Reproducibility in Modeling: Technology for the Stepping Stones of Science

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1. Reproducible science is much too rare.
2. A template: an example package with data, with test for verification and validation.
3. Cost and benefits. Does reproducibility pay off?

Advancing Science through Research

- Hypothesize
- Figure out how to test the hypothesis
  - State the hypothesis precisely, so it's testable:
    - An equation: $E = mc^2$
    - A verbal description? Probably not!
    - A mathematical model?
      - » Predict responses to lowering pressure at baroreceptor
      - » Predict nerve transmission velocity with nerve gas
  - Design the experiment to test it.
  - Alternative hypothesis? Design the experiment distinguishing the two ideas. One must be disproved.

Platt JR. Strong Inference. Science 146:347-353, 1964

SIMULATION: THE SCIENTIFIC CONTEXT

Modeling, Simulation is for:

- Discovery: gaining insight into systems, understanding
- Decision support: medicine, engineering, manufacturing

Goal: To find answers to particular questions

- The answers must be inferred from numerical values output by the simulations of the specified problems.
- The numerical values are rarely precise and, as such, contain intrinsic uncertainty, which should be regarded as essential to quantify as part of the simulation activity. We desire “confident prediction”.

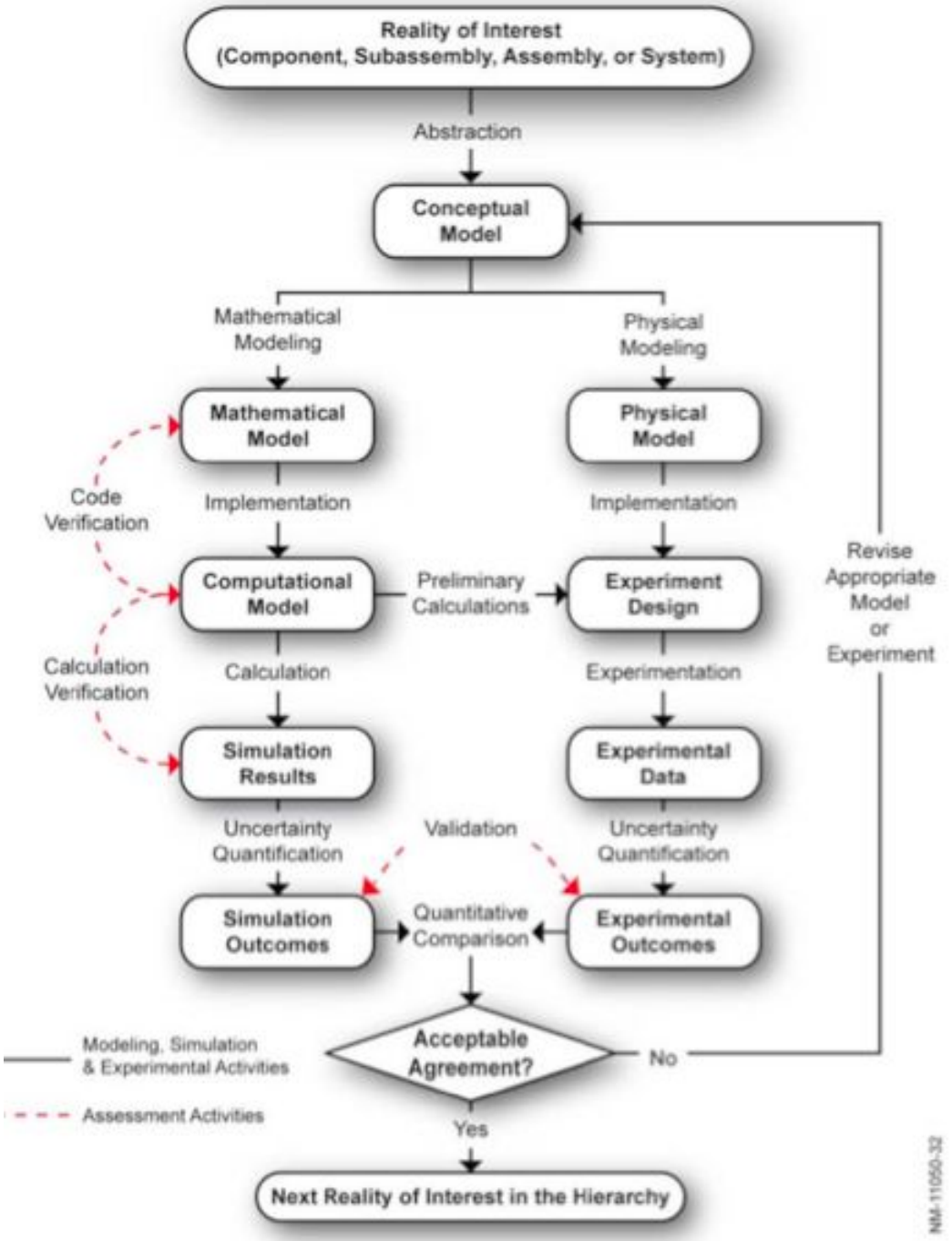
A Strategy: VVUQ = Verification, Validation, Uncertainty Quantification

Dissemination: Reviewing, revising, publishing, depositing, retrieving.

GOALS:

Define the hypothesis
Code the model
Verify - math
- computation
Validity testing vs. data
Define parameter confidence ranges
Uncertainty Quantification
Assess hypothesis
Predict consequences
- test the predictions

(Flowchart taken from the ASME)



Strong Inference

John R. Platt[5]

Science 16 October 1964: 347-353.

[DOI:10.1126/science.146.3642.347]

- The inference cycle:

1. Devising alternative hypotheses
2. Devising the distinguishing experiments to exclude one
3. Carrying out the experiment to get a clean result

1’. Recycle and refine the possibilities

Errors are the norm!

Kristin Sainani reports:

What is published is often untrue.

•The science is not reproducible because of:

- Errors in data
- Errors in software
- Errors in methods
- Typographical errors
- Incompleteness
- Falsification

And because

- Models not available
- Data not available
- The review system failed to find the inadequacies.

Modeling errors are costly!

David Nickerson reports: There are a few hundred models in the CellML repository. “I think there are maybe 5 or 6 of these that didn’t have errors in the original publication” and actually *none* were directly reproducible.

Nic Smith (in Exptl Physiol 2009) reports that model parameters for caridac electrophysiology remained untested through generations of models even though derived from a variety of species.

Nicolas Lenovere: All but 5 of 800 models required going back to the authors.

Model Phylogeny: Cardiac

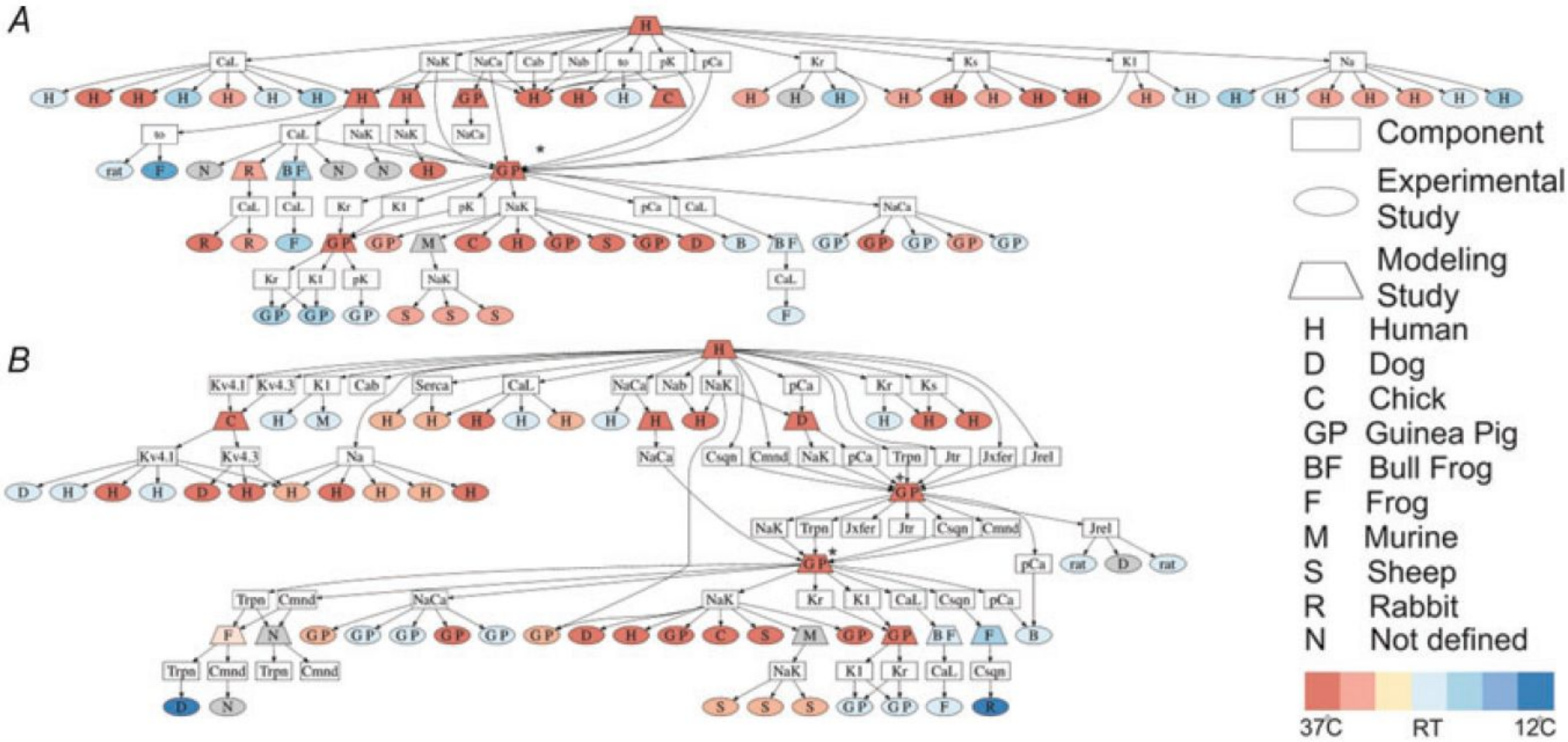
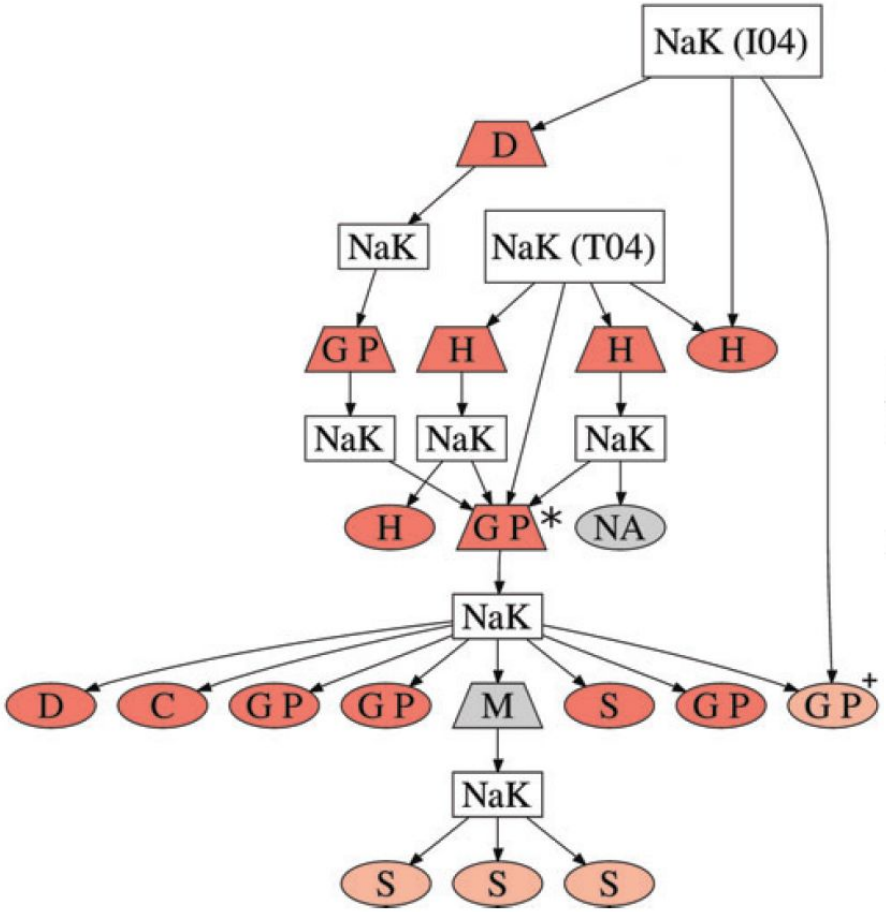
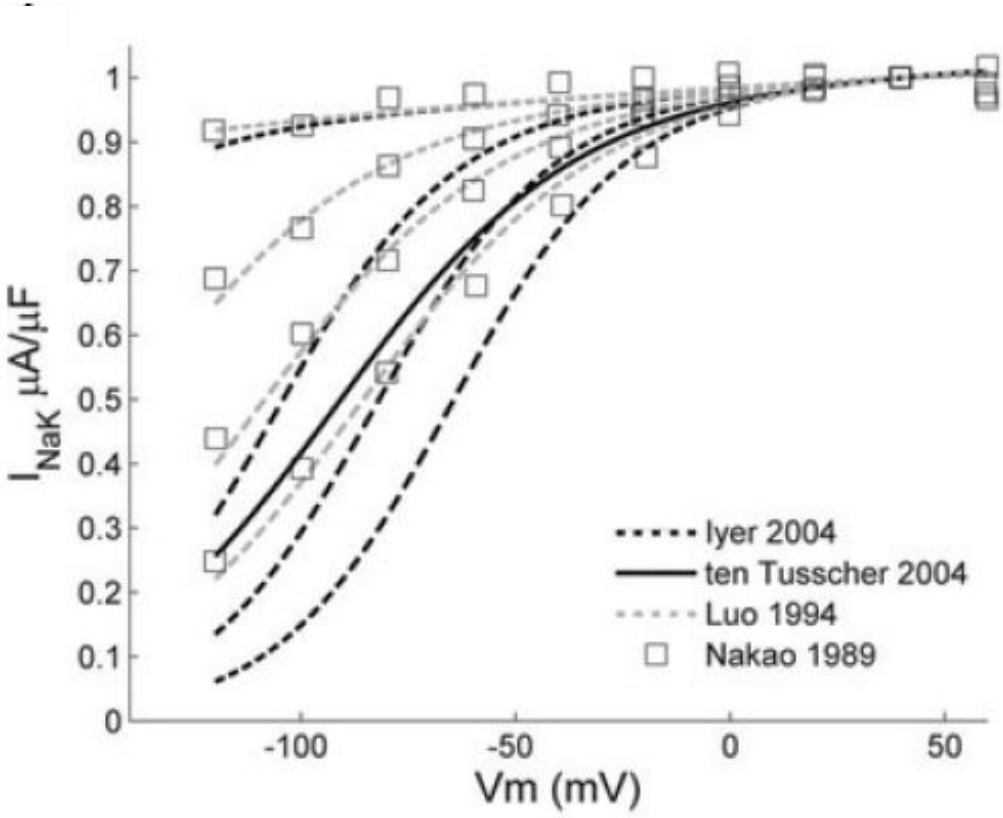


Figure 1. Phylogenetic schematic for the ten Tusscher *et al.* (2004; *A*) and the Iyer *et al.* (2004; *B*) cell models (*B*), showing the links between modelling (trapeziums) and experimental studies (ellipses)
Modelling studies are broken up into components (boxes), with connections (arrows) between components and published studies. ∗ Luo & Rudy (1994) model; and + Jafri *et al.* (1998) model.

From S.A.Niederer, M. Fink, D Noble and NP Smith. A meta-analysis of cardiac physiology computational models. Exp Physiol.94.5: 485-495, 2009.

Model Phylogeny: The NaK pump

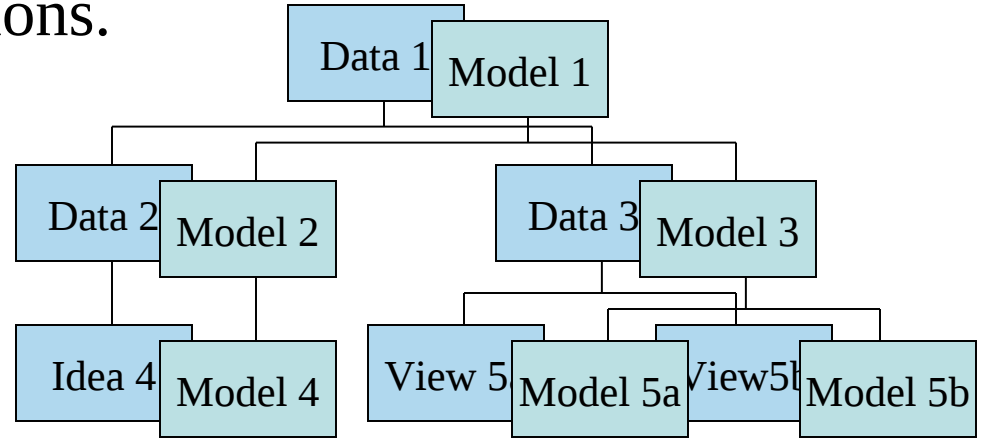




From S.A.Niederer, M. Fink, D Noble and NP Smith. A meta-analysis of cardiac physiology computational models. Exp Physiol.94.5: 485-495, 2009. The tree shows dependencies of the Iyer (2004) and Ten Tusscher (2004) models on the guinea pig (*) models of Luo and Rudy (1994) and data (+ , squares) of Nakao and Gadsby (1989) with comments on irreproducibility.

Physiome Projects depend on reproducibility of the models, the modeling process, the data, and the data analysis.

- Models (descriptive, theoretical, or mechanistic) are designed to represent data or ideas about real systems.
- Data and models are complementary, matched sets.
- Good data are a treasure, a permanent reference source.
- Models are transients: they capture snapshots of evolving perceptions.



NSF Grants: General Conditions

http://www.nsf.gov/pubs/policydocs/gc1_607.pdf

38. Sharing of Findings, Data, and Other Research Products

NSF expects significant findings from research and education activities it supports to be promptly submitted for publication, with authorship that accurately reflects the contributions of those involved. (Like NIH re PubMed)

It expects investigators to share with other researchers, the data, samples, physical collections and other supporting materials created or gathered in the course of the work.

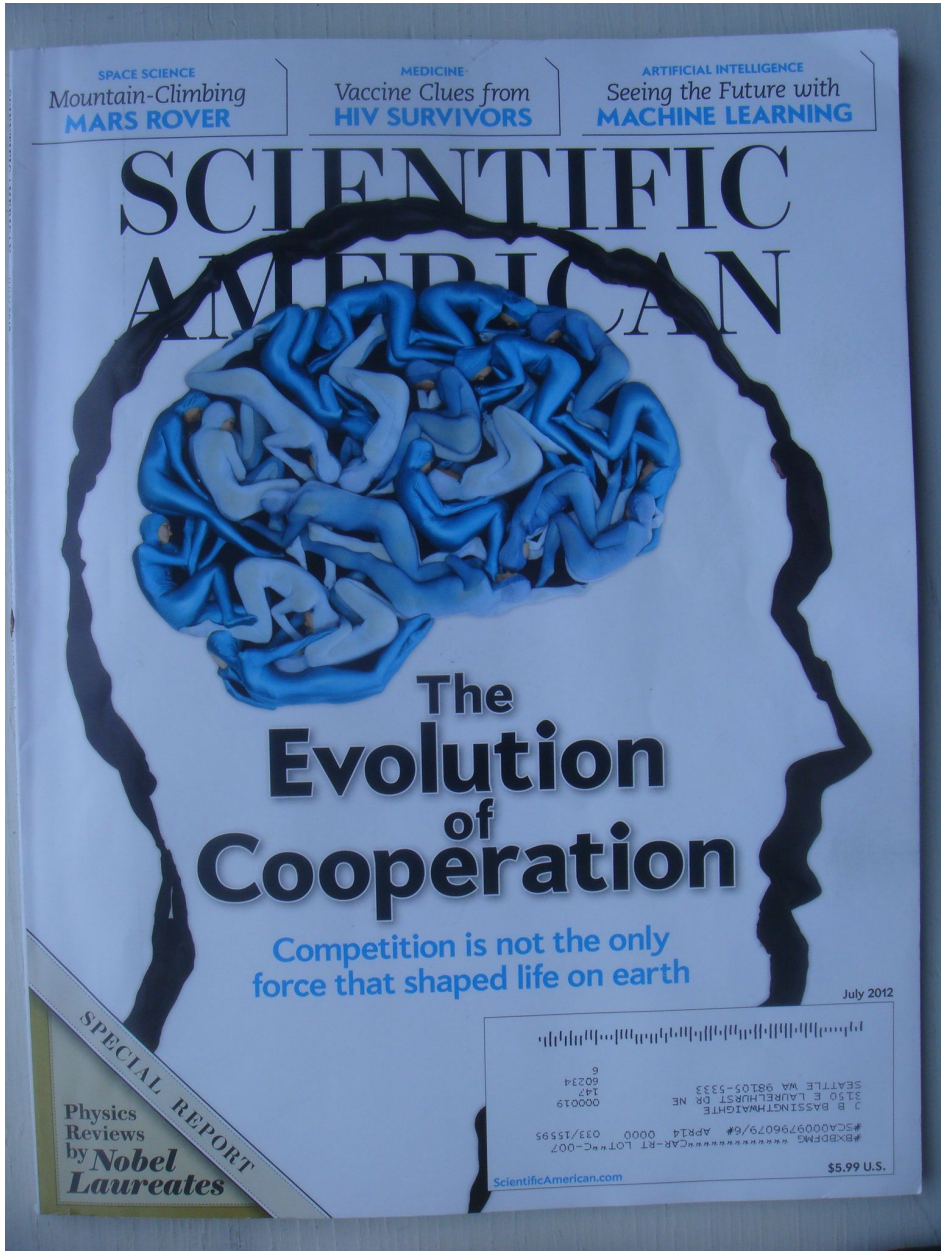
It also encourages grantees to share software and inventions or otherwise to make the innovations they embody widely useful and usable.

Collaborative Science Programs

This is a new era:

Beyond P01s and RRs to P51s and U01s:

Initiatives in physical and biological science are based ever more strongly on coherent collaborative programs

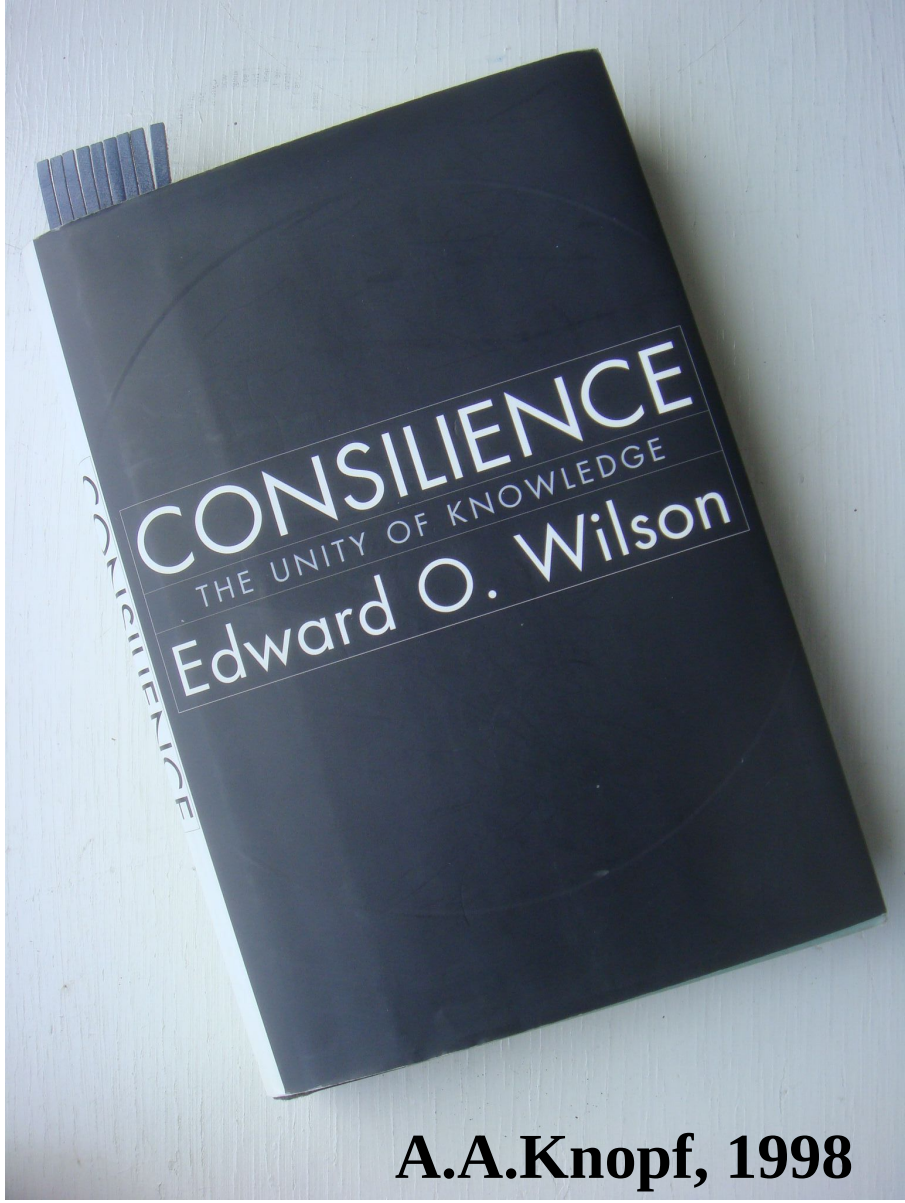


Consilience:

A “jumping together” of knowledge by the linking of facts and fact-based theory across disciplines from different disciplines to create a common groundwork of explanation. ….William Whewell 1840.

Fact: A particular truth known by direct observation, as opposed to what is merely inferred. A datum of experience. ….OED.

Planned consilience = integrative multiscale modeling in collaborations



A.A.Knopf, 1998

Convergence and Collaboration

- **Promoting Convergence in Biomedical Science**

Phillip A. Sharp and Robert Langer

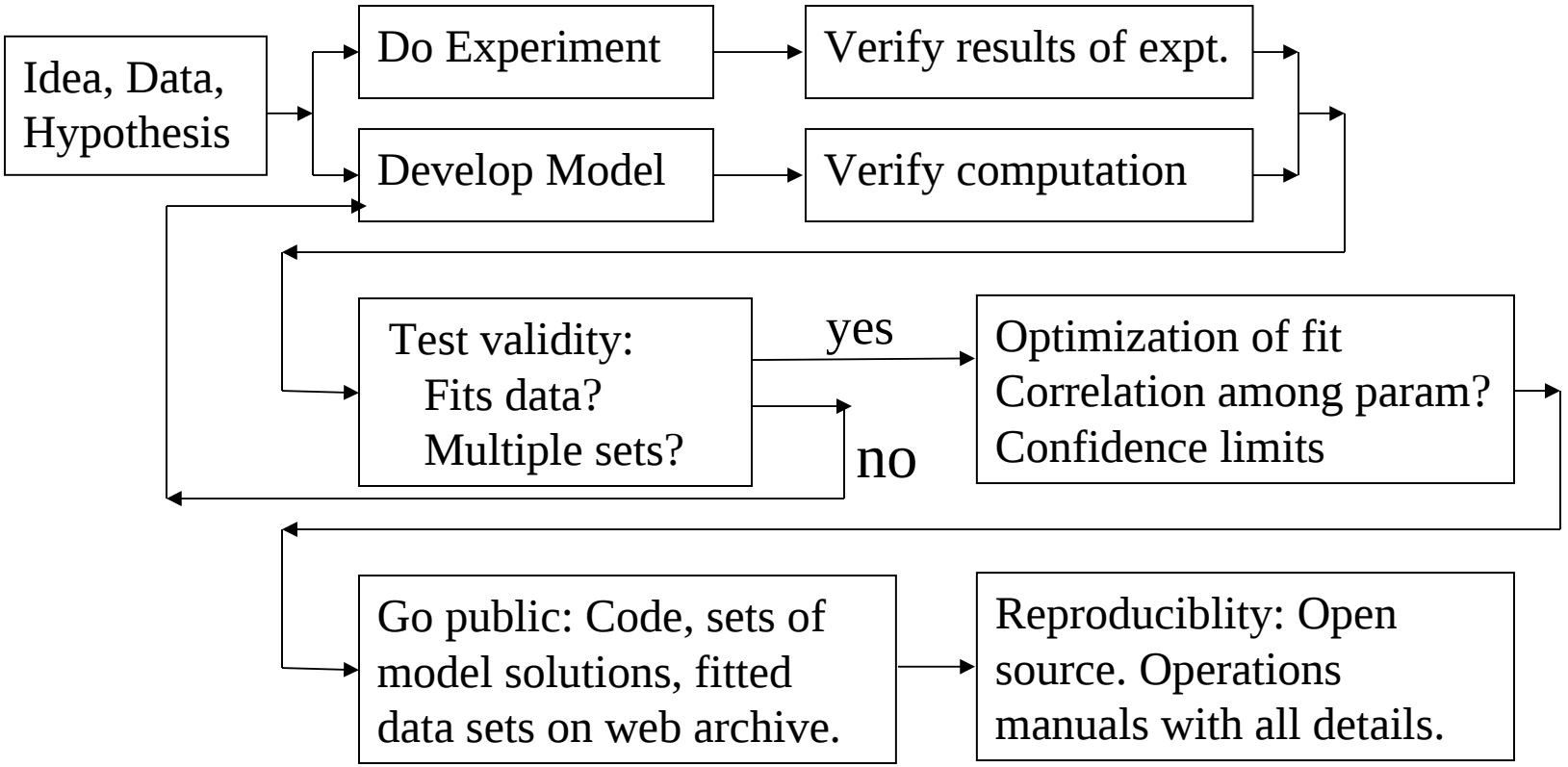
Science 333: 527, 29 July 2011.
[DOI:10.1126/science.1205008]

Multidisciplinary thinking and analysis will permit the emergence of new scientific principles and opportunities!

- cutting across silos
- collaborations
- new think tanks
- perspectives on data
- sharing + skepticism
- combined training

The prerequisite:
Reproducible Science, a creator of trust.

Making the Modeling Process Reproducible

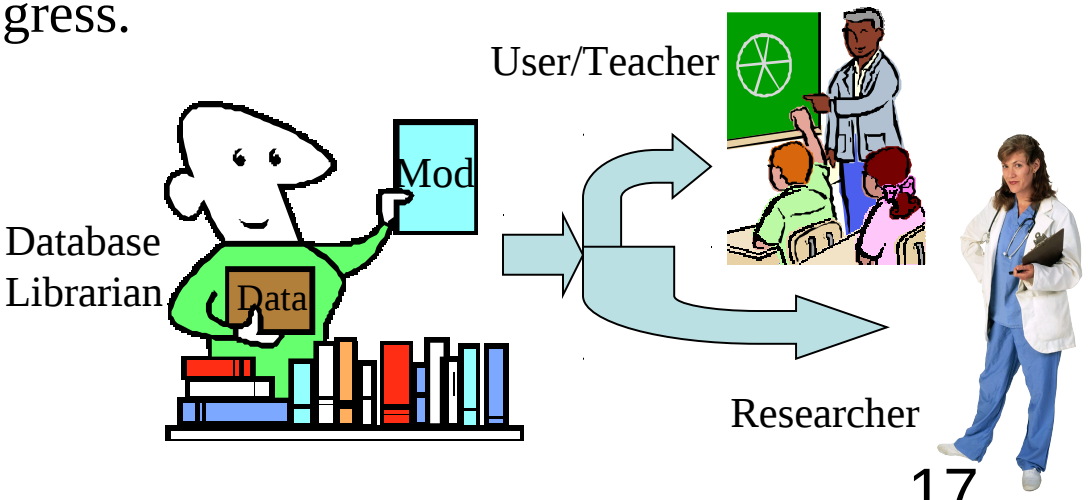


Reproducing the science (data, models, modeling process, and data analyses) is both tedious and difficult

- Reproducible models are building blocks and milestones of science
- They should capture the development: Models evolve through iterative refinements: multiple data sets → more comprehensive models integrating information and reconciling contradictions.
- More complex models describe more of the biology, but put higher demands on verification and validation measures.
- Integrative models define mechanisms, and fit more data sets. They infer a higher level of validity, i.e. greater generality.
- Having the data together with the models is more critical as complexity increases.
- For some examples of incremental development from primitive models see Tutorials at www.physiome.org/Models/tutorial.html

Reproducibility, capability, and computability aid experiment design and model improvement

- Reconciling disparities, and broadening the factual basis improves predictive capability of a model. Maintain your "*thaetige Skepsis*", *active doubt*. (Goethe)
- A broad range of predictions makes the model more susceptible to *invalidation*.
- Invalidation, disproof, by the next experiment creates the setting for the next advancement of the science.
- Archiving the data and model at each phase of the iterative process documents the progress.



Current Markup Languages (MLs) Are Inadequate

- Model markup languages, SBML, CellML, are serious attempts toward the public sharing of models. They provide a forum for curation and improvement.
- Curation is greatly improved, units and Initial Conditions have been added
- Current MLs provide bare-bones models, not enough for reproducible science.

The MLs fail to provide elements essential to the scientific process:

- Model heritage, their relationships, deviations and improvements
- Explanations of model configuration, and relation to the experiments
- Derivation of the mathematics, but do refer to published papers
- References for all parameters and how they were evaluated and selected.
- Methods of solution, numerical (stochastic, deterministic) or analytical, left to user.
- Cannot run or store PDEs, needed for spatial and convection-diffusion problems.
- Exemplary solutions over a wide range of parameter values, verification test suites.
- Examples of validation tests against varied data sets, models fitted to data, residuals, goodness of fit assessments.
- Parameter confidence limits, covariances, conditions under which these are obtained.
- Interpretation of the analysis, and meaning and role of the model relative to other models.

Technical Requirements for Reproducibility

The processes providing reproducible modeling go beyond the original intellectual beginnings, but are basically technical:

- Adhere to *standards* of information content. (www.imagwiki.nibib.gov)
- Use common *ontologies*, specify the ontology for each term.
- Describe the model *completely*, with diagrams.
- Give all equations, ICs. BCs, constraints.
- Define assumptions *explicitly*.
- *Verify* that computer solutions match the mathematics with the numerical and analytical methods used. Use conservation tests (mass, energy, etc.)
- *Validate* by testing against suites of data.
- *Archive the data with the models*.
- Write an operation manual to guide users.
- Show data analyses for *multiple data sets*.
- *Interpret* parameter values and confidence limits.
- *Publish* full manuscript.

The Project File Concept

- Store all experimental data sets, along with:
  - Model: Design, diagrams, equations, code for ODEs, DAEs and PDEs
  - Numerical methods and Parameter sets and plots for each data set
  - Optimizer settings and results of data fitting:
    - Goodness of fit, covariance matrix, confidence limits, Monte Carlo assessment
  - Sensitivity functions, Residuals
  - Notes for describing analyses and interpretations
    - General notes or data set specific
  - Plots or numeric output for model solutions against data
- Features for users and reviewers:
  - Source code, editable, with recompile and run
  - Automated unit balance checking, automated unit conversion
  - Ability to infer units (where model code was non-committal)
  - Automated parameter exploration: Loops with varied Param values
  - Behavioral Analysis, a display of matrices of solutions
  - Browser: Connectivity Diagrams between nodes in the system model
  - View Java text. Translations: XMML, SBML, CellML, Antimony, GraphML
- All of these are in the current JSim Project File.
  - Archival versions preserved (CVS)

The JSim Project File: Data-Models-Analyses

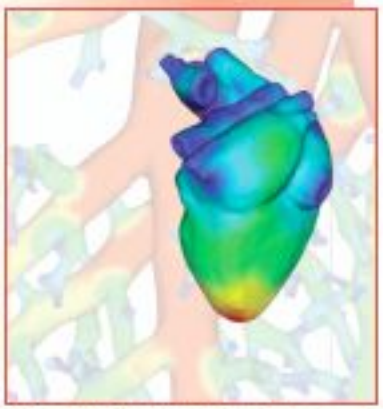
- JSim is a Java-based, project-file-based simulation analysis system. It runs models from MML, SBML, CellML
- JSim is ***open source***, at www.physiome.org
- Its archival forms are MathML and XMML
- The "MODEL.proj" file contains:
  - One or more models, for DAEs, ODEs, PDEs, events
  - Data sets, even hundreds of them
  - Multiple choices of numerical solvers, continuous or stochastic
  - Eight optimizers for automated data fitting, covariance analysis.
  - Model diagrams, connectivity diagrams automated.
  - Plots: Yon X, contour, movies, phase plane, 2D and 3D
  - Stored parameter sets, notes, optimizer and solver settings
  - Function generators, procedural and event capability
  - Translation to Java, GraphML, SBML and CellML (for ODE/DAE models, not PDEs). Matlab via SBML.
- Models are *open source* at www.physiome.org

Verify: Does the model solution match the math?

- Equations and phrases have units balancing?
- Match analytical solutions, at least in limiting cases?
- Insensitive to changes in time step size? Space step size?
- Same solutions on different platforms?
- Independent of software revisions in the basic languages or in the use of software modules?
- Steady state solutions independent of starting values? (Or operating on an attractor?)

Verification, the first step: Checking units

MULTISCALE MODELING PART 2



© Images courtesy of Daniel Einstein

Error Detection and Unit Conversion

Automated Unit Balancing in Modeling Interface Systems

BY HOWARD JAY CHIZECK, ERIK BUTTERWORTH, AND JAMES B. BASSINGTHWAIGHTE

Unit balance checking is the first of a series of checks for achieving correctness and validity of models.

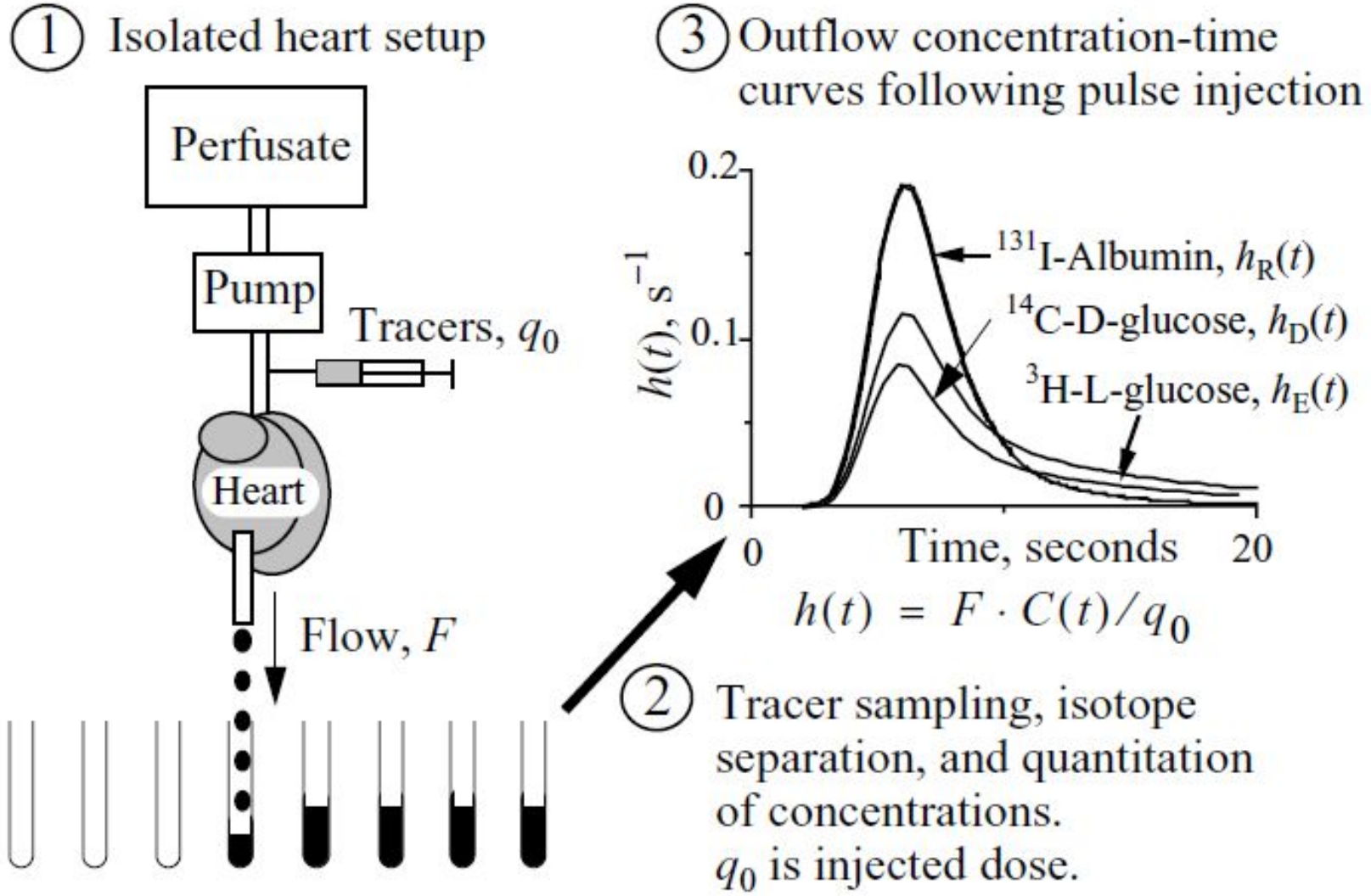
The incentives to *automate* unit balance checking in computer programs include speed and reproducibility.

```
// fundamental units
kg = fundamental,                    // kilograms
m = fundamental,                     // meters
sec = fundamental prefixable,        // seconds
amp = fundamental prefixable,        // amperes
degK = fundamental,                  // deg Kelvin
mol = fundamental prefixable,        // moles
candela = fundamental prefixable, // candela
```

Example project:

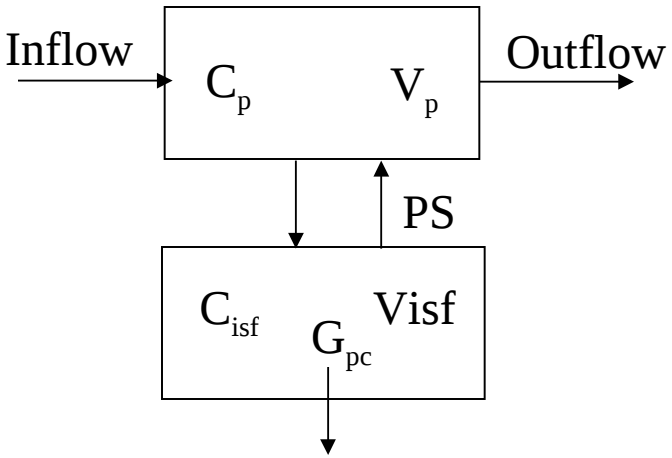
Glucose uptake in the heart. Can we distinguish cardiomyocyte uptake from endothelial uptake?

The Multiple-Tracer Indicator Dilution Experiment



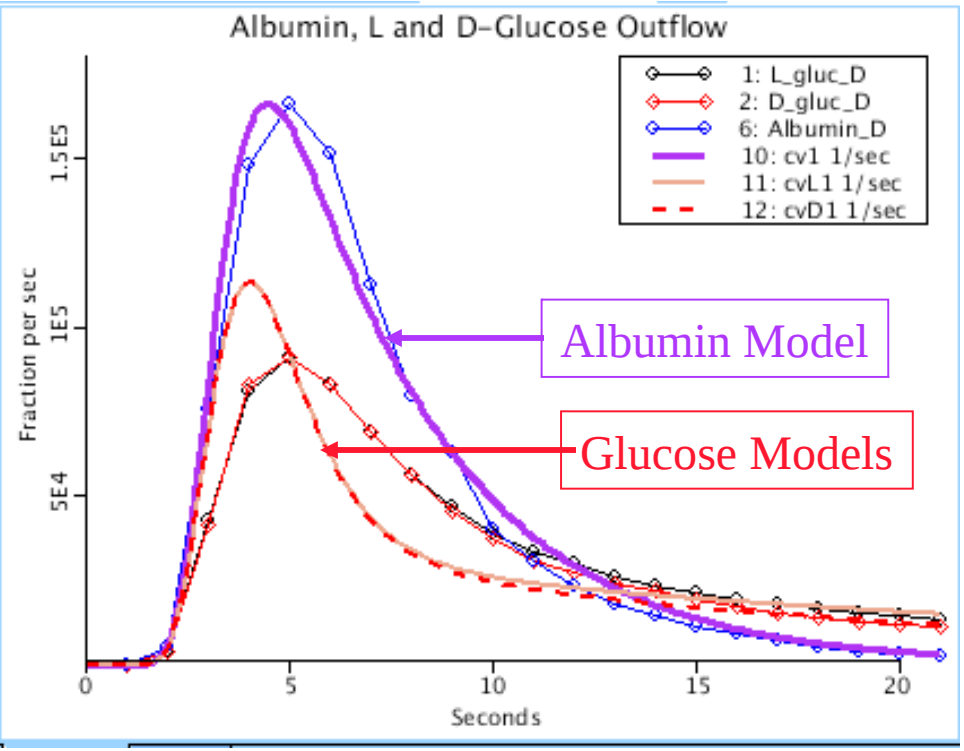
Einstein said “keep your model as simple as possible, … but not too simple!”

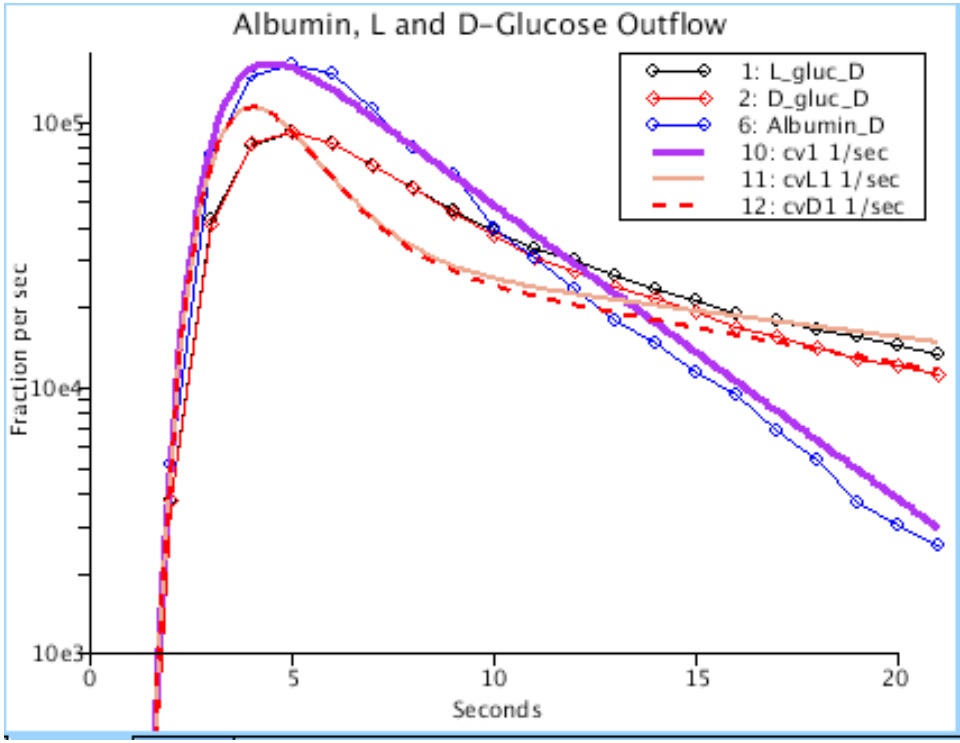
Two compartmental stirred tank model:
Vascular space, p, and extravascular space, isf



G_{pc} is a consumption process, cellular uptake (pc = parenchymal cell).

Too simple! A 2-compartment model fails.





Linear plot.

Semilog plot.

_D denotes Data = outflow Concn(t)
Albumin fits not too badly.
Neither L- nor D-glucose are fitted at all, except at the tail.

The model was wrong. Good!

For then we must learn to revise the model.

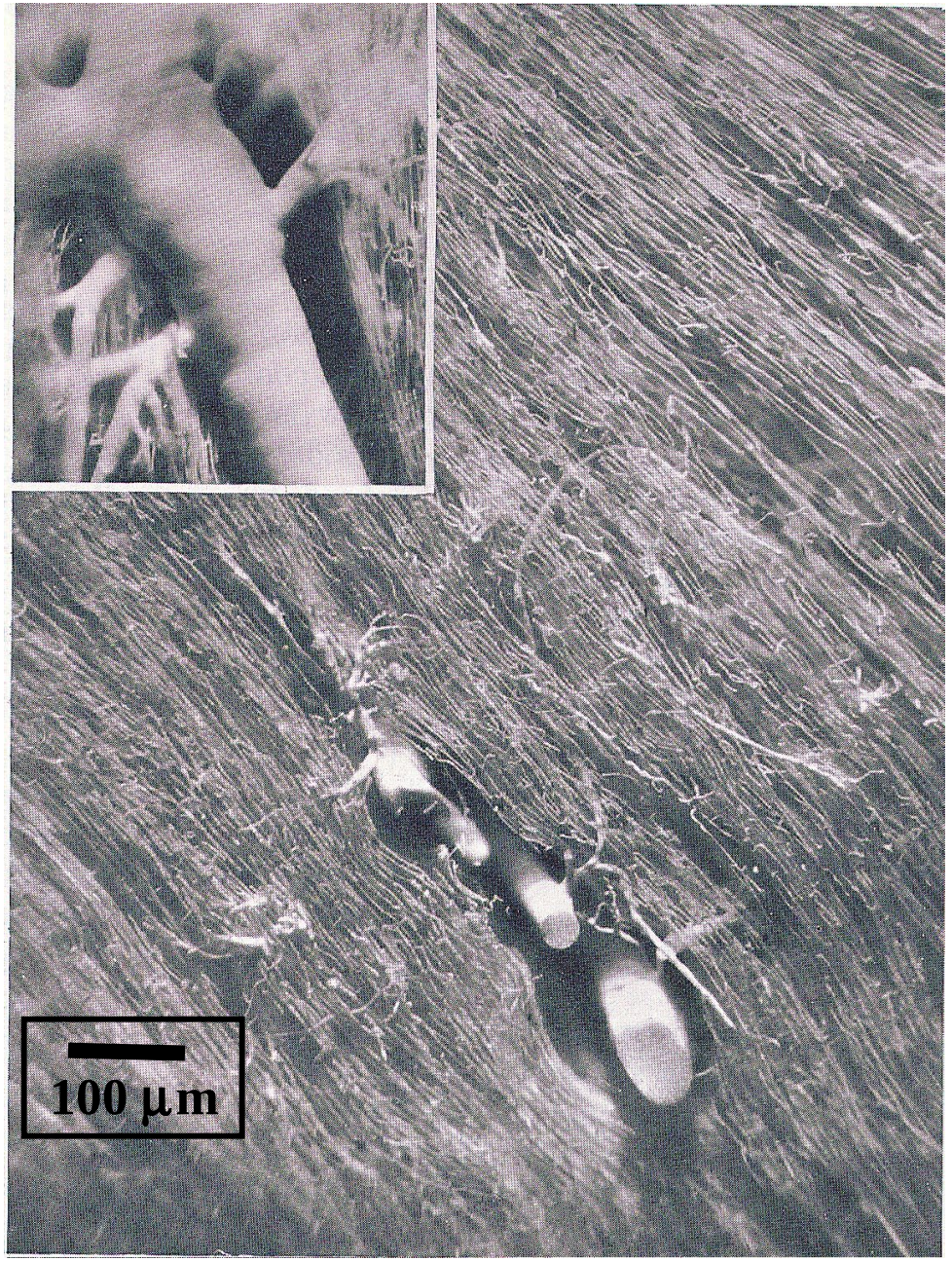
- We had neglected to ask “what is the anatomy” and how do we approximate it in this case? Can we use actual dimensions
  - Anatomic data provide constraints. Capillary lengths are 200 times capillary diameters. Fast mixing over such an aspect ratio is physically impossible.

- Did we think like a molecule?
  - What processes does each molecule undergo?
  - What influences its reactions, or its binding, or its diffusion?

- Check! Did we actually use the logical elements advocated?
  - Distinguish alternative hypotheses (Platt ‘64: Strong inference)
  - Did we build hypotheses by eliminating self contradictions, even while maintaining our “thätige Skepsis”, our *active doubt.*

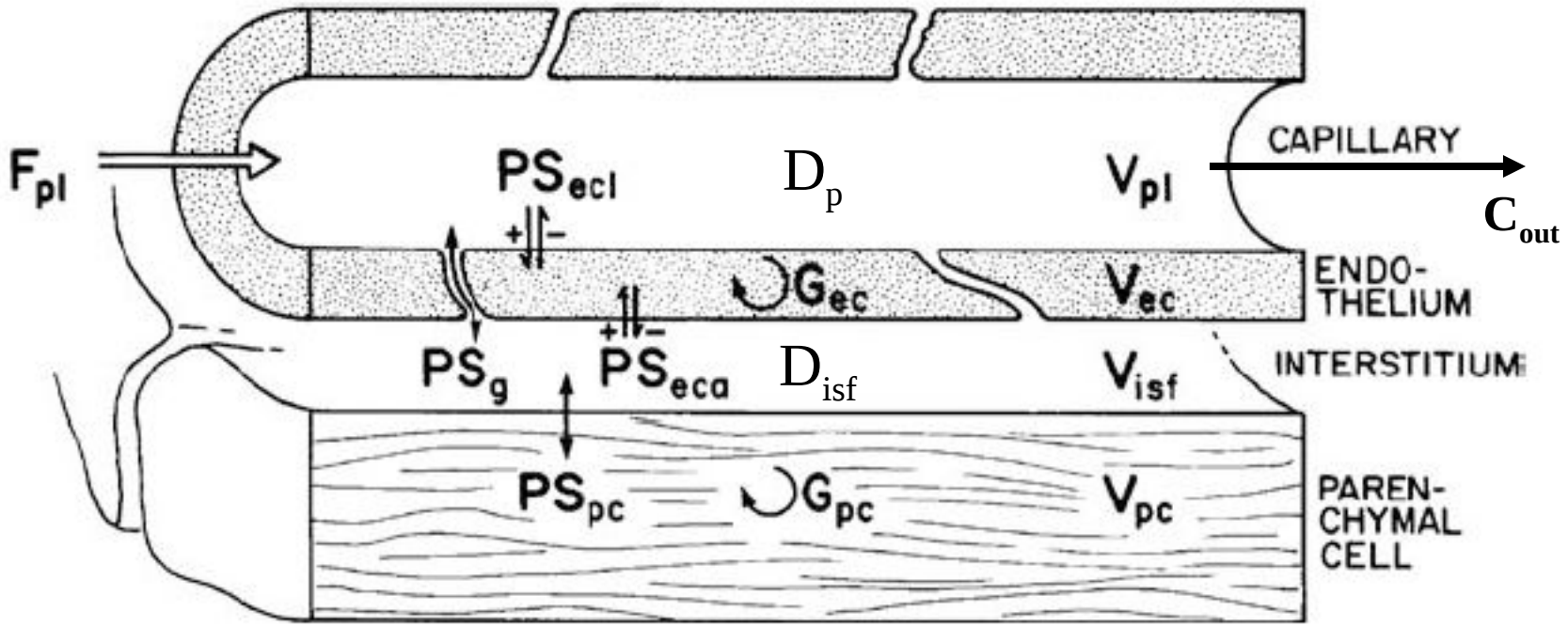
The Capillary Arrangements

Capillaries are parallel to the cardiomyocytes.
Dimensions: 5 μm diam., 800 μm long.
Radial intercapillary distances for diffusion are 17-20 microns.



(Bassingthwaighte, Yipintsoi & Harvey, Microvasc Res 1974)

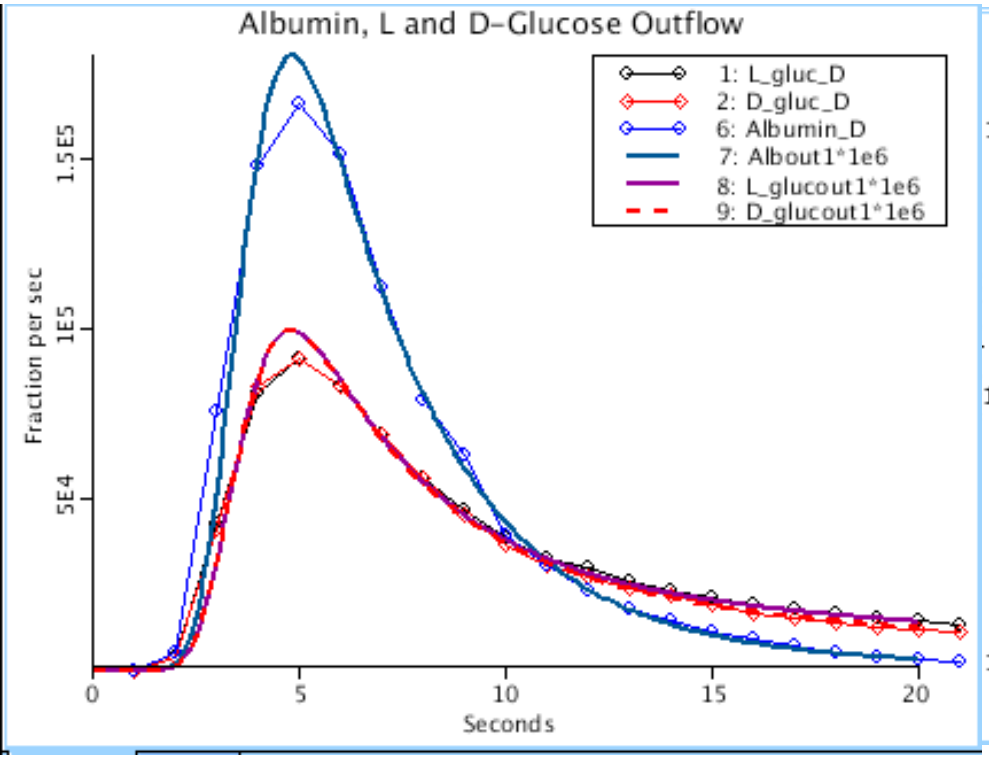
A capillary-tissue exchange unit

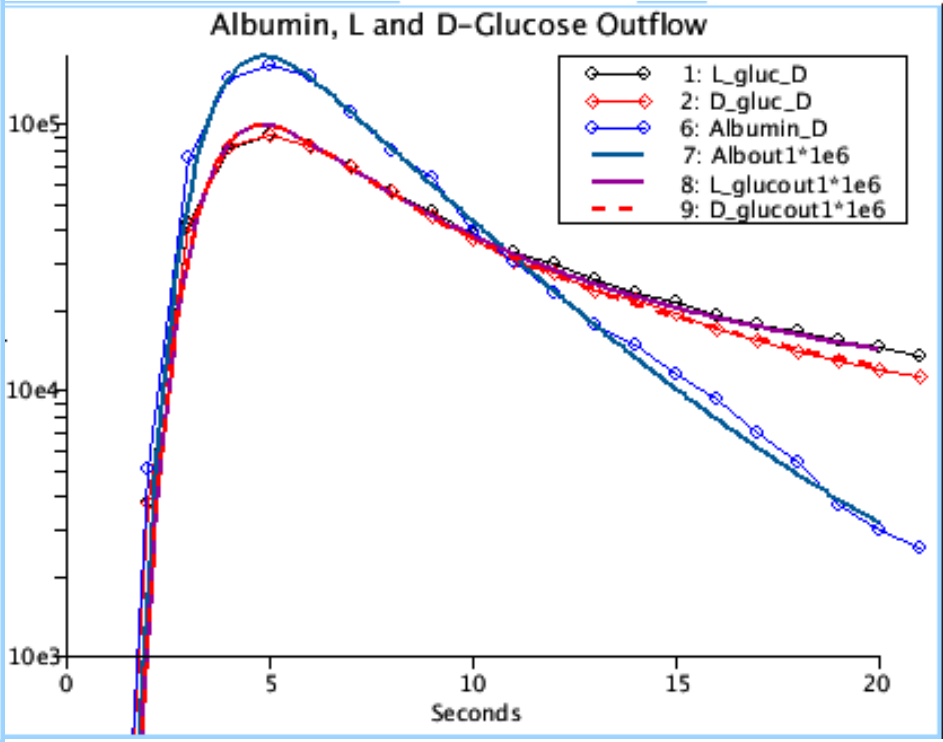


Tracer-labeled albumin, L-glucose, and D- glucose all have identical kinetics in passage through the intravascular path from artery to vein.

L- and D-glucose, stereoisomers, have identical permeabilities through the interendothelial clefts, and identical volumes of distribution and diffusion coefficients within the ISF. Only D-glucose enters cells.

The single-path axially distributed 3-region capillary-isf-cell model fits the data better, but not yet very well.





Linear plot. Albumin fits not too badly, except for the peak. Neither L- nor D-glucose are fitted well at the peak, but are very good at the tails.

Semilog plot. Albumin "looks" better. L- and D-glucose are fitted well at the tails. Their close similarity of D- and L-glucose data at the peaks means that endothelial uptake of D-glucose is not measurable.

The model was still wrong. Oh! (#%$*@!), regroup!

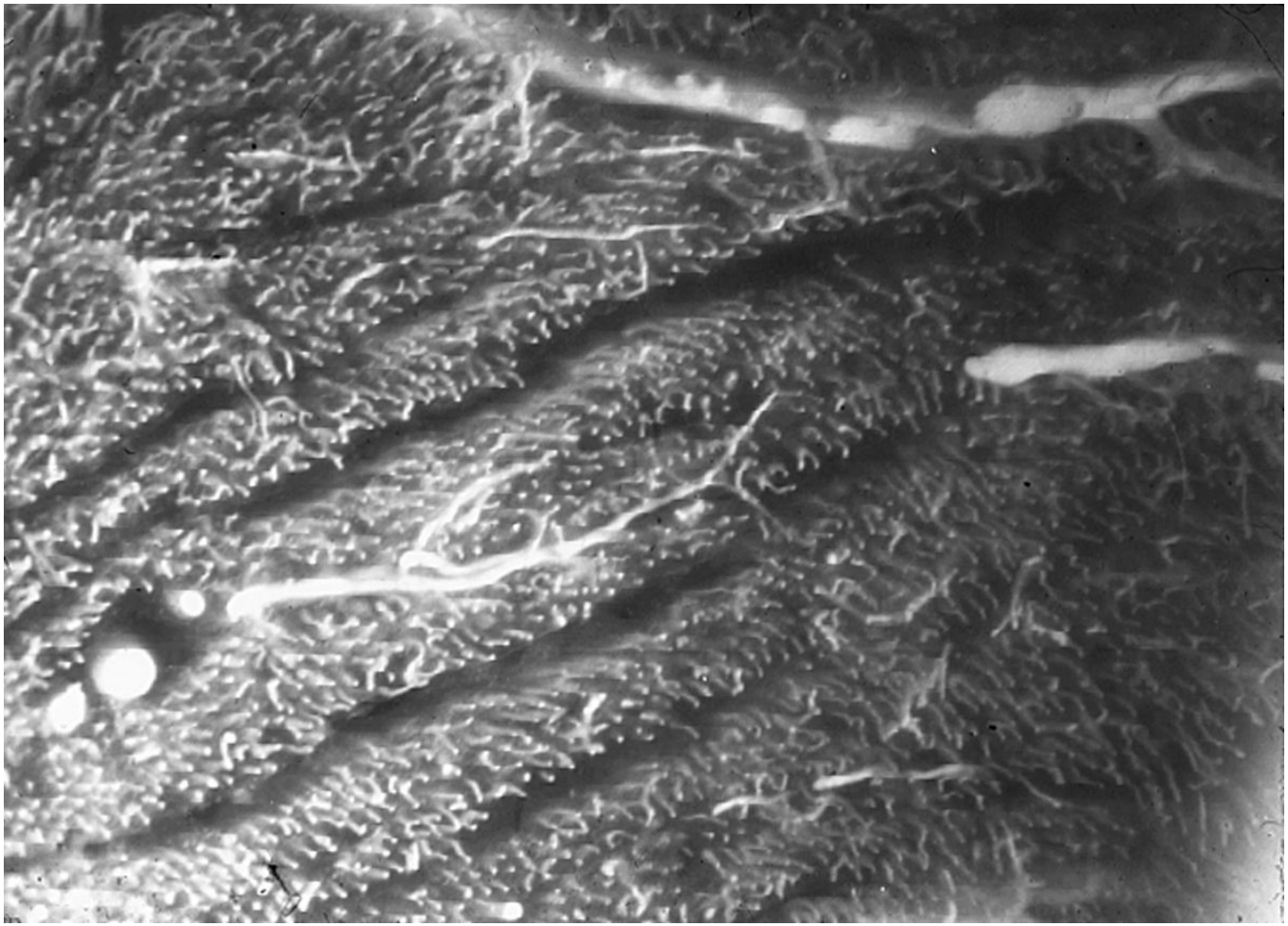
- Re-examine the anatomy
- Do all capillary tissue have the same flows? Check for heterogeneity of tissue perfusion.

Our next hypothesis: Heterogeneity of regional flows must be represented in the model.

Reminder: No hypothesis can be proven, but it may survive enough challenges to be useful. Thus evolves the “working hypothesis”.

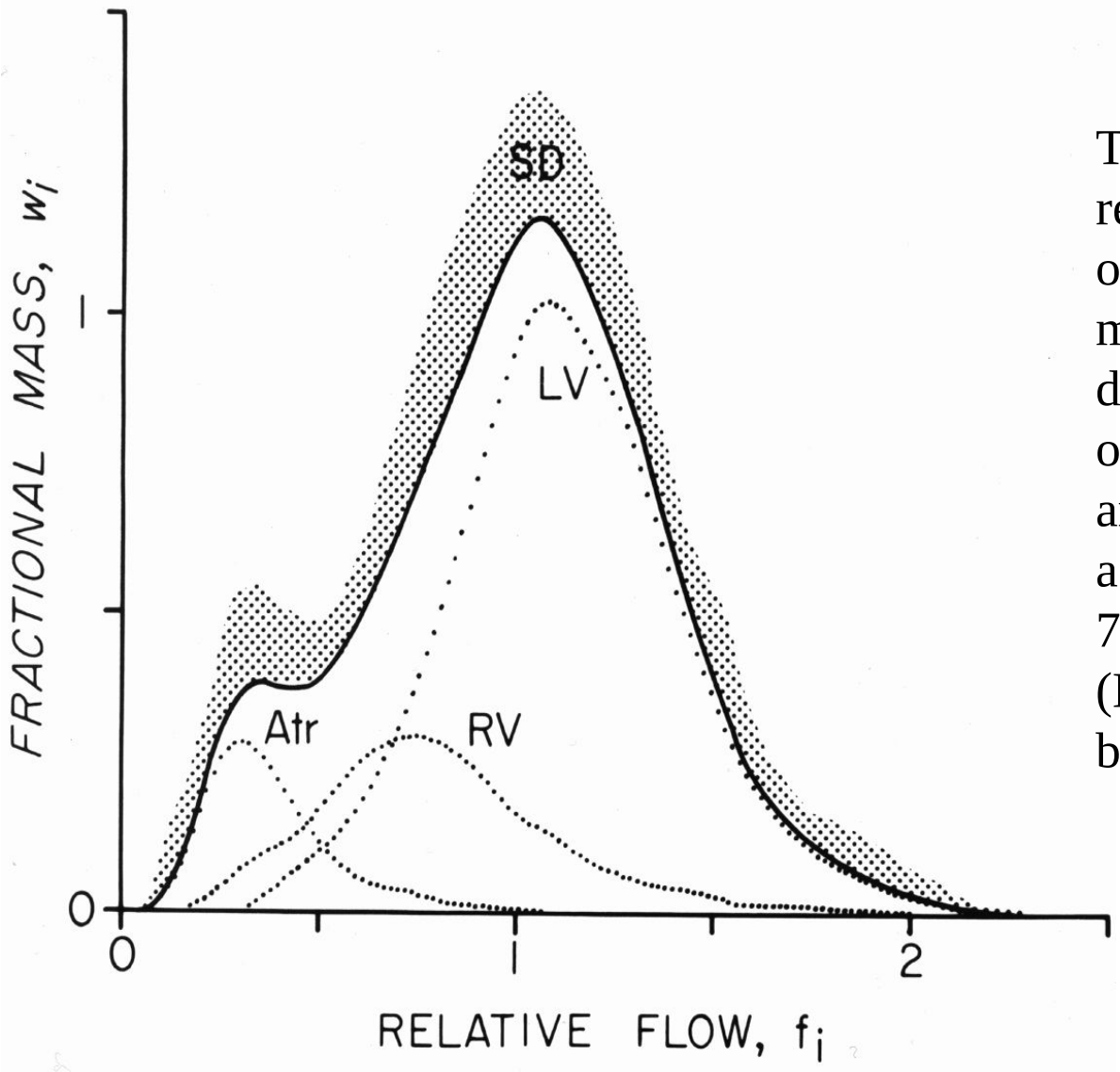
Myocardial capillaries within sheets of cardiac muscle: Differing workloads; expect differing flows.

Capillaries parallel muscle fibers within myocardial sheets (one capillary per cell)



from Bassingthwaighte, Yipintsoi and Harvey, Microvasc. Res. 1964

Myocardial Flow Heterogeneity in Awake Baboons

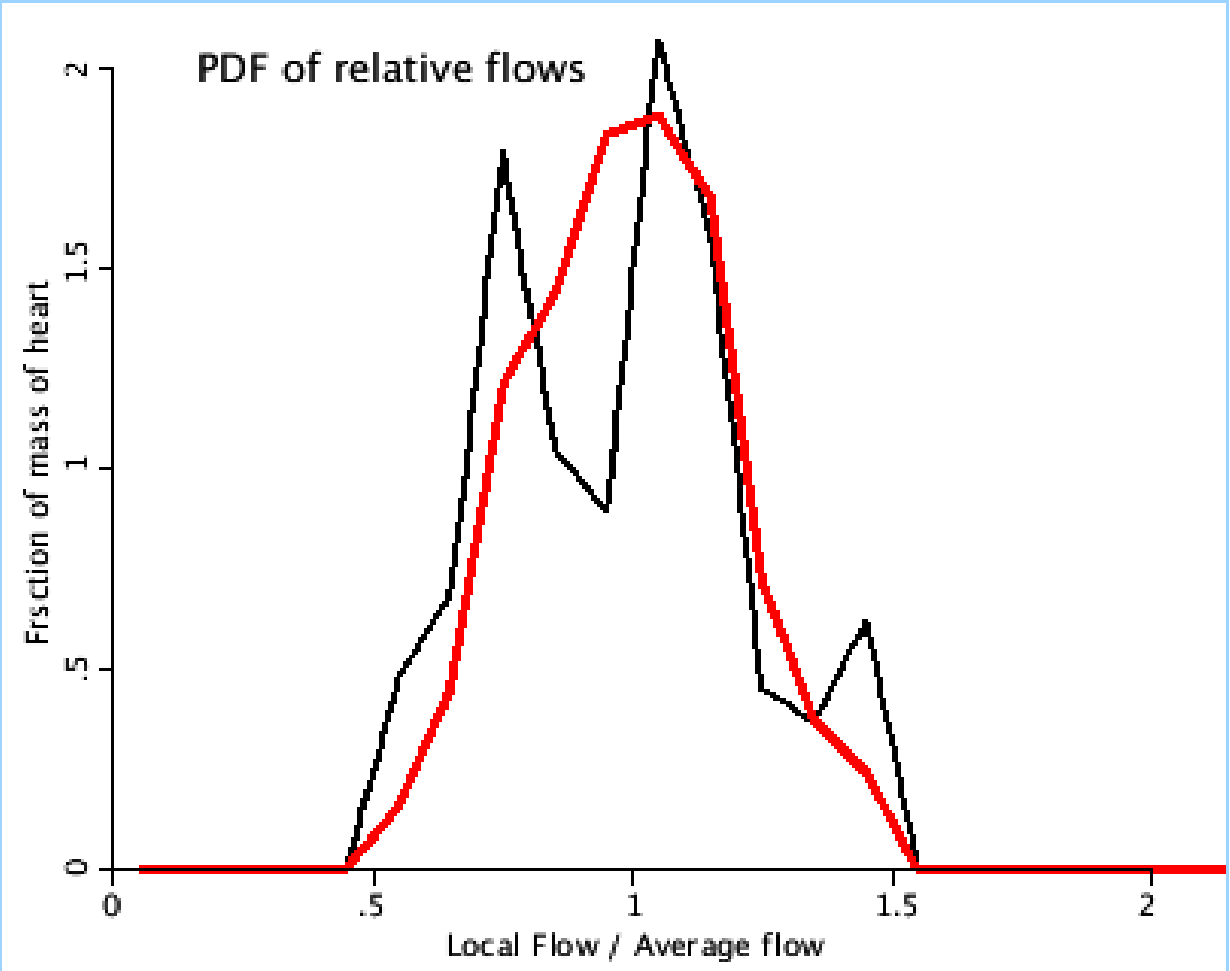


The distribution of regional flows, in voxels of about 0.5% of LV mass, shows a relative dispersion (SD/mean) of 25 to 30% in the LV, and more in the heart as a whole. RV flows are 70% of LV flows. (Data from 13 awake baboons at rest.)

(The same pattern is found in sheep, dogs, rabbits, guinea pigs,hamsters, and pigs.)

(King, Bassingthwaighte, Hales, and Rowell. Circ Res.57: 285-295, 1985. Fig 4)

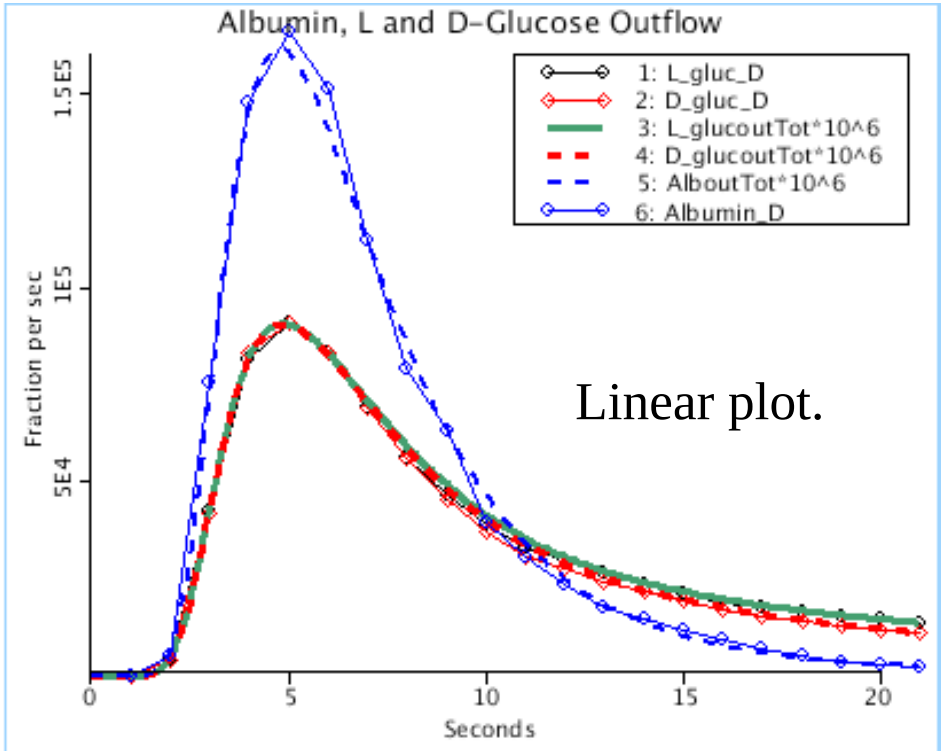
The data on this rabbit heart also provide the probability density function of relative regional flows

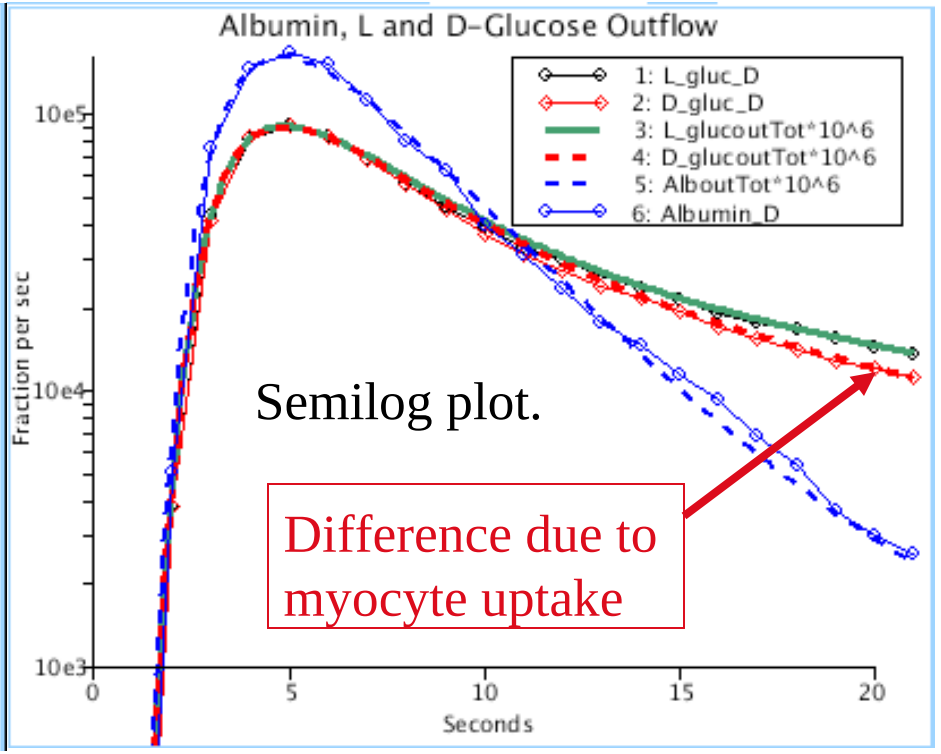


Two measures of the regional myocardial blood flows in this same rabbit heart. We took an average of the two sets of data to represent the flow heterogeneity in a multipath model.

Kuikka J, Levin M, and Bassingthwaighte JB. Am J Physiol Heart Circ Physiol 250: H29-H42, 1986.

The best working hypothesis! A multipath, heterogeneous flow model using the measured vascular, ISF and cell volumes to analyze multiple tracer outflow dilution data.

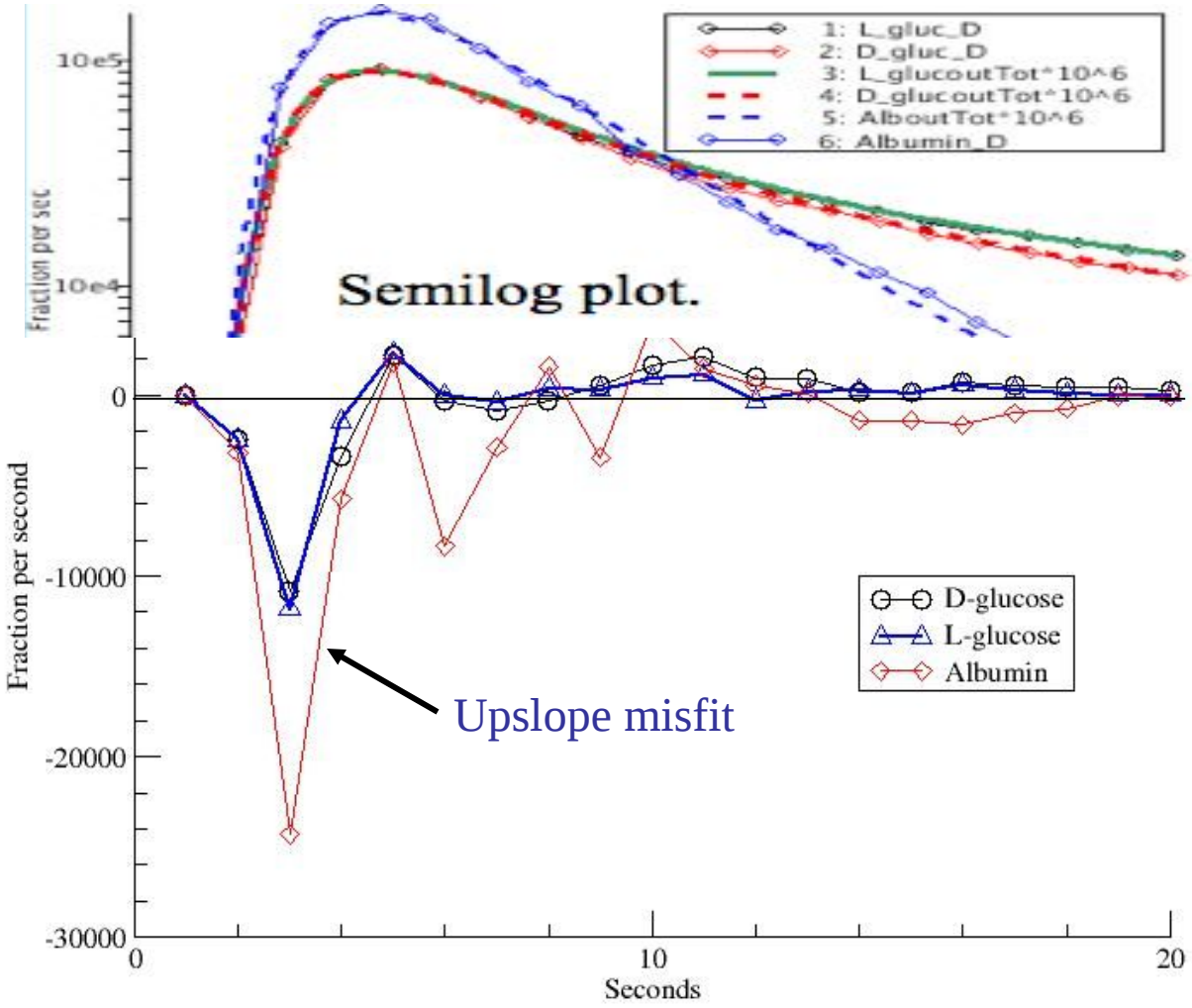




A first assessment: Albumin fits well. The L- and D-glucose are also fitted well. The D-glucose cellular uptake is quantitated clearly by the difference between D- and the L-glucose outflow concentration-time curves *after* t = 10 seconds.

Data: Kuikka, Levin, and Bassingthwaighte. Am J Physiol Heart Circ Physiol 250: H29-H42, 1986.

Assessment 2: Any systematic residual differences between Model and Data?



A third assessment:
Parameter Values and the Correlation Matrix

Parameter	**Value**	**+/- 1SD**	**+/- 95%**
PSL_gluc	1.1	0.103	0.206
GD_gluc	0.18	0.069	0.138
Visf	0.21	0.024	0.47
Vp	0.035	0.034	0.071
Fmean	1.68	0.147	0.29

Normalized correlation matrix:

	PSL_gl	GD_gluc	Visf	Vp	Fmean
PSL_gluc	1	.3325	.7397	.894	.9028
GD_gluc	.3325	1	.082	.182	.1848
Visf	.7397	.082	1	.7306	.730
Vp	.894	.182	.7306	1	.9959
Fmean	.9028	.1848	.730	.9959	1

Look for high correlations that indicate where the model should be simplified. Transit time = Vp / Fmean: such high correlation is thus inevitable. It is best to measure the flow, not to treat it as a free parameter. Or just fix the estimate of Vp, whose value has little influence on estimates of other parameters.

Parameter Values and Correlation matrix

Parameter	Value	+/- 1SD	+/- 95%
PSL_gluc	1.1	0.044	0.0878
GD_gluc	0.18	0.068	0.1349
Visf	0.21	0.016	0.0322
Vp	0.035	0.0006	0.0013

Normalized covariance matrix:

	PSL_gl	GD_gluc	Visf	Vp
PSL_gluc	1	.3919	.2744	-0.1331
GD_gluc	.3919	1	-0.0788	-0.0234
Visf	.2744	-0.0788	1	.0574
Vp	-0.1331	-0.0234	.0574	1

The very high correlations are gone after reducing the number of free parameters by removing that for flow (and which was measured in the experiment anyway). (The glucose model, with data sets, is model #126 at www.physiome.org.)

Conclusions from the analysis of multiple indicator dilution data on glucose

- **General: An adequate model was constructed, by iterative improvements in the anatomy and physiology.**

- **Technical: The project file holds the set of models, the data sets and the validation tests, graphic and numeric.**

- **Scientific: Cellular glucose uptake by cardiomyocytes is quantitatively measurable, but for endothelial cells is below resolution limits, as D-glucose uptake did not differ from that of L-glucose.**

The JSim Project File supports reproducible science:

- Archival storage of Data and Models in XMML format
- Publicly available models and data on a website (www.physiome.org/Models)
- Models and simulation analysis system, JSim, are open source
- Coding is easy, basically just write the equations
- Behavioral analysis, parameters scanning, sensitivity analysis
- Modeling analysis of data: optimization, goodness of fit, residuals, covariance and confidence limits on parameters, all in one package
- Data analysis preserved with data.
- JSim's MML translates to Java, XMML, GraphML, SBML and CellML (for ODE/DAE models only), Matlab (limited).

The Project File: Reproducing Physiome Models

Archiving of data sets, model sets, and analyses.

Open source for data, models, and simulation system, JSim.

Multilaboratory collaboration in model building and experimental testing.

Reproducibility in science requires effort

- The publication of a paper is a good start, if it provides:
  - Complete description of all experimental methods and results
  - The experimental data, in full and open form
  - The methods of analysis, including how the models are used
  - Model source code, verification tests, representative solution sets
  - Validity tests against the experimental data
  - Parameter evaluation, correlation matrices, confidence ranges

- Archiving Models in a public repository does better:
  - The complete code, with its mathematical and scientific basis
  - The explicit methods of solution, with example solutions for users' comparisons
  - Behavioral analysis and parameter exploration
  - Validation tests: data analyses, residuals, parameter sensitivities
  - Parameter covariances, parameter reduction methods
  - Assumptions, weaknesses and limitations.
  - Archiving with data

Strangers! Beware!

- Donoho 2011: *If everyone in a research team knows that everything they do is going to someday be published for reproducibility, they will behave differently and do better work.*
- *"It is a fundamental fact that in striving for reproducibility, we are producing code for the use of strangers".*

- Old Adage: *"Here's a stranger. Throw a brick at him!"*

- A stranger*: Anyone not in possession of the author's current short term memory and experiences:*
  - *Our coauthors*
  - *Current graduate students. Future graduate students.*
  - *The new postdoctoral fellow.*
  - *Anonymous referees of our papers and grant proposals.*
  - *Future employees.*
  - *Me, the author, a year or so from now.*

Executable Publications

International Conference on Computational Science, ICCS 2011.
Elsevier Special Issue on Executable Paper Grand Challenge:

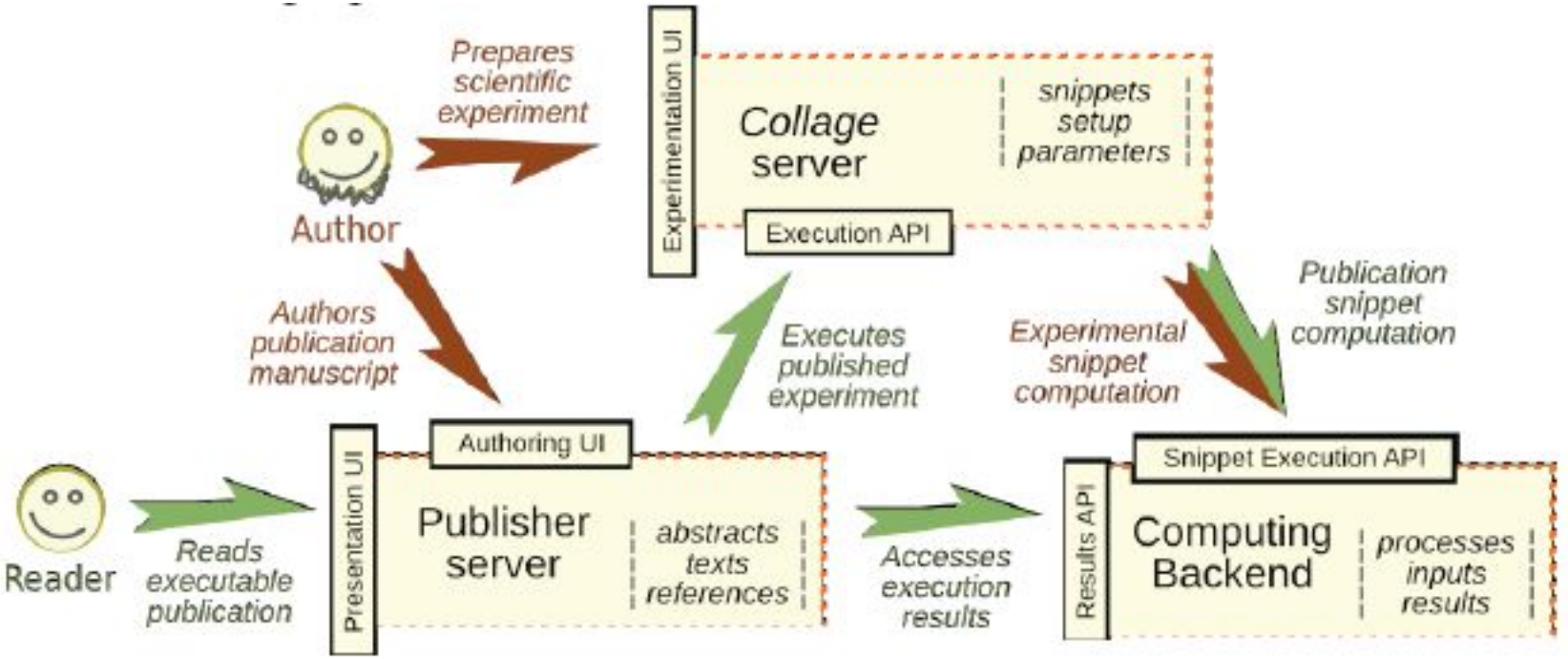
Peter Van Gorp and Steffen Mazanek. *SHARE: a web portal for creating and sharing executable research papers.* Procedia Computer Sci. 4: 589-597, 2011.
… a shared virtual machine with data and software plots diagrams, proofs theorems, and interactively transforms inputs into a complex output document.

Piotr Nowakowski et al. *The Collage authoring environment*. Procedia Computer Sci. 4: 608-617, 2011. …datasets, static content, and executable code recreating the authors materials, results, and publication.

Matan Gavish and David Donoho. *A universal identifier for computational results*. Procedia Computer Science 4: 637-647, 2011. … a verifiable computational result (VCR), a VCR repository, a verifiable result identifier, VRI, that is a DOI-like string for each element of a computational study from inception to publication.

Executable Publications

Piotr Nowakowski et al. *The Collage authoring environment*. Procedia Computer Sci. 4: 608-617, 2011. …datasets, static content, and executable code recreating the authors materials, results, and publication.



Why is reproducibility worth the effort for society?

- One builds “upon the shoulders of giants” (The “giants” are the one whose work is reproducible. Check the Nobel winners.)
- Reliable source code defining a specific hypothesis presents a target for one’s skepticism: comparison with an alternative well-defined hypothesis advances scientific understanding.
- In a skeptical society, having a clearly defined concept to argue against is the first step in modifying and advancing new ideas.
- Reproducing a model from open source publications, data repositories, websites (archival, operational, tutorial) saves months to years of an investigator’s time in refuting or improving it.

What shall we do for modeling reproducibility?

- Follow best standards and practices for model coding.
- Contribute to open source: publications, data repositories, websites (archival, operational, tutorial)
- Establish national repositories for:
  - Data (physiological, experimental, physico-chemical)
  - Models (modules or elements, integrative models)
  - Toolkits (Simulation systems, executable paper systems)
- Persuade scientific societies and journals to upgrade review systems by identifying reproducible research.

Now, as you maintain your “active doubt” …

- Does the “reproducible package” store concepts in concrete and inhibit development?
- Is is truly worth the cost?
- Is it really the best training to push for the highest quality?
- Should postdocs be pushed to be relentlessly reproducible or can only graduate students be so trained?
- Do citations indices represent acknowledgement of leadership in the field, or mere notoriety!
- Will promotion committees recognize reproducibility?

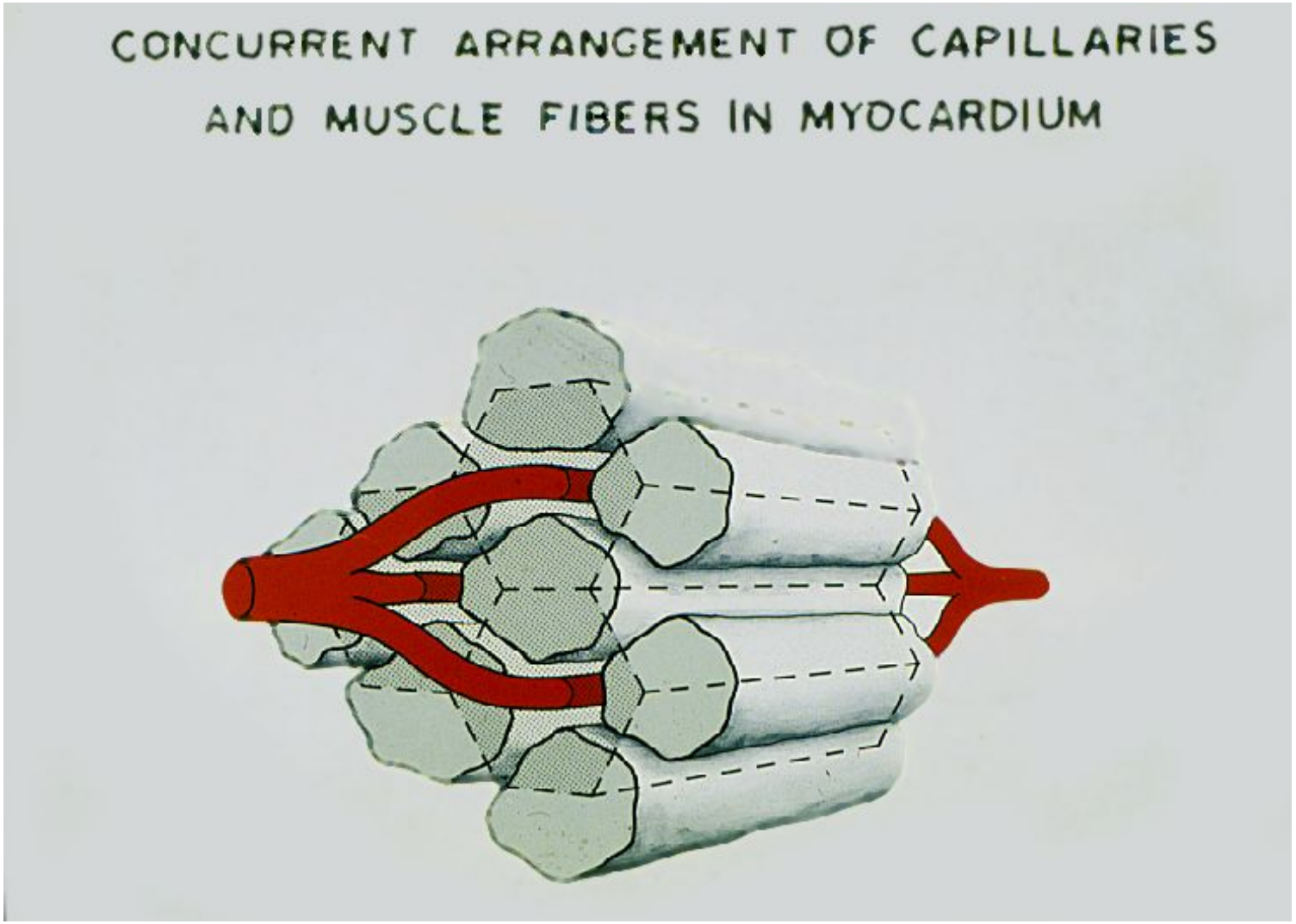
Credits for the Simulation Resource Facility

- Erik Butterworth: JSim
- Lucian Smith: Antimony, MML--> SBML, CellML
- Gary Raymond: The 2D PDE movies
- Bart Jardine: Models on the Website
- Jyrki Kuikka: The glucose studies
- Max Neal: SemSim and SemGen: Ontologies

University of Washington, Seattle
(Lake Washington in the background)

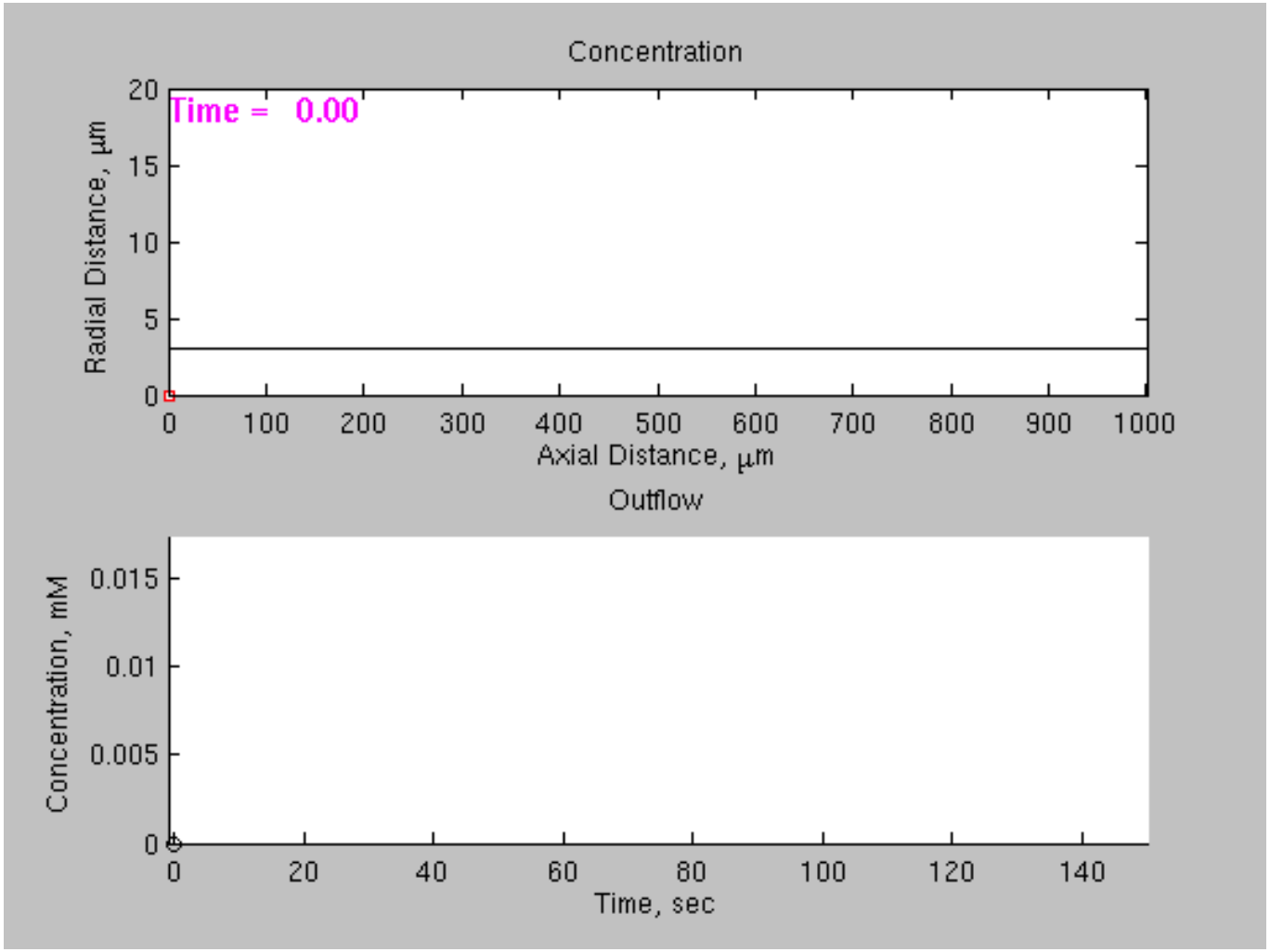
THE END

Hexagonal arrangement of capillaries and muscle fibers allows simplified computation



Capillary-tissue pulse response:

Spatial profile stabilizes as washout becomes exponential

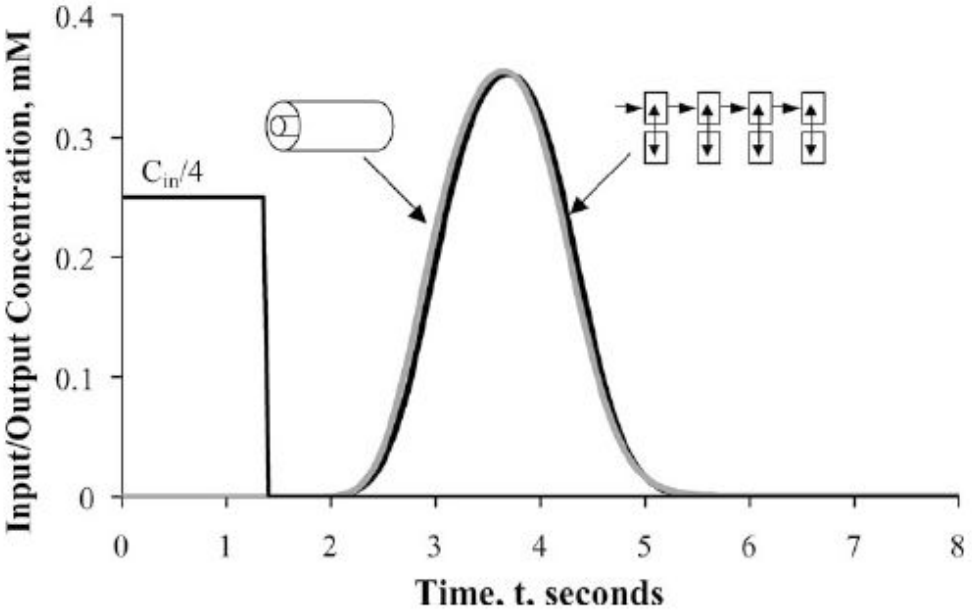


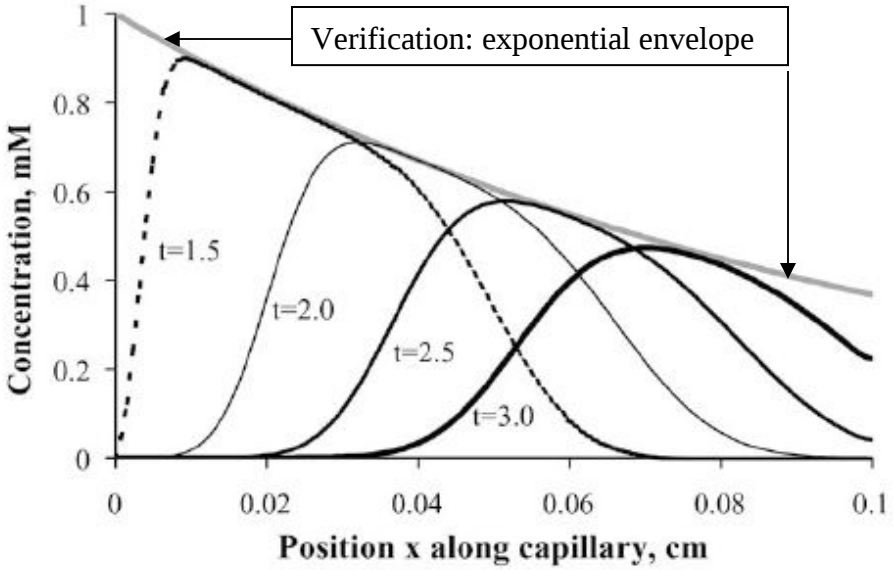
Upper: Concentration profiles in capillary, at bottom of panel, and in tissue. The center of mass of retained tracer is mapped.

Lower: Outflow concentration-time curve shows initial spike of non-extracted tracer followed by return flux from tissue.

PSdivFeq10: L = 1000 microns; F = 1 ml/(g*min); PS = 10 1 ml/(g*min); Dr = 2e-7 cm^2/s; DLp = 1e-4; DLt = 6e-5.

Serial Compartments vs Axially-distributed





The axially-distributed capillary (grey line) and the serial stirred tank model (black) are shown here as having almost identical outflow dilution curves in response to the square wave input.(Verification test.) No. of tanks = 109.

The spatial spread of the input function is by molecular dispersion axially. The mixing chamber model (stirred tanks) has a uniform concentration in each tank (not shown).

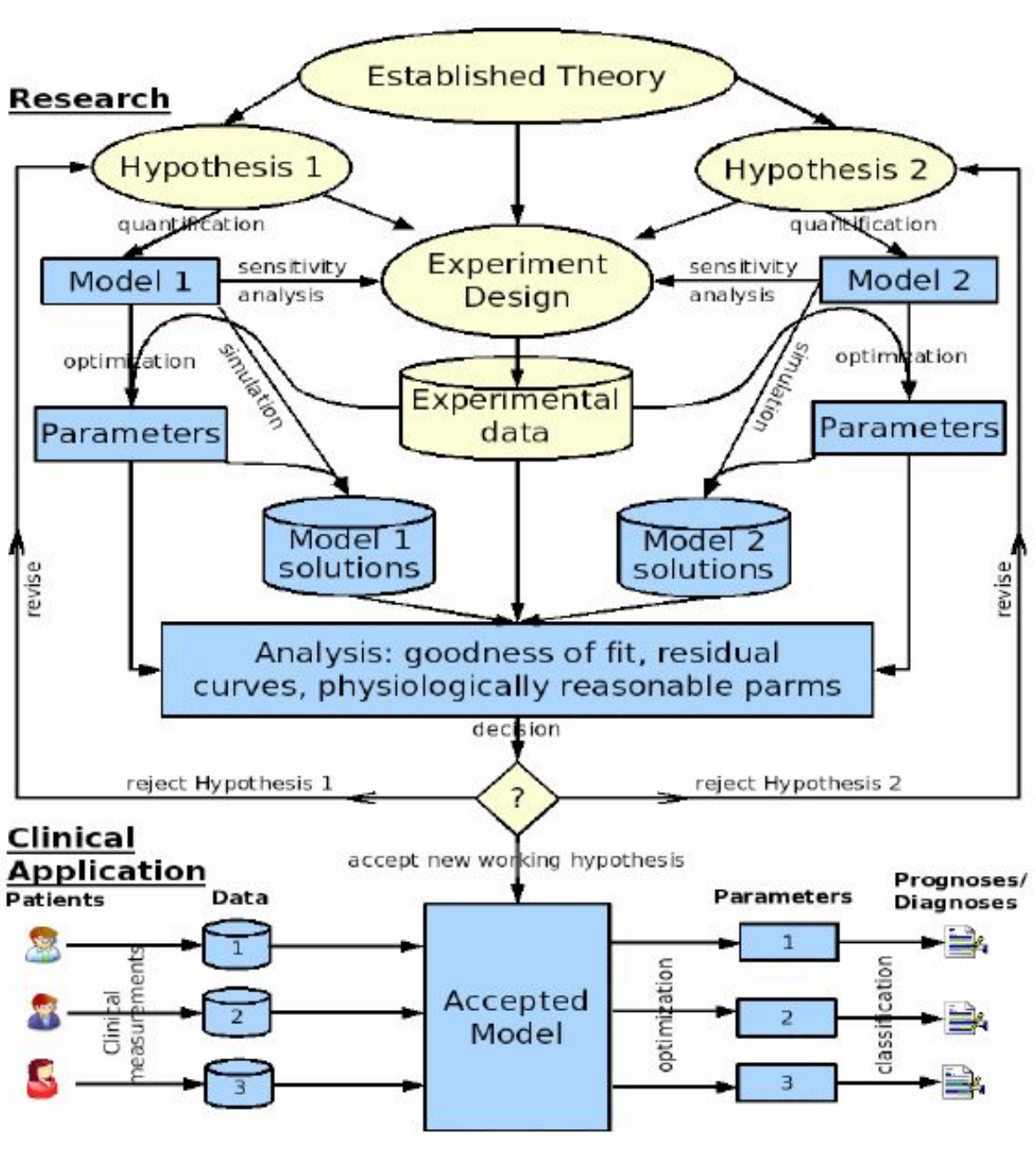
From Anderson JC and Bassingthwaighte JB. Tracers in physiological systems modeling. In: Mathematical Modeling in Nutrition and Agriculture. edited by MD Hanigan JA Novotny and CL Marsteller. Virginia Polytechnic Institute and State University Blacksburg, VA, 2007, pp 125-159. http://www.physiome.org Model #45

“Strong Inference”

JR Platt
Science 111: 222-223, 1964

A qualified hypothesis must be strong enough to provide a prediction. Design an experiment whose results can distinguish between *two alternative hypotheses*, deny one or other of the predictions, and prove one hypothesis wrong.

Thomas Henry Huxley:
“The great tragedy of science:
A beautiful hypothesis slain by an ugly fact!”



Again, and Again, and Again,…

- Science 334: 1225-1235, Dec 2011
- Computer Science
- Behavioral Research and Cognition
- Biology in the Field
- Systems Biology, “Omics”
- Global warming:
  - Santer et al: multiple groups examine the same data, generate new data, and come to robust conclusions.

Data Replication & Reproducibility

CONTENTS

Perspectives