A Multiscale Systems Biology Framework to Model mBDNF–proBDNF-Mediated Bifurcation Dynamics in CNS Neurotrophin Signaling

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VISUAL ABSTRACT

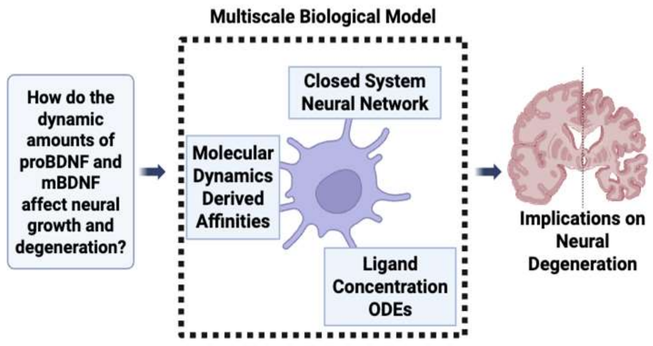

Fig 1. A visual abstract detailing the pipeline towards the model's implications on degeneration

INTRODUCTION

Brain-Derived Neurotrophic Factor (BDNF) is a protein that plays a significant role in the development and maintenance of plasticity of neurons inside of the central nervous system (CNS). **BDNF's role in neuronal modulation makes it a crucial regulator of brain health** (Wurzelmann et al., 2017).

- Mature BDNF (**mBDNF**) is synthesized by the cleavage of **proBDNF** (Wang et al., 2021)
- **mBDNF** binds to the Tropomyosin receptor kinase B (**TrkB**), which activates a signaling cascade for **neuronal growth**
- **proBDNF** activates a contrasting **apoptotic** signaling cascade through the **p75** neurotrophin receptor
- However, both mBDNF and proBDNF also have capabilities to bind to their opposite receptors

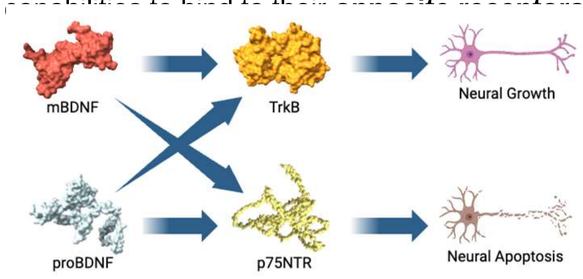

Fig 2. The interactions between the ligands and receptors that lead to their respective signaling cascades

Although widely regarded as important, **the complex dynamics of BDNF have been minimally explored in past literature** (Treble-Barna et al., 2023). This research aims to uncover the direct associations between BDNF levels and neuronal degeneration and a "tipping point" within BDNF concentrations that reveals onset of neurodegeneration.

METHODOLOGY

ORDINARY DIFFERENTIAL EQUATIONS

- Each neuron in the network contains a set of Ordinary Differential Equations (**ODEs**)
- Model concentrations of ligands, receptors, and complexes
- Affected by neuronal activity

$$\begin{aligned}\frac{d[\text{mBDNF}]}{dt} = &+ k_{\text{cleave}} \cdot [\text{tPA}] \cdot [\text{proBDNF}] \\ &- k_{\text{TrkB/on}} \cdot \text{aff}_{\text{TrkB}} \cdot [\text{mBDNF}] \cdot [\text{TrkB}] \\ &+ k_{\text{TrkB/off}} \cdot [\text{TrkB/mBDNF}] \\ &- k_{\text{p75/on}} \cdot \text{aff}_{\text{p75}} \cdot [\text{mBDNF}] \cdot [\text{p75}] \\ &+ k_{\text{p75/off}} \cdot [\text{p75/mBDNF}] \\ &- k_{\text{deg/mBDNF}} \cdot [\text{mBDNF}]\end{aligned}$$

CLOSED SYSTEM NEURAL NETWORK

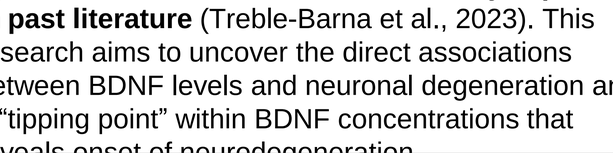

Fig 3. A simplified model of the layers within the neural network

- Neuron state determined by ODEs growth/apoptosis signal calculated through a monotonically increasing **hill function**
  - mBDNF and proBDNF densities would be input through **two sigmoid-type functions** that would determine a cell's growth and apoptotic response signals, respectively
- Stimulation Arbitrarily Applied to Layer 4
  - Activity **propagation** throughout network
  - **Activity levels** for each neuron are inputted to their internal ODE mechanisms
- **Synaptic edge weights** are controlled by the **states of the two neurons** they connect

DOCKING ANALYSIS

HOMOLOGY MODELING ALGORITHM

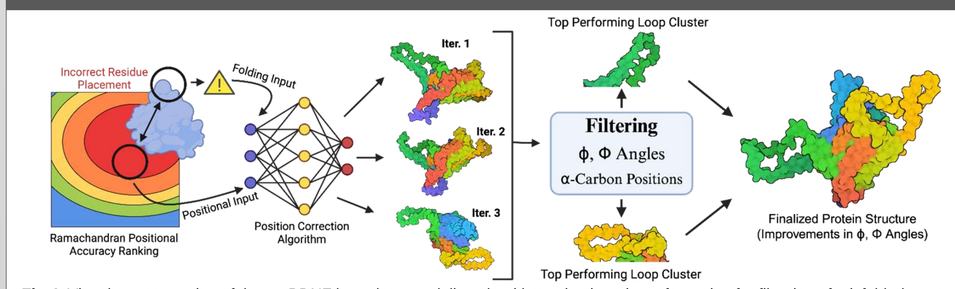

Fig 4. Visual representation of the proBDNF homology modeling algorithm using iterative reformation for filtration of misfolded structures

HOMOLOGY MODELING RESULTS

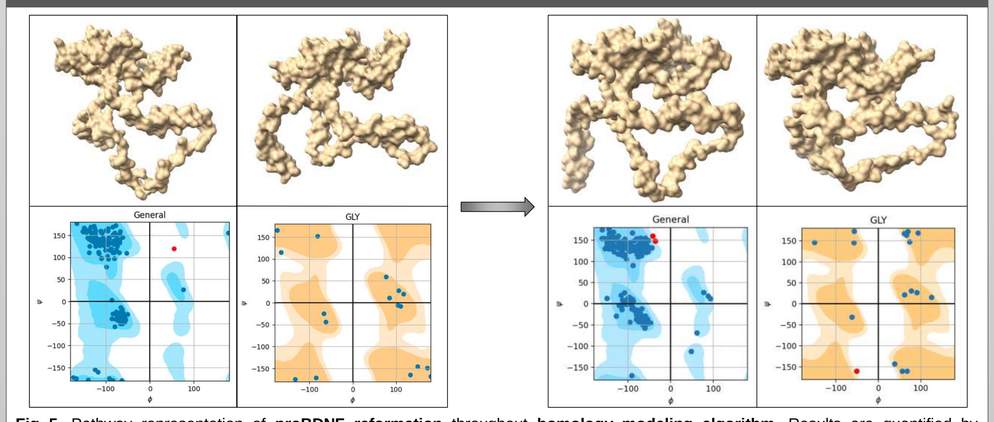

Fig 5. Pathway representation of **proBDNF reformation** throughout **homology modeling algorithm**. Results are quantified by analyzing Ramachandran plots of **regular amino acid residues** vs **glycine-specific (flexible) residues**

LOW-RESOLUTION DOCKING AND MOLECULAR DYNAMICS

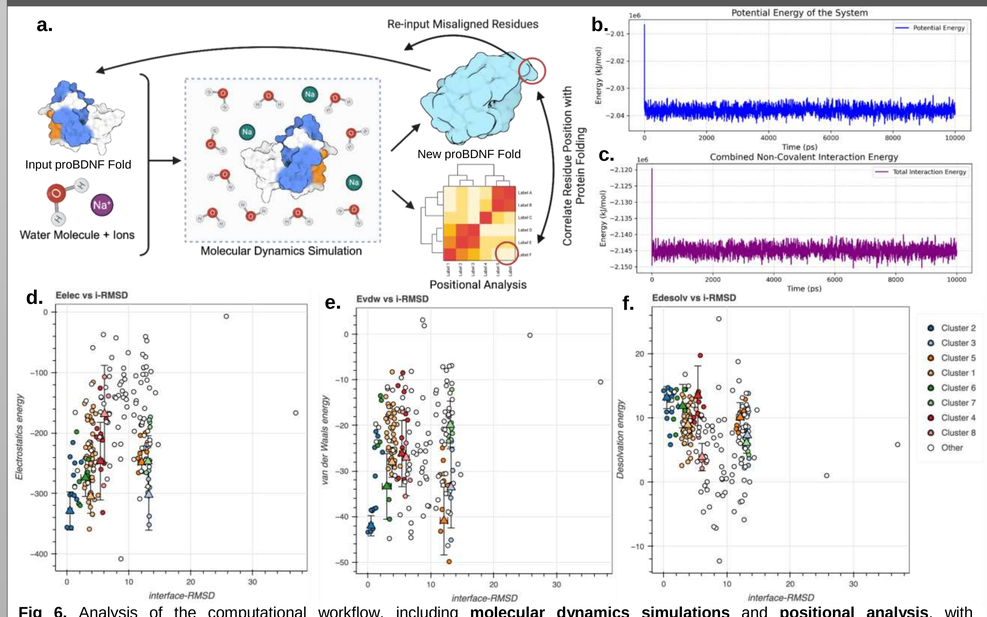

Fig 6. Analysis of the computational workflow, including **molecular dynamics simulations** and **positional analysis**, with corresponding plots showing (b) potential energy, (c) combined non-covalent interaction energy, and the **relationship** between interface-RMSD and (d) electrostatic energy, (e) van der Waals energy, and (f) desolvation energy.

RESULTS

Fig. 7: Connection Survival vs proBDNF/mBDNF Ratio Analysis identifies a initial critical ratio of 7.1 proBDNF/mBDNF that governs a system-wide bifurcation from neuronal survival to apoptosis. Pearson Correlation: r=-0.512, p=0.0006 (Significant), Spearman Correlation: ρ=-0.449, p=0.0033 (Significant), Linear Regression: R^2=0.262, Piecewise R^2=0.650, Breakpoint=7.1, Improvement from Linear=38.9% better fit.

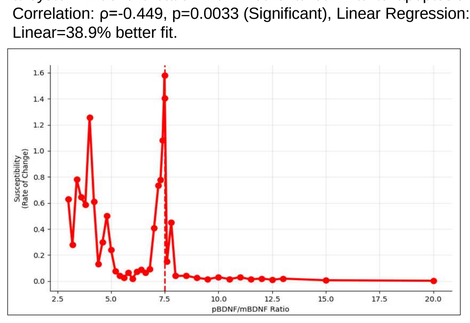

Fig. 8: System susceptibility identifies critical BDNF ratio Neural Network collapse

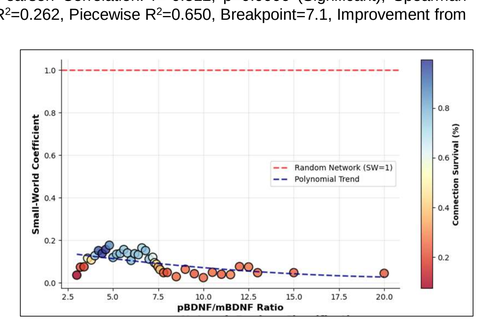

Fig. 9: Small-World Property vs Ratio shows linear decline in small-world network efficiency with increasing BDNF ratio

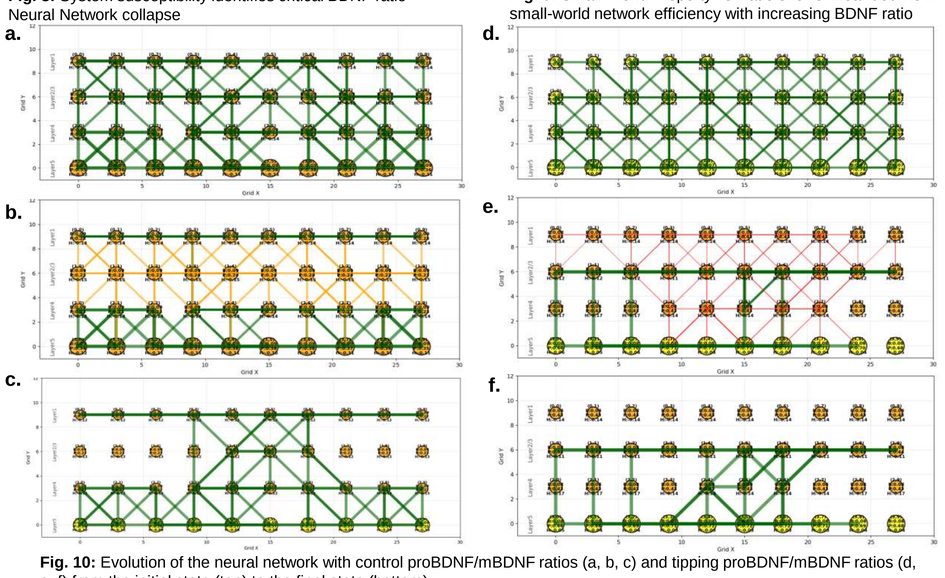

Fig. 10: Evolution of the neural network with control proBDNF/mBDNF ratios (a, b, c) and tipping proBDNF/mBDNF ratios (d, e, f) from the initial state (top) to the final state (bottom).

DISCUSSION

CONCLUSIONS

- Modeling mBDNF, proBDNF, and conjugate receptor activity holds potential to identify **"tipping-point" ratios** which signal the **onset of neuronal degeneration.**
- A ratio of 7.1 between proBDNF and mBDNF was found to be a **critical point** where the graph upsets in its trend (Fig. 7).
- A **piecewise regression** had a 38.9% improvement in R^2 value compared to a linear regression (Fig. 7). This further supports that a **"tipping point" exists**.

The framework provides a **quantifiable approach** to assess and optimize the efficacy of treatments for neurodegenerative disorders.

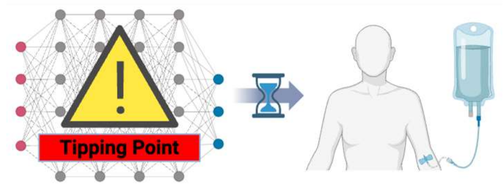

Fig 11. A utilization of the tipping point in improving therapeutic efficiency

LIMITATIONS

Conclusions are drawn under a **closed-system assumption**, accounting only for the modeled proBDNF/mBDNF–receptor dynamics **without external modulatory influences**. (Fig. 10)

- **Limited data on auxiliary pathway components** means the model omits certain factors, thereby not comprehensively reflecting in vivo biological complexity

FUTURE WORK

- Research and integrate intermediaries and feedback loops in **post-complex-activation** signaling cascades to improve biological accuracy
- Perform in vitro experiments to measure actual proBDNF/mBDNF ratios and **validate the predicted bifurcation threshold**
- Creation of **bispecific antibodies** to activate the TrkB cascade

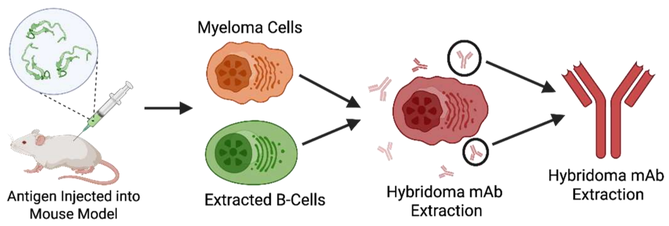

Fig 12. Visual representation of mAB development pipeline

The de novo structural elucidation of a previously uncharacterized isoform of proBDNF not only allows for further research in this space but may **inform the design of artificial proteases to precisely cleave proBDNF and promote neuroprotection.**

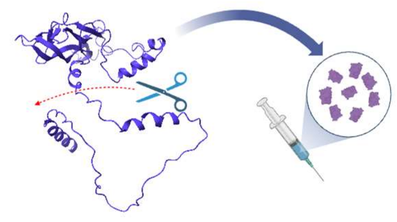

Fig. 13 A proposed extraction of mBDNF from proBDNF for degeneration therapy

REFERENCES

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