has identified a network of conserved regions common to the Hsp90 chaperones that could play a universal role in coordinating functional dynamics, principal collective motions and allosteric signaling of Hsp90. We have found that these functional motifs may be utilized by the molecular chaperone machinery to act collectively as central regulators of Hsp90 dynamics and activity, including the inter-domain communications, control of ATP hydrolysis, and protein client binding. These findings have provided support to a long-standing assertion that allosteric](https://pubmed.ncbi.nlm.nih.gov/22624053/" \l ":~:text=of%20Hsp90%20regulatory%20interactions%20to,standing%20assertion%20that%20allosteric" \t "_blank)

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[Probing Molecular Mechanisms of the Hsp90 Chaperone: Biophysical Modeling Identifies Key Regulators of Functional Dynamics | PLOS One](https://dx.plos.org/10.1371/journal.pone.0037605" \l ":~:text=to%20dissect%20for%20the%20first,and%20biochemical%20studies%20have%20proposed" \t "_blank)

[to dissect for the first time functionally coordinated kinetics of CTD and NTD upon nucleotide binding, providing a compelling evidence of anti-correlated motions of the C-terminal open and an N-terminal closed state [73]. The occupancy of the C-terminal open conformation was found to be modulated by nucleotides bound to the N-terminal domain, thus providing a strong evidence of long-range communication between the two terminal domains of the molecular chaperone [73]. Collectively, structural and biochemical studies have proposed](https://dx.plos.org/10.1371/journal.pone.0037605" \l ":~:text=to%20dissect%20for%20the%20first,and%20biochemical%20studies%20have%20proposed" \t "_blank)

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[Spontaneous Quaternary and Tertiary T-R Transitions of Human Hemoglobin in Molecular Dynamics Simulation | PLOS Computational Biology](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774" \l ":~:text=His,on%20the%20simulation%20results%2C%20we" \t "_blank)

[His(β)146, and they sum up to a total length of 5.6µs. We observe spontaneous and reproducible T→R quaternary transitions of the Hb tetramer and tertiary transitions of the α and β subunits, as detected from principal component projections, from an RMSD measure, and from rigid body rotation analysis. The simulations reveal a marked asymmetry between the α and β subunits. Using the mutual information as correlation measure, we find that the β subunits are substantially more strongly linked to the quaternary transition than the α subunits. In addition, the tertiary populations of the α and β subunits differ substantially, with the β subunits showing a tendency towards R, and the α subunits showing a tendency towards T. Based on the simulation results, we](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774" \l ":~:text=His,on%20the%20simulation%20results%2C%20we" \t "_blank)

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[Spontaneous Quaternary and Tertiary T-R Transitions of Human Hemoglobin in Molecular Dynamics Simulation | PLOS Computational Biology](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774" \l ":~:text=projections%2C%20from%20an%20RMSD%20measure%2C,on%20the%20simulation%20results%2C%20we" \t "_blank)

[projections, from an RMSD measure, and from rigid body rotation analysis. The simulations reveal a marked asymmetry between the α and β subunits. Using the mutual information as correlation measure, we find that the β subunits are substantially more strongly linked to the quaternary transition than the α subunits. In addition, the tertiary populations of the α and β subunits differ substantially, with the β subunits showing a tendency towards R, and the α subunits showing a tendency towards T. Based on the simulation results, we](https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000774" \l ":~:text=projections%2C%20from%20an%20RMSD%20measure%2C,on%20the%20simulation%20results%2C%20we" \t "_blank)

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[Modulation of the conformational landscape of the PDZ3 domain by perturbation on a distal non-canonical α3 helix: decoding the microscopic mechanism of allostery in the PDZ3 domain - PubMed](https://pubmed.ncbi.nlm.nih.gov/39076021/" \l ":~:text=extensive%20molecular%20dynamics%20simulations%20corroborated,Covariance" \t "_blank)

[extensive molecular dynamics simulations corroborated with principal component analysis (PCA), ligand binding free energy calculations, energetic frustration analysis and Markov state model analysis are employed to uncover such molecular details. We demonstrate the definite presence of a binding competent closed-like state in the conformational landscape of wild-type PDZ3. The population modulations of this closed state and other binding incompetent states in the landscape due to α3-truncation/mutation of PDZ3 are explored. A correlation between the closed state population and calculated binding free energy is established, which supports the conformation selection mechanism. Covariance](https://pubmed.ncbi.nlm.nih.gov/39076021/" \l ":~:text=extensive%20molecular%20dynamics%20simulations%20corroborated,Covariance" \t "_blank)

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[Modulation of the conformational landscape of the PDZ3 domain by perturbation on a distal non-canonical α3 helix: decoding the microscopic mechanism of allostery in the PDZ3 domain - PubMed](https://pubmed.ncbi.nlm.nih.gov/39076021/" \l ":~:text=landscape%20due%20to%20%CE%B13,got%20further%20away%20from%20the" \t "_blank)

[landscape due to α3-truncation/mutation of PDZ3 are explored. A correlation between the closed state population and calculated binding free energy is established, which supports the conformation selection mechanism. Covariance analysis identified the presence of correlated motion between two distant loops (β1-β2 and β2-β3) in the wild-type PDZ3 system, which weakened due to truncation/mutation in the distant α3 helix. It has also been observed that whenever the α3 helix was perturbed, the β2-β3 loop got further away from the](https://pubmed.ncbi.nlm.nih.gov/39076021/" \l ":~:text=landscape%20due%20to%20%CE%B13,got%20further%20away%20from%20the" \t "_blank)

[www2.chemistry.msu.edu](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=of%20a%20common%20force%20constant,In%20this%20work%2C%20we%20use" \t "_blank)

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[of a common force constant. A GNM analysis of apo-AKE points to the Lid and Amp-bd domains as the ones with the largest fluctuations. When substrates bind to proteins, a recurring theme is that of induced fit whereby the substrates are largely responsible for the protein conformational changes. On the other hand, it may be that protein fluctuations are responsible for setting up conformations that are predisposed to capture substrates to yield the final substrate-bound structure.12-15 In this work, we use](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=of%20a%20common%20force%20constant,In%20this%20work%2C%20we%20use" \t "_blank)

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[No Job Name](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=Mode%202%2C%20High%20T,appear%20correlated%20over%20the%20first" \t "_blank)

[Mode 2, High T. Figure 14 shows that the mass center distance does come close to 20 Å, which indicates closure of the Lid. Two snapshots are shown in Figure 16 (top panel), which illustrates the closure of the Lid toward the Core. Snapshots of the CA atom displacements obtained from mode 2 are presented in Figure 17, confirming that the Lid is closing to the Core region. The time courses shown in Figure 14 of the Lid-to-Core mass centers distance and mode 2 appear correlated over the first](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=Mode%202%2C%20High%20T,appear%20correlated%20over%20the%20first" \t "_blank)

[www2.chemistry.msu.edu](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=description%20of%20the%20important%20protein,the%20second%20change%20in%20RMSD" \t "_blank)

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[description of the important protein motions. First, the Lid closes toward the Core region. This closure corresponds to the first changes in RMSD (0-600 ps). In terms of RMSD relative to the AP5A-bound X-ray structure,41 the Lid has closed in a fashion similar to the AP5A-bound form. Then, with the Lid remaining closed, it performs a conformational change, reflected in mode 1. The resulting conformation is different from the X-ray structure conformation of both closed and open forms. This transformation corresponds to the second change in RMSD](https://www2.chemistry.msu.edu/faculty/cukier/manuscripts/jpcb%20110%2012796%2006.pdf" \l ":~:text=description%20of%20the%20important%20protein,the%20second%20change%20in%20RMSD" \t "_blank)

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[Allosteric transitions in the chaperonin GroEL are captured by a dominant normal mode that is most robust to sequence variations - PubMed](https://pubmed.ncbi.nlm.nih.gov/17557788/" \l ":~:text=favorable%20collective%20motions%20encoded%20in,parametric%20perturbations%20caused%20by%20sequence" \t "_blank)

[favorable collective motions encoded in the R''T structure. By comparing each normal mode with the observed conformational changes in the R''T --> TR'' transition, a single dominant normal mode provides a simple description of this highly intricate allosteric transition. A detailed analysis of this relatively high-frequency mode describes the structural and dynamic changes that underlie the positive intra-ring and negative inter-ring cooperativity. The dynamics embedded in the dominant mode entails highly concerted structural motions with approximate preservation of sevenfold symmetry within each ring and negatively correlated ones between the two rings. The dominant normal mode (in comparison with the other modes) is robust to parametric perturbations caused by sequence](https://pubmed.ncbi.nlm.nih.gov/17557788/" \l ":~:text=favorable%20collective%20motions%20encoded%20in,parametric%20perturbations%20caused%20by%20sequence" \t "_blank)

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[Allosteric transitions in the chaperonin GroEL are captured by a dominant normal mode that is most robust to sequence variations - PubMed](https://pubmed.ncbi.nlm.nih.gov/17557788/" \l ":~:text=variations%2C%20which%20validates%20its%20functional,transmitting%20allosteric%20signals%20between%20subunits" \t "_blank)

[variations, which validates its functional importance. Response of the dominant mode to local changes](https://pubmed.ncbi.nlm.nih.gov/17557788/" \l ":~:text=variations%2C%20which%20validates%20its%20functional,transmitting%20allosteric%20signals%20between%20subunits" \t "_blank)