THERMODYNAMIC INHIBITION OF AMYLOID FIBRILLIZATION VIA LATTICE TERMINATION

A Crystallographic Approach to Alzheimer's Therapeutics using the Cabrera-Vermilyea Step-Pinning Model

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Abstract

We propose a therapeutic strategy for Alzheimer's Disease based not on biological receptor antagonism, but on **crystal growth inhibition physics**. Amyloid-β (Aβ) fibrils are formally treated as one-dimensional crystals growing via the screw-dislocation mechanism (BCF theory) along the crystallographic b-axis (4.7Å). We derive the specifications for **GeoNeuro-Alz1**, a peptide mimetic engineered to act as a "poison" impurity. Using the Cabrera-Vermilyea model, we demonstrate that a surface coverage of inhibitors satisfying the critical distance condition $L < 2r_c$ induces a thermodynamic arrest of fibril elongation ($v \to 0$) by increasing the Gibbs free energy of the step edge. This approach targets the invariant cross-β diffraction signature rather than mutable epitopes.

Keywords: Amyloid, BCF Theory, Cabrera-Vermilyea, Step Pinning, N-methylation, Steric Zipper, Crystallography.

1. Introduction: The Amyloid as a Crystal

The pathogenic agent in Alzheimer's is the Aβ(1-42) fibril. Structural biology (Eisenberg & Sawaya, 2005) has identified the fundamental unit as the **Steric Zipper**: a pair of β-sheets interdigitated with dry interfaces. From a physics perspective, the fibril is a 1D crystal growing anisotropically. The growth rate R is governed by the addition of monomers to the active "face" of the crystal.

1.1 Crystallographic Parameters

The target structure belongs to the Class 1 steric zippers (face-to-face, up-up).

- **Space Group:** $P2_1$ (typical for cross-β spines).
- **Unit Cell Dimensions:**
  - $a \approx 9.6\text{Å}$ (Inter-sheet distance)
  - $b = 4.7\text{Å}$ (Inter-strand distance, H-bonding axis)
  - $c \approx \text{variable}$ (Peptide length dependent)
- **Growth Vector:** $\vec{G} \parallel \vec{b}$.

Our objective is to reduce the growth rate along $\vec{b}$ to zero: $\lim_{t \to \infty} \frac{db}{dt} = 0$.

2. Theoretical Framework: Growth and Inhibition Kinetics

2.1 BCF Theory (Burton-Cabrera-Frank)

Fibril elongation is not diffusion-limited but reaction-limited at the crystal face. The growth rate v of a step on the crystal surface is given by:

$$v = \beta\Omega(C - C_e)$$

Where:

- β: Kinetic coefficient of the step.
- Ω: Atomic volume of the monomer.
- C: Bulk concentration of Aβ.
- C_e: Equilibrium solubility (critical concentration).

2.2 The Cabrera-Vermilyea (C-V) Model of Step Pinning

We introduce GeoNeuro-Alz1 as an immobile impurity adsorbed on the growth terrace. According to C-V theory (1958), the step front (the growing layer of the fibril) must curve to squeeze between two inhibitor molecules separated by a distance L.

The critical radius of curvature r_c is defined by the Kelvin-Gibbs equation:

$$r_c = \frac{\gamma\Omega}{k_B T \ln(S)}$$

Where:

- γ: Step edge free energy (surface tension).
- $S = C/C_e$: Supersaturation ratio.

The Inhibition Condition: If the distance L between adsorbed GeoNeuro molecules is less than the diameter of the critical nucleus ($2r_c$), the step cannot pass. It becomes "pinned".

$$v_{imp} = v_0 \sqrt{1 - \frac{2r_c}{L}}$$

When $L \to 2r_c$, then $v_{imp} \to 0$. **Conclusion:** We do not need to cover 100% of the surface. We only need a surface density σ of GeoNeuro such that the average spacing $L \approx \sigma^{-1/2}$ satisfies the pinning condition.

3. Molecular Design: The "Capping" Mechanism

To function as a C-V impurity, GeoNeuro-Alz1 must fulfill two thermodynamic criteria:

1. $\Delta G_{bind} \ll 0$**:** High affinity for the fibril tip (Adsorption).
2. $\Delta G_{elong} > 0$**:** Prohibit the addition of the next monomer (Termination).

3.1 The Scaffold: KLVFFA (Aβ_{16-22})

We utilize the hydrophobic core sequence Lys-Leu-Val-Phe-Phe-Ala.

- **Recognition:** This sequence creates the "dry interface" of the steric zipper (Sawaya et al., 2007).
- **Modulation:** We employ a macrocyclic constraint to pre-organize the peptide in β-strand conformation, reducing the entropic penalty of binding (ΔS_{bind}).

3.2 The Perturbation: N-Methylation

Standard peptide bonds allow Hydrogen Bonding: $N-H\cdots O=C$. We introduce **N-Methylation** ($N-CH_3$) at the amide nitrogen of Phenylalanine-19 (F_{19}).

Thermodynamic Consequence: The presence of $-CH_3$ instead of $-H$:

1. **Deletes the H-bond donor:** Energy penalty $\approx +3 \text{ to } +5 \text{ kcal/mol}$ for the incoming monomer.
2. **Steric Clash:** The Van der Waals radius of Methyl (2.0Å) is significantly larger than Hydrogen (1.2Å). In a lattice with spacing $b = 4.7\text{Å}$, a protrusion of 2.0Å perpendicular to the axis disrupts the stacking geometry.

The energy barrier for adding a new monomer ($\Delta G^{\ddagger}$) becomes:

$$\Delta G^{\ddagger}_{blocked} = \Delta G^{\ddagger}_{native} + \Delta H_{steric} + \Delta H_{H-bond\_loss}$$

This raises the activation energy effectively to infinity for biological timescales.

4. Falsifiable Predictions & Experimental Validation

To rigorously test this hypothesis, we propose the following experimental protocol:

4.1 ThT Fluorescence Kinetics (Macroscopic)

- **Prediction:** In the presence of GeoNeuro-Alz1 at sub-stoichiometric ratios (1:10), the lag phase (t_{lag}) should not change, but the elongation rate k_{app} must decrease asymptotically to zero.
- **Falsification:** If k_{app} remains constant, the C-V pinning model is incorrect.

4.2 Atomic Force Microscopy (AFM) (Mesoscopic)

- **Setup:** Observe individual fibril elongation on mica surfaces in fluid.
- **Prediction:** Addition of GeoNeuro should stop growth at the tips. The morphology should show "tapered" ends due to step curvature before pinning.

4.3 Micro-Electron Diffraction (MicroED) (Microscopic)

- **Setup:** Co-crystallize GeoNeuro with Aβ microcrystals.
- **Prediction:** The diffraction pattern should show high resolution (structure is ordered) but the crystal size along the c-axis (fibril axis) should be truncated. The electron density map

must show the Methyl group protruding into the solvent/interface layer.

5. Conclusion

Alzheimer's disease is treated here as a problem of **pathological crystallization**. By applying the BCF and Cabrera-Vermilyea theories of crystal growth, we have designed a specific "crystal poison" (GeoNeuro-Alz1). This molecule exploits the 4.7Å lattice constraint to create a thermodynamic barrier to elongation. This is not chemical suppression; it is geometric termination of a solid-state lattice.

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