Investigating the Role of Cholesterol in Alzheimer's Disease using Systems Biology:

A Preliminary Report

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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting 1 in 8 individual over the age of 65. A growing body of evidence is suggesting that cholesterol levels in both the brain and the plasma may play significant roles in AD pathogenesis; however, the exact nature of this role is currently not well understood. Building on previous experiments, we have approached this problem using two, complementary methods- a systems biology model for biomolecular networks in the brain that is based on empirical data gathered from the literature and *in vivo* experiments. The systems-level network consists of 6 nodes: 5 nodes representing the various cell types present in the brain and a node representing the brain ECM. Each cellular node contains a sub-network representing the biomolecular (proteomic, metabolic and lipidomic) network of that specific cell type. Sub-nets are capable of interacting and influencing each other, leading to shifts in the weights of sub-network nodes. We have simplified the network described here to specifically study the effect of regulation that is believed to exist between cholesterol and the production of the beta amyloid protein.

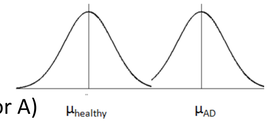
Background:

- Brain contains the highest level of cholesterol of all organs in the human body (~25%; Bjorkhem 2004):
  - 80% necessary for producing myelin
  - Remainder necessary for:
    - Maintenance of plasma membrane fluidity
    - Synaptic vesicle & synapse formation
    - Neurite extension
- In AD, the level of cholesterol in both the blood plasma and the brain is believed to play a role in pathogenesis:
  - High plasma cholesterol, due to hypercholesterolemia or heart disease, leads to ↑ Aβ deposition (Refolo 2000, Puglielli 2003)
  - Increased APP levels lead to:
    - ↓ in LRP-1 & cholesterol
    - ↑ in apoE (Liu 2007)
- Synthesis & regulation of cholesterol in the brain is just starting to be understood
  - Cholesterol is believed to inhibit BACE activity, preventing generation of Aβ (Crameri 2006)
  - Aβ is believed to inhibit AcetylCoA production by inhibiting the action of pyruvate dehydrogenase (Hoshi 1996)
- Currently no quantitative model to study this
  - Would provide a method to study this possible regulation using control & systems theory, reducing the difficulty to study the system

Simplifying the Complex: Model Assumptions

- Every cell of the same type has a similar biochemical network, with only minor variations between different cells
  - Implications:
    - Single or small groups of aberrant cells do not have an effect on the entire system
    - Outliers are removed via apoptosis
- External or environmental cues will act on all cells similarly, with only minor variations between cells
- Aside from synaptic transmission, there is minimal, direct chemical cross talk between cells of the same type
  - Implication:
    - The biochemical network between cells of the same type are independent of each other
- This allows us to represent each cellular node as a network with a sample distribution given by:

~ Normal($\mu_{j,k}$, $\sigma_{j,k}$/sqrt($n_{j,k}$)),
where:
n = # cells of type j in sample (>10^6 cells, except for A)
k = molecule of interest



Modeling Equations:

Ordinary differential equations (ODEs) were developed to model the interactions between cholesterol and Aβ to study the role of feedback inhibition.

$$\frac{dACoA}{dt} = k[PDH][pyruvate] - k_1[A\beta] - k_{chol}k_T[ACoA] - k_{FA}k_T[ACoA]$$

$$\frac{dHmgCoA}{dt} = k_{chol}k_T[ACoA] - [HmgCoA] - k_l[chol]$$

$$\frac{dMCoA}{dt} = k_{FA}k_T[ACoA] - [MCoA]$$

$$\frac{dmev}{dt} = [HmgCoA] - [mev]$$

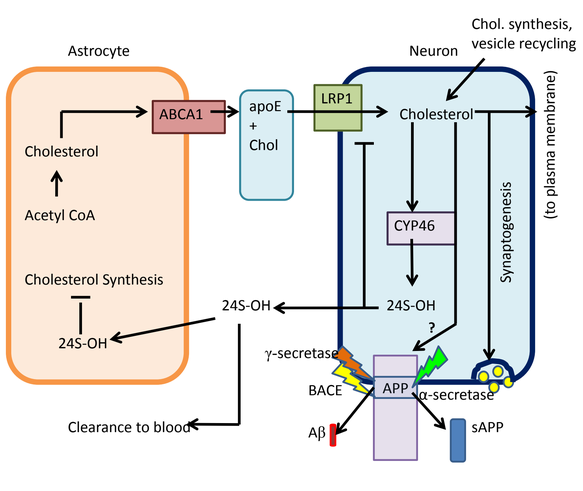
$$\frac{dchol}{dt} = [mev] - k_D$$

With regulation:

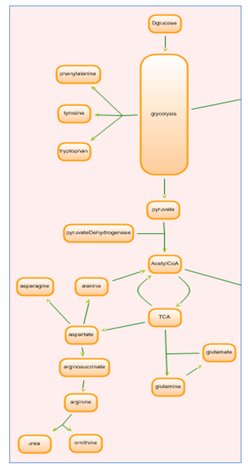
$$\frac{dA\beta}{dt} = k_2[BACE][APP] - k_R[chol]$$

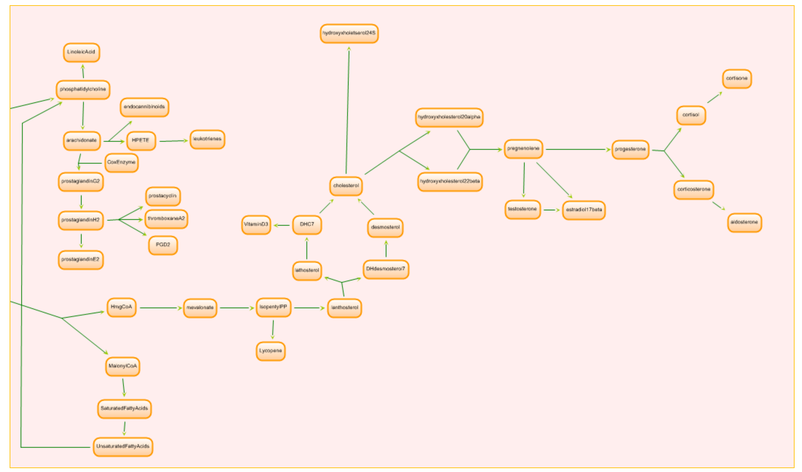
$$\frac{dA\beta}{dt} = k_{BACE}\left(1 - \left(\frac{chol}{1000}\right)\right)[APP]$$

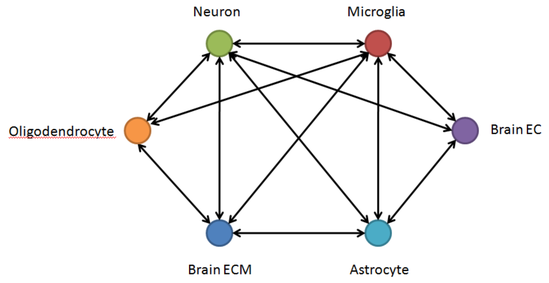
Networks:



Cholesterol & Aβ: (Above) The current understanding of cholesterol synthesis in the brain. Note that in the adult, it is believed that all cholesterol is synthesized by astrocytes and transported to neurons the ABCA1/LRP-1 route with apoE as the carrier protein.



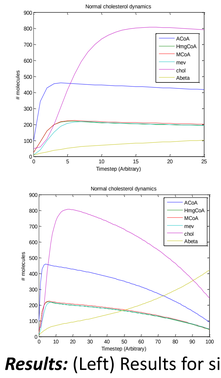




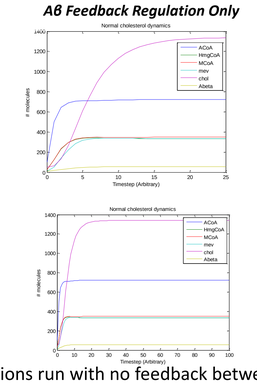
Network Hierarchies: (Above) The metabolic and lipidomic network that we are studying is given above. The simulations in this study focused on the network described by cholesterol and fatty acid synthesis from AcetylCoA. It is believed that regulation by Aβ modulates cholesterol synthesis, in addition to the inhibition of BACE activity by cholesterol that has been observed. (Left) The top level, cellular network that we have developed. Given the assumptions that we derived, each cell type in this network can be described by a normal distribution with some mean value for each biomolecule.

Simulation Results:

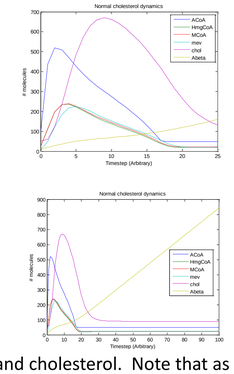
No Feedback Regulation



Aβ Feedback Regulation Only



Cholesterol & Aβ Feedback Regulation



Results: (Left) Results for simulations run with no feedback between Aβ and cholesterol. Note that as the # of timesteps increases, the simulation becomes unstable. (Center) Feedback regulation of Aβ is studied by introducing a term for inhibition of BACE activity via cholesterol. The simulation quickly converges. (Right) Both cholesterol and Aβ have been regulated by each other here in a simplified feedback loop. Our results are interesting since they show cholesterol and fatty acid synthesis converge to low levels quickly, though Aβ continues to rise. Further simulations are needed to verify if this is accurate.

Discussion & Conclusion:

- We have developed a simplified model to study feedback regulation between cholesterol and Aβ in the brain
- We have also started to develop a systems-level model to integrate metabolic, proteomic and lipidomic networks to have more accurate simulations
- We have shown that a top-down approach is valid by developing a high level network consisting of interactions between various cellular components and the brain ECM, each containing sub-networks describing the distribution of biomolecules
- In the future, we would plan on identifying key nodes in the biomolecular network & performing further, more detailed simulations
- We are also conducting *in vivo* experiments to study the effect of decreased cholesterol on the distribution of key protein (Aβ, LRP, apoE).

References:

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Acknowledgments: Research is partially funded by industrial collaboration funds of the HyNet Center at the University of Maryland, College Park.