Understanding L-dopa Transport and Metabolism in the Human Brain

Final Presentation for REU program

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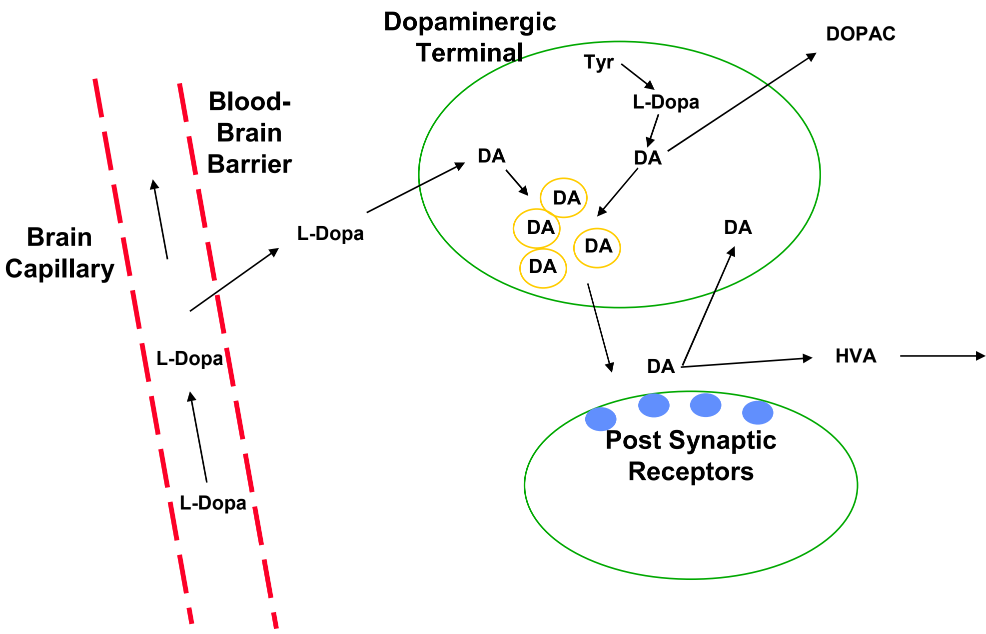
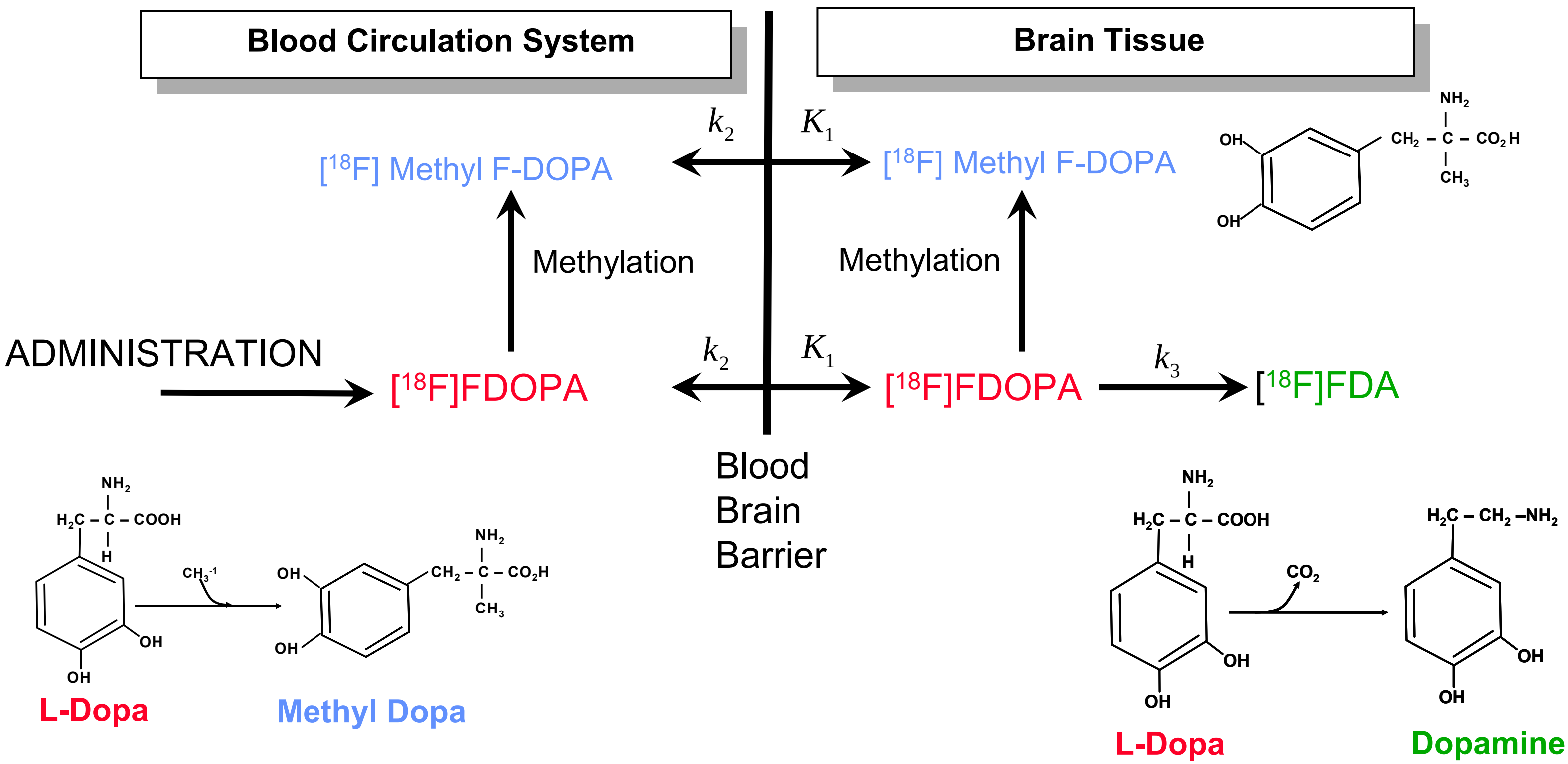
Motivation: Dopamine Metabolic in Human Brain

- **Neurotransmitter and hormone**
- **Insufficient supply of dopamine causes Parkinson's disease**
  - Approximately 1 out of every 100 adults over the age of 55 suffers from Parkinsonism
  - Dopamine is involved in muscle inhibition and without it patients lose muscle control
- **Dopamine cannot pass the blood brain barrier so it cannot be administered as a drug**
  - Only small, non polar, lipid soluble molecules can pass the tight junctions of endothelial cells
  - L-dopa can pass and is used instead of dopamine



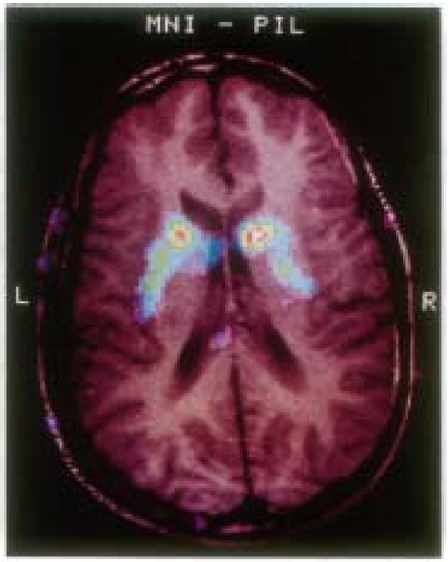
Metabolic Mechanism for L-DOPA



All L-dopa reactions be included in the mathematical model

PET Scanning and F-dopa

- **Positron Emission Tomography**



- **F-dopa (6-[^{18}F]fluoro-L-DOPA)**
  - radiopharmaceutical ^{18}F will emit gamma rays when struck by a positron and thus is visible to the scanner.
  - produces methyl-F-Dopa or fluorodopamine just as L-dopa becomes methyldopa or dopamine.

- **PET scanner measures total radioactivity, so it measures F-dopa, methyl-F-dopa, and fluorodopamine combined**
  - Several techniques have been developed to account for dopamine production only
    - » Using the ratio of radioactivity between the striatum and the cerebellum
    - » Subtracting out the total radioactivity of the cerebellum from the striatum

$$^{18}F = K_1^D * e^{-[K_1^D/V_e]t} * \int_0^T C_1(t) * e^{[K_1^D/V_e]t} dt + qK_1^D * e^{-q[K_1^D/V_e]t} * \int_0^T C_2(t) * e^{q[K_1^D/V_e]t} dt + V_0 * C^*(t)$$

Grid Model of Brain Compartments

Caudate Nucleus

Putamen

Thalamus

Hippocampus

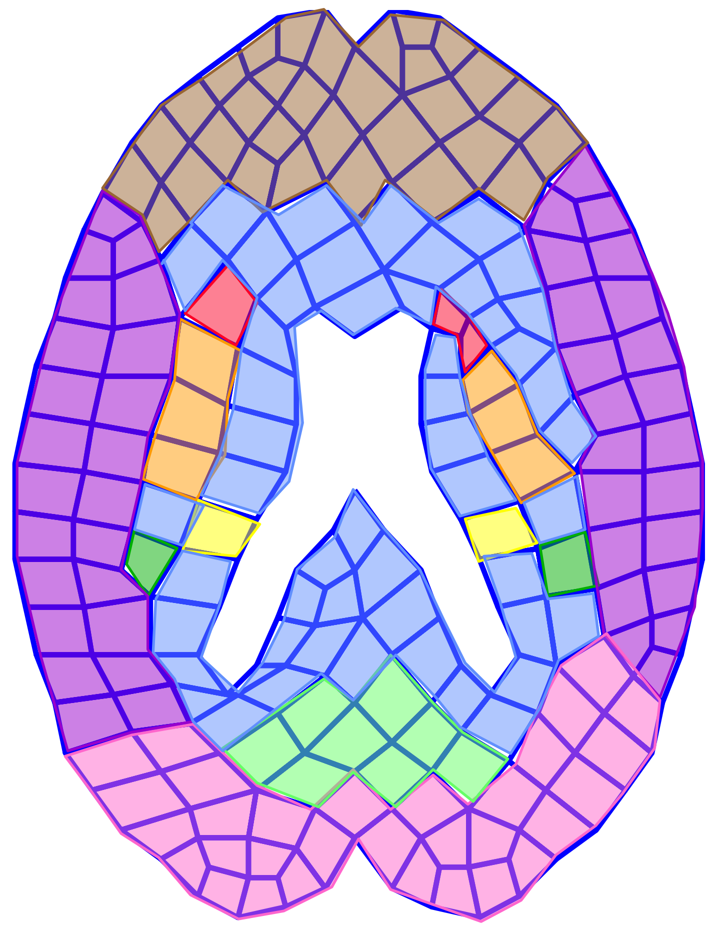
Midbrain

Superior Frontal Gyrus

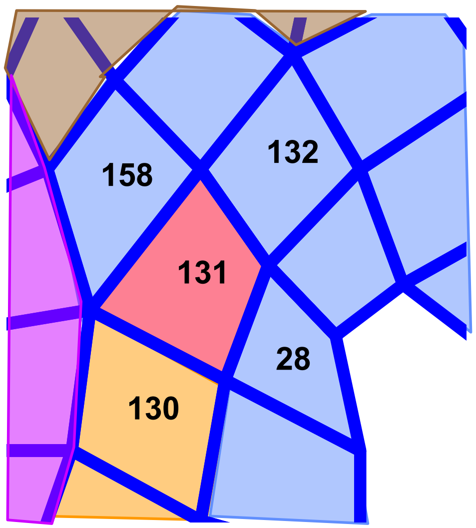
Inferior Temporal Gyrus

Middle Occipital Lobe

Posterior Occipital Lobe



Developing 2-D Model



- **Three equations for every compartment in the unstructured grid**
  - Diffusion and loss of L-dopa to methyldopa or dopamine
  - Diffusion and production of methyldopa
  - Diffusion and production of dopamine

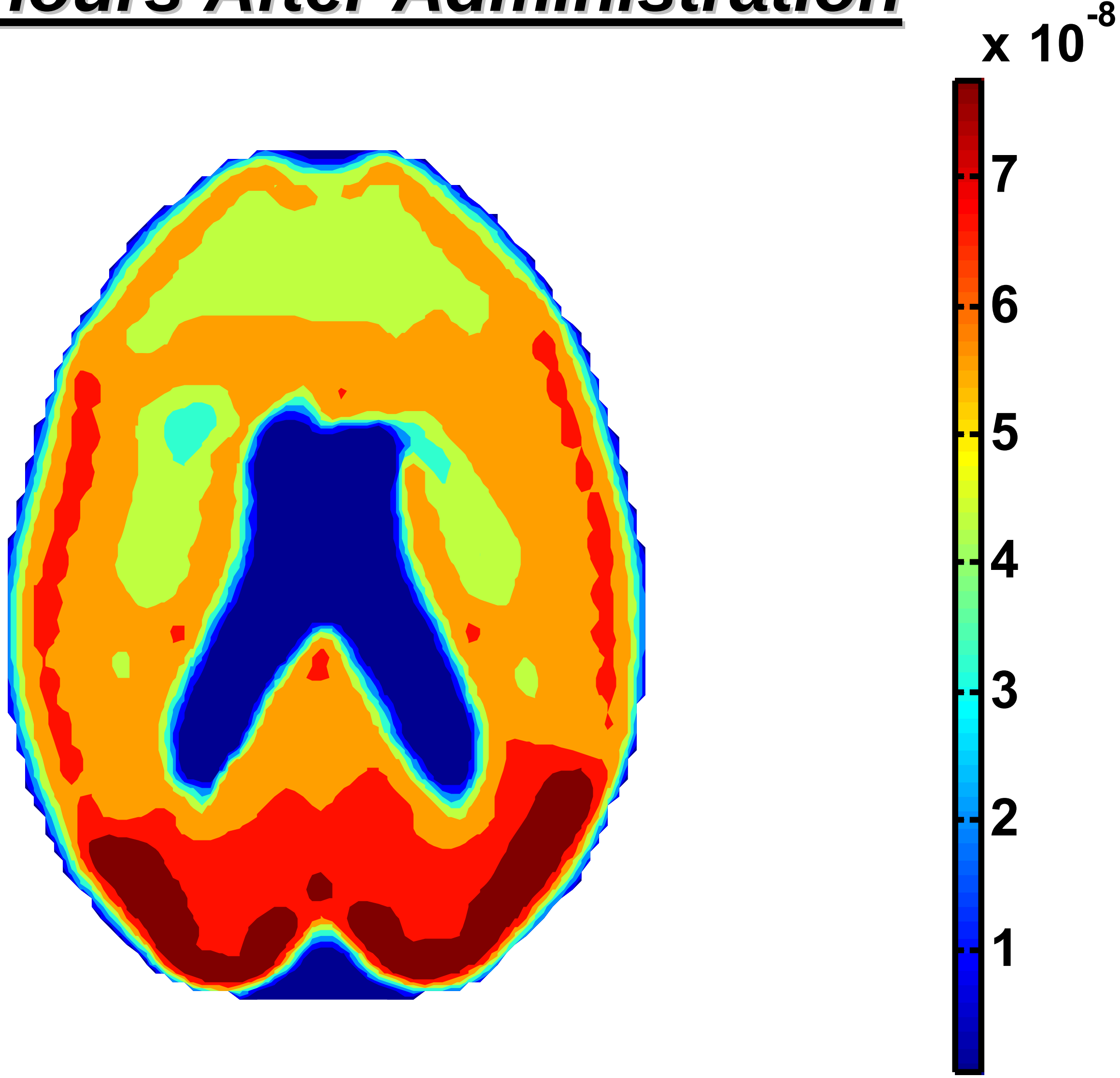
- **Example: Compartment 131, Caudate Nucleus**
- **Can diffuse to any compartment sharing a boundary**
  - 28, 130, 132, 158
- **Uses reaction rate coefficients specific to the Caudate Nucleus**

$$\frac{dC131a(t)}{dt} = D(C131a - C28a)/\Delta x + D(C131a - C130a)/\Delta x + D(C131a - C132a)/\Delta x + D(C131a - C158a)/\Delta x + \ldots$$

$$\ldots + \mathrm{k}_{1\ \mathrm{Caud}}^{\mathrm{D}} \mathrm{C}_{\mathrm{Ldopa}} - \mathrm{k}_2^{\mathrm{D}} \mathrm{C131a} - \mathrm{k}_{3\ \mathrm{Caud}}^{\mathrm{D}} \mathrm{C131a} - \mathrm{k}_5^{\mathrm{D}} \mathrm{C131a}$$

L-Dopa Two Hours After Administration

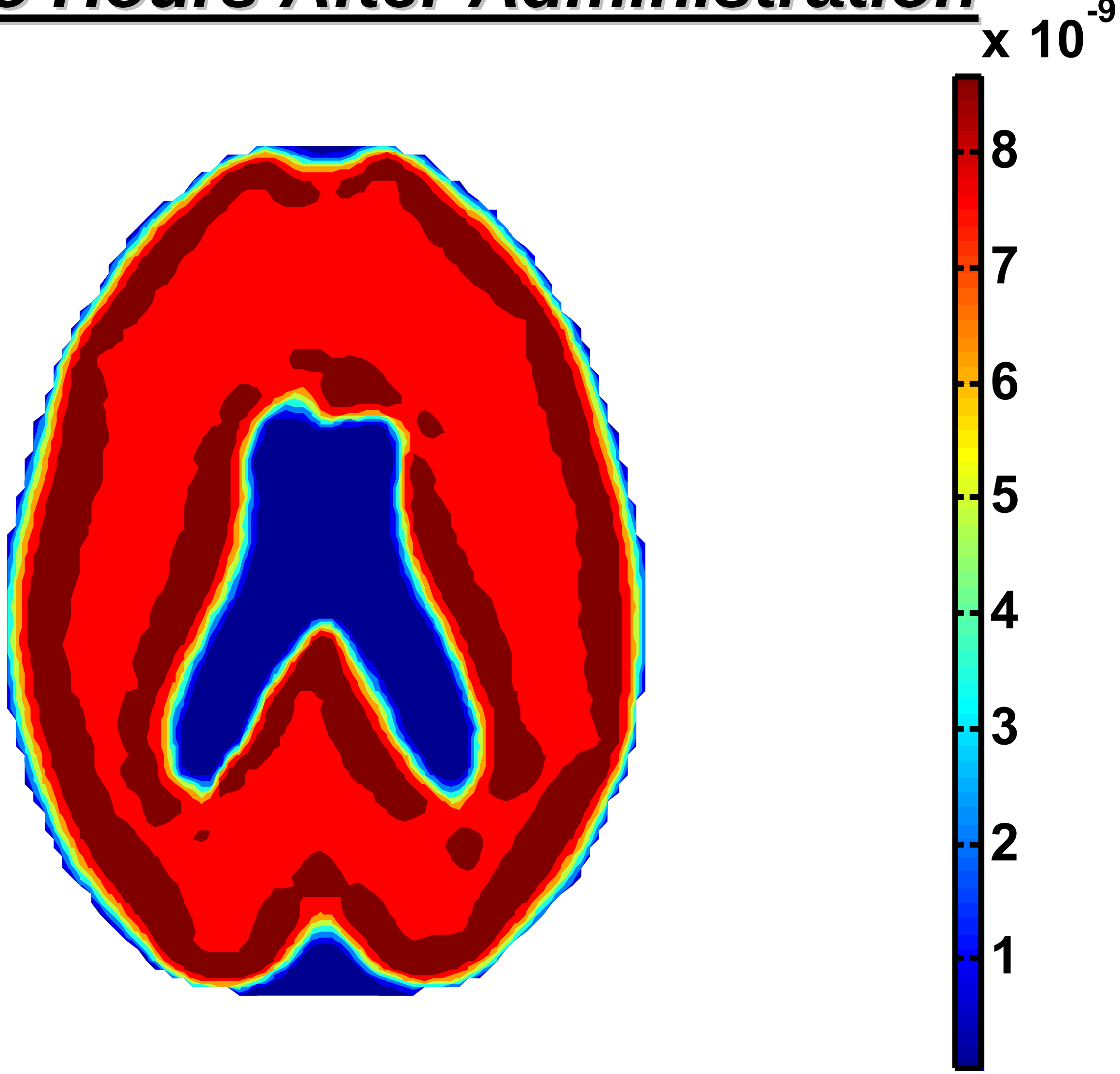
- **Highest concentration, .07 μM, found in the posterior occipital lobe**
  - Highest blood brain barrier transport constant
- **Lowest concentration, .03 μM found in the caudate nucleus**
  - L-dopa consumed to make dopamine in the caudate nucleus and putamen



Methyldopa Two Hours After Administration

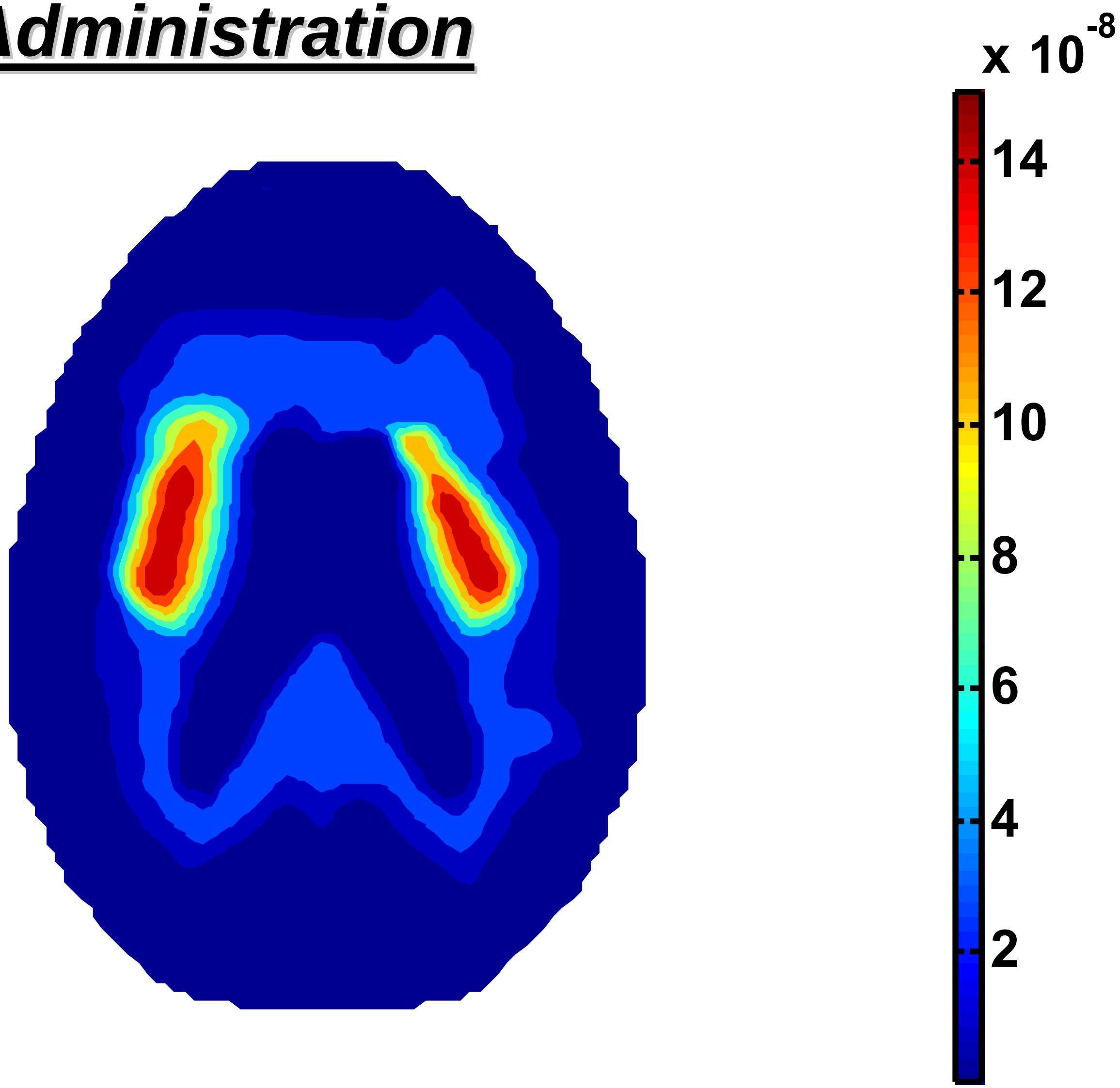
- **Even distribution throughout brain**
  - Between .007 μM and .009 μM of methyldopa everywhere

- **Methyldopa can be produced anywhere in the brain**

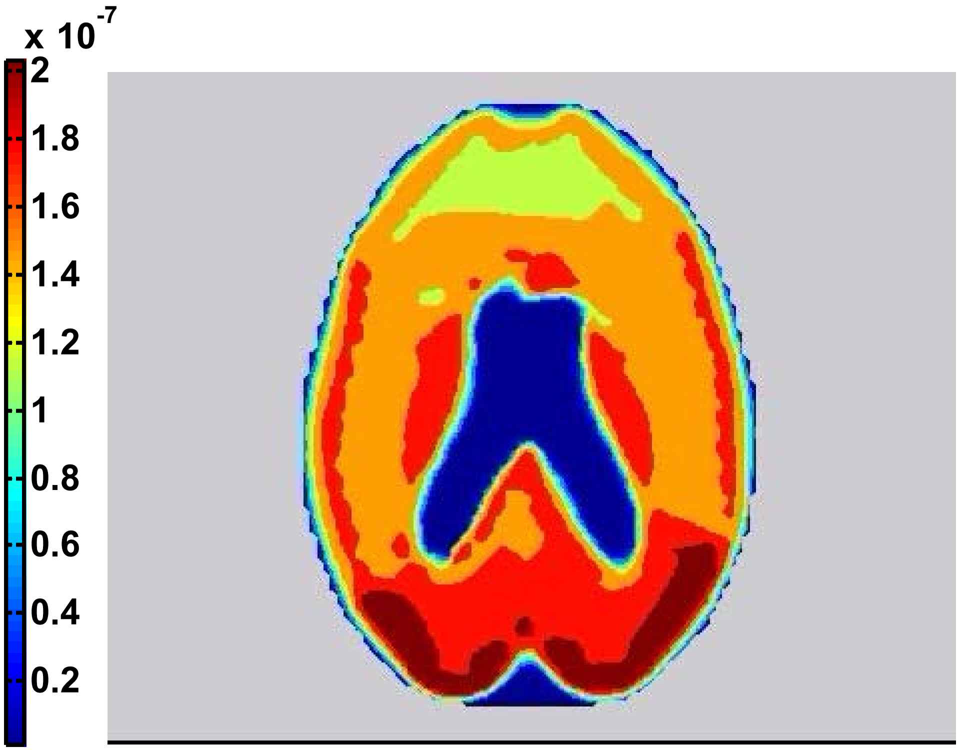


Dopamine and Metabolites Two Hours After Administration

- **Highest concentration, .14 μM, found in the caudate nucleus and putamen**
  - Highest L-dopa → dopamine reaction constant
  - Twice highest concentration of L-dopa
- **Lowest concentration, 0 μM found in outer regions**
  - No dopamine production

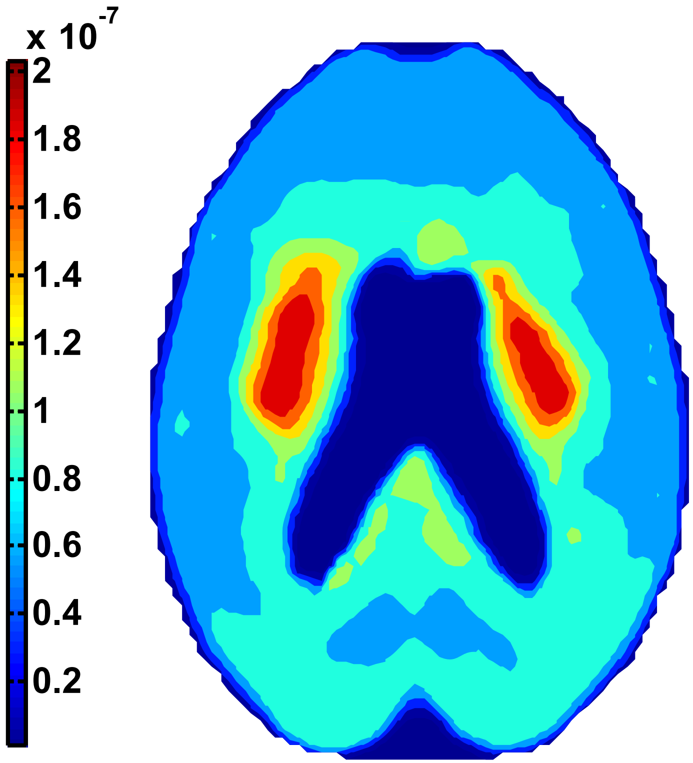


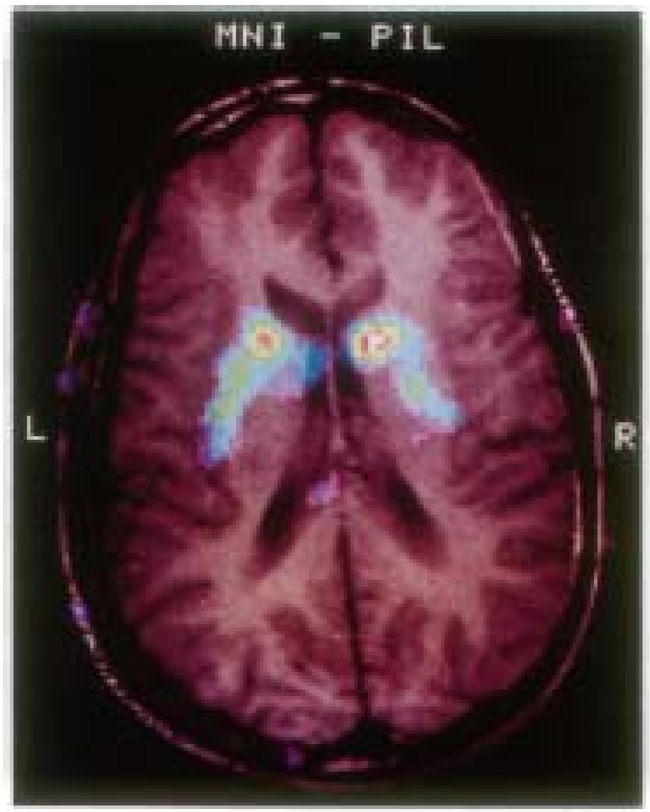
Transient Behavior of Dopa Administration in Human Brain



- **Scale:**
  - 1 second = 15 minutes
- **Duration:**
  - 3 hours
- **Concentrations outside of the caudate nucleus and putamen will comparatively drop with time as dopamine is produced and stored.**
- **Other regions of the brain will turn green and blue, meaning lower concentrations.**

Compare to PET Image





- **Highest concentration, .20 µM, found in the caudate nucleus and putamen**
- **Recall: Maximum dopamine and metabolites were twice maximum L-dopa and an order of magnitude higher than methyldopa**

Conclusions

- The compartment models are limited to describe the Ldopa metabolic mechanism in human brain.
- The combination of one dimensional plasma and two dimensional brain model.
- Model generation, unstructured grid and generalized curvilinear transformation help us to solve this problem.
- The distributed system model of the brain produces results that are similar to data from PET images of the brain

Future work:

- Discover the tissue properties and metabolic constant from PET images based on this rigorous model
- Combine the ventricular network and two or three dimensional brain model;

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Happy Birthday Marisa!