A systems biology model studying the role of cholesterol in Alzheimer's disease pathogenesis

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Abstract: A simplified network describing the interactions between the cholesterol and beta amyloid (Aβ) synthesis pathways was generated using information available from the KEGG database and literature. A system of ordinary differential equations was developed and modeled using Matlab. Rate constants and molecular concentrations were approximated using ratiometric data. Simulations demonstrated the importance of negative feedback control by cholesterol in the regulation of beta amyloid levels.. Eliminating negative feedback by beta amyloid on cholesterol, as well as decreasing the initial levels of cholesterol or Aβ, led to no changes in the steady state levels of molecules studied. Future work will look further at the role of the negative feedback loop that cholesterol provides both *in silico* as well as *in vivo* with an APP/PS1 transgenic mouse model.

Background & Introduction

- 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

Model Assumptions:

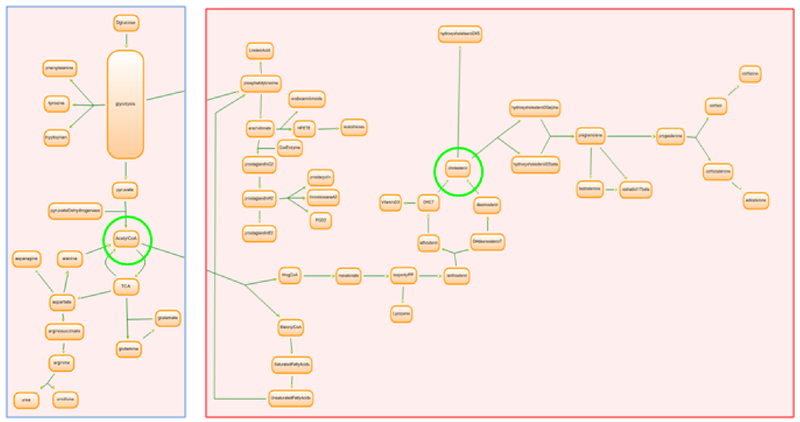
- Every cell of the same type has a similar biochemical network, with only minor variations between different cells
  - Implications:
    - Single or small groups of aberrant cells do not have an effect on the entire system
    - Outliers are removed via apoptosis
- External or environmental cues will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

$$\sim \text{Normal}(\mu_{j,k}, \sigma_{j,k}/\text{sqrt}(n_{i.k})),$$

where:
n = # cells of type j in sample
k = molecule of interest

- *This model focuses on **the interrelationship between the biochemical pathways for cholesterol and Aβ** in general*

Visual Node Identifications: Nodes with High Degree or Impact



Model Basics: Negative Feedback & Related Equations

$$\frac{dACoA}{dt} = k\left(\frac{1}{1+k_\beta[A\beta]}\right)[PDH][pyruvate] - k_S[ACoA] - k_{chol}k_T\left(\frac{1}{1+k_\gamma[chol]}\right)[ACoA] - k_{FA}k_T[ACoA]$$

$$\frac{dHmgCoA}{dt} = k_{chol}k_T\left(\frac{1}{1+k_\gamma[chol]}\right)[ACoA] - k_2[HmgCoA]$$

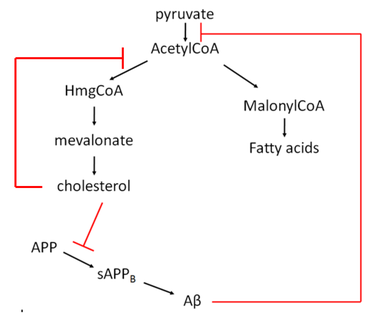
$$\frac{dMCoA}{dt} = k_{FA}k_T[ACoA] - [MCoA]$$

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

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

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

Cholesterol & Aβ: (Above) Feedback regulation between cholesterol & Aβ



***Simulation Results**: Role of Negative Feedback Regulation*

Role of AcetylCoA Degradation Rate

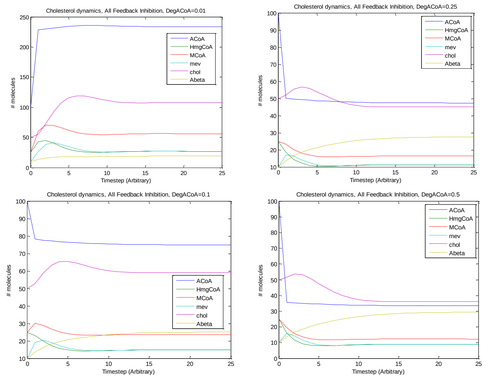


Figure 1: Simulation results for various AcetylCoA degradation rates (k_{deg} = 0.01, 0.1, 0.25, 0.5). Low levels of AcetylCoA lead to slightly increased levels of beta amyloid.

Role of Feedback Inhibition

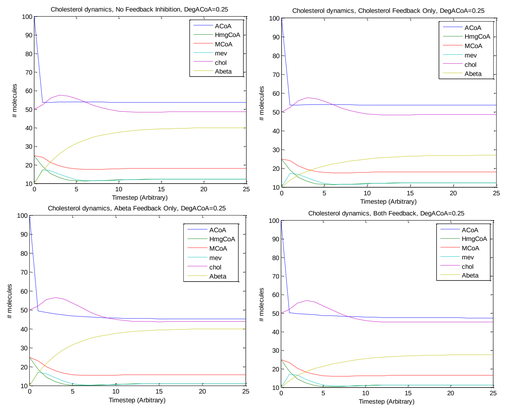


Figure 2: ~50% increased levels of beta amyloid when no feedback control by cholesterol. When feedback by Aβ is removed, normal levels of cholesterol and Aβ observed.

Effect of Initial ACoA + Feedback

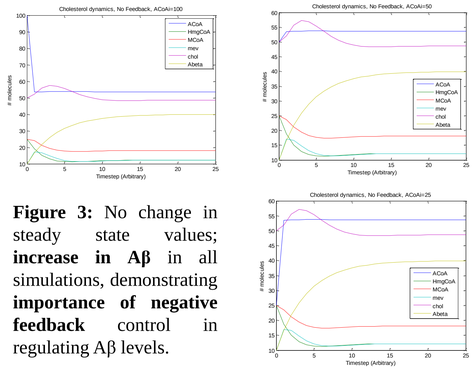


Figure 3: No change in steady state values; **increase in Aβ** in all simulations, demonstrating **importance of negative feedback** control in regulating Aβ levels.

Role of Cholesterol Levels

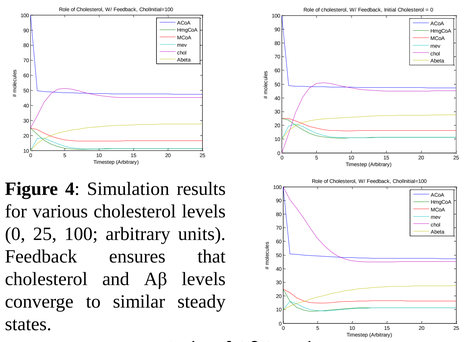


Figure 4: Simulation results for various cholesterol levels (0, 25, 100; arbitrary units). Feedback ensures that cholesterol and Aβ levels converge to similar steady states.

Role of Aβ Levels

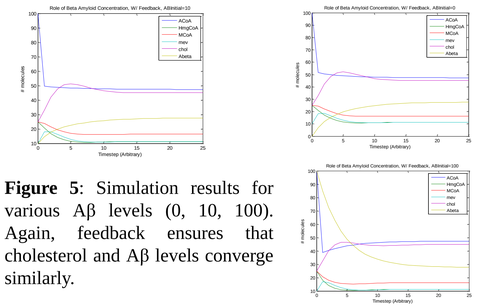


Figure 5: Simulation results for various Aβ levels (0, 10, 100). Again, feedback ensures that cholesterol and Aβ levels converge similarly.

Preliminary Biology Experiments:

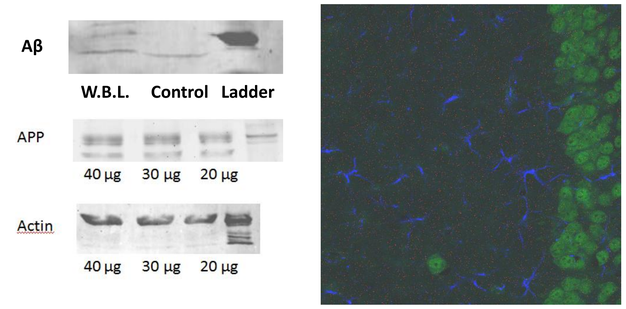


Figure 6: (Left) Western blot preliminary results for Aβ and APP, with an actin control. (Right) Immunohistochemistry of hippocampal slices (p30-35 CBL57 WT mice). Neurons (green, NeuN), astrocytes (blue, GFAP), beta amyloid (red, DE2B4), taken with a Zeiss confocal microscope, 60x oil.

Discussion & Conclusion:

- We have developed a simplified model to study feedback regulation between cholesterol and Aβ in the brain, showing that **feedback regulation between cholesterol and Aβ is essential**
- 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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Acknowledgements

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