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 basic parameter estimation. Initial 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. The model was then adapted to include compartmentalization of cholesterol and ApoE into neuronal, astrocytic and free ApoE. This adapted model was used to study the effect of decreasing ApoE, decreased neuronal cholesterol, decreased acetyl CoA, as well as decreased LRP-1 expression. Future work will continue to expand on the model to include further compartmentalization, where applicable, as well as the possible effect of statin treatments on the concentration levels of key proteins (Aβ, ApoE, LRP-1). Future models will also use a Monte Carlo simulation method to study the effect of noise on such a system.

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
  - Could also help identify key chemicals or regulatory steps that could be used in future treatments

Basic Model Basics: Negative Feedback & Related Equations

$$\frac{dACoA}{dt} = k\left(\frac{1}{1+k_\beta[A\beta]}\right)[PDH][pyruvate] - k_5[ACoA] - k_{chol}k_T\left(\frac{1}{1+k_\gamma[chol]}\right)[ACoA] - k_{FA}k_T[ACoA]$$

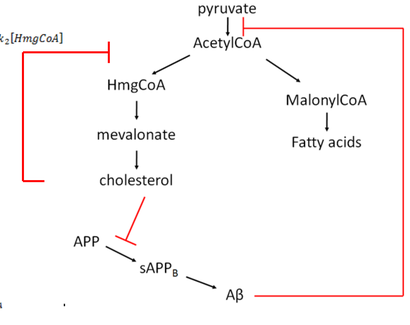
$$\frac{dHmgCoA}{dt} = k_{chol}k_T\left(\frac{1}{1+k_\gamma[chol]}\right)[ACoA] - k_2[HmgCoA]$$

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

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

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

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



Simulation Results: Role of Negative Feedback Regulation

Standard Simulation

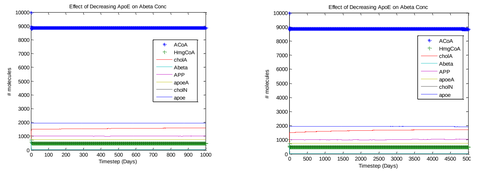


Figure 1: Standard run (**left**) Short term (**right**) Long term run

Effect of Decreasing Levels of ApoE

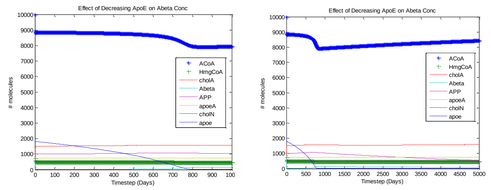


Figure 2: Decreased levels of ApoE lead to slightly increased levels of beta amyloid with an initial decrease in AcetylCoA concentration. (**left**) Short term (**right**) Long term run

Effect of Decreasing Levels of Acetyl CoA

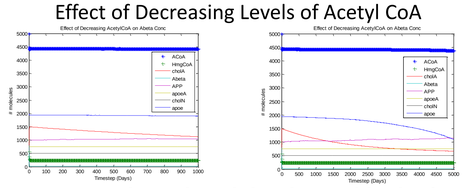


Figure 3: Decreased AcetylCoA led to decreased levels of astrocytic cholesterol and free ApoE, while increasing APP levels & mildly increasing Aβ levels

Effect of Decreasing Levels of Neuronal Cholesterol

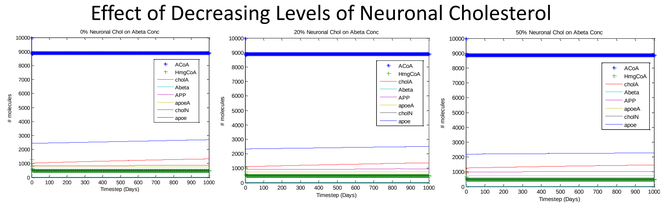


Figure 4: Decreased AcetylCoA led to decreased levels of astrocytic cholesterol and free ApoE, while increasing APP levels & mildly increasing Aβ levels

Effect of Decreasing Levels of LRP

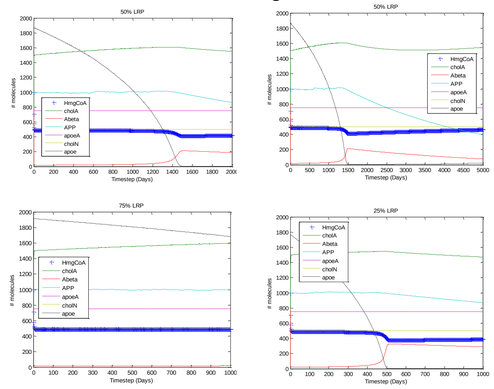


Figure 5: Decreased LRP led to significantly decreased levels of free ApoE, decreased levels of APP, and increased Aβ levels when LRP is decreased by 50% or more

Simulation Results: Role of Negative Feedback Regulation

Role of AcetylCoA Degradation Rate

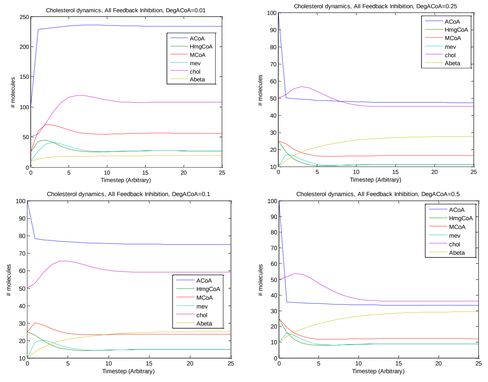


Figure 1: Simulation results for various AcetylCoA degradation rates (k_{deg} = 0.01, 0.1, 0.25, 0.5). Low levels of AcetylCoA lead to slightly increased levels of beta amyloid.

Role of Feedback Inhibition

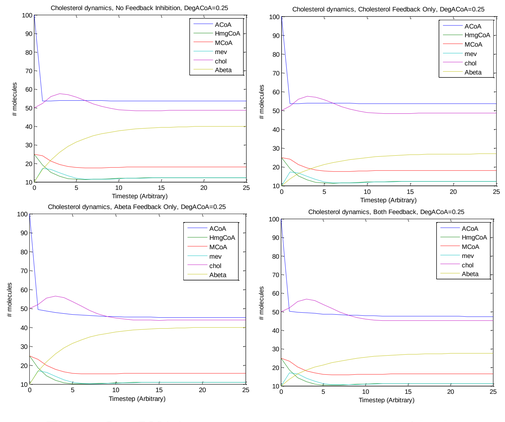


Figure 2: ~50% increased levels of beta amyloid when no feedback control by cholesterol. When feedback by Aβ is removed, normal levels of cholesterol and Aβ observed.

Effect of Initial ACoA + Feedback

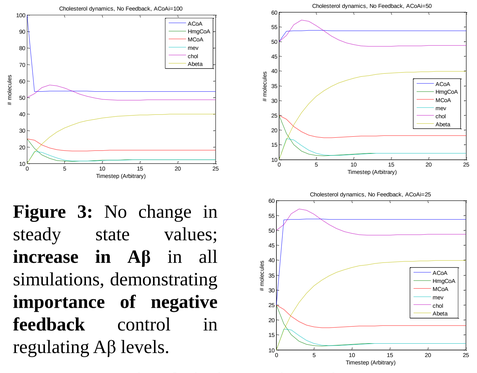


Figure 3: No change in steady state values; **increase in Aβ** in all simulations, demonstrating **importance of negative feedback** control in regulating Aβ levels.

Role of Cholesterol Levels

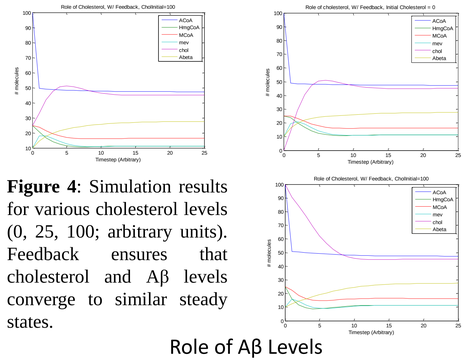


Figure 4: Simulation results for various cholesterol levels (0, 25, 100; arbitrary units). Feedback ensures that cholesterol and Aβ levels converge to similar steady states.

Role of Aβ Levels

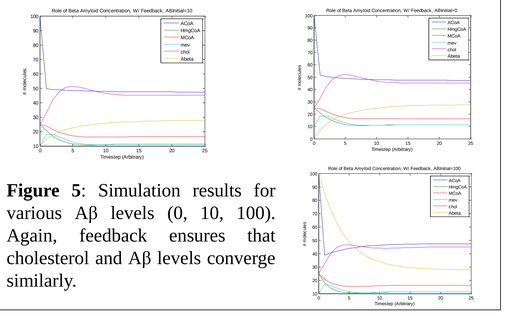
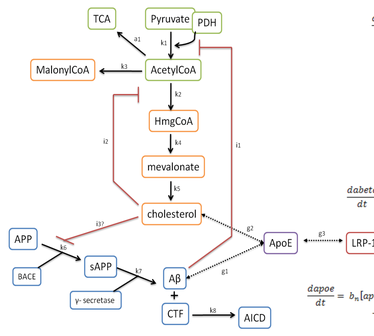


Figure 5: Simulation results for various Aβ levels (0, 10, 100). Again, feedback ensures that cholesterol and Aβ levels converge similarly.

Model Network & Equations for Compartmental Model:



$$\frac{dACoA}{dt} = k_1[pyruvate] - k_2[ACoA] - k_3[ACoA] - a_1[ACoA]$$

$$\frac{dHmgCoA}{dt} = k_2[ACoA] - k_4\left(\frac{1}{1+\gamma cholN}\right)HmgCoA$$

$$\frac{dmev}{dt} = k_4[HmgCoA] - k_5 mev$$

$$\frac{dAPP}{dt} = b_1 APP - k_6\left(\frac{1}{1+\beta cholN}\right)[APP] - d_3[APP][ACoA]$$

$$\frac{dsAPP}{dt} = k_6\left(\frac{1}{1+\beta cholN}\right)[APP] - k_7[sAPP]$$

$$\frac{dabeta}{dt} = k_7[sAPP] - endo[Abeta] - k_{f1}[Abeta][apoe] - k_t[Abeta][lrp]$$

$$\frac{dchol}{dt} = k_5 mev - t_1 cond[apoeA] - d1$$

$$\frac{dapoeA}{dt} = b_a - [apoeA]$$

$$\frac{dapoe}{dt} = b_a[apoe] - k_{f1}[Abeta][apoe]((kf2 + kf3)[lrp]((Abeta * apoe)/(Abeta + (((kf2 + kf3)/kf1) * lrp)))) - d5[apoe * mev] - t_1 cond[apoeA] - d1$$

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 plan on expanding on the current networks, as well as complete Monte Carlo simulations to study the effect of noise on the system
- We are also conducting *in vivo* experiments to study the effect of decreased cholesterol and inflammation on the distribution of key protein (Aβ, LRP, apoE).

References:

1) Bjorkhem, I. and S. Meaney (2004). "Brain cholesterol: long secret life behind a barrier." Arterioscler Thromb Vasc Biol 24(5): 806-15.
2) Refolo, L. M., M. A. Pappolla, et al. (2001). "A cholesterol-lowering drug reduces beta-amyloid pathology in a transgenic mouse model of Alzheimer's disease." Neurobiol Dis 8(5): 890-9.
3) Puglielli, L., R. E. Tanzi, et al. (2003). "Alzheimer's disease: the cholesterol connection." Nat Neurosci 6(4): 345-51.
4) Crameri, A., E. Biondi, et al. (2006). "The role of seladin-1/DHCR24 in cholesterol biosynthesis, APP processing and Abeta generation in vivo." Embo J 25(2): 432-43.
5) Liu, Q., C. V. Zerbinatti, et al. (2007). "Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1." Neuron 56(1): 66-78.
6) Hoshi, M. et al (1997). "Nontoxic Amyloid β Peptide 1-42 Suppresses Acetylcholine Synthesis." J.Biol.Chem. 272(4):2038-2041.

Acknowledgements

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