Model Credibility Report: U01 HL133362
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Project title: Multiscale modeling of cerebral blood flow and oxygen transport

Summary of the project topic: Distribution of blood flow according to the needs of tissues, particularly for oxygen, is achieved by local regulation of blood flow, through the adjustment of diameters of small arteries and arterioles. The overall goal of this project is to gain quantitative understanding of blood flow and oxygen transport to brain tissue through the development of multiscale theoretical models. For more details please see the IMAG wiki.

Model credibility plan: In the following, we provide the requested information, organized according to the CPMS 'Ten not-so-simple rules.' All activities are ongoing. Specific items of progress in the past 12 months are noted.

Rule 1 – Define context clearly.
Plan and develop the M&S activity with clear definition of the intended purpose or context accommodating end-users needs.

- The goals of our models are clearly defined by the Specific aims of the project, as follows. Specific Aim 1 is to develop predictive multiscale models for blood flow and oxygen transport in the mouse cerebral cortex, and validate these models using experimental data derived from multimodal imaging of the cortex microvasculature. Specific Aim 2 is to develop multiscale models for blood flow autoregulation and neurovascular coupling in the mouse cerebral cortex, and to test and refine these models using experimental data derived from multimodal imaging of the cortical microvasculature. The computational tools are being developed in such a way that they can be used by others for studies in any tissue for which detailed information is available about microvascular structure.

Rule 2 – Use appropriate data.
Use data relevant to the M&S activity, which can ideally be traced back to the source.

- The project is carried out in close collaboration between an experimental group and a theoretical group, facilitating frequent comparisons and "reality checks." In the past 12 months, our collaborators have provided additional high-quality data sets that we are using to test our modeling methods.
- Specific Aim 1 is structured to allow model testing with experimental data other than those used in the initial model development. The model for flow and oxygen transport is parameterized using data in the resting state. Then flow rates and oxygen levels in main inflow and outflow vessels are 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 are compared with independently measured values.

Rule 3 – Evaluate within context.
Evaluate the M&S activity through verification & validation, uncertainty quantification, and sensitivity analysis faithful to the context/purpose/scope of the M&S efforts, with clear and a-priori definition of evaluation metrics and including test cases.

- 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.
- In Specific Aim 2, the models are 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 carry out sensitivity analyses of model results to key unknown parameters. These analyses are 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.

Rule 4 – List limitations explicitly.
Provide an explicit disclaimer on the limitations of the M&S to indicate under what conditions or applications the M&S may or may not be relied on.

- Simplifying assumptions and limitations of our methods are explicitly described in publications describing our theoretical models.

Rule 5 – Use version control.
Implement a version control system to trace the time history of the M&S activities, including delineation of contributors' efforts.

- Within the past year, we have established repositories on GitHub for two key pieces of computer software: *FlowEstimateV1*, Estimation of blood flows in microvascular networks, version 1; and *GreensV4*, Greens function method for simulation of solute transport, version 4. They can be found at https://github.com/secomb.

Rule 6 – Document adequately.
Document all M&S activities, including simulation code, model markup, scope and intended use of M&S activities, users' and developers' guides.

- 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.

Rule 7 – Disseminate broadly.
Disseminate appropriate components of M&S activities, including simulation software, models, simulation scenarios and results.

- We make experimental data sets, model code with sample input data files, and sample output files publicly available via the internet, both on our website https://physiology.arizona.edu/people/secomb and on GitHub https://github.com/secomb.

Rule 8 – Get independent reviews.
Have the M&S activity reviewed by independent third-party users and developers, essentially by any interested member of the community.

- Our consultants (Drs. Roy and Devor) contribute to the assessment of model credibility. We have met with both consultants within the past 12 months.
- The assessment of our work through peer review of the resulting manuscripts remains an important component of establishing model credibility.
- Several other groups are using pieces of our software and we are highly responsive to requests for assistance and fixes to problem or limitations that they encounter.

Rule 9 – Test competing implementations.
Use competition of multiple implementations to check the conclusions of different implementations of the M&S processes against each other.

- As already mentioned, we test the code for simple geometric configurations where the correct behavior is known or can be calculated independently.

Rule 10 – Conform to standards.
Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and standards accepted as best practices.

- At present the file format that we use for describing microvascular network structure, geometry and flow distributions is the nearest thing to a standard for this application, and we promote its use.

Critical issues and concerns: 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 outcomes and drive further conceptual and model development. These processes are continuous throughout all stages of modeling.

Other factors contributing to credibility: We have not identified any issues that are not covered by the CPMS 'Ten not-so-simple rules.'

Data Management Plan

Experimental imaging data. The proposed three-dimensional imaging of microvascular structure, oxygen levels and blood flow in the mouse cerebral cortex will yield very large raw data sets. The storage and management of these data will be performed at the Martinos Center for Biomedical Imaging, Massachusetts General Hospital. A server farm of over 25 Linux servers handles central storage, email, web and other shared services, with overall storage capacity of more than exceeds 200 terabytes, with a further 2 petabytes associated with a 128-node computing cluster. The budget includes fees for backup storage of imaging data in these facilities.

Network-level data and variables. As described elsewhere (Approach), software already developed in-house will be used to segment and skeletonize image stacks to derive vascular network structures in terms of nodes and segments. We have developed a standardized data format for describing such structures. Each segment is described by an identifying string (typically an integer), the index numbers of the nodes that it connects, its reference diameter, and a flexible set of other descriptive parameters, such as parameters describing assumed active response characteristics. Each node is identified by its index number and its three-dimensional coordinates are specified. Curved segments are represented by a set of linked straight segments. Examples of such network data files are available online (see below). This file format has the advantage of being compact and easy to read, particularly given that networks analyzed may contain 10^3 to 10^4 or more segments. Model results in the form of variables describing each segment, such as oxygen partial pressure, saturation, vessel tone, active diameter, flow rate and hematocrit are incorporated as additional fields associated with each segment. It is possible in principle to describe network structures in terms of a markup language such as CellML (https://www.cellml.org/specifications/cellml_1.1), although the resulting descriptions may be cumbersome due to the need to specify each segment as a separate model component. If a description based on a markup language proves desirable for model interoperability, we will create programs to automate the conversion between different formats.

Field-level data and variables. The Green's function method will be used to compute three-dimensional fields of oxygen partial pressure in tissue region. The results are defined in terms of distributions of sources and sinks at specified positions, which are stored as arrays of numerical data, providing a compact method for encoding the field. The oxygen level at any given location can be computed later as needed by convoluting this distribution of sources and sinks with the Green's function. Due to the fundamentally different computational approach being used here, existing methods for storage of field data, such as methods based on finite element methods, or the approaches envisaged in the still-developing FieldML markup language (http://physiomeproject.org/software/fieldml) are unlikely to be suitable for the proposed work.

Plan for sharing models and software. Under the sponsorship of the International Union of Physiological Sciences, the Physiome Project (http://physiomeproject.org) grew out of a series of discussion in the 1990s and was formally initiated in 2000. As part of this project, we established a web site in December 1998 with the goal of sharing information about microvascular network structures, hemodynamics and mass transport simulations: http://physiology.arizona.edu/people/secomb. Although modest in scale, this remains a unique resource for network structural data and has been utilized by several other independent groups. The current content includes: (i) /network - two and three-dimensional network structures; (ii) /greens - C code for the Greens function method; (iii) /netflow - C code for microvascular network flow simulations; (iv) /contours - C code for efficient line and color contour plotting. This site will provide the initial framework for sharing data, models and results arising from the proposed work. As part of the current proposal, we will update and enhance this site, as follows:

- addition of existing datasets on several tissues that we have acquired but not yet made available;
- publication of version 4.0 of the Greens function method, whose development is well advanced and contains significance enhancements;
- transition to GitHub or another source repository, to provide a more consistent structure and more secure continuity of access;
- addition of data, models and results specific to this project as they become available.

To date, our policy in making these materials available has been to publish them online upon acceptance of related journal publications, so that the online materials are thoroughly documented and to avoid issues of pre-empting publication. We may modify this policy according to current standards in the MSM community.

Project Timeline: U01 HL133362

Year	Experiments	Model development	Model sharing
1	Resting conditions, with and without anesthesia	Flow and oxygen model development and testing with preliminary data sets	Transition to Github, Greens version 4
2	Effects of hypoxia and hypotension	Flow and oxygen model under resting conditions	GreensGPU version 1 NetFlow version 2
3	Effects of neural activation	Models for flow regulation, including effects of hypoxia and hypotension	Flow regulation modeling framework for arbitrary networks
4	Effects of hypoxia, hypotension and neural activation	Models for flow regulation, including effects of neural activation	Add modules for specific regulation mechanisms
5	Effects of hypoxia, hypotension and neural activation	Models for flow regulation, including effects of hypoxia, hypotension and neural activation	Add modules for specific regulation mechanisms