Studying Alzheimer's disease pathogenesis using a systems biology approach

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Abstract: Alzheimer's disease (AD) is the most common form of dementia among the elderly, affecting approximately 1 in 6 individuals over the age of 65. To help study the progression of AD, we have developed a mixed metabolic-lipidomic-proteomic network to represent the key interactions in pathways that have been linked to AD. We will present simulation results which study how robust feedback plays an important role in the disease process, as well as how varying cholesterol and LRP concentration levels affects the level of beta amyloid in the system, such as is seen in AD.

Introduction:

Alzheimer's disease (AD) is:
- most common form of dementia among the elderly
- affects about 1 in 6 over age 65 (or 5.3 million people in the US)
- a growing socioeconomic issue

Diagnosis is given post-mortem by observation of brain pathology & pre-mortem behavior:
- presence of diffuse beta amyloid plaques and oligomers in brain parenchyma & cerebrovasculature
- hyperphosphorylated tau protein in neuronal axons
- loss of short- and long-term memory
- loss of spatial orientation
- loss of voluntary muscle control

Other pathologies that are present and may be contributing factors to AD are:
- neuroinflammation
- mitochondrial dysfunction & other metabolic abnormalities
- decrease in expression of LRP-1 (low density lipoprotein receptor-related protein)

Several risk factors have been suggested:
- presence of ApoE4 allele
- cardiovascular & cerebrovascular disease
- plasma hypercholesterolemia
- traumatic brain injury (TBI)
- infections

The **unifying factors** in many of the risk factors is the presence of **chronic inflammation** & **alterations in cholesterol metabolism**. This poster will discuss a systems biology model that has been developed to study how alterations in cholesterol and LRP levels affect generation of beta amyloid and APP (the amyloid precursor protein).

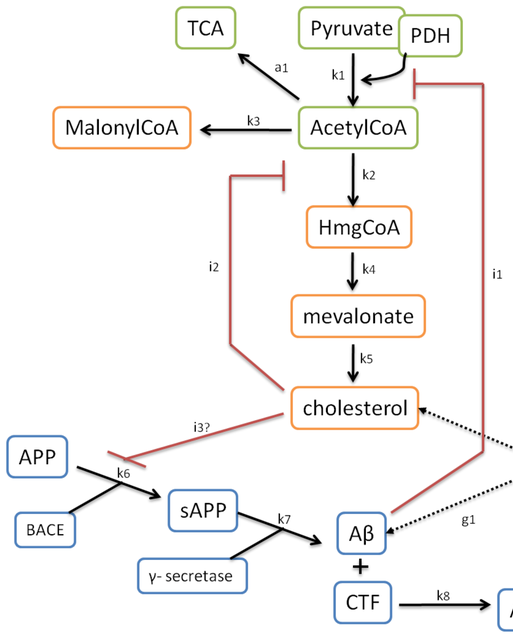
Model Goals:

- Develop the **first** systems biology model for Alzheimer's disease to study the role of cholesterol.

- The ideal model will be capable of answering the following questions:
  - What are the key nodes and regulatory points in the described network?
  - Does inhibition of BACE activity by cholesterol fit with the known data?
  - How does varying the expression levels of LRP-1 alter steady state levels of Aβ?

Model Assumptions:
- Molecules reside in two possible compartments:
  - brain (limited concentration levels)
  - blood (infinite sink)
- Within the brain, there are several cell types or areas that can contain molecules of interest:
  - **Neurons:** Contains cholesterol, interacts with ApoE at the cell membrane
  - **Astrocytes:** Produces cholesterol and ApoE to interact with neurons
  - **Parenchyma:** Contains free cholesterol and ApoE

Network Topology: A topological network describing the interactions between the simplified proteomic, lipidomic and metabolic pathways have been derived (Figure 1). The network was simplified to include only those molecules that are most relevant from a biological standpoint and directly relevant to the questions that we were trying to ask. There are 15 rate constants and a total of 17 molecules in the network. The degree of each major node was calculated and is listed in Table 1.



Node	Degree
AcetylCoA	5
HmgCoA	3
Mevalonate	2
Cholesterol	4
Aβ	3
ApoE	3
LRP-1	2

Figure 1: Network topology for mixed proteomic-lipidomic network to study AD. Precursor molecules (green boxes), lipidomic molecules (orange), and proteomic molecules (blue, purple and red) are described. Inhibitory interactions are given by a red line with a blunted bar, metabolic reactions between precursor and product are described by solid black lines, and binding interactions between molecules are given by dotted, black lines. **Table 1 (right inset): Degree of Key Nodes.** AcetylCoA has the highest degree, followed by cholesterol. **Acronyms used: APP**: amyloid precursor protein; **ApoE:** apolipoprotein E; **AICD:** APP intracellular domain; **Aβ:** beta amyloid; **CTF:** C-terminal fragment; **HmgCoA:** 3-hydroxy-3-methylglutaryl-coenzyme A; **LRP-1:** low density lipoprotein receptor-related protein; **PDH:** pyruvate dehydrogenase; **TCA:** the citric acid cycle

Equations: The following system of equations was derived to describe the above network. Acetyl coenzyme A is generated from its precursor, pyruvate, at a rate that is inhibited by beta amyloid:

$$\frac{dACoA}{dt} = k_1\left(\frac{1}{1+\alpha[A\beta]}\right)[pyruvate] - k_2[ACoA] - a_1[ACoA]$$

ApoE is either found in astrocytes or as a free form in the parenchyma:

$$\frac{dapoe}{dt} = b_n - k_{f1}[Abeta][apoe] + \left(\frac{k_{f2}+k_{f3}}{\left([Abeta]+\left(\frac{k_{f2}+k_{f3}}{k_{f1}}\right)[LRP]\right)}\right)[LRP][Abeta][apoe] + t_1[ApoE_A] - d_5[apoe]$$

$$\frac{dapoE_A}{dt} = b_a - t_1[ApoE_A] - ([apoe_A] - [cholA])$$

Beta amyloid is generated from APP through a series of 2 cleavages:

$$\frac{dAbeta}{dt} = k_7[sAPP] - endo[Abeta] - k_{f1}[Abeta][apoe] - k_t[Aeta][LRP] \qquad \frac{dAPP}{dt} = b_1[APP] - k_6[APP]\left(\frac{1}{1+\beta[cholN]}\right) - d_3[APP]$$

Cholesterol can be either astrocytic or neuronal, and is generated from mevalonate:

$$\frac{dmev}{dt} = k_4\left(\frac{1}{1+\gamma[cholN]}\right)[HmgCoA] - k_5[mev] \qquad \frac{dcholA}{dt} = k_5[mev] - t_1[ApoE_A] - d_2[cholA]$$

$$\frac{dchol_N}{dt} = t_1[ApoE_A] - d_2[cholN]$$

Simulation Results:

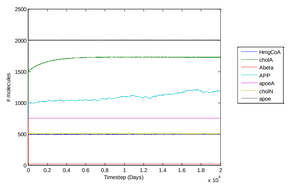


Figure 2: Reference Simulation. Convergence was reached for all simulated molecules within the first 6000 days of the simulation. Only APP continued a slowly upward trend during the entirety of the simulation, increasing from an initial value of 1000 to a final value of 1183. Not shown is AcetylCoA levels, which converged from 10,000 to 8845.

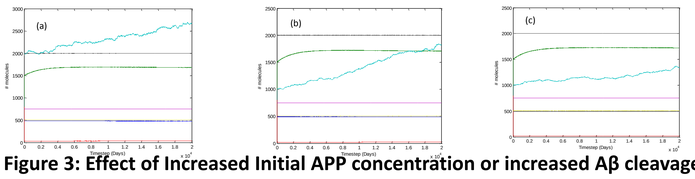


Figure 3: Effect of Increased Initial APP concentration or increased Aβ cleavage. (a) Initial APP levels were doubled, leading to a significant increase in the amount of APP and Aβ present in the system. HmgCoA levels began to drop slightly as Aβ levels started to increase. Final APP level: 2672; final Aβ level: 40 (b) Aβ generation rates were increased by 25%, leading APP levels to nearly double. Ironically, Aβ levels did not change significantly. Final APP level: 1821; final Aβ level: 27 (c) Aβ generation rates were increased by 12.5%, leading APP levels to increase slightly. Aβ levels did not change significantly. Final APP level: 1345; final Aβ level: 20

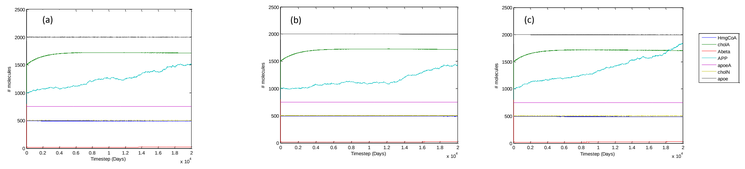


Figure 4: Effect of Decreased LRP: (a) LRP levels decreased by 25%. Final APP: 1520; final Aβ: 23. (b) LRP levels decreased by 50%. Final APP: 1431; final Aβ: 22. (c) LRP levels decreased by 75%. Final APP: 1828; final Aβ: 29.

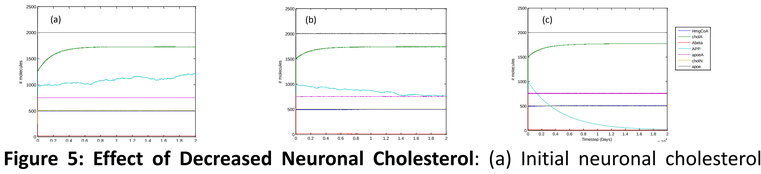


Figure 5: Effect of Decreased Neuronal Cholesterol: (a) Initial neuronal cholesterol decreased by ½. Final APP: 1207; final Aβ: 18. (b) Cholesterol transfer rate decreased by 50%. Final APP: 781; final Aβ: 12. (c) Cholesterol transfer rate decreased by 90%. Final APP: 14; final Aβ: 0.

Conclusion:

We have developed a systems biology model with a graph theoretic approach to studying processes in the development of AD

Future Directions:

We are currently expanding the model to include a network to describe a basic inflammatory pathway, as well as transition to a bipartite graph theoretic approach to reduce possible variability inherent in our current approach

References:

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