

# A First Principles Approach to Understanding Why Proteins Fold

Technical Report and Experimental Log

Recognition Science Collaboration  
protein-folding project

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## Abstract

We present a first-principles approach to protein folding that derives structural predictions from geometric and thermodynamic principles rather than statistical learning. Starting from the Recognition Composition Law (RCL) and the unique J-cost function it implies, we develop a hierarchical folding model that predicts secondary structure from steric properties, tertiary contacts from directional hydrophobicity, and sheet topology from multi-partner hydrogen bonding patterns. Our model achieves a mean RMSD of approximately 11.5Å on a diverse panel of 7 proteins without fitting any parameters to structural data. We document both successful mechanisms and failed hypotheses, maintaining strict separation between theory-derived and data-fitted components. This work represents an attempt to *understand* protein folding rather than merely predict it.

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# 1 Introduction: The Goal is Understanding

## 1.1 Why Prediction is Not Enough

AlphaFold and similar deep learning methods achieve remarkable accuracy in protein structure prediction, often approaching experimental resolution. However, these methods function as sophisticated pattern matchers—they can tell us *what* a protein’s structure is, but not *why* it folds that way.

We adopt a different goal:

**We are trying to UNDERSTAND how and why proteins fold.**

Prediction accuracy is not the goal. It is merely the *evidence* that our understanding is correct.

A model that correctly explains *which forces dominate, in what order, and why* is more valuable for our purposes than a black-box predictor, even if the black-box is more accurate.

## 1.2 What Constitutes Understanding

We claim to *understand* protein folding when we can answer:

1. **Why does the protein fold at all?** A derivable energy principle, not just “it minimizes energy.”
2. **Why this particular fold?** A mechanistic sequence-to-structure mapping.
3. **What sets the timescale?** Derived from physical constants, not fitted to folding rates.
4. **What would prevent folding?** Specific, testable predictions.

## 1.3 The Circularity Problem

Any model that improves by fitting to known structures is circular—it uses the answer to generate the answer. We maintain a strict **Circularity Watchlist**:

- No fitting weights to minimize RMSD on known structures
- No using “typical protein” statistics as targets
- No adding terms “because they improve the benchmark”
- No cherry-picking proteins where we perform well

Every parameter in our model is either (a) derived from first principles, (b) a fundamental physical constant, or (c) explicitly flagged as a model assumption requiring future derivation.

# 2 Theoretical Foundation

## 2.1 The Recognition Composition Law

The Recognition Science framework begins with the **Recognition Composition Law (RCL)**, which constrains how any system can compose or recognize sub-patterns:

**Theorem 1** (Recognition Composition Law). *For a recognition operation  $R$  acting on composite pattern  $A \circ B$ :*

$$R(A \circ B) = R(A) \circ R(B) \circ \Delta(A, B)$$

where  $\Delta(A, B)$  captures the interaction between  $A$  and  $B$ .

## 2.2 The J-Cost Function

From RCL, we derive the unique cost function that satisfies the composition requirement:

**Theorem 2** (Uniqueness of J-Cost). *The function*

$$J(r) = \frac{1}{2} \left( r + \frac{1}{r} \right) - 1$$

*is the unique smooth cost function (up to scaling) that:*

1. *Has a minimum at  $r = 1$  (scale invariance)*
2. *Satisfies  $J(r) = J(1/r)$  (reciprocal symmetry)*
3. *Composes additively under RCL*

This function replaces arbitrary harmonic or Lennard-Jones potentials with a principled form. It penalizes deviations from target distances in both directions equally.

## 2.3 $\phi$ -Forcing and the Golden Ratio

A key result from discrete self-similarity is that stable recursive structures must satisfy:

**Theorem 3** ( $\phi$ -Forcing). *If a pattern  $P$  contains a self-similar subpattern, and both must satisfy RCL, then the scaling ratio  $r$  satisfies:*

$$r^2 = r + 1 \implies r = \phi = \frac{1 + \sqrt{5}}{2} \approx 1.618$$

This forces the golden ratio to appear in geometric relationships. We derive several structural distances from this:

Distance	Formula	Value
Backbone C $\alpha$ -C $\alpha$	$\phi^2 \times$ N-C $\alpha$ bond	3.85 Å
Helix i $\rightarrow$ i+4	$\phi \times$ backbone	6.23 Å
$\beta$ -strand interstrand	$\sqrt{\phi} \times$ backbone	4.90 Å
Helix-helix packing	$\phi^2 \times$ backbone	10.08 Å

These derived values match experimental observations within 5%, providing evidence that the  $\phi$ -forcing principle captures real physics.

## 3 Strategy: Rigorous Exploration

### 3.1 The Exploration Protocol

We follow a strict experimental protocol to prevent overfitting and ensure reproducibility:

1. **Preregistration:** Every experiment is documented before running, including hypothesis, falsification criterion, and confidence level.
2. **Panel Separation:** Proteins are divided into DEV (iteration), SEALED (milestone testing), and STRESS (adversarial) panels.
3. **Baseline Tournament:** Claims only “pass” if they beat increasingly sophisticated baselines.
4. **The Graveyard:** Failed ideas are explicitly buried to prevent resurrection without new evidence.

### 3.2 The Graveyard: What Didn't Work

Transparency about failures is essential. The following ideas were tested and explicitly killed:

Dead Idea	Cause of Death
W-token contact prediction	E1: No channel achieves consistent signal across proteins. Mean lift $0.72\times$ (below random).
W-token secondary structure	E6/E7: DFT on chemistry properties fails across all window sizes [4..16]. Anti-correlated with DSSP.
Binary HP motifs	E8: Balanced accuracy 0.47 (worse than random 0.50).

The “W-token” approach (spectral analysis of chemistry properties via DFT) consumed significant effort before being definitively falsified. This failure redirected us toward simpler, more physical encoders.

## 4 What Works: The Successful Mechanisms

### 4.1 Mechanism 1: Steric Propensity for Secondary Structure

**Principle 1** (Steric Propensity). *The local secondary structure preference of an amino acid is determined by its sidechain geometry:*

- **$\beta$ -strand:** Beta-branched (V, I, T) or bulky aromatics (Y, F, W) resist  $\alpha$ -helix backbone torsion
- **Coil:** Flexible (G), rigid breakers (P), or short polar (D, N, S) disrupt regular structure
- **$\alpha$ -helix:** All others (A, L, M, E, Q, R, H, C) accommodate helical geometry

**Physical basis:** Beta-branched sidechains (V, I, T) have a carbon at the  $\beta$  position that sterically clashes with the  $i+3/i+4$  backbone in an  $\alpha$ -helix. This is not a statistical preference—it is geometric impossibility.

**Context-aware extension:** We improve strand detection by using a sliding window. If neighboring residues are bulky, even non-strand residues (L, M, C) can participate in strands:

$$\text{Score}_i = \sum_{j=i-1}^{i+1} w(aa_j)$$

where  $w(V,I,T) = +1.0$ ,  $w(Y,F,W,L,M,C) = +0.5$ ,  $w(A,E,K,Q,R,H) = -0.5$ ,  $w(G,P,D,N,S) = -1.0$ .

If  $\text{Score}_i > 0.5$ , residue  $i$  is predicted as strand.

**Experimental support:** E10 showed  $1.55\times$  lift over random baseline. E16 recovered 4/5 strands in Ubiquitin (vs 2/5 with rigid rules).

### 4.2 Mechanism 2: Directional Hydrophobic Attraction

**Principle 2** (Directional Hydrophobicity). *Hydrophobic residues attract each other only when their sidechains face each other. Isotropic attraction leads to collapsed globules; directional attraction preserves local geometry.*

**Physical basis:** Hydrophobic sidechains must interdigitate to exclude water. This requires specific orientation—the “ridges into grooves” packing of helix bundles, or the interleaved sidechains of  $\beta$ -sheets.

**Implementation:** For each residue  $i$ , we compute a virtual sidechain direction:

$$\vec{v}_i = \text{normalize} \left( C\alpha_i - \frac{C\alpha_{i-1} + C\alpha_{i+1}}{2} \right)$$

The directional factor for a pair  $(i, j)$  is:

$$f_{\text{dir}} = \max(0, \vec{v}_i \cdot \hat{r}_{ij}) \times \max(0, \vec{v}_j \cdot \hat{r}_{ji})$$

where  $\hat{r}_{ij}$  is the unit vector from  $i$  to  $j$ . Both sidechains must point toward each other for attraction to occur.

**Experimental support:** E13 (isotropic) destroyed helix geometry in 1ENH (RMSD 16.75Å). E14 (directional) recovered it (RMSD 13.74Å), a 3Å improvement.

### 4.3 Mechanism 3: Multi-Partner $\beta$ -Sheet Topology

**Principle 3** (Sheet Formation).  *$\beta$ -sheets are sheets, not pairs. Each strand can hydrogen-bond to neighbors on both sides. A greedy 1-to-1 pairing algorithm fails to capture sheet topology.*

**Implementation:** We allow each strand to have up to 2 partners (one on each side). This is implemented by tracking a “used count” per strand rather than a binary “used” flag.

**Experimental support:** E17 increased strand pairs in 2GB1 from 1 to 3, improving RMSD from 15.81Å to 14.53Å.

### 4.4 Mechanism 4: Salt Bridges

**Principle 4** (Electrostatic Stabilization). *Oppositely charged residues (K/R vs D/E) attract via electrostatic forces. These salt bridges stabilize helix caps, surface contacts, and domain interfaces.*

**Implementation:** Same directional constraint as hydrophobic attraction, with target distance 6.5Å and weight 0.8.

**Experimental support:** E18 showed consistent small improvements across 6/7 proteins.

### 4.5 Mechanism 5: Disulfide Bonds

**Principle 5** (Covalent Constraints). *Disulfide bonds (C-C) are covalent and provide strong distance constraints. Proteins with multiple disulfides cannot fold correctly without modeling them.*

**Implementation:** Add strong J-cost term (weight 10.0) at target C $\alpha$ -C $\alpha$  distance of 5.5Å for known disulfide pairs.

**Experimental support:** E22 improved 1AKI (lysozyme, 4 disulfides) from 17.85Å to 15.96Å.

## 5 Current Results

### 5.1 Best Achieved Accuracy

After 22 experiments (E1–E22), our best results with 4000 optimization steps are:

Protein	Type	Residues	RMSD (Å)	Status
1L2Y	Miniprotein (Trp-cage)	20	<b>5.87</b>	Excellent
1VII	$\alpha$ -helical (Villin)	36	<b>10.16</b>	Good
1PGB	$\alpha/\beta$ (Protein G)	56	<b>10.76</b>	Good
1ENH	$\alpha$ -helical (Engrailed)	54	<b>11.22</b>	Good
1UBQ	$\alpha/\beta$ (Ubiquitin)	76	<b>13.07</b>	Pass
2GB1	$\alpha/\beta$ (Protein G alt)	56	<b>13.79</b>	Pass
1AKI	Large + SS (Lysozyme)	129	<b>15.96</b>	Improved
Mean			<b>11.5</b>	

## 5.2 Comparison to Baselines

Our model beats the following baselines:

- **B0 (Random)**: Uniform random structure. Our model is dramatically better.
- **B1 (Separation-matched random)**: Random contacts with correct sequence separation distribution. Our model is better.
- **B2 (Hydrophobicity only)**: Simple burial term without directional constraints. Our model is better, proving the directional mechanism adds value.

For context: AlphaFold achieves  $\sim 1\text{\AA}$  RMSD. We are at  $\sim 11\text{\AA}$ . However, AlphaFold uses 170,000 proteins for training; we use zero.

## 5.3 Radius of Gyration Accuracy

A notable success is the accuracy of predicted compactness:

Protein	Native Rg (Å)	Predicted Rg (Å)	Error
1L2Y	7.00	6.16	12%
1VII	8.82	8.27	6%

Getting the “Goldilocks density” correct—not too tight, not too loose—without fitting is evidence that our compaction mechanism (hydrophobicity +  $\phi$ -scaling) captures real physics.

# 6 Open Questions

## 6.1 Q5: Breaking the $10\text{\AA}$ Barrier

Only 1 of 7 proteins (1L2Y) achieves sub- $10\text{\AA}$  accuracy. What limits the others?

**Hypotheses:**

1. **Optimization convergence**: The energy landscape has local minima. Evidence: E20 showed that doubling iterations from 2000 to 4000 improved mean RMSD by  $2.4\text{\AA}$ .
2. **Missing physics**: We don’t model backbone hydrogen bonds explicitly, only C $\alpha$ -level constraints.
3. **Entropic effects**: We use a pure energy model without temperature/entropy.

**First-principles approach**: The  $\phi$ -forcing principle might constrain the number of optimization steps required. If the energy landscape has a hierarchical structure with neutral windows at specific beats, annealing schedules derived from this structure could help.

## 6.2 Q6: Deriving the Remaining Weights

Several weights in our model are “algorithmic choices” rather than derived values:

Weight	Current Value	Circularity Risk
Rg penalty	2.0	HIGH
Burial weight	0.3	HIGH
Hydrophobic weight	0.5	MEDIUM
Salt bridge weight	0.8	MEDIUM

**First-principles approach:** The ratio of these weights might be constrained by  $\phi$ -scaling. If backbone bonding is the “base unit,” other terms might scale as  $\phi^{-1}$ ,  $\phi^{-2}$ , etc. This is speculative but testable.

## 6.3 Q7: The 1AKI Problem

Lysozyme (1AKI) remains our hardest case, even with disulfide modeling. At 15.96Å, it’s significantly worse than smaller proteins.

**Hypotheses:**

1. **Size effects:** At 129 residues, the conformational space is vastly larger.
2. **Domain structure:** Lysozyme has distinct  $\alpha$  and  $\beta$  domains that must pack correctly.
3. **Missing  $\beta$ -sheet:** We detect only 1 strand; native has more.

**First-principles approach:** The contact budget theorem predicts  $N/\phi^2$  stabilized contacts. For 1AKI, this is  $\sim 50$  contacts. Are we forming the right 50?

# 7 Planned Experiments

## 7.1 E23: Extended Optimization

- **Goal:** Test if 8000 steps improves on 4000.
- **Hypothesis:** We are still under-converged.
- **Risk:** Low. If it helps, great; if not, we know convergence is not the bottleneck.

## 7.2 E24: Simulated Annealing

- **Goal:** Escape local minima using temperature-based exploration.
- **Hypothesis:** The energy landscape has kinetic traps.
- **First-principles constraint:** The annealing schedule could be tied to the 8-beat neutral window hypothesis (large moves at beats 0 and 4).

## 7.3 E25: $\phi$ -Derived Weights

- **Goal:** Derive the Rg and burial weights from  $\phi$ -scaling.
- **Hypothesis:** If backbone bond weight is 50, then secondary structure weight should be  $50/\phi \approx 31$ , tertiary weight  $50/\phi^2 \approx 19$ , etc.
- **Risk:** High. This is speculative theory.

## 7.4 E26: Stress Panel

- **Goal:** Find failure modes with adversarial proteins.
- **Candidates:** Multi-domain proteins, repeat proteins, intrinsically disordered regions.
- **Purpose:** A model that only works on “easy” proteins doesn’t demonstrate understanding.

## 8 Conclusion

We have developed a protein folding model from first principles that:

1. **Derives** key distances from the golden ratio via  $\phi$ -forcing
2. **Predicts** secondary structure from steric geometry (no fitting)
3. **Forms** tertiary structure via directional hydrophobicity
4. **Achieves**  $\sim 11\text{\AA}$  mean RMSD on diverse proteins
5. **Documents** failures as rigorously as successes

This is not competitive with AlphaFold for prediction accuracy. That is not the goal. The goal is to understand *why* proteins fold, and to build that understanding from derivable principles rather than learned correlations.

The model in its current form represents a proof of concept: geometric and thermodynamic first principles *can* drive folding without data fitting. The open questions (sub-10 $\text{\AA}$  accuracy, weight derivation, large proteins) define the path forward.

### 8.1 What We Claim to Understand

- Why secondary structure forms where it does (steric constraints)
- Why hydrophobic cores form (directional burial)
- Why  $\beta$ -sheets have specific topology (multi-partner H-bonding)
- Why the protein is as compact as it is ( $\phi$ -scaling of  $R_g$ )

### 8.2 What We Don’t Yet Understand

- Why some proteins fold to  $<10\text{\AA}$  and others don’t
- The precise numerical weights (currently model assumptions)
- Folding kinetics and timescales
- Misfolding and aggregation

The journey continues.

## A Model Parameter Audit

Every number in the model is classified by source:

Parameter	Value	Source	Circularity
$\phi$	1.618...	THEOREM	None
C-H bond	1.09 Å	MEASUREMENT	None
N-C $\alpha$ bond	1.47 Å	MEASUREMENT	None
Backbone distance	3.85 Å	DERIVED ( $\phi^2 \times$ N-C $\alpha$ )	None
Helix i $\rightarrow$ i+4	6.23 Å	DERIVED ( $\phi \times$ backbone)	None
$\beta$ interstrand	4.90 Å	DERIVED ( $\sqrt{\phi} \times$ backbone)	None
Backbone weight	50.0	ALGORITHMIC	Low
Helix weight	3.0	ALGORITHMIC	Low
Sheet weight	2.0	ALGORITHMIC	Medium
Steric penalty	50.0	ALGORITHMIC	Low
Rg penalty	2.0	MODEL ASSUMPTION	<b>High</b>
Burial weight	0.3	MODEL ASSUMPTION	<b>High</b>

## B Experimental Log Summary

ID	Experiment	Result	Key Finding
E1	W-token contacts	FAIL	No universal signal
E6	W-token SS	FAIL	Worse than random
E10	Steric Propensity	PASS	1.55 $\times$ lift
E14	Directional hydrophobic	PASS	Recovered helix geometry
E16	Context-aware sterics	PASS	Strand recovery
E17	Multi-partner sheets	PASS	Proper topology
E18	Salt bridges	PASS	Consistent small gains
E19	Aromatic stacking	MARGINAL	Protein-dependent
E20	4000 iterations	PASS	-2.4Å mean RMSD
E22	Disulfide bonds	PASS	1AKI improved by 2Å