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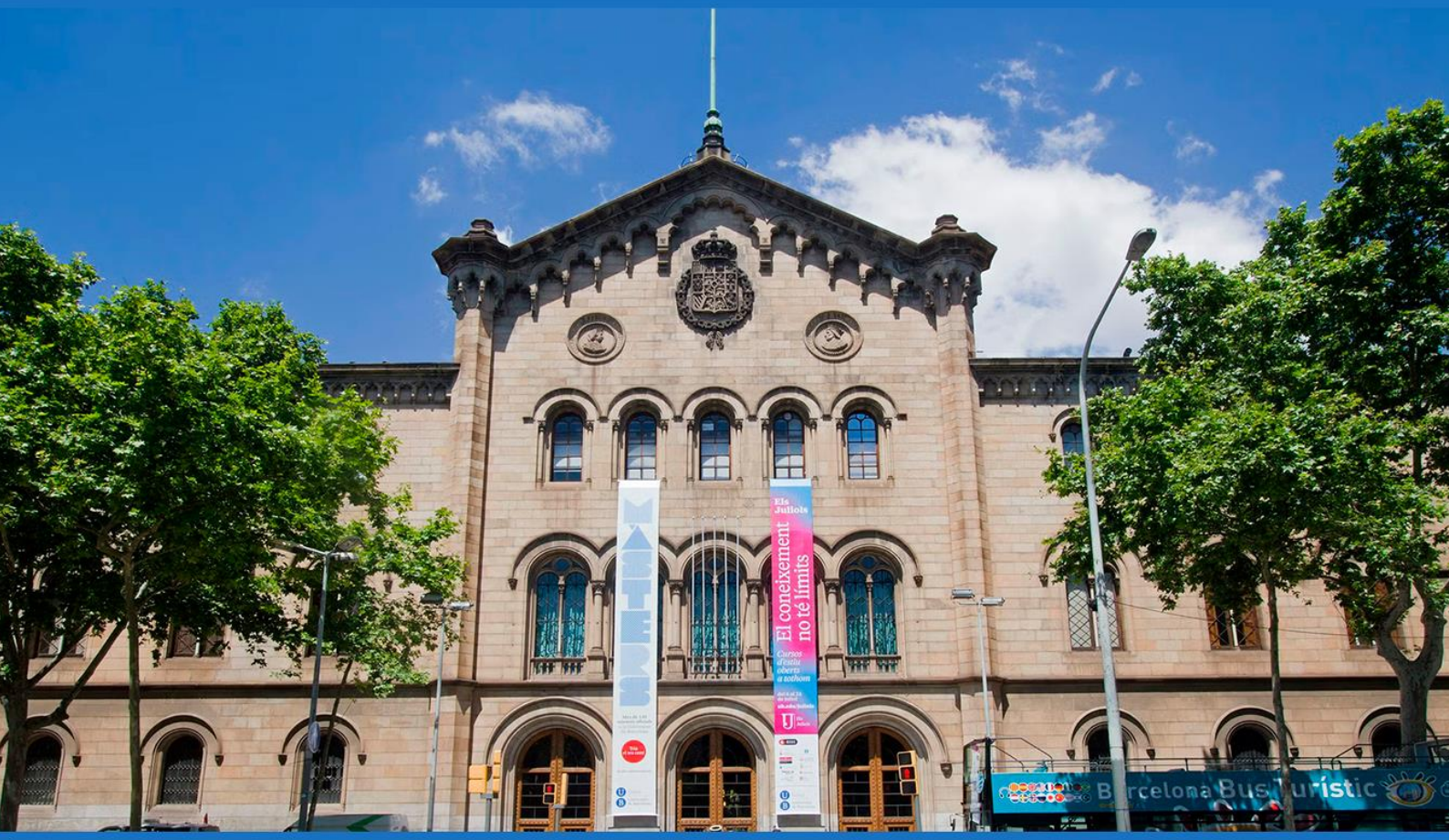

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AN ANTITRANSITIVE APPROACH TO NEURO-METABOLIC DISORDER: COMPUTATIONAL DESIGN OF TARGET COMBINATIONS TO DISRUPT PATHOLOGICAL FEEDBACK LOOPS

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Introduction. Neuronal and glial networks are governed by intricate molecular interactions that stabilize specific operational states. Within the framework of systems biology, health is characterized by a stable, homeostatic attractor state – a condition maintained by robust negative feedback control loops [1]. Chronic neurodegenerative conditions, e. g. Alzheimer's Disease (AD), represent a basic departure from this ideal, manifesting as a shift into a robust, high-pathology attractor state that resists spontaneous reversal. The observed clinical resilience of AD progression is structurally enforced by self-sustaining molecular circuitry.

The primary molecular architects of this pathological stability are positive feedback loops (PFLs), referred as "vicious cycles" [2]. PFLs could be described within switch-like, irreversible behavior known as bistability or multi-stationarity [3]. Bistability means the system can stably exist in two distinct states – a low-pathology (healthy) state and a high-pathology (diseased) state – without needing continuous stimulation to remain diseased. The transition into the high-pathology one often triggered by age or environmental factors, is highly robust, requiring a large external perturbation or, ideally, a structural alteration of the network itself to force a return to the healthy equilibrium [5].

The pathology of AD is entangled network of mutually reinforcing vicious cycles, encompassing Amyloid-β (Aβ) accumulation, tauopathy, oxidative stress (OS), inflammation, and calcium dysregulation [2]. The canonical loop often

modeled involves Aβ, OS, and Inflammation.

Topologically, this cycle forms a series of interlocking positive triangles: Aβ accumulation induces OS [12], OS promotes glial activation and inflammation [13], and inflammation, in turn, accelerates Aβ production and aggregation [14]. Specifically, OS is known to increase the expression and activity of β-secretase (BACE1), thereby accelerating Aβ production [12]. Aβ exposure generates Reactive Oxygen Species (ROS) via protein kinase C and NADPH-dependent oxidases [11]. Activated glial cells (microglia and astrocytes) responde to inflammatory cues via releasing toxic radicals, which exacerbates neuronal damage and amplifies the inflammatory response [13].

The high density of positive connections (triangles) within this core AD pathway implies that the local topology of the neuro-metabolic network is profoundly altered in a high local transitivity index among the nodes governing Aβ, OS, and inflammation is a quantifiable structural biomarker of the established, robustly stable disease state. Any effective intervention must aim to structurally reduce this local transitivity, to turn the densely clustered pathological motif into a controllable, linear, or dampening circuit [14].

Aim. To propose the computational design of MTDLs to disrupt pathological PFLs by enforcing a structural, non-transitive relationship within the molecular network, thereby qualitatively reversing the net feedback sign and forcing a system-wide transition from a pathological bistable state back to a stable, healthy monostable state.

Materials and Methods. The study uses a comprehensive computational approach (in silico) based on systems biology and network control theory to develop a novel therapeutic strategy against AD. The basic principle is to structurally alter the topology of the biochemical network that supports the pathological state.

Results and discussion. In mathematical graph theory, a binary relation R is transitive if, given three values A, B and C, the conditions ARB and BRC necessitate ARC. Antitransitivity is the property where this condition fails: one can find A, B, C such that A→B and B→C, but A→C does not exist in the expected cascading manner

[15].

The therapeutic goal is to design a Multi-Target Drug Ligand (MTDL), D_{anti}, that introduces a structural failure of transitivity into the AD vicious cycle. If we define the PFL in AD as the sequential activation chain:

$$A\beta \xrightarrow{Activation} \text{OS} \xrightarrow{Activation} \text{Inflammation}$$

Transitivity dictates that Aβ ultimately drives inflammation. The antitransitive drug D_{anti} is designed to enforce:

$$A\beta \rightarrow OS \; and \; OS \rightarrow Inflammation \; but \; A\beta \nrightarrow Inflamation \; due \; to \; D_{anti}$$

This is achieved by D_{anti} simultaneously targeting an upstream component, A, and a downstream component, C, in such a way that the net effect of the upstream component on the downstream component is neutralized or reversed, thereby short-circuiting the positive feedback sign. This structural change is what converts the pathological positive (vicious) loop into a negative (dampening) loop.

The proposed strategy is fundamentally distinct from traditional polypharmacology. While many MTDLs seek quantitative synergy – where the combined effect exceeds the simple additive sum (often quantified using metrics like the Combination Index (CI) [11] or comparison against null reference models such as Loewe additivity or Bliss independence [4]) – antitransitivity demands a qualitative, structural reversal of the pathological dynamics.

The therapeutic gain must manifest as the introduction of an inhibitory link, drasticly changing the sign of the overall feedback loop from positive to negative. The combined inhibitory effects of the MTDL must be strong enough to overcome the entrenched resilience of the PFL. The MTDL achieves therapeutic selectivity because the structural disruption is most potent in the environment where both targets are pathologically hyperactive (inflamed), e. g. OS-laden AD brain [7].

The successful outcome of an antitransitive intervention is the establishment of a stable, therapeutic, homeostatic state governed by negative feedback principles [1]. Negative feedback loops (NFLs) are primal for stabilizing regulatory systems, allowing them to approach a steady state rapidly [9]. The design must account for the specific dynamics of NFLs: if the feedback is too strong or the loop is too long, the

system may become unstable, potentially generating limit cycle oscillations rather than returning to a steady state [9]. The D_{anti} must therefore introduce a highly constrained NFL that is strong enough to dominate the PFL's influence but optimized to avoid overshooting or oscillatory instability.

The core mathematical demonstration of therapeutic success is the elimination of the pathological attractor state. PFLs generate bistability because of specific reaction kinetics, notably "ultrasensitive" positive feedback and specific back reactions that saturate [4]. These systems exhibit multiple stable fixed points. The introduction of the antitransitive intervention must fundamentally alter the system's kinetic parameters to eliminate these conditions.

The therapeutic D_{anti} aims to shift the balance of production and degradation rates of the key pathological components (Aβ, OS, Inflam) such that the bifurcation point is crossed [5]. The intervention must guarantee that the high-concentration pathological fixed point is annihilated, leaving only the low-concentration (healthy) monostable state as the single viable steady state [5] This proves a systemic reset.

The success of the antitransitive strategy can be monitored by assessing the topological change in the pathological network cluster. The loss of metabolic homeostasis associated with disease is reflected by measurable changes in network topology. We employ the weighted transitivity index, which quantifies local triangle density [14]. Successful D_{anti} intervention should result in a return of the locally weighted transitivity index of AD-relevant network nodes (Aβ, OS, Inflammation) to the value observed in the healthy, tightly regulated network state. This index serves as a quantitative structural indicator of the system's transition from a persistently clustered pathological state to a stable homeostatic topology.

Ordinary differential equations (ODE) provide the necessary kinetic framework for modeling the coupled feedback loops of AD [2]. The basic kinetic model will be a system of coupled ODEs describing the rates $\frac{d[A\beta]}{dt}, \frac{d[OS]}{dt}, \frac{d[Inflammation]}{dt}$. These equations must include nonlinear terms, typically represented by generalized Hill functions, to accurately capture the switch-like activation dynamics inherent in PFL [10]. Linear models are insufficient to describe the bistability that defines the disease

state.

The MTDL intervention, D_{anti}, is incorporated into this system as an inhibitory term, I(D_{anti}), affecting the rate equations of the targeted species [8]. Crucially, to model antitransitivity accurately, the model must move beyond simple additive or multiplicative inhibition. The response surface models based on generalized Hill-type models are required to explicitly parameterize the non-linear interaction terms ($\delta_{\alpha\beta}, \delta_{xy}$, etc.) that quantify the unique non-additive gain arising from the combination [12]. This mathematical rigor is essential because kinetic models attempting combination interventions have previously found caution is necessary, as clear synergy is not always guaranteed, even when targeting vicious cycles [2]. Modeling these explicit drug interaction terms ensures accurate quantification and modeling of antitransitive amplification.

As ODEs provide quantitative kinetic data, Boolean Networks (BNs) offer a computationally efficient method for analyzing regulatory logic and identifying system attractors [3]. BNs model regulatory interactions discretely (ON/OFF states), allowing rapid identification of stable fixed points (corresponding to the diseased attractor state) or limit cycles [4].

Main application of BNs in this framework is the identification of the positive feedback vertex set (P) [3]. This set represents the minimum collection of nodes whose external control (inhibition or activation) is necessary to force the network into a desired (healthy) fixed point. Trough analyzing the regulatory graph of the Aβ/OS/Inflammation network, we can identify the smallest and most impactful set P that guarantees the collapse of the positive cycle dynamics jointly targeted by the MTDL [5].

Target selection must maximize topological disruption. Computational network fragility analysis with tools like NetworkPrioritizer, is created to compute various centrality measures (Degree, Betweenness, Closeness). High centrality indicates that a node is an interaction hub of many molecules, making us suggest that its modulation will yield the greatest systemic effect [6].

To optimize antitransitive design we need to select two or more highly central

nodes that are topologically separated but yet connect the key components of the PFL. The MTDL must exploit the scale-free nature of biological networks with information funneling hubs [6], by targeting multiple points around these hubs simultaneously to prevent compensatory signaling [7].

Conclusions. The conceptualization of neurodegenerative disease as a robust dynamical system stabilized by positive feedback loops necessitates a therapeutic paradigm shift. The antitransitive intervention strategy offers a path toward a fundamental therapeutic reset. By enforcing a non-transitive relation across the vicious cycle, the MTDL structurally reverses the net feedback sign, breaking the pathological bistable state into a stable, healthy monostable attractor. The integration of ODE kinetics, Boolean network analysis for critical node identification, and advanced parameterized synergy modeling provides the necessary computational rigor to transition this control theory concept into a viable, disease-modifying strategy for AD.

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