

Data Availability Statement

Data sources

Thermodynamic data for the four validation proteins (Trp-cage, Villin HP35, CI2, ACBP) were obtained from the following published sources:

- **Trp-cage (TC5b):** Neidigh, J.W. et al. (2002) *Nature Struct. Biol.* 9, 425–430; Streicher, W.W. & Makhatadze, G.I. (2007) *Biochemistry* 46, 2876–2880.
- **Villin HP35:** Kubelka, J. et al. (2003) *J. Mol. Biol.* 329, 625–630.
- **CI2:** Jackson, S.E. & Fersht, A.R. (1991) *Biochemistry* 30, 10428–10435.
- **ACBP:** Kragelund, B.B. et al. (1995) *J. Mol. Biol.* 256, 187–200.

Alzheimer mutation clinical data were compiled from published clinical genetics and biochemistry literature, including onset ages, aggregation propensities, and clinical phenotypes documented in the Alzforum Mutations Database (<https://www.alzforum.org/mutations>).

Code availability

All simulation code is available at:

<https://github.com/forgottenforge/protein-sigma>

The repository contains:

All scripts are implemented in Python 3 and require only NumPy, SciPy, and Matplotlib. No proprietary software, specialized hardware, or molecular dynamics packages are needed. Results are fully reproducible with the provided random seeds.

Additional materials

Supplementary materials include: complete $\sigma(T)$ tables for all proteins (S1), Go model specification (S2), simulation parameters (S3), full temperature scan data (S4), complete α scan data (S5), Alzheimer mutation mapping details (S6), intervention simulation results (S7), dose–response data (S8), experimental validation data (S9), large-scale validation across 20 proteins (S10), ClinVar VUS predictions (S11), code availability (S12), transthyretin validation data with leave-one-out, within-phenotype, and onset-data sensitivity analyses (S13), benchmark against alternative early-warning indicators (S14), hereditary lysozyme amyloidosis validation (S15), gelsolin amyloidosis validation (S16), and negative control data for SOD1, PRNP, and A β 42 (S17).

File	Description
<code>protein_folding_cbfi.py</code>	Thermodynamic $\sigma(T)$ computation for real proteins
<code>protein_telescope_v2.py</code>	Single-basin Go model validation
<code>protein_dual_basin.py</code>	Dual-basin model with α scan and transient σ
<code>protein_dual_basin_intervention.py</code>	Therapeutic intervention simulations
<code>protein_alzheimer_mutations.py</code>	Alzheimer mutation analysis
<code>protein_validation.py</code>	Experimental $\Delta\Delta G$ validation across 37 mutations
<code>protein_largescale_validation.py</code>	Large-scale validation (20 proteins, 277 mutations, ClinVar VUS predictions)
<code>robustness_sweep.py</code>	Parameter sweep: early-warning robustness across N , S , contact topologies
<code>ttr_validation.py</code>	Transthyretin mutation validation against clinical onset ages
<code>hdx_proxy.py</code>	HDX-MS/NMR order parameter proxy for σ
<code>drift_sensitivity.py</code>	Drift-rate sensitivity analysis (0.02–0.05/decade)
<code>benchmark_early_warning.py</code>	Benchmark: σ vs. 4 alternative early-warning indicators
<code>lyz_validation.py</code>	Hereditary lysozyme amyloidosis validation
<code>gelsolin_validation.py</code>	Gelsolin amyloidosis validation
<code>sod1_validation.py</code>	SOD1/ALS negative control analysis
<code>prnp_validation.py</code>	Prion disease negative control analysis
<code>structure_based_ddg.py</code>	DynaMut2 + ESM-1v cross-method analysis for A β 42
<code>paper5_figures.py</code>	Figure generation for main text and supplementary