Mathematical Modelling Approach of WntSignalling PATHWAY Analyse in Alzheimer Disease

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Abstract. Alzheimer disease is followed by accumulation of amyloid plaques and neurofibrillary tangles in neural cells of brain, what leads to toxicity and cell dead. These physical brain impairment or damage is followed with intellectual and cognition fall, and loss of capabilities. Beneath these impairments is production of amyloid beta protein and tau protein, that is interfered with signalling pathways that provide important functioning to organism, cells, or central nervous system, like cell proliferation, differentiation, adhesion, survival, and apoptosis, as an examples of functions that are provided with Wnt signaling pathway. Other pathways found to be included in pathology of Alzheimer's disease are AMPK, mTOR, Sirtuin1, and PCB-1. They crosstalk with other molecular mechanisms, biological functions, and cell signaling in normal cell functioning and in disease. However, disease appears in case of abnormalities, irregularities or dysfunctions. Causes of Alzheimer disease are environmental, biological, or genetics factors. It can be also triggered earlier if other diseases are present like pneumonia, diabetes, injuries and strokes, HIV, or other specific diseases. It is interesting to examine connections between these abnormalities, irregularities, and dysfunctions with physical causes of disease, in case of Alzheimer disease formation of amyloid plaques and neurofibrillary tangles. Further, it is important to discover what causes dysfunctions of signaling pathways, or how they fight against risks and factors that cause the disease. In further research we will explore complexity and cross talk between the pathways and connection with diseases. In this paper we are particularly interested for *Wnt signaling pathway* since it has important cell functions, and cause transcription of genes that provide normal functioning and also have protective and neuroprotective effect in preventing and fighting off risk factors of disease. Wnt signaling is also found in other human diseases such as cancer, metabolic diseases, coronary disease, diabetes and obesity, etc. Our aim is to set framework for research examination of Alzheimer disease via understanding molecular mechanisms, biochemical reactions and mathematical modelling, and to perform dynamical analyze with simulation results, stability and bifurcation tests, in order to get better understanding of signaling pathways and connection with diseases.

Keywords: Alzheimer disease · Cross talk of signalling pathways
Wnt signaling pathway · Molecular mechanism · Biochemical reactions
Mathematical model

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1 Introduction

Alzheimer disease is neurodegenerative disorder which appears in people 65 years old or older, but early onset can appear after 40-ies. It prevents people from ordinary activities, social relationships, and it cause sharper intellectual fall. It is named after Alois Alzheimer who was the first to study Alzheimer disease. Disease can be confirmed only after autopsy, and in living person it is only diagnosed as "probable Alzheimer disease". It is similar with dementia or senile dementia, but pathological and functional signs and brain damage in Alzheimer disease is much harder, [1].

Alzheimer disease is followed with neuropathology which signs are accumulated amyloid plaques on extra cellular surface of brain cell and neurofibrille tangles inside brain cell that prevents brain and neuronal cells form normal functioning. Amyloid plaques and neurofibrille tangles presents specific physical abnormalities in brain.

Alzheimer disease is progressive, what means that symptoms are worsen when disease advance. The earliest symptoms of Alzheimer disease are mild memory loss, forgotten last conversation data, or what year is. It can be present some form of disorientation, problems with routine tasks, changes in personality, or in judgment. As disease progresses, symptoms get worse in everyday life, so 24 h help is needed. It can be present anxiety, suspiciousness and agitation, wondering, difficulties in recognizing members from close family or friends, and dream disturbances. In more advanced form, patient loss ability to talk, have weight and appetite loss. It is not directly fatal, but it can leave patients with disease over decades. It can also cause infections and other diseases like pneumonia which can be ultimate cause of death. Often, people are exhausted and die earlier, but patients who are normally healthy can survive over decades.

Alzheimer disease is characterised with anatomical changes that forms amyloid plaques and neurofibrille tangles that can be perplexed. Tangles and plaques prevents normal functioning and different functions of neurons and neuronal cells in brain, what causes general slowness and loss of capabilities. Amyloid plaques are formed, stacked, and accumulated on extracellular side of neuronal cell in brain. Amyloid is protein that is normally present in whole body. In AD it is unequally divided creating the substance called beta amyloid that is toxic for nerve cell. As amyloid plaques are accumulated brain cells starts to die. Neurofibrille tangles which can be perplexed are second anatomical sign of Alzheimer disease. Normally, each cell in brain contains long fibres made from proteins which serves as scaffold and supports brain cell in right form. It also helps in transport of food materials and nutrients in cell. In AD these fibres starts curling and clewing. Brain cell lose its form and becomes incapable to transfer food and nutrients in right way, what cause cell to eventually die. As plaques and tangles are accumulated in brain, wide cells dying in brain is present.

There are reported several possible causes in development of AD. It seems that Alzheimer disease is caused environmentally and that biological and genetic factors are included. If specific other diseases are present the risk is wider or higher. Scientists have discovered that many people with this form of the disease have a *specific genes abnormality*: mutation in genes located on chromosomes 1, 14, and 21. Furthermore, chromosome 19 contains a gene called APOE which helps in carrying cholesterol in the

blood and in recovering nerves after injury. It is observed that people with apoE4 gene have increased risk of developing AD. In addition to genetic factors, *manybiological factors* have been implicated in AD: for example, free radicals which are formed when the body metabolizes oxygen. Free radicals serve important functions - such as helping the immune system to fight disease. However, too many free radicals cause problems. It is observed that brain cells in AD produce the mutated form of amyloid protein and produce more free radicals. However, free radicals can also enforce beta amyloid protein production. Third, *several environmental factors* contribute to AD: aluminium as common contaminant in drinking water, since it is observed that both the plaques and tangles in AD contain aluminium. Important environmental factors are also zinc, smoking, high exposure to paint solvents, exposure to electromagnetic fields and power lines.

Alzheimer disease can also be developed in patients who already have some disease, like injuries, pneumonia, diabetes, strokes, viral infections, HIV, or other. It is important to conduct research to find relationships with these and other diseases. Environmental factors can trigger Alzheimer disease or cause symptoms to appear earlier. Currently, much more research is needed to identify other triggering factors, and to learn what can be done to prevent it.

In order to treat AD drugs are developed and clinically tested. It is needed 10–20 years of research of new drug, prior clinical tests and medical use. The only allowable drugs today are so called cholinergic drugs as tacrine, donepezil, rivastigmine, and galantimine. So far, these drugs had limited success in treating AD. Tacrine causes side effects and is rarely prescribed. Aside of cholinergic drugs, researchers looks for other kinds of drugs that can influence other chemicals in brain, or which interfere with forming plaques or tangles in AD, or enforce brain activity for producing new neurons in order to substitute dead neuronal cells. Also, dietal supplements can help, prevent or slow AD. Damage in brain caused by free radicals can be treated with antioxidants that can be found in Vitamin C, E, beta carotene which is associated to Vitamin A. Other antioxidants found are ginko biloba and phosphatidylserinme. However, supplements with high dosage of antioxidants can cause specific side effects. Safer way in consuming antioxidants is by diet, taking fruits and vegetables, brown rise, integral grain, meat, eggs, and milky food. It can be also used anti flammation drugs like aspirin or pain relief drugs.

It is unclear so far why plaques and tangles start to form in AD brain. Many researchers try to answer these questions and try to develop ways of preventing or healing this neurodegenerative disease. Last researches discovered vaccine that promise preventing and treating of AD since it has possibility of solubility of plaques. However, it is still not found vaccine which will dissolution or solve problems with tangles which is considered to have complicated role in AD, [1].

Research of AD is actual today, but it is considered that will be needed years or decades to solve this problem and to find drug for people altered or ill from AD. In order to find relationship of formation of amyloid plaques and neurofibrille tangles in Alzheimer disease research is conducted to find molecular mechanisms or signalling pathways that cause or influence abnormal or irregular functioning or signalling, what consequently cause formation of these neuronal physical abnormalities, alteration in function, or different cell function, and what lead to development of Alzheimer disease.

For that reason we present findings of signalling pathways that are connected with Alzheimer disease. They cross talk with other molecular mechanisms, signalling pathways, or cause gene transcription that might lead to genetic mutation and alter or change cells functions or fate. Irregularity or dysfunction of signalling pathways can cause AD related problems. Signalling pathways can also act neuroprotectively to neural cells in brain, or heal them after injury or take off the risks if they are attacked.

2 Roles of Signalling Pathways and Crosstalk of Complex Network of Signalling Pathway

Alzheimer disease is characterized with progressive loss of cholinergic neurons that lead to severe behavioural, motor and cognitive impairments. Extracellular amyloid beta plaques and neurofibrillary tangles containing hyper phosphorylated tau are frequently present in brain of patients with AD. Energy failure in neurons and brain in AD is also hallmark of this disease. Energy demands are prerequisite for neuronal communication. It is a question what causes these impairments, energy failure and accumulation of amyloid plaques and neurofibrillary tangles?

In order to answer this question there are attempts to discover metabolic pathways that might lead to pathogenesis of AD. So far, several signalling pathways are discovered, with attempts to discover mechanism behind these pathways: AMPK pathway, mTOR pathway, Sirtuin1 pathway, PGC-1 pathway, and Wnt pathway (name derived after *wingless* gene in *Drosophilia*). Short names are for biomolecules that play important role in cell, [2, 3]. They are able to *modulate several pathological events* in AD. These include *reduction of amyloid beta aggregation and inflammation*, *regulation of mitochondrial dynamics*, and *increased availability of neuronal energy* [1]. They can provide new therapeutic to slow down or prevent development of AD. These pathways normally increase transcription of genes that are important for normal functioning. For example, in case of dis-functioning caused by oxidative or inflammation insult, genes are transcripted in mitochondria to stabilize the functioning. It is important to reach greater understanding of the molecular basis of these pathways and ways how they interact within cell in order to slow down or attenuate metabolic deficits observed in AD.

In this paper we will consider Wntsignalling pathway, in particular canonical Wnt/Beta catenin signalling pathway in order to show in which cellular processes it is included, to show main components of the pathway, and to set up biochemical and mathematical model of this signalling pathway in order to obtain simulation results and better insight into biological mechanism. It is question of further research to see what genes are transcribed and with what cell function, how it relates to proteins, genes, or other compounds in developing amyloid plaques and neurofibrillary tangles in developing Alzheimer disease, and in order to find targets for potential drug development.

Molecular mechanism is still unclear with several genes or proteins associated that leads to Alzheimer disease. The aim of this paper is to present clues how to investigate pathways. For modelling we use computational approach. It is presented biochemical and mathematical framework for dynamical analysing of signalling pathways. More

complex problems will be focus of further research, since thorough investigation of the results from literature is needed.

Wntsignalling pathway is involved in several key cellular processes associated with cell proliferation, differentiation, adhesion, survival, and apoptosis in several catabolic and anabolic cells, including neuronal and glial cells which are key residents of Central Nervous System. Wnt is family of secreted cysteine rich glycosylated protein that are named after Drosophilae protein wingless and mouse protein int-1. So far 19 of 24 Wnt genes are identified in humans, with 80 Wnt target genes in humans, mice, *drosophilae*, *xenopus*, *zebrafish* [4, 5].

Wntsignalling pathway is induced with Wnt that binds to frizzled transmembrane receptors located on the cell surface leading to the induction of at least three downstream signalling pathways, [5]:

1. The first is known as *canonical Wnt pathway* which regulates gene transcription through beta catenin, also called Wnt/beta catenin.
2. The second is *non canonical Wnt pathway* that modulates Ca+ release, also called *Wnt/Ca2+ signalling pathway*.
3. Third one is *Wnt cell polarity signalling pathway*, in which Jun N-terminal kinase (JNK) plays a key role and is also called *Wnt/PCP-JNK signalling pathway*.

In this paper we are interested in canonical Wntsignalling pathway.

3 WntSignaling Pathway

The *canonical Wnt/β-catenin signalling pathway* is important for essential cellular functions where it plays key role and is implicated in many diseases. It has role in cell proliferation and specification during development, in cell maintenance and in wound repair [1]. Dysfunction of *Wntsignalling pathway* leads to many diseases or pathological conditions that include neurodegenerative diseases. The pathway dynamics is still not well understood and further clarifications are needed.

It is known that Alzheimer disease is followed with accumulation of amyloid plaques and neurofibrillary tangles, but the question is *how are they related to Wntsignalling pathway (and other pathways) and how they are caused in AD in general*? It is known that Wntsignalling pathway components are altered in AD. Also, it is known that beta catenin levels in AD are *reduced* what consequently causes inherited mutations in presenilin gene, as an example [2].

4 Description of the Mechanism

Here we present *canonical Wntsignalling pathway* with simple mechanism and key components that are identified to be important for which we set biochemical reactions and derive mathematical model.

Molecular mechanism [5] on which the model is based is described as: Wnt binds to cell-surface receptors that transduce a signal via a multistep process involving Dishevelled (Dsh) to the so-called destruction complex (Y), which contains forms of

Axin, adenomatous polyposis coli (APC), and glycogen synthase kinase (GSK-3). In the absence of a Wnt signal, the Y actively degrades β-catenin by phosphorylation and degradation. Following Wnt stimulation, degradation of β-catenin is inhibited through phosphorylation of Y members, leading to accumulation in the cytoplasm of free β-catenin, which is able to translocate to the nucleus where it can form a complex with T-cell factor (TCF) and lymphoid-enhancing factor proteins and influence the transcription of target genes, [6].

The presented model is focused on activation, sequestration, biochemical interactions, phosphorilation, and degradation of key components of main components Dsh (Disheveled), Y (destruction complex), Beta-catenin, and P (phosphatases), TF (transcription factor)in signalling pathway, and localization of these components in cytoplasm and nucleus, and their transport from cytoplasm-to-nucleus, and from nucleus-to cytoplasm.

5 Biochemical Reactions

From the molecular mechanism described above, set of biochemical reactions is obtained. In order to present the model, we first need table of biochemical species which are used in biochemical model, with corresponding symbols and mathematical variables (Table 1).

Table 1. Biochemical species with symbols and mathematical variables

Species	Symbol	Variable
Dishevelled inactive in cytoplasm	D_i	x_1
Dishevelled active in cytoplasm	D_a	x_2
Dishevelled active in nucleus	D_{an}	x_3
Destruction complex inactive in cytoplasm	Y_i $(APC/Axin/GSK3\beta)_i$	x_4
Destruction complex inactive in cytoplasm	Y_a $(APC/Axin/GSK3\beta)_a$	x_5
Destruction complex inactive in nucleus	Y_{ni} $(APC/Axin/GSK3\beta)_{in}$	x_6
Destruction complex inactive in nucleus	Y_{na} $(APC/Axin/GSK3\beta)_{an}$	x_7
Phosphatase in cytoplasm	P	x_8
Phosphatase in nucleus	P_n	x_9
Beta catenoin in cytoplasm	β-catenin	x_{10}
Beta catenoin in nucleus	$\beta\text{-catenin}_n$	x_{11}
Gene transcription factor in nucleus	TF_n	x_{12}
Transcription complex in nucleus: Beta catenin:TCF	IC_{xt}	x_{13}
Intermediate complex in cytoplasm: Beta catenin: Dishevelled	IC_{yd}	x_4

(*continued*)

Table 1. (*continued*)

Species	Symbol	Variable
Intermediate complex destruction complex in nucleus: Beta catenin: Dishevelled	IC_{xdn}	x_{15}
Intermediate complex in cytoplasm: Destruction complex: Phosphatase	IC_{yp}	x_{16}
Intermediate complex in nucleus: Destruction complex: Phosphatase	IC_{ypn}	x_{17}
Intermediate complex in cytoplasm: Beta catenin: Destruction complex	IC_{xy}	x_{18}
Intermediate complex in nucleus: Beta catenin: Destruction complex	IC_{xyn}	x_{19}

Next, we give set of biochemical reactions, with forward and backward reactions rate for each of the reactions.

Here we state few proofs from the literature: Studies have shown that exposure of hippocampal neurons to amyloid beta results in *inhibition* of canonical Wnt signaling that is important for cell proliferation, differentiation, adhesion, survival, and apoptosis. It is also shown that in hippocampal neurons amyloid beta cause induction of Dkk1 protein that acts as Wnt antagonist and *prevents* normal cell proliferation, differentiation, adhesion, survival, or apoptosis. In AD protein Dkk1 is elevated. Protein Dkk3 is also elevated and is present in plasma and cerebral fluid in AD. Neuronal impairment in brain and amyloid plaques prevents Wnt signaling and leads to induction of Dkk1 proteins that cause genes mutations or variations. Further, Apo lipoprotein E is found to be *risk factor* for AD that inhibits canonical Wnt signaling. Also, low density of receptor related LRP6 leads to genetic variations, and AD progression. Dkk1 protein also *reduce* amount of synaptic proteins inducing synaptic disassembly at pre and post synaptic sites. Clustering is found to be a *susceptibility factor* for late onset AD, and it *regulates* amyloid beta toxicity via Dkk1 driven induction of the non-canonicalWnt/PCP-JNK pathway, which *contributes* to tau phosphorylation and cognitive impairments. *Early event* in AD is synaptic failure which is caused by amyloid beta oligomers that are *soluble* to nerve cells and are responsible for synaptic pathology prior plaque deposition and neuronal death. Studies summarized in (2) support the idea that alterations in Wnt signaling pathway, are involved in modulation of synaptic development as well as in progression of AD. The activation of signaling pathways that crosstalk with Wnt pathway, support the neuroprotective potential of Wnt signaling cascade in AD.

In basal forebrain there is a loss of cholinergic neurons and due to cortical deficiencies in cholinergic neurotransmission there is impairment of cognitive functions and behavioral disturbances in AD. This is found after postmortem AD autopsy that disturbances are found in the metabolism of acetylcholine. Decrease of cholinergic neurons leads to the alteration of several proteins in the cholinergic system, such as

decreased activity of acetylcholinesterase AChE and cholineacetyl transferase. Macromolecule found in synapsis interacts with amyloid beta and form complex which alters synaptic function in hippocampal neurons. Amyloid beta AChE complexes are more neurotoxic then amyloid beta alone depending on level of AChE, suggesting that AChE plays key role in neurodegenerative changes in AD, [2].

There are many proofs and data in the literature, and our aim here was to give clues how brain damage or impairment is caused by neurotoxicity of amyloid plaques and neurofibrillary tangles and more complex oligomers, and to show that above mentioned signaling pathways have protective or neuro protective effects in fighting these physical abnormalities, with inferring that possible cross talk with other mechanisms and pathways might influence signaling in pathway, transcription of genes, protein synthetized, cell functions or fate, and diseases that include Alzheimer disease as well. Impairment or damage of neural cells in brain cause functional and cognitive decline and in general loss of capabilities.

It is therefore important to investigate these pathways, and in this paper particularly Wnt signaling pathway. We focus on canonical Wnt/beta catenin signaling cascade, in order to show simple model, to set computational framework for analyzing more complex pathways and cross talks in further research.

Biochemical reactions in cytoplasm,

$$
\begin{gathered}
D_i \Leftrightarrow D_a, \mathrm{k}_1, \mathrm{k}_2, \\
D_a + \mathrm{Y}_i \Leftrightarrow \mathrm{IC}_{\mathrm{xd}} \rightarrow D_a + \mathrm{Y}_a, \mathrm{k}_3, \mathrm{k}_4, \mathrm{k}_5, \\
Y_a + \mathrm{P} \Leftrightarrow \mathrm{IC}_{\mathrm{yp}} \rightarrow Y_i + \mathrm{P}, \mathrm{k}_6, \mathrm{k}_7, \mathrm{k}_8 \\
Y_i + \mathrm{x} \Leftrightarrow \mathrm{IC}_{\mathrm{xy}} \rightarrow Y_i + 0, \mathrm{k}_9, \mathrm{k}_{10}, \mathrm{k}_{11} \\
0 \rightarrow \mathrm{x}, \mathrm{k}_{12} \\
x \rightarrow 0, \mathrm{k}_{13}
\end{gathered}
$$

Biochemical reactions in nucleus,

$$
\begin{gathered}
D_{\mathrm{an}} + \mathrm{Y}_{\mathrm{in}} \Leftrightarrow X_{\mathrm{dyn}} \rightarrow D_{\mathrm{an}} + \mathrm{Y}_{\mathrm{an}}, \mathrm{k}_{14}, \mathrm{k}_{15}, \mathrm{k}_{16} \\
Y_{\mathrm{an}} + \mathrm{P}_n \Leftrightarrow \mathrm{IC}_{\mathrm{ypn}} \rightarrow Y_{\mathrm{in}} + \mathrm{P}_n, \mathrm{k}_{17}, \mathrm{k}_{18}, \mathrm{k}_{19} \\
Y_{\mathrm{in}} + \mathrm{x}_n \Leftrightarrow \mathrm{IC}_{\mathrm{xyn}} \rightarrow Y_{\mathrm{in}} + 0, \mathrm{k}_{20}, \mathrm{k}_{21}, \mathrm{k}_{22} \\
x_n \rightarrow 0, \mathrm{k}_{23} \\
x_n + \mathrm{TF} \Leftrightarrow \mathrm{IC}_x\mathrm{TF}_n, \mathrm{k}_{24}, \mathrm{k}_{25}
\end{gathered}
$$

Biochemical reactions in Cytoplasm to Nucleus,

$$
\begin{gathered}
D_a \Leftrightarrow D_{\mathrm{an}}, \mathrm{k}_{26}, \mathrm{k}_{27} \\
Y_a \Leftrightarrow Y_{\mathrm{an}}, \mathrm{k}_{28}, \mathrm{k}_{29}
\end{gathered}
$$

6 Mathematical Model of Wnt Signalling Pathway

Next, we give mathematical model of Wnt/β catenin signalling pathway, [6]:

$$\dot{x}_1 = -k_1 x_1 + \mathrm{k}_2 x_2 \tag{1}$$

$$\dot{x}_2 = \mathrm{k}_1 x_1 - (k_2 + \mathrm{k}_{26}) x_2 + \mathrm{k}_{27} x_3 - k_3 x_2 x_4 + (k_4 + \mathrm{k}_5) x_{14} \tag{2}$$

$$\dot{x}_3 = \mathrm{k}_{26} x_2 - k_{27} x_3 - k_{14} x_3 x_6 + (k_{15} + \mathrm{k}_{16}) x_{15} \tag{3}$$

$$\dot{x}_4 = -k_3 x_2 x_4 - k_9 x_4 x_{10} + \mathrm{k}_4 x_{14} + \mathrm{k}_8 x_{16} + (k_{10} + \mathrm{k}_{11}) x_{18} \tag{4}$$

$$\dot{x}_5 = -k_{28} x_5 + \mathrm{k}_{29} x_7 - k_6 x_5 x_8 + \mathrm{k}_5 x_{14} + \mathrm{k}_7 x_{16} \tag{5}$$

$$\dot{x}_6 = -k_{14} x_3 x_6 - k_{20} x_6 x_{11} + \mathrm{k}_{15} x_{15} + \mathrm{k}_{19} x_{17} + (k_{21} + \mathrm{k}_{22}) x_{19} \tag{6}$$

$$\dot{x}_7 = \mathrm{k}_{28} x_5 - k_{29} x_7 - k_{17} x_7 x_9 + \mathrm{k}_{16} x_{15} + \mathrm{k}_{18} x_{17} \tag{7}$$

$$\dot{x}_8 = -\dot{x}_{16} = -k_6 x_5 x_8 + (k_7 + \mathrm{k}_8) x_{16} \tag{8}$$

$$\dot{x}_9 = -\dot{x}_{17} = -k_{17} x_7 x_9 + (k_{18} + \mathrm{k}_{19}) x_{17} \tag{9}$$

$$\dot{x}_{10} = \mathrm{k}_{12} - (k_{13} + \mathrm{k}_{30}) x_{10} - k_9 x_4 x_{10} + \mathrm{k}_{31} x_{11} + \mathrm{k}_{10} x_{18} \tag{10}$$

$$\dot{x}_{11} = -k_{23} x_{11} + \mathrm{k}_{30} x_{10} - k_{31} x_{11} - k_{20} x_6 x_{11} - k_{24} x_{11} x_{12} + \mathrm{k}_{25} x_{13} + \mathrm{k}_{21} x_{19} \tag{11}$$

$$\dot{x}_{12} = -\dot{x}_{13} = -k_{24} x_{11} x_{12} + \mathrm{k}_{25} x_{13} \tag{12}$$

$$\dot{x}_{14} = \mathrm{k}_3 x_2 x_4 - (k_4 + \mathrm{k}_5) x_{14} \tag{13}$$

$$\dot{x}_{15} = \mathrm{k}_{14} x_3 x_6 - (k_{15} + \mathrm{k}_{16}) x_{15} \tag{14}$$

$$\dot{x}_{18} = \mathrm{k}_9 x_4 x_{10} - (k_{10} + \mathrm{k}_{11}) x_{18} \tag{15}$$

$$\dot{x}_{19} = \mathrm{k}_{20} x_6 x_{11} - (k_{21} + \mathrm{k}_{22}) x_{19} \tag{16}$$

Conservation laws are,

$$0 = (x_1 + \mathrm{x}_2 + \mathrm{x}_3 + \mathrm{x}_{14} + \mathrm{x}_{15}) - c_1 \tag{17}$$

$$0 = (x_4 + \mathrm{x}_5 + \mathrm{x}_6 + \mathrm{x}_7 + \mathrm{x}_{14} + \mathrm{x}_{15} + \mathrm{x}_{16} + \mathrm{x}_{17} + \mathrm{x}_{18} + \mathrm{x}_{19}) - c_2 \tag{18}$$

$$0 = (x_8 + \mathrm{x}_{16}) - c_3 \tag{19}$$

$$0 = (x_9 + \mathrm{x}_{17}) - c_4 \tag{20}$$

$$0 = (x_{12} + x_{13}) - c_5 \tag{21}$$

Some research on biomolecules and signalling pathways in Alzheimer disease is analysed in [7–9]. Further, NfkB and MAPK signalling pathways that are also important for biological functions are modelled in [10, 11].

Interesting biological phenomena in molecular mechanisms, signalling pathways or biological networks can also be approximated or modelled as singular or impulsive phenomena. Therefore system theory developed for singular and impulsive systems [12–14] can be used. Results are given in [15]. For example, we could state general dynamical model by including conservation laws, to obtain differential – algebraic model, i.e. singular system. Thresholds in biological models can be modelled as impulsive phenomena.

7 Simulation Results

In order to obtain simulation results we give table of initial conditions and rates of reactions that we will use in simulations (Table 2).

Table 2. Rate of reactions

Rate of reaction	Value	Rate of reaction	Value
k_1	92.331732	k_{17}	0.61699064
k_2	0.86466471	k_{18}	0.61699064
k_3	79.9512906	k_{19}	37.913879
k_4	97.932525	k_{20}	0.86466471
k_5	1	k_{21}	0.86466471
k_6	3.4134082	k_{22}	0.99326205
k_7	0.61409879	k_{23}	0.99326205
k_8	0.61409879	k_{24}	1
k_9	3.4134082	k_{25}	5.9744464
k_{10}	0.98168436	k_{26}	1.7182818
k_{11}	0.98168436	k_{27}	1.7182818
k_{12}	4.7267833	k_{28}	1.7182818
k_{13}	0.17182818	k_{29}	1.7182818
k_{14}	0.68292191	k_{30}	0.55950727
k_{15}	1	k_{31}	1.0117639
k_{16}	3.2654672		

Conserved quantities are given in Table 3.

Table 3. Conserved quantities

Conserved quantities	Value
c_1	4.9951026
c_2	16.4733784
c_3	1.6006340
c_4	1.2089126
c_5	2.7756596

Next, we state set of initial conditions.

Table 4. Initial conditions

Variable	Initial value	Variable	Initial value
x_1	4.9951	x_{11}	0
x_2	0	x_{12}	2.77566;
x_3	0	x_{13}	0
x_4	16.4734	x_{14}	0
x_5	0	x_{15}	0
x_6	0	x_{16}	0
x_7	0	x_{17}	0
x_8	1.60063	x_{18}	0
x_9	1.20891	x_{19}	0
x_{10}	0		

Initial conditions are chosen in such a way that certain quantities are present for inactive Disheveled, inactive destruction complex, phosphatase in cytoplasm, phosphatase in nucleus, and transcription factor in nucleus. Other quantities and intermediate complexes are at initial time equal to zero (Fig. 1). Therefore, quantities chosen for initial conditions given in Table 4 straightforwardly correspond to conservation quantities given in Table 3.

From the simulation results above we see that Disheveled inactive in cytoplasm and active in cytoplasm and nucleus rise from initial value to steady state. Rise of inactive Disheveled is due to inactivation from active Disheveled that is produced when Wnt signaling is on. Destruction complex inactive in cytoplasm decrease from initial state to zero, since it reacts with active Disheveled to form intermediate complex and produce active destruction complex. It is consumed as more active Disheveled is formed. Active destruction complex both in cytoplasm and nucleus and inactive destruction complex in nucleus rise from zero to steady state, since active Disheveled is produced that react with destruction complex. Phosphates both in cytoplasm and nucleus decrease from initial state to steady state, since they are consumed in biological process with active destruction complexes to form intermediate complexes, and inactivate destruction complexes. Beta catenin has impulse rise in cytoplasm to steady state, due to production, and in nucleus also rise from zero to steady state. It also degrades but rate of

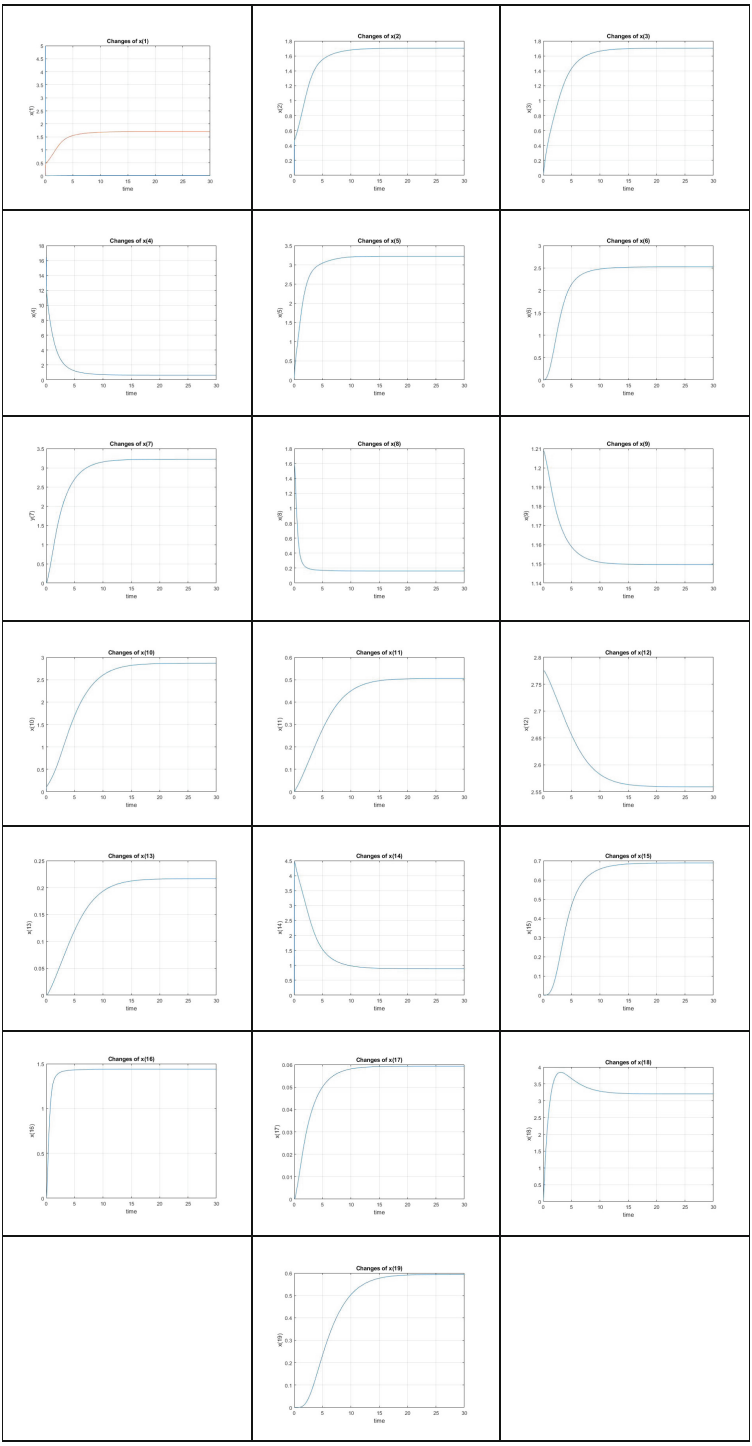

Fig. 1. Simulation results

degradation k_{13} is lower than rate of production k_{12}. Transcription factor decrease from initial state to steady state, since it is consumed for transcription due to release of beta catenin that promotes process of transcription. Intermediate complex of beta catenin and disheveled in cytoplasm decrease, while complexes of beta catenin-transcription factor, beta catenin disheveled in nucleus, complex of destruction complex and phosphate in cytoplasm and nucleus rise. Intermediate complex of beta catenin and destruction complex rise, have transient behavior and reach steady state. Intermediate complex of beta catenin and destruction complex in nucleus rise.

8 Analysis of Mathematical Model

Mathematical model we have obtained is nonlinear with 19 states and 31 rate reactions. Since it is nonlinear it can show multiple responses and multistability of Wnt signalling pathway under certain different conditions. By investigating the model in Mathematica software we have obtained two sets of equilibrium states that can lead to different cell functions (for example, stem cells proliferation or differentiation) depending of the chosen equilibria of the model. Equilibrium points are functions of rate of reactions as parameters, what leads to different steady states obtained. Further, it can be performed bifurcation analysis of biochemical rates parameters in order to show changes in system dynamics that leads to different responses, like bistability, switch-like transition, hysteresis, or graded response [2]. Model resembles two steady states switching between committed state and stem like state. In the bi stable regime the low level of gene transcription is associated with a committed cell state and the high level with a stem-like phenotype over long time periods. As the value of a parameter, for example β-catenin shuttling into the cytoplasm k_{25}, decreases below a threshold, the bifurcation diagram predicts that cells will differentiate. If the shuttling rate was adequately increased these cells would dedifferentiate to a stem-like state. If the parameter regime were known, bifurcation analysis and singularity analysis could also predict parameters governing reversible and irreversible behaviour, like parameter k_5 that leads to irreversible behaviour. This is a topic of further research.

Nonlinear systems in general exhibit multiple equilibrium points, limit cycles - oscillations of constant amplitude and frequency, chaos phenomena: randomness, complicated steady state behaviours, and multiple modes of behaviour. For the model presented we have found two sets of equilibrium states, and by performing linearization around equilibrium point, we have obtained linear matrix that we have tested for eigenvalues in order to determine stability, but we have found three positive equilibria states with other ones being generally negative or zero eigenvalues. From First or indirect method of Lyapunov we could not conclude stability of matrix of linearized system and therefore nonlinear system, although simulation results shows that states attained steady values.

In mathematical models governing biochemical processes or signalling pathways there are present large number of system states and is therefore hard to perform analytical study, rather we use computational approach, numerical, stability, and bifurcation studies in order to show graphically how system states are changed due time, dependence of variables, or parameter values that lead to different state responses, or

state changes depending of parameters. Even numerical study becomes impossible for large number of system states, since time needed for simulation is large, and hardware requirements for components are more demanding. This is a problem that follows biochemical modelling, simulation, and dynamical analysis of signalling pathways.

Further research will focus on more detailed model of signalling pathway including other key actors. We will consider cross talk with other pathways, and analyse each of them. We will attempt to show dependence of signalling pathway actors with amyloid beta protein and plaques and tau proteins neurofibrily tangles. We will perform extensive research of the literature in order to connect and find clues from the results already proved, and try to explain them in line with mutations, variations of genes, dysfunctions of pathways, irregularities, abnormal proteins, etc. In order to decipher connections with Alzheimer disease pathology.

9 Conclusion

In this paper we have explained what the Alzheimer disease is, what are signs and pathological abnormalities that follow this disease, main symptoms, causes that can be environmental, biological, or genetics, or interfered with specific other diseases that can trigger AD earlier. We have explained possible crosstalk of different signalling pathways that are found to be key acters in Alzheimer disease: AMPK, mTOR, Sirtu1, PCB-1, Wnt. We left complex analyse for further research and we focused on canonical Wnt/beta catenin signalling pathway, since we are interested to find connections and clues between neural cell damage or impairment in brain, accumulation of amyloid plaques and neurofibrillary tangles, amyloid beta protein and their complexes, tau protein and explain taupatologies that appear in Alzheimer disease, and their connection with signalling pathways and other compounds and molecular mechanisms and their crosstalk. We are particularly interested to set computational model consisted of set of biochemical reactions that are based on molecular mechanism beneath, and mathematical model, for which we are interested in order to find responses of states or components in signalling pathway due time, and their responses. Of our interest is beta catenin and beta catenin destruction intermediate complex that triggers gene transcription and determine cell function between two possible states: stem-cell or differentiation. Thorough analytical and numerical investigation is topic of further research, and this paper presents initial base with concept, framework and results that will be used in future work.

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