From Data to Models

or…
a biological
“Theory of Everything”?

Arthur Thomas

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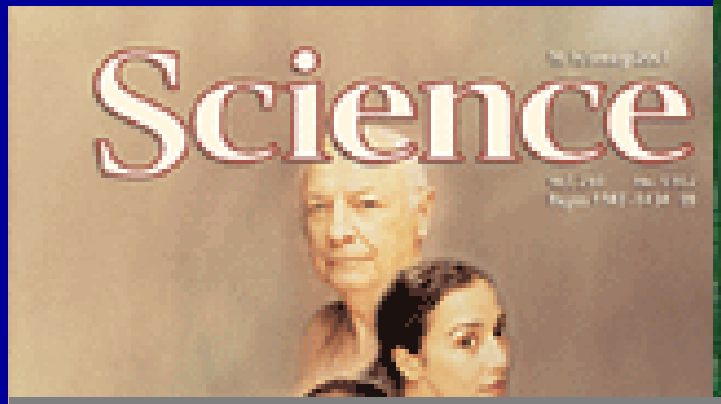
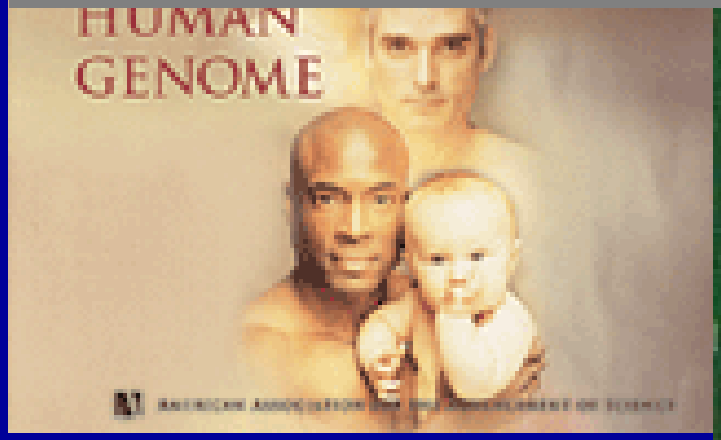
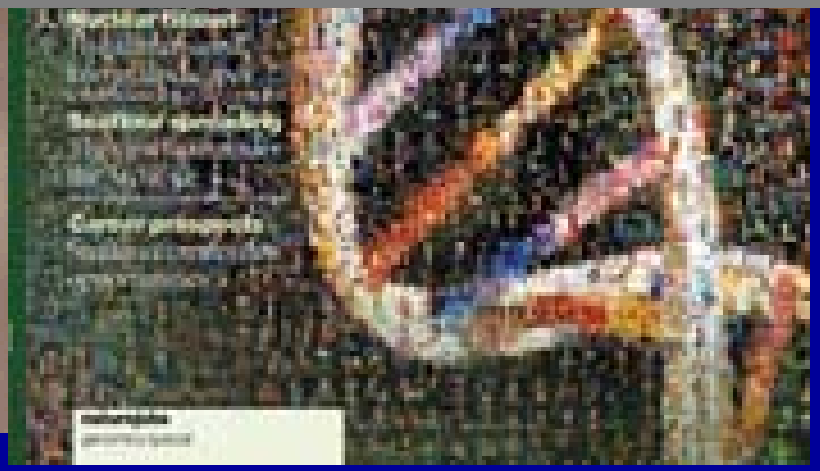
February 15, 2001

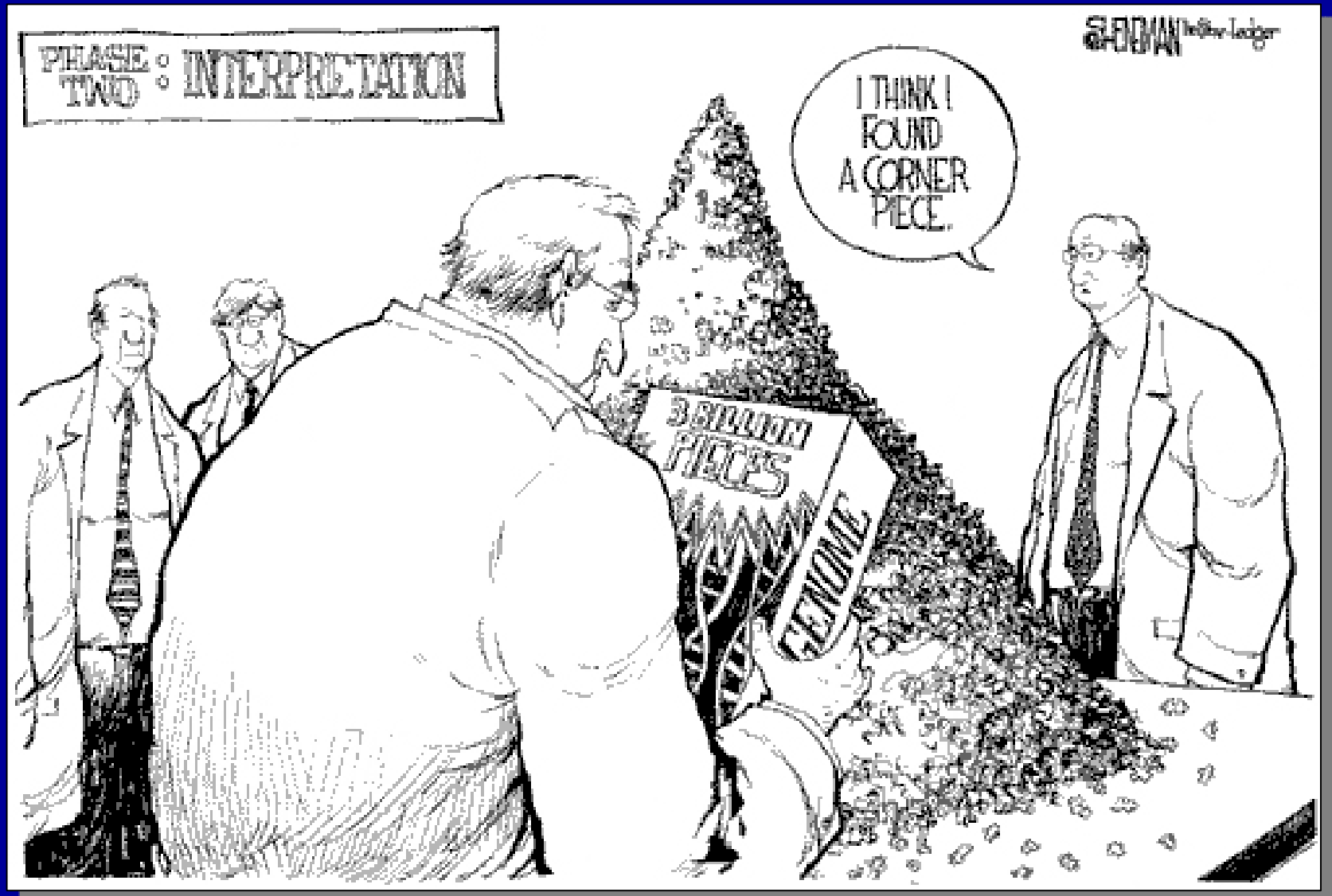


"The end of the beginning"?





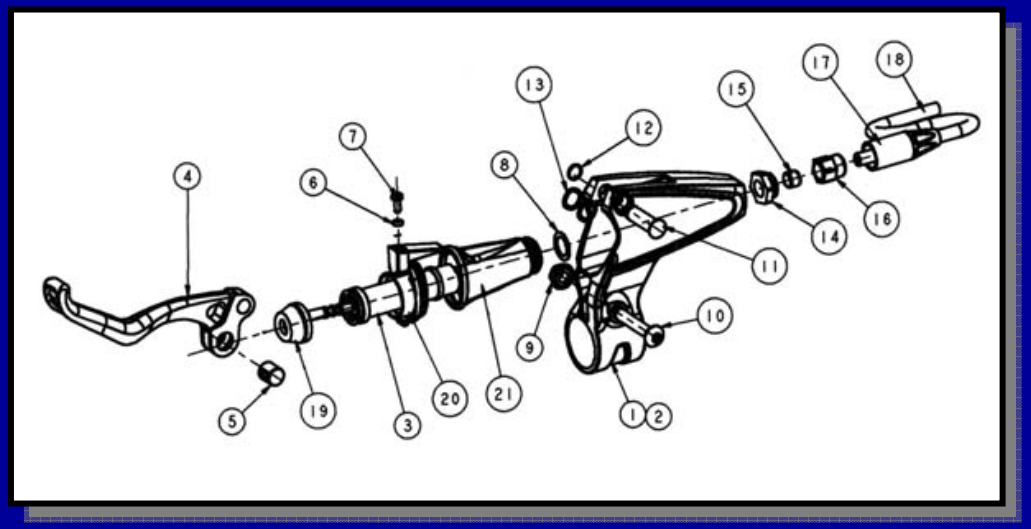
The Challenge



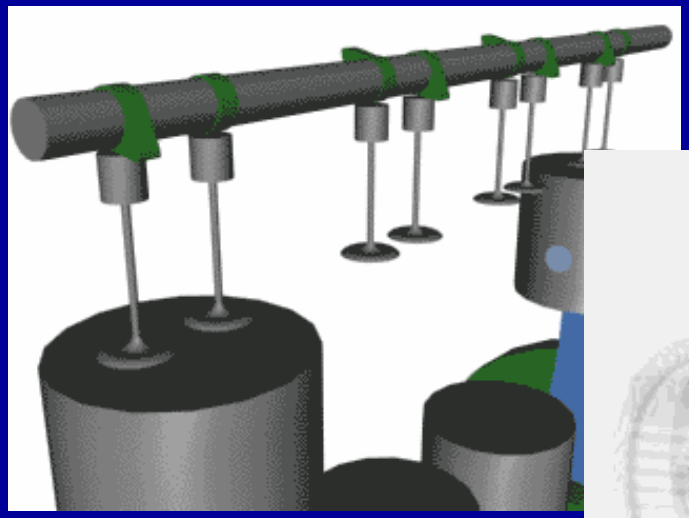
It’s even worse than that…

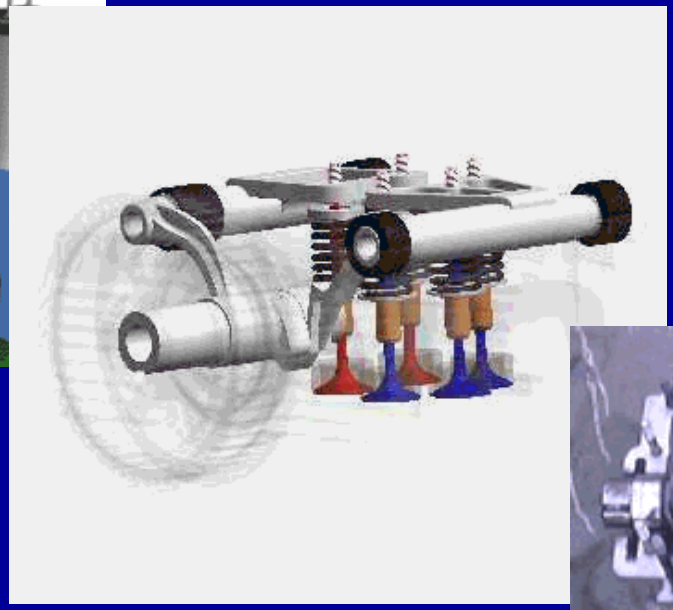
Getting from… To… To…

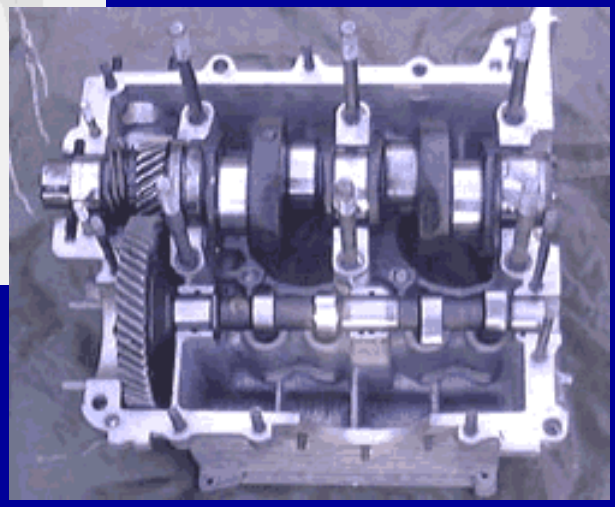
Part #	***Description***	*Label*
100-306	Master Cylinder Body Left	1
100-223	Master Cylinder Body Right	2
225-777	Cartridge Assembly	3
100-876	Lever	4
101-888	Adjustable Bushing	5
332-863	Master Cylinder Bleeder O-	6
444-754	ring	7
100-328	Master Cylinder Bleeder Screw	8
100-111	Cartridge Gasket	9
274-000	Clamp Nut	10
273-875	Clamp Screw	11
273-876	Lever Pivot Pin	12
700-201	Lever Pivot Retaining Ring	13
700-202	Wave Washer	14
202-343	Jam Nut	15
209-876	Compression Bushing	16
209-875	Hose Nut	17
209-874	Nose Cone	18
300-888	Hose	19
503-987	Push Rod Seal	20
503-972	Bladder Retainer	21



But, a static picture is not enough…





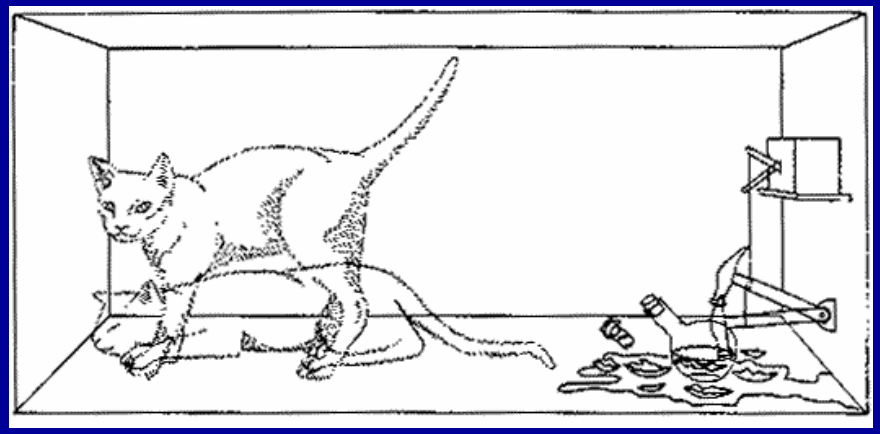


Outline

- Steps towards a biological “Theory of Everything”
  - What would it take to get there?
    - Challenges to modelling: getting the data, doing the computations
  - How would we know we’d got there?
    - Completeness, accuracy
- Illustrative examples
  - Biological pathways as graphs
    - Inferring pathway graphs from data
    - Global properties of graphs: robustness and evolution
  - Integrative whole-organ modelling
    - The “Human Physiome Project”
    - Inferring whole-organ behaviour from molecular and other data
  - Super-organism modelling
- Some Implications
  - Drug discovery
  - “Wellness”
  - Environmental

Q: What's the difference between a live cat and a dead one?

A1: an *alpha* particle



A2: Systems Biology!

A long time coming…

1968

1969

1970

1972

2002

Elements of Systems Biology

- Understanding of
  - Structure (components and structural relationships)
  - Behaviours and their phase spaces
  - Factors controlling states and behaviours
  - Methods for controlling systems and influencing/synthesizing desired behaviours
- Main subjects
  - Genetic regulatory networks
  - Signal Transduction Networks
  - Metabolic networks

  } *Pathway Models*

  - Organ/organism/super-organism *physiology*
    - biochemistry in structural context
    - inter-cell, inter-organism communication

From Kitano (2000)

Biology as an “Information Science”

“Genes can only specify the properties of the proteins they code for, and any integrative properties of the system must be ‘*computed’ by their interactions*.”

S. Brenner (emphasis added)

“We need to design a theoretical framework that can take account of the *flow of information* through biological systems.”

S. Brenner (emphasis added)

"So few genes, so many functions?"

- Gene function not directly specified in the code
- Genes may play multiple roles, and code for multiple proteins
  - splice variants, post-translational modifications, RNA silencing, …
    - Extreme: 1 gene = 38,000 proteins in *Drosophila*
- Highly non-linear relationship between genome size and functional complexity: many functions result from cooperation between multiple genes;
  - for *n* genes and *r* genes/function there are

    $nPr = n(n-1)(n-2) \ldots\ldots (n-r+1) = n!/(n-r)!$ possible functions
    - 2 genes/function = 0.5 x 40000 x 39999 = 799,980,000 possible functions
    - 100 genes/function ~ 10^{300} possible functions(1)
- Re-use of functional "modules": nature has only explored a small sub-space
- Functions depend on extra-genetic factors (water, etc.)

Feytmans, E., Noble, D. & Peitsch, M. "Genome Size and Numbers of Biological Functions," *Trans. Comp. Systems Biology* 1:44-49 (2004)

Basic Challenges

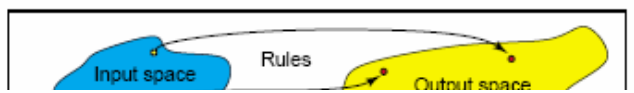
- Experimental:
  - Developing non-invasive techniques for measuring *in vivo* parameters down to the sub-cellular level, with appropriate accuracy
- Computational:
  - Multi-scale, multi-source, multi-physics modelling
  - Unifying frameworks (models, ontologies)
  - Interactive visualization of complex temporal data sets: “modelling at the speed of thought”

Experimental Challenges

- Need for *tight (two-way) coupling* with experimental work
- *Accuracy* of measurements: PCR is noisy, low copy number, thermodynamic effects, stability, statistical criteria
- *Identifiability/Controllability*: what could we *possibly* observe/control?
- Importance of *structure* (cytoskeleton, compartments): need for high-spatial resolution intra-cellular measurements (e.g. *FISH,* reporter genes)
- Need kinetic data under uniform conditions

How Much Data Do We Need?

- No framework for deciding when a model is complete or consistent with data
- How much accuracy is “enough”?



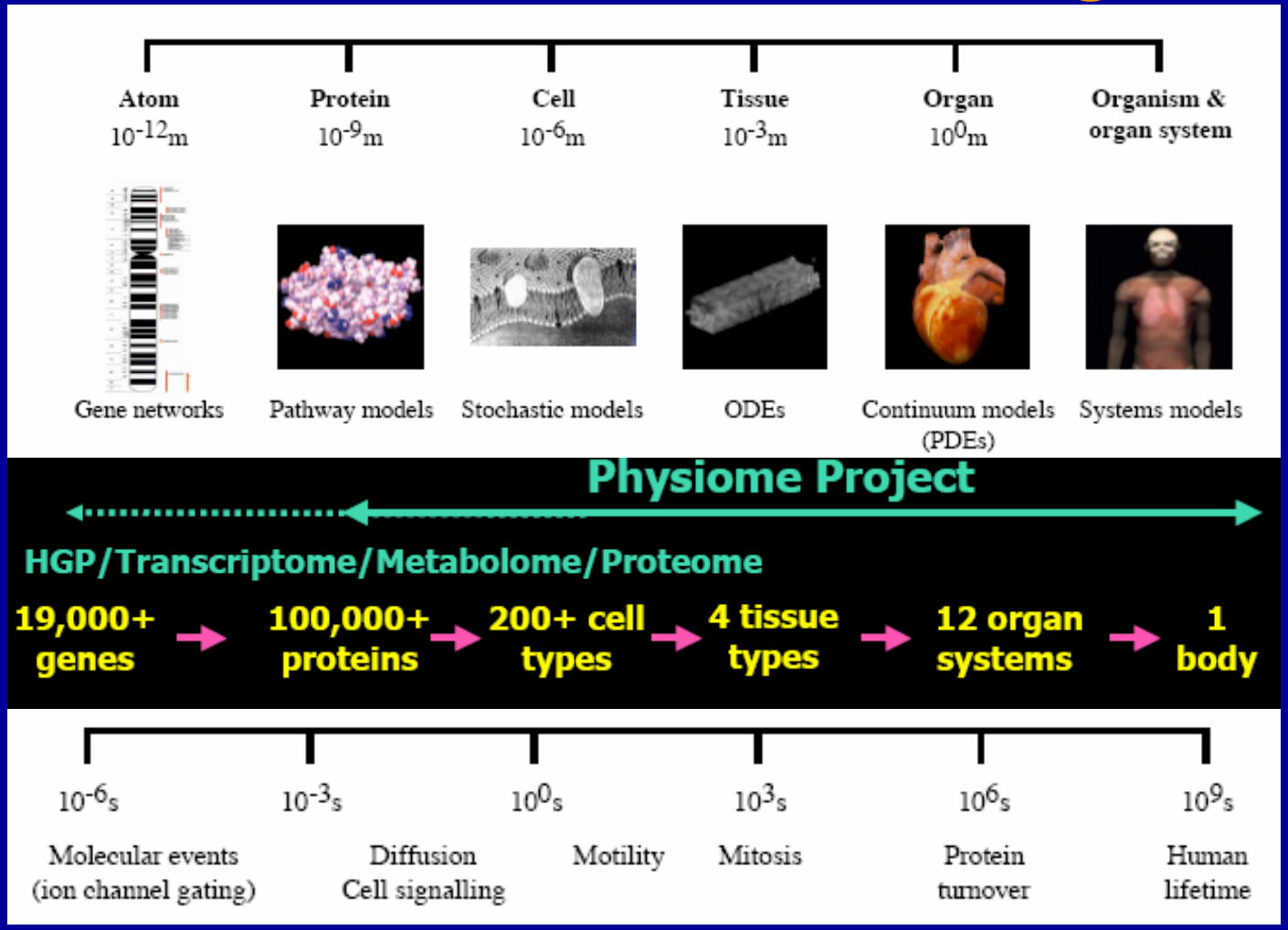
Model	Scope	Applicable Rules
Atomic	Cell *c* at time *t*	Physics
Molecular	Cell *c* at time *t*	Chemistry
Biomolecular (discrete)	Cell *c* at time *t*	Molecular mechanic
Biomolecular (statistical)	Biochemically equivalent cells	Chemical kinetics an thermodynamics des by differential equati
Biomolecular (steady-state)	Genetically equivalent cells, similar growth conditions, steady state	Flux balance, physic and chemical constr
Boolean	Genetically equivalent cells	Genetic and metabo ‘circuits’

Organism	N	K	Estimated number of microarrays	
			Lower bound	Upper bound
M. pneumoniae	688	1	10	80
E. coli	4,288	3	50	40 000
H. sapiens	50 000	4	100	700 000

Upper and lower bounds on the number of microarrays (or equivalent transcriptome-wide experiments) to complete discrete transcriptional network models for various organisms, calculated according to Krupa [10]. N represents the number of nodes (genes in this example). K represents the maximum number of regulatory connections per node. The expression level of each gene is categorized as high, medium, or low ($\xi = 3$). The lower bound (information-theoretic) is given by $\xi^K + K\log_\xi(N/K)$. The upper bound is given by $\xi^{2K}(2K(\ln N + \ln\xi) + \ln C)$, where the measurements fail to determine the model with probability 1/C. Here we set 1/C equal to 0.01. It is important to note that the upper bound estimate increases exponentially with K, making it the dominant parameter.

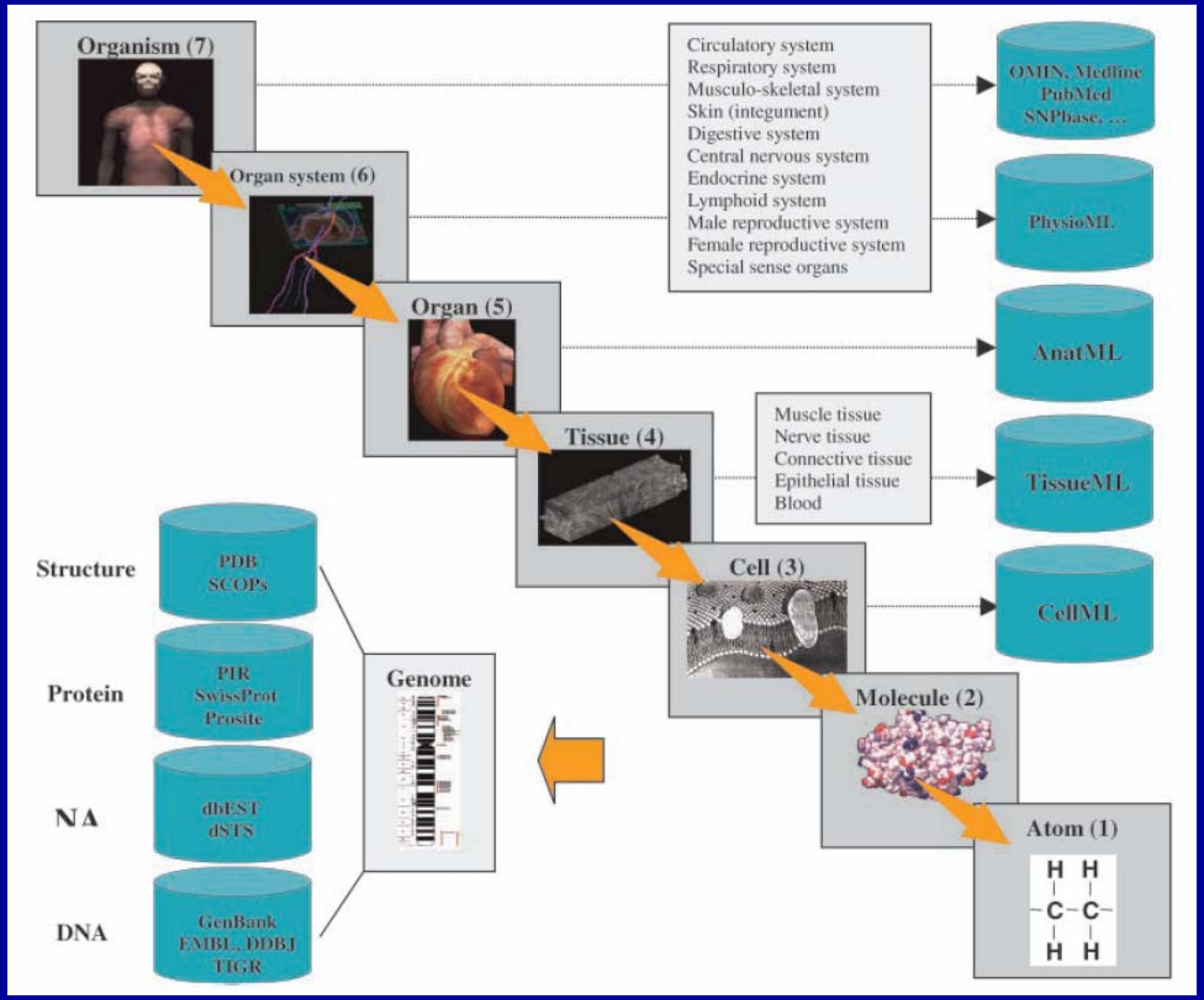
Selinger et al. *Trends in Biotech.* (2003)

Multi-scale Modelling



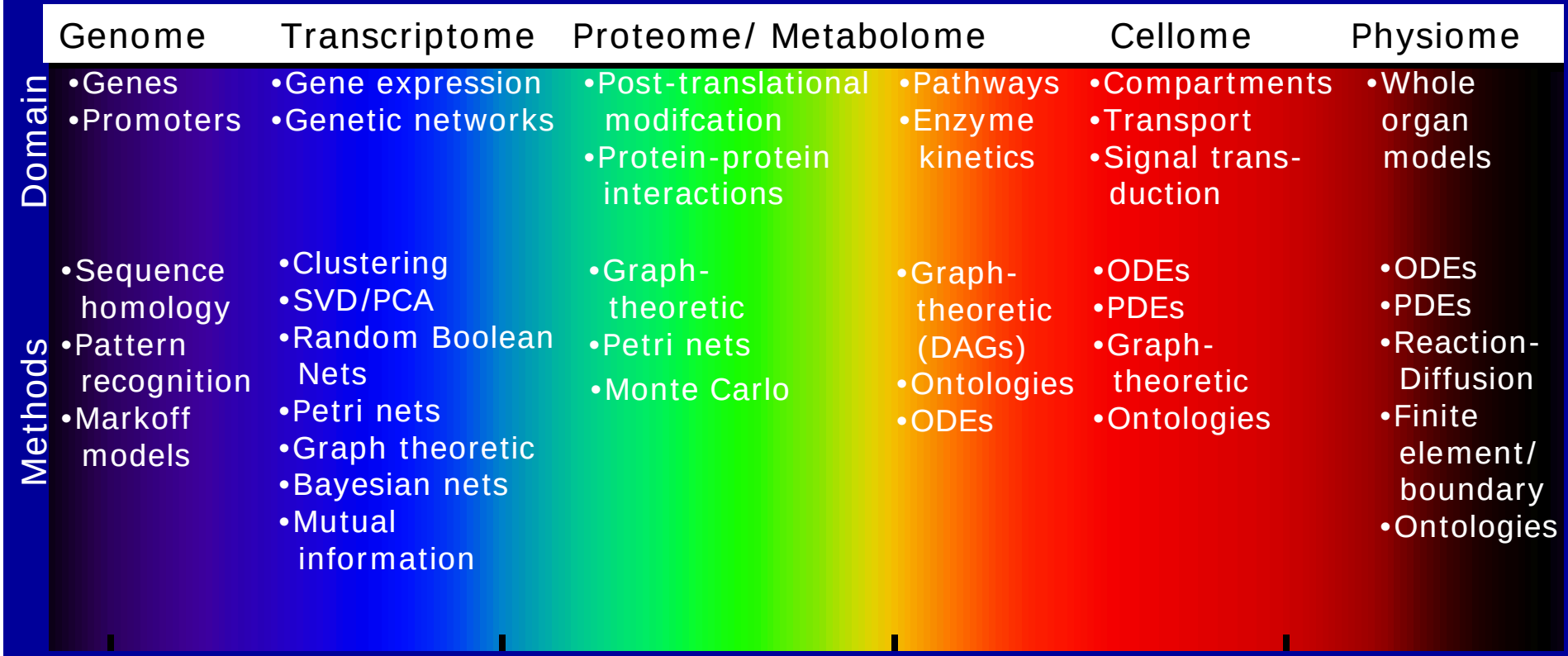
Adapted from P. Hunter, P. Robbins, D. Noble "The IUPS human physiome project" *Eur J Physiol* 445:1–9 (2002) and P. Hunter "An Update on the Human Physiome Project," in *Proc. IUPS Satellite Workshop on Computational Physiology, San Diego, CA (2005)*

Multi-source Modelling

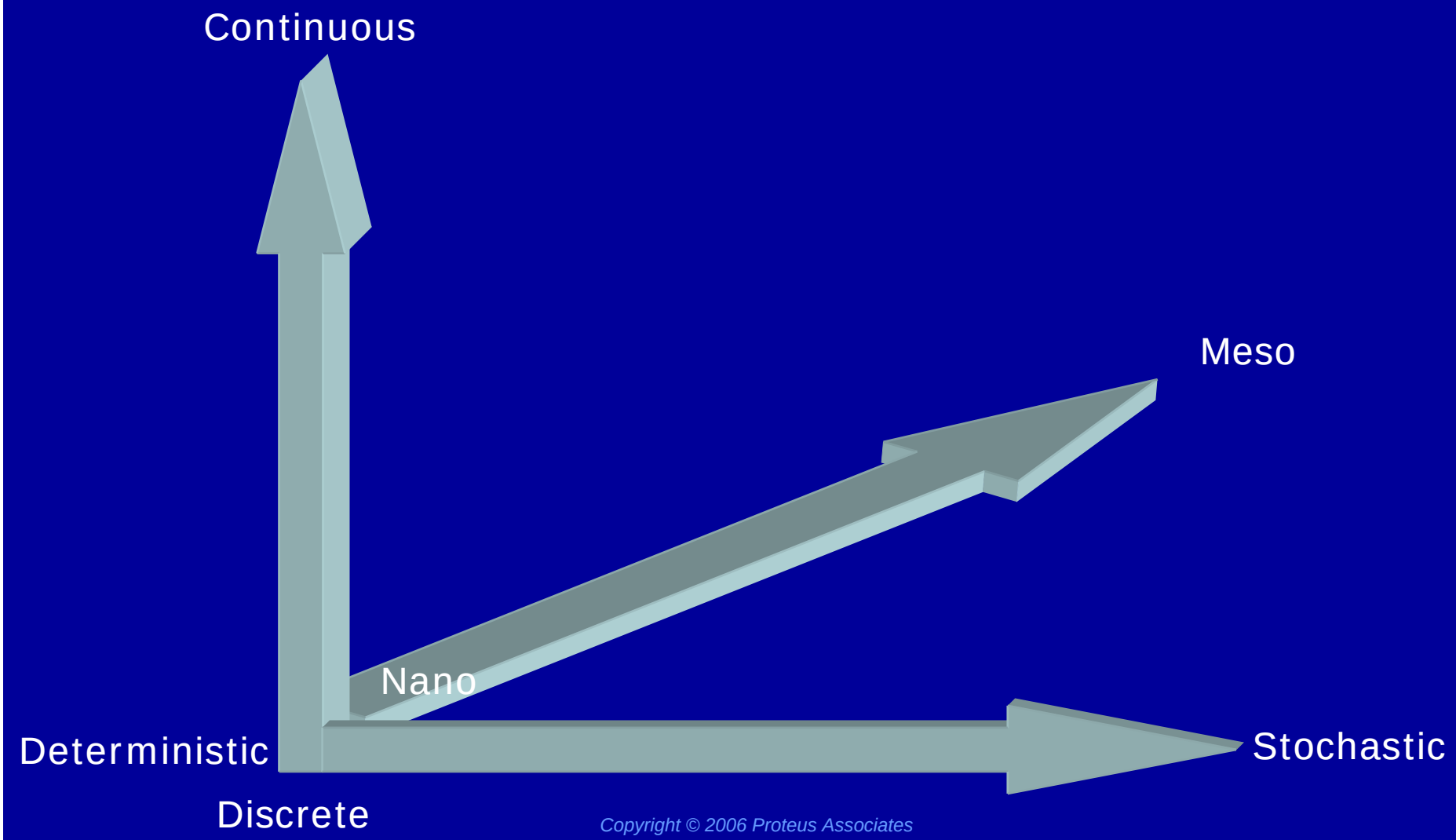


P. Hunter, P. Robbins, D. Noble "The IUPS human physiome project" *Eur J Physiol* 445:1–9 (2002)

Multi-physics Modelling



Modelling Methods

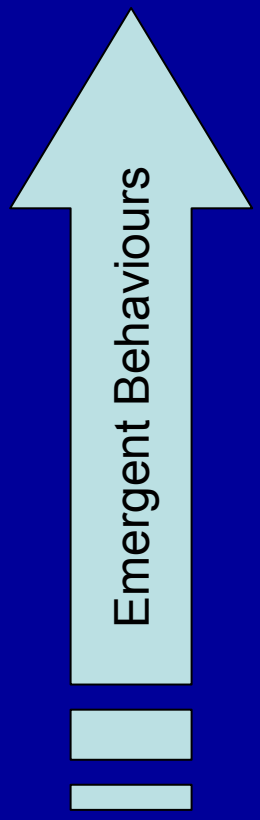


Networks

"The emergent theory that describes how non-biological networks constitute themselves, how they react dynamically to perturbations and how their behaviour translates into predictable and measurable properties of the system… should provide a *general theoretical framework for systems biology*."

Rudi Aebersold (2005)

Hierarchies of Networks



Biological Systems

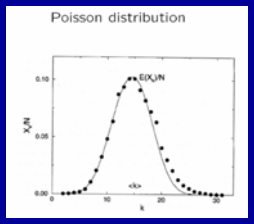
Interaction Networks

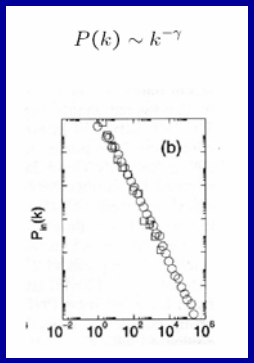
General Theory of Networks

(Condensed-matter physics!)

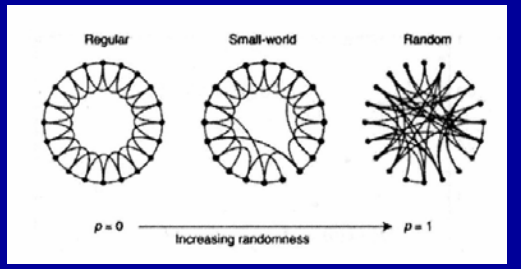
Properties of Biological Networks

- Degree distribution
  - frequency distribution *P(k)* of nodes of degree *k*
- Random*: P(k)* follows a Poisson law
- Scale-free: *P(k)* follows a power law





- "Small world": average separation between nodes is small compared to the overall size of the network



Properties of Biological Networks

- "Rich get richer": likelihood of attachment to a node is proportional to the node's degree
- Evolution of "hubs"
  - Trade-off between diversity and robustness
- Scale free networks are
  - Robust against random failure but not loss of hubs
  - Low congestion/efficient transport/energetics
- Move away from looking at single protein functions to studying networks of interactions (protein complexes)

Robustness & Evolution

- Uneven degree connectivity makes networks resilient to mutations
- Importance of feed-back/-forward loops in network stability
  - But, sometimes rare perturbations lead to catastrophic failure

Not robust to turbulence

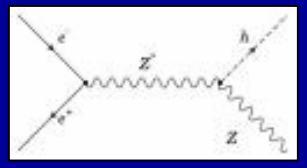
Robust to turbulence, but fragile to power failure!

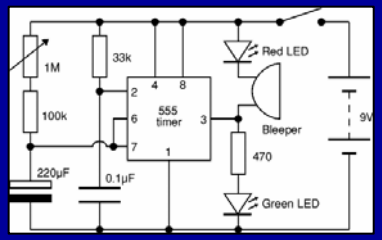
- Modularity: maintain function by localizing damage

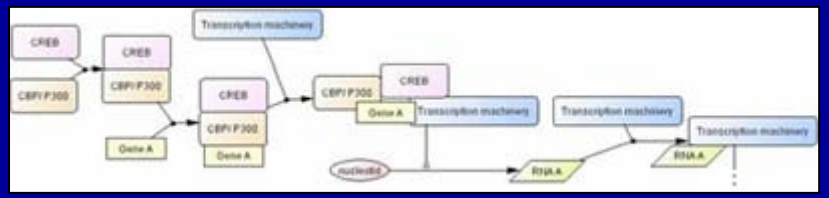
Importance of Notation

- Visual

www.sbgn.org







- Computational

SU(3) x **SU**(2) x **U**(1)/Z_6

$$\nabla \cdot \mathbf{D} = 4\pi\rho$$

$$\nabla \times \mathbf{H} = \frac{4\pi}{c}\mathbf{J} + \frac{1}{c}\frac{\partial \mathbf{D}}{\partial t}$$

$$\nabla \times \mathbf{E} + \frac{1}{c}\frac{\partial \mathbf{B}}{\partial t} = 0$$

$$\nabla \cdot \mathbf{B} = 0$$

www.sbml.org

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1"
      level="1" version="2">
  <model name="gene_network_model">
    <listOfUnitDefinitions>
      ...
    </listOfUnitDefinitions>
    <listOfCompartments>
      ...
    </listOfCompartments>
    <listOfSpecies>
      ...
    </listOfSpecies>
    <listOfParameters>
      ...
    </listOfParameters>
    <listOfRules>
      ...
    </listOfRules>
    <listOfReactions>
```

Reaction	Rate
$src \rightarrow RNAP$	$V_i/(1+P/K_i)$
$RNAP \rightarrow waste$	$V_{kd} \cdot RNAP$
$RNA_{nuc} \rightarrow mRNA_{nuc}$	$\frac{V_{m1} \cdot RNAP \cdot RNA_{nuc}}{K_{m1} + RNA_{nuc}}$
$mRNA_{nuc} \rightarrow mRNA_{cyt}$	$k_1 \cdot mRNA_{nuc}$
$mRNA_{cyt} \rightarrow RNA_{cyt}$	$\frac{V_{m2} \cdot mRNA_{cyt}}{mRNA_{cyt} + K_{m2}}$
$RNA_{cyt} \rightarrow RNA_{nuc}$	$k_2 \cdot RNA_{cyt}$

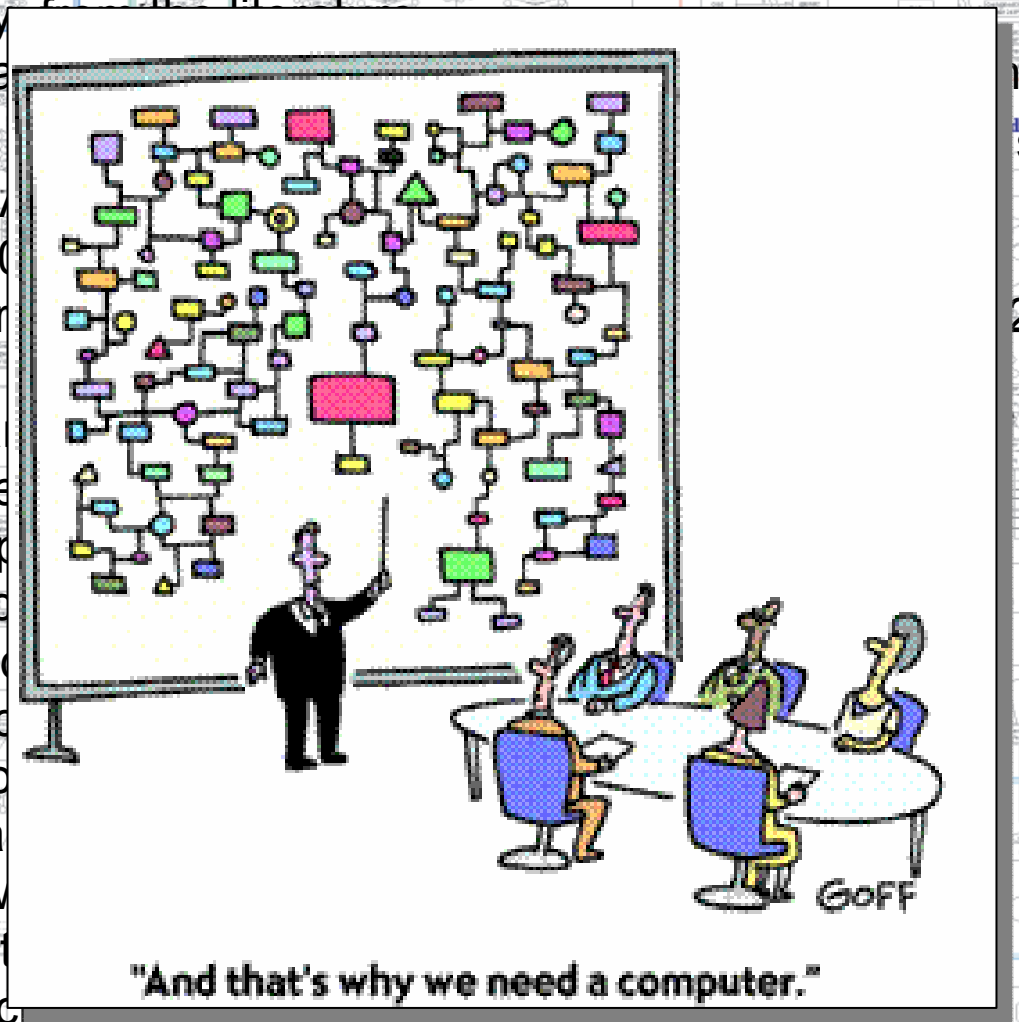
```
ode(Xr1, time) = 50.0{dimensionless}/
                 (1.0{dimensionless}+exp(-(V-5.0{millivolt})/9.0{millivolt}))*
                 (1.0{dimensionless}-Xr1)- 0.05{dimensionless}*
                 exp(-(V-5.0{millivolt}));
```

$$\frac{dXr1}{dtime} = \frac{50.0}{1.0+e^{\frac{-(V-5.0)}{9.0}}}\cdot(1.0-Xr1) - 0.05\cdot e^{\frac{-(V-20.0)}{15.0}}$$

www.cellml.org

Epidermal Growth Factor Receptor Pathway Map

- Pathway inference:
  - Manually
  - Computa
- 202 proteins,
and seven RN
- 10 ligands, 1
channels, 10 tr
proteins.
- Reactions ca
  - 131 state
  - 34 transp
  - 32 assoc
  - 11 disso
  - two trunc
- 247 interactio
  - 206 cata
  - 9 unknov
  - 16 inhibit
  - 12 transc
  - 4 transcriptional inhibitions.



Kitano et al *Molecular Systems Biology* (2005)

- Machine-readable, application-neutral format for representing computational models in systems biology
  - Expressed in XML
  - Intended for software tools
- Supported by >90 modelling packages
- API, Conversion tools (KEGG, CellML), Mathematica/Matlab plugins

www.sbml.org

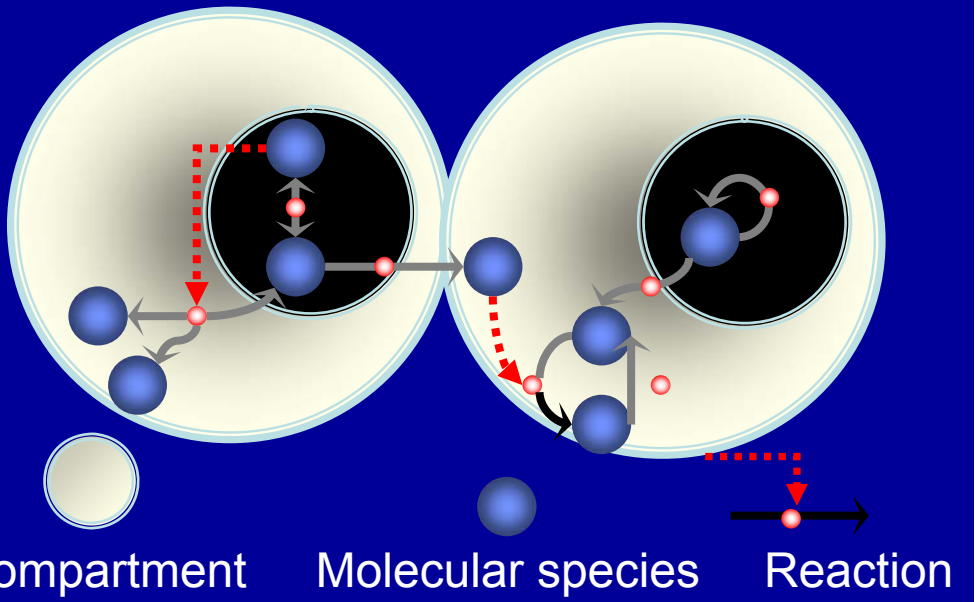
SBML Systems Biology Markup Language

- Focus: systems of biochemical reactions

$$\alpha A + \beta B \xrightarrow{f([A],[B],[C],\overline{X})} \gamma C$$

$$\mu C + \nu D \xrightarrow{f([C],[D],[E],\overline{Y})} \rho E + \eta F$$

- Also include:
  - Compartments
  - Rules/constraints
  - Discrete events



Source: M. Hucka, CalTech

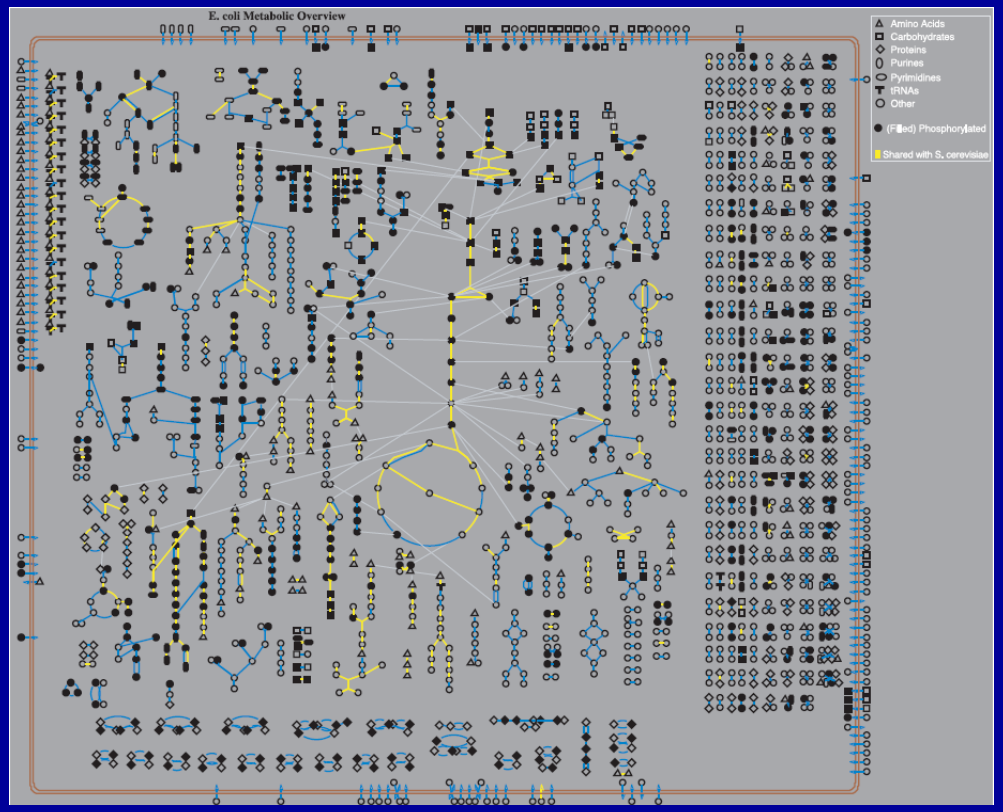
- Level 3 Model (forthcoming) adds:
  - Graphical layout of models
  - Model composition (submodels)
  - Multistate complex species
  - Arrays of elements
  - 2-D & 3-D geometry

Computational Pathway Inference

- ANOVA, hierarchical and k-means clustering, discriminant analysis, SOMs, SVMs
- Different methods give divergent results
- Data quality a *major* issue
- Mutual Information Methods
  - Systematic analysis of mutual information in
  - Boolean network state transition tables to extract minimal network architectures ("reverse engineering")
  - Performs well for "low-*k*" networks (small number of inputs per gene); being extended to higher-*k*
  - Impact of measurement errors?
- Correlation Metric Methods
  - Use a time-lagged correlation metric as a measure of distance between reacting species

Pathway Analysis: *BioCyc*

206 pathway databases, derived from literature and by computation www.biocyc.org

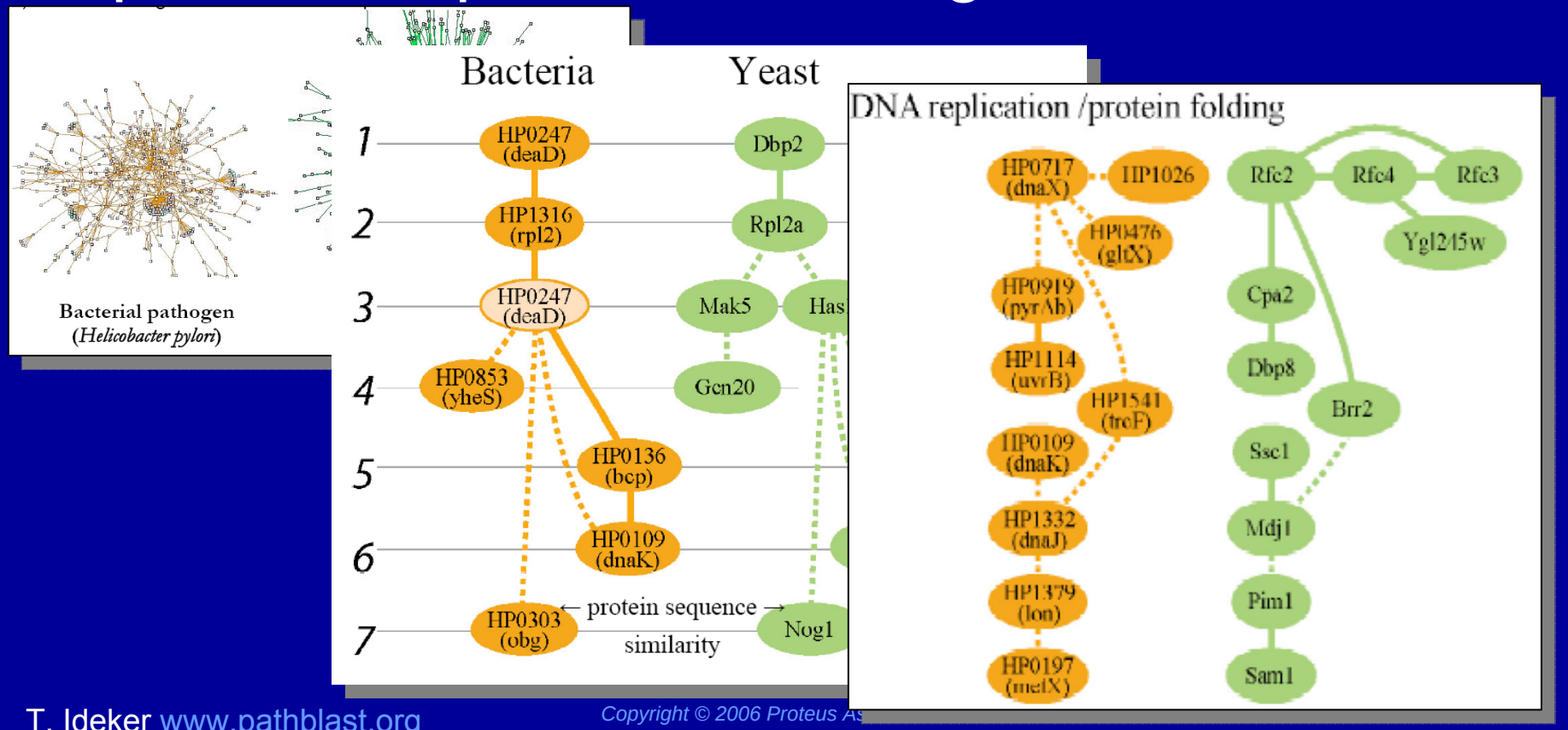


P. Karp, *Science* 293 (2001)

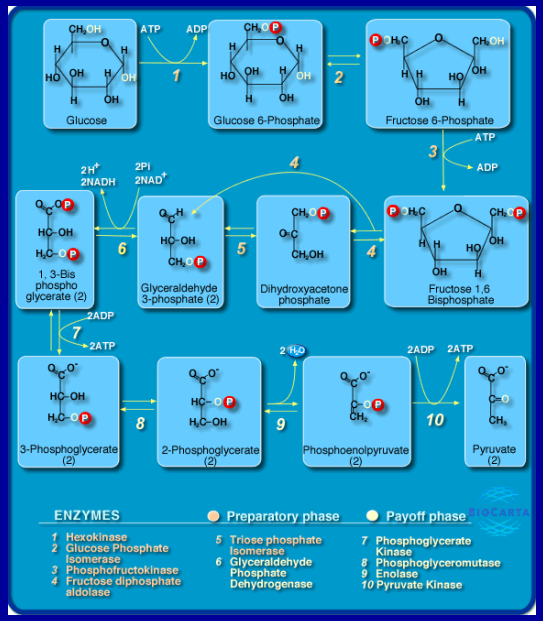
- Qualitative simulation by symbolic computation on the network:
  - represent network as a set of "production rules" A^B →X
  - answer questions such as "can this network produce X?"
- *PathoLogic*: pathway inference from whole genome data
  - two inputs
    - annotated genome sequence that includes locations and predicted functions of genes within the genome,
    - reference pathway DB.
  - output
    - new PGDB that includes a set of pathways predicted to be present
  - match enzymes in the annotated genomes against enzymes in the *MetaCyc* DB
  - compute a score for presence of different pathways on basis of number of matching enzymes, and their positions within the pathway

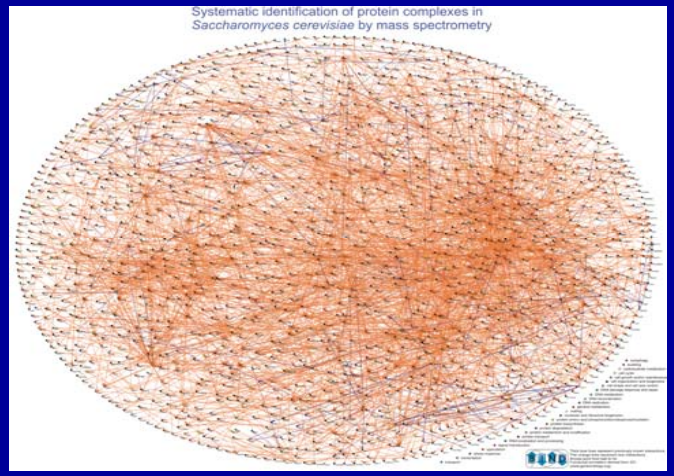
Pathway Analysis: *PathBlast*

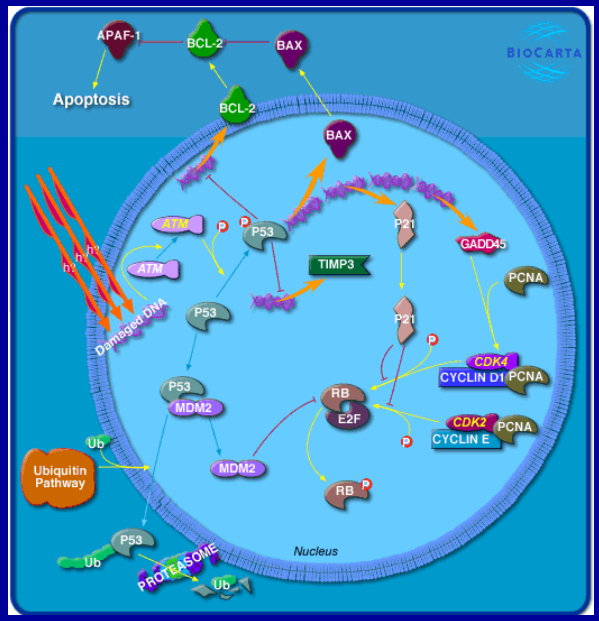
- Function prediction by cross-species protein sequence matching



BioPAX: ontology and data exchange format for pathways





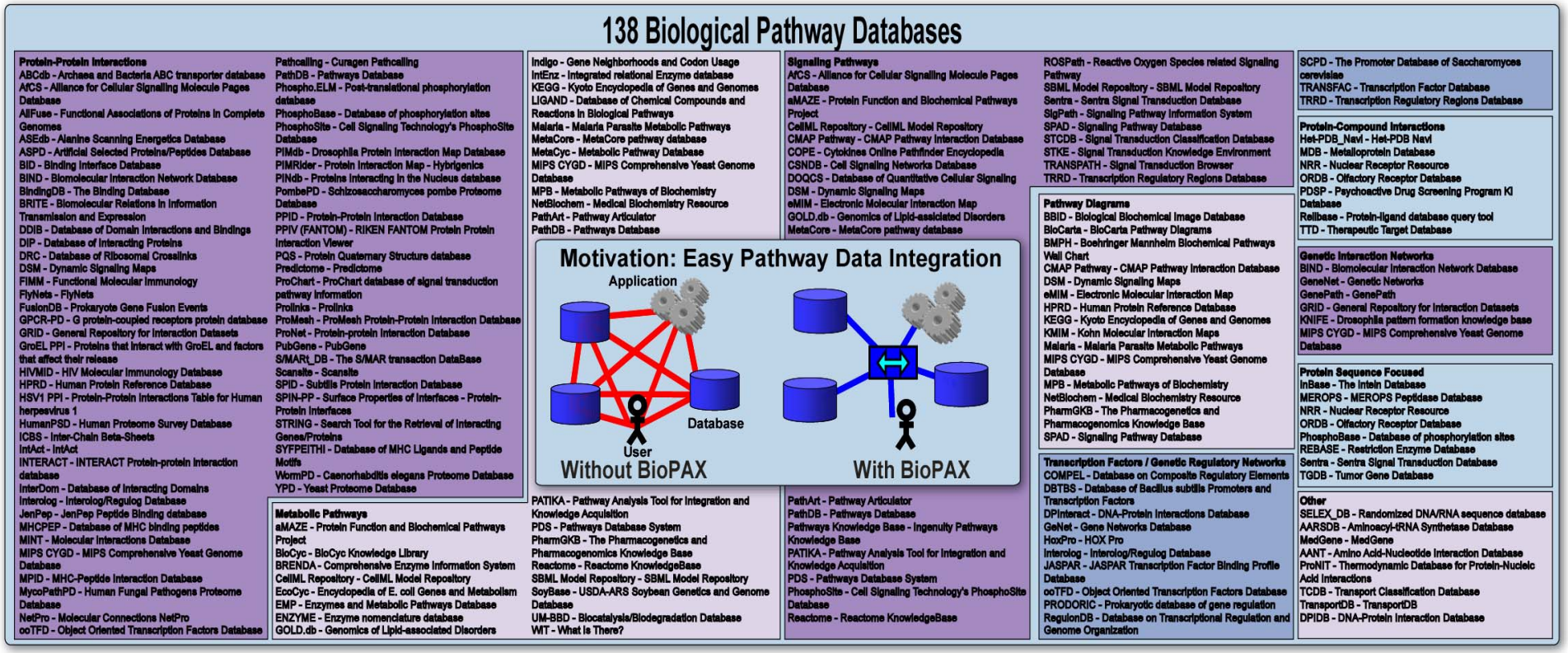


Metabolic Pathways

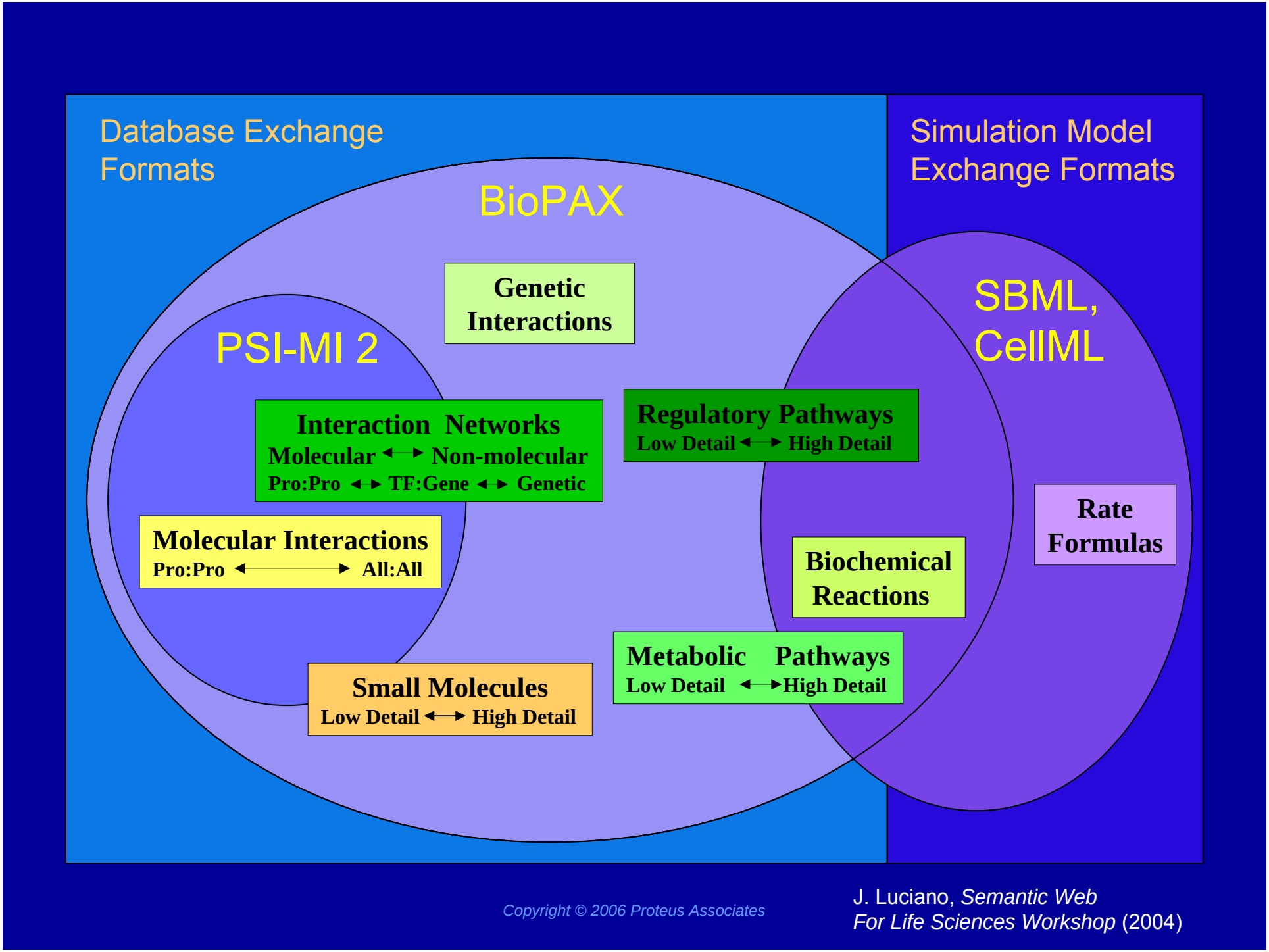
Molecular Interaction Networks

Signaling Pathways

BioPAX: so many databases…



Pathway Resource List http://cbio.mskcc.org/prl/



J. Luciano, *Semantic Web For Life Sciences Workshop* (2004)

Aggregation, Integration, Inference

1. Multiple kinds of pathway databases
   - metabolic
   - molecular interactions
   - signal transduction
   - gene regulatory
2. Constructs designed for integration
   - DB References
   - XRefs (Publication, Unification, Relationship)
   - Synonyms
   - Provenance (not yet implemented)
3. OWL DL – to enable reasoning

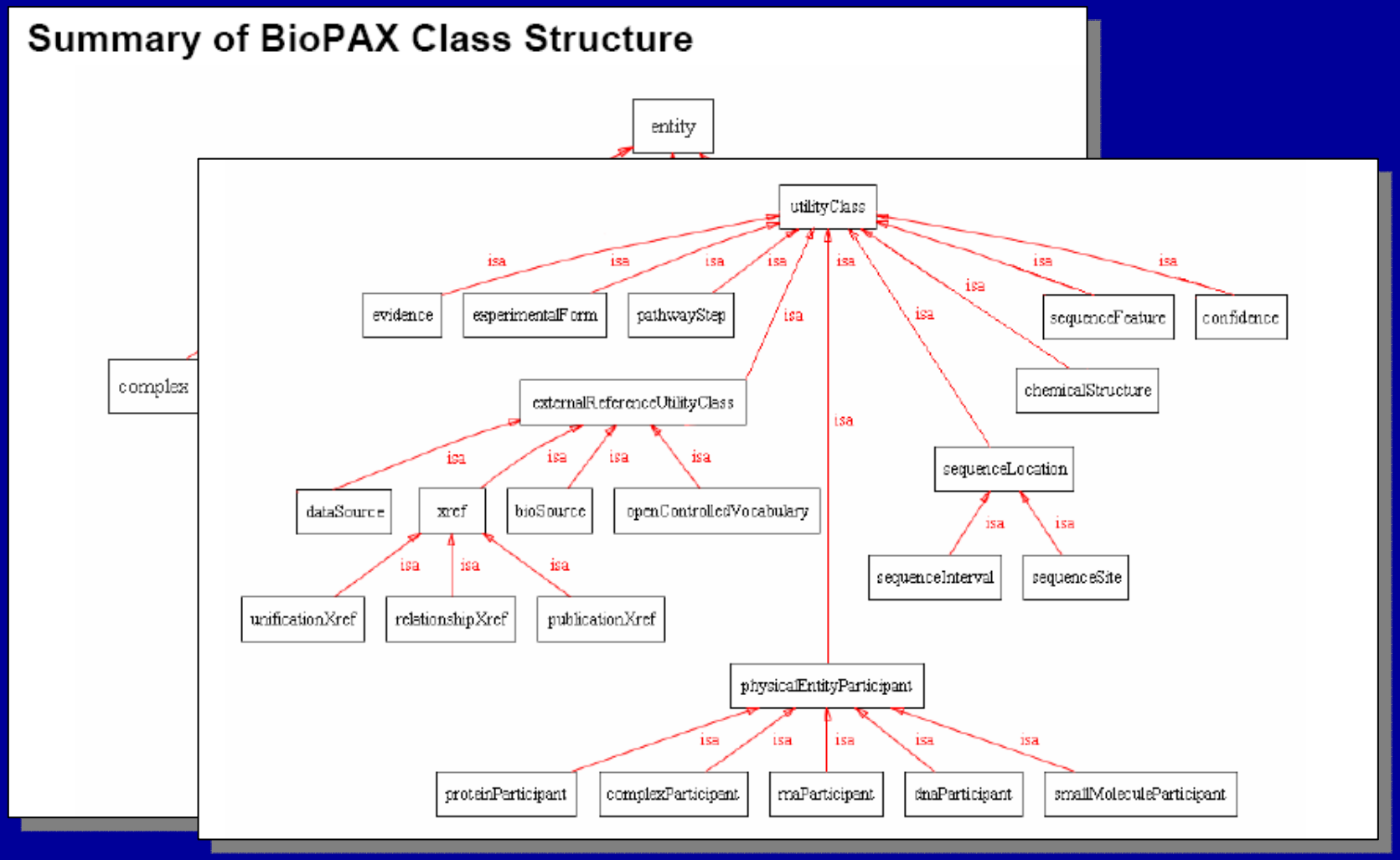
J. Luciano, *Semantic Web For Life Sciences Workshop* (2004)

BioPAX: use of other ontologies

- Conceptual framework based upon existing DB schemas:
  - *aMAZE*, *BIND*, *EcoCyc*, *WIT*, *KEGG*, *Reactome*, etc.
  - Allows wide range of detail, multiple levels of abstraction
- Uses pointers to existing ontologies to provide supplemental annotation where appropriate
  - Cellular location → *GO* Component
  - Cell type → *Cell.obo*
  - Organism → NCBI *taxon* DB
- Incorporate other standards where appropriate
  - Chemical structure → *SMILES*, *CML*, *INCHI*
- Interoperate with existing standards (*RDF/OWL, LSID, SBML, PSI, CellML Metadata Standard*)

J. Luciano, *Semantic Web For Life Sciences Workshop* (2004)

BioPAX Ontology



BIOMODELS.NET

- Store, search and retrieve published mathematical models of biological interests
- Annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.
- *MIRIAM*: *Minimum information requested in the annotation of biochemical models*

	Release 1 (April 2005)	Release 2 (June 2005)	Release 3 (July 2005)	Release 4 (January 2006)
Models	20	30	44	50
Species	322	425	596	761
Reactions	631	736	943	1163
Annotations	1084	1609	2373	3126

Topic	# models
Cell communication	24
Cell cycle	6
Metabolism	10
Circadian rhythm	7
Other	3

Whole-organ Models: “Physiomics”

Organ Systems

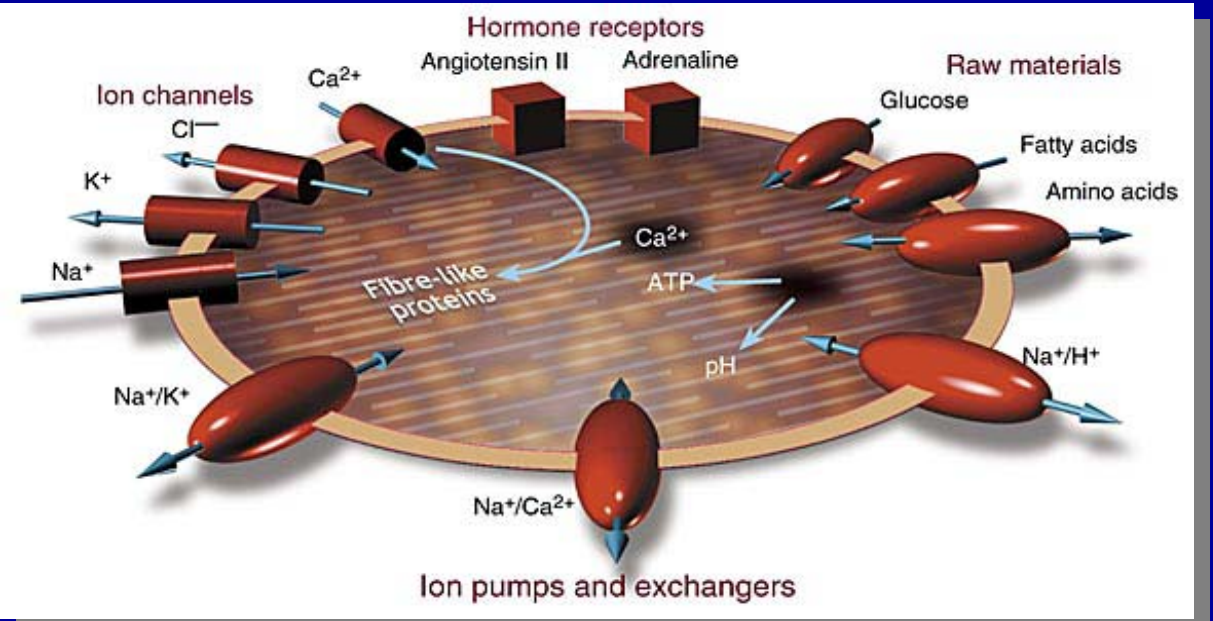
- Epitheliome – cell interactions
- Immune System
- Central Nervous Systems

P. Hunter “An Update on the Human Physiome Project,” in *Proc. IUPS Satellite Workshop on Computational Physiology, San Diego, CA (2005)*

Cardiac Modelling Domains

- Cardiac Myocyte Models
  - Membrane currents
  - Intracellular Ca^{++} transport
  - Excitation-contraction coupling
  - Interval/force relationships
- Micro/Meso-scale Anatomical Structure
  - Histological models
  - DTMR imaging
  - Electrical bundle/node geometry
  - Vascular system dynamics

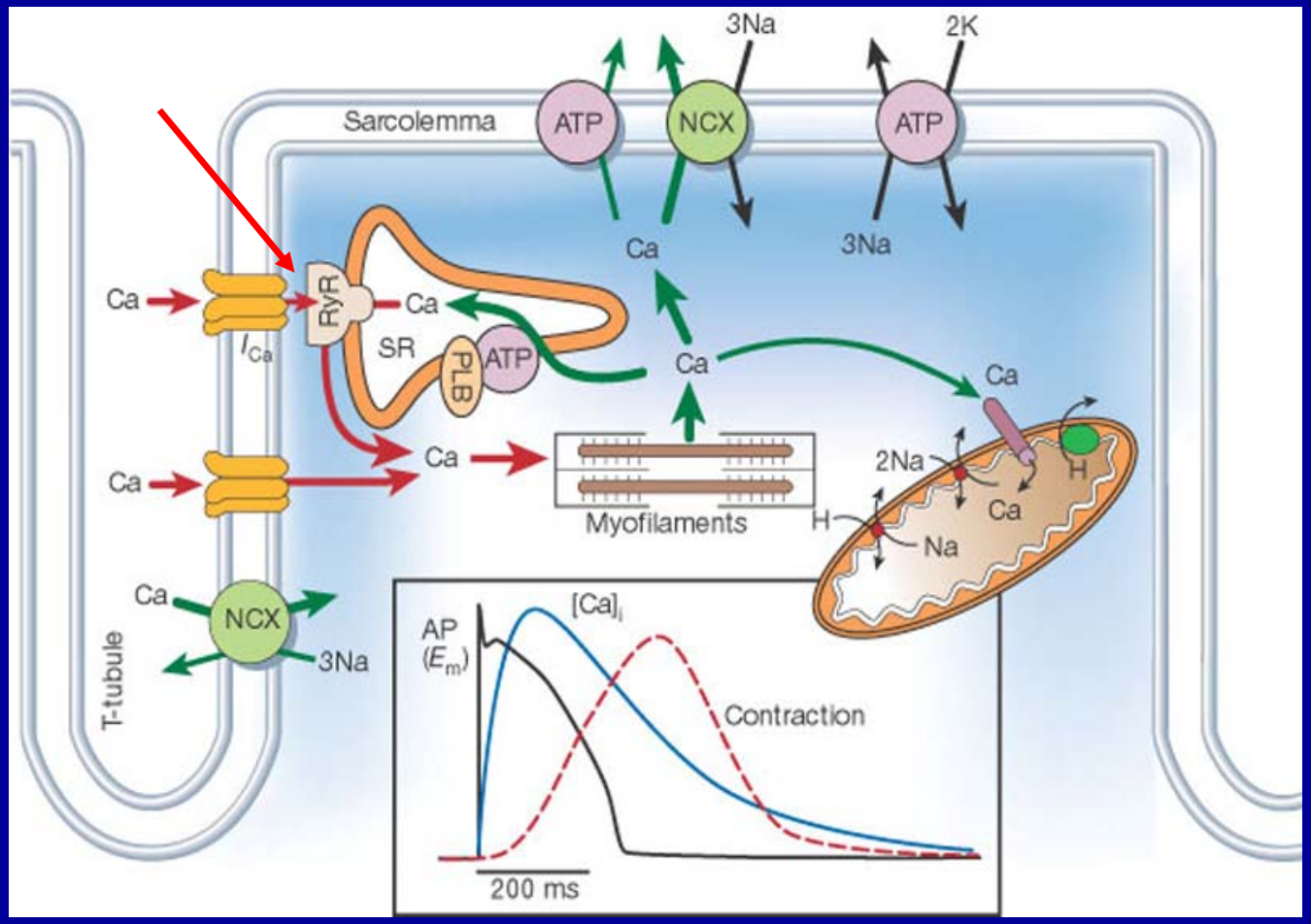
Cardiac Myocyte Model



Source: New Scientist

- Model of voltage-gated membrane currents, membrane transporters, Ca^{2+} sequestration, intracellular Na^{+}, Ca^{2+} and K^{+}
- Voltage- and time-dependent behaviour described by systems of non-linear ODEs

Cardiac Myocyte Model



Bers *Nature* 415: 198-205 (2002)

Modelling Ventricular Myocytes

Single Cell

$$dV/dt = -\frac{I_{ion} + I_{stim}}{C_m}$$

2-D continuous sheet of cells

$$\partial V/\partial t = -\frac{I_{ion} + I_{stim}}{C_m} + \frac{1}{\rho_x S_x C_m}\left(\frac{\partial^2 V}{\partial x^2}\right) + \frac{1}{\rho_y S_y C_m}\left(\frac{\partial^2 V}{\partial y^2}\right)$$

where I_{stim} is the externally applied stimulus current, C_m is the cell capacitance per unit surface area, ρ_x and ρ_y are the cellular resistivity in the x and y direction, S_x and S_y are the surface to volume ratio in the x and y direction, and I_{ion} is the sum of all transmembrane ionic currents given by the following equation:

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa}$$

Ten Tusscher K. H.W. J., Noble D., Noble P. J. and Panfilov A. V. "A model for human ventricular tissue," *Am J Physiol Heart Circ Physiol* (December, 2003)

Membrane Current	Model
Fast Na^+ current: I_{Na}	$I_{Na} = G_{Na} m^3 h j (V - E_{Na})$
L-type Ca^{2+} current: I_{CaL}	$I_{CaL} = G_{CaL} d f f_{Ca} 4 \frac{VF^2}{RT} \frac{Ca_i e^{2VF/RT} - 0.341 Ca_o}{e^{2VF/RT} - 1}$
Transient outward current: I_{to}	$I_{to} = G_{to} r s (V - E_K)$
Slow delayed rectifier current: I_{Ks}	$I_{Ks} = G_{Ks} x_s^2 (V - E_{Ks})$
Rapid delayed rectifier current: I_{Kr}	$I_{Kr} = G_{Kr} \sqrt{\frac{K_o}{5.4}} x_{r1} x_{r2} (V - E_K)$
Inward rectifier K^+ current: I_{K1}	$I_{K1} = G_{K1} \sqrt{\frac{K_o}{5.4}} x_{K1\infty} (V - E_K)$
Na^+/Ca^{2+} exchanger current, Na^+/K^+ pump current, plateau and background currents	$I_{NaCa} = k_{NaCa} \frac{e^{\frac{\gamma VF}{RT}} Na_i^3 Ca_o - e^{\frac{(\gamma-1)VF}{RT}} Na_o^3 Ca_i \alpha}{(K_{mNai}^3 + Na_o^3)(K_{mCa} + Ca_o)(1 + k_{sat} e^{\frac{(\gamma-1)VF}{RT}})}$ $I_{NaK} = P_{NaK} \frac{K_o}{K_o + K_{mK}} \frac{Na_i}{Na_i + K_{mNa}} \frac{1}{1 + 0.1245 e^{-0.1VF/RT} + 0.0353 e^{-VF/RT}}$
I_{pCa} I_{pK}	$I_{pCa} = G_{pCa} \frac{Ca_i}{Ca_i + K_{pCa}}$ $I_{pK} = G_{pK} \frac{V - E_K}{1. + e^{(25-V)/5.98}}$
background sodium and calcium leakage currents	$I_{bNa} = G_{bNa} (V - E_{Na})$ $I_{bCa} = G_{bCa} (V - E_{Ca})$

Ten Tusscher K. H.W. J., Noble D., Noble P. J. and Panfilov A. V. "A model for human ventricular tissue," *Am J Physiol Heart Circ Physiol* (December, 2003)

Intracellular Ion Dynamics

Calcium

$$
\begin{aligned}
I_{leak} &= V_{leak}(Ca_{SR} - Ca_i) \\
I_{up} &= \frac{V_{maxup}}{1 + K_{up}^2 / Ca_i^2} \\
I_{rel} &= (a_{rel}\frac{Ca_{SR}^2}{b_{rel}^2 + Ca_{SR}^2} + c_{rel})dg \\
Ca_{ibufc} &= \frac{Cai \times Buf_c}{Cai + K_{bufc}} \\
dCa_{itotal}/dt &= -\frac{I_{CaL} + I_{bCa} + I_{pCa} - 2I_{NaCa}}{2V_c F} + I_{leak} - I_{up} + I_{rel} \\
Ca_{srbufsr} &= \frac{Ca_{sr} \times Buf_{sr}}{Ca_{sr} + K_{bufsr}} \\
dCa_{srtotal}/dt &= \frac{V_c}{V_{sr}}(-I_{leak} + I_{up} - I_{rel}),
\end{aligned}
$$

Na_i and K_i

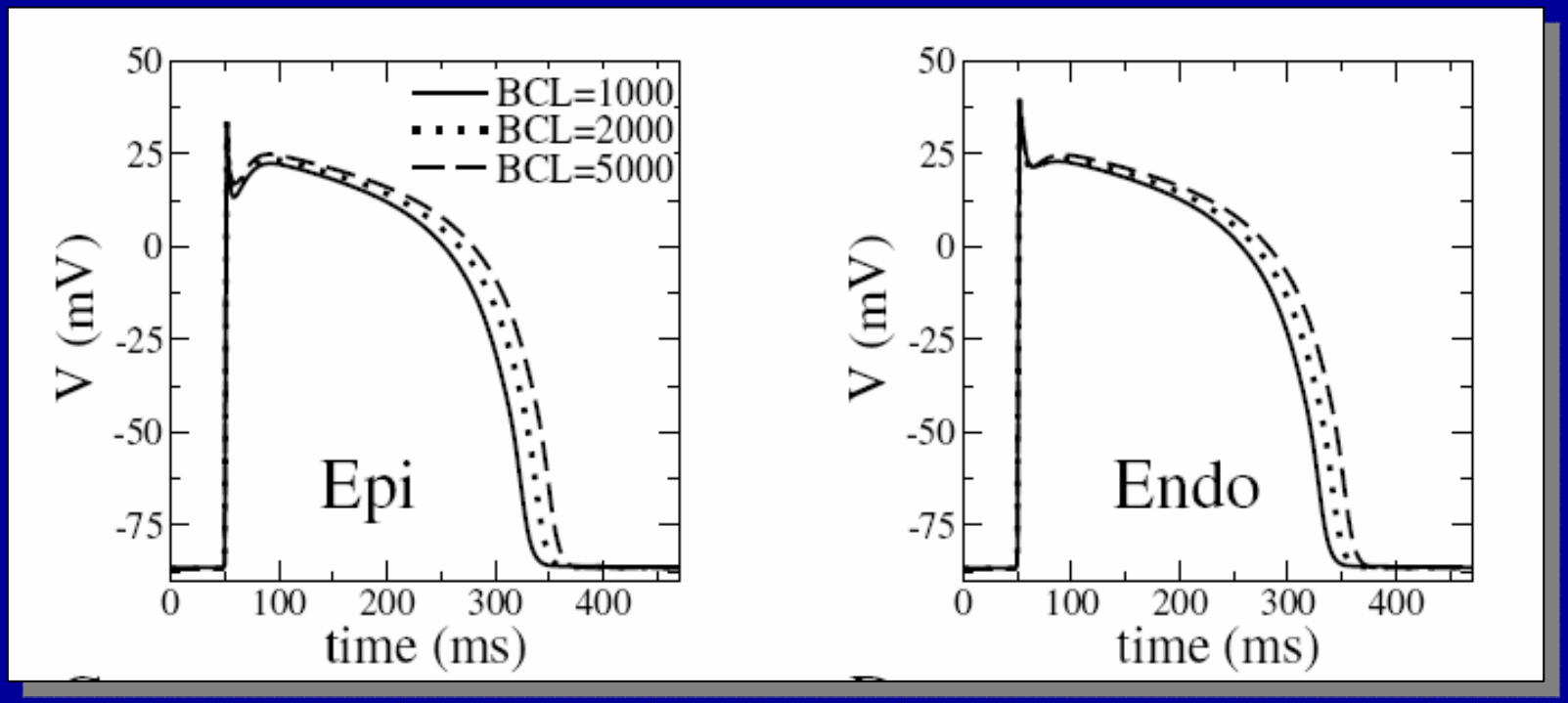
$$
\begin{aligned}
dNa_i/dt &= -\frac{I_{Na} + I_{bNa} + 3I_{NaK} + 3I_{NaCa}}{V_c F} \\
dK_i/dt &= -\frac{I_{K1} + I_{to} + I_K - 2I_{NaK} + I_{pK} + I_{stim} - I_{ax}}{V_c F}
\end{aligned}
$$

Ten Tusscher K. H.W. J., Noble D., Noble P. J. and Panfilov A. V. “A model for human ventricular tissue,” *Am J Physiol Heart Circ Physiol* (December, 2003)

Myocyte Model Parameters

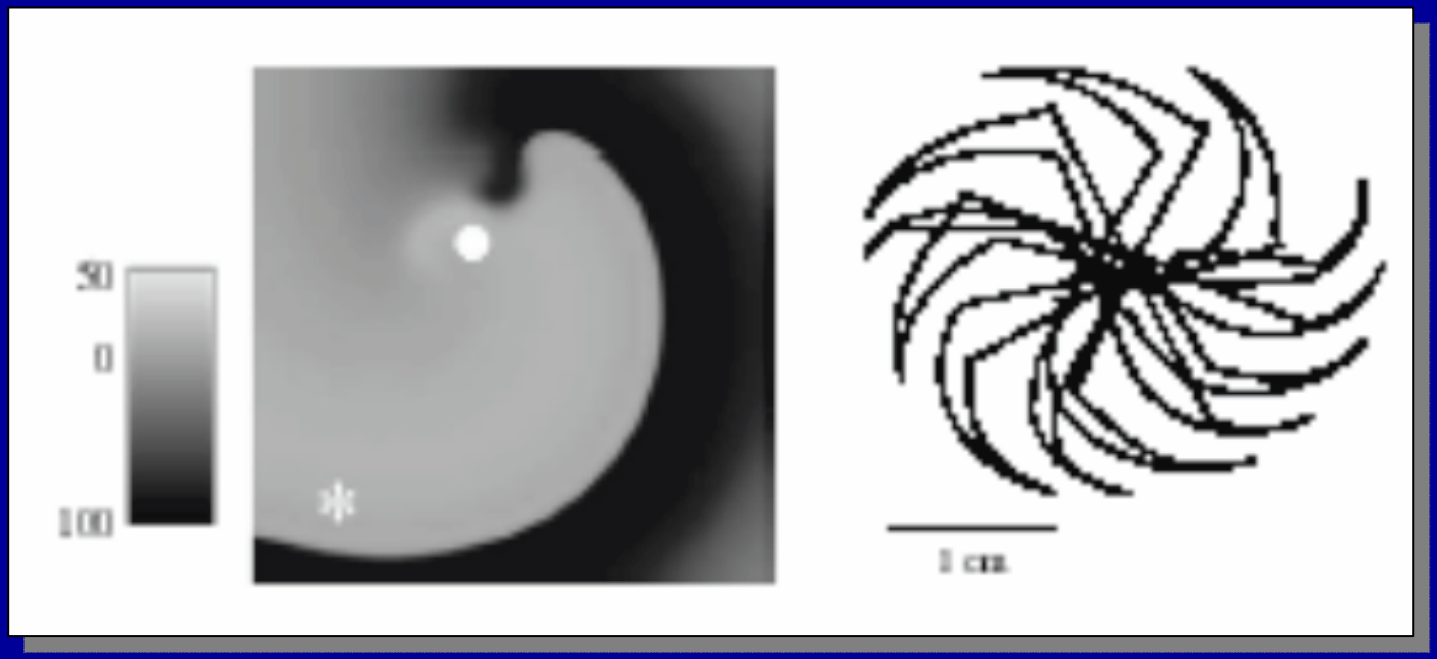
- $3x10^7$ myocytes/heart, each unique in geometry, orientation
- 34 coupled non-linear ODEs/myocyte
- Integrated using modified Runge-Kutta 4^{th}-order adaptive step algorithm
  - Maximum step size = 100 μsec
  - Maximum error tolerance = 10^{-6}
- Some processes have very rapid kinetics, so use a stiff integrator (DVODE) to improve performance

Myocyte Model: the calculated Action Potential



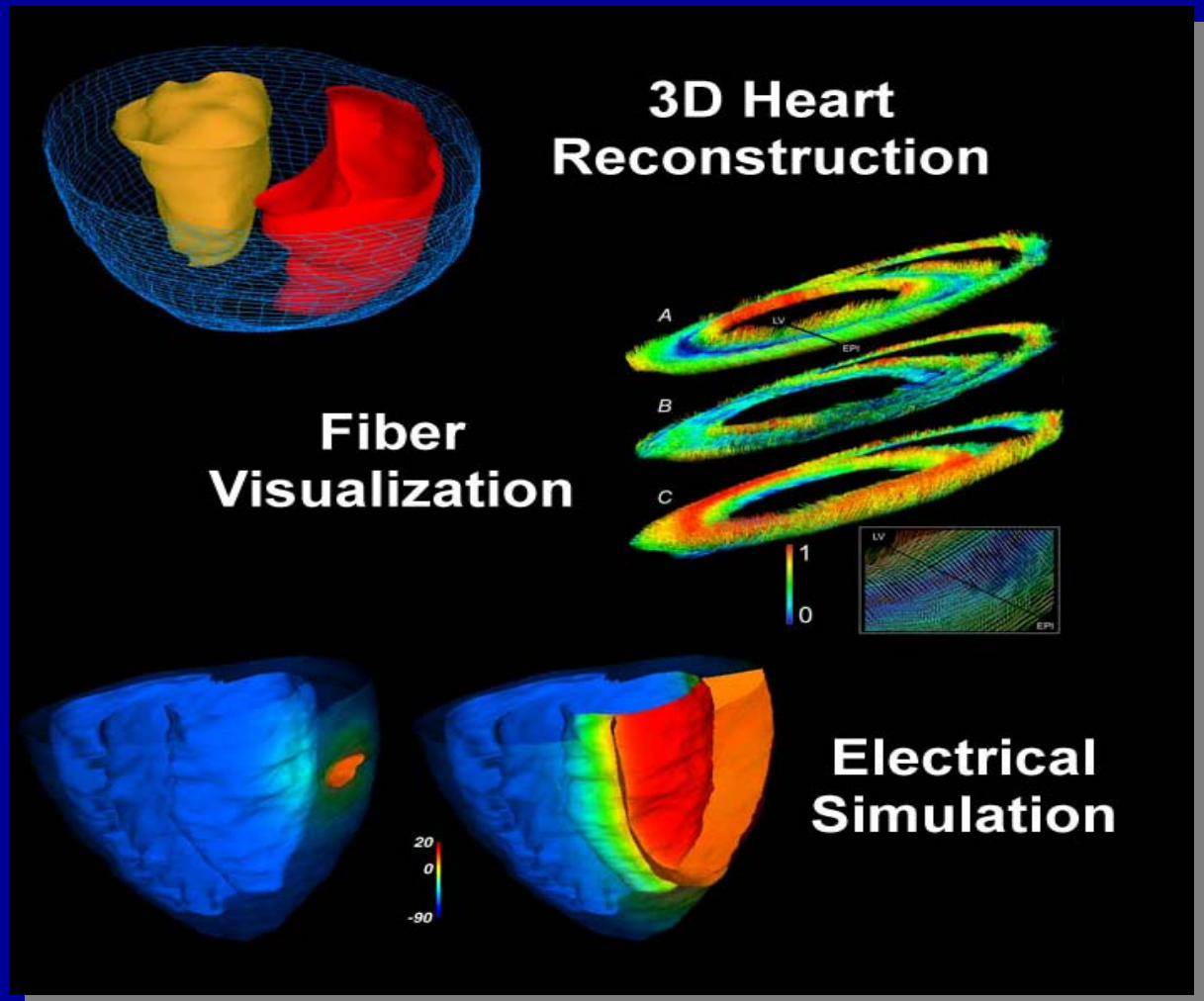
Ten Tusscher K. H.W. J., Noble D., Noble P. J. and Panfilov A. V. "A model for human ventricular tissue," *Am J Physiol Heart Circ Physiol* (December, 2003) [BCL = "basic cycle length"]

Myocyte Model: complex non-linear phenomena



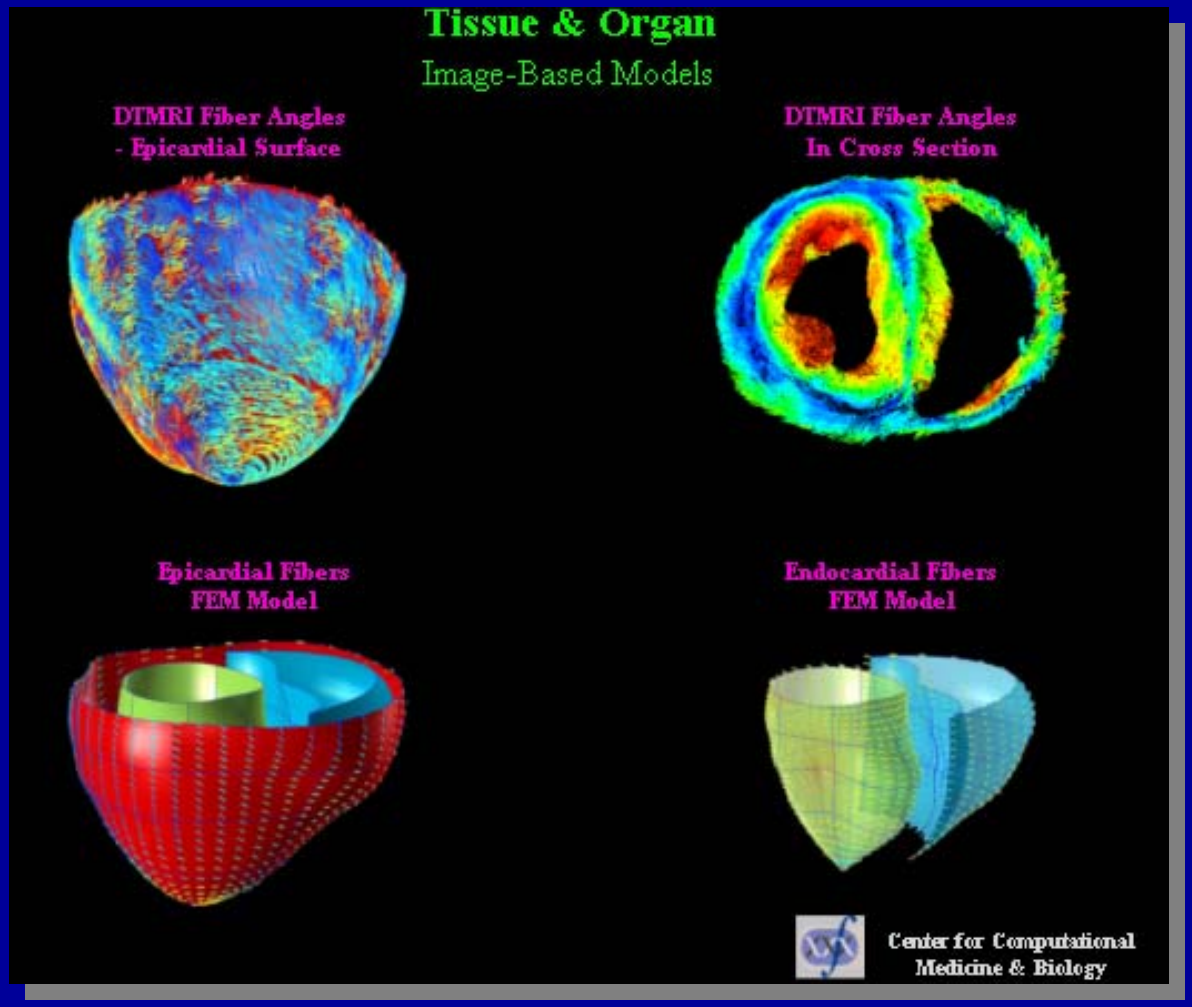
Ten Tusscher K. H.W. J., Noble D., Noble P. J. and Panfilov A. V. “A model for human ventricular tissue,” *Am J Physiol Heart Circ Physiol* (December, 2003) [BCL = “basic cycle length”]

Whole-heart Modelling



R. Winslow JHU

Image-based Models



R. Winslow JHU

Integrated Excitation Model

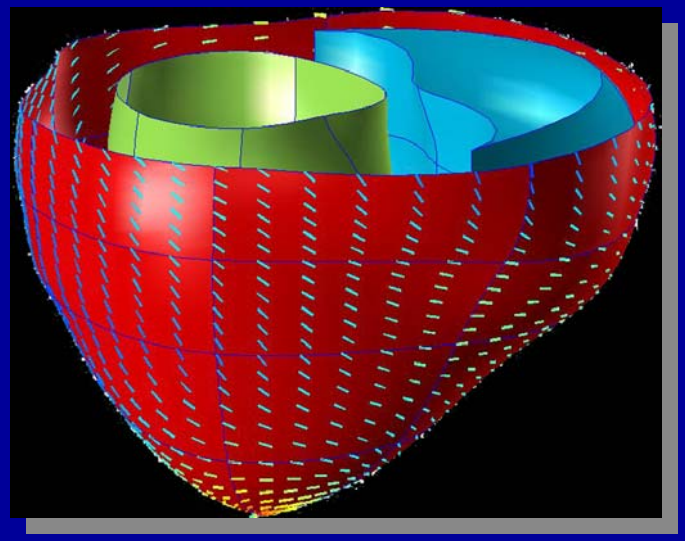
- Treat each myocardial domain as a continuum: use average conductivity, trans-membrane voltages
- Coupled parabolic and elliptic equations which must be satisfied by the myocardium and the surrounding medium (can be reduced to a parabolic reaction-diffusion equation)

Integrated Excitation Model

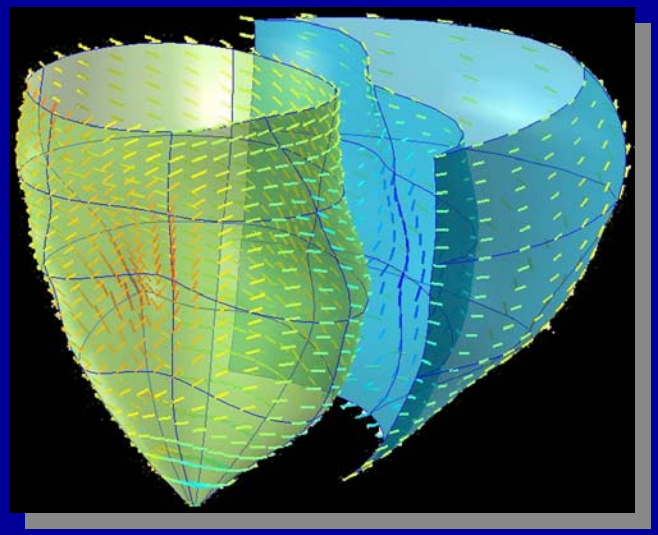
- Parallelized and solved on a 4-node x 8-processor IBM SP Power^3 using OpenMP
- ~250 μm mesh = 3x10^6 lattice points =
  3x10^7 coupled non-linear ODEs;
  2.5 μs time step; 30 ms cycle
- Solved using:
  - Forward Euler method
  - 4th-order non-adaptive Runge-Kutta method
- Parallelized by creating one sub-grid for each processor

Finite Element Modelling

Epicardial Fibers – FEM Model

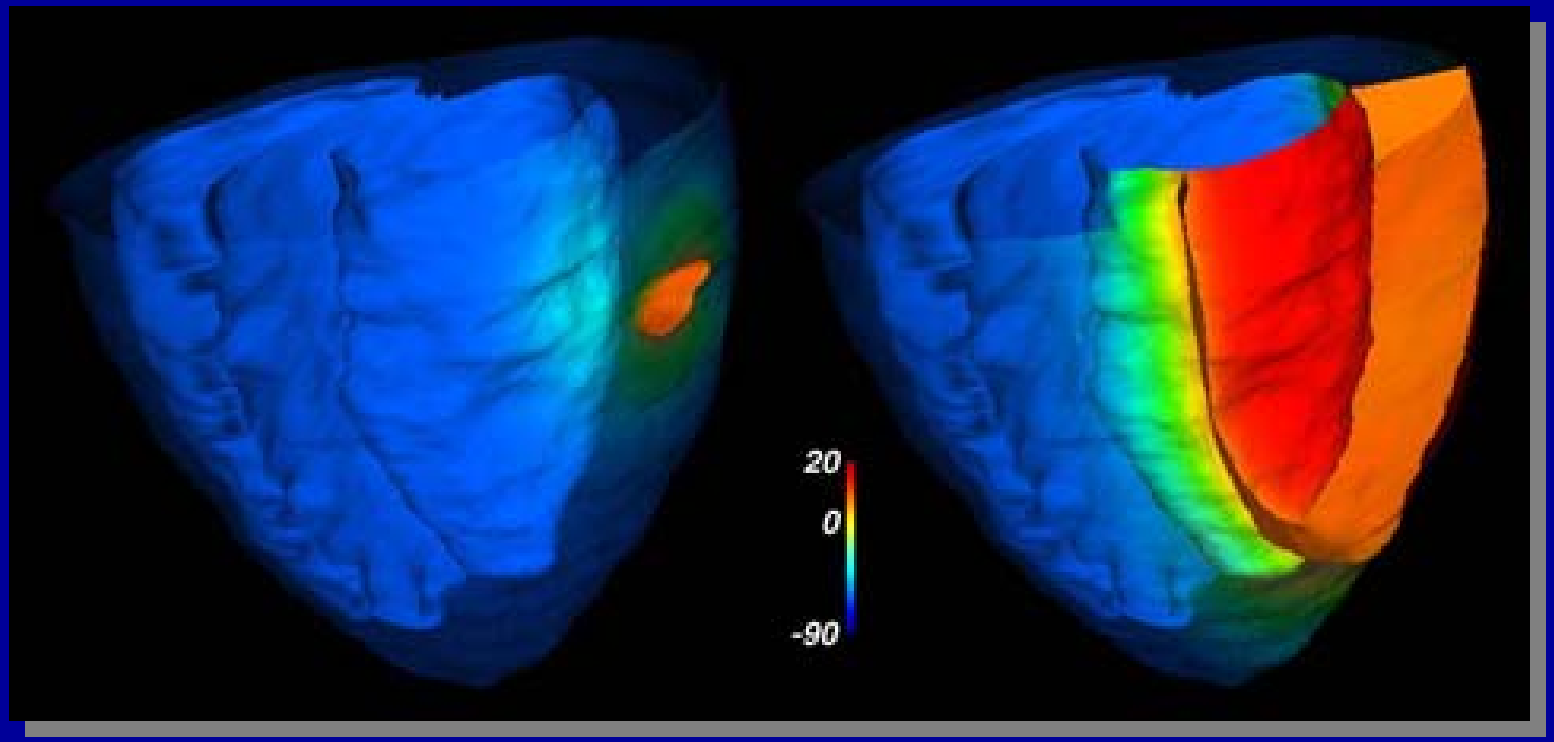


Endocardial Fibers – FEM Model



R. Winslow, Johns Hopkins Univ.

Electrical Model



Geometry and fiber structure from DTMRI converted to a computational domain over which PDEs governing the spread of current in the myocardium were solved

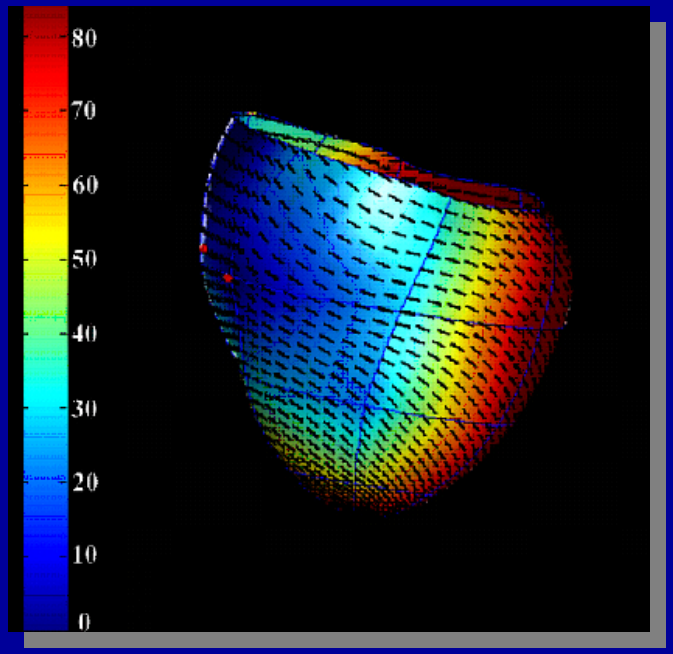
R. Winslow (Johns Hopkins)

Reaction-Diffusion Equation

$$\frac{\partial v(\underline{x},t)}{\partial t} = \frac{1}{C_m}\left[-I_{ion}(v(\underline{x},t)) - I_{app}(\underline{x},t) + \frac{1}{\beta}\left(\frac{\kappa}{\kappa+1}\right)\nabla\bullet\left(M_i(\underline{x})\nabla v(\underline{x},t)\right)\right], \cdots \forall \underline{x} \in H$$

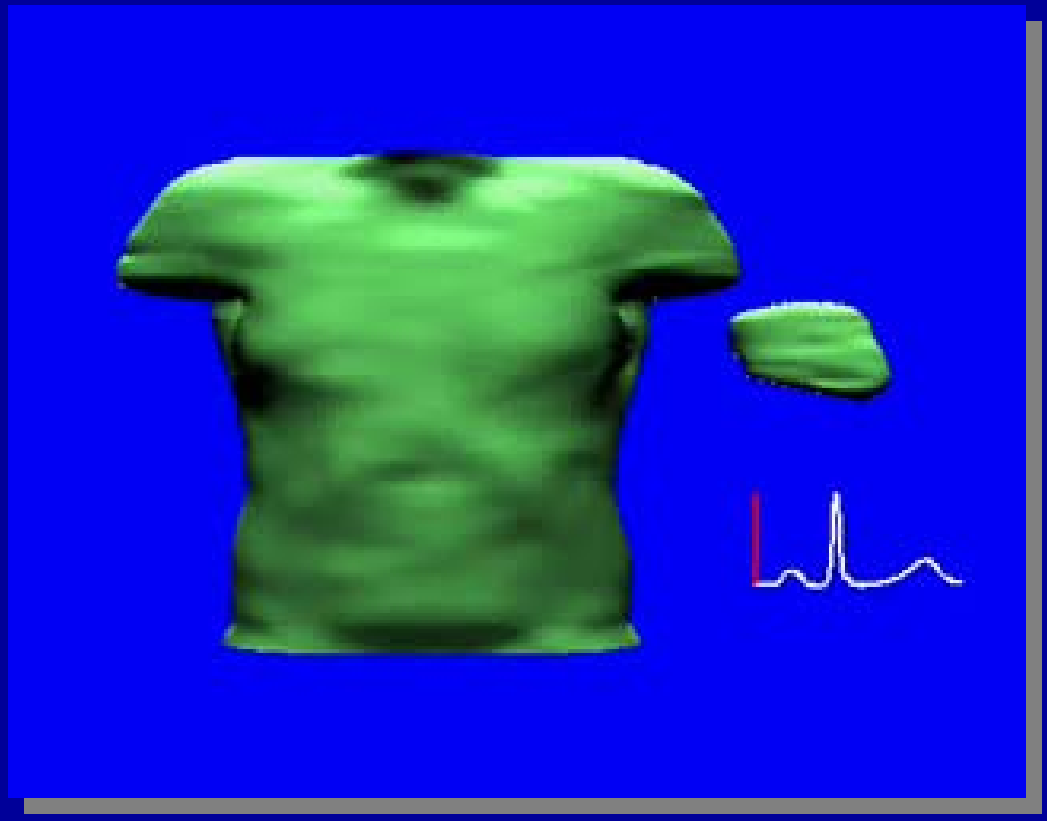
From Ionic Models

From DTMRI



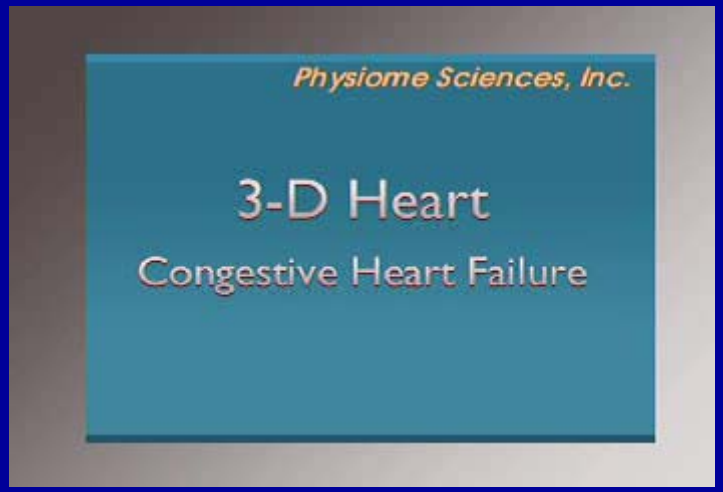
Courtesy of R. Winslow/Physiome Sciences

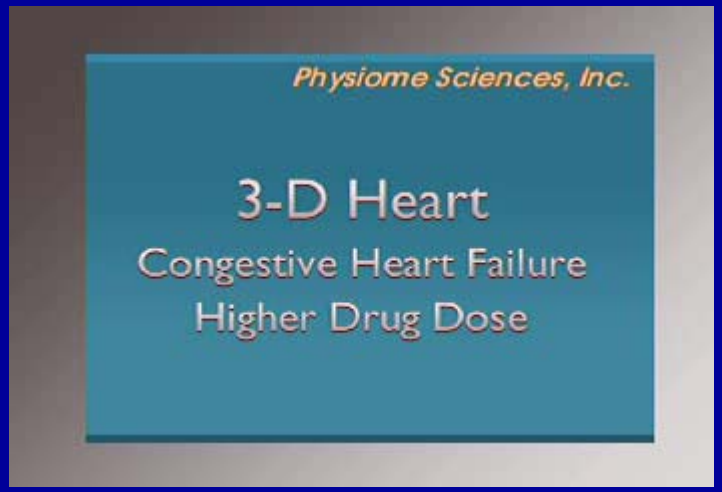
Heart in torso model



R. Winslow et al.

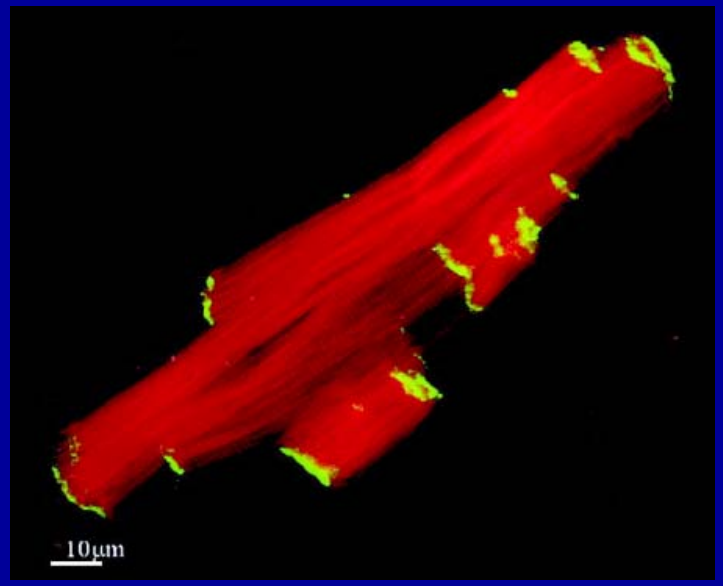
Modelling Arrhythmias

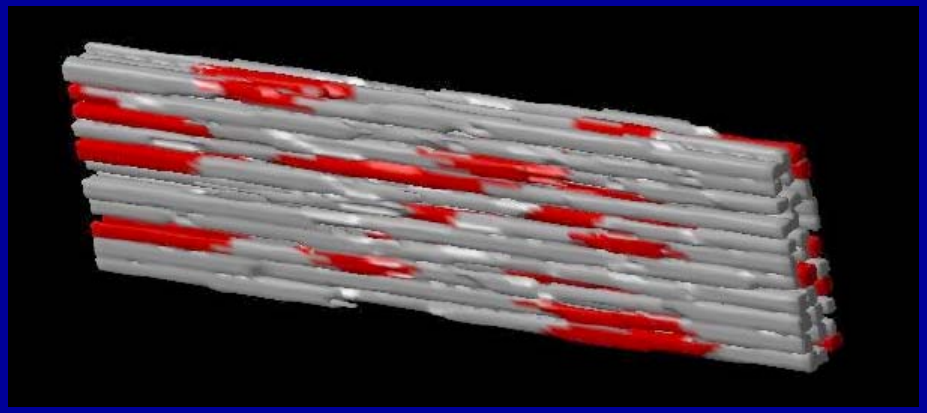


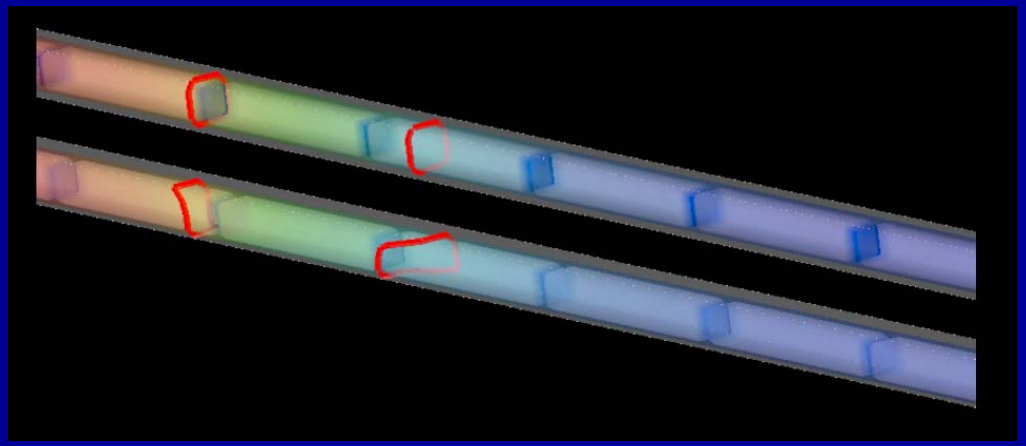


R. Winslow, JHU/Physiome Sciences

But reality is more complex…





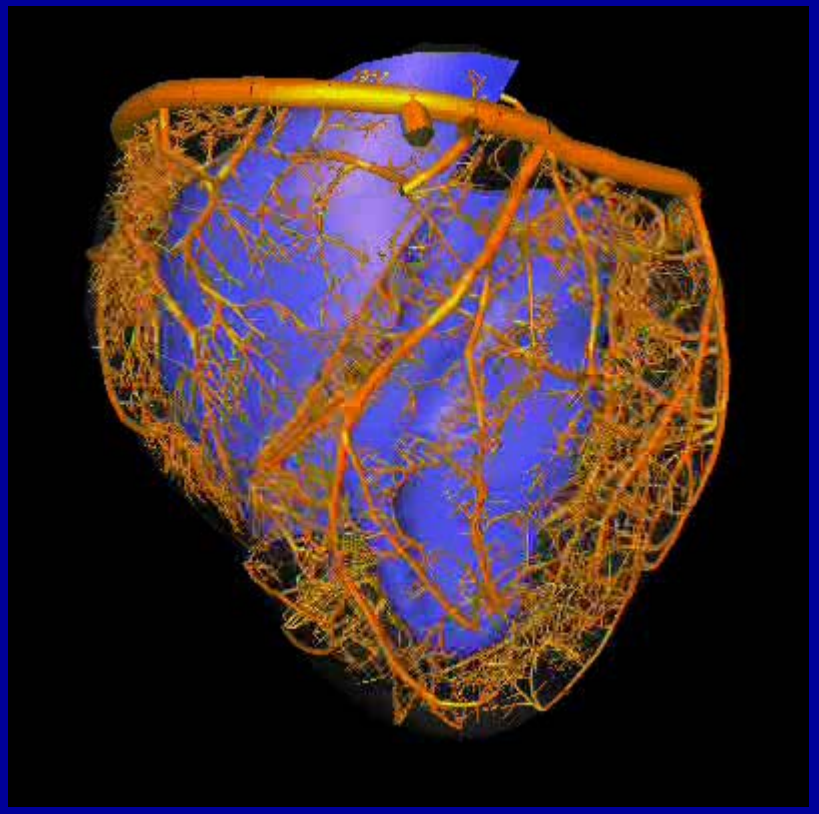


- Cell to Cell Coupling
- Cell Size
- Action potential Heterogeneity
- Fibrosis

C.S. Henriquez, S.F. Roberts "3D Microstructural Modeling of Cardiac Tissue," in *Proc. IUPS Satellite Workshop on Computational Physiology, San Diego, CA (2005)*

Coronary Vasculature

- 1mm spatial resolution for larger vessels
- fractal model for smaller vessels



Source: N. Smith and P. Hunter 1998

Coronary Vasculature: Simulating Ischaemia

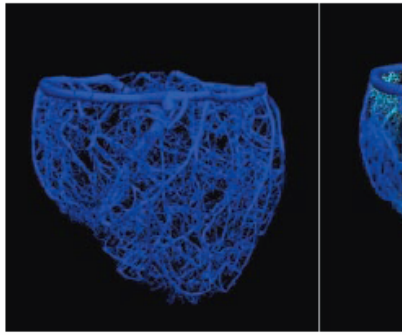
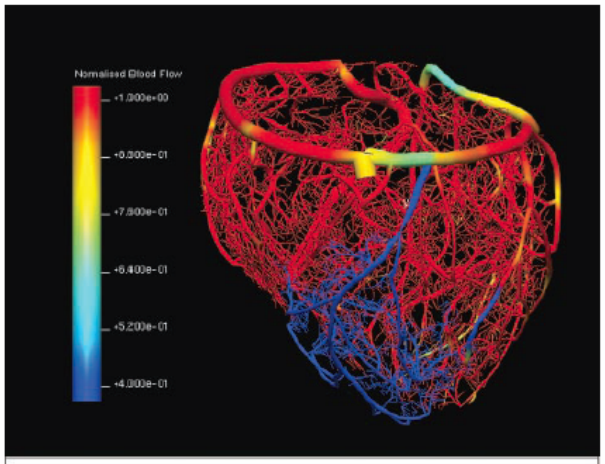
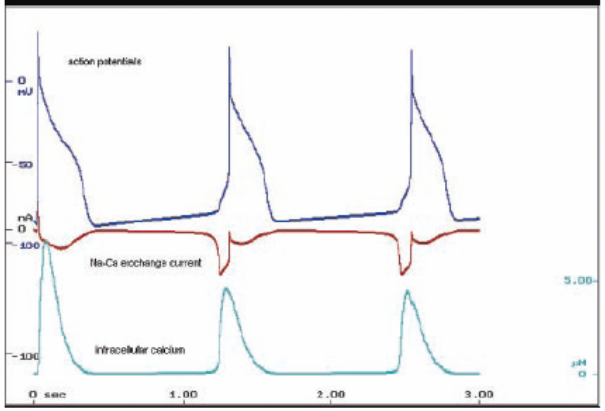


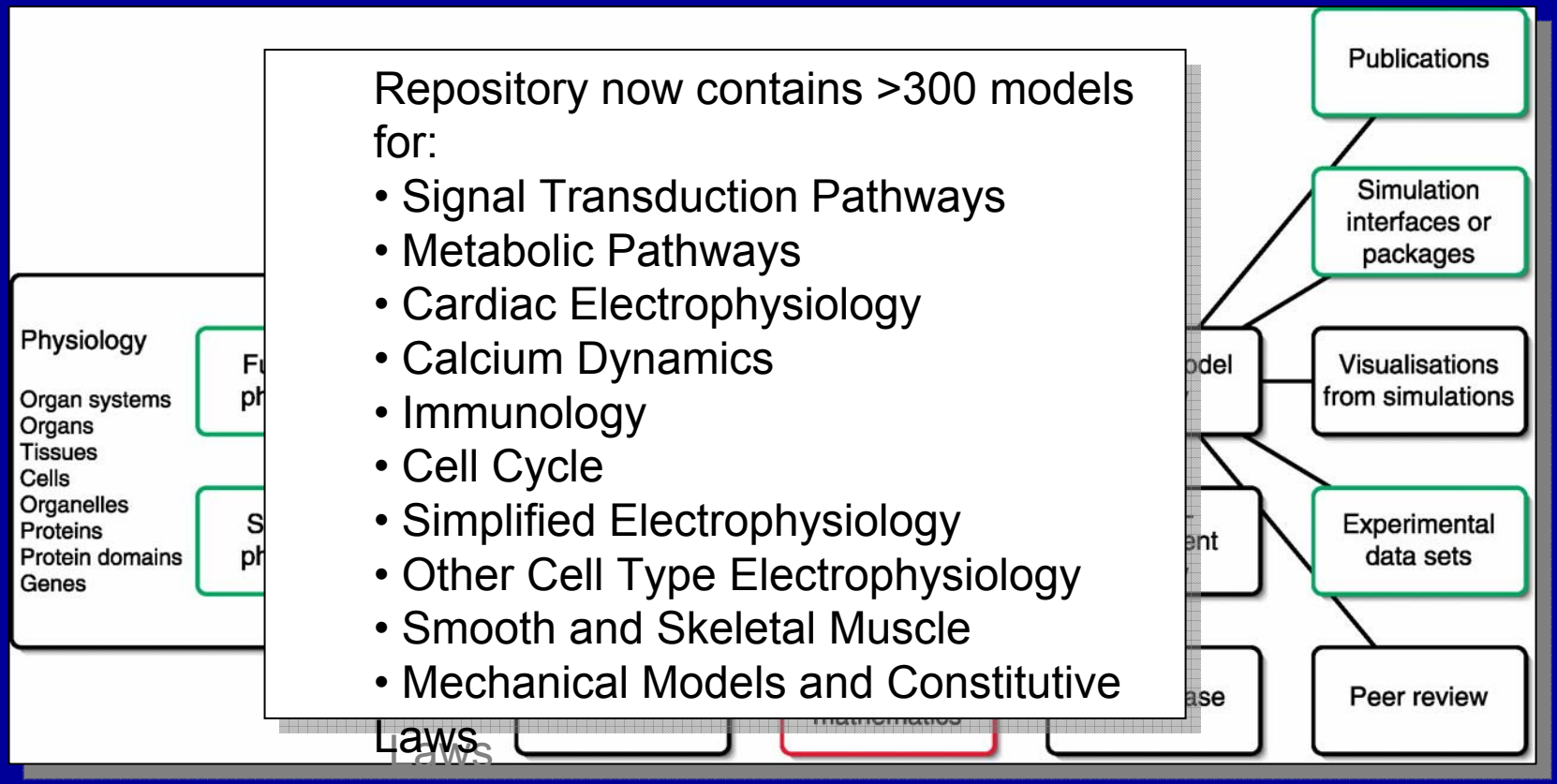
Fig. 3. Flow calculations coupled to the deforming myocardium. The color coding represents transmural pressure acting on the coronary vessels from the myocardial stress (dark blue, zero pressure, red, peak pressure). The deformation states are (from left to right) zero pressure, end-diastole, early systole, and late systole (*26*).

Fig. 4. Left, the coronary circulation model shown in Fig. 3 has been subjected to a constriction of one of the main branches leading to blocked blood flow in the regions colored blue. Right, simulation of ectopic beats in a Purkinje fiber model in conditions of calcium overload of the kind that occurs in ischemic tissue. Oscillatory calcium changes (bottom) induce inward sodium-calcium exchange current (middle) leading to initiation of action potentials (above).





Noble, D. "Modeling the Heart: from Genes to Cells to the Whole Organ," *Science* 295: 1678 (2002)



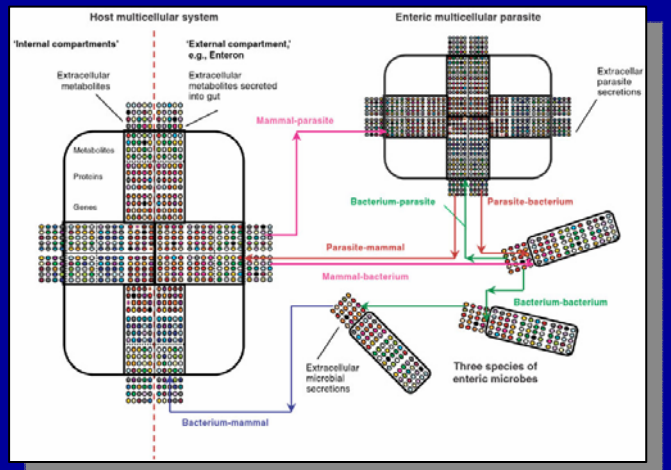
Repository now contains >300 models for:

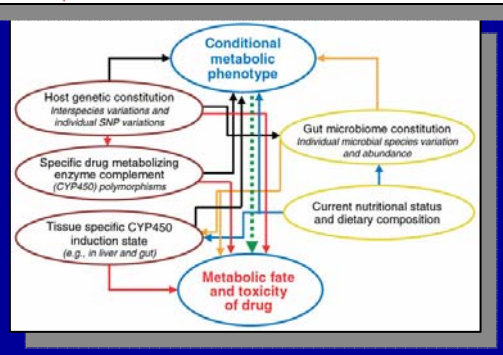
- Signal Transduction Pathways
- Metabolic Pathways
- Cardiac Electrophysiology
- Calcium Dynamics
- Immunology
- Cell Cycle
- Simplified Electrophysiology
- Other Cell Type Electrophysiology
- Smooth and Skeletal Muscle
- Mechanical Models and Constitutive Laws

www.cellml.org

Some Implications

- Drug Discovery and "Wellness" Nestlé Good Food, Good Life
  - Metagenomics: "super-organisms"
    - Intestinal microbiome
      - 1000+ species, 1Kg = 10^{11} cells
      - Milk a "molecular cocktail"?
  - Drug interactions with multiple proteins e.g. arrhythmia
    - Look for small molecules which can alter behaviour of entire networks, not single proteins

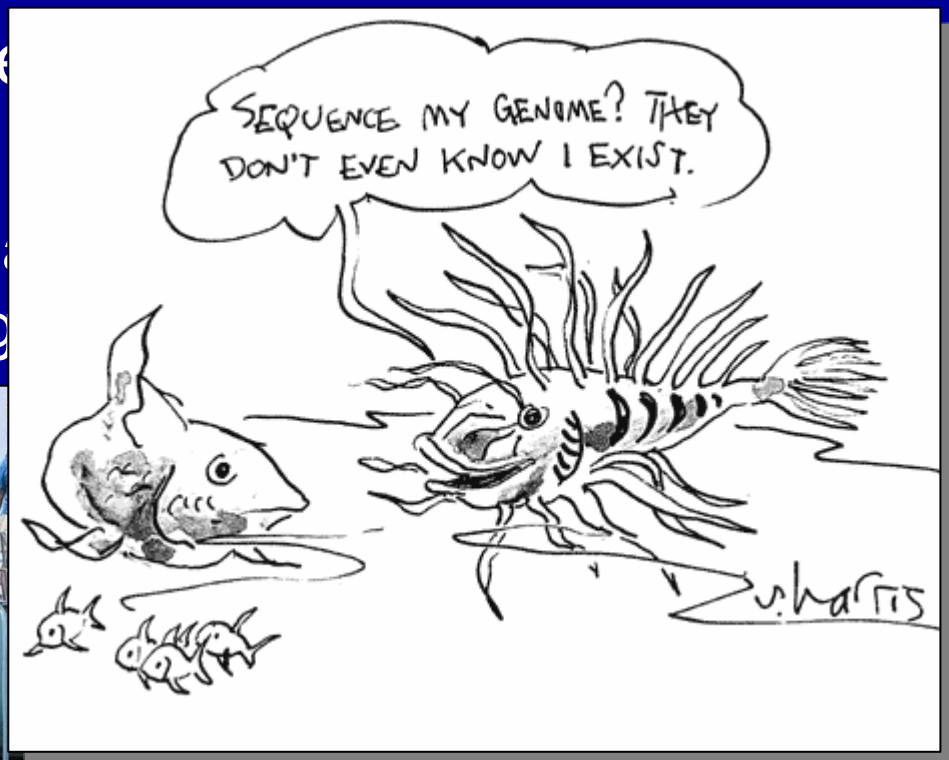


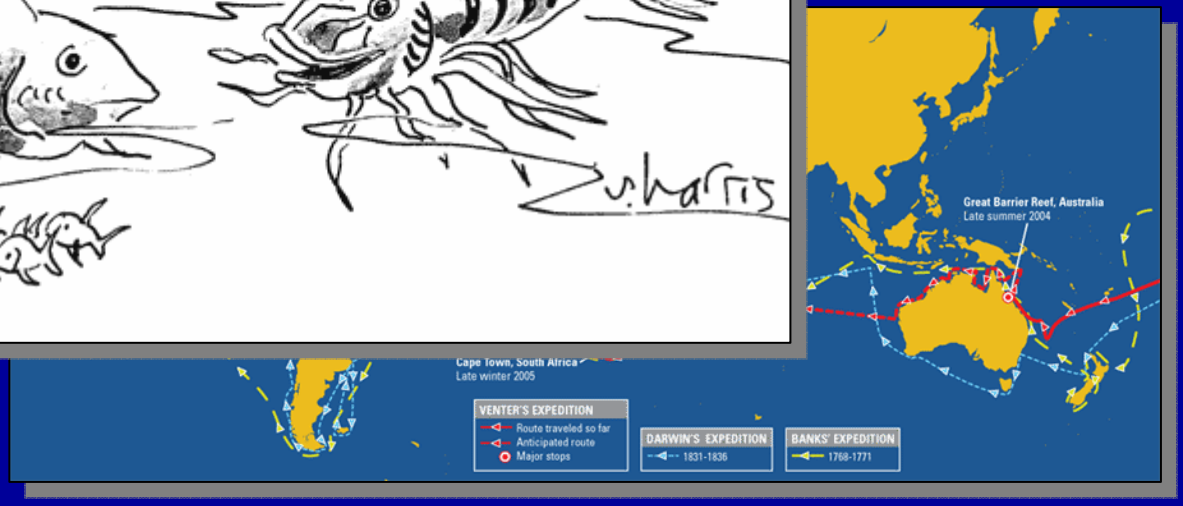


Nicholson et al *Nature Biotech* 22:2268 (2004)

Some Implications

- Understanding the planet
  - – Meta-ge ents
    - 6000 crobes?
    - 1 oce s, 1.2 million new g





Not quite there yet…

Thank You!

Merci!

Danke schön!

Grazie!

БЛАГОДАРНОСТЬ!

由於

Diolch!