Proposal for Fields-MITACS Industrial Problem-Solving Workshop (FMIPW) August 16-20, 2010

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Background:

The clinical value of monitoring patterns of variation of physiologic parameters such as heart or respiratory rate is being increasingly recognized. This interval-in-time variability analysis provides complementary value to traditional point-in-time analysis. In addition to the clinical evaluation of the utility of continuous variability monitoring, we are actively exploring the etiology and origins of both healthy variability and altered variability with illness. One of the characteristic patterns associated with healthy variation is a scale-invariant or fractal pattern. A linear relationship on a log-log graph of frequency of occurrence versus amplitude of variation provides a measure of this fractal or self-similar pattern, demonstrating similarity across time-scales. At present, there is no current theory regarding the origins of fractal variability.

Andrew JE Seely is a surgeon, intensivist and scientist in Ottawa Hospital Research Institute and the University of Ottawa. Dr Seely leads the Dynamical Analysis Laboratory at the Ottawa Hospital, and is engaged in several clinical research projects to uncover the clinical value of Continuous Individualized Multiorgan Variability Analysis (CIMVA^{TM}). Dr Seely also founded Therapeutic Monitoring Systems (TMS) in order to commercialize CIMVA with the aim of improving care for patients with critical illness by improving their monitoring, providing earlier detection of deterioration and improved prognostication of severity of illness. In conjunction with Dr Seely, Andre Longtin, Professor of Physics at the University of Ottawa, and Alexandre Iolov, PhD student, Department of Mathematics, University of Ottawa, are engaged in a program of research to understand the origins of healthy variability, in particular, fractal variability. This trans-disciplinary research utilizes mathematical models, physics fundamentals, and physiologic concepts to generate novel theories with clinical and commercial value. We propose to present and participate the following in the FMIPW, Aug 16-20, 2010.

Hypotheses:

Given that fractal structures in time and space are ubiquitous in nature, and pre-supposing that nature seeks to breakdown energy gradients in the most expedient means possible, we hypothesize that: (1) fractal structures in time and space offer the most efficient means to dissipate energy gradients (and optimize entropy production), and (2) fractal structures in time and space are spontaneous, self-organizing emergent structures because of (1).

General approach to first hypothesis:

We intend to utilize mathematical models of circulation to evaluate if a fractal structures (anatomic structures and temporal structures) offers optimal means to dissipate energy gradients between a source and a body, or in physiologic terms, optimize O_2 delivery and/or CO_2 elimination.

Initial ideas regarding mathematical models:

1. Impact of spatial fractal structures: construct a vascular tree as in (Pindera, Ding, & Chen, 2008), simulate RBC's flow down the tree as in (Pozrikidis, 2009), evaluate oxygenation using the Green's function formalism as in (Secomb, Hsu, Park, & Dewhirst, 2004), reparametrize the vascular tree (different branching ratios etc.) and iterate. See which geometry gives you best O_2 delivery and/or CO_2 elimination or max CO_2 elimination given a fixed O2 influx.
2. Impact of temporal fractal structures: Come up with temporal structures for the blood influx (monotonic vs. scale-invariant variable) and again see which is 'best' vis-a- O_2 delivery and/or CO_2 elimination.

General approach to second hypothesis:

To prove that it fractal structures in time and space are emergent and due to the optimization of energy dissipation, we need to create a model and determine if fractal anatomy is a result of a system trying to optimize flow.

Initial ideas regarding mathematical models:

3. Consider a network of cells bathed in an aqueous solution, containing a low level of O_2 and CO_2. There is a slight space in between cells such that fluid can flow around the cells, through capillaries all of which are the

same small size. All cells have a very low metabolic rate, and burn a small amount of O_2 to create CO_2. If exposed to more O_2, cells will burn greater CO_2, presumably in a sigmoid relationship. Now we introduce an O_2 tap at the top of this grid, and we also add a CO_2 drain at the bottom. The tap pumps O_2 into the aqueous solution at one point, and the CO_2 drain draws out CO_2 at a specific point elsewhere. And, last but not least, greater quantities of either O_2 and CO_2 cause a dilation, a swelling, of the capillaries in between cells, thus allowing for greater flow. Btw, this is based on real physiology. If the above hypothesis is correct, then turning on this model will yield fractal anatomy as an emergent phenomenon. In other words, a river delta like fractal should slowly develop from the tap, and a river delta should collect at the drain. It would be interesting to experiment with growing systems, different locations for the tap and drain, 2D and 3D, and more. One could study the increase in flow, measured by CO2 output over time, in conjunction with the observation of what happens to the network of capillaries. Though the vasculature remodelling models discussed in (Pries & Secomb, 2008) and (Peirce, 2008) include metabolic factors, the following relationships may need to be further developed: (a) cells have a very low metabolic rate, and burn a small amount of O_2 to create CO_2, (b) if exposed to more O_2, cells will burn greater CO_2, presumably in a sigmoid relationship, and (c) greater quantities of either O_2 and CO_2 cause a dilation of the capillaries in between cells, thus allowing for greater flow.

Relevance:
Variability analysis offers the potential for a breakthrough in terms of a bedside application of complex systems science. The understanding of the origins of healthy variability and the breakdown of pathologic variability is a critical component to this clinical application, one which mathematical modelling has a potentially critical and definitive role to play. This workshop represents simply the beginning of an extensive research program.

BIBLIOGRAPHY:

For abstracts of References: (also see: http://www.mendeley.com/research-papers/collections/3148381/Math-Medicine-Workshop/)

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Study evaluating the kinetics of a tracer and its association with morphological information about the vessels through which the tracers flow.

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Peirce, S. M. (2008). Computational and mathematical modeling of angiogenesis. *Microcirculation (New York, N.Y. : 1994)*, *15*(8), 739-51. doi: 10.1080/10739680802220331.

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This paper implements blood flow through a capilary network with a single arterial entrance, treating single RBC's as particles.

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This paper implements blood flow through a capilary network with a single arterial entrance, treating single RBC's as particles.

Pries, A. R., & Secomb, T. W. (2008). Modeling structural adaptation of microcirculation. *Microcirculation (New York, N.Y. : 1994)*, *15*(8), 753-64. doi: 10.1080/10739680802229076.

This paper is the state-of-the-art in vessel remodelling, focusing on capillary diameter evolution subject to wall-shear stress and metabolic demands.

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This paper simulates oxygenation in tissue based on the most up-to-date knowledge of vasculature and blood rheology. It treats the blood as a continuum and focuses on the performance of different blood substitutes (HBOCs) at oxygen delivery. It generates a computer-based capilary network around muscle tissues that is based on hamster anatomy.