Resetability (R): A Deterministic Geometric Metric Revealing Allosteric and Immunotherapeutic Rigidity Patterns in Proteins

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Abstract

We introduce resetability (R), a deterministic geometric metric that quantifies residual coupling after replaying a scaled backbone rotation history twice in SU(2). R approaches zero for single-axis, rigid-like motions and increases with non-commutative mixing. Using public PDB/mmCIF structures, we validate R on hemoglobin T↔R allostery, PD-1 loop locking by pembrolizumab, and HLA/TCR systems. R recovers classical hinges, reports rigidification at therapeutic epitopes, and maps allele- and ligand-dependent groove mechanics from single structures.

Introduction

Rigidity and flexibility underlie allosteric regulation and immune recognition. While dynamics are often inferred from ensembles, static structures are widely available. We derive a geometry-only metric, R, from local backbone frames to detect rotational coupling that correlates with functional mechanics.

Methods

Local right-handed frames (tangent, normal, binormal) are built from successive Cα positions. Rotations between consecutive frames are mapped to SU(2). The net rotation defines a scale $\lambda=\pi/\theta\_net$. The scaled sequence $(\lambda\cdot\theta\_i)$ is applied twice to a spinor aligned with the chain principal axis; $R = 1 - \text{fidelity}(\text{initial}, \text{final})$. Whole-chain R and sliding-window R (25-residue window, 5-residue step) are computed. Profiles are normalized by residue index for cross-chain comparisons.

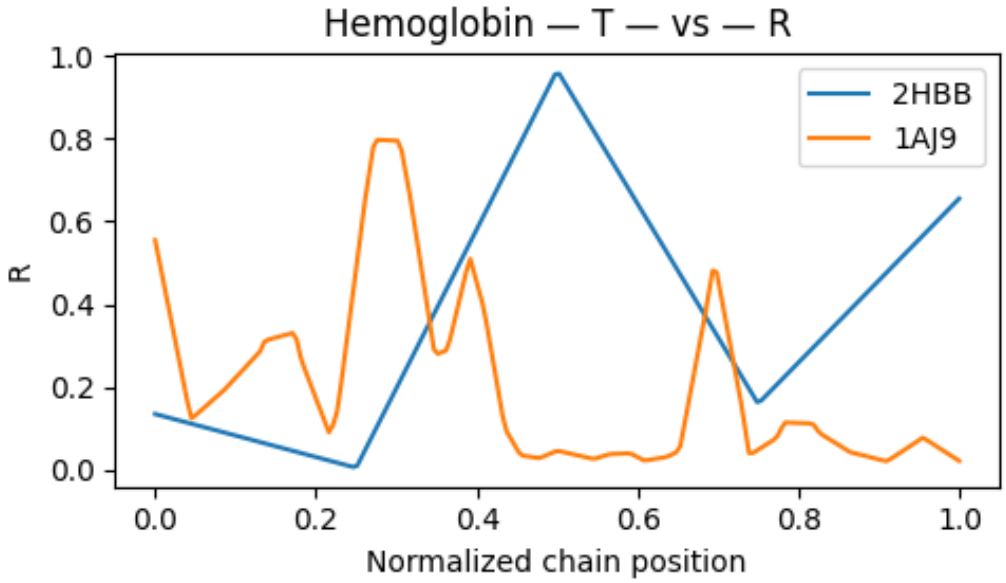
We analyzed public structures: hemoglobin (2HBB T-state; 1AJ9 R-state), PD-1 apo (3RRQ, 3B71) and pembrolizumab-bound (5GGS), HLA-A*02:01 (1A1N), HLA-B*27 (1HSA), and TCR-bound HLA-A2 (1AO7).

Results

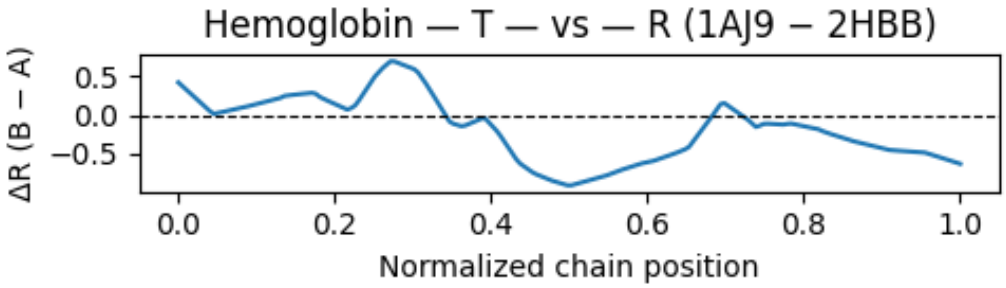
Hemoglobin — T — vs — R

R distinguishes T vs R with higher hinge-region R in the T state.

Normalized R-profiles:



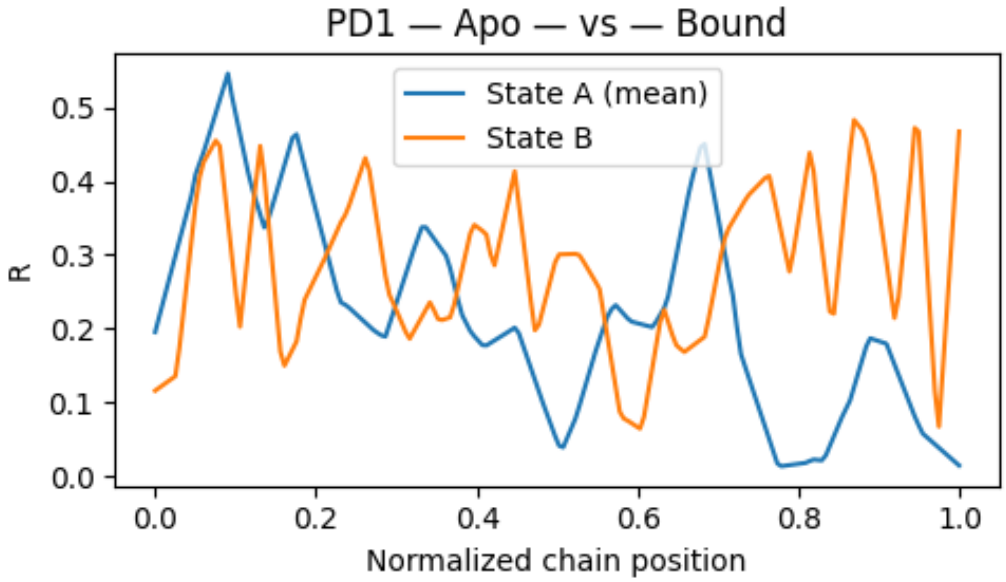
ΔR profiles (B − A):



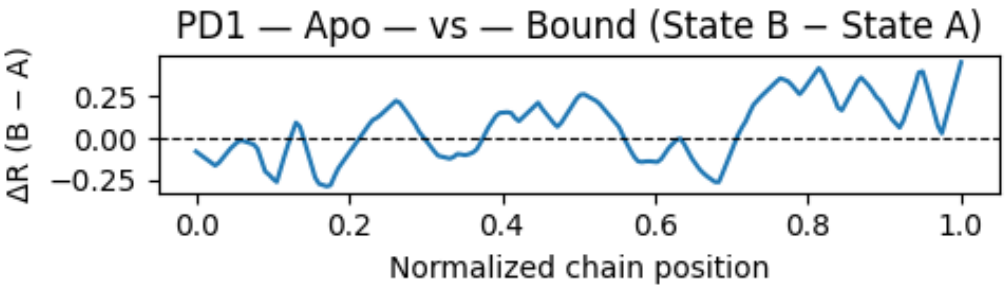
PD1 — Apo — vs — Bound

Antibody binding reduces PD-1 R in loop regions (e.g., C′D loop), consistent with loop locking.

Normalized R-profiles:



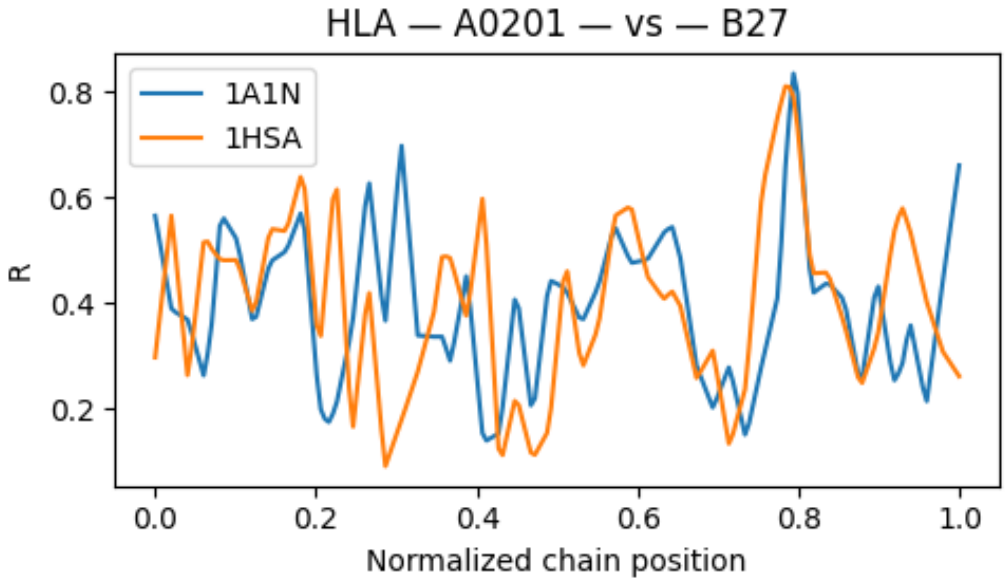
ΔR profiles (B − A):



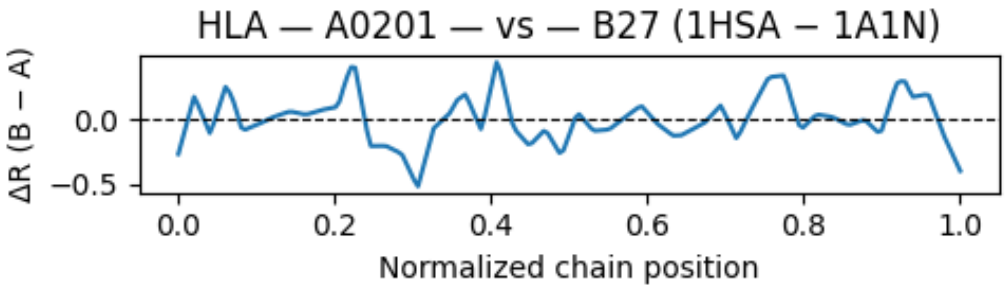
HLA — A0201 — vs — B27

Allele-specific mechanics along the HLA groove (A*02:01 vs B*27).

Normalized R-profiles:



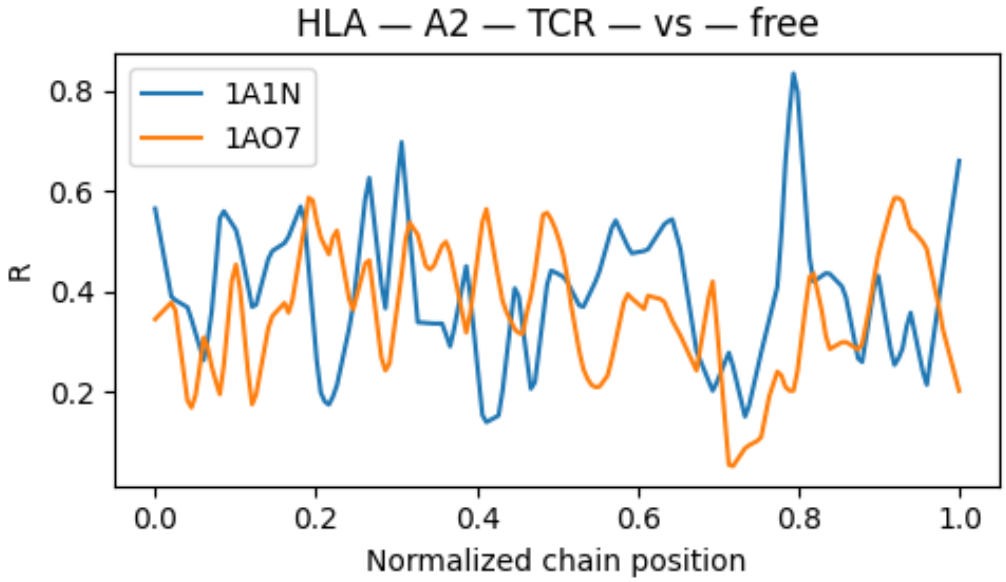
ΔR profiles (B − A):



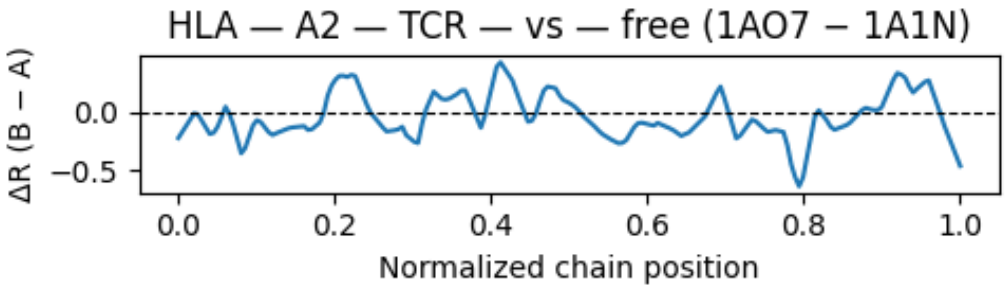
HLA — A2 — TCR — vs — free

TCR engagement rigidifies HLA-A2 groove segments (ΔR < 0).

Normalized R-profiles:



ΔR profiles (B − A):



Quantitative summaries

Mean/median/max/min R per file/chain (sliding windows). Full details in CSV.

file	chain	mean_R	median_R	max_R	min_R	n_windows
1A1N.cif	A	0.305	0.260	0.945	0.000	50
1A1N.cif	B	0.503	0.629	0.969	0.001	15
1AJ9.cif	A	0.193	0.095	0.944	0.001	23
1AJ9.cif	B	0.224	0.059	0.983	0.000	24
1AO7.cif	A	0.378	0.236	0.989	0.000	50
1AO7.cif	B	0.357	0.265	0.994	0.000	15
1AO7.cif	D	0.346	0.218	0.945	0.002	18
1AO7.cif	E	0.309	0.182	0.967	0.000	37
1BD2.cif	A	0.322	0.217	0.998	0.000	50
1BD2.cif	B	0.459	0.413	0.977	0.002	15
1BD2.cif	D	0.264	0.222	0.934	0.001	33
1BD2.cif	E	0.330	0.328	0.986	0.000	44

1CG9.cif	A	0.380	0.330	0.992	0.000	51
1CG9.cif	B	0.415	0.319	0.989	0.017	15
1F3J.cif	A	0.371	0.369	0.928	0.001	32
1F3J.cif	B	0.322	0.273	0.991	0.000	33
1F3J.cif	D	0.416	0.355	0.990	0.000	32
1F3J.cif	E	0.338	0.195	0.940	0.005	33
1FNE.cif	A	0.325	0.178	0.990	0.001	32
1FNE.cif	B	0.214	0.166	0.859	0.000	38

Discussion

Across benchmarks, R from single structures recovers classical mechanics: hemoglobin hinge behavior, PD-1 loop rigidification by antibody, and HLA allele/TCR effects. R is fast and deterministic, enabling large-scale triage (e.g., on AlphaFold models) and mechanistic prioritization for drug design and immuno-oncology.

Conclusion

Resetability (R) offers a reproducible geometry-only readout of rotational coupling. Combined with public coordinates, it reveals therapeutically relevant rigidification patterns and complements simulations and experiments.

Data and Code Availability

All input structures are public PDB/mmCIF. This script reproduces the analysis end-to-end.