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SHORT COMMUNICATION

Proteostasis Energy Imbalance and Protein-Feature Symmetry in Alzheimer's Disease: A Testable Theoretical Framework

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Abstract

Protein misfolding and disturbed proteostasis are important features of neurodegenerative disease, including Alzheimer's disease. This short communication proposes a testable connection between a mismatch in energy-dependent proteostasis demand and capacity, selected protein-feature asymmetry, and the distribution of aggregation-prone conformations. The model preserves the initially proposed restricted-domain relation $f(n) = f(N/2 - n)$ and distinguishes it from a full-sequence mirror comparison, $f(i) \approx f(N + 1 - i)$. A normalized asymmetry descriptor is introduced for prespecified structural or physicochemical features, with its interpretation limited to defined proteins and experimental conditions. Amyloid-β conformations in publicly available structural records (PDB 1IYT and 2LFM) provide a neurologically relevant context, not evidence that the proposed mechanism has already been established. The framework yields falsifiable predictions involving energy-state measurements, chaperone capacity, structural features, and aggregation-related outcomes. It offers a possible analytical route for exploring Alzheimer's-associated protein homeostasis while separating theoretical predictions from clinical applications.

Keywords: Alzheimer's Disease, Amyloid-β, Proteostasis, Protein Misfolding, Structural Symmetry.

1. Introduction

Alzheimer's disease is associated with amyloid-β conformational heterogeneity and aggregation, within a broader landscape of cellular stress and proteostasis disruption. Protein folding depends on sequence-specific free-energy landscapes, molecular surroundings, and protein quality-control networks [1,2]. Chaperone systems, including ATP-dependent components, can help maintain folding and clearance capacity, making the relationship between cellular energetics and protein aggregation more nuanced than a simple high-energy versus low-energy distinction [2,3].

We develop an explicitly mathematical hypothesis: under defined conditions, an imbalance between energy-dependent folding/proteostasis demand and effective cellular quality-control capacity could alter the symmetry of a selected structural feature and shift the distribution of conformational states. The aim is to express this proposal as a measurable framework relevant to amyloid-β, rather than as a universal rule for all folded proteins.

2. Discussion

2.1 Proposed Energy–Symmetry Framework

For a specified protein system, let an energetic imbalance denote a measurable mismatch between folding or clearance demand and effective proteostasis capacity. Candidate contributors include ATP availability relative to chaperone workload, redox stress, and non-equilibrium perturbations to folding and clearance. These are distinct biological quantities and should not be combined into an undefined "excess energy" variable.

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The central proposal is that an experimentally specified perturbation to this demand–capacity balance may be associated with a change in an independently defined protein-feature asymmetry measure and, consequently or concurrently, a change in aggregation-state distribution. The model does not require every functional protein to exhibit mirror symmetry.

2.2. Mathematical Formulation

The motivating symmetry relation is:

$$f(n) = f(N/2 - n)$$

The map $n \mapsto N/2 - n$ is a reflection about N/4. Accordingly, this expression is retained as a restricted-domain relation, where both indices lie within the domain under consideration; it is not presented as reflection about the midpoint of an entire sequence.

For residue indices i = 1, …, N, define a separate whole-sequence feature comparison:

$$f(i) \approx f(N + 1 - i)$$

Here f may be a prespecified residue-level structural descriptor, normalized flexibility measure, or accessibility score. A normalized asymmetry statistic may then be written:

$$A(f) = [\Sigma_{i=1}^{N} (f(i) - f(N + 1 - i))^2] / [\Sigma_{i=1}^{N} f(i)^2 + \varepsilon]$$

where $\varepsilon > 0$ is a stated stabilizing constant. A(f) is an illustrative, not experimentally calibrated, descriptor. Its use requires an explicitly chosen feature, normalization, conformational reference, and comparison set. It neither proves correct folding nor independently identifies Alzheimer's pathology.

2.3 Neurological Relevance and Structural Context

Disturbed proteostasis is a relevant setting in neurodegeneration, and aging-associated changes in chaperone networks provide a biological rationale for studying folding-capacity constraints [2,3]. Public Protein Data Bank entries 1IYT and 2LFM offer experimentally derived amyloid-β structural examples [4,5]. Entry 2LFM describes a partially folded amyloid-β(1–40) conformation; neither entry is a direct test of the energy–symmetry relationship advanced here. Future structural comparisons should include sufficiently broad conformational ensembles and controlled conditions rather than assume that two reference structures establish the proposed effect.

2.4 Falsifiable Predictions

The model yields the following experimentally assessable predictions when the feature, energetic perturbation, and statistical analysis are specified before data collection:

- In an amyloid-β-relevant system, a defined demand–capacity imbalance should be associated with an increase in the selected asymmetry statistic, after controlling for known folding and aggregation influences.
- Perturbations that alter effective proteostasis capacity in opposite directions should produce prespecified directional changes in both the asymmetry statistic and conformational-state distribution.
- The symmetry descriptor should add predictive information beyond peptide concentration, sequence composition, temperature, redox status, and chaperone-related measures.
- The effect should be evaluated in independent experimental batches, held-out conformations, and suitable negative controls; failure to generalize would limit the model's scope.
- If the association disappears when ATP supply and chaperone capacity are measured separately, the proposed energetic interpretation should be reconsidered.

2.5 Proposed Evaluation and Alternative Explanations

A prospective evaluation could pair energy-state indicators with controlled folding or aggregation assays, biophysical conformational readouts, and residue-resolved structural features. Molecular-dynamics calculations, if undertaken, would require transparent force-field settings, replicates, equilibration procedures, and convergence checks. Outcomes and directional predictions should be prespecified, with appropriate negative controls.

Alternative explanations include intrinsic sequence-specific aggregation propensity, peptide concentration, oxidative modifications, clearance dynamics, chaperone occupancy, and temperature-dependent conformational shifts. A reproducible association between energy imbalance and feature asymmetry would still need mechanistic analysis before causal or clinical claims could follow. Diagnostic biomarkers, energy buffering, and symmetry-directed chaperone mimetics remain possible future research questions, not demonstrated interventions.

3. Conclusion

The proposed framework combines an energy-dependent proteostasis concept with a restricted

symmetry relation and a separate, quantifiable whole-sequence feature descriptor. In the setting of Alzheimer's-associated amyloid-β misfolding, it defines testable relationships among energetic state, structural-feature asymmetry, and conformational outcomes. Its potential contribution is a mathematically explicit route for investigating molecular patterns in neurodegeneration, with experimentally distinguishable predictions and competing explanations.

Declarations

Data Availability

This theoretical communication reports no new datasets, experiments, molecular-dynamics runs, or patient data. Published structural examples are available through the RCSB Protein Data Bank (PDB 1IYT and 2LFM).

Ethics Approval and Consent

No human participants, animal experiments, or clinical interventions were involved in preparing this theoretical manuscript.

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Competing Interests

The author declares no conflicts of interest

Author Contributions

Begüm Yıldırım: conceptualization and original theoretical proposal.

Generative AI Disclosure

OpenAI ChatGPT (GPT-6) assisted with English-language editing, manuscript organization, and adaptation to the target journal's submission format. No measurements or simulation results were generated. The author is responsible for reviewing the scientific content, references, and final submission.

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