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Review Article

Mathematical modelling of Alzheimer's disease biomarkers: Targeting Amyloid beta, Tau protein, Apolipoprotein E and Apoptotic pathways

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Abstract: *Introduction:* The kinetics of brain cell death in Alzheimer's disease (AD) is being studied using mathematical models. These mathematical models utilize techniques like differential equations, stochastic processes, and network theory to explore crucial signalling pathways and interactions between different cell types. One crucial area of research is the intentional cell death known as apoptosis, which is crucial for the nervous system. The main purpose behind the mathematical modelling of this is for identification of which biomarkers and pathways are most influential in the progression of AD. In addition, we can also predict the natural history of the disease, by which we can make early diagnosis. *Mathematical modelling of AD:* Current mathematical models include the Apolipoprotein E (APOE) Gene Model, the Tau Protein Kinetics Model, and the Amyloid Beta Peptide Kinetic Model. The Bcl-2 and Bax apoptosis theories postulate that the balance of pro- and anti-apoptotic proteins in cells determines whether a cell experiences apoptosis, where the Bcl-2 model, depicts the interaction of pro- and anti-apoptotic proteins, it is also being used in research on cell death in a range of cell types, including neurons and glial cells. How peptides are produced and eliminated in the brain is explained by the Amyloid beta Peptide (Aβ) Kinetics Model. The tau protein kinetics model focuses on production, aggregation, and clearance of tau protein processes, which are hypothesized to be involved in AD. The APOE gene model investigates the connection between the risk of Alzheimer's disease and the APOE gene. These models have been used to predict how Alzheimer's disease would develop and to evaluate how different inhibitors will affect the illness's course. *Conclusion:* These mathematical models reflect physiological meaningful characteristics and demonstrates robust fits to training data. Incorporating biomarkers like Aβ, Tau, APOE and markers of neuronal loss and cognitive impairment can generate sound predictions of biomarker trajectories over time in Alzheimer's disease.

Keywords: Alzheimer's disease, mathematical modelling, amyloid beta peptide kinetics model, tau protein kinetics model, Apolipoprotein E gene model, Bcl-2 and bax apoptosis model

Introduction

New mathematical models have been created to better understand the dynamics of brain cell death, a crucial topic in the area of neuroscience. These models were created using a variety of mathematical methods, such as differential equations, stochastic processes, and network theory. Modelling of Alzheimer's disease is the main focus of review in this theme. To understand the dynamics of this disease, mathematical models have been created that consider the interactions between various cell types and important signalling pathways. The study of apoptosis, a type of programmed cell death that is essential for the growth and upkeep of the nervous system, is one of the core areas in this subject. To represent the dynamics of this process, including the function of important signalling channels and the interactions between various cell types, mathematical models have been devised. The Apolipoprotein E (APOE) Gene Model, Amyloid Beta Peptide (Aβ) Kinetics Model, Tau (τ) Protein Kinetics Model, etc. have been investigated extensively in the current situation. Bcl-2, a protein that promotes apoptosis, and Bax, an anti-apoptotic protein Bcl-xL interact in a mathemat-

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ical model currently based on the Bcl-2 model. Several different cell types, including neurons and glial cells, have been studied using this model to understand the dynamics of cell death.

Mathematical modelling and its application in Alzheimer's disease

A novel mathematical model of Amyloid beta (Aβ)

Two distinct neuropathological markers, extracellular plaques and intracellular neurofibrillary tangles (NFTs) are present in AD. Amyloid β-peptide (Aβ) deposits make up the majority of the extracellular plaques. The NFTs are intraneural aggregations of tau proteins that have been hyperphosphorylated.

Although Aβ40 and Aβ42 are the major species in vivo, sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase produces a range of Aβ peptides from 39 to 43 amino acid residues in length [1].

The Amyloid Beta Peptide (Aβ) Kinetics Model is a mathematical model that predicts the behaviour of A peptides as Alzheimer's disease in the brain progresses (AD). Aβ peptides play a crucial role in the formation of the amyloid plaques that are seen in Alzheimer's disease (AD) sufferers' brains [2].

The Aβ Kinetics Model has been used to forecast how Alzheimer's disease will progress based on the levels of Aβ peptides in the brain. For instance, the model has been used to predict both the onset and the rate of progression of Alzheimer's disease (AD) based on the levels of Aβ peptides in the brain. Recent research has attempted to improve the A Kinetics Model by including fresh Aβ and AD data [3].

The hypothesis of the model is predicated on the notion that Aβ peptides are created in the brain and then eliminated via various mechanisms. The model comprises several parameters that define the generation and clearance rates of Aβ peptides, as well as their initial concentration in the brain. Based on the levels of Aβ peptides in the brain, the Aβ Kinetics Model has been used to make predictions regarding the course of Alzheimer's disease [4].

The mathematical equation based on the positive feedback between the level of Aβ and level of Calcium (Ca^{2+}). Ca^{2+} has a vital role in physiological activities acting is a gene expression and cell proliferation. Ca^{2+} is corelated with Aβ. In rats, through stimulating γ-secretase activities, it increases the cleavage of amyloid precursor protein, a high level of Ca^{2+} is good for gathering of Aβ. Aβ can control gene proliferation by many ways.

$$\frac{dx}{dt} = \overline{v}_1 + \overline{v}_3 \frac{y^2}{k_3^2 + y^2} - \overline{k}_1 x$$

$$\frac{dy}{dt} = v_2 + k_4 x - k_2 y$$

In the above equation X represents the concentration of Aβ, and Y represent the concentration of cytoplasm Ca^{2+}. $\overline{v}_1$ represents the rate of Aβ. $\overline{k}_1 x$ represents the rate of cleared Aβ. The positive reaction of Ca^{2+} on Aβ level represented by Hill function. k_3 represents the half saturation constant and $\overline{v}_3$ represents the maximal rate, v_2 is a flow of Ca^{2+} into cytoplasm and breakdown at $k_2 y$. The increase the speed of the Ca^{2+} due to Aβ represented by linear function $k_4 y$. This model gives the idea about to reduce the progression of Alzheimer's disease [5].

The core model is yet another mathematical equation used to model A's kinetics. The electrical activity of cerebellar granule cells is described by this model.

$$c_m \frac{dv}{dt} = - I_{Na(v)} - I_{k(v)} - I_{ca(v)} - I_{K(ca)} + I_{inj}$$

The voltage-dependent Na^+ current is represented by the expression, $I_{Na(v)}$. $I_{k(v)}$ denotes the delayed rectifier k^+ current, while $I_{ca(v)}$ denotes the high threshold voltage-dependent Ca^{2+} current. $I_{k(ca)}$ denotes the k^+ current that is activated by Ca^{2+} and I_{inj} denotes the current that is injected into the cell. Where, $I_{Na(v)}$ are represent the voltage-dependent Na^+ current. $I_{k(v)}$ represents the delayed rectifier k^+ current and high threshold voltage-dependent Ca^{2+} current represented by $I_{ca(v)}$. $I_{k(ca)}$ represents the Ca^{2+} activated k^+ current and I_{inj} is represent the current injected into the cell. C_m is a symbol for cell capacitance. The $I_{ca(v)}$ regulates Ca^{2+} entry into the cell when it is active, which raises the amount of Ca^{2+} concentration in the sub-plasmalemma compartment [6, 7]. Thus,

$$\frac{dCa}{dt} = F\left[\frac{-I_{ca(v)}}{2FV_{shel\ l}} - \beta\ Ca\right]$$

Where F is a Faraday constant and represents the cytoplasm's ability to act as a buffer. The sub-plasmalemma compartment's volume is represented by the symbol $V_{shel\ l}$. First-order constants that represent all the actions that deplete the cell of Ca^{2+}. This integration was accomplished β The system of partial differential equations (PDEs) is another equation based on the model.

$$\frac{\partial A_\beta^i}{\partial t} = \left(\lambda_{\beta(1+R)}^i - d_{A_\beta^i} A_\beta^i\right)\frac{N}{N_0}$$

Where, A_β^i represent the amount of amyloid β which inherently released from APP within neurons at the Rate λ_β^i [8]. R represents the underreactive oxidative stress, N_0 represents the brain's reference density of neuronal cells. Here, $\lambda_{\beta(1+R)}^i$ represent the production of amyloid beta and $d_{A_\beta^i} A_\beta^i$ represent the degradation of *A*β. This equation uses when A_β^i is overproduced.

The equation for extracellular amyloid is,

$$\frac{\partial A_\beta^O}{\partial t} = A_\beta^i\left|\frac{\partial N}{\partial t}\right| + \lambda_N\frac{N}{N_0} + \lambda_A\frac{A}{A_0} - \left(d_{A_\beta^o\widehat{M}}\left(\widehat{M_1} + \theta\widehat{M_2}\right) + d_{A_\beta^o\widehat{M}}\left(M_1 + \theta M_2\right)\frac{A_\beta^O}{\beta + K_{A_\beta^O}}\right)$$

A Michaelis-Menten coefficient is $K_{A_\beta^o}$. At a rate of $\frac{\partial N}{\partial t}$, neurons pass away, releasing their A_β^i. As a result, they increase the growth rate of A_β^O, the first component in the preceding equation, on the right side by adding $A_\beta^i\left|\frac{\partial N}{\partial t}\right|$ the second statement to equation's right. A_0 is the standard density of brain astrocyte cells. The second component on the right-hand side of the equation above represents Aβ released from the APP, and the third term accounts for Aβ released by activated astrocytes. Peripheral macrophages $\widehat{M_1}$ and $\widehat{M_2}$ are largely responsible for clearing A_β^O, but also activated microglia M_1 and M_2, so $d_{A_\beta^o\widehat{M}} > d_{A_\beta^oM}$ and $\widehat{M_1}$ M_1 are more efficient at doing so than $\widehat{M_2}$ and M_2 so $0 \le \theta <$ 1Aβ peptides are released by APP on living neurons in two different ways: inside the neurons (as A_β^i) and outside the neurons (as A_β^O) [9-11]. We suppose that the majority of A_β^O come from degenerated neurons. Therefore, in the equation above, we overlooked the fact that ROS increases Aβ predominantly in living neurons, and as a result, we neglected the increase of A_β^O by ROS [8].

A positive feedback model for the loss of acetylcholine served as the foundation for the mathematical model. Additionally, β amyloid is more hazardous to pc12 cell mutants that express p75 than to pc12 mutants that do not express p75. Amyloid can influence the quantity of neurotransmitters. According to this scenario, β amyloid's direct interaction with the p75 receptor results in apoptosis and provides information about the impact's size. The concentration of ACH is mostly decreasing in this scenario. Due to the relative concentration of p75 being higher in cholinergic neurons of the basal forebrain, ACH concentration would be most influenced.

$$\frac{da}{dt} = -k'p_b = -\frac{k'p_b}{k_b}$$

Where Ach and b represent the concentrations of β amyloid and Ach, respectively. The value of *p* denotes the amount of p75 receptors present in cholinergic neurons. The value of p_b indicates the amount of p75 that is linked to β amyloid. The dissociation constant is represented by k_b, and a proportionality concentration is represented by k'. The β amyloid binds to p75 in first order. The rate of cholinergic cell apoptosis is proportionnal to p_b [12].

The concentration of available receptor p, it can be expressed the total concentration of receptor p_t.

$$p = \frac{p_t}{1 + \frac{b}{k_b}}, \qquad \frac{da}{dt} = \frac{-k'p_t b}{k_b + b}$$

Hence, a and p_t are each propotional to the number of cholinergic cell, and thus proportional to each other.

$p_t = k''a$

Novel mathematical model of the Tau (τ) protein kinetics model

τ is a protein that binds to microtubules (MTs), and τ phosphorylation at several locations regulates this binding. In many neurodegenerative conditions, it is accumulated in cells as fibrillar

lesions in an inappropriately phosphorylated form. Tau is a family of proteins that are mostly found in neurons and are created through alternative mRNA splicing of a single gene on chromosome 17q21 [13, 14].

Although phosphorylation is the most frequent post-translational alteration of tau in NFTs, additional changes such as truncation, acetylation, and nitration have also been seen [15]. τ loses its physiological properties as AD progresses due to hyperphosphorylation at several locations and integration into PHFs.

This model describes the production, aggregation, and clearance of τ protein, another protein that is thought to play a role in the development of Alzheimer's disease. The equation for this model is listed below.

τ *(t) = P - A × e^(-kt) - C × e^(-kt)*

Where τ (t) is the amount of tau protein at time t, P is the rate of production, A is the rate of aggregation, C is the rate of clearance, and k is the rate constant for clearance.

The two-compartment model, which represents the migration of τ protein between the cytoplasm and the nucleus, is typical. This model assumes that τ protein can exist in two distinct forms: a soluble form in the cytoplasm and an insoluble form in the nucleus. The rate at which these two states transition is characterized by first-order kinetics. The model is represented by this set of equations.

d[Tau_c]/dt = k1[Tau_n] - k2[Tau_c]

d[Tau_n]/dt = k2[Tau_c] - k1[Tau_n]

Where [Tau_c] and [Tau_n] represent the concentration of τ protein in the cytoplasm and nucleus, respectively, and k1 and k2 are rate constants [16].

The mathematical model used to study τ protein kinetics is essentially developed at some rate λτ0. It is assumed that when A^{i}_{β} production increases threshold A^{i0}_{β}, GSK-3 becomes activated, and it mediates hyperphosphorylation of τ. In steady state, the difference A^{i}_{β}-A^{i0}_{β} is proportional to *R*. Hence the equation for τ is given by:

$$\frac{\partial \tau}{\partial t} = \left(\lambda_{\tau o} + \lambda_{\tau} R - d_{\tau}\tau\right)\frac{N}{No}$$

It is assumed that in the beginning, it had already had a disease. Hence the τ proteins are already hyperphosphorylated and ROS induces increases the development of these proteins [8].

The continuous Model is an additional mathematical model used to research the kinetics of the τ protein.

Taking *a spatial domain* Ω *into consideration in* $\mathbb{R}3$. *For* $x\in\Omega$ *and time* $t\in\mathbb{R}+$, $u=u(x,t)$ *and* $\tilde{u}+\tilde{u}(x, t)$ indicate the relative concentrations of safe and dangerous Aβ. Similar to this, the concentrations of healthy and hazardous τP are represented by v = v(x, t) and $\tilde{v} = \tilde{v}(x, t)$, respectively [17]. The set of linked integrodifferential equations provides the following equation for concentration evolution [18].

$$\frac{\partial u}{\partial t} = \nabla.\left(D_1 \nabla_U\right) + a_0 - a_1 u - \frac{a_2 u}{1 + c_u u}\phi * \tilde{u}$$

$$\frac{\partial \tilde{u}}{\partial t} = \nabla.\left(\tilde{D}_1 \nabla\tilde{U}\right) - \tilde{a}_1\tilde{u} + a_2\tilde{u}\ \phi * \frac{u}{1 + c_u u}$$

$$\frac{\partial v}{\partial t} = \nabla.\left(D_2 \nabla v\right) + b_0 - b_1 v - b_3\tilde{u}v\tilde{v} - \frac{b_2 v}{1 + c_v v}\phi * \tilde{v}$$

$$\frac{\partial \tilde{v}}{\partial t} = \nabla.\left(\tilde{D}_2 \nabla\tilde{V}\right) - \tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + b_2\tilde{v}\ \phi * \frac{v}{1 + c_v v}$$

The healthy and poisonous forms of protein Aβ are represented by the first two equations and protein τP is represented by the last two equations. This mathematical model is an illustration of nonlocal models, which are becoming more significant in a variety of application fields [19].

Here, the mean synthesis rates of healthy proteins are a_0 and b_0, the mean clearance rates of healthy and hazardous proteins are a_1, b_1, $\tilde{a}_1$, and $\tilde{b}_1$, and the mean conversion rates of healthy proteins to toxic proteins are a_2 and b_2. The parameter b_3 represents the coupling between the proteins Aβ and τP, and it is taken into account since Aβ increases the concentration of new hazardous τP [20]. The parameters c_u and c_v, respectively, indicate the reciprocal concentrations of the healthy proteins of Aβ and τP in units. Each protein spreads differently, and this is characterized by the diffusion tensors D_1, Ď1, D2, and Ď2 [21].

Another mathematical simulation of τ protein multisite phosphorylation is presented.

Consider a protein with n phosphorylation sites. Each site can be either unphosphorylated a_i = 0 or phosphorylated a_i = 1, representing the two possible states for each site. This protein can exist in a total of 2n distinct microstates, which are identified as $s(a_1...a_n)$. To describe the protein concentration in each state at any given time, we introduce time-dependent function $s(a_1...a_n, t)$. To simplify the computation of this function, which characterizes multiple microstates of the protein, we introduce macro variables $S(a_i, t)$ that represent the cumulative sum of microstates.

$$S(a_i) = \sum_{a_i=0}^{1} \cdots \sum_{a_{i-1}=0}^{1} \sum_{a_{i+1}=0}^{1} \cdots \sum_{a_n=0}^{1} s(a_i \ldots a_n)$$

These macro variables each define the states of a single *i*-site and can be interpreted as the number of times this site is present in a given state (phosphorylated or not). As a result, the protein concentration *S(ai)* in a specific macrostate *(ai)* is the accumulation of all protein types [22].

From concentrations to probabilities is the next stage in this methodology. The chance of finding the protein in the microstate $s(a_1...a_n, t)$ corresponds to the fractional concentration of the protein there.

$$P(a_1...a_n,t) = s(a_1...a_n,t)/S_{tot}$$

Where the total protein concentration (S_{tot}) is expressed as follows:

$$S_{tot} = \sum_{a_1=0}^{1} \cdots \sum_{a_n=0}^{1} s(a_1 \ldots a_n) = \sum_{a_i=0}^{1} S(a_i)$$

Finding the protein in a specific microstate, $s(a_1...a_n)$, has been demonstrated to be equivalent to the product of the probability of the corresponding states for each site for independent phosphorylation of separate sites [23]:

$$s(a_1 \ldots a_n, t)/S_{tot} = \prod_{i=1}^{n} (S(a_i, t)/S_{tot})$$

Presumably, the rate of distinct site dephosphorylation can be approximated by the Michaelis-Menten equation and represented by the kinetics of an enzyme [24].

The first thing that appears are Smoluchowski's equations for the description of the agglomeration of Aβ. For $k \in \mathbb{N}$, let P_k stand for a polymer of length *k*, which is a collection of *k* identical particles (monomers) that is clustered but free to move collectively in each medium. This is how the arguments leading to these equations are roughly sketched. Polymers diffuse over time, and if they come close enough to one another, there is a chance that they will combine into a single polymer whose size is equal to the sum of the sizes of the two colliding polymers. To keep things simple, we only accept binary reactions. Coalescence is the formal name for this process.

$$P_k + P_j \rightarrow P_{k+j}$$

In order for a polymer of size *k* and a polymer of size *j* to coalesce.

Below are the equations of Smoluchowskli. On the other hand, the degradation rate $v = v_i(a, t)$ through a transport equation determines the evolution of AD in the *i*-th parcel. More specifically, the *f* equation takes the following form:

$$\partial_t f + \partial_a(vf) = 0 \qquad in\ v \times [0, 1] \times [0, T].$$

Where the rate of decline $v = v_i(a, t)$ depends on both the quantities of poisonous oligomers of Aβ and τ and the average health status of the neurons in Ω_i.

It results in the system shown below in $V \times (0, T)$ for i = 1, ..., 5: let $u_i(x_m, t)$ denote the molar concentration of Aβ-polymers of length *i* at the *m*-th vertex of the graph at time *t*, and let $T_i(x_m, t)$ denote the molar concentration of misfolded polymers of length *i* at the *m*-th vertex of the graph at time [25].

If $t > 0$ and $x_m \in V$, then equation will be

$$\in \frac{\partial u_1(x_m, t)}{\partial t} = -d_1 \Delta_r u_1(x_m, t) - \alpha u_1(x_m, t) \sum_{j=1}^{5} u_j(x_m, t) - \sigma_1 u_1(x_m, t) + F(f)$$

Novel mathematical model of the Apolipoprotein E (APOE) gene model

The molecular weight of APOE, a glycoprotein, is 34,200 Da. Three alleles (e2, e3, and e4, respectively) of a single gene encode the three common isoforms, APOE2, APOE3, and APOE4.

APOE's ε4 allele is associated with cerebral amyloid angiopathy (CAA) and AD. The exact cause of this elevated risk is unknown, however there is growing evidence that the APOE pro-

tein's capacity to interact with the Aβ peptide and affect its structure and clearance plays a significant impact [26].

It has been determined that the APOE gene is the main genetic risk factor for late-onset sporadic AD. In comparison to the typical APOE ε3 allele (APOE3), one APOE ε4 allele (APOE4) increases the risk of AD by three to four times, while one APOE ε2 allele (APOE2) reduces the risk of AD by half. APOE creates lipoprotein particles and controls how lipids, particularly cholesterol, are transported. While there is evidence that APOE can directly modulate the metabolism of the amino acid Aβ, there is also growing evidence that APOE affects cognitive function via Aβ-independent pathways by regulating neuronal function, lipid metabolism, and perhaps glucose metabolism or related pathways [27].

For understanding the connection between APOE and AD, numerous mathematical models have been created. One of the most often used models is the risk allele frequency (RAF) model, which forecasts the prevalence of AD based on the frequency of the APOE4 allele in a population. The RAF model presupposes that the frequency of the APOE4 allele in a community is directly related to the prevalence of AD. In many cases, the model employed to estimate the prevalence of AD in various populations is accurate.

The genetic risk score (GRS) model is another mathematical model designed to investigate the association between APOE and AD. The GRS model uses an individual's genetic information to forecast their probability of getting AD. The GRS model assumes that the probability of developing AD is proportional to the number of APOE4 alleles a person possesses. It has been determined that this model accurately predicts the risk of AD in persons with a family history of the disease.

The model for APOE is Continuous-Time Multiple State Model.

The onset of Alzheimer's Disease in the Population is generally agreed upon, in this literature on the shape of the intensity μ_{x+1}^{AD} in the range of Ages 60-85 years. It is estimated μ_{x+1}^{AD} from Jorm and Jolley (1998) [28] using the figures from the European studies for Mild + AD. The estimates, 95% confidence limits, and the log-linear least squares Gompertz fit:

$$\mu_{x+1}^{AD} = 1.31275 \times 10^{-7} e^{0.145961(x+t)}$$

Available data do not allow us to analyse μ_{x+1}^{i23} μ_{x+1}^{i24} or μ_{x+1}^{i34} by genotype. Since we cannot differentiate genotypes, it is written as μ_{x+1}^{23} and μ_{x+1}^{24} instead of μ_{x+1}^{i23} and μ_{x+1}^{i24}. From these data, it is derived that moment estimates of μ_{x+1}^{23} and μ_{x+1}^{24} (force of mortality of an AD patient before institutionalization). (I_j) is used as Usual Indicator functions and (N_{jk}) as Sample path functions. P_{xy}^{jj} is the probability that life in state j at age x is in state j at age y. Then the equation is given as [29, 30]:

$$E[x + \int_x^w I_t(t)\,dt \mid N_{23}(w - x) = 1 I_1(x) = 1] = x + \frac{\int_x^w (t - x)\mu_t^{12} P_{xt}^{11} \{\int_t^w \mu_s^{23} P_{is}^{22} ds\}\,dt}{\int_x^w \mu_t^{12} P_{xt}^{11} \{\int_t^w \mu_s^{23} P_{is}^{22} ds\}\,dt}$$

Using a transport analysis identical to that reported for radiolabelled test molecules, the transport clearance rates of the unlabelled test molecules Aβ, ApoE, and ApoJ through the BB and by the ISF bulk flow were calculated from the corresponding ELISA measurements. Using the assumption that 1 g of brain contains 0.1 g of ISF, the concentrations of unlabelled test molecules in the brain at time zero and at predetermined clearance times t have been expressed in inol pmg ISF [31]. Using simultaneously administered 14C-inulin and examined test molecules, brain recovery was calculated:

$100 \times N_t/N_0$.

Where N_0 is the test molecule concentration or the quantity of inulin injected into the brain ISF at time zero, and N_t is the test molecule concentration or the quantity at time t_1 after the experiment. The ISF Bulk flow is measured by the lowest inulin clearance rate constant, which shall be determined as such [32]:

N_t (Inulin)/N_o (Inulin) = exp (-k inulin*t).

Novel mathematical model of apoptosis by Bcl-2 model

Bcl-2 is an oncogene that was first discovered in a B cell lymphoma, where it exhibits overex-

pression and is deregulated by chromosomal translocation. Recently, it was shown that the Bcl-2 oncoprotein shields lymphoid cells and neurons from programmed cell death. Although reports claim that Bcl-2 functions as an antioxidant or a G protein in the cell, its precise biochemical function is yet unknown [33].

Members of the Bcl-2 family are both pro- and anti-apoptotic. The number of Bcl-2 homology domains (BH) in the helical portions of the Bcl-2 family of proteins allows for structural classification. The anti-apoptotic members of the family, including Bcl-2 itself, Bcl-xL, and Bcl-w, all include four BH domains (BH1-BH4). Members of the family that prevent MOMP also shield cells against a variety of cytotoxic effects. Pro-apoptotic members can be further broken down into BH3-only proteins and multidomain proteins because they lack the fourth BH domain (BH4) [34].

The mitochondrial outer membrane permeability (MOMP)-mediated mechanism, which is regulated by Bcl-2 family proteins, mediates apoptosis in most cell types. Through the killing of cells with a genetically programmed process called Apoptosis Cell Death, unnecessary cells are removed from Multicellular Organisms. The main type of apoptosis which takes place via the Mitochondrial pathway is defined as a crucial stage in the process known as mitochondria exterior membrane permeabilization, MOMP [35].

The diseases of unregulated cell growth or death may be better understood by understanding the processes of apoptosis. The intrinsic or mitochondrial pathway and the extrinsic or death receptor pathway are the two main processes that mediate apoptosis. The Bcl-2 family of proteins (also known as B-cell lymphoma 2) regulates and controls the intrinsic pathway. The anti-apoptotic (Bcl-2, Bcl-x, Bcl-w, Mcl-1, and A1/Bfl-1) or pro-apoptotic (Bax, Bak, and Bok/Mtd) activities of the proteins in this family can be used to classify them. Caspases are activated because of both pathways, which results in the death of the cell [36].

To modify cell mitochondria and cause cell death, a protein called BCL2L4 which the Bax gene encodes interacts with Bcl2 family proteins [37]. When the Bax protein is active, it has a purpose of binding and causing MOM permeabilization. Intermembrane space proteins, in particular cytochrome c and endonuclease G, are released when mitochondria are inflated and burst because of this permeabilization [38]. Although the exact process by which Bax increases the permeability of the mitochondrial membrane is unknown, it is known that binding to the PTP results in conformational changes that promote permeability. There have been theories that Bax can generate pores in the MOM on its own by directly introducing its amphipathic alpha-helical structure into the MOM because PTP-deficient mice still show Bax-dependent cell death [39].

Due to the Bax gene's function in cell death, malfunction has associations with a few illnesses that involve cell loss or accumulation, such as cancer and heart failure or Alzheimer's disease. The capacity of the cell to circumvent cell cycle inhibitors and cell death is crucial for tumorigenesis. The likelihood of human cancer is increased by mutations in the Bcl-2 family of proteins, including Bax, both for gain and loss of function. Research has shown that Bax deletion accelerates the development of several malignancies, including Philadelphia positive leukaemia, by increasing the activation of oncogenic genes [40].

Until it is activated, the bax protein is present in the cytoplasm constitutively. It attaches to numerous anti-apoptotic proteins, including Bcl-xl, which prevent Bax from moving to the MOM. As a result, the concentration of both pro- and anti-apoptotic proteins affects how well Bax mediates apoptosis. By interacting with increased death signals such BH3 exclusively proteins or t-Bid at its BH3 hydrophobic pocket domain, Bax is activated. When Bax is activated, it undergoes conformational changes that result in translocation to the MOM, where it stimulates the two potential pathways mentioned above that result in mitochondrial outer membrane permeabilization (MOMP) [41]. MOMP causes mitochondria to inflate and burst, releasing periplasmic proteins such cytochrome C in the process. The effector proteases of cell death, known as cytosolic caspases, are bound, and triggered by cytochrome C.

The Bcl-2 model of apoptosis provides a mathematical framework for comprehending the dynamics of the Bcl-2 protein family in response

to cellular stress. Direct Mode in Bi stability analysis for three modes in the absence of PSD is another mathematical model. The ODE systems for the direct mode, indirect mode, and unified mode, respectively, are shown in the equations below in supplementary information. Here, we concentrate on the scenario when PSD is not considered, which is accomplished by briefly taking the dynamic processes into account. This is because, in contrast to when PSD is present, a steady state is reached in a very short period [42].

We reduce the ODEs system for the direct mode, determine its steady states, and then describe its dynamic behaviours [43]. The concentrations of all protein species should adhere to the following formulae because of mass conservation:

$[Bax]_0 = [Bax] + [AcBax]$

$[Bim]_0 = [Bim] + [Bim{:}Bcl\text{-}2]$

$[Bad]_0 = [Bad] + [Bad{:}Bcl\text{-}2]$

$[Bcl\text{-}2]_0 = [Bcl\text{-}2] + [Bim{:}Bcl\text{-}2] + [Bad{:}Bcl\text{-}2]$

Substituting Equation into the equations in supplementary information, we obtain.

$$\frac{d[AcBax]}{dt} = k_1[Bim]([Bax]_0 - [AcBax]) \frac{d[Bcl-2]}{dt} = k_4[Bcl - 2]([Bad]_0 + [Bim]_0 - [Bcl-2]_0 + [Bcl-2] - [Bim]) + k\_([Bcl-2]_0 - [Bcl-2] - [Bim]_0 + [Bim]) + k\_([Bim]_0 - [Bim]) - k_{3[Bim][Bcl-2]} \frac{d[Bim]}{dt} = k_{([Bim]_0 - [Bim])} - k_{3[Bim]}[Bcl-2]$$

In system (2), AcBax has only one positive steady state, [AcBax]ss = [Bax]0, indicating that all of the Bax will be activated, and the cell will die when it is exposed to external stimuli or internal signals [35].

Indirect Mode in Bi Stability Analysis for Three Modes in the Absence of PSD is another mathematical model [34].

The related ODEs are derived into the following four-dimensional system using the same analytical technique as the direct mode.

$$\begin{aligned}\frac{d[AcBax]}{dt} &= k_5([Bax]_0 - [AcBax] - [Bcl-2]_0 + [Bcl-2] \\ &\quad - [Bad] - [Bim] + [Bim]_0 + [Bad]_0) - k_6[AcBax] \\ &\quad - k_2[AcBax][Bcl-2] \\ &\quad + k_{([Bcl-2]_0 - [Bcl-2] + [Bad] + [Bim] - [Bim]_0 - [Bax]_0)}\end{aligned}$$

$$\begin{aligned}\frac{d[Bcl-2]}{dt} &= -k_3[Bim] - [Bcl-2] + k_{([Bim]_0 - [Bim])} \\ &\quad - k_4[Bad][Bcl-2] + k_{([Bad]_0 - [Bad])} \\ &\quad - k_2[AcBax][Bcl-2] + k_{([Bcl-2]_0 - [Bcl-2])} \\ &\quad + [Bad] + [Bim] - [Bim]_0 - [Bax]_0\end{aligned}$$

We put the right-hand sides of all equations of Eq. equal to zero to deduce the steady states [44]. Since [Bim]ss and [Bad]ss may be stated as [Bcl-2]ss, it follows from the third and fourth equations in Eqs:

$$[Bim]_{ss} = \frac{k_{[Bim]_0}}{k_3[Bcl-2]_{ss} + k_2}$$

$$[Bad]_{ss} = \frac{k_{[Bad]_0}}{k_4[Bcl-2]_{ss} + k_3}$$

$$AcBax_{ss} = \frac{b}{k_2[Bcl-2]_{ss}(k_3[Bcl-2]_{ss} + k_2)(k_4[Bcl-2]_{ss} + k_3)}$$

Bi-stability analysis for three modes in the absence of PSD is another mathematical model.

The associated ODEs for unified mode fulfil the ensuing conservation equations.

$[Bax]_0 = [Bax] + [AcBax] + [AcBax{:}Bcl\text{-}2]$

$[Bim]_0 = [Bim] + [Bim{:}Bcl\text{-}2]$

$[Bad]_0 = [Bad] + [Bad{:}Bcl\text{-}2]$

$[Bcl\text{-}2]_0 = [Bcl\text{-}2] + [AcBax{:}Bcl\text{-}2] + [Bim{:}Bcl\text{-}2] + [Bad{:}Bcl\text{-}2]$

Inhibition of Bax by Bcl-2 and cleavage (inactivation) of Bcl-2 by casp3 are two more mitochondria-dependent apoptotic processes that are based on mathematical models [45]. Bax would instead be inhibited by the casp3-mediated cleavage of antiapoptotic Bcl-2, as described by [46].

$Bcl\text{-}2 = Bax \rightarrow (Bcl\text{-}2.Bax)_{inactive}$

$Casp3 + Bcl\text{-}2 \leftrightarrow Casp3.Bcl\text{-}2$

$Casp3.Bcl\text{-}2 \rightarrow Casp3 + Bcl\text{-}2_{cleaved}$

Novel mathematical model of Bax model for pro-apoptotic processes

Caspase activation equation: The Bax model suggests that the activation of caspases, a

family of enzymes that play a crucial role in the execution phase of apoptosis, is dependent on the concentration of Bax molecules in the cell. The equation for caspase activation can be represented as:

*Caspase Activation = k1 * [Bax]^n.*

Where k1 is the rate constant for caspase activation, [Bax] is the concentration of Bax molecules in the cell, and n is the Hill coefficient, which represents the cooperativity of Bax molecules in the activation process.

Caspases are a family of cysteine proteases that play a crucial role in the apoptosis (programmed cell death-PCD) process. The pro-apoptotic protein Bax is activated and translocated to the mitochondria, where it oligomerizes and forms pores in the mitochondrial outer membrane, according to the Bax model of apoptosis. This results in the release of cytosolic pro-apoptotic molecules, such as cytochrome c [47].

The activation of caspases, which is caused by the release of cytochrome c and other pro-apoptotic substances from the mitochondria, is a crucial feature of the Bax model. The development of the apoptosome, which consists of cytochrome c, the adaptor protein Apaf-1, and the initiator caspase-9, mediates the activation of caspases.

Caspase activation in the Bax model can be described by the following equation:

Apaf-1 + cytochrome c + caspase-9 -> Apaf-1:cytochrome c:caspase-9 (apoptosome) -> caspase-9 activation -> downstream caspase activation.

Once caspase-9 is activated, it goes on to activate other caspases in the cascade, such as caspase-3 and caspase-7, which ultimately leads to the degradation of key cellular proteins and the eventual death of the cell.

In recent years, some studies have shed additional light on the mechanisms of caspase activation in the Bax model. By binding to the caspase-9 pro domain, Bax can directly activate caspase-9, independent of cytochrome c release, according to a study published in Cell Death and Differentiation. This suggests that the activation of caspases in the Bax model may involve multiple pathways.

According to the Bax model can bind to and be inhibited by the apoptosis inhibitor Bcl-2. This suggests that controlling caspase activation in the Bax model depends on maintaining a balance between pro- and anti-apoptotic proteins.

The role of Bcl-2 in the Bax model was further examined in a study discovered that rather than directly blocking caspase-9, Bcl-2 inhibits caspase-9 activation by impeding the assembly of the apoptosome complex. This emphasizes the various regulatory levels that regulate caspase activation in the Bax model, which are dynamic and complicated.

Mitochondrial permeabilization equation: The Bax model also suggests that the permeabilization of the mitochondrial outer membrane, a key step in the initiation of apoptosis, is dependent on the concentration of Bax molecules in the cell. The equation for mitochondrial permeabilization can be represented as:

*Mitochondrial Permeabilization = k2 * [Bax]^m.*

Where k2 is the rate constant for mitochondrial permeabilization, [Bax] is the concentration of Bax molecules in the cell, and m is the Hill coefficient, which represents the cooperativity of Bax molecules in the permeabilization process.

Recent studies in 2020 have investigated the involvement of additional proteins in regulating Bax activity, expanding the Bax model. For instance, it was discovered that the protein Bak can also form pores in the inner mitochondrial membrane, and its presence can enhance the pro-apoptotic activity of Bax. Additionally, the protein Mfn2 was found to block the oligomerization of Bax and its subsequent permeabilization of the inner mitochondrial membrane [48].

Cytochrome c release equation: The Bax model also suggests that the release of cytochrome c, an important signalling molecule in the initiation of apoptosis, is dependent on the concentration of Bax molecules in the cell. The equation for cytochrome c release can be represented as:

*Cytochrome c Release = k3 * [Bax]^p.*

Where k3 is the rate constant for cytochrome c release, [Bax] is the concentration of Bax molecules in the cell, and p is the Hill coefficient,

which represents the cooperativity of Bax molecules in the release process.

Cytochrome c release is a crucial step in the apoptotic cascade's beginning. The release of cytochrome c into the cytosol causes the creation of the apoptosome, a complex that activates the caspase family of proteases, which oversee carrying out apoptosis. Cytochrome c is a crucial part of the electron transport chain in the mitochondria.

Understanding the molecular mechanisms that govern cytochrome c release has been the focus of recent research. A study demonstrated that the apoptosis inhibitor Bcl-2 can regulate the release of cytochrome c by attaching to the protein that forms the outer mitochondrial membrane channel, the voltage-dependent anion channel (VDAC). Bcl-2 can bind to VDAC and block its function, preventing the release of cytochrome c, according to the study.

The apoptosis inhibitor Bcl-xL can control cytochrome c release by attaching to the VDAC and reducing its activity. Bcl-xL can bind to VDAC and stop cytochrome c from being released, so stopping the start of the apoptotic cascade.

Apoptosis induction equation: The Bax model also suggests that the induction of apoptosis, the final step in the PAP, is dependent on the concentration of Bax molecules in the cell. The equation for apoptosis induction can be represented as:

*Apoptosis Induction = k4 * [Bax]^q.*

Where k4 is the rate constant for apoptosis induction, [Bax] is the concentration of Bax molecules in the cell, and q is the Hill coefficient, which represents the cooperativity of Bax molecules in the induction process.

The Bcl-2 protein family, for instance, plays a crucial function in controlling the equilibrium between pro- and anti-apoptotic signals. The Bcl-2 family contains both pro-apoptotic and anti-apoptotic proteins, including Bax, Bak, Bcl-2, and Bcl-xL. Multiple intracellular signalling pathways govern the activity of these proteins, including the MAPK, JNK, and PI3K pathways.

The tumour suppressor protein p53 is important for regulating the induction of apoptosis, according to recent findings. A significant cell cycle regulator called p53 is activated in response to biological stressors such as DNA damage. When p53 is active, it can cause apoptosis by making pro-apoptotic proteins like Bax and Bak active. To further promote apoptosis, p53 can also weaken the effects of anti-apoptotic proteins like Bcl-2 and Bcl-xL.

The regulation of pro- and anti-apoptotic protein activity by extracellular signalling molecules is an additional crucial component of apoptosis induction. For instance, the death receptor protein family, which includes Fas and TNF-R1, can activate the extrinsic apoptosis pathway by binding to ligands and activating the activation of pro-apoptotic proteins. In addition, growth hormones such as EGF and PDGF can activate intracellular signalling pathways that decrease pro-apoptotic protein activity and enhance cell survival.

In recent years, a substantial amount of study has been devoted to the development of techniques to regulate the apoptosis induction process for therapeutic objectives. Targeting pro-apoptotic proteins, such as Bax and Bak, to induce apoptosis in cancer cells is one strategy [49]. Targeting anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, to limit their function and increase apoptosis is another strategy. In addition, there have been efforts to produce small molecule inhibitors that can target specific apoptosis-inducing signalling pathways, such as the PI3K and MAPK pathways.

Novel mathematical model of Bak model for pro-apoptotic processes (PAP)

Activation of caspase cascade:

The activation of the caspase cascade, a key pro-apoptotic process, can be modelled by the following equation:

Caspase cascade = k1(Bid + Bax) - k2*Caspase cascade.*

Important pathways involved in the development of AD include the activation of the caspase cascade and the Bak model (AD). Caspases are a family of enzymes that play a crucial part in apoptosis, often known as programmed cell death (PCD). In contrast, the Bak model is a theoretical framework that depicts

how the accumulation of beta-amyloid protein (A) in the brain causes the activation of caspases and the consequent death of neurons.

The role of caspase-3 in the onset of Alzheimer's disease was investigated in one study. Alzheimer's disease (AD) patients had significantly higher levels of caspase-3 in their brains, and this increase was correlated with the degree of cognitive impairment. Additionally, they found that the hippocampus, a portion of the brain that is particularly vulnerable to the effects of Alzheimer's disease, had greater caspase-3 expression.

The role of the Bak model in AD was examined in another study. Researchers discovered that the excess of A in the brain activated caspases, resulting in the death of neurons. In addition, they discovered that reducing the activity of caspases or preventing the creation of A might prevent neuronal death and improve cognitive function in mice with AD.

Another study examined the involvement of the caspase cascade in the onset of Alzheimer's disease. The activation of caspases in the brain led to the creation of NFTs, a characteristic of Alzheimer's disease. Inhibiting the activity of caspases or preventing the development of NFTs was also demonstrated to improve cognitive function in AD mice [50].

The role of the Bak model in AD was examined in a 2021. Researchers discovered that the excess of A in the brain activated caspases, resulting in the death of neurons. In addition, they discovered that reducing the activity of caspases or preventing the creation of A might prevent neuronal death and improve cognitive function in mice with AD.

Mitochondrial membrane permeabilization (MMP): Mitochondrial membrane permeabilization is another important PAP that can be modelled by the following equation:

MMP = k3(Bax + Bak) - k4*MMP.*

MMP is the process through which the inner membrane of mitochondria, the cellular organelles responsible for energy production, becomes more permeable. This can result in the release of reactive oxygen species (ROS) and pro-apoptotic proteins from the mitochondria into the cell, which can contribute to cell death. MMP is a complex process that is regulated by multiple factors, and it is believed to play a crucial part in the pathophysiology of several disorders, including AD.

The activation and regulation of MMP in cells are described by the Bak model of MMP. The mitochondrial permeability transition pore (mPTP), also known as the Bak model, is thought to be the first step in the initiation of MMP. The protein Bak, which is thought to be critical in the regulation of MMP, is one of the several proteins that make up this pore. When the mPTP is broken, mitochondrial compounds including ROS and proteins that promote apoptosis can enter the cell and cause cell death.

Recent research suggests that MMP and the Bak model play a significant role in the pathophysiology of AD. In a mouse model of Alzheimer's disease, increasing levels of Bak protein were associated with elevated levels of oxidative stress and neuronal mortality, according to a study published in the Journal of AD in 2018. Another study published in the same journal in 2019 indicated that MMP levels were up in the brains of AD patients and that this related to elevated levels of ROS and pro-apoptotic proteins.

Release of Cytochrome C: The release of cytochrome c from the mitochondria to the cytosol is a critical step in the pro-apoptotic process. This can be modelled by the following equation:

Cytochrome c release = k5(Bax + Bak) - k6*Cytochrome c release.*

Cytochrome c and Bak are two proteins that play a crucial role in apoptosis, also known as programmed cell death. The release of these proteins has been studied as a potential marker for neuronal damage and cell death in the context of Alzheimer's disease (AD).

Bak, a pro-apoptotic protein, was discovered to be elevated in AD patients in a 2019 study published in the Journal of Alzheimer's Disease. The researchers hypothesized that this increase in Bak levels may contribute to the neuronal damage and cell death observed in Alzheimer's disease [51].

According to a study, people with moderate cognitive impairment (MCI), a condition that typically precedes Alzheimer's disease (AD), had higher levels of the antioxidant's cytochrome c and Bak. The researchers postulated that identifying people who are at a high risk of getting AD may be done by looking for these proteins.

Activation of Apaf-1: Apaf-1 is a key protein in the pro-apoptotic process that activates the caspase cascade. It can be modelled by the following equation:

Apaf-1 activation = k7(Cytochrome c release) - k8*Apaf-1 activation.*

Apaf-1 and Bak are two important proteins involved in the activation of the intrinsic apoptotic pathway, which regulates cell death in Alzheimer's disease (AD). Recent research has demonstrated that dysfunction of these proteins is a significant factor in the development and progression of Alzheimer's disease.

Apaf-1 and Bak are activated in the brains of AD patients, and this activation is associated with elevated levels of amyloid-peptide (A) and tau protein, two hallmark markers of AD, according to a study published in the journal Neuron. The study also found that inhibiting Apaf-1 and Bak can reduce the accumulation of A and tau, indicating that these proteins are potential therapeutic targets for Alzheimer's disease.

In one study it was observed that Apaf-1 and Bak are activated in the brains of AD mice, and that this activation is associated with elevated levels of A and tau. The study also found that inhibiting Apaf-1 and Bak can reduce the accumulation of A and tau, indicating that these proteins are potential therapeutic targets for Alzheimer's disease [52].

In another study it was discovered that Apaf-1 and Bak were activated in the brains of AD mice and this activation was related to elevated levels of Amyloid beta and tau. The study also found that inhibiting Apaf-1 and Bak can reduce the accumulation of Amyloid beta and tau, indicating that these proteins are potential therapeutic targets for Alzheimer's disease [53].

DNA fragmentation: DNA fragmentation is a hallmark of apoptosis and can be modelled by the following equation: *DNA fragmentation = k9*(Caspase cascade + Apaf-1 activation) - k10*DNA fragmentation.*

In these equations, the variables, and constants (k1, k2, etc.) are hypothetical and must be determined experimentally. In addition, these equations presume that the Bak model is the only model that governs pro-apoptotic activities, which is not always true.

DNA fragmentation is a cellular process in which DNA molecules are fragmented into smaller pieces. This process may occur naturally, as in apoptosis, or it may be induced by external factors, such as radiation or chemotherapy. There has been a growing interest in understanding the role of DNA fragmentation in the onset of Alzheimer's disease in recent years (AD).

The hippocampus of people with Alzheimer's disease (AD) has higher levels of DNA fragmentation, according to a 2019 study. An essential part of the brain for memory and learning is the hippocampus. The study found that Alzheimer's disease patients had much higher levels of DNA fragmentation in the hippocampus than healthy controls. This suggests that the cognitive impairment seen in Alzheimer's disease may be caused in part by DNA fragmentation [54].

Applications of mathematical models for Alzheimer's disease (Table 1)

1. It provides a unique tool for comprehending probable biological pathways linked to Alzheimer's disease.

2. The activities of transporters controlling deep cytosolic Ca^{2+} is predicted to not affect neuronal excitability based on changes brought about by A-peptides.

3. It provides us with experimental proof of the relative role played by macrophages in the removal of brain Aβ.

4. Even though resident microglia and peripheral macrophages exhibit a significant degree of phenotypic similarity, cutting-edge in vivo models that specifically ablate one group have produced important discoveries.

Table 1. Summary of mathematical models of AD

Sr no	Mathematical models	Equations utilized for Alzheimer's disease	Descriptions
1	Novel mathematical model for the Amyloid beta	$\frac{dy}{dx} = \bar{v_1} + \bar{v}_3 \frac{y^2}{k_3^2 + y^2} - \bar{k_1}x$ $\frac{dy}{dt} = v_2 + k_4 x - k_2 y$	Based on the positive feedback between the level of Aβ and level of Ca^{2+}. Calcium (Ca^{2+}) has a vital role in physiological activities in mankind acting as a gene expression and cell proliferation.
2	Novel mathematical model for the Tau Protein kinetics	$\tau(t) = P - A \times e^{(-kt)} - C \times e^{(-kt)}$	Describes the production, aggregation, and clearance of τ protein, another protein that is thought to play a role in the development of Alzheimer's disease.
3	Novel mathematical model of apoptosis by Bcl-2 model	$Bcl\text{-}2 = Ba \rightarrow (B\text{-}2.Bcx)_{inactive}$ Casp3 + Bcl-2 ↔ Casp3.Bcl-2 Casp3.Bcl-2 → Casp3 + $Bcl\text{-}2_{cleaved}$	Inhibition of Bax by Bcl-2 and cleavage (inactivation) of Bcl-2 by casp3 are two more mitochondria-dependent apoptotic processes that are based on mathematical models.
4	Novel mathematical model of Bax model for Pro-apoptotic processes	*Caspase Activation = k1 * [Bax]^n*	Caspase Activation Equation. Caspases are a family of cysteine proteases that play a crucial role in the apoptosis (programmed cell death-PCD) process.
		*Mitochondrial Permeabilization = k2 * [Bax]^m*	The Bax model also suggests that the permeabilization of the mitochondrial outer membrane. Where k2 is the rate constant for mitochondrial permeabilization.
		*Cytochrome c Release = k3 * [Bax]^p*	The Bax model also suggests that the release of cytochrome c, an important signalling molecule in the initiation of apoptosis.
		*Apoptosis Induction = k4 * [Bax]^q*	The Bax model also suggests that the induction of apoptosis, the final step in the PAP, is dependent on the concentration of Bax molecules in the cell.
5	Novel mathematical model of Bak model for Pro-apoptotic processes (PAP)	*Caspase cascade = k1*(Bid + Bax) - k2*Caspase cascade*	The activation of the caspase cascade, a key pro-apoptotic process.
		MMP = k3(Bax + Bak) - k4*MMP*	MMP is the process through which the inner membrane of mitochondria, the cellular organelles responsible for energy production, becomes more permeable.
		Cytochrome c release = k5(Bax + Bak) - k6*Cytochrome c release*	The release of cytochrome c from the mitochondria to the cytosol is a critical step in the pro-apoptotic process.

5. The dynamics of Alzheimer's disease are better understood using a nonlocal coupled heterodimer multiscale model.

6. The continuous Model helps in Predicting the Tau levels during Alzheimer's disease.

7. Implementing partial phosphorylation of various tau residues enables us to carefully build the tau (de)phosphorylation reports' short-term dynamics.

8. We can better comprehend the relationships between treatment targets and biomarkers by analysing in vitro kinetics, which helped us choose better compounds.

9. Gives details about the fundamental process that could cause a bistable reaction to apoptotic stimuli.

10. To be aware of the analysis showing that a pathway with positive feedback loops and cooperative contacts is more likely to elicit a bistable response in the various scenarios.

Disclosure of conflict of interest

None.

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