Multiscale modeling of cerebral blood flow and oxygen transport: Model credibility plan

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Project title and description

Multiscale modeling of cerebral blood flow and oxygen transport; U01 HL136662, start date 08/01/2017

The overall goal of this proposal is to gain quantitative understanding of the relationship between neural activation, blood flow and tissue oxygenation in the brain cortex, using multiscale theoretical models for blood flow, oxygen transport and flow regulation in networks of microvessels.

Context of models

- The model development in this project serves two main purposes:
  - to provide methods to study blood flow and oxygen transport in the brain;
  - to provide tools for studies of blood flow and mass transport in other tissues, by us and by other groups.
- The audience is similarly twofold:
  - investigators in the field of neurovascular coupling;
  - theoreticians working on mass transport to tissue by blood.

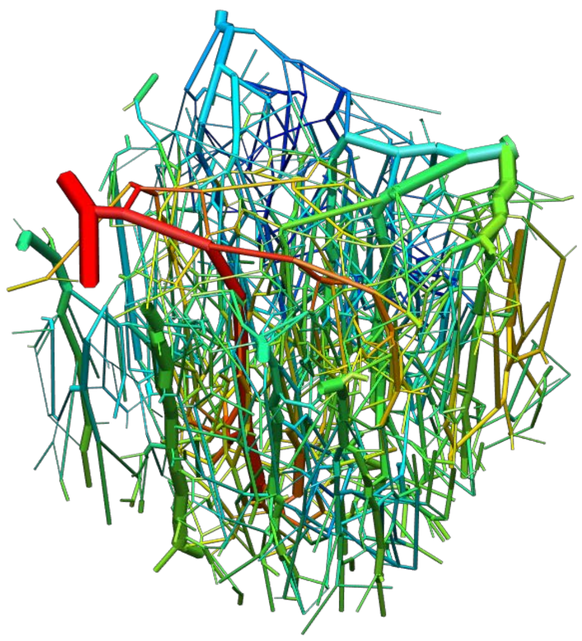
Aspects of model validity/credibility

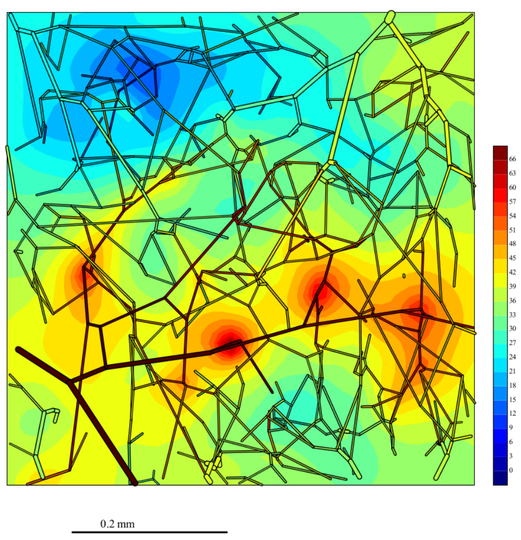
- **Technical validity**: are assumptions underlying the model accurately represented by the mathematical or computational method?
- **Biological credibility**: does the model faithfully represent relevant aspects of the biological system behavior?

Technical validity

The assurance of technical validity is continuously considered during our model development, mostly in C++. We use a number of techniques to ensure that the resulting code is technically valid:

- While developing model code, we simultaneously write a draft of a paper describing the model. In this way, we keep the code in close correspondence with the methods and assumptions of the model.
- We test the code under conditions for which the correct behavior is known or can be calculated independently. For example, our Greens function method for oxygen transport was tested by comparing its solution with corresponding solutions using the Krogh cylinder model.
- We continuously generate graphical output during program execution, to check for Inconsistent or unexpected behavior. Graphics files showing network structure, hemodynamic variables, oxygen fields on slices through 3D domains, histograms of relevant variables, etc., are generated and monitored.





Biological credibility

The following approaches are used to establish biological credibility of our models.

- The project is carried out in close collaboration between an experimental group and a theoretical group, facilitating frequent comparisons and “reality checks.”
- The model for flow and oxygen transport will be parameterized using data in the resting state. Then flow rates and oxygen levels in main inflow and outflow vessels will be measured in conditions of reduced blood pressure or blood oxygen levels, and used as boundary conditions for model simulations to predict flow rates and tissue oxygen fields throughout the observed region. These predictions will be compared with independently measured values.
- The models will be used to test hypotheses regarding the mechanisms of flow regulation in the brain, by generating multiple models in which specific mechanisms are turned on or off. We anticipate that many of these models will be unable to predict behavior consistent with observations, regardless of assumed parameter values. These “failures” will guide the choice of mechanisms to be included in the eventual model. Comparisons with observed responses to several types of experimental conditions will aid in establishing the credibility of these models.
- We will carry out sensitivity analyses of model results to key unknown parameters. These analyses will be used to assess model robustness, to obtain estimates of uncertainty of model predictions where key parameters are not precisely known, and to predict the effects of parameter changes that occur in various physiological and pathological conditions. For example, we will examine the dependence of tissue oxygen distribution and hypoxic fraction on oxygen consumption rate and on perfusion.

Third party assessment of model credibility

- We make experimental data sets, model code with sample input data files, and sample output files publicly available via the internet.
- Our two consultants will be asked to contribute to the assessment of model credibility.
- The assessment of our work through peer review of manuscripts remains an important component of establishing model credibility.

Conclusion

Due to the complexity of biological systems and the difficulty of characterizing all aspects of their behavior, biological validity is not absolute, and its assessment is subjective. Theoretical models can and often do fail to represent biological reality in significant ways. In our experience, such failures are often very informative and drive further conceptual and model development. These processes are continuous throughout all stages of the project.