

## The Resource Facility for Population Kinetics at the University of Washington

An Executive Summary – January 1, 2005

**R F P K**



<http://www.rfpk.washington.edu>

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The Resource Facility for Population Kinetics (RFPK) at the University of Washington promotes the application of scientific data modeling in biomedical research, focusing on population kinetic analyses. RFPK is developing and will maintain new software systems designed to address issues in population kinetics, and supports the application of these systems in biomedical research through collaborative studies, service, training and dissemination.

The overall **purpose** of the Resource Facility is to provide scientific modeling assistance to the biomedical research community. To achieve this goal, we pursue the following objectives:

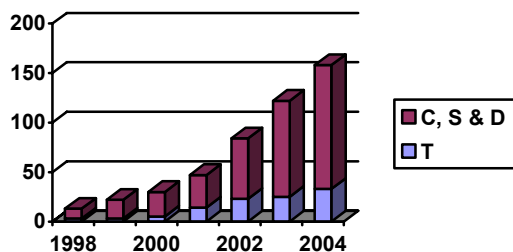
1. develop *new modeling methodologies and technologies* and apply them to study biological systems;
2. specify, design, develop, test, validate and maintain *new software systems* which incorporate state-of-the-art methods of estimating black-box, structural and statistical model parameters in kinetic studies;
3. provide *service* to the biomedical community via consultation in scientific modeling, and in the experimental design and analysis of kinetic data;
4. *educate and train individuals* in the use of modeling technology in biomedical research; and
5. *disseminate* our software products, technology, expertise and accomplishments.

The resource was founded in 1998 by Prof. David Foster at the UW. It is mainly supported in its efforts by a grant from the **National Institutes of Health**, National Institute of Biomedical Imaging and Bioengineering (P41 EB-001975). Its administrative center is at the University of Washington, while subcontracting institutions are the University of Western Australia, Perth; the University of Padova, Italy; and the University of Pittsburgh. Each subcontracting laboratory brings unique expertise and visibility to the RFPK project. Scientific journals where RFPK members have published peer-reviewed articles include:

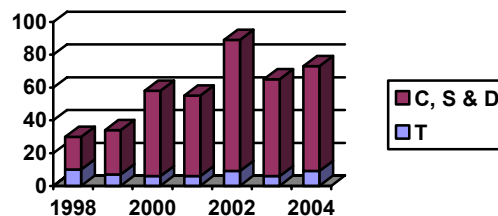
- American Journal of Physiology
- Annals of Biomedical Engineering
- Antimicrobial Agents and Chemotherapy
- Arteriosclerosis, Thrombosis, and Vascular Biology
- Biophysical Journal
- Circulation
- Clinical Cancer Research
- Clinical Pharmacology and Therapeutics
- Diabetes
- IEEE Transactions in Medical Imaging
- Journal of Clinical Endocrinology and Metabolism
- Journal of Lipid Research
- Journal of Pharmaceutical Sciences
- Journal of Pharmacokinetics and Pharmacodynamics
- Proceedings of the National Academy of Sciences of the USA (PNAS)

Quantitative measures of **impact** of the resource activities include the following<sup>1</sup>:

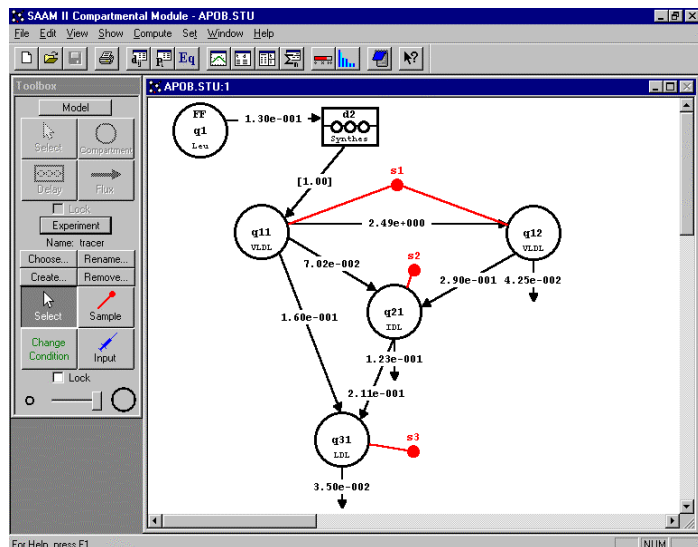
Number of Subprojects, 1998-2004



Number of Publications, 1998-2004



- The resource has supported the work and research of 152 users since inception; 74 of these were directly involved in collaborative projects; 282 papers and abstracts have been published under the auspices of the resource since 1998.
- We develop novel software tools for data modeling and analysis. The predecessor of RFPK, the Resource Facility for Kinetic Analysis, originally developed the popular software SAAM II, licensed to the SAAM Institute, Inc. RFPK plans to release the System for Population Kinetics, a novel population kinetic modeling web service.

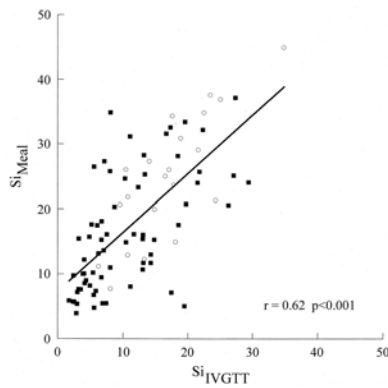


A SAAM II screen shot showing a compartmental model of lipoprotein kinetics with multiple sampling sites. The model definition is easily accomplished by interactive building of the compartmental structure using a modeling and experimental design toolbar (left side). Nonlinearities and complex dosing structures can also be interactively defined by typing in the relevant equations. The SAAM II program was licensed to the SAAM Institute, inc., in 1998, the year when RFPK started. It continues to be widely used in the research community for the analysis of time-dependent biological, biomedical, pharmacokinetic and pharmacodynamic data. More information is available at <http://www.saam.com>.

<sup>1</sup> (in the graphs below, T indicates Core R&D Technology projects, while C, S and D group collaborative, service and dissemination subprojects, using the classification of the National Center for Research Resources; the publication count includes journal articles, conference proceedings and abstracts)

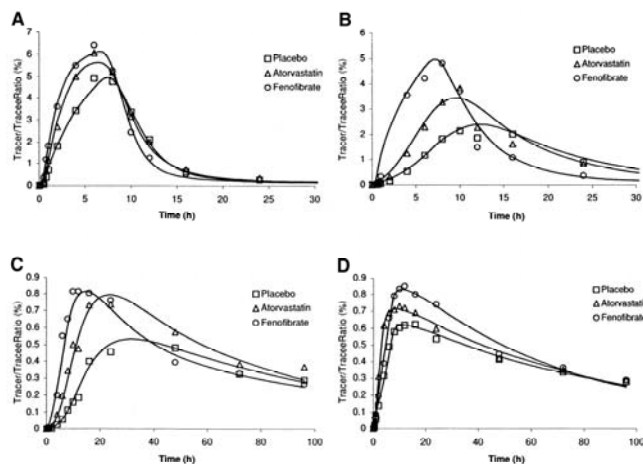
The Resource serves users in **six main application areas**. Within our Collaborative Projects, we work closely with collaborators to build and apply physiological and biomedical models that include uncertain knowledge, in order to better understand and predict the behavior of intact systems. The areas are (highlights are also shown):

1. **Intermediary metabolism:** the study of glucose and insulin regulation during physiological perturbations. Claudio Cobelli at the Padova site developed modeling paradigms to extract indices of insulin action and secretion from oral glucose data.



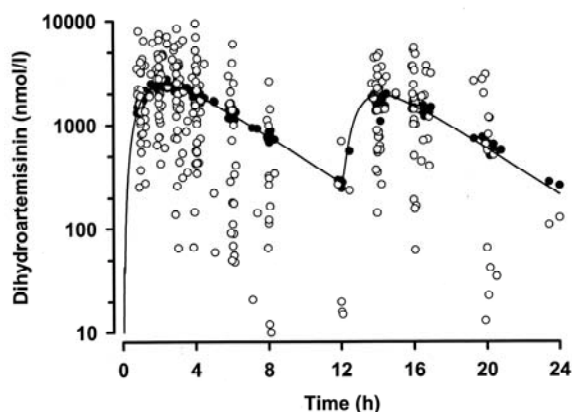
It is of increasing importance to be able to measure indices of insulin resistance cheaply and reliably in a single individual. This plot shows the correlation between insulin action indexes obtained with the minimal model applied to meal ( $S_{i_{Meal}}$ ) and intravenous ( $S_{i_{IVGTT}}$ ) glucose disappearance data. Both elderly (full squares) and young (open circles) participants were included. The meal and IV glucose minimal models assess insulin secretion, in response to stimuli administered by different routes. This agreement is encouraging.  $S_{i_{Meal}}$  correlations with various covariates suggest that the degree of fatness rather than age per se is the primary determinant of insulin action (from Basu et al., *Mechanisms of the Age-Associated Deterioration in Glucose Tolerance*, Diabetes 52:1738-1748, 2003 © 2003 by the American Diabetes Association, Inc.)

2. **Lipid metabolism:** Hugh Barrett's group at our site in Perth develops models of lipoprotein kinetics elucidating their role in insulin resistance and the metabolic syndrome, using a variety of experimental and modeling approaches.



The figure shows tracer data for VLDL apoB (panel A), IDL apoB (B), LDL apoB (C), and HDL ApoAI (D) after the administration of [d3]-leucine in a representative subject during treatment with atorvastatin, fenofibrate, and placebo. The tracer rate of appearance within the VLDL and LDL apoB fractions was increased by treatment. Continuous lines are predictions made with a linear compartmental model of tracer kinetics (from Watts et al. *Differential Regulation of Lipoprotein Kinetics by Atorvastatin and Fenofibrate in Subjects With the Metabolic Syndrome*, Diabetes. 2003 Mar;52(3):803-11, © 2003 by the American Diabetes Association, Inc.)

3. **Pharmacokinetics and pharmacodynamics**, the study of drug biodistribution and effect, takes place both at the Seattle and the Pittsburgh sites, under the coordination of Robert Bies. Projects are sought both in academia and industry.



Uncomplicated malaria can be treated with artesunate (ARTS). The figure shows a population model (full circles) and measurements (open circles) of dihydroartemisinin (DHA, ARTS primary active metabolite) concentration against time. The solid line shows plasma DHA concentration simulated by using the mean parameters for the model, a 12.75-mg/kg dose at zero time and 72% of that dose at 12 h. (from Karunajeewa et al., *Disposition of Artesunate and Dihydroartemisinin after Administration of Artesunate Suppositories in Children from Papua New Guinea with Uncomplicated Malaria*, *Antimicrobial Agents and Chemotherapy*, August 2004, p. 2966-2972, © 2004, American Society for Microbiology).

4. The collaborations in the **environmental toxicology** area are focused on the determination of physiologically based pharmacokinetic models for the determination of toxicant exposure and effect, e.g. in the workplace.
5. The **cellular biochemical networks** area groups mathematical and statistical models of data (in vivo and in vitro) gathered at the cellular or subcellular level.
6. **Parametric models of imaging data** we develop aim at extracting quantitative physiological information from dynamic imaging protocols, via model-based analysis of image sequences. This enables estimation, e.g. of local permeability or perfusion.

Parametric maps in atherosclerosis. (a) Histology specimen with a region of hemorrhage (long arrow), and microvessels throughout the plaque. (b), Model-based map of fractional blood volume: the vessel lumen is bright, indicating 100% blood volume, the area of hemorrhage (long arrow) shows a large blood volume. (from Kerwin et al. *Quantitative magnetic resonance imaging analysis of neovascularity volume in carotid atherosclerotic plaque*. *Circulation*. 2003;107:851 © 2003 American Heart Association, Inc.)

