Modeling the Kinetics of ^{99m}Tc-HMPAO in the Lungs of Rats

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ABSTRACT

The objective of our work is to develop an understanding of the mechanisms involved in the lung uptake of radiopharmaceuticals that may be useful clinically for evaluating lung injury. A four compartment model to describe the kinetics of Technetium labeled Hexamethylpropyleneamine Oxime (^{99m}Tc-HMPAO) in the blood and lung tissue of rats has been developed and implemented in MATLAB. The four partial differential equations of the model are solved using a finite difference approximation to determine the distribution of the four existing species of HMPAO in the blood and lung tissue of rats. Preliminary results demonstrate that this model is capable of fitting the model rate constants to experimentally gathered mass data, which, with further refinement, will allow for the quantification of the difference in the kinetics of ^{99m}Tc-HMPAO in healthy lungs versus diseased lungs.

INTRODUCTION

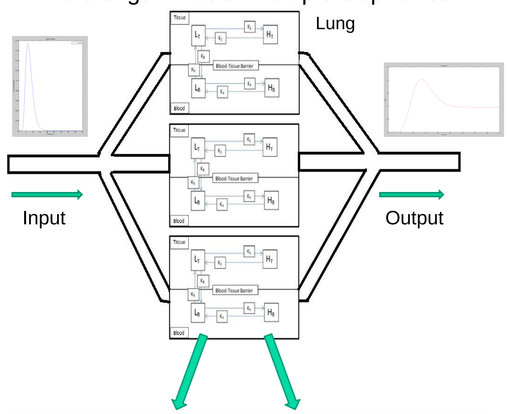
^{99m}Tc-HMPAO has previously been used as a radioactive imaging tracer to quantify cerebral blood flow. The compound crosses the blood-brain barrier and is retained in the brain tissue, allowing it to be imaged. The present research concerns the kinetics of ^{99m}Tc-HMPAO in the lungs of rats. ^{99m}Tc-HMPAO exists in two conformational forms: a lipophilic form which can cross from the blood in the capillaries into the cells of the lung tissue and a hydrophilic form which cannot cross the blood-tissue barrier. A model is needed which describes the amount of ^{99m}Tc-HMPAO in each form in the blood and tissue and quantifies the rate constants associated with the transport and conversion kinetics. A region of damaged lung tissue may have different rate constants associated with uptake of ^{99m}Tc-HMPAO. Quantification of the differences in these parameters will allow for the identification of regions of damaged lung tissue from the images.

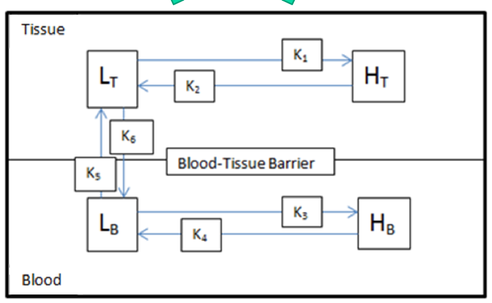
OBJECTIVES

- Create a model capable of fitting rate constants (K_1 – K_6) to the experimentally gathered ^{99m}Tc-HMPAO mass data.
- Determine the sensitivity of the concentrations of the four species of ^{99m}Tc-HMPAO to changes in the rate constants and other model parameters.
- Create an algorithm capable of generating an input concentration function (Random Walk Function [1]) given the experimentally gathered mass curve.

METHODS

Whole Organ Model: Multiple Capillaries





The One Big Capillary: A four compartment model. HMPAO can exist as four different species: lipophilic in the blood (L_B), lipophilic in the tissue (L_T), hydrophilic in the blood (H_B) and hydrophilic in the tissue (H_T).

$$\frac{\partial L_B}{\partial t} = (-v)\frac{\partial L_B}{\partial x} + (K_4)H_B + \left(\frac{K_6 V_T}{V_B}\right)L_T - (K_3 + K_5)L_B$$

$$\frac{\partial H_B}{\partial t} = (-v)\frac{\partial H_B}{\partial x} + (K_3)L_B - (K_4)H_B$$

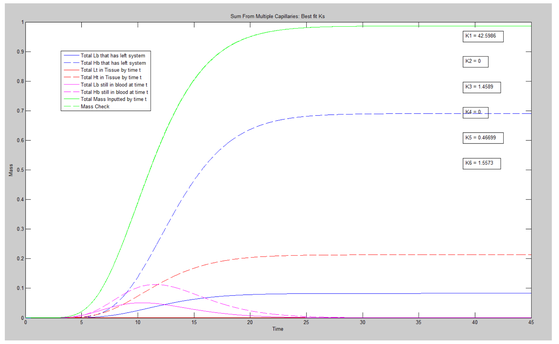
$$\frac{\partial L_T}{\partial t} = \left(\frac{K_5 V_B}{V_T}\right)L_B + (K_2)H_T - (K_6 + K_1)L_T$$

$$\frac{\partial H_T}{\partial t} = (K_1)L_T - (K_2)H_T$$

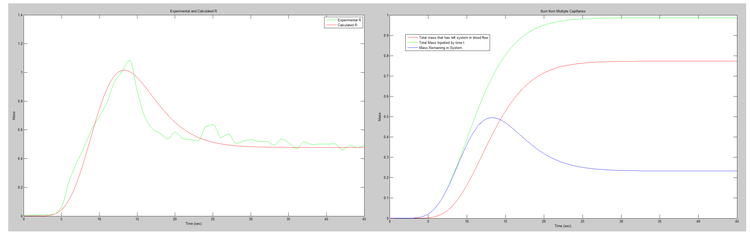
This system of partial differential equations describes the distribution of each species of ^{99m}Tc-HMPAO in the blood and lung tissue at each point in space and time along the One Big Capillary. Once this system is solved, we compute the mass, R, of HMPAO in the lung at time t, i.e.

$$R(t) = V_B{*}L_B + V_B{*}H_B + V_T{*}L_T + V_T{*}L_T$$

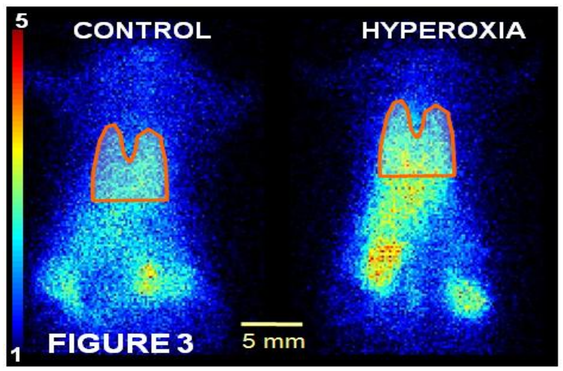
DATA and RESULTS



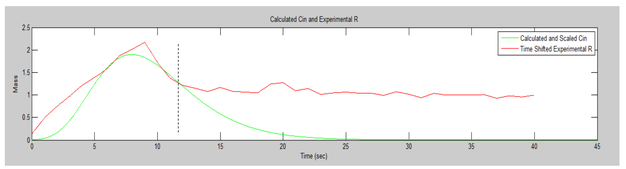
Solving the system of partial differential equations allows us to simulate the amount of each species present in the system at each point in time.



These output curves from the model demonstrate the model's ability to fit rate constants to the experimental data (left) and simulate the kinetics of ^{99m}Tc-HMPAO using those constants (right). A GUI has been developed that allows the user to choose rate constants to remain fixed. For this example: K_1 = 42.6, K_3 = 1.46, K_5 = 0.467, K_6 = 1.56, and K_2 and K_4 have been fixed at zero.

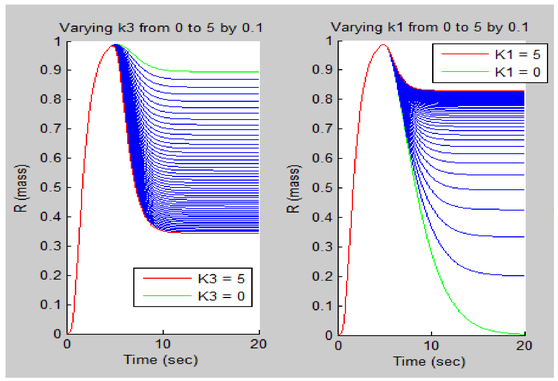


A control and diseased rat showing ^{99m}Tc-HMPAO uptake. The outline overlaying the image defines the boundary of the lung region. Activity within the lung is quantified during each second and is plotted and corresponds to R(t) in the model simulations.



The function that describes the amount of tracer inputted to the system at each time step is not recorded experimentally but is a vital part of the model. We fit a random walk function [1] representing the input function to an initial segment of the experimental mass data curve to obtain Cin(t).

Sensitivity Analysis



Rate constant sensitivity analysis was conducted to determine which parameters could be fixed to a predetermined value and which should be passed to the nonlinear least squares regression (MATLAB function lsqnonlin()) for optimization. The effect on R(t) of changing K_3 and K_1 is shown here for example.

DISCUSSION and CONCLUSIONS

- This PDE model appears to contain the dominant processes involved in lung uptake of ^{99m}Tc-HMPAO.
- Estimated parameters produced an R(t) function that matched the measured data.
- Subsequent experiments should measure the input function directly.
- The model will be useful for determining changes in the K parameters that occur with lung injury/disease. For example, we should be able to identify changes in the blood-tissue barrier versus biochemical changes within the lung cells.

SELECTED REFERENCES

[1] Audi, S. H., J. H. Linehan, G. S. Krenz, C. A. Dawson. Accounting for the Heterogeneity of Capillary Transit Times in Modeling Multiple Indicator Dilution Data. *Annals of Biomedical Engineering*. 26:914-930, 1998.

[2] Matsuda, H., H. Oba, H. Seki, S. Higashi, H. Sumiya, S. Tsuji, H. Terada, K. Imai, K. Shiba, H. Mori. K. Hisada. Determination of Flow and Rate Constants in a Kinetic Model of [^{99m}Tc]-Hexamethyl-Propylene Amine Oxime in the Human Brain. *Journal of Cerebral Blood Flow and Metabolism*. 8:S61-S68, 1988.

[3] Ramakrishna, M., Z. Gan, A. V. Clough, R. C. Mothen, D. L. Roerig, S. H. Audi. Distribution of Capillary Transit Times in Isolated Lungs of Oxygen-Tolerant Rats. *Ann. Biomed. Eng.* 38: 3449-3465, 2010.