ESTIMATION OF BLOOD BRAIN BARRIER PERMEABILITY BY STATISTICAL AND ANALYTICAL METHODS

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Abstract: This work proposes a statistical approach for estimating blood brain barrier permeability. The statistical model simulates crossing of contrast agent according to permeability and lesions of Blood Brain Barrier (BBB). It considers passing of contrast agent through the capillary and BBB as intrinsically statistical processes and simulate them by Monte Carlo method. We exact real arterial input function (AIF) from magnetic resonance images (MRI) and consider it as input to the model. We derive the concentration of contrast agent as a function of time in the extravascular space for abnormal capillary and different permeabilities. Next, the real data is extracted from each pixel of rat brain. The curves of simulated and the real data of rat brain are compared and permeability map of rat brain is obtained. The results of analytical method are compared to Monte Carlo simulation results. The main advantage of Monte Carlo simulation is its use of real data directly. It does not fit a mathematical model to real data, therefore, it is accurate and easy to use.

Introduction

The history of quantitative blood-brain barrier (BBB) permeability estimates goes back to at least forty years[1],[2]. In all such measurements, the concentration of an indicator, usually a radioactive substance or contrast agent, is measured in blood over time and estimated in tissue either at several times or at the end of the experimental period. These data are used to calculate a blood-to-tissue permeability.

Magnetic Resonance Imaging (MRI) is the ideal imaging technique for evaluating brain tumors because of its high tissue contrast and ability to show injury of BBB [3].

Generally, two major models were used for calculating permeability, compartmental model and Tissue Homogeneity (TH). Johnson and Wilson [4] introduced a Tissue Homogeneity (TH) model for the capillary. In the TH model, tissue is divided into the extra-vascular space (EVS) and the intra-vascular space (IVS). These two spaces are separated by a vessel wall whose permeability surface area product (PS) is used as a measure of vascular permeability to a given tracer.

In these works, real AIF was not used directly as the input to the capillary and the following questions were not answered. How can the problem be solved with the real data as the capillary input? How can the models be practically used for calculating permeability form the real data?

We presented an approach similar to these studies of the diffusion of water in a complex vascular model before [5]. The method used Monte Carlo procedures and the modified Patlak model to estimate the concentration of the contrast agent as a function of time and distance in the capillary for a measured AIF in normal (*i.e.* not permeable due to the presence of BBB) and abnormal capillaries with uniform and non-uniform permeability.

Herein, the statistical model of BBB exchange is used for calculating tissue permeability. First, a real AIF extracted from real images is considered as input of statistical model and contrast agent concentration curves vs time are foundfor different permeability. Next by comparing the curves with extracted informationfrom each pixel, the nearest curve is chosen and permeability of pixel is specified. Using the permeabilities, a map of permeability is made. Finally, this procedure is executed for TH model with a fitted curve to AIF as input and permeability map is made.

Materials and Methods

Tissue Homogeneity (TH) Model

The TH [6] model and Patlak's [7] model are first described. Following that, we describe the solution of TH quations by Laplace transform. The new model, which uses the TH model, the Patlak model, and Monte Carlo simulation, is then introduced.

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Tissue Homogeneity (TH) Model

This model describes the BBB using two compartments: IVS and EVS, which are separated by a membrane having a given PS product [6]. The contrast agent represented by the AIF enters the capillary (IVS) from the left side and varies with position across the capillary's length due to the permeability of the BBB. The PS determines the rate of diffusion of the contrast agent across the EVS-IVS boundary. From conservation of the mass of the tracer in the IVS and EVS, the following adiabatic equations are derived:

$$a_{iv}\frac{\partial C_{iv}(x,t)}{\partial t} = -F\frac{\partial C_{iv}(x,t)}{\partial x} - \frac{PS}{L}[C_{iv}(x,t) - C_{ev}(t)]$$
$$a_{ev}L\frac{\partial C_{ev}(t)}{\partial t} = \frac{PS}{L}\int_0^L [C_{iv}(x,t) - C_{ev}(t)]dx \qquad (1)$$

where x and t are position and time, respectively, $C_{iv}(x,t)$ and $C_{ev}(t)$ are the concentrations in mM of tracer in the IVS and the EVS, L is the length of the capillary in cm, F is the flow in $ml.\ min^{-1}.g^{-1}$, a_{iv} and a_{ev} represent the cross-sectional area of each compartment in $cm^2.g^{-1}$, and PS is the permeability surface area products in $ml.\ min^{-1}.g^{-1}$.. By finding the numerical inversion of the Laplace transforms, the concentrations of the contrast agent as a function of time and distance in IVS and as a function of time in EVS are derived.

The Patlak's Model

The Patlak's model [7] is a compartmental model and introduced for the transport of particles in tissue and plasma. The model consists of three compartments: plasma, irreversible region and reversible region. The following assumptions are made about the transport model. Plasma is the single source of the contrast agent in the system. Concentration of the contrast agent in plasma may be time variant. There may be a relatively rapid exchange of the contrast agent between plasma and a tissue region, built up of n compartments. Transfer of the contrast agent among the plasma and the compartments of the first region (reversible compartments) are reversible. The contrast agent may flow directly or indirectly from plasma into any of these compartments, move freely among these tissue compartments, and flow back readily into the plasma. The contrast agent may also enter a second tissue region from the plasma but it will stay there (irreversible compartments)

Under these assumptions, Patlak and co-workers [7] showed that the blood-to-tissue transfer or influx constant (K_i) may be obtained by a graphical analysis of the time series of the tissue and arterial concentrations, using the following equation:

$$C_{tis}(t) = K_i\int_0^t C_{Pa}(\tau)d\tau + C_{Pa}(t)V_P$$

where $C_{tis}(t)$ is the tissue concentration of the contrast agent (amount per unit weight) at the end of the experimental period (t), $C_{Pa}(\tau)$ is the arterial plasma concentration (amount per unit volume) at a series of times over the duration of the experiment (used to calculate the arterial concentration-time integral), K_i is the blood-to-brain transfer constant of the contrast agent, and V_P is the tissue volume in which the blood-borne contrast agent mixes and fills on its way to crossing the rate-limiting barrier. This volume includes the plasma space in all instances and sometime other intravascular and capillary wall compartments.

Implemented Methods

Analytical Method (Laplace Transform)

For solving equation (1), we used the numerical inversion program written by Hollenbeck (INVLAP.M: a Matlab function for numerical inversion of Laplace transforms by the de Hoog algorithm, http://www.Mathwork.com or http://www.netlib.org/toms), which is a variation of the de Hoog algorithm [8]. Several algorithms exist for this numerical inversion, but only this particular one is written for Matlab. A binomial series of order four is fitted to the data of real AIF with these coefficients:

$$AIF(t) = p_1 t^4 + p_2 t^3 + p_3 t^2 + p_4 t + p_5 \qquad (2)$$

where t is time, p_1=-1.5X10^{-14}, p_2=5.89X10^{-11}, p_3= -0.042X10^{-8}, p_4=4.35X10^{-5}, and p_5 = -0.004717. The mean relative error with respect to real data is 10.6%. In Figure 1, the fitted curve and real AIF are shown. By taking the Laplace transform of (2) and substituting it in the Laplace transform of equations (1) and using de Hoog algorithm, the contrast agent concentration curves are calculated for different permeabilities.

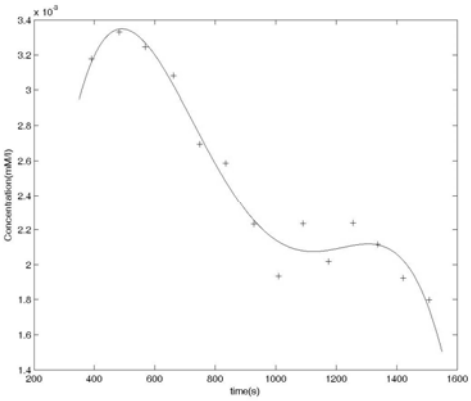

Figure 1: real AIF data and fitted curve to it. A binominal of order 4 is fitted to real AIF. Their coefficients are brought in text.

Statistical Method (Monte Carlo)

In this work, the brain tissue is considered to be composed of two compartments: a) capillary or IVS; and b) extra-vascular space or EVS. These

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compartments are divided into several sections similar to Patlak's model. Additionally, the capillary is divided into multiple sections. The exchangeable compartments of the Patlak's Model consist of bi-directional parts and, depending on the permeability of the region; the contrast agent may transfer into the compartments or out of them. Particles enter the capillary in specific times and move to other compartments according to different probabilities. The position of a particle at time $t + \Delta t$ is given by:

$$P(t+\Delta t) = P(t) + r(\Delta t) \qquad (3)$$

where $P(t)$ is the position at time t and $r(\Delta t)$ is a random displacement vector of arbitrary direction.

In the capillary and adjacent sections, the probabilities of particle motion are calculated by the permeability values, flow of blood, and equilibrium partition coefficient according to the adiabatic equations (1):

$$Prc = \frac{F}{\frac{PS \times \Delta x}{L} + F} \qquad (4a)$$

$$Poc = \frac{\frac{PS \times \Delta x}{L}}{\frac{PS \times \Delta x}{L} + F} \qquad (4b)$$

$$Pic = \frac{\frac{PS \times \Delta x}{L}}{\frac{PS \times \Delta x}{L} + F} = Poc \qquad (4c)$$

where Prc and Poc add up to one and are the probabilities for a tracer particle to move forward inside the intra-vascular space and go outside of the intra-vascular space into the extra-vascular space, respectively. Also, Pic is the probability for a tracer particle that is in the extra-vascular space to move back into the intra-vascular space. The probability for a contrast particle that is in the extra-vascular space to remain within the extra-vascular space equals $(1- Pic)$. Finally, Δx is the length of each section of the capillary and the rest of the parameters are defined before, after equation (1).

The time step (Δt) in the capillary is obtained by:

$$t_n = L/nv \qquad (5)$$

where L is the length of the capillary, n is the number of sections of the capillary, and v is the velocity of the blood in the capillary. For the average blood velocity of $0.05\ cm/s$, $L=61\mu m$ and $n = 120$, t_n is about 0.001 s.

The average random walk or travel path along one direction is described by Einstein as:

$$\langle l^2 \rangle = 2\Delta t(ADC) \qquad (6)$$

where ADC is apparent diffusion coefficient (usually given in cm^2/s or mm^2/s) and Δt is the observation time (seconds). The Δt is set to $40ms$, ADC to $8\text{x}10^{-6} cm^2/s$, and l to $9\mu m$.

Results

At first, to evaluate the proposed algorithm and compare it to previous methods, the AIF is considered as a Gamma function. According to our proposed Monte Carlo procedure, particles enter the network and their positions and times are recorded in each step. For BBB with different uniform abnormalities, the ratio of the concentrations in the output of the capillary to the input of the capillary is then measured, which also can be measured using the Laplace transform and Gamma function as the AIF.

For further evaluation and validation of the proposed method a real AIF, extracted from MRI of a rat brain acquired in the NMR laboratory in the Department of Neurology at Henry Ford Heath System, Detroit, Michigan, USA, is used. It is assumed that $\Delta R(t)$ is linearly proportional to the concentration of the contrast agent.

For the making of the permeability map, these steps are taken:

- At first, the brain is separated from ΔR1 images.
- The AIF data is extracted and is considered as the input of the simulation and concentration curves obtained for different permeability.
- The simulation curves are compared to extracted information from each pixel and the closest curve is chosen. Criterion of choosing is the least relative error between real curve and the simulated curves. After choosing the nearest curve, its permeability is given to the pixel.
- By setting the permeability, each pixel is made into the permeability map.

This procedure is executed for TH model, but a fitted curve to real AIF data is used as input. The permeability map of these models are shown in Figure 2.

In the Monte Carlo simulation, max. and min. permeability for a tumor is 0.17, 0.47 $mLit.min^{-1}.g^{-1}$ and for normal tissue is 0.01, 0.17 $mLit.min^{-1}.g^{-1}$, respectively. For TH model, tumor permeability is between 0.39-0.79 $mLit.min^{-1}.g^{-1}$ and normal tissue permeability is between 0.02-0.15 $mLit.min^{-1}.g^{-1}$. The results of the models are different because of the statistical error in Monte Carlo simulation and fitting error in the analytical method. For all of the procedures in this and other parts, we used a home-written software in "Matlab". In evaluation of noise (white noise 1%) in the two approches, we observed that the Monte Carlo simulation has noise but the fitting curve errort exists in the analytical method and usually is larger than the statistical error in the Monte Carlo simulation.

Discussion

This work estimates the contrast agent concentration inside and outside of a capillary with abnormal BBB permeability by two methods: analytical and statistical.

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Different models have different error sources. In the Monte Carlo simulation, a mathematical function (for example, a gamma function) or real AIF may be used as the input to the capillary. However, in the analytical method, a mathematical function or a sum of mathematical functions must be used as the AIF. Fitting of the mathematical functions to the real data has intrinsic errors and limits the accuracy of the results. Although in the Monte Carlo method statistical error exist , but the number of particles may be selected large enough to reduce the error to a desirable low level. For example, in the experiments presented in this paper, the average error percentage was about 1.8% - 2.1% using a real AIF.

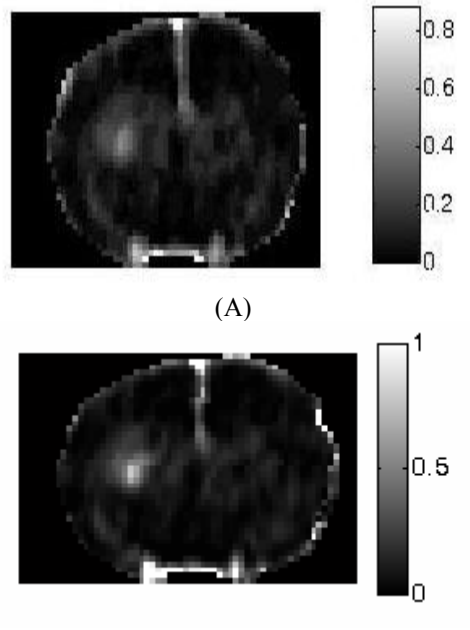

Figure 2: Permeability map is obtained by A) the Monte Carlo simulation and B) analytical method (Laplace transform). The region of tumor has larger permeability with respect to the normal tissue.

In the Monte Carlo method, the partition coefficient, return of the tracer to the plasma and gradual mixing can be considered. Although an important issue in this method is how to find the required probabilities, once the coefficients and probabilities are determined, the distribution of the contrast agent in the EVS without the assumption of prefect mixing can be found. In the future, high resolution MRI (comparable to the average capillary length) and the Monte Carlo simulation may be used to detect capillary injury and calculate its abnormality level.

Advantage of the Monte Carlo simulation compared to the other methods can be summarized as follows:

- Real AIF may be used in the model.
- No need to fit mathematical models to the real data.
- No need to solve complicated equations.
- New parameters may be included using appropriate probability density functions.
- Non-uniformity of the capillary may be studied using this model.
- Monte Carlo simulation is easier to use f because it dose not require the curve.

A disadvantage of the method is its long execution time, especially when a large numbers of particles are used for reducing the error. However, these calculations are usually done off-line, for which the execution speed is not critical.

Conclusions

In summary, both models can be used for calculating permeability. The statistical error, fitting curve error are sources of the error. An operator can use the Monte Carlo simulation easier because it does not need to fit a mathematical model and can directly use the real AIF data.

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