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In vivo estimation of regional oxygen consumption using positron emission tomography

An ongoing project at NSR is, in collaboration with investigators in the Departments of Radiology and Cardiology, to develop new methods for estimating regional myocardial oxygen consumption (MRO_2) *in vivo*.

The most direct measure of oxidative tissue metabolism is the conversion rate of oxygen to water via mitochondrial respiration. Technological advances in positron emission tomography (PET) enable us to obtain good-quality time-activity curves (TAC) in small areas in the heart after injection of [O-15]oxygen. To calculate oxygen consumption from the analysis of tissue residue curves or outflow dilution curves, realistic mathematical models that account for convection, diffusion, binding, and transformation in the tissue are needed. Because the transit time for untransformed [O-15]oxygen is so much less than that for the [O-15]water produced by metabolism, the model separates the oxygen from the water component in the total O-15 outflow or tissue residue curves, and thus estimates the oxygen uptake and consumption (Fig. 1).

We have developed a dual oxygen-water model that accounts fully for the nonlinearity of binding by hemoglobin (Hb) within erythrocyte and by myoglobin (Mb) within myocytes (Li et al., 1997). This model is accurate and easy to use since the local volumes of distribution for oxygen (including Hb and Mb binding space) are calculated automatically from oxygen supply and demand at steady state. The model's potential for parametric imaging, thought by many to be impractical because of the numerical complexity, is being explored.

The PET studies on dog and human hearts for the estimation of regional MRO_2 used a new technique: a single breath inhalation of about 30

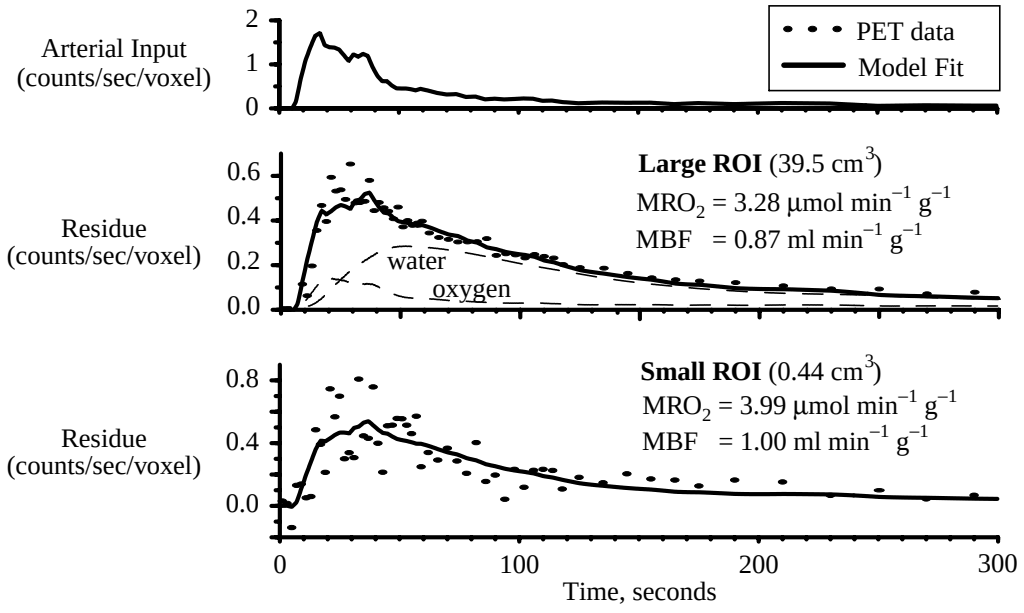

Figure 1. Two examples of fitting the nonlinear oxygen model to the PET data following an inhalation of [O-15]oxygen. The top panel shows the arterial input function of the model. The bottom two panels show the model fits to the myocardial TAC's from two ROI's of different size.

Contents

Staff

Jim Bassingthwaighte, Director
jbb@nsr.bioeng.washington.edu

Steve Bangs, System Mgmt.
steve@nsr

William Chan, Software Librarian
wchan@nsr

Rita Jensen, Administration
jensen@nsr

Rick King, Asst. Dir., Software
rick@nsr

Keith Kroll, Asst. Dir., Applications
keith@nsr

Eric Lawson, Publications
eric@nsr

Zheng Li, Modeling Applications
zhengl@nsr

Gary Raymond, Applications
garyr@nsr

to 60 mCi of [O-15]oxygen. This technique gave rise to a good sharp intra-atrial or intraventricular time-activity curve as the model input function, and provided consistently analyzable tissue residue curves, even on regions of interest (ROI) as small as 0.3 g of tissue.

Table 1: Global comparison of MRO_2 ($\mu mol\ min^{-1}\ g^{-1}$) estimates by PET and direct measurements.

	Control 1	Control 2	Stimulation
Heart 1:			
Fick	2.4	2.3	5.4
PET	2.8	2.8	6.6
Heart 2:			
Fick	2.5	2.5	8.1
PET	2.3	2.4	9.0
Heart 3:			
Fick	2.6	2.0	5.8
PET	3.2	3.0	6.7

Table 2: Estimates of myocardial blood flow ($ml\ min^{-1}\ g^{-1}$) and MRO_2 ($\mu mol\ min^{-1}\ g^{-1}$) on two human subjects.

	Heart 1 n = 36	Heart 2 n = 48
ROI Mass	0.7 ± 0.2 g	0.7 ± 0.3 g
Mean Flow	1.0 (±20%)	0.7 (±26%)
Mean MRO_2 (Control 1)	3.7 (±30%)	4.2 (±22%)
Mean MRO_2 (Control 2)	4.0 (±26%)	4.0 (±30%)

For the open chest dog studies, the whole left ventricular (LV) MRO_2 estimates by PET imaging were compared to those by the Fick method using blood samples from the aorta and coronary sinus. The studies were done during two control states and dobutamine stimulation. Table 1 shows good agreement of the two methods on the estimate of MRO_2 from three hearts.

For the human studies, the left ventricle was divided into 4 ROIs per ring in each of the 9 to 12 rings. For each heart, two oxygen studies, separated by about 15 minutes, were done for comparison. The mean values of regional estimates at the two control states were very close (Table 2), and they are virtually identical to the global estimates obtained from the whole LV as a single ROI (not shown). This shows the robustness of the model in the presence of noise. The present study suggests the feasibility of using PET to assess the heterogeneity of flow and oxygen consumption in small areas (~0.7 g) of the human heart.

The development of parametric imaging technology is in progress. We are combining a powerful image display and manipulation system (XMODIMG), with the "mixture analysis" of Dr. O'Sullivan, our collaborator in the Dept. of Statistics, to produce parametric images of regional oxygen consumption and flows.

This new technique, for the first time, provides direct information on regional myocardial oxygen consumption *in vivo*. It has great potential clinical usage, because information such as mismatch of regional myocardial blood flow and oxygen metabolism can be obtained without invasion. From the physiological point of view, this is also a big step forward in our effort to understand the metabolic basis for regional flow distribution, and the correlation of local blood flow, local metabolism and local cardiac work.

References

Li, Z., T. Yipintsoi and J.B. Bassingthwaighte, Nonlinear model for oxygen transport and metabolism. *Ann. Biomed Eng.*, 1997 (in press)

Li, Z., T. Yipintsoi, J. H. Caldwell, J. M. Link, K. A. Krohn, and J. B. Bassingthwaighte. Modeling of [O-15]oxygen kinetics for estimating regional oxygen consumption in canine hearts. *J. Nucl. Med.* 37:110P, 1996a.

Li, Z., T. Yipintsoi, J. H. Caldwell, C. Zuurbier, K. A. Krohn, J. M. Link, T. K. Lewellen, and J. B. Bassingthwaighte. Single breath inhalation of [O-15]oxygen for estimating regional oxygen consumption in human hearts via PET. *J. Nucl. Med.* 37:146P, 1996b.

Zheng Li

NSR and the World Wide Web

NSR has a World Wide Web (WWW) home page at the Uniform Resource Locator (URL) address http://nsr.bioeng.washington.edu/. You can use Mosaic™ or your favored WWW browser to access general information about NSR at our site: development of the site continues, however, so tune in from time to time for more goodies. While you're there, check out the link to the home page of the *Annals of Biomedical Engineering*, where you will find the tables of contents for previous and forthcoming issues of the journal, as well as information for authors. To go directly to the *Annals* website, use URL http://nsr.bioeng.washington.edu/ABME/annals.html.

XSIM available on the World Wide Web

The distribution package for Version 2.0 of XSIM for SunOS is available at our WWW site. You can get to the distribution page by following the "XSIM distribution page" link from the NSR home page, http://nsr.bioeng.washington.edu. The package contains all the files required for a standalone version of XSIM.

A release of XSIM for Solaris is scheduled for March 15, 1997.

Send questions or report problems to

librarian@nsr.bioeng.washington.edu.

Rick King

NSR grant renewal

On June 1, 1996, we submitted to the National Center for Research Resources (NCRR) a competitive renewal of the grant that funds the research activities of the National Simulation Resource. This proposal contains the continuation of projects started in the previous cycle and also some new projects which have resulted from progress made over the last five years. The research proposals in this application are divided into three sections: Simulation Analysis (tool development), Modeling (model development for biological research), and Research Projects (application of these tools and models to specific projects at the University of Washington and other institutions). The funding is provided by NCRR primarily for Sections 1 and 2, and the support Section 3 via consultation and the provision of models and modeling tools.

Modeling and simulation research at NSR

I. Research in Simulation Analysis: General simulation tools, including the new interface XSIM, are being developed for simulation and data analysis using new techniques from mathematics, statistics, and data presentation.

A. Simulation Interface Development, XSIM (*King*)
B. Precision of parameter estimates in distributed models: a Monte Carlo strategy (*Cobelli*)
C.1. Refinement and Validation of Mixture Analysis for Application to [O-15] PET Studies of the Heart (*O'Sullivan*)
C.2. Image Display and Analysis Toolkit and User Interface (*King*)
C.3. Functional Imaging Packages for Clinical Research (*King*)
D. Statistical Analysis and Synthesis of Fractal Processes (*Percival*)
E. Analysis of Mathematical Models through Visualization (*Harris*)

II. Research in Modeling Mass Transport and Exchange: The research in these projects defines and refines the models and the approaches to using them for biological research. Most of these models serve a variety of purposes beyond the initial target suggested by the project title.

A. General Multipath, Multispecies, Nonlinear Models (*King*)
B.1. Nonlinear modeling of adenosine pathways in the heart (*Kroll*)
B.2. Nonlinear modeling of myocardial high energy phosphate system. (*Kroll*)
C. Glucose and FDG Imaging of Cancer (*Graham*)
D. Diffusional Facilitation in Tissues with Barriers (*Bassingthwaighte*)
E.1. Estimating Regional Flow by External Detection of Water (*Zheng Li*)
E.2. Flow Estimation From Tracers Undergoing Transcapillary Exchange (*Bassingthwaighte*)
F. Oxygen Transport from Red Blood Cells to Mitochondria (*Zheng Li*)
G. The Modeling of Water Fluxes (*Bassingthwaighte*)
H.1. Vascular Growth Patterns (*Beard and Wang*)
H.2. Biomechanical models for tissue remodeling: angiogenesis & wound contraction (*Murray*)
I. Model of intracellular bioenergetics and energy balance (*Kushmerick*)

Research projects using NSR tools

III. Applications in Modeling Analysis: Research in cardiac physiology and pathophysiology, at NSR and elsewhere, applies Resource tools to modeling analysis projects.

A.1 Metabolic Imaging of Cancer and Its Response to Therapy (Core C: Analysis)
A.2. Mechanisms of Heterogeneity in the Lung
A.3. Mathematical Modeling and Prediction of Consequences of Hypertension on Microvascular Network Function
B.1. Metabolic Basis for Myocardial Flow Heterogeneity
B.2. Imaging Regional Cardiac Sympathetic Dysfunction
B.3. Dispersion of Diffusible Indicators in the Body
B.4. Cardiac protection by adenosine in ischemia.
B.5. Adenosine and K^+ATP channels in coronary flow regulation.
B.6. PET imaging of myocardial adenosine
B.7. Oxygen Transport in the Heart.
B.8. Glucose Transport in the Human Muscle Tissue
B.9. Regulation of pyruvate dehydrogenase in pancreatic β-cell lines.
B.10. The local rate of myocardial aerobic metabolism in relation to local blood flow in the heart, estimated in multiple small tissue samples with [C-13]-enriched substrates.
B.11. CT Analysis of Myocardial Microcirculatory Function
B.12. Fractal Geometric Analysis of Brain Microcirculation
B.13. Adenosine formation and metabolism in hypoxia
B.14. Adenosine kinetics in cultured endothelial cells
B.15. Perfusion Modeling of Magnetic Resonance Imaging of the Heart using MMID4

Rita Jensen

Anonymous ftp at NSR

You may get files from NSR by using anonymous ftp. If you are using a UNIX system, use the following steps to get the "Readme" file, then read it carefully for detailed instructions. The "Readme" file is a text file that can be read with your usual text editor or word processing application. Macintosh and PC users may use similar procedures specific to their system and communication software.

1. Enter `ftp nsr.bioeng.washington.edu` at the system prompt.
2. Enter `anonymous` at the resulting `Name` prompt.
3. Enter a complete electronic mail address at the `Password` prompt.
4. Enter `get Readme` at the `ftp` prompt.
5. Enter `quit` to return to your system.

Computing facilities at NSR

The computing facilities of the Simulation Resource are centered on a network of 19 Sun workstations that range from the entry-level SparcStation 1+ to our newest acquisition, a Creator series Ultra Model 170. The Ultra is a state-of-the-art computer designed for high speed graphics and especially fast floating-point numerical work.

In addition to the Sun workstations, the Resource has one DEC AlphaStation 200 running OSF/1, two Intel-based computers running LINUX, and several X-terminals. These additional computers and terminals are fully integrated into the workstation network, which allows our UNIX hosts to communicate with each other and the rest of the world through the University campus backbone at a speed of ten million bits per second.

All workstations are accessible over the Internet. For access from remote systems not currently on the Internet, NSR maintains three inbound V.34 modems (28.8kb).

A total of 14.8 GB of disk storage is available for storage of users' files.

To aid biomedical researchers in performing advanced simulation of biological systems, NSR provides a variety of computing tools including optimizing FORTRAN, C, and C++ compilers, model libraries, and symbolic math packages such as Maple, Matlab, and S+.

Our facilities are constantly being expanded, upgraded, and otherwise improved in an effort to keep pace with rapidly evolving hardware and software technology. This stance is reflected in our shift from Berkeley UNIX to the industry standard UNIX System V, which is in progress.

Rick King and Steve Bangs

One-dimensional fractal signals

NSR has developed computer programs that generate and analyze one-dimensional fractal series. Generation methods for one-dimensional fractal signals include Successive Random Addition (sra), Spectral Synthesis Method (ssm), and Fractional Gaussian Process (fgp). Code for these three techniques is available from the NSR website at URL http://nsr.bioeng.washington.edu/, by following the links to "Available Software" and then "Fractal Analysis Programs."

The recommended algorithm for generating a fractional Gaussian noise signal is fgp. It has the correct falloff in power spectral density (psd) and the correct autocorrelation. The other two methods, sra and ssm, do not have the correct psd at high frequencies.

Two more methods of analysis available at the URL given above are dispersional analysis (disp) and rescaled range analysis (hurst). Both methods work only for signals that are fractional Gaussian noises (fGn). They give incorrect results for fractional Brownian motions (fBm) (commonly taken to be the running sum of an fGn). The preferred method is disp, which generates less bias and variance for the estimated Hurst coefficient. The rescaled range method is an unacceptable method of analysis because of the large bias and variance of its results (Bassingthwaighte and Raymond, 1994). An improved version of the disp algorithm which iterates for a correction to the estimation of variance in the data is being tested and shows promise for reducing both bias and variance in the Hurst estimates.

Three additional methods of analysis available from the NSR website in beta test versions include scaled windowed variance analysis (swv), variants bridge detrended swv (bdswv), and linearly detrended swv (ldswv). The scaled windowed variance methods are used to analyze fBm and are as successful as disp is for fGn (Cannon et al., 1997).

Other methods for analyzing one-dimensional signals which are well developed and will soon be available at the NSR website include calculating the probability density function and statistics (pdf) and autocorrelation function analysis (acf).

Additionally, three different methods for analyzing the spectrum of a time series for its correlation structure are currently being tested and will be made available when ready.

References

Bassingthwaighte, J. B., and G. M. Raymond. Evaluating rescaled range analysis for time series. *Ann. Biomed. Eng.* 22:432-444, 1994.

Cannon, M., D. B. Percival, D. Caccia, G. M. Raymond, and J. B. Bassingthwaighte. Evaluating scaled windowed variance methods for estimating the Hurst coefficient of time series. *Phys. Rev. A*, 1997 (in press).

Gary M. Raymond

Precision of parameter estimates in distributed models

When mathematical models of physiological systems are used to indirectly "measure" parameters not directly accessible to measurement, their *a priori* unique identifiability is mandatory. Often, however, models are *a priori* unidentifiable, i.e., the model is either too complex or the experiment is poorly informative. In this case, one possibility for achieving unique identifiability is to assign a given value to some model parameters. However, when moving to the parameter estimation arena, care must be taken in assessing results.

Parameter estimation techniques, e.g., weighted nonlinear least squares, provide an estimate of the parameters of interest and a measure of their precision (from the inverse of the Fisher Information Matrix), i.e., of their *a posteriori* (numerical) identifiability. However, if some parameters are given assigned values and therefore are not involved in the estimation process, *a posteriori* identifiability will be overestimated. In addition, parameter bias may occur if the assigned values are unrealistic. It is worth emphasizing that a reliable measure of *a posteriori* identifiability is of utmost importance when models are used to "measure" directly inaccessible physiological events. This is a general issue that involves distributed parameter models and compartmental lumped-parameter models alike.

The aim of our research is to develop methods and software tools for a reliable assessment of precision of parameter estimates (*a posteriori* identifiability) of distributed models in the presence of assigned model parameters. In particular, we are developing a Monte Carlo method which takes into account both measurement error and the uncertainty associated with the fixed parameters. To briefly illustrate the method: the basic idea is to take the fixed parameters as means of an assumed probability distribution (which might be Gaussian, or uniform, with experimentally determined or assumed standard deviation). By now generating a large number of fixed parameter values according to their distribution, an equally large number of synthetic data sets is generated. To these data, noise (resembling the experimental noise) is added. Estimating the parameters in each of these synthetic data sets will allow the researcher to derive a Monte Carlo mean and standard deviation, which gives a realistic measure of parameter precision.

Work is also in progress to compare this approach with less computationally intensive approaches, such as the approach invoking linearization of the objective function. Preliminary results on real and simulated data sets with the Monte Carlo approach with a two-region distributed parameter model show that the uncertainty on the capillary wall parameters (permeability-surface area product and interstitial fluid volume) increases with respect to that derived from weighted least squares only, but it remains within acceptable limits.

The Monte Carlo methodology we describe is quite general, and can in principle be applied to any model, with any number of extravascular regions.

Claudio Cobelli, Paolo Vicini

Papers by NSR collaborators

These three recently published papers by our collaborators deserve special notice because of the insight they offer:

Bosan, S., and T. R. Harris. A visualization-based analysis method for multiparameter models of capillary tissue-exchange. *Ann. Biomed. Eng.* 24:124-138, 1996.

Roselli, R. J., G. Tack, and T. R. Harris. A model for fluid, erythrocyte, and solute transport in the lung. *Ann. Biomed. Eng.* 25:46-61, 1997.

Sparacino, G., and C. Cobelli. A stochastic deconvolution method to reconstruct insulin secretion rate after a glucose stimulus. *IEEE Trans. Biomed. Eng.* 43:512-529, 1996.

Recent NSR publications

Bassingthwaighte, J. B., and G. M. Raymond. Evaluation of the dispersional analysis method for fractal time series. *Ann. Biomed. Eng.* 23:491-505, 1995.

Bassingthwaighte, J. B. Toward modeling the human physionome. In: *Molecular and Subcellular Cardiology: Effects on Structure and Function*, edited by S. Sideman and R. Beyar. New York: Plenum, 1995, pp. 331-339.

Bassingthwaighte, J. B., and D. A. Beard. Fractal ^{15}O-water washout from the heart. *Circ. Res.* 77:1212-1221, 1995.

Bassingthwaighte, J. B., D. A. Beard, D. B. Percival, and G. M. Raymond. Fractal structures and processes. In: *Chaos and the Changing Nature of Science and Medicine: An Introduction*, edited by D. E. Herbert. Woodbury, New York: AIP Press, 1996, pp. 54-59.

Bassingthwaighte, J. B., B. Winkler, and R. B. King. Potassium and thallium uptake in dog myocardium. *J. Nucl. Med.* 38:264-274, 1997.

Deussen, A., and J. B. Bassingthwaighte. Modeling [^{15}O]oxygen tracer data for estimating oxygen consumption. *Am. J. Physiol.* 270 (*Heart Circ. Physiol.* 39):H1115-H1130, 1996.

King, R. B., G. M. Raymond, and J. B. Bassingthwaighte. Modeling blood flow heterogeneity. *Ann. Biomed. Eng.* 24:352-372, 1996.

King, R. B. Modeling membrane transport. In: *Advances in Food and Nutrition Research*, 1996, pp. 243-262.

Kroll, K., and G. V. Martin. Comparison of myocardial ATP, blood flow, and cytosolic adenosine in demand ischemia and coronary occlusion. *Am. J. Physiol.* 269 (*Heart Circ. Physiol.* 38):H819-H828, 1995.

Kroll, K., N. Wilke, M. Jerosch-Herold, Y. Wang, Y. Zhang, R. J. Bache, and J. B. Bassingthwaighte. Modeling regional myocardial flows from residue functions of an intravascular indicator. *Am. J. Physiol.* 271 (*Heart Circ. Physiol.* 40):H1643-H1655, 1996.

Kroll, K., and D. W. Stepp. Adenosine kinetics in the canine coronary circulation. *Am. J. Physiol.* 270 (*Heart Circ. Physiol.* 39):H1469-H1483, 1996.

Stapleton, D. D., T. C. Moffett, D. G. Baskin, and J. B. Bassingthwaighte. Autoradiographic assessment of blood flow heterogeneity in the hamster heart. *Microcirculation* 2:277-282, 1995.

Stepp, D. W., R. van Bibber, K. Kroll, and E. O. Feigl. Quantitative relation betweeen interstitial adenosine concentration and coronary blood flow. *Circ. Res.* 79:601-610, 1996.

Sweet, I. R., L. Peterson, K. Kroll, C. J. Goodner, M. Berry, and M. M. Graham. Effect of glucose on uptake of radiolabeled glucose, 2-deoxyglucose and 3-O-methylglucose by the perfused rat liver. *Am. J. Physiol.* 271 (*Endocrin. & Metab* 40):E384-E396, 1996.

Wang, C. Y., P. L. Liu, and J. B. Bassingthwaighte. Off-lattice Eden-C cluster growth model. *J. Phys. A: Math. Gen.* 28:2141-2147, 1995.

Wilke, N., K. Kroll, H. Merkle, Y. Wang, Y. Ishibashi, Y. Xu, J. Zhang, M. Jerosch-Herold, A. Mühler, A. E. Stillman, J. B. Bassingthwaighte, R. Bache, and K. Ugurbil. Regional myocardial blood volume and flow: First-pass MR imaging with polylysine-Gd-DTPA. *J. Magn. Res. Imaging* 5:227-237, 1995.

Eric Lawson, Publications
Bioengineering, Box 357962
University of Washington
Seattle, WA 98195-7962

61-8300