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. Here, we adapt recent discoveries in rotational mathematics **(1, 2)** to derive a geometry-only metric, R, from local backbone frames to detect rotational coupling that correlates with functional mechanics. This principle establishes that any sequence of rotations, when scaled by $\lambda = \pi / \theta_{\text{net}}$ and replayed twice, returns to the origin2, allowing us to quantify geometric reversibility.

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 λ=π/θ_net. The scaled sequence (λ·θ_i) is applied twice to a spinor aligned with the chain principal axis; R = 1 − fidelity(initial, 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.

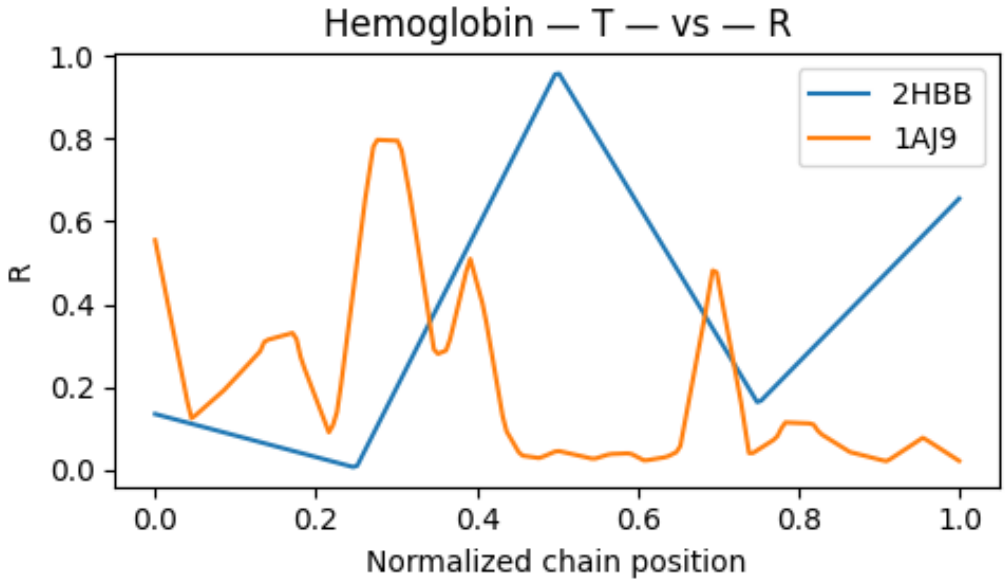
We analyzed public structures: hemoglobin (2HBB T-state; 1AJ9 R-state), PD-1 apo (3RRQ, 3B71) and pembrolizumab-bound (5GGS), HLA-A*02:01 (1A1N), HLA-B*27 (1HSA), and TCR-bound HLA-A2 (1AO7).

Results

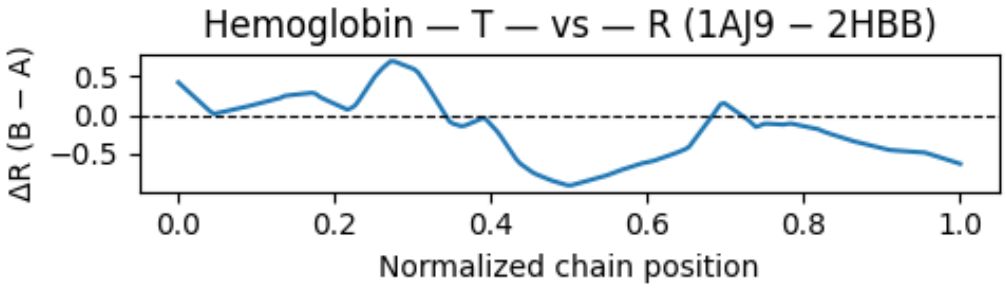
Hemoglobin — T — vs — R

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

Normalized R-profiles:



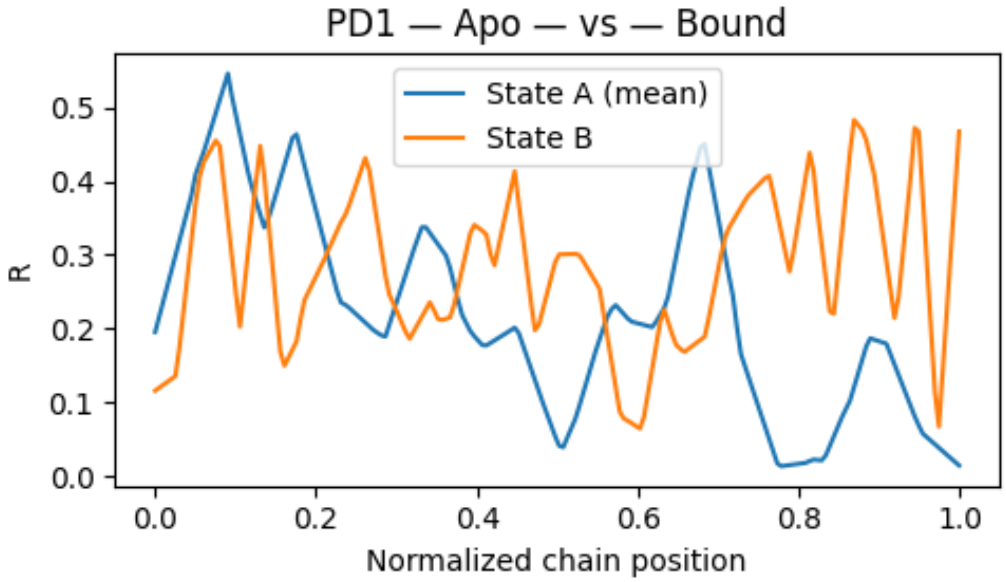
ΔR profiles (B − A):



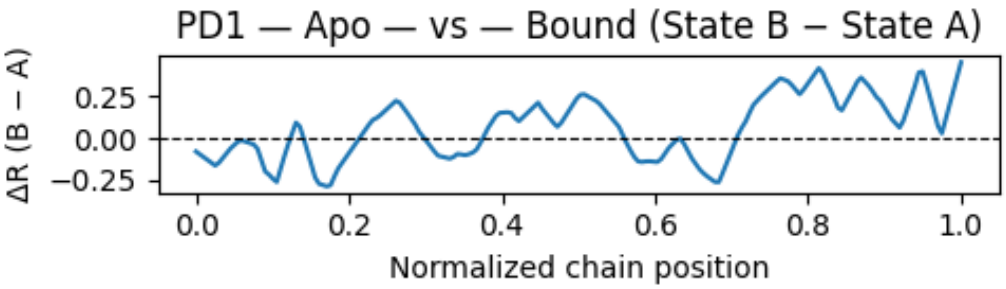
PD1 — Apo — vs — Bound

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

Normalized R-profiles:



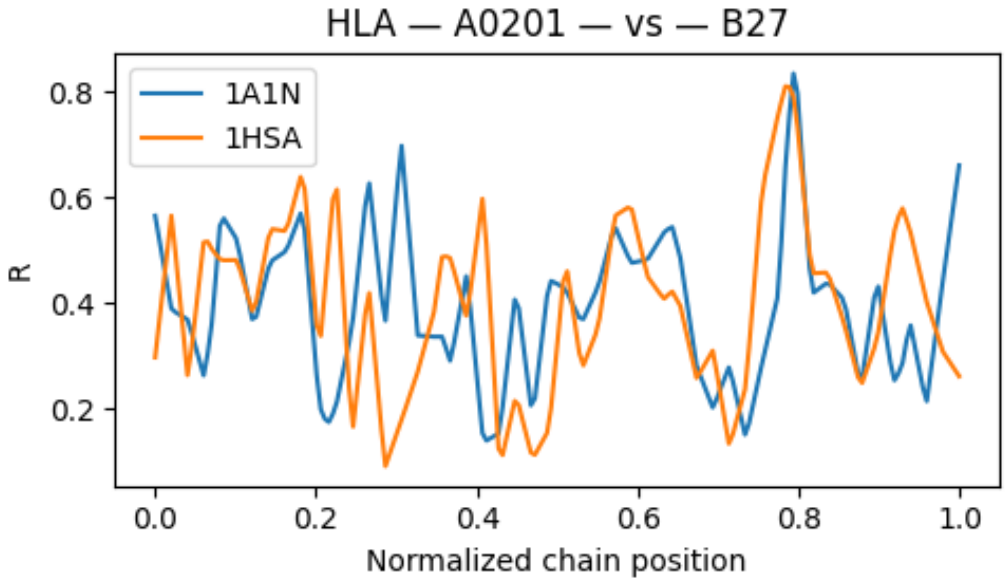
ΔR profiles (B − A):



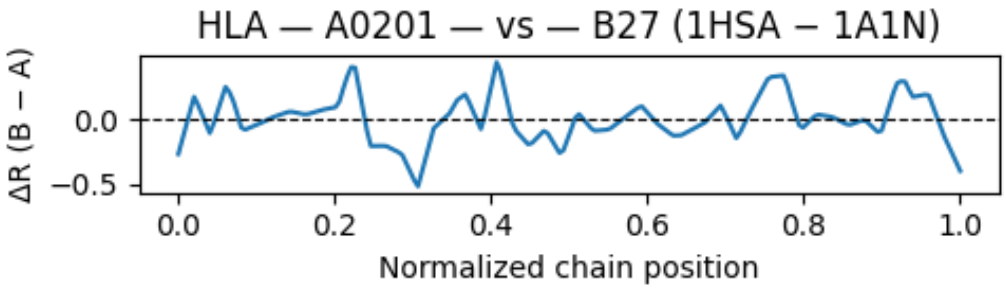
HLA — A0201 — vs — B27

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

Normalized R-profiles:



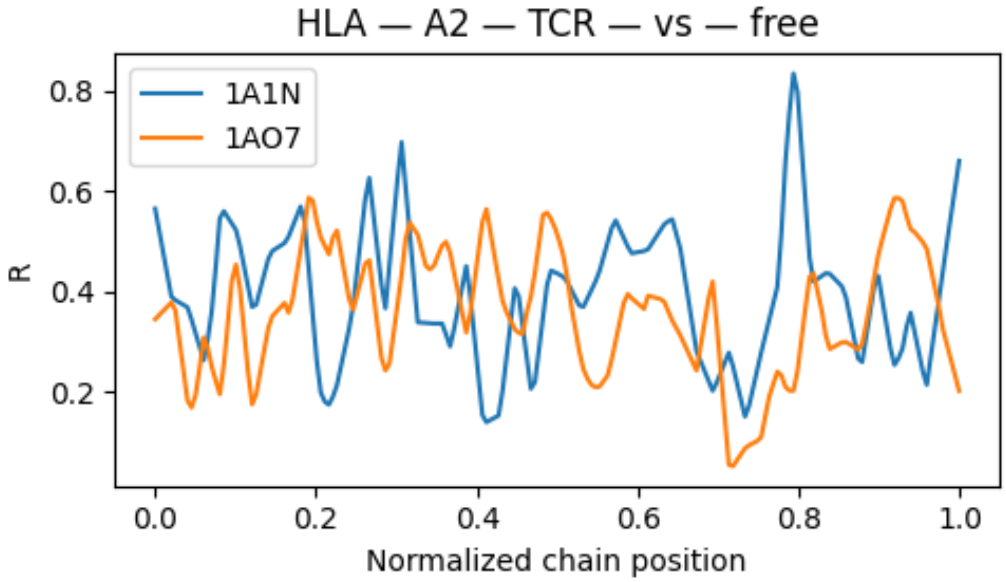
ΔR profiles (B − A):



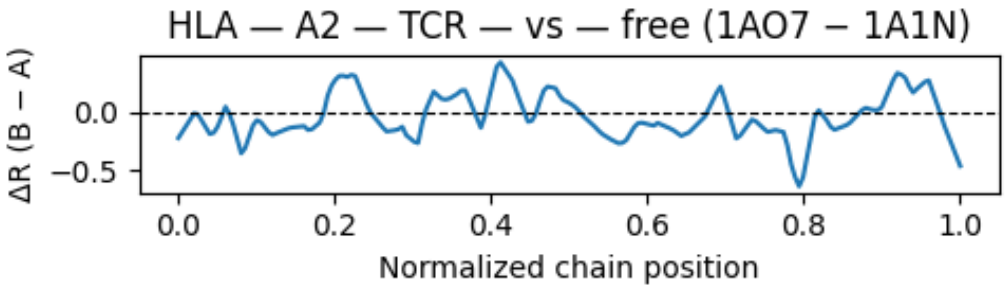
HLA — A2 — TCR — vs — free

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.

Corresponding References

1. Eckmann, J.-P., & Tlusty, T. (2024). Tumbling Downhill along a Given Curve.

2. Eckmann, J.-P., & Tlusty, T. (2025). Walks in Rotation Spaces Return Home when Doubled and Scaled. Physical Review Letters.