Protein Structure Explorer: Mutation Analysis of 1AKE

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1. Research question & motivation

Adenylate kinase (1AKE) is a benchmark model for studying conformational switching in energy-metabolism enzymes.

Goal: Quantify how single-point mutations alter 1AKE's structural geometry and potential stability.

Why it matters: Understanding mutation-induced perturbations informs protein engineering, inhibitor design, and the interpretation of disease-linked variants.

2. Methods

Data source: crystal structure downloaded from the RCSB PDB (mmCIF format).

Parsing: BioPython (PDB / MMCIF parsers) used for coordinate extraction and atom mapping.

In-silico mutagenesis:

- Residue renamed to target amino acid.
- Side-chain reoriented by **120° rotation about the local Cα–Cβ bond axis** (geometry-based approximation).
- For glycine or residues lacking Cβ, only renaming performed.

Metrics:

- **RMSD:** computed after **backbone-based superposition** of wild-type vs. mutant structures.
- **Center-of-mass shift (ΔCOM):** distance between **mass-weighted atomic centers of mass**, not limited to Cα atoms.

3. Mutation panel

Fifteen mutants spanning functional / structural categories:

#	WT res	Pos	Mut	Category
1	K	13	A	Catalytic neutralisation
2	R	36	A	Catalytic neutralisation
3	A	37	G	Flexibility increase
4	I	53	P	Fold-kink probe
5	L	82	D	Hydrophobe → charged
6	D	93	N	Charge removal

7	R	119	E	Charge swap
8	F	120	A	Hydrophobe → Ala
9	G	122	P	Proline rigidification
10	L	134	P	Helix breaker
11	V	148	W	Bulky hydrophobe → Trp
12	R	156	A	Catalytic neutralisation
13	D	158	N	Charge removal
14	Y	171	F	Aromatic H-bond loss
15	T	175	A	Ser/Thr → Ala scan

4. Key results

Mutation	RMSD (Å)	ΔCOM (Å)	Comment
R36A	4.46	0.006	largest global distortion
K13A	2.84	0.003	catalytic Lys removal
L134P	4.32	0.005	helix kink introduced
mean (15)	2.6	0.003	most mutants localised

RMSD distribution: *0.0 Å (G122P) → ~4.8 Å (R119E).*
COM shifts: *≤ 0.01 Å → global fold preserved.*

Figures: mutation_rmsd.png, mutation_com_shift.png.

5. Limitations

- Geometry-only modelling; no molecular-mechanics relaxation or solvation effects.
- Residue mapping limited to single chains without insertion codes.
- Side-chain clashes and energetic penalties not explicitly evaluated.
- Near-zero RMSD/ΔCOM values for certain mutations (e.g., Gly→Pro) result from absence of comparable side-chain atoms and lack of relaxation.

6. Future work

- Integrate energy minimisation (e.g., OpenMM or Modeller) for realistic relaxation.
- Extend residue mapping between PDB and UniProt to support insertion codes.
- Apply workflow to other kinases and correlate geometric perturbations with activity assays.