

Dynamics of Amyloid Beta Protein Signaling under Complexity Reduction: A Mathematical Modeling and BooleSim Simulation Approach

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Abstract. Understanding how complex biological systems behave over time is essential for predicting their future states, especially when studying Alzheimer's disease. Mathematical modeling of such systems offers a valuable approach to exploring not only theoretical aspects of network behavior but also their biological and medical implications. This study investigates how reducing the complexity of the amyloid-beta signaling pathway influences its dynamic behavior. We apply Boolean modeling and network simulations in BooleSim using data from the SIGNOR database under different initial conditions that reflect healthy and disease-related cellular states. Complexity reduction involved removing non-essential interactions and simplifying regulatory motifs. Our findings show that while simplification can shorten the time to reach steady states, it does not eliminate important regulatory pathways unless critical nodes are removed. Importantly, pro-disease nodes such as BAX and GSK3 β retained their functional significance even in simplified models, confirming their central role in Alzheimer's pathology and supporting their relevance as potential therapeutic targets, consistent with current Alzheimer's drug development strategies. This work illustrates how simplified Boolean modeling can provide a practical framework for analyzing neurodegenerative systems while preserving essential biological insights.

Keywords: *Mathematical modeling, Complexity, Alzheimer's disease, Boolean model, Signaling pathway*

1. Introduction

In modern biomedicine, understanding and interpreting the complicated interplay of molecular entities within biological systems and linking it with a specific diagnosis or health issues is eventually a fundamental challenge and is additionally on the attention of

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scientists [1, 2]. The complexity that encompasses all the interactions between genes, proteins, and other biomolecules underlies the dynamic behavior of these systems and gives us all the motivation to study such complex networks [3, 4]. This type of research is as complex as the system dynamic behavior we want to study, as it requires the combination of systems biology principles, network theory analysis, and mathematical background to construct suitable mathematical models (discrete or continuous) that can capture the time-dependent dynamics of the complex interactions characterizing the biological network [3]. Through these models, we can further integrate experimental data and use computational simulations of cell signaling pathways, protein–protein interactions, and gene regulatory networks, enabling us to highlight and analyze the roles of key molecular actors in nonlinear behavior, uncover hidden interactions and feedback loops, and predict different system responses to perturbations as primarily suggested by Kauffman [5] and from other scientists later on [6–8]. On this focus, this research delves into the intriguing question of how reducing complexity within a network related to a specific health condition influences its dynamic behavior and the attainment of its steady states. Our study employs various strategies, including the removal of less important influential connections from the network, simplification of regulatory motifs, and reduction of network size. Through rigorous analysis, we uncover how such simplifications alter the speed, stability, and trajectory of the network’s transition towards steady states.

We conduct our study on a biological network associated with a specific health condition such as Alzheimer’s and represented by the signaling Alzheimer Pathway of Amyloid beta precursor protein (App) generated by SIGNOR [9]. We aim to study this system’s behavior by unraveling its represented network structural dynamics and analyzing its stable states with the purpose to understand the dynamics of such a neurodegenerative disease [10]. Alzheimer’s disease is the most common cause of dementia in humans, affecting over 50 million people worldwide [11, 12]. It is driven by the accumulation of amyloid beta plaques and tau tangles, which lead to the degeneration and death of neurons. This high prevalence results in an enormous global economic and social burden, arising both from patient care and from the ongoing need for research into the causes, mechanisms, and treatment strategies for Alzheimer’s. Currently, there is no definitive cure or reliable method for early diagnosis and treatment. For this reason, Alzheimer’s remains an active area of study not only at the experimental and clinical levels but also through computational and mathematical approaches. In particular, mathematical modeling provides a low-cost tool for understanding the molecular mechanisms that underlie this disease and for identifying potential therapeutic strategies. Using network analysis of the network on focus, we dissect its structural topology and explore network properties to define the most important elements of the system that have key roles in signaling pathways [13–15]. Dynamic evolution of the system depends precisely on the behavior of these most important elements of the biological network, for the study of which mathematical modeling is necessary to be implemented [16]. We base our study on Boolean modeling, a discrete simplified mathematical model applied to make other evaluations of the most important nodes that are now distinguished by less complexity [17, 18].

In combination with Boolean modeling, BooleSim simulation is used to investigate the impact of complexity reduction on the attainment of fixed points—stable states [17, 19]. This methodology is an important tool to understand how biological mechanisms interact with each other, and on the other hand to understand why some medical interventions fail even though experimental data seemed to promise success. For this reason, where there is a lack of in-depth experimental data or where it is difficult to conduct experiments initiated even by clinical indications, the mathematical models such as Boolean model can intervene by shedding light on finding the reasons for the malfunction of a specific treatment or on the initiation of a new treatment [10, 20, 21]. In most of the cases, considering very big

networks, complexity reduction may lead to the loss of critical pathways and critical regulatory nodes that can be crucial for signaling pathways [22, 23]. Interestingly, in our case, we found out that complexity reduction decreases a bit the time of convergence to steady states but it did not make the system lose its critical pathways or change the behavior of the most important nodes. This outcome can indicate that the biological network of signaling Alzheimer Pathway of Amyloid beta precursor protein (App) possesses inherent robustness or redundancy, where multiple pathways can be chosen to transmit the biochemical signals and biological information without affecting the system behavior, indicating we have a symmetric biological network [24, 25]. Moreover, network analysis shows that the most important nodes of the system, which are not affected by the complexity reduction rules, coincide with those identified by experimental data. This indicates that the eliminated nodes are not biologically critical for the dynamics captured by the Boolean model [22]. As a result, the future state of the system depends only on the initial state of these key nodes and the network inputs [22, 26]. It is worth noting that if a crucial node such as GSK3 β is removed, the system becomes asymmetric and the signal transmission is interrupted, leading to a pathological situation [24, 27]. The final fate of the cell—Apoptosis—is therefore defined by the state of a small set of essential nodes, including TNF, APP, GSK3 β , BAX, CASP8, BCL2, and PSEN1. Altogether, these findings enhance our understanding of how network architecture and complexity shape dynamic behavior, highlighting the trade-offs between simplification and biological accuracy.

2. Materials and Methodology

SIGNOR is a website that often integrates curated experimental evidences [9]. In this study we used the Amyloid Beta Precursor Protein (APP) signaling pathway from SIGNOR, which is composed of 28 elements where there are 25 different proteins and three different phenotypes, and 50 links indicating activation (green link), inhibition (red link), and one link connecting APP with GSK3B (grey link) that indicates there is an unspecified interaction between these two elements. This type of link is there because scientists working on building this biological network believe that there is an interaction between the two elements but there is not enough experimental evidence to show if it represents an activation or inhibition [9]. In this network, all links are accompanied by a confidence score between 0 and 1, showing a coefficient that is attributed to each interaction based on experimental evidence and giving assurance of existence for each link separately (Fig. A1).

The Boolean network of Amyloid Beta Precursor Protein (APP) signaling pathway was first modeled and simulated via BooleSim [19] as a full system, with the purpose to later identify the differences in results after the complexity reduction is applied. For this reason, Boolean rules were built according to the information we received from the full biological network and experimental data available. Nevertheless, there are cases where there is a lack of information and in these cases suitable Boolean rules are assumed based on logical reasoning, as described in previous studies [17, 28]. Generally speaking, the Boolean model is based on logical rules AND, OR, NOT, which are defined upon the need for activating or inhibiting each element by more than one biological neighbor affecting its behavior. Logical operator OR can be used when more than one independent node can activate/inhibit the same node, while AND operator is used when it is necessary for all nodes to act simultaneously at the same time on the same node. Each node can have two possible binary states: 1 (ON) indicating a healthy or active state of the node and 0 (OFF) indicating an unhealthy or inactive state of it [20, 26]. After building the Boolean model, we ran it to finalize Boolean modeling using BooleSim simulation to synchronously update the state of the nodes [19, 20]. Worth emphasizing is that this simulation works every time under the

condition of starting the evolution by just one specific initial state of the system. This initial state was determined according to the experimental and clinical evidence reported in several previous studies. Our purpose is to explore how our system behaves when its most important nodes are supposed to be initially in different states from what evidence shows [29].

2.1 Boolean model of the biological networks

As mentioned above, the evolution of the biological system depends on the logical rules for all the key elements of that system. This is why we are interested in explaining the logic and the methodology we have followed to build Boolean rules for all these elements. According to the experimental evidence, CASP8 is activated if both adaptor proteins TRADD and FADD are active (ON). Initially, TRADD is activated by the TNF receptor and then it recruits FADD to both activate CASP8 at the same time [30, 31]. If one of them is missing then CASP8 is not properly activated, and for this reason logical operator AND must be used. Experimental evidence shows that CASP3 is active if either CASP8 or apoptosome. Although these two entities are not fully independent, as shown in the network, the operator OR can be used in this case because, biologically, CASP8 and apoptosome contribute to an active state of CASP3 through independent pathways of formation [32, 33, 40].

CASP8	FADD && TRADD
CASP3	CASP8 Apoptosome

Apoptosome is a complex protein which is activated through the green edge coming from APAF1, and this means that APAF1 positively contributes to the active formation and function of the apoptosome, and this is done through a complex formation. CYCS is activated when CASP8, BID, and BAX are active (ON) and BCL2 is not active (OFF). Experimental evidence shows that an active BCL2 inhibits CYCS [33]. Edges represented by dashed lines are shown by SIGNOR 3 to represent indirect interactions between nodes that are connected through them. The presence of these links affects the Boolean rules because the entities connected through dashed links are supposed not to be included as direct inputs unless the intermediate nodes that mediate their effect are included. In cases where biological data are not enough, then all nodes should be considered [7, 28, 29]. In our case, a biologically accurate Boolean rule for the activation of CYCS requires all nodes included and the use of AND because all of them are required to be present.

CYCS	CASP8 && BID && BAX && !BCL2
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BAX is inhibited by BCL2, while being activated by either GSK3β or BID, since they both can activate BAX independently from each other [34], so the operator OR should be used between them.

BAX	!BCL2 && (BID GSK3B)
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PSEN2 is independently activated by either CASP3, CASP8, or NCSTN. The other complex protein, γ-secretase, is up-regulated by NCSTN, which activates it through a complex formation (green edge), and by PSEN1 simultaneously because both are essential

for an active γ -secretase. PSEN1 is active when being activated by either active NCSTN, CASP8, or CASP3, and an inactive GSK3 β [35, 36].

PSEN1	(NCSTN CASP8 CASP3) && !GSK3B
PSEN2	CASP3 CASP8 NCSTN

Between nodes APP and GSK3 β there is shown to be a grey link which, according to SIGNOR 3, indicates an undefined causal relationship, but the nature of its effect—activation or inhibition—is unknown or not specified. Nevertheless, evidence shows that in Alzheimer’s disease GSK3 β leads to increased APP processing, meaning that there might be a positive up-regulated effect of GSK3 β on APP [37]. For this reason, this activation link is considered part of our Boolean model.

APP	gamma_secretase GSK3B
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CDK5/CDK5R1 is a kinase catalytic subunit that, to be active (ON), requires both activators CDK5R1 and CAPN1 to be active at the same time [38], so AND should be used to maintain the biological conditions. The network shows that MAPT is active if none of the nodes—CDK5/CDK5R1, CAPN1, GSK3A, and GSK3 β —are inactive (OFF) [39,40]. Thus, if any of them is active, MAPT will be inhibited, so the logical operator OR can be used.

MAPT	!CDK5_CDK5R1 !CAPN1 !GSK3A !GSK3B
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There are three phenotypes for the cell indicated by this network that are related to Alzheimer’s disease (AD): Amyloid_fibril_formation, Neurofibrillary_tangle_formation, and Apoptosis [9]. The first two phenotypes are activated by only one other protein—APP and MAPT, respectively—while Apoptosis is upregulated independently by seven entities, and only one of them, BCL2, inhibits it. The network shows indirect edges between phenotypes and proteins indicating activation through a complex formation. According to this network, it seems that despite there being three different phenotypes, there is only one that determines the final state of the cell, i.e., Apoptosis, and this is a crucial element to consider in Boolean modeling of our network.

Apoptosis	(Amyloid_fibril_formation NAE1 BAX CASP3 CASP8 Neurofibrillary_tangle_formation) && !BCL2
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2.2 Network Complexity Reduction Strategy and the New Boolean Modeling

In this study, we reduced the complexity of the original biological network by filtering the network based on the confidence score coefficient that characterizes each link, as well as considering the topological characteristics of the network, as described in Table A1. The reduction was not done immediately at once, but step by step, with the purpose of observing any small difference that might occur from one simulation to the other. The first reduction process resulted in a smaller network with fewer nodes (20 nodes, 3 of which are still the phenotypes and 17 are proteins) and 38 links. “Leaf” and “Intermediate” nodes were removed in this step, along with the links connecting them to their neighbors (Tab. A2). It is important to emphasize that while some intermediate nodes were removed, others were

created as a result of this process, which were also subsequently removed from the network. Here, we did not remove phenotypes that could also be considered intermediate (Amyloid fibril formation and Neurofibrillary tangle formation) or a “Leaf” node (Apoptosis). Finally, the Boolean model, unlike the first one explained above, is now simplified, and only one rule is different: the one for Apoptosis.

Apoptosis	(Amyloid_fibril_formation APP BAX CASP3 CASP8 Neurofibrillary_tangle_formation) && !BCL2
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The second reduction consisted in choosing from SIGNOR the Aβ pathways that reflect only the connections that have confidence score coefficients greater than or equal to 0.5. As a result of this, the new reduced biological network is characterized by fewer links (28 links) because this process had a direct effect primarily on the number of links, and 19 nodes (Fig. 1). Nevertheless, because of this reduction, GSK3A was removed as a consequence of the removal of links connected to it. For this new biological simplified network, the new and final Boolean model is the most simplified one and the Boolean rules for the most important nodes are presented in Table A3.

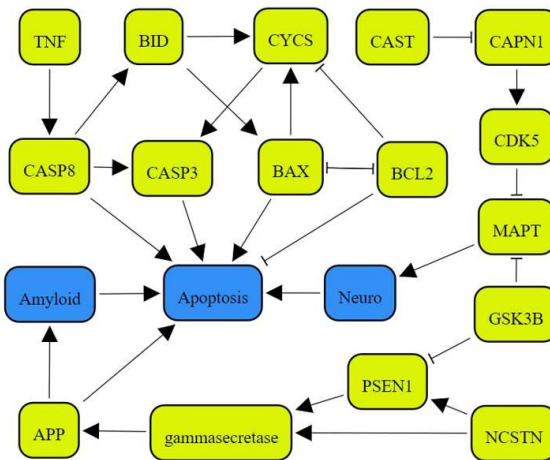


Figure 1. The most simplified biological network, produced by BooleSim, after two processes of network complexity reduction.

3. Results

When nodes that are pro-disease (Tab. A4) are in an active state (ON) this can indicate the Alzheimer’s disease presence because of the active pathological state that a patient can be. On the contrary, when these nodes are inactive (OFF) this indicated a healthy state of the system and the patient, consequently is not a target of getting the disease. Our results show that sometimes the final state of the system is a fixed point and in some other cases it enters into a limit cycle (Tab. A5). While the conclusions above are related to the fixed points, i.e. stable states of the system, our simulations show also few different results when instead of stable states, limit cycles are reached. We suggest that limit cycle in the (Aβ) signaling

pathways indicates unresolved signaling so that the system fails to commit to active apoptosis. Since, the state of the pro-disease proteins switch continuously from active to passive and vice versa, the biological state of the system indicates instability of the system, stress and/or confusion that might reflect a chronic disease or an unsolved pathological state.

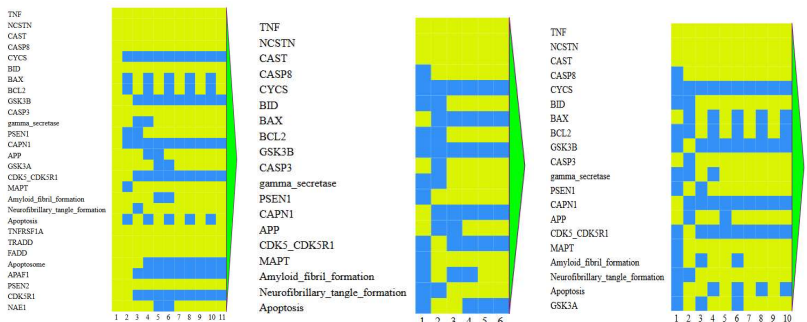


Figure 2. Dynamic simulation cases of three different systems starting from different initial states. Full simulations are given in the Appendix.

As a result of our simulations, partially presented in Fig. 2, (full simulations are given in the Appendix section in Fig. A2, Fig. A3, Fig. A4) we see that, despite the reduction, when all nodes are initially active the system enters in a limit cycle composed by 2 different states, causing Apoptosis to jump from active to inactive infinitely. On the contrary, when the initial state is composed by nodes that are all inactive we see that the system converges in a fixed point. In this case a healthy final stable state is reached where Apoptosis is OFF, indicating a cell survival.

When the system is initially in a healthy state or in an early stage disease it converges in a healthy final stable state, while when the system is initially in a moderate to severe disease state it converges in a SICK final stable state. In both cases the final state is determined by the final state of Apoptosis which remains OFF (healthy) and ON (sick), respectively.

All the results reached so far were same for all networks. The differences between the full network and the reduced ones begin to appear when the system is initially in an apoptotic trigger with all the inputs being active (ON). In this case, the system converges in a healthy final stable state, where Apoptosis remain OFF, and this is same for the full and the 2nd reduced networks. For the 1st reduced network system enters in a limit cycle composed by two states causing Apoptosis to jump from active to inactive infinitely. The simulation gives a different approach of the system when it is initially in an apoptotic trigger with all inputs being inactive (OFF). In this situation, the system converges in a healthy final stable state only in the 2nd reduced network while for the full and the 1st reduced network system enters in a limit cycle composed by 2 states causing Apoptosis to jump from active to inactive infinitely.

4. Discussion

When pro-disease nodes remain in an inactive state the biological processes connected to the disease are not yet triggered, but when these pro-disease entities are initially active this

indicates that amyloid cascade may start (if APP = 1), or hyper activation of it is about to start. Furthermore, if the final state of the Apoptosis is active (ON) it means that some disease symptoms are already present and that the disease is ongoing indicating a degenerative process of cell that will send it to death. On the other side, when the final state of Apoptosis is inactive (OFF) then the cell remains alive, despite the fact that some pro-disease proteins might be initially active. As a result, the patient is in a healthy state indicating that there is not enough dysregulation and the signaling cannot trigger death pathways. It is very important to emphasize that protein BCL2 is an active protector and when it is initially ON, or when it evolves toward the active state, than the protection against amyloid cascade is activated, leading to an inactive Apoptosis. In this state the system's protective response to the disease is dominant and neurons are avoiding death. Interestingly, when being in the early stage disease, apoptosis is initially ON but then it evolves toward an inactive state and gets stuck in the OFF state, indicating that the patient remains somehow healthy, although some biological processes connected to the disease might have appear.

It is worth noting that despite the complexity reduction we have applied most of the results reached are same for all three networks indicating that the complexity reduction we have followed does not change the fate of the system. Moreover, we see that reducing the complexity in general reduces the number of steps needed to enter in the limit cycle, so the system dynamics evolves faster. When reducing the complexity through topological reduction, limit cycles may appear due to the fact that some key stabilizing nodes or links are removed, but when the complexity is reduced following the topology of the network, then we believe that this may lead the system to hide the true disease behavior. This is not present in our study because we did not remove the main nodes because of their biological importance for the AD. This is the reason why the final states simulated for the three systems do not have big differences.

Regardless of these results, we think that there is another reason why we cannot see more differences between the dynamic behaviors of the three systems taken into consideration. This study is based on BooleSim simulation only, which simulates the Boolean network (system) starting by only one initial specific state. Although this specific state might be very important and relevant to the AD – signaling pathway, the situation might completely change if we simulate the system considering all possible initial states, represented by 2^N states (where N is the number of nodes in the network), as indicated by Boolean model. Working on this path will require another Boolean simulator that can support the complexity of the network, and we believe that some results related to the health conditions of the system might be different. Consequently, extending the analysis to the full 2^N state space may uncover alternative pathways or attractors, shedding further light on the mechanisms that drive either protective or pathological outcomes in Alzheimer's signaling.

Appendix: Supplementary Information

This section provides supplementary information to support the research presented in this paper. The content of this appendix is composed by tables and figures which are part of the methodology and analysis followed during this work and the results achieved. This information was not included in the main body of the paper with the purpose to maintain clarity and conciseness of this research work, despite the fact that it provides further transparency of our work and give opportunity to reproducibility of the results.

Table A3. Boolean Rules of the most important nodes for the final simplified network presented in Fig. 2.

CASP8	TNF
CYCS	BID && BAX && !BCL2
BAX	!BCL2 && (BID GSK3B)
PSEN1	NCSTN && !GSK3B
APP	gamma secretase
MAPT	!CDK5 !GSK3B
CASP3	CASP8 CYCS
Apoptosis	(Amyloid_fibril_formation APP BAX CASP3 CASP8 Neurofibrillary_tangle_formation) && !BCL2

Table A4. Biological motivation and final state effects after which the initial states are determined and the final states are analyzed. Focus is given to the main nodes that are pro-disease.

Node	Biological Meaning		Biological Role for AD	Network Topology	
	Active: ON = 1	Inactive: OFF = 0		In-degree	Out-degree
All Nodes	Hyper activation in the cellular state: Chronic stress; Oxidative damage; amyloid accumulation	Healthy or non-pathological cellular state: minimal signaling activity			
TNF	Disease is Active	Process of degradation is OFF	Inflammatory cytokine => promotes neural damage	0	1
APP	Disease is Active	Process of degradation is OFF	Amyloid Precursor Protein / source of Aβ plaques	2	3
GSK3B	Disease is Active	Process of degradation is OFF	Tau hyper phosphorylation => promotes neurodegeneration	1	4
BAX	Disease is Active	Process of degradation is OFF	Pro – apoptotic => triggers cell death	3	3
CASP8	Moderate or severe AD presence	Disease is OFF	Initiator of apoptosis	2	5
BCL2	Protection ON	Protection OFF: chances for activation of the disease increase	Anti-apoptotic (protective)	1	3
PSEN1	Amyloid production ongoing	No effect on Amyloid production	Familial AD mutations => affects Aβ production	4	1
Apoptosis	Cell is dying: The disease is giving effect	Cell survives	Output phenotype – cell death	7	0

Table A5. Simulation outcomes of the Boolean model under different initial states, showing the evolution toward fixed points or limit cycles.

Network	Simulation							
	Initial to Final (a)	Initial to Final (b)	Initial to Final (c)	Initial to Final (d)	Initial to Final (e)	Initial to Final (f)	Initial to Final (g)	
Original Full Network	Final State	Limit Cycle	Fixed Point	Fixed Point	Fixed Point	Fixed Point	Limit Cycle	
	No. of Steps	7	6	6	6	7	7	
	Inputs	ON	OFF	OFF	ON	ON	ON	
	APP	ON – ON	OFF – ON	OFF – ON	ON – ON	ON – ON	ON – ON	
	BCL2	ON – (ON-OFF)	OFF – ON	ON – ON	ON – ON	OFF – OFF	OFF – (ON-OFF)	
	GSK3B	ON – OFF	OFF – ON	OFF – ON	ON – OFF	ON – OFF	OFF – OFF	
	CAPN1	ON – OFF	OFF – ON	OFF – ON	OFF – OFF	ON – OFF	ON – OFF	
Apoptosis	ON – (ON-OFF)	OFF – OFF	OFF – OFF	ON – OFF	ON – ON	OFF – OFF		
1st Reduced Network	Final State	Limit Cycle	Fixed Point	Fixed Point	Fixed Point	Fixed Point	Limit Cycle	
	No. of States	7	5	5	6	7	7	
	Inputs	ON	OFF	OFF	ON	ON	ON	
	APP	ON – ON	OFF – ON	OFF – ON	ON – ON	ON – ON	ON – ON	
	BCL2	ON – (ON-OFF)	OFF – ON	ON – ON	ON – ON	OFF – OFF	OFF – (ON-OFF)	
	GSK3B	ON – OFF	OFF – ON	OFF – ON	ON – OFF	ON – FF	OFF – OFF	
	Apoptosis	ON – (ON-OFF)	OFF – OFF	OFF – OFF	ON – OFF	ON – ON	OFF – (ON-OFF)	
2nd Reduced Network	Final State	Limit Cycle	Fixed Point	Fixed Point	Fixed Point	Fixed Point	Fixed Point	
	No. of States	5	3	3	4	5	5	
	Inputs	ON	OFF	OFF	ON	ON	ON	
	APP	ON – ON	OFF – OFF	OFF – OFF	ON – ON	ON – ON	ON – ON	
	BCL2	ON – (ON-OFF)	OFF – ON	ON – ON	ON – ON	OFF – OFF	OFF – ON	
	GSK3B	ON – ON	OFF – OFF	OFF – OFF	ON – ON	ON – ON	OFF – OFF	
	Apoptosis	ON – OFF	OFF – ON	OFF – ON	OFF – OFF	ON – OFF	ON – OFF	

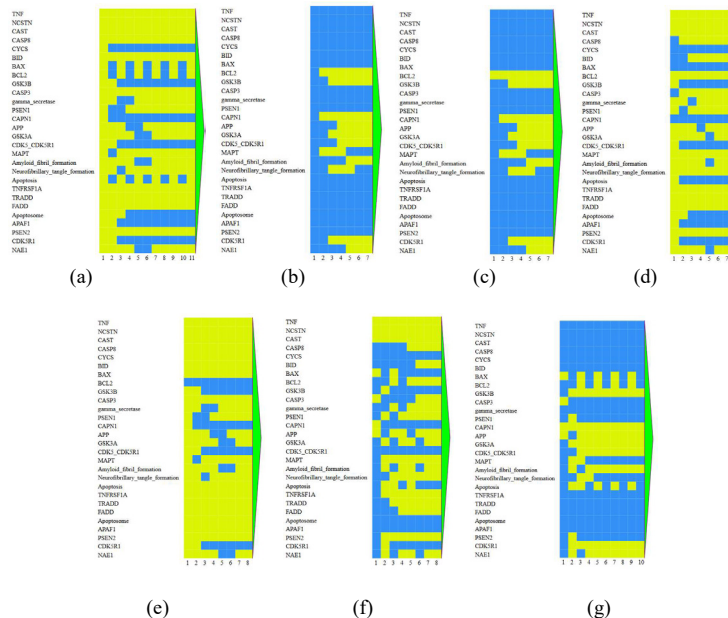


Figure A2. Full network – (a) initial state: all nodes ON; (b) initial state: all nodes OFF; (c) Healthy State; (d) Early stage disease; (e) Moderate to Severe disease; (f) Apoptotic trigger with input ON; (g) Apoptotic trigger with input OFF.

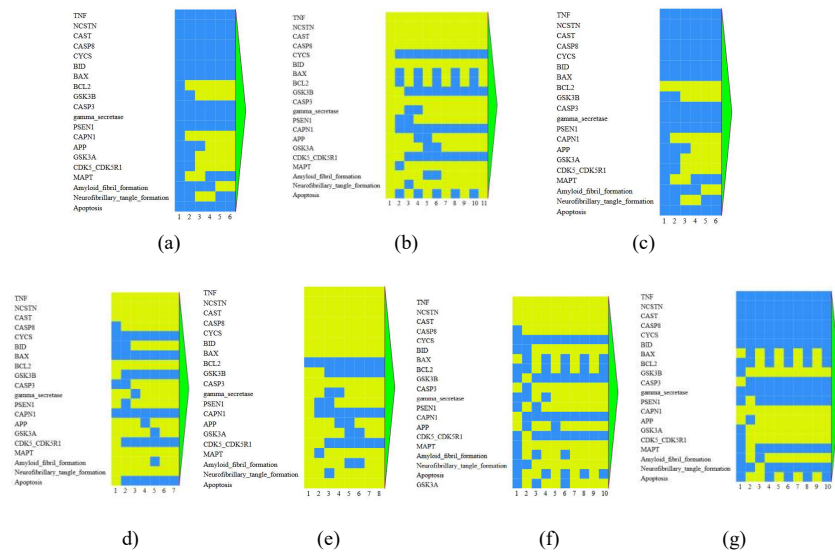


Figure A3. First reduced network composed by 20 nodes and 38 links. Here “Leaf” and “Intermediate” nodes are removed from the original network.

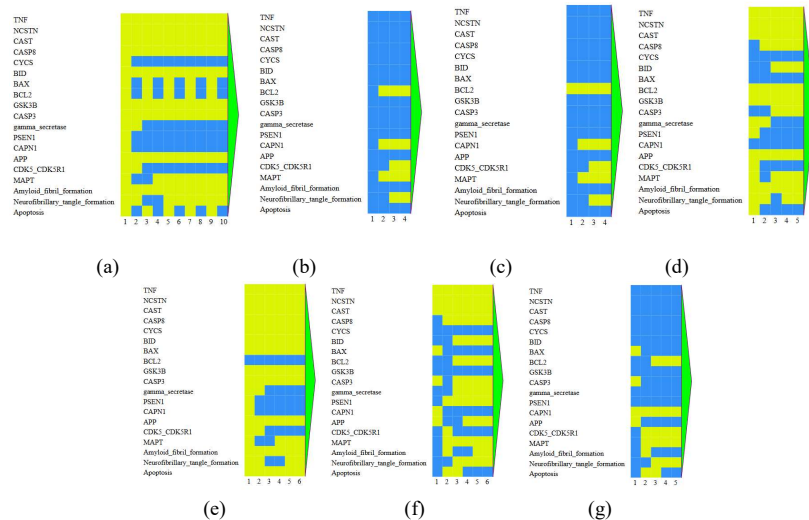


Figure A4. Second reduced network composed by 19 nodes and 38 links. Here “Leaf” and “Intermediate” nodes are removed from the original network.

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