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University LDRD Student Progress Report on Descriptions and Comparisons of Brain Microvasculature via Random Graph Models

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University LDRD Student Progress Report on Descriptions and Comparisons of Brain Microvasculature via Random Graph Models

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Abstract

Brain tissue includes a close interaction of neurons, glial cells, and microvasculature. This university LDRD project supported a student, Mr. Nathan Cornelius working with Professor Peter C. Doerschuk of Cornell University, in developing techniques extracting maps of the microvasculature from 2-photon optical 3-D imagery, in describing such maps as random graphs, and in developing statistical tools for comparing the graphs.

Summary

Area of work: Quantitative neuroscience

Four related projects in Nathan's thesis research:

1. A mathematical model of the neurovascular system, neural excitation to optical intrinsic signal imaging (OISI), based on circuit ideas. Key aspects are description of both oxygenated and deoxygenated hemoglobin and their interconversion and both cerebral blood flow and cerebral blood volume.
2. Pose and solve an inverse circuit problem for determining a complete network model for the microvasculature in a volume of cerebral cortex tissue from a limited number of flow measurements. Use the resulting model in experimental design and in understanding the effects of a microstroke on brain perfusion.
3. An abstract description of vascular networks focusing on the location of branches using point process ideas and a maximum likelihood estimator for the parameters leading to a novel partitioning of the cerebral cortex into layers based purely on vascular properties.
4. Image processing in support of measuring flow speeds in vessels based on video 2-photon scanning laser microscopy data.

Introduction

The funds have supported a Graduate Research Assistantship for Mr. Nathan Cornelius for 5 years. As a part of his curriculum, Nathan was required to be a Teaching Assistant and during that period he was paid by the Department. So the 5 years of Sandia support will actually support Nathan for 5.5 years. My expectation as his advisor is that he will have a successful thesis defense late in Fall 2012 and graduate officially in January 2013.

As described in the following sections, Nathan's Ph.D. research is in four major directions all concerned with using electrical engineering tools in neuroscience.

Circuit model of the neurovascular network

Despite extensive study, the mechanisms of the local control of cerebral blood flow and cerebral blood volume by neuronal activity are not resolved [1, 2, 3, 4, 5, 6]. A mathematical model has been developed and demonstrated whose purpose is to relate cortical electrical activity to flows and volumes of cerebral oxygenated and deoxygenated hemoglobin. While parts of the model are completely specified, e.g., by conservation laws, other parts have

flexibility that can be used to describe alternative mechanisms. To provide a concrete connection to at least one class of experimental result, the basic model is augmented with an optical model that allows it to describe Optical intrinsic signal imaging (OISI) [7], essentially space-resolved and time-resolved optical reflectance spectroscopy measurements on surgically exposed cortex. Applications include the understanding of natural or induced epilepsy, the planning of surgical excision of surface cortical foci of epilepsy, and the planning of electrical stimulation paradigms for increasing cerebral blood flow.

The model is a combination of new ideas and standard ideas. The following items describe the model in terms of the goals that it achieves:

1. To describe both cerebral blood flow and cerebral blood volume. Therefore, when described in terms of an electrical circuit analog, the model has both resistors and capacitors.
2. To describe behavior when the space resolution is $10^2 \mu\text{m}$ implying that blood that enters the microvasculature in one pixel might exit in a different pixel.
3. To have a model that incorporates physical constraints. Therefore, Kirchhoff's current and voltage laws are obeyed throughout and Laplace's and Poiseuille's laws are used to describe flow through a vessel where the contractile state of the vessel is described by the Young's Modulus of the vessel wall which is controlled by other quantities in the model.
4. To model both oxygenated and deoxygenated hemoglobin, including the conversion of oxygenated to deoxygenated. This requires a generalization of the usual Kirchhoff's laws to the situation where two types of current (oxygenated and deoxygenated) flow in the circuit and one type (oxygenated) can be converted to the second type (deoxygenated).
5. Since the neurovascular interaction is not completely understood, to provide a model that is sufficiently flexible such that different interactions can be included in the model.
6. To use a set of parameters that is sufficiently limited such that the parameters in the model can be determined for individual subjects rather than for populations of subjects.
7. To demonstrate the presence or absence of an initial decrease in HbO_2 in response to an excitation is not necessarily due to a different structure for the mathematical model but rather could be due to the choice of parameters in a mathematical model of fixed structure. The presence or absence of such an initial decrease in HbO_2 is much discussed in the neuroscience literature.
8. To connect the model, with a typical spatial scale of roughly $10\mu\text{m}$, to the macroscopic world which is done by deriving Grubb's law [8] (a macroscopic relationship between cerebral blood volume and flow derived from whole-body medical imaging) from the model. Grubb's law can be interpreted as specifying the effective exponent in Poiseuille's law.

Because the model is nonlinear, it describes total signals and not perturbations in signals superimposed on an unmodeled baseline signal. Therefore, especially when modeling the neurovascular interaction, we focus on feedback models (the “metabolic hypothesis” [7]) in order to achieve long term homeostasis.

Because the model is connected to an OISI measurement model, the model is a 2-D array of pixels. Generalization to a 3-D array of voxels, suitable for a 3-D measurement modality, would be relatively straightforward, although it would likely be desirable to modify the neuroscience contained in the model for the depth direction relative to the two lateral directions.

Because (1) spatial resolution is too coarse to show cells, (2) the OISI data [7] is two dimensional rather than three dimensional, and (3) the goal is a simple model that can be personalized, the emphasis is on continuum models rather than models constructed of interacting cellular submodels. While the models are continuum models, in order to facilitate computation, spatially discretized versions of the continuum models are emphasized where the discretization is pixel-by-pixel. In the mathematics of the models, the spatially discretized model is a set of ordinary differential equations for each pixel and, if the pixel size is allowed to approach zero, the set of ordinary differential equations becomes a set of partial differential equations which is what is typically meant by a continuum model.

The cortical vasculature has a complicated 3-D structure as is shown, for instance, in Ref. [9, Figure 1a]. While such a network could possibly be modeled as some form of random network, such a choice would make it difficult to determine the parameters in the model for individual subjects. Therefore, very simple deterministic networks are used.

The model has four interacting components, electrical, metabolic, vascular, and optical. The components are interconnected as is shown in Figure 1.

An important part of the model is the interaction of spatial dimensions and time. It has been difficult to publish the model because there has not been OISI data that includes both spatial and temporal variability and therefore the model, which intrinsically connects space and time, has appeared to be over complicated. Such data is now becoming available and we will soon submit an enhanced manuscript where the complexity of having coupled spatial and temporal variability is justified by its ability to describe corresponding data.

Flows in the microvasculature of the cerebral cortex

The work described in the final section of this report (“Determination of flow speeds in the microvasculature from video 2-photon laser scanning microscopy”) allows the measurement of flow speeds in the microvasculature of the cerebral cortex by two photon laser scanning microscopy (2PLSM). In addition, also by 2PLSM, the vessel diameters and the topology of the interconnected vessels can be determined. However, there are limitations. First, the number of flows that can be measured per hour of anesthesia is limited. Second, the

Figure 1. The four components of the model and their interactions shown as arrows which indicate the direction of the interaction.

microvasculature extends beyond the volume of cortex that can be imaged so there are flows into and out of the volume that is imaged. For the laminar flows in these small vessels, a resistive circuit analogy is well developed with a resistance that is proportional to vessel length times a resistance per unit length for a vessel of the measured diameter. The resistance per unit length is a complicated but well-studied subject which is usually described with a diameter-dependent viscosity.

In collaboration with Professor Chris Schaffer and Dr. Nozomi Nishimura (both Cornell BME), we have developed a circuit inverse problem that allows computation of all of the flows from the experimental data. The resistive circuit model of the flows in the vessels is a fragment of a circuit because of the limited volume in which measurements can be performed. We complete the circuit by the addition of voltage sources (i.e., pressure sources) of unknown values and by the addition of resistors of known values describing the capillary bed. We then solve a least squares problem using the measured currents (i.e., flows) to determine the unknown voltage (i.e., pressure) values. Once these values have been estimated, estimates of any current (i.e., flow) can be done by solving circuit equations. There are two main neuroscience contributions. First, we investigate experimental design issues. In particular, with measurements of a given quality, how many measurements have to be taken in order to achieve predictions with a particular level of accuracy throughout the circuit. Second, we investigate how a stroke effects cortical perfusion. We describe strokes by setting the resistance corresponding to the vessel branch in which the stroke occurs to infinity. Then, using unchanged values for the voltage sources (i.e., pressure sources), we compute how much

the total flow into the brain is changed and the spatial distribution of the changes. This has been an experimental topic of great interest to Professor Schaffer's group for many years and these results corroborate the experimental evidence that the vascular network contains a class of vessel that are not redundant so that a stroke in such a vessel reduces flow to the corresponding region of the cortex. A manuscript describing this work is in the final stages of preparation for submission to *J. Cerebral Blood Flow and Metabolism*.

Abstract descriptions of vascular networks

The model of the neurovascular network described in the "Circuit model of the neurovascular network" section of this report is at the physical level of conservation laws, *etc.* Just as electrical circuits can be described at various levels of detail, so can the neurovascular networks of the cerebral cortex. An important feature of the vascular network is the location of branches. A 3-D Poisson random process model of the location of branches has been developed parameterized by a 3-D rate function and a maximum likelihood estimator for the rate function has been implemented.

In collaboration with Dr. Nozomi Nishimura (Cornell BME), the model and estimator have been applied to archived mouse data. The cortex of all mammals is organized into layers parallel to the surface of the cortex. The standard definitions of layers are based on histology, primarily the types and numbers of cells and the neuronal connectivity. The maximum likelihood estimator definitely detects a layer organization based on the location of branches in the vascular network, not on the traditional types and numbers of cells, *etc.* We are currently collaborating with Dr. Nishimura in order to develop an explanation of these observations that relates the layers detected in the vascular network with the traditional layers.

Determination of flow speeds in the microvasculature from video 2-photon laser scanning microscopy

By adding an fluorescent molecule to blood which is excluded from the volume of the red blood cells, the plasma but not the cells can be labeled. Two photon laser scanning microscopy can be operated such that a single line in 3-D is repeated scanned at high rates. When the scan line is along a blood vessel and the blood has been labeled as described, the each image shows dark spots (the cells) in a tube of fluorescence (the plasma) and the cells move from one scan to the next scan.

In collaboration with Professor Chris Schaffer (Cornell BME) and especially Schaffer's Ph.D. student Thom Santisakultarm, we have developed image processing tools that can take the quite noisy video of moving spots and estimate flow speeds. The approach is to make an image of the line scans, high pass filter the image to remove large-scale artifacts, compute the

Radon transform, and estimate the direction of the moving spots (which corresponds to red blood cell speed) by finding the Radon transform direction such that the variance of the 1-D projection is minimized. This work has been published in the context of Santisakultarm's thesis research on the effect of the cardiac cycle and the respiration cycle on the flow of blood in the cerebral cortex microvasculature [10].

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