

PCA-BASED ASSESSMENT OF CONFORMATIONAL ENSEMBLES OF AChE AND BChE FOR SELECTIVE CHOLINESTERASE INHIBITOR SEARCH

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Introduction

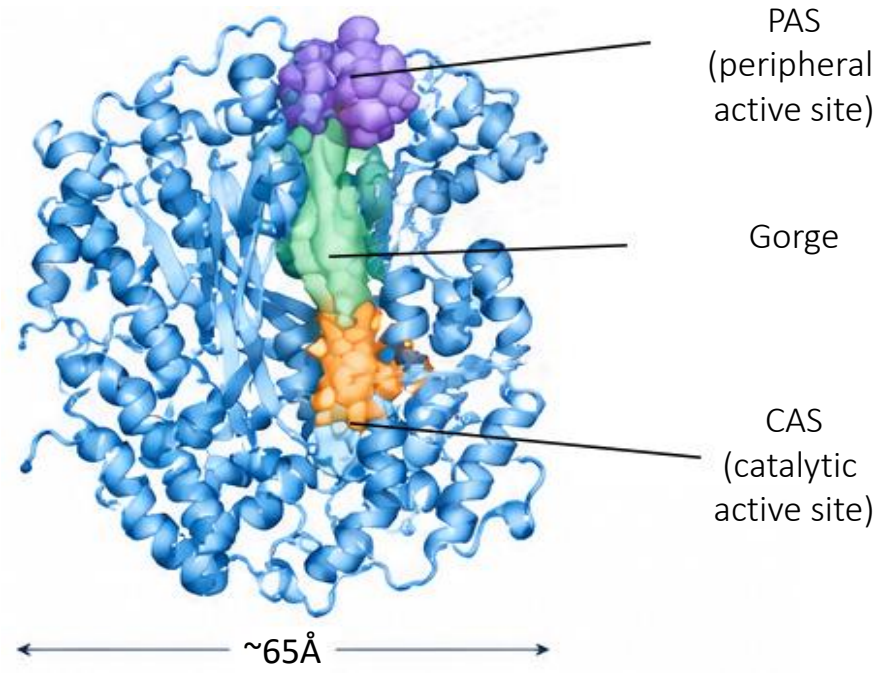


Fig. 1 — AChE structure (7XN1, chain A)

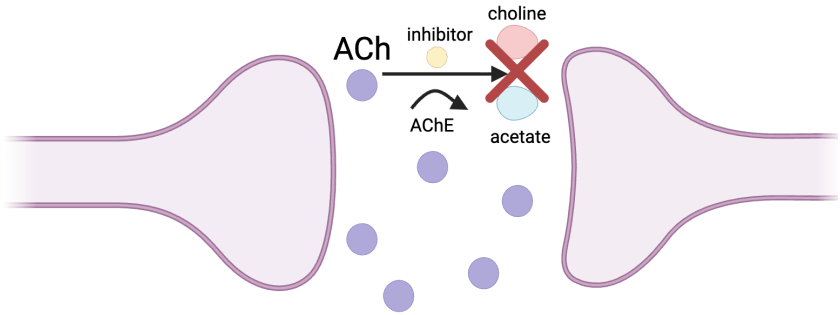


Fig. 2 — Schematic representation of AChE's action

Introduction

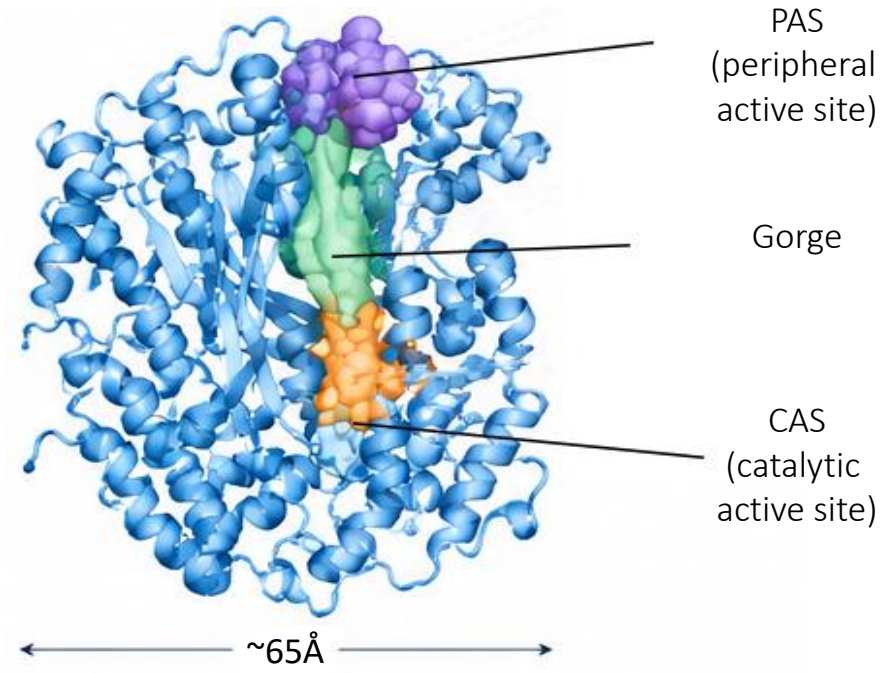


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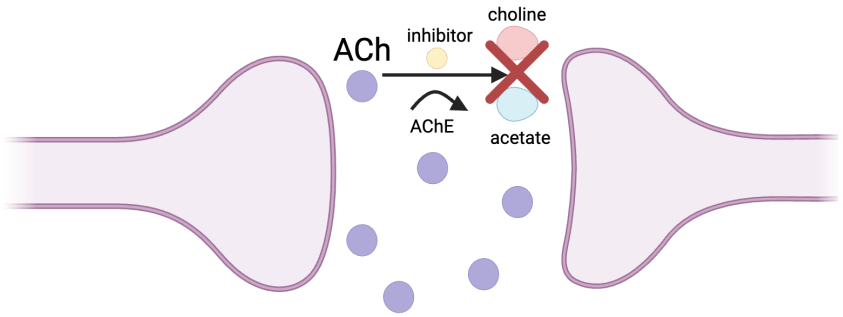


Fig. 2 — Schematic representation of AChE's action

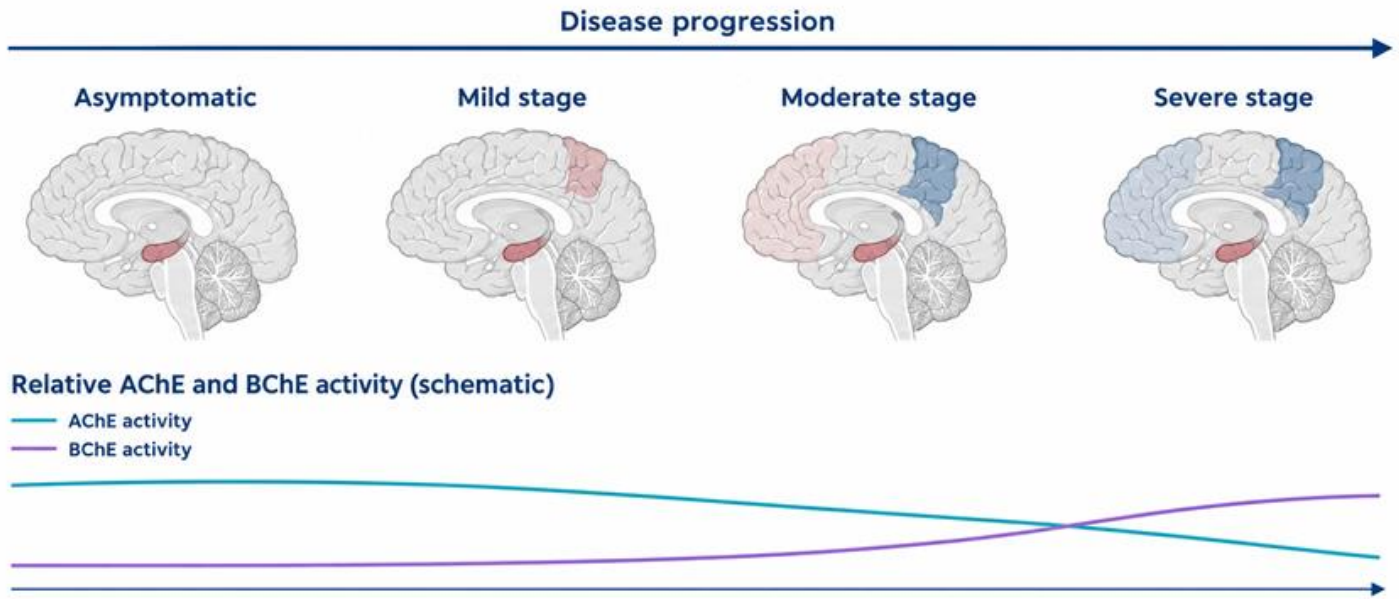


Fig. 3 — Schematic representation of the progression of Alzheimer's disease and changes in the relative activity of AChE/BChE

With the progression of Alzheimer's disease, the level of acetylcholinesterase (AChE) decreases while butyrylcholinesterase (BChE) is compensatorily overexpressed

Selective BChE inhibition a promising strategy for severe stage disease

Introduction

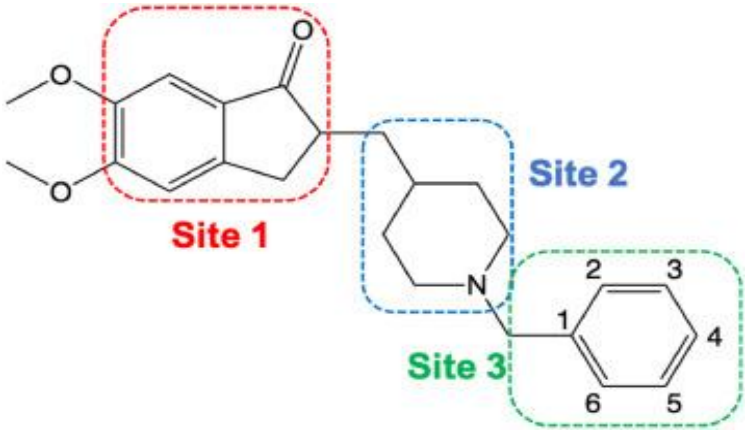


Fig. 1 - Donepezil structure

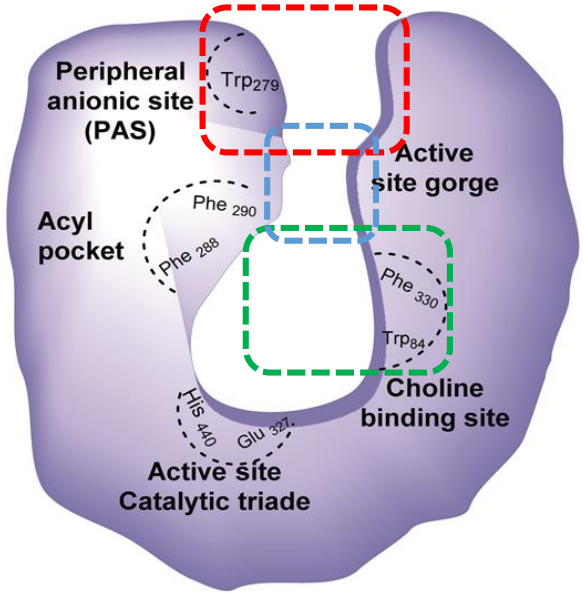


Fig. 2 — Schematic representation of AChE binding site [1]

[1] - 10.1039/d1ra03718h; * - Molecular Dynamics

Introduction

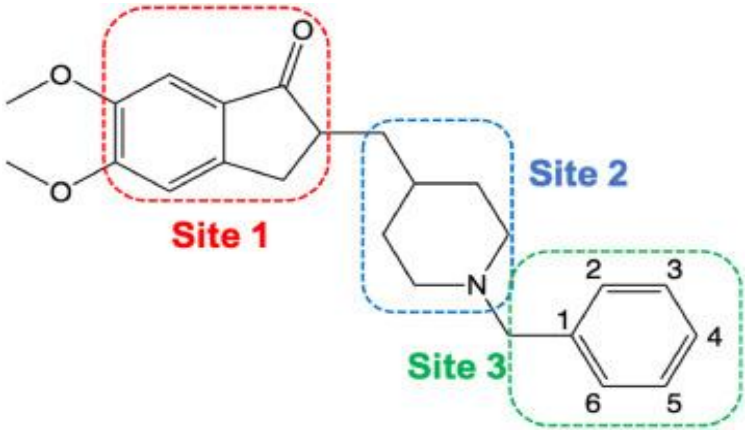


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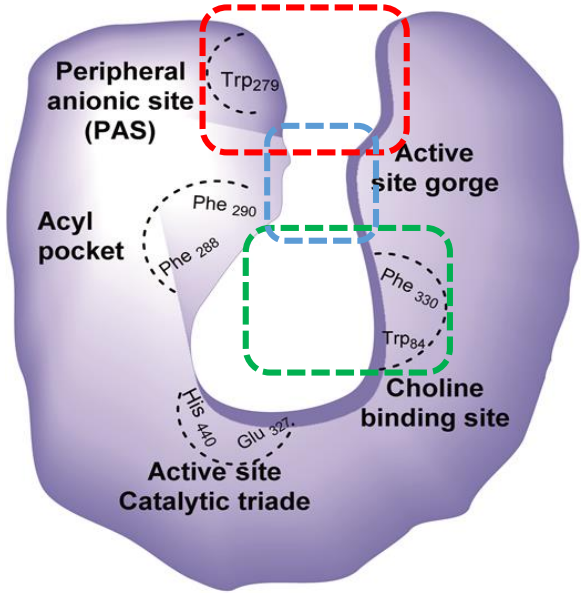


Fig. 2 — Schematic representation of AChE binding site [1]

Hypothesis: An ensemble approach can simplify the identification of unique pharmacophoric features as well as search of selective inhibitor

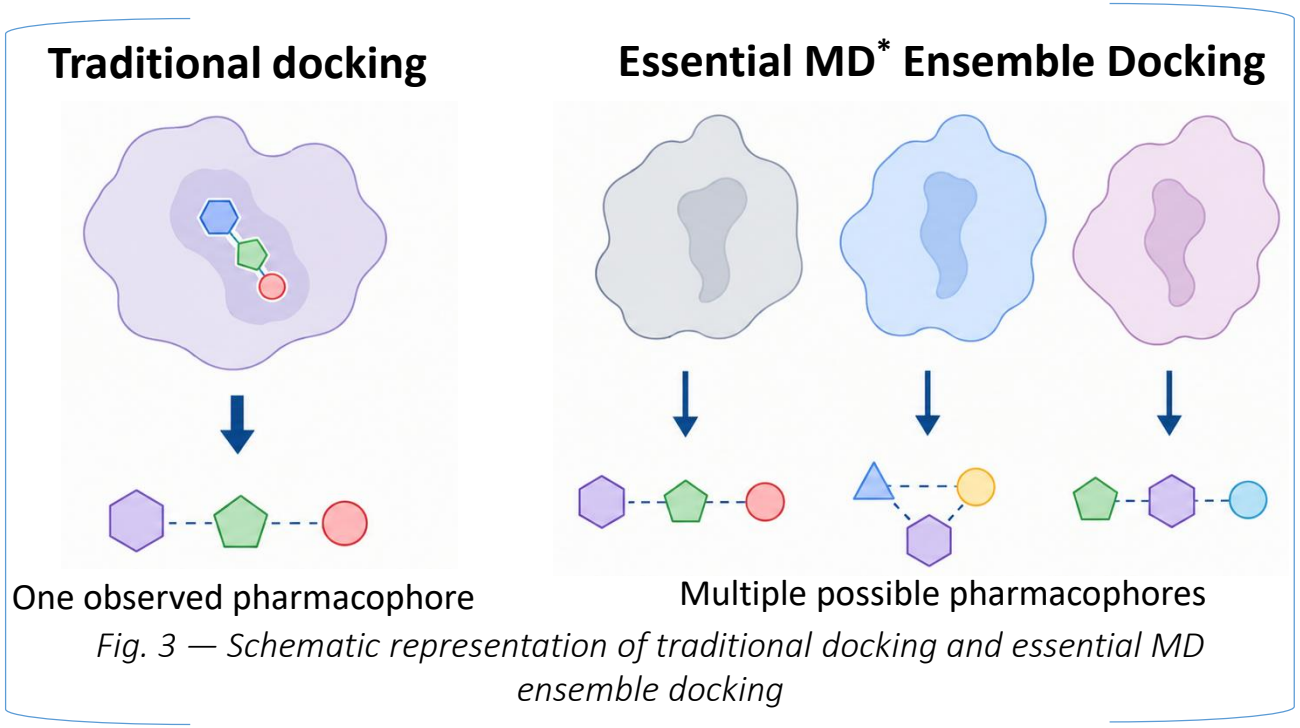


Fig. 3 — Schematic representation of traditional docking and essential MD ensemble docking

Development of an approach to assess whether conformational heterogeneity is relevant for molecular docking

[1] - 10.1039/d1ra03718h; * - Molecular Dynamics

Objective and methodology

Objective: To assess the relevance of conformational heterogeneity for molecular dynamics-based ensemble docking of AChE and BChE using PCA



Protonation states and protein charges were standardized within each pair**, and a consistent simulation protocol was applied

* - trajectory analysis to assess system stability; ** - 7RB7 with 6O4X and 5DYY with 5K5E

Result

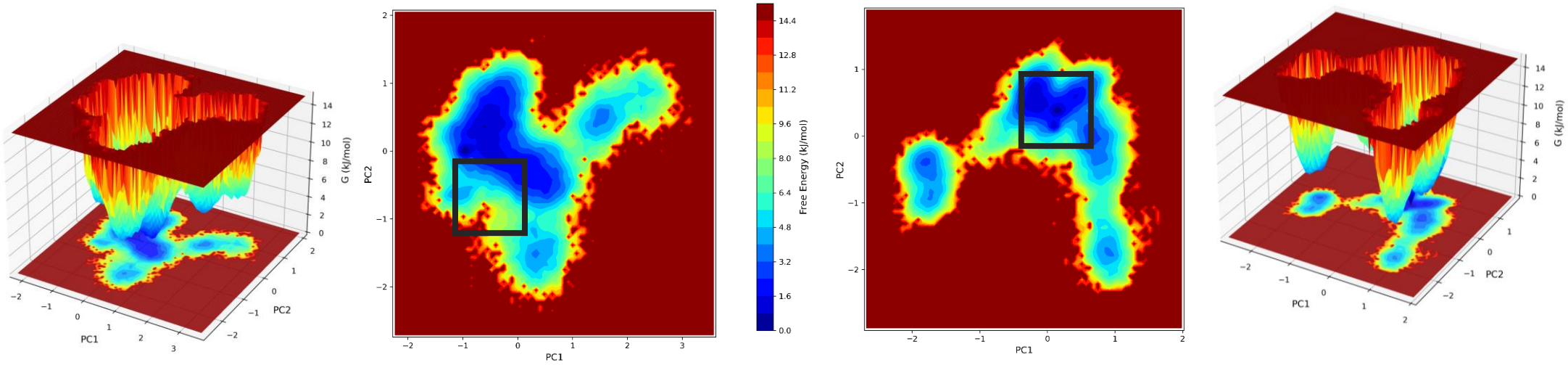


Fig. 1 — PCA-based free-energy landscape of the combined trajectories projected onto PC1 and PC2 of 3 replica for AChE **(A)** and BChE **(B)***

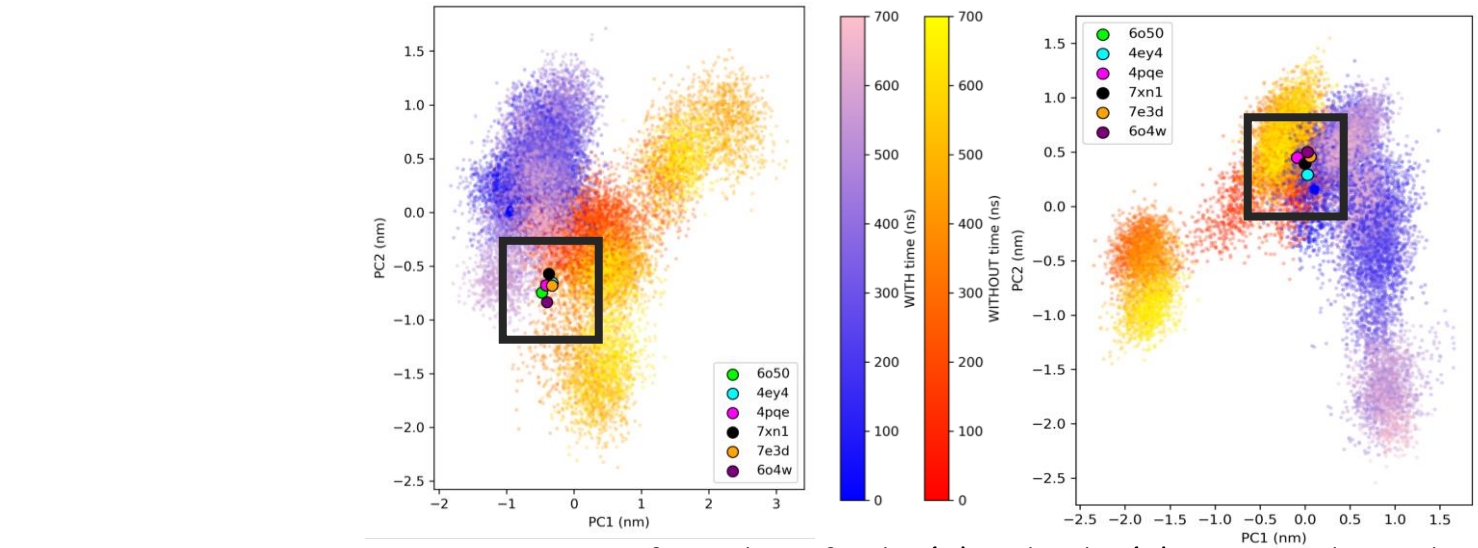


*Fig. 2 — PCA space of 3 replica of AChE **(A)** and BChE **(B)** using residues selected by RMSF filtering and ligand-proximity criteria (within 6 Å)**

* - high-RMSF residues potentially involved in ligand binding subsequently restored

Result

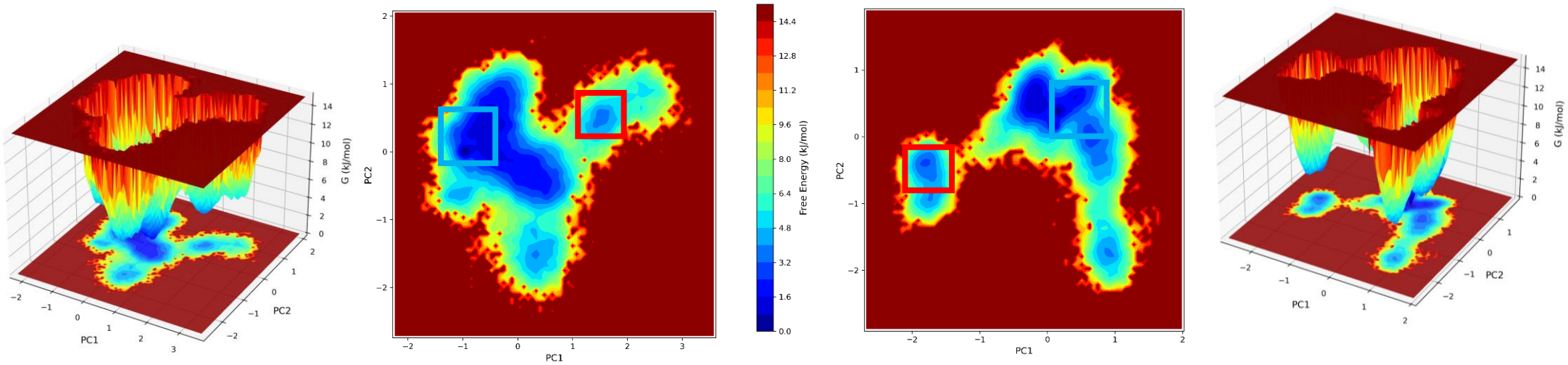
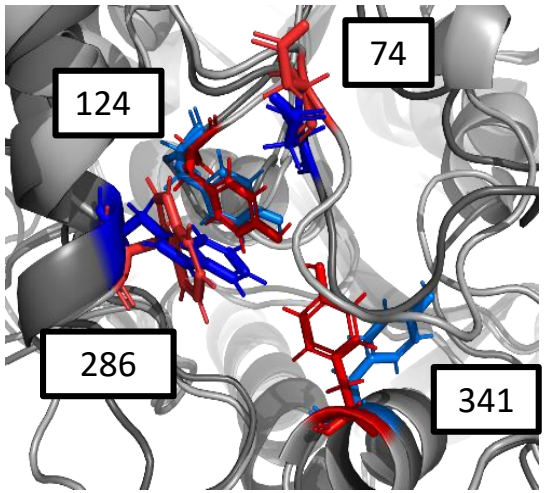
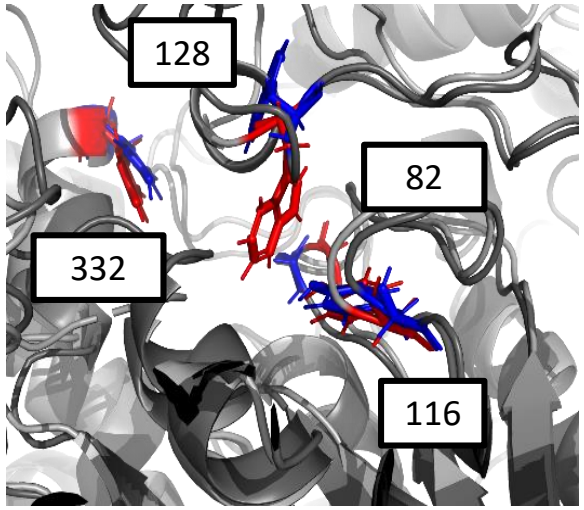


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* - high-RMSF residues potentially involved in ligand binding subsequently restored

Conclusion

BChE exhibited larger collective displacement vectors, while inter-residue distances changed between conformational clusters in both enzymes.

The crystallographic structures covered only a subset of the conformational states sampled during MD.

PCA-defined conformational clusters can guide the selection of representative MD structures for ensemble docking.

Результаты согласуются с Previous исследованиями где molecular dynamics studies have demonstrated link between conformational dynamics and substrate specificity.[1]

Significance

The proposed workflow of conformational heterogeneity provides a rational basis to assess the relevance for essential MD ensemble docking.

[1] -