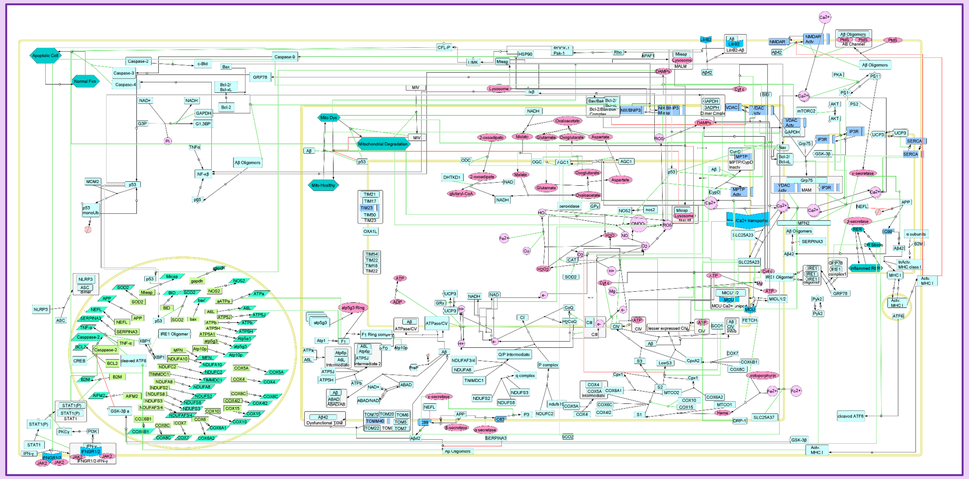
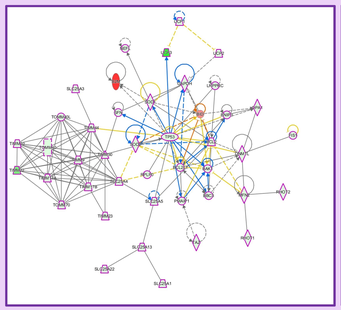
A mathematical model of Alzheimer's Disease simulates different gene therapy treatments and their effects on mitochondrial activity

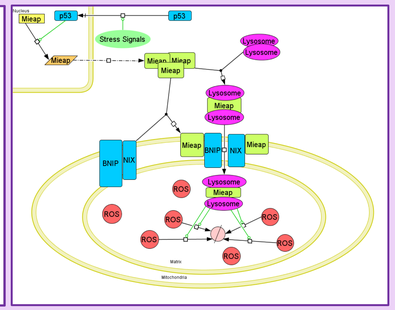
Morgan Shelton, BS, Sonali Shirali, Zhenyu Han, Sean Holden-Kapshuck & Randolph A. Coleman, PhD College of William & Mary, Williamsburg, VA, USA
Frank J Castora, PhD, Eastern Virginia Medical School, Norfolk, VA, USA

As Alzheimer's disease progresses there is an increase in mitochondrial dysfunction and reactive oxygen species (ROS) production. One potential goal of treatment is to restore normal mitochondria function. Computer models based on tissue analysis can be used to simulate CRISPR Cas9-based therapies that will change cellular activity related to mitochondrial viability.



Model Design





Collaborator Dr. Frank Castora, researcher at Eastern Virginia Medical School, created an IPA interactome map from R2 PCR array data (upper left figure). This data indicates that gene expression related to ROS homeostasis maintenance and energy production is important to the progression of Alzheimer's disease.

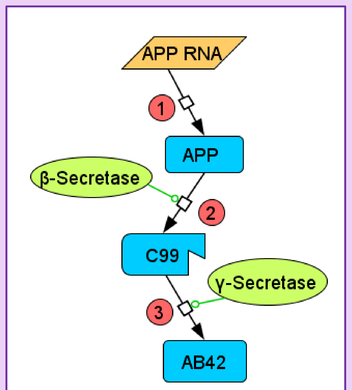
The upper right figure depicts a mitochondria quality control pathway that is activated to decrease the concentration of ROS in the mitochondria.

Method

Flux Equations

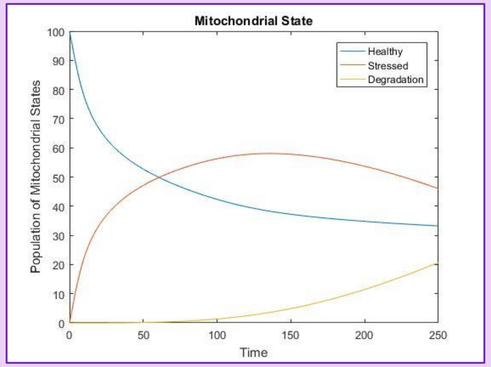
$$J_1 = k_1 * APP\ RNA$$
$$J_2 = k_2 * APP\ * \beta Secretase^{p_\beta}$$
$$J_3 = k_3 * C99\ * \gamma Secretase^{p_\gamma}$$

The Biochemical Systems Theory equation system was used to simulate the model in the upper middle column. These equations contain a relative rate constant (k), species concentrations and a power-law (p) applied to the enzymes to approximate the efficacy of the enzyme. The equations above represent the system to the right.



Results

The model was calibrated using Alzheimer's tissue PCR array data as an endpoint for the baseline simulation protein expression. During time course simulations performed in MATLAB, there is a predicted decrease in mitochondria viability. As viability decreases, a stressed state is favored until the mitochondria are degraded.

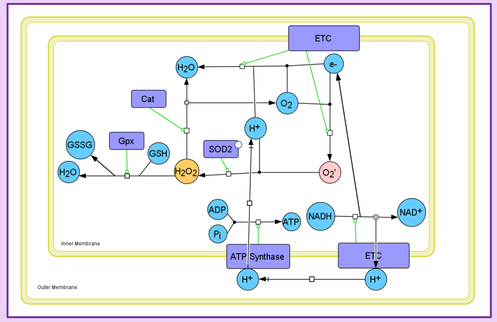


Simulated gene therapies did not indicate a good target, but do hint to the importance of electron transport chain regulation as being susceptible to CRISPR-based therapies

Control (uM)	Oligomers	AbetaProduction	Bax	mPTP	CytC	ATP	FreeROS
'BACEBaseline'	0.005	0.071	1.38	0.0007	1.14E-06	-9.36E-07	3.19E-06
'APPBaseline'	0.0006	0.015	0.197	0.0001	1.76E-07	-1.18E-07	4.99E-07
Crispr Cas9 Therapy Targets and difference from disease state (uM)							
Gene Therapies	Oligomers	AbetaProduction	Bax	mPTP	CytC	ATP	FreeROS
'B2M'	-1.24E-09	-4.70E-06	-0.0014	-1.66E-08	-1.00E-10	2.38E-08	-3.12E-10
'NDUFA10'	-1.45E-12	-2.41E-11	-1.01E-07	-2.07E-10	-1.03E-13	3.61E-11	-4.24E-13
'NDUFS3'	-8.67E-19	-2.78E-17	-8.94E-11	-8.88E-16	-1.08E-19	5.55E-17	-6.51E-19
'COX4I2'	3.74E-09	-1.05E-07	-0.0029	-3.39E-08	-2.42E-10	7.83E-08	-2.13E-10
'COX7A2'	2.20E-09	-4.63E-08	-0.0013	-1.47E-08	-1.64E-10	3.33E-08	-4.56E-10

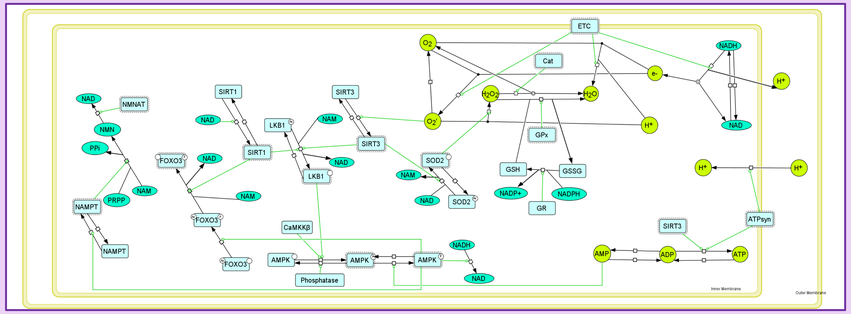
Large-scale models provide a good overview of function and dysfunction. They do not effectively model the fine details becoming relevant in recent literature; this includes ion oscillations, and robust responses to changes in environment.

Future Work



The Electron Transport Chain is the primary producer of Reactive Oxygen Species (ROS) in the mitochondria. The neuron's response to changes in ROS has become the focus of future modeling.

The programs CellDesigner, SBMLsqueezer, and COPASI are being used to create and analyze pathways. These programs allow for more detailed modeling as well as advanced analytical techniques. The model below will be simulated using these programs.



Method

The model above uses Michaelis-Menten and mass action equations to describe mitochondrial activity. The equation to the right describes the import and use of NADH during respiration and redox reactions. In the above model.

$$\frac{d(NADH \times V_{matrix})}{dt} = V_{matrix} \times k1 \times NAD - V_{matrix} \times AMPK2\left(\frac{k6_{cat} \times NADH}{k6_{mc} + NADH}\right) - V_{matrix} \times ETC\left(\frac{k7_{cat} \times NADH}{k7_{mc} + NADH}\right)$$

Analysis will be done using parameter scanning to observe the effects of varying rate constants or initial substrate concentrations. The concentration of ROS or the rate of production can also be varied during a simulation to observe the changes in pathway equilibrium.

Acknowledgements
Chemistry Department
Associate Provost of Research
Office of Graduate Research Studies
Student Assembly

alzheimer's association AAIC 18