



Computational Neuroscience Working Group

What do we mean by multi-scale modeling?

“You know it when you see it”

But

Is ‘seeing it’ enough??

(Report from CNS 2011 workshop in Stockholm)

James M. Bower, UTHSCSA; UTSA

Ilya Rybak, Drexel University

1st NIBIB MSM review panel meeting

Nov. 17, 2011

“What constitutes a multi-scale model?”

“What does model availability mean?”

General question: “how to review complex multi-scale proposals?”

20th CNS Meeting in Stockholm, 2011

1st IMAG Computational Neuroscience Working group Workshop:

Multi-Scale Modeling in Computational Neuroscience: Challenges and Opportunities

Organizers:

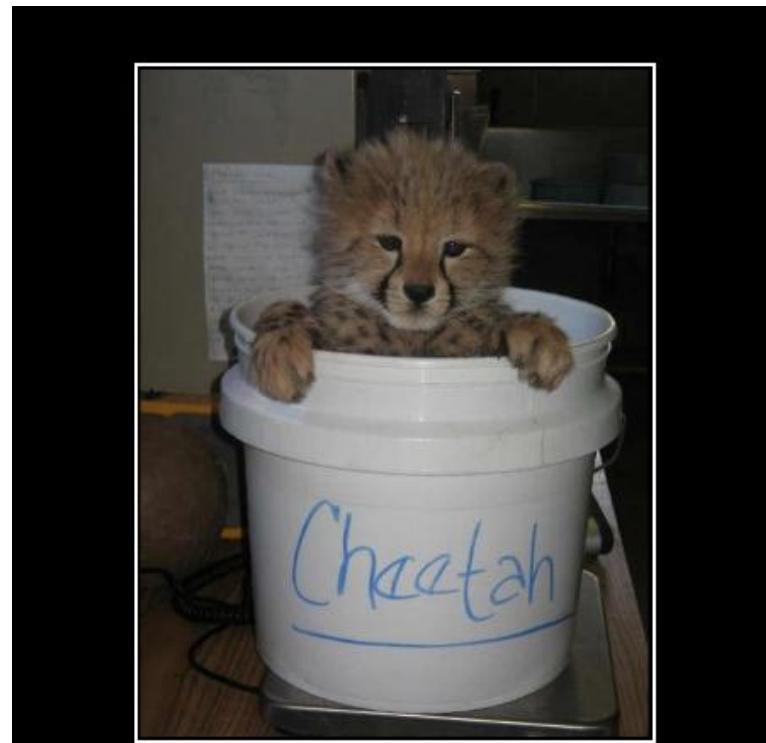
James M. Bower, UTSA

Ilya Rybak, Drexel University



Principle conclusion from Stockholm:

“We need a taxonomy of models”



ALL BUCKETS MUST
BE CLEARLY LABELED

JOANNA'S CHEESEBURGER.COM © OSHA demands it

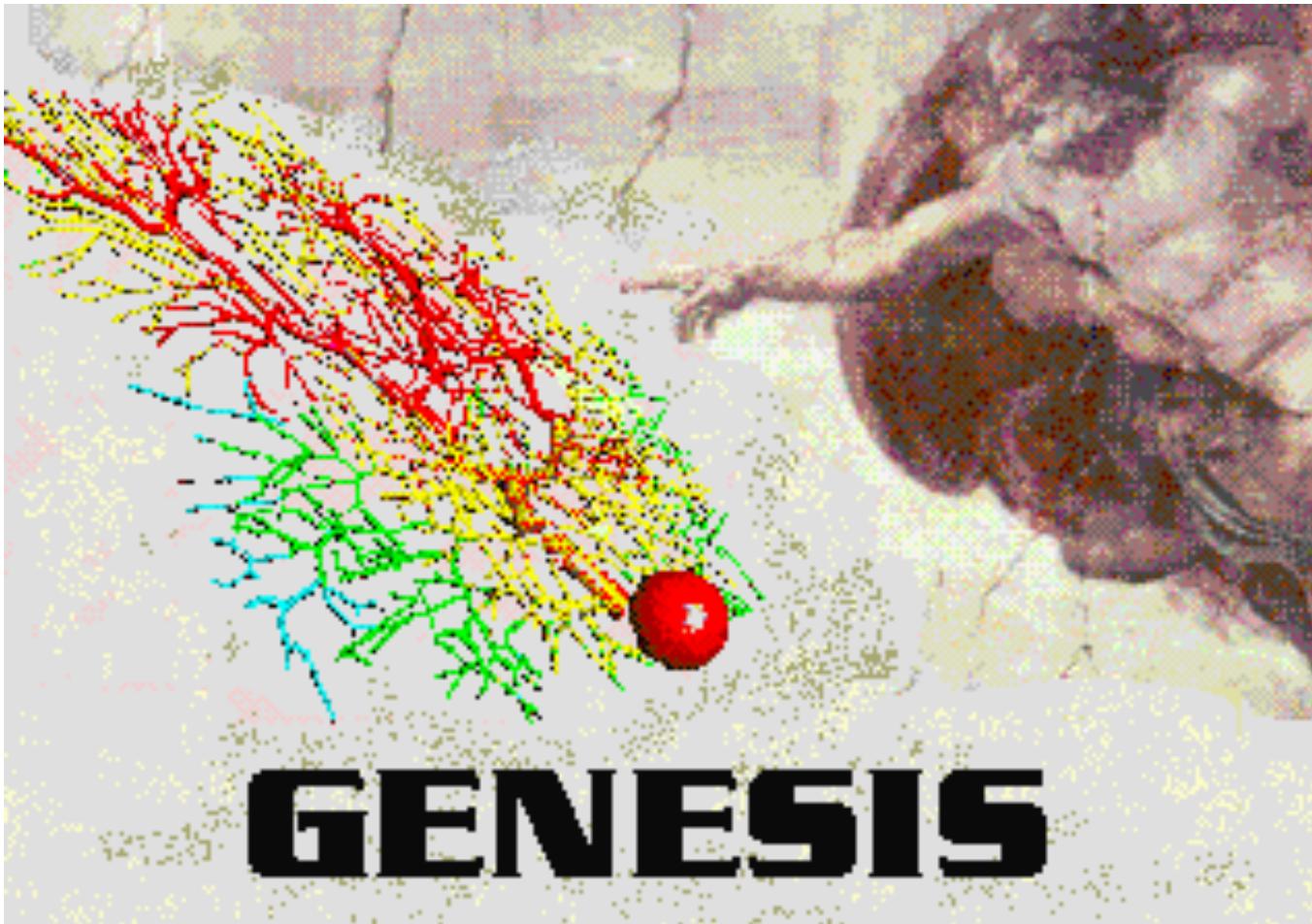
“OSHA
demands”

Caveat: GENESIS: “Name the Animals”



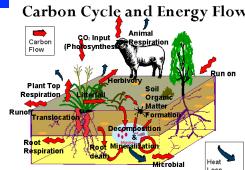
(Human (academic) tendency)

Advertisement: Name the Models

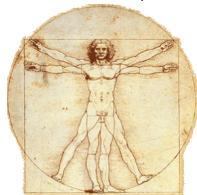


G3

Ecology

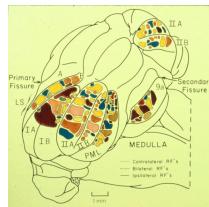


Behavior

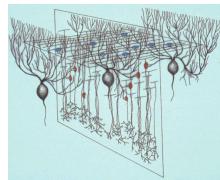


Many levels of biological scale

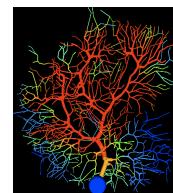
Systems



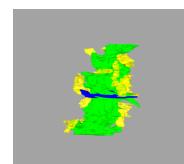
Network



Cellular

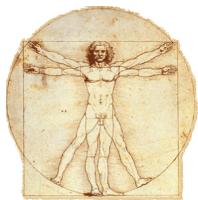


Subcellular

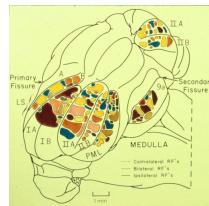


BIOLOGICAL SCALE

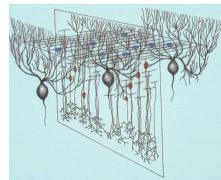
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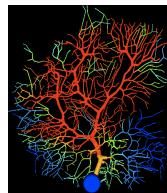
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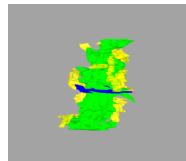
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Cellular



Subcellular



“Multi-?scale? modeling”

“Scale” = “Level”

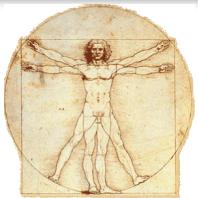
Model A

Model B

BIOLOGICAL SCALE

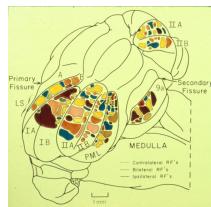
BIOLOGICAL DETAIL

Behavior



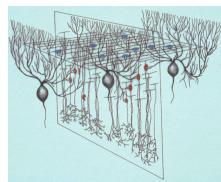
“Multi-?scale? modeling”

Systems

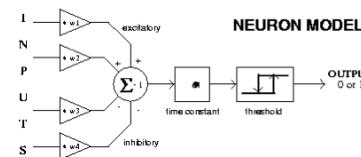
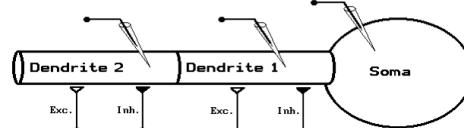
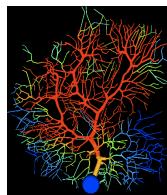


“Scale” = “Space / Time”

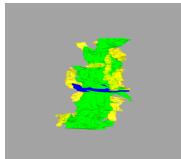
Network



Cellular



Subcellular

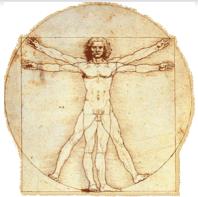


“Element complexity”

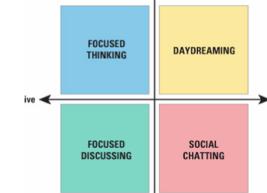
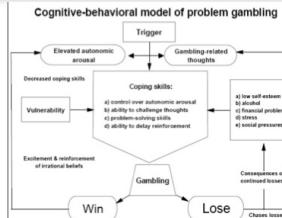
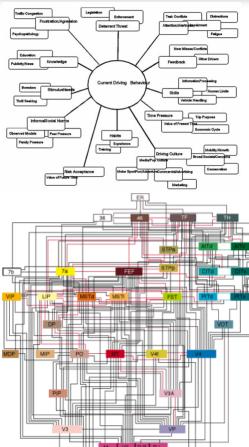
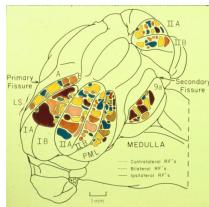
Applies to all biological levels

BIOLOGICAL SCALE

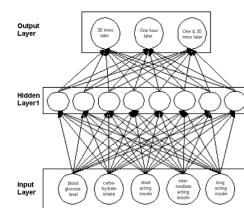
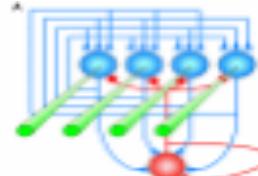
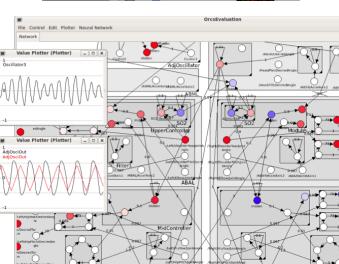
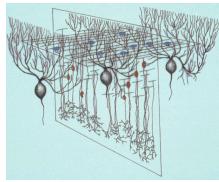
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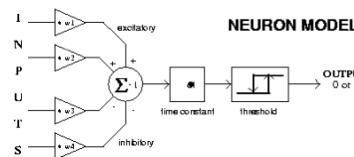
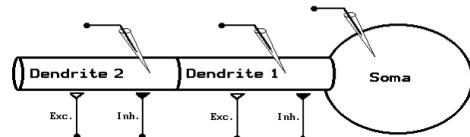
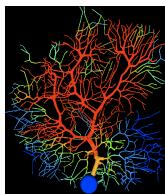
Systems



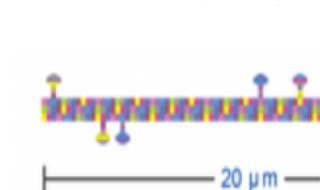
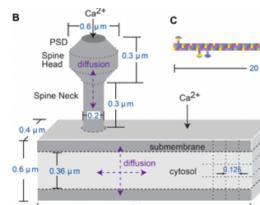
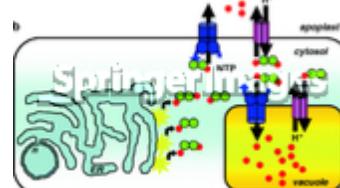
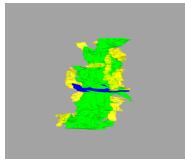
Network



Cellular

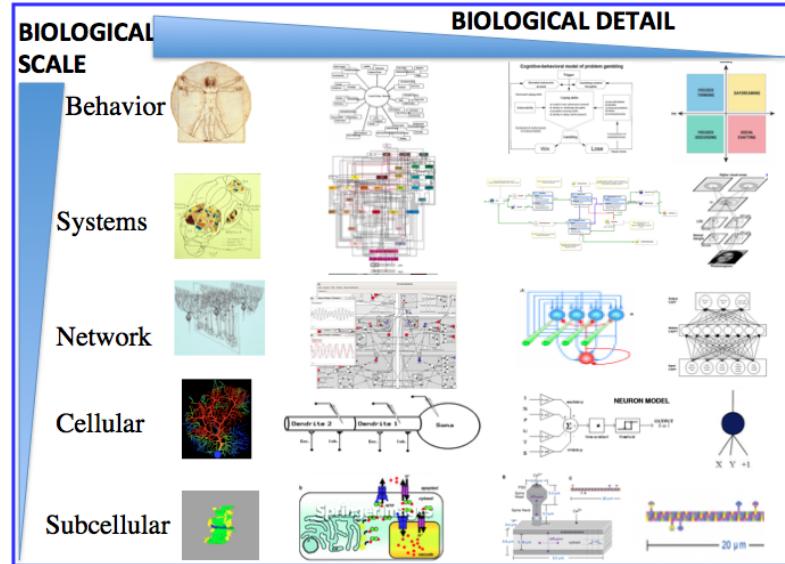


Subcellular



One application of a taxonomy:

A structure around which
to organize computational tools

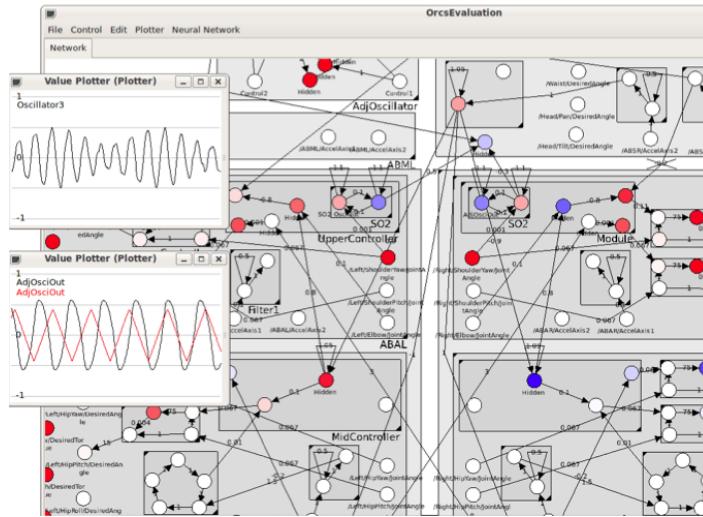


Different locations in the taxonomy differ in:

- Mathematical structures
- Computational requirements and tools
- Data structures and requirements
- Relationship to biological data and experiments
- Computational behavior
-

In neuroscience, perhaps biology as a whole: Taxonomy applies even within single models

Multi-scale (level and space/time) within single models

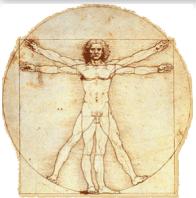


Lets Exercise the Taxonomy

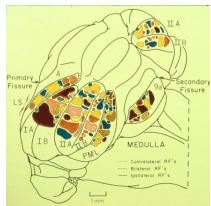
Especially at higher levels of biological scale

BIOLOGICAL SCALE

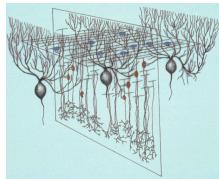
Behavior



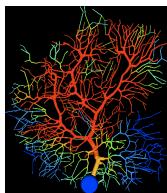
Systems



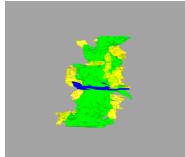
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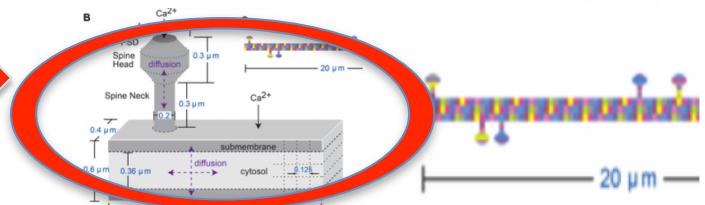
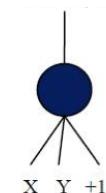
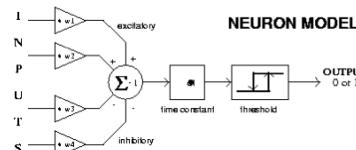
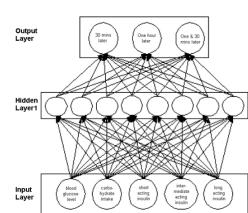
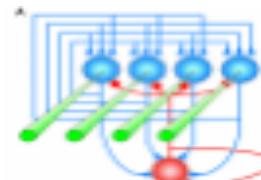
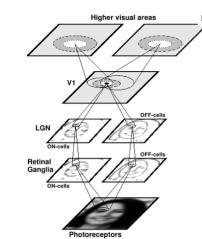
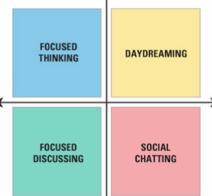
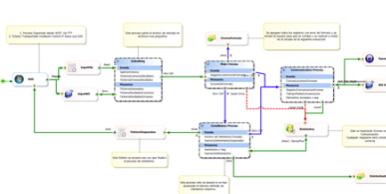
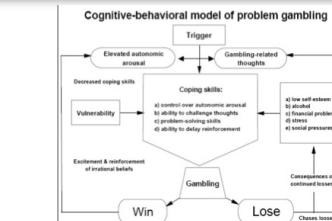
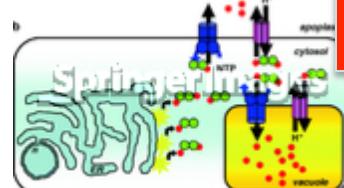
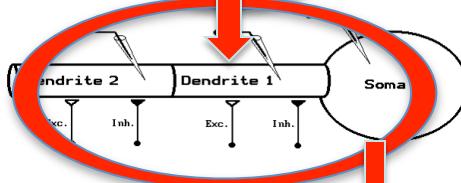
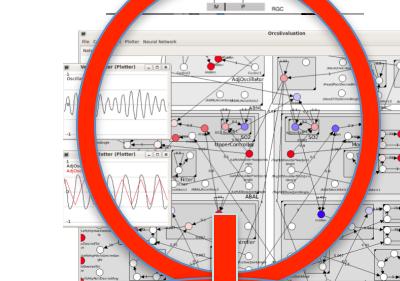
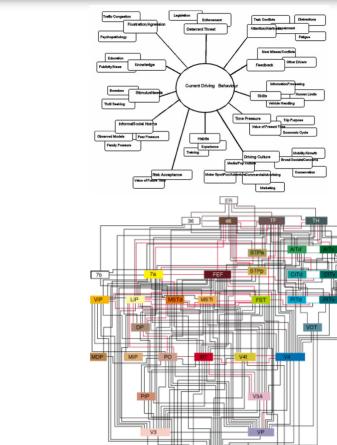
Cellular



Subcellular



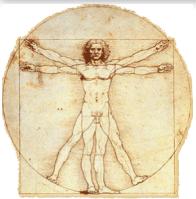
BIOLOGICAL DETAIL



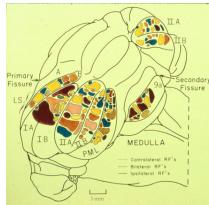
More loosely linked to higher levels

BIOLOGICAL SCALE

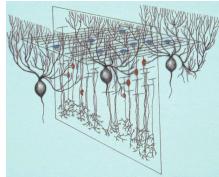
Behavior



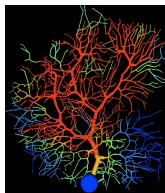
Systems



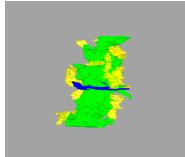
Network



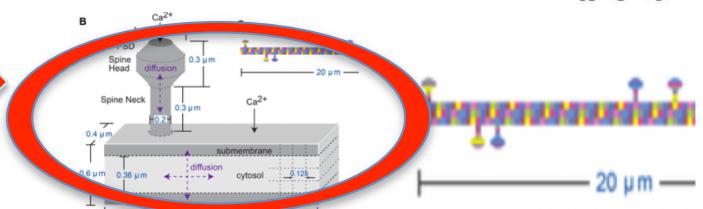
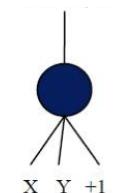
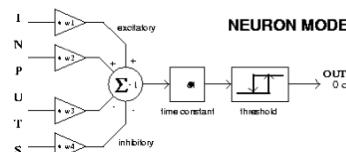
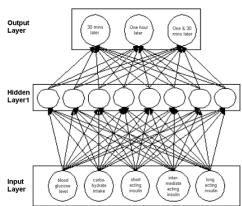
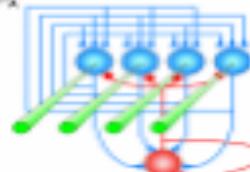
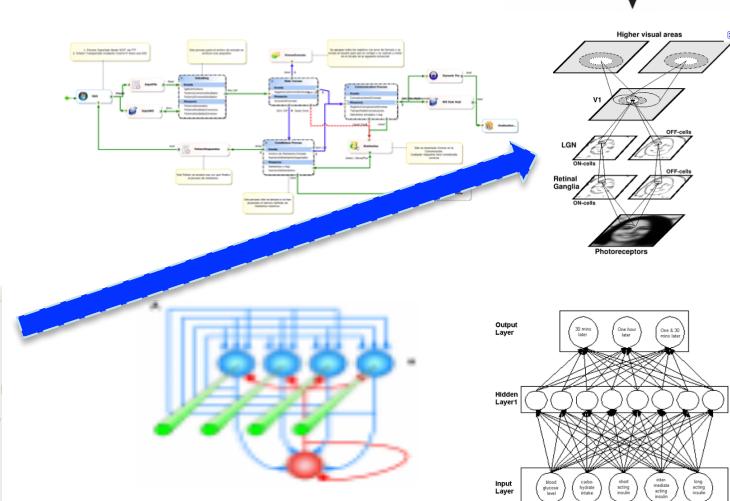
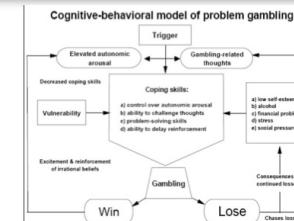
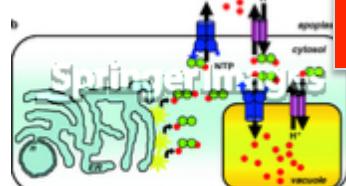
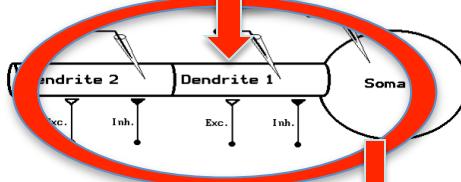
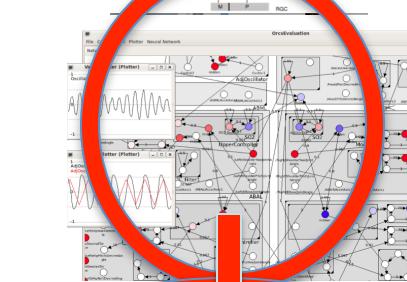
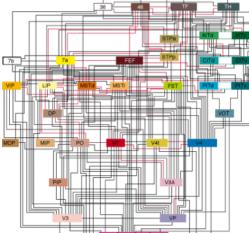
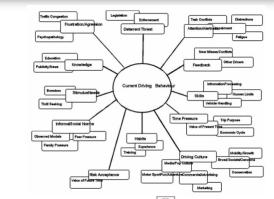
Cellular



Subcellular



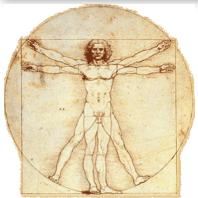
BIOLOGICAL DETAIL



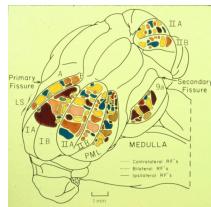
Value of taxonomy

BIOLOGICAL SCALE

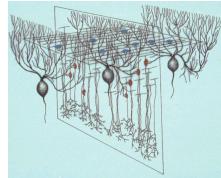
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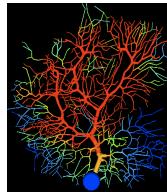
Systems



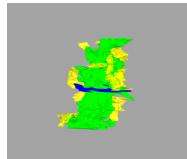
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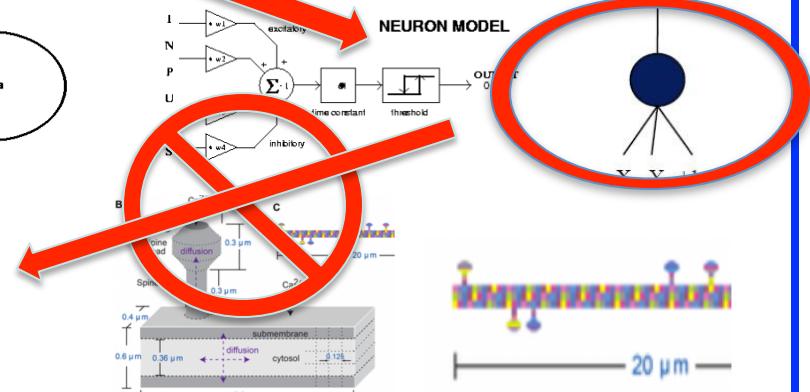
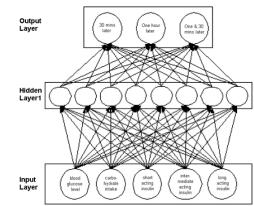
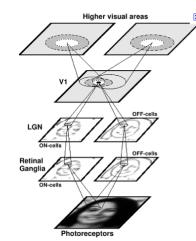
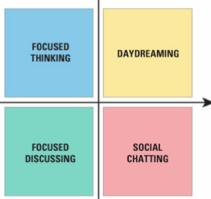
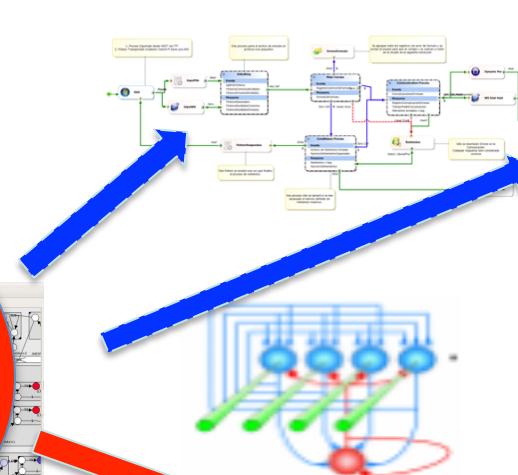
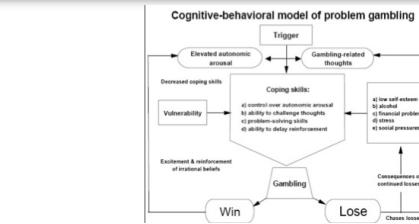
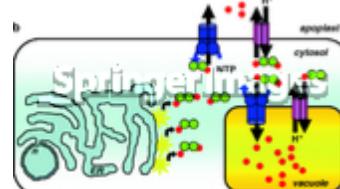
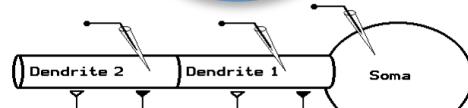
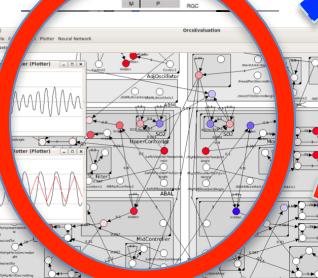
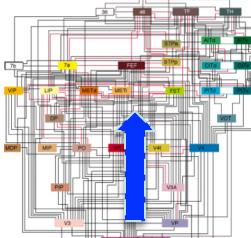
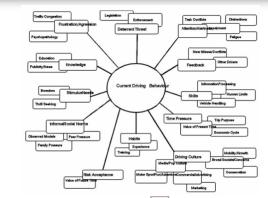
Cellular



Subcellular



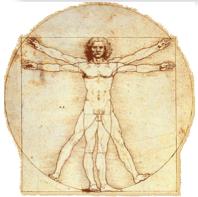
BIOLOGICAL DETAIL



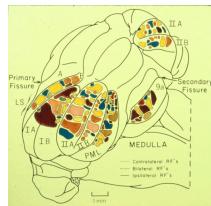
Value of taxonomy

BIOLOGICAL SCALE

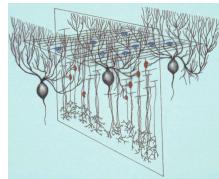
Behavior



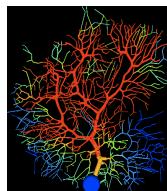
Systems



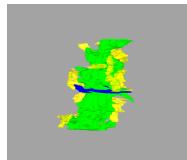
Network



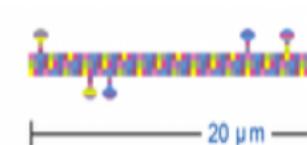
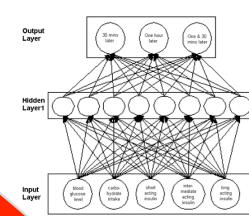
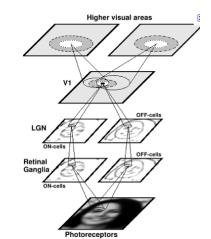
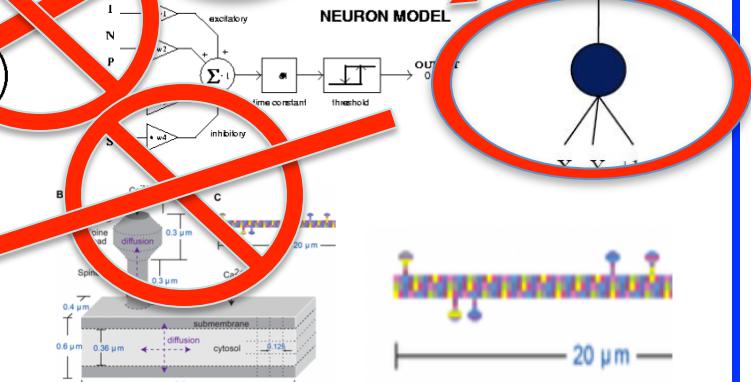
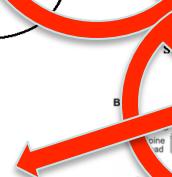
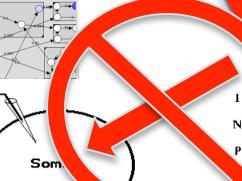
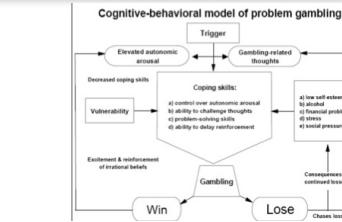
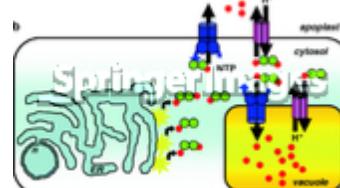
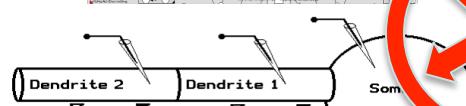
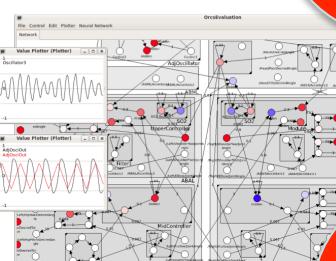
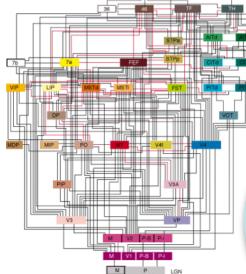
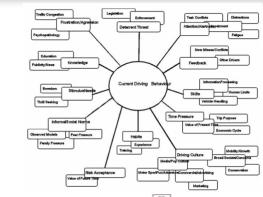
Cellular



Subcellular



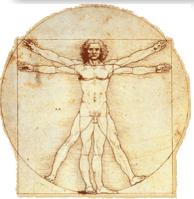
BIOLOGICAL DETAIL



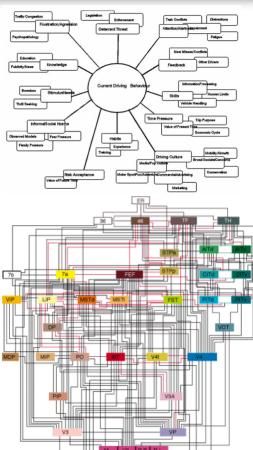
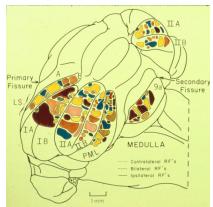
More to the right often excludes lower levels

BIOLOGICAL SCALE

Behavior

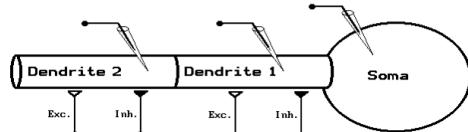
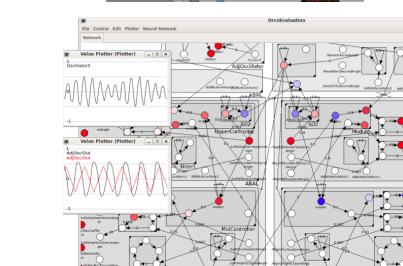
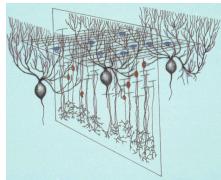


Systems

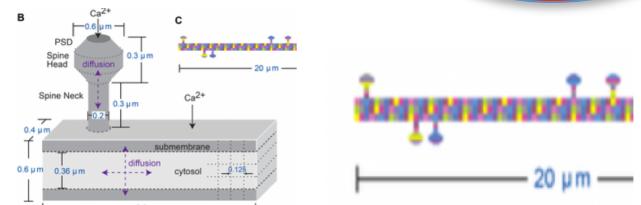
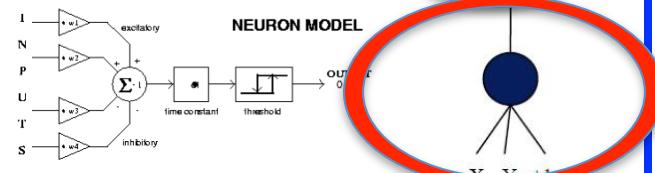
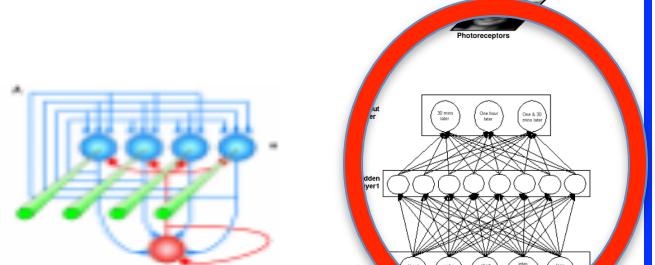
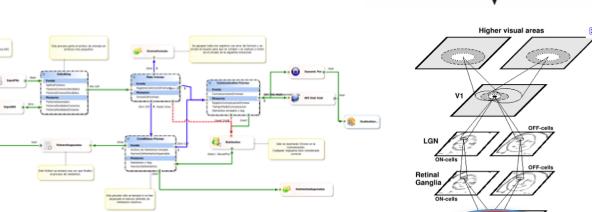
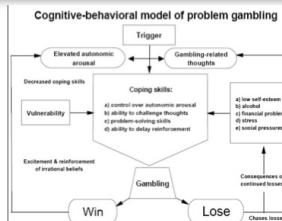
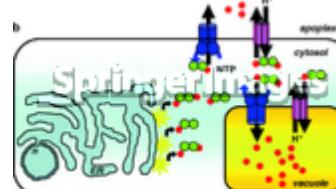
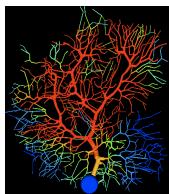


BIOLOGICAL DETAIL

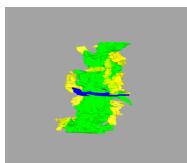
Network



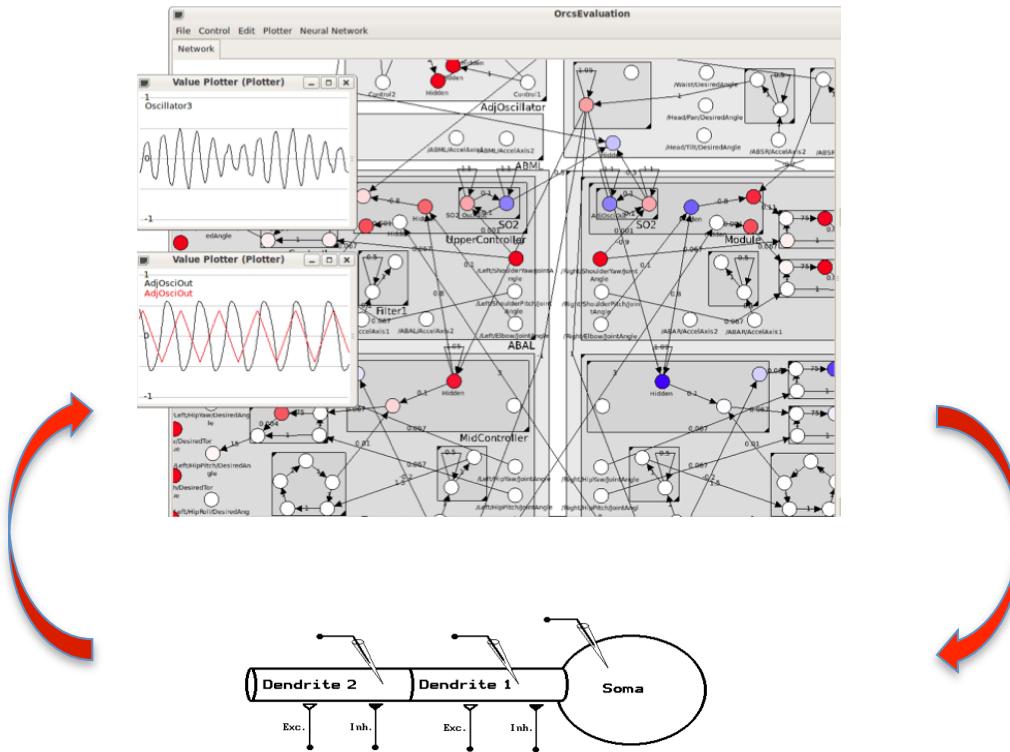
Cellular



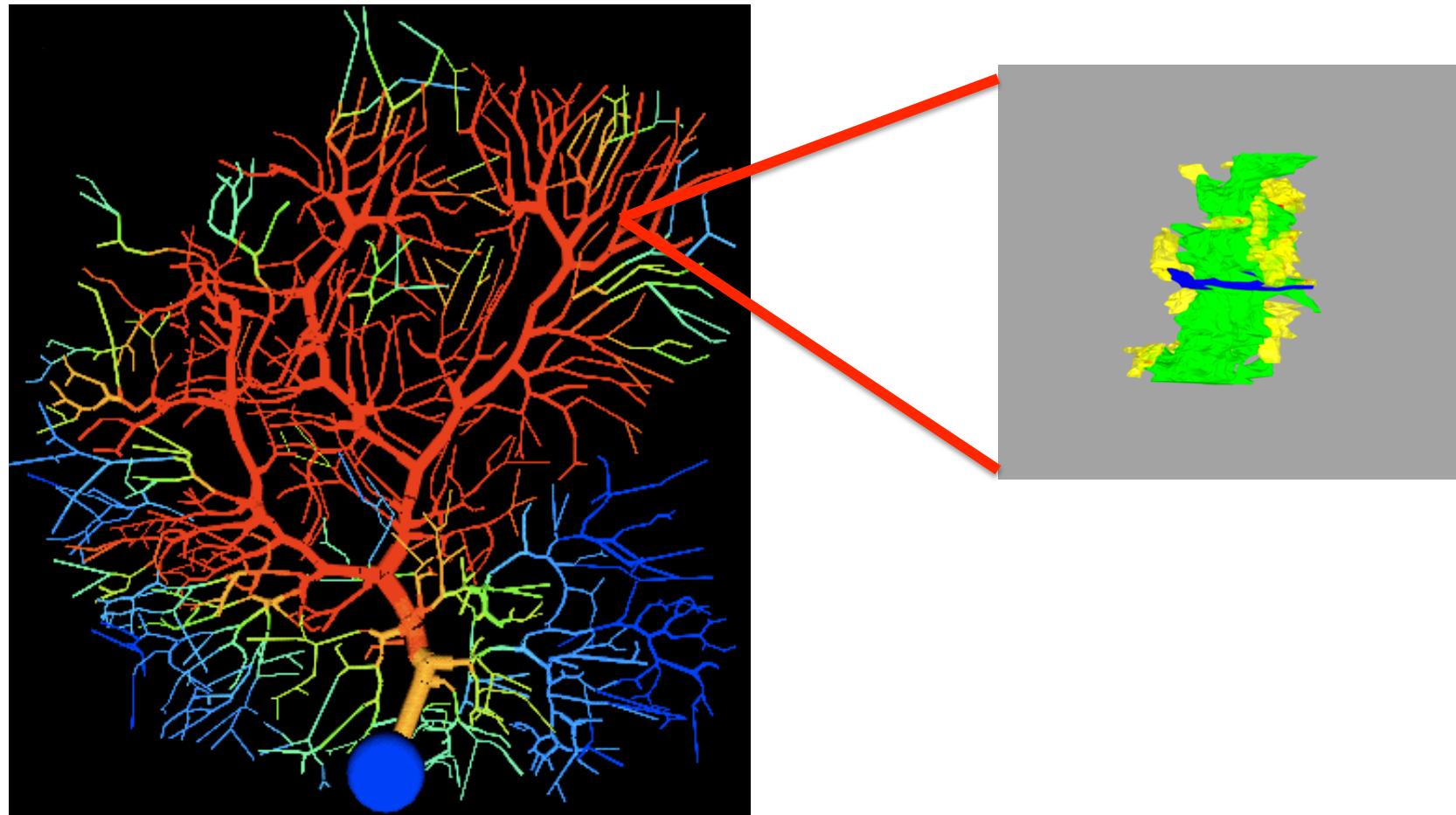
Subcellular



Multi-scale (level and space/time) in multiple articulated models

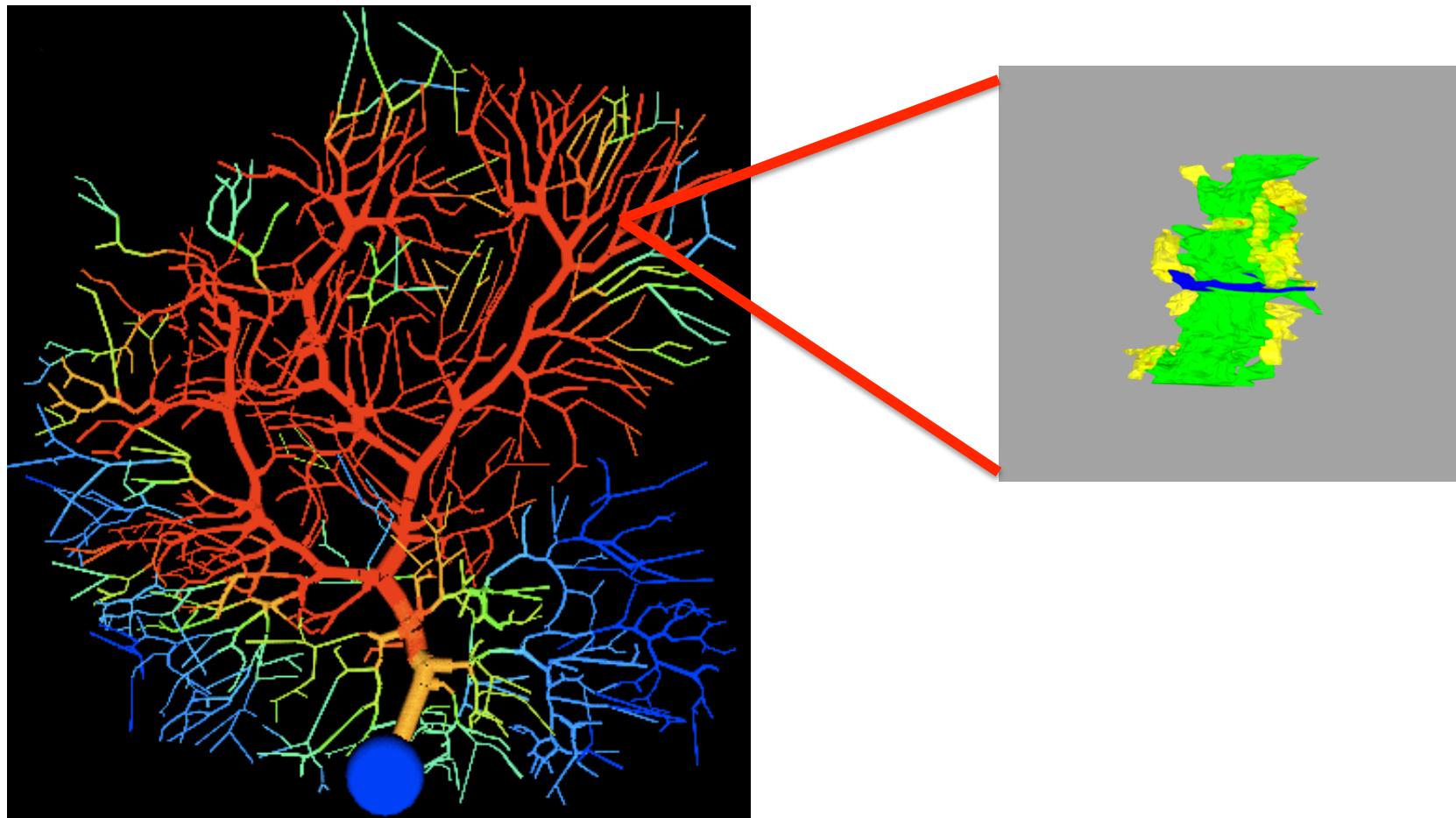


Embedded Scale Simulations



A significant current technical challenge:

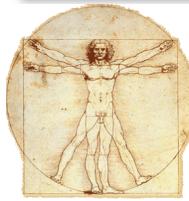
Because it mixes time and space



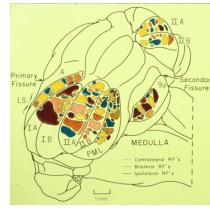
Switching articulation

BIOLOGICAL SCALE

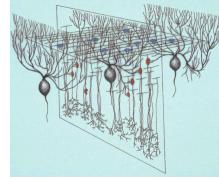
Behavior



System



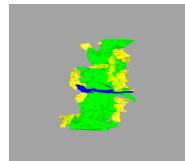
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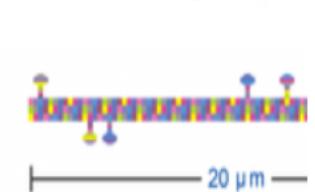
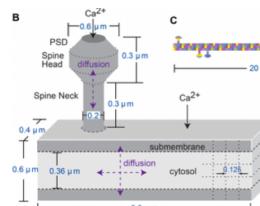
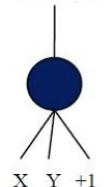
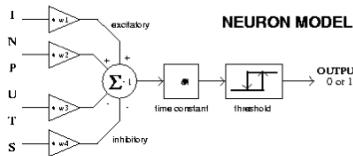
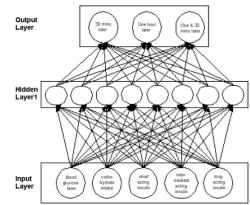
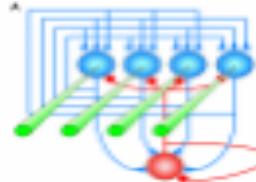
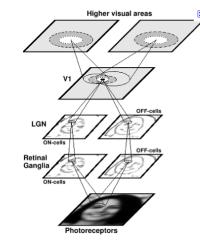
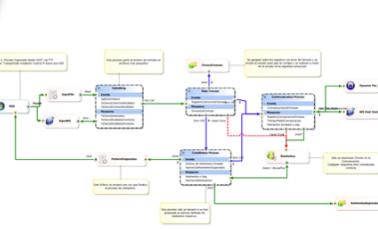
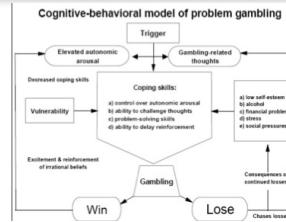
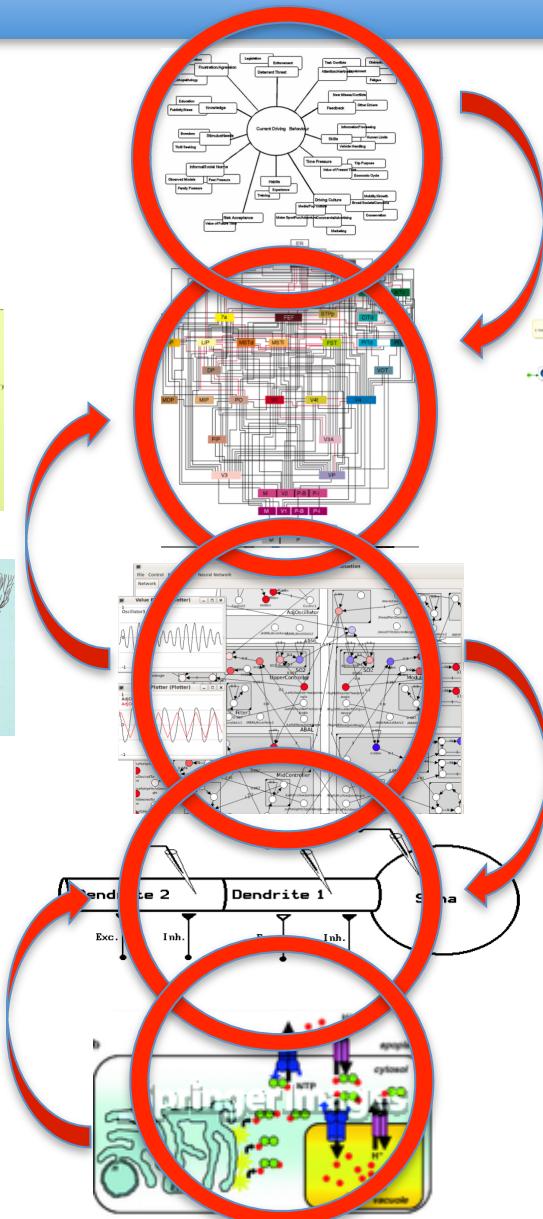
Cellular



Subcellular

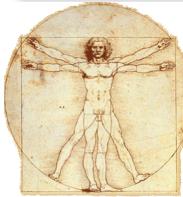


BIOLOGICAL DETAIL

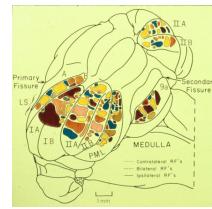


BIOLOGICAL SCALE

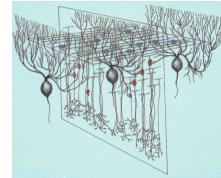
Behavior



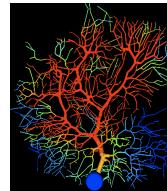
System



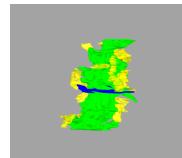
Network



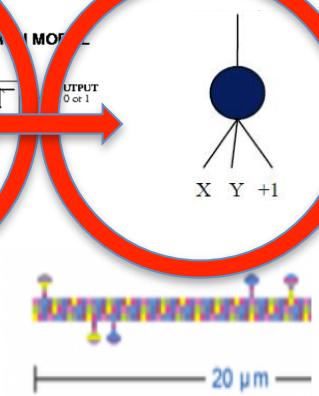
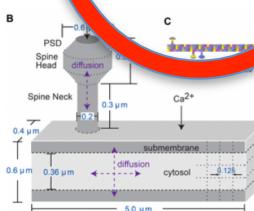
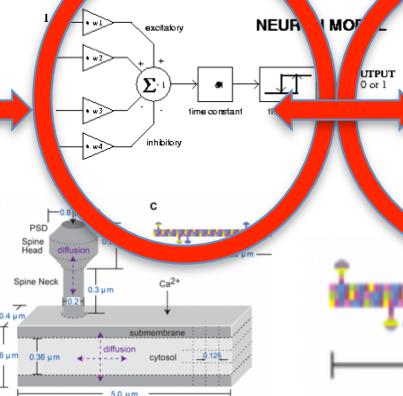
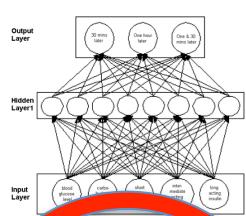
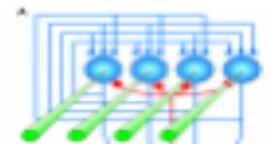
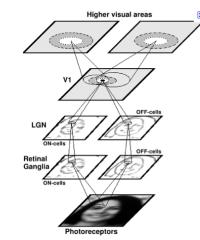
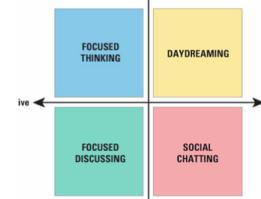
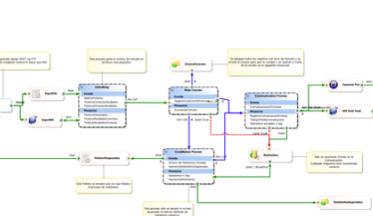
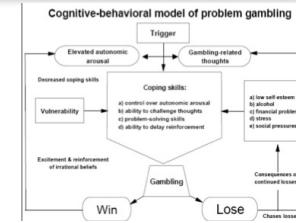
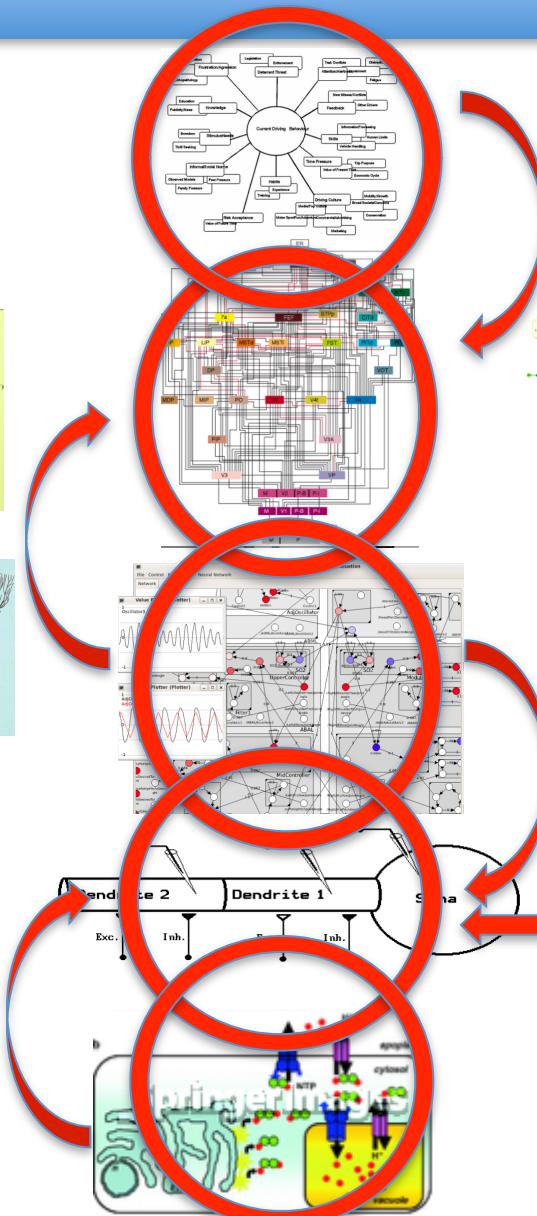
Cellular



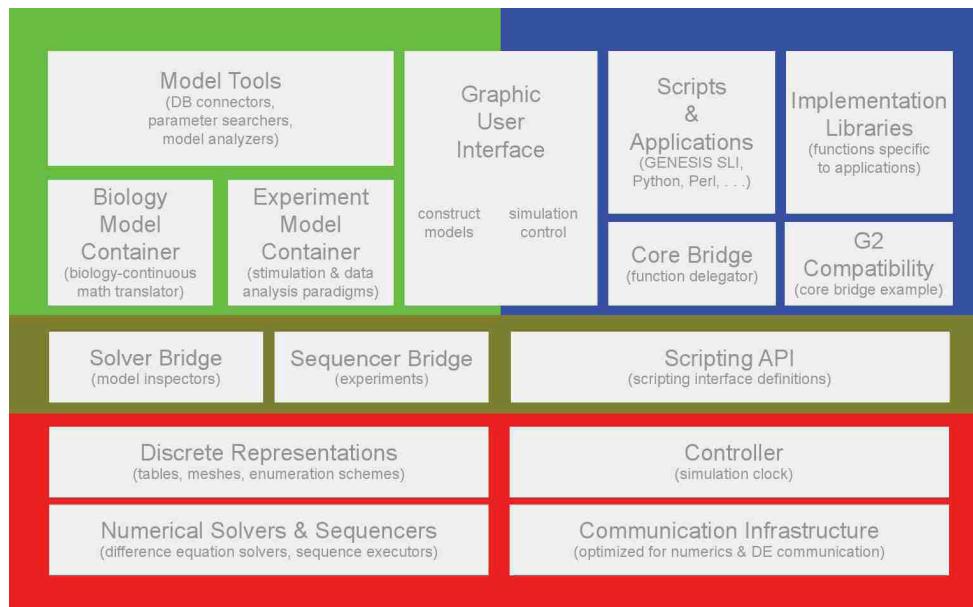
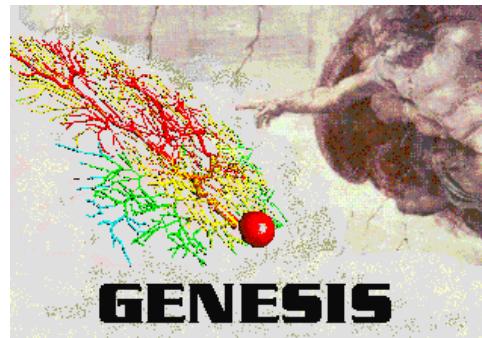
Subcellular



BIOLOGICAL DETAIL



Requires a simulation system with the right architecture



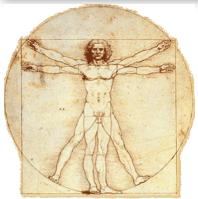
PONE-D-11-06475R1

A Federated Design for a Neurobiological Simulation Engine: The CBI federated software architecture.

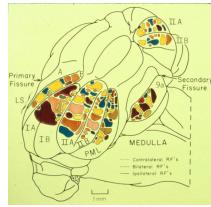
PLoS ONE

BIOLOGICAL SCALE

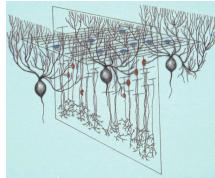
Behavior



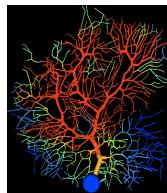
System



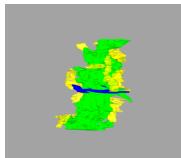
Network



Cellular



Subcellular



BIOLOGICAL DETAIL

Taxonomy

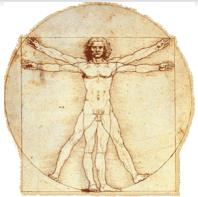
Used to organize:

- What type of model do you have?
- Computational requirements
- Appropriate data sources
- Appropriate experimental questions
- Simulators
- Federal funding opportunities:
 - Technical challenges
 - Holes in understanding
- What do you know?

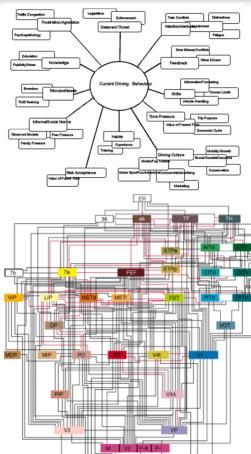
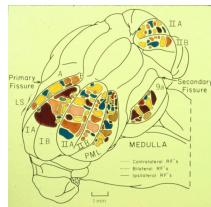
What constitutes “understanding”?

BIOLOGICAL SCALE

Behavior

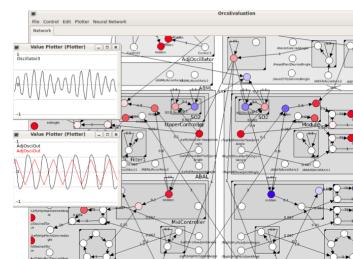
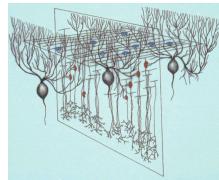


Systems

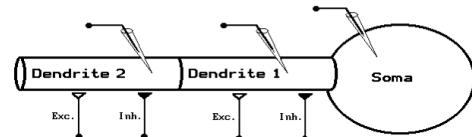
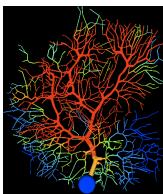


BIOLOGICAL DETAIL

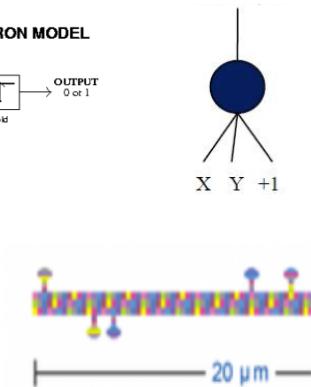
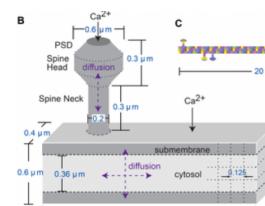
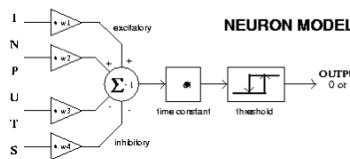
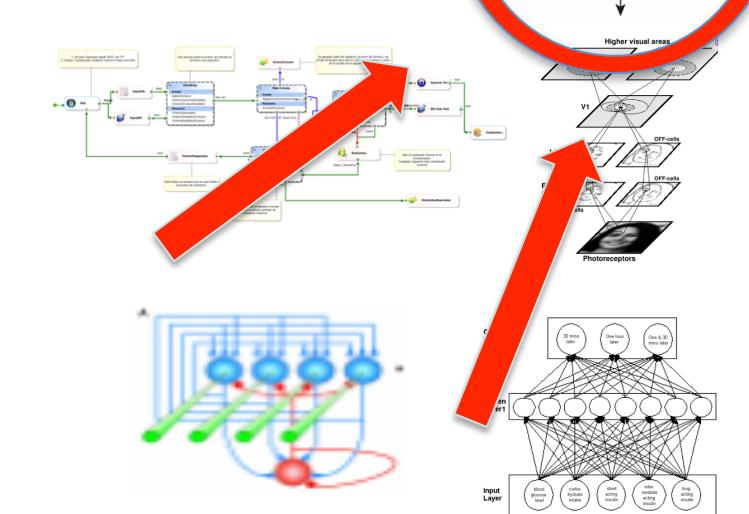
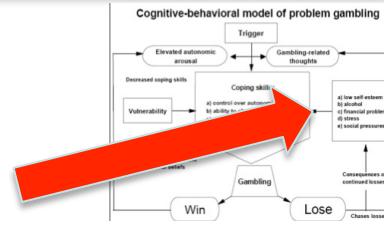
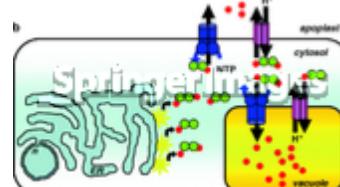
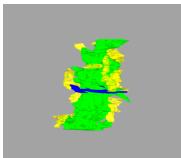
Network



Cellular



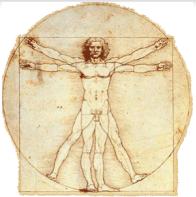
Subcellular



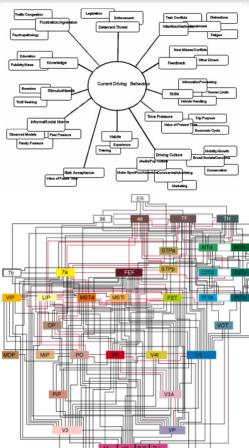
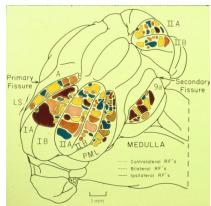
Where is most likely clinical intervention?

BIOLOGICAL SCALE

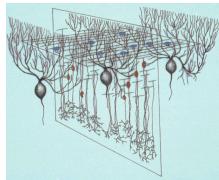
Behavior



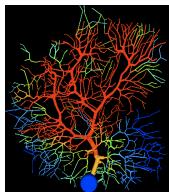
Systems



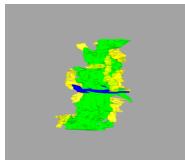
Network



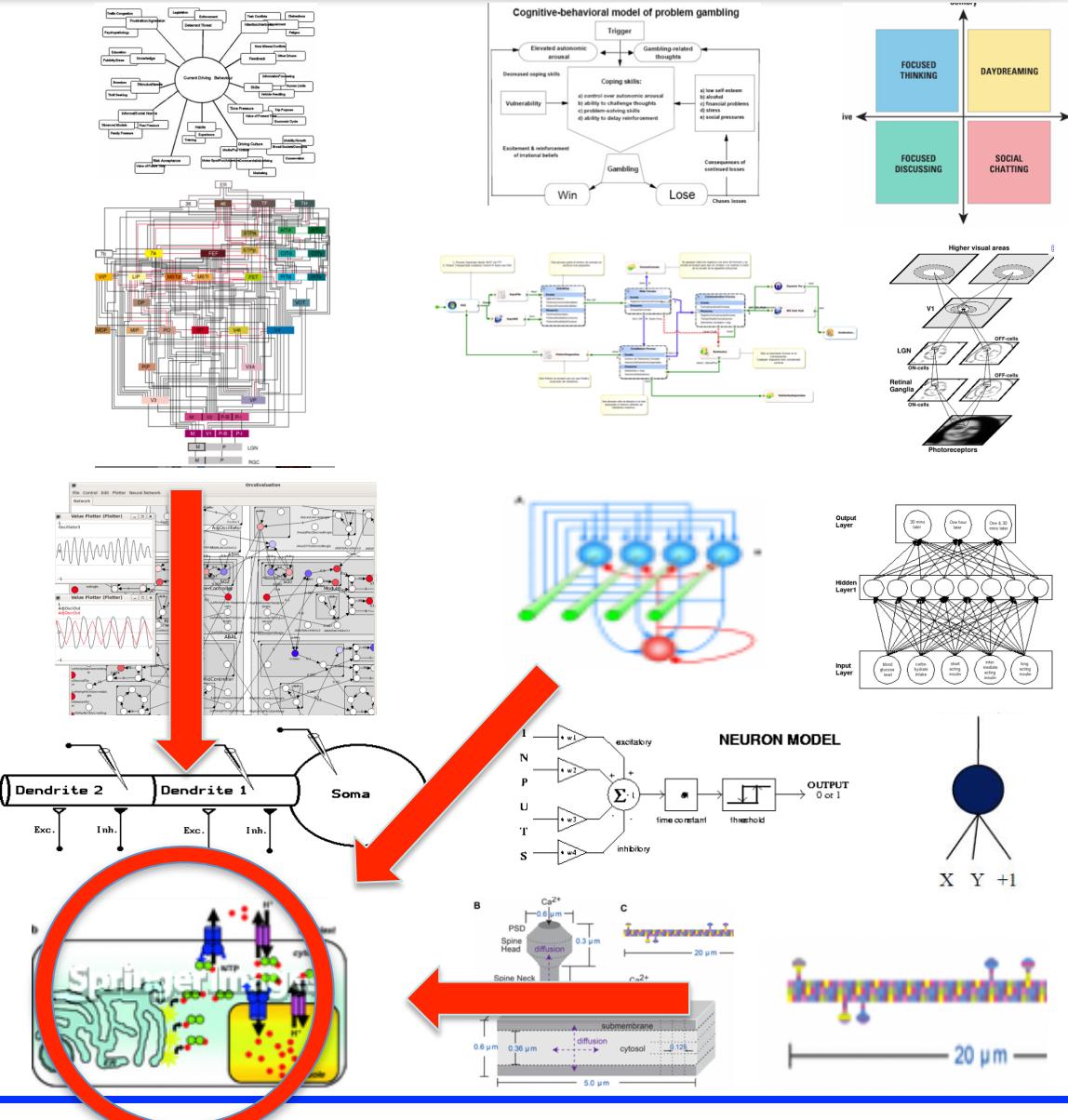
Cellular



Subcellular



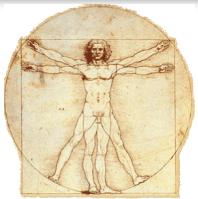
BIOLOGICAL DETAIL



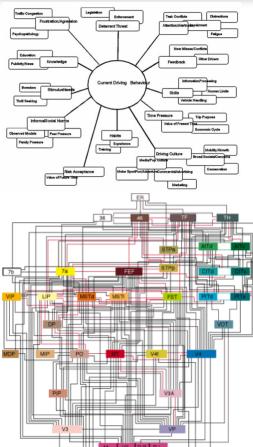
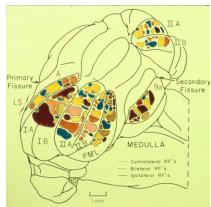
Likely ultimate outcome?

BIOLOGICAL SCALE

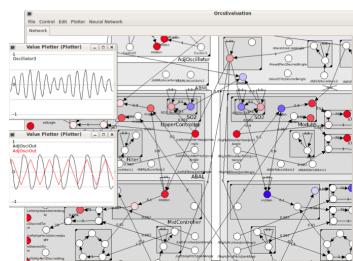
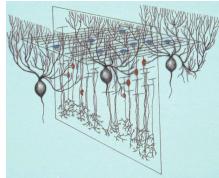
Behavior



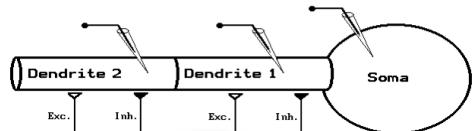
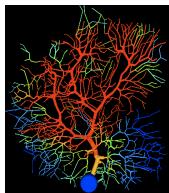
Systems



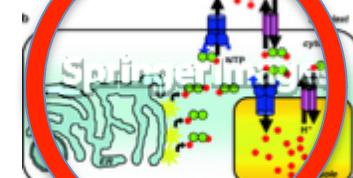
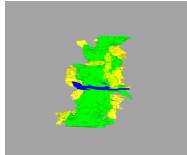
Network



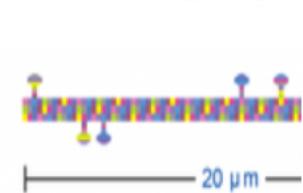
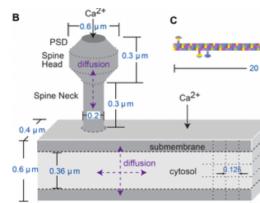
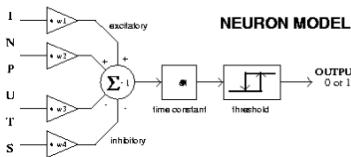
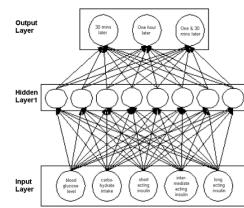
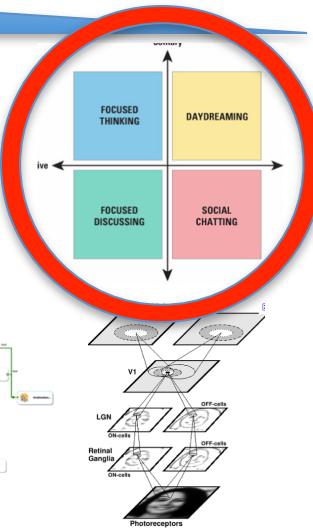
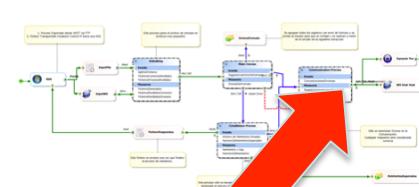
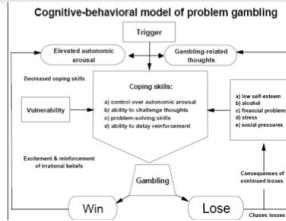
Cellular



Subcellular



BIOLOGICAL DETAIL



Then what are we really about?

“Building a quantitative infrastructure for biological science that captures what we currently know and don’t know and informs us what to do next”

“Using this quantitative infrastructure to link multiple kinds of expertise into a coherent enterprise”

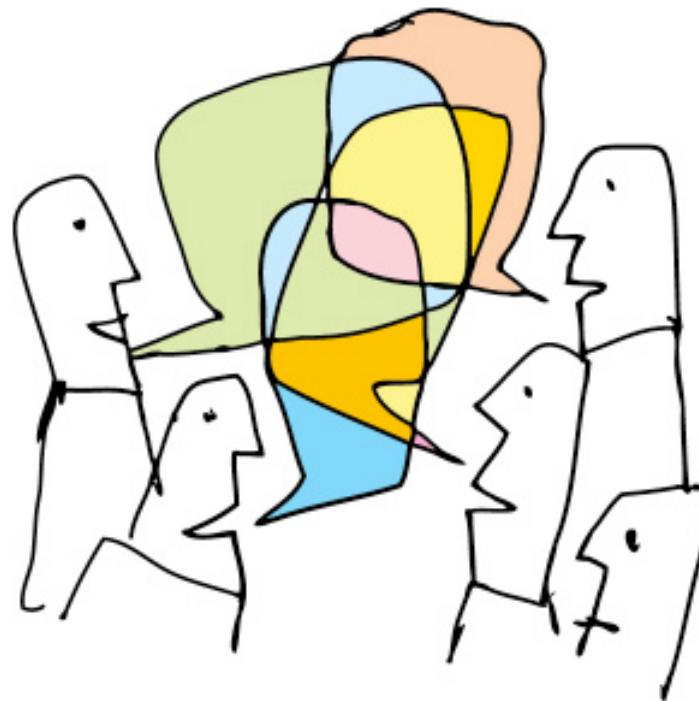
“Have a taxonomy of models will be critical”

“Making biology into a science”

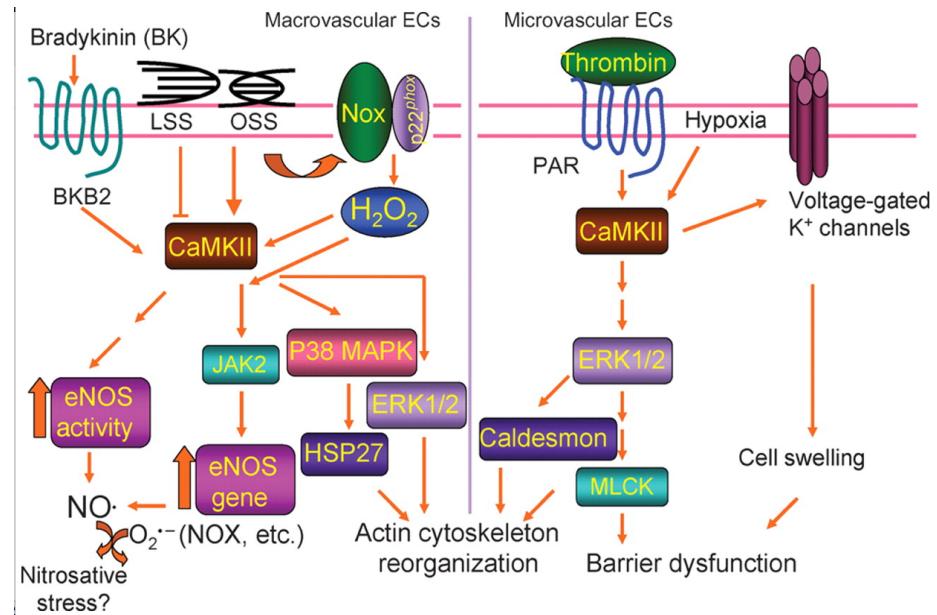
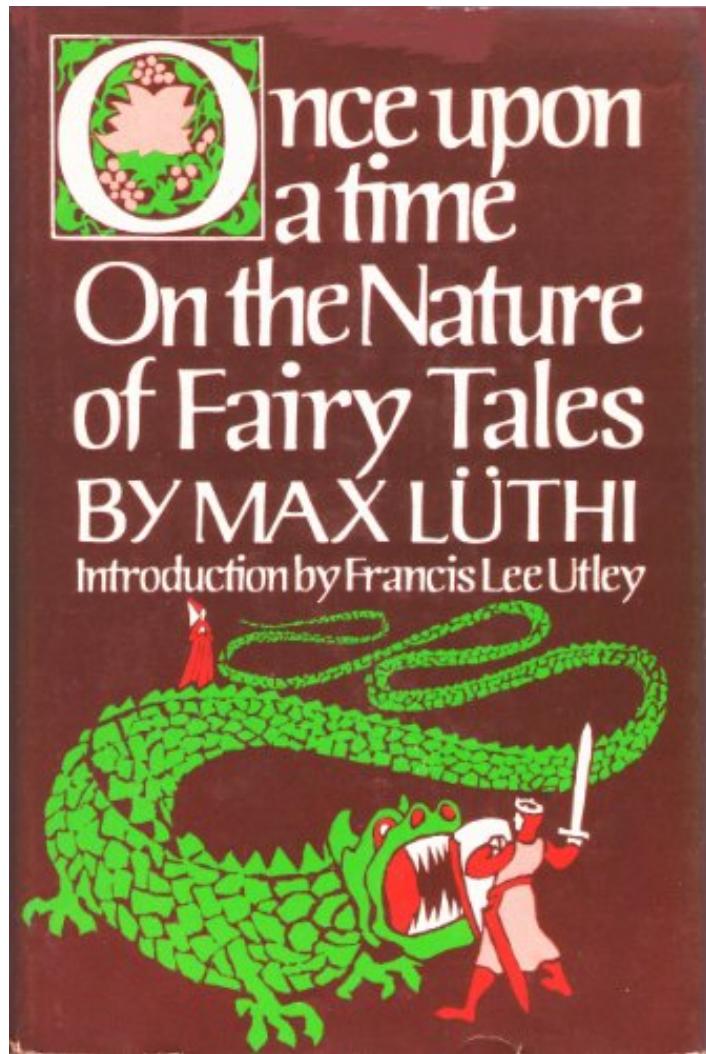
The Tower of IMAG

IMAG

How do we communicate now?



We tell stories



This is not a “model” this is a story
“no numbers, no model”

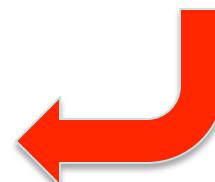
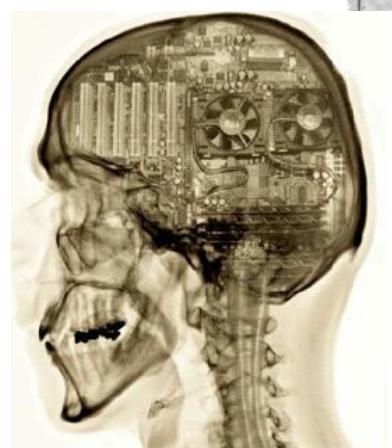
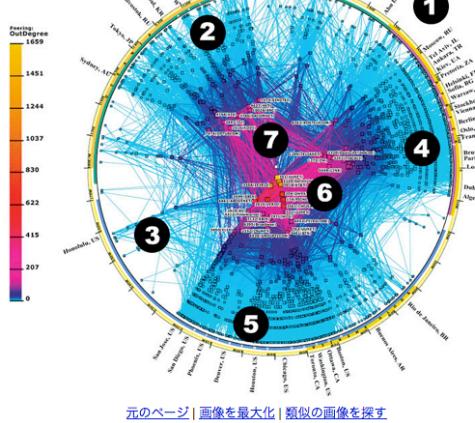
WE USE METAPHORES

THE BRAIN IS:

Humors flowing in aqueducts?

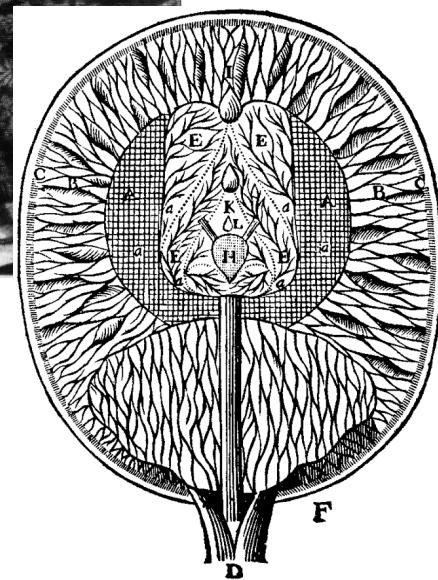


A mechanical machine



A connected cloud

A digital computer

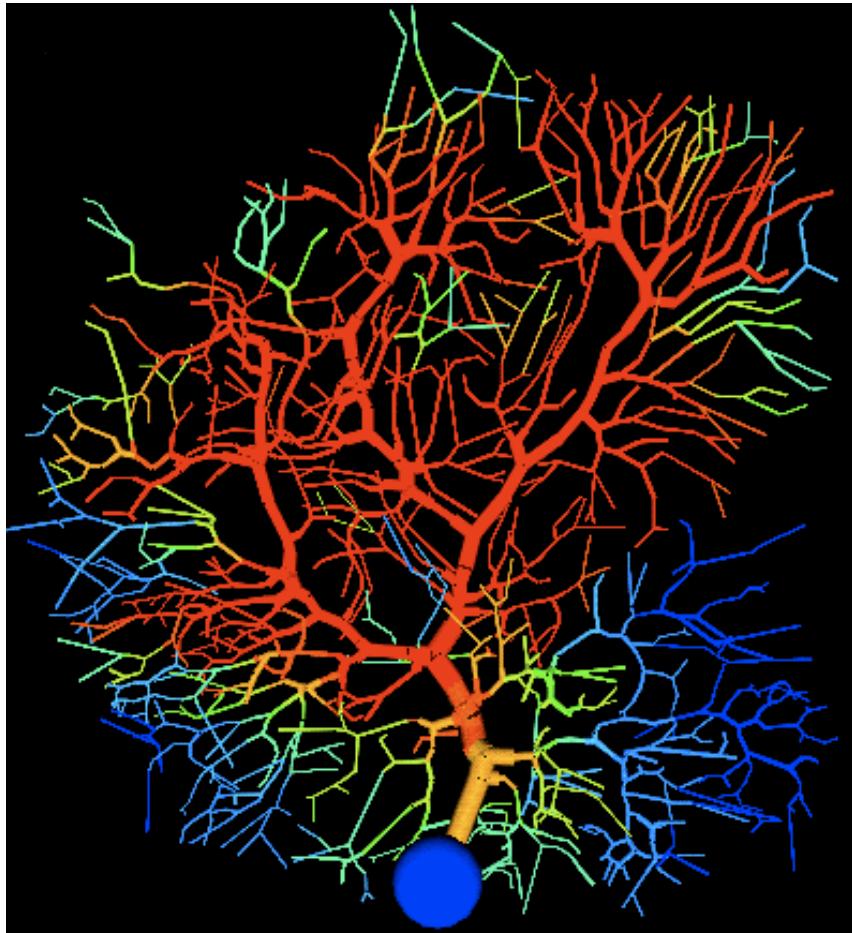


Neurobiological Metaphors

- “Synaptic Integration”
- “Connectome”
- “Cortical column”
- “Plasticity”
- “Synchronous”
- “Model”
- “Multi-scale”

This structure is not metaphorical:

Total number of coupled equations: 25,471



4,548 rows in a sparse matrix

1600 morphology compartments,
two compartments for each of the 1474 spines

Combined using Crank-Nicolson integration with:

16,039 ODEs for voltage gated channels

soma: 13 voltage gates
9 main dendritic compartments: 14 voltage gates each
105 smooth dendritic compartments: 10 voltage gates each
1485 spiny dendritic compartments: 10 voltage gates each

1,600 exponential decay equations for Ca concentration
one per reconstructed morphology compartment

1,474 second order ODEs for ligand gated channels

one parallel fiber per spine

10 second order ODEs for ligand gated channels

one basket axon per main dendritic compartment + soma

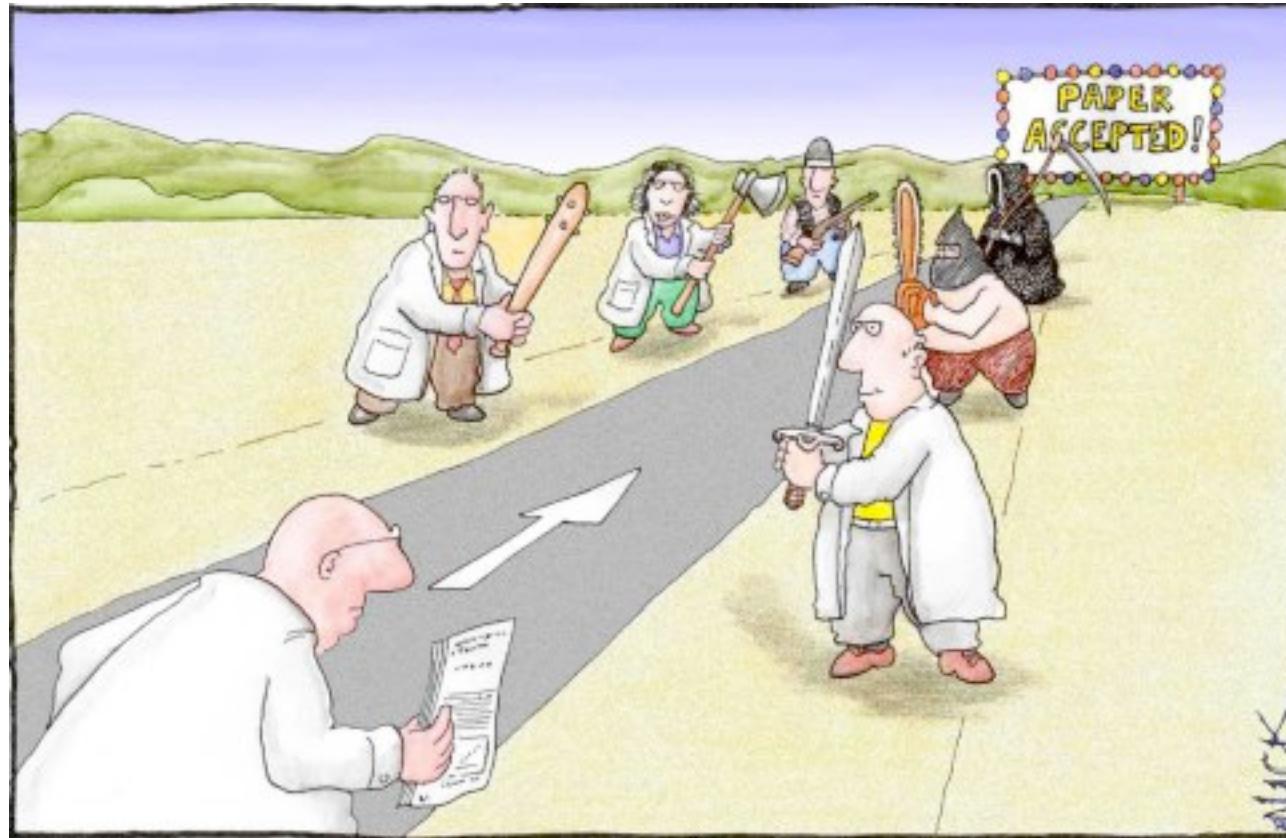
1,695 second order ODEs for ligand gated channels

two stellate axons per smooth dendritic compartment
one stellate axon per spiny dendritic compartment

105 second order ODEs ligand gated channels

one climbing fiber synapse per smooth dendr. comp.

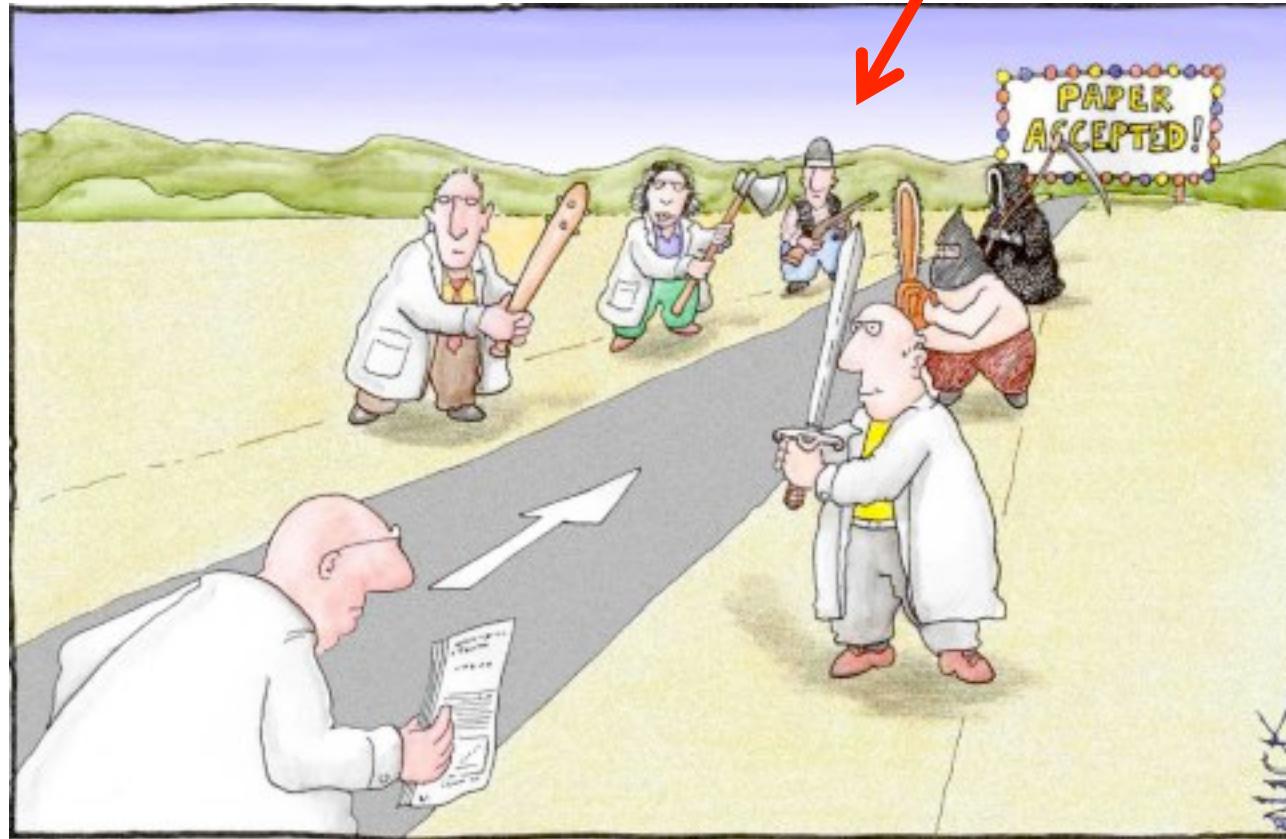
How do we evaluate?



Peer Review

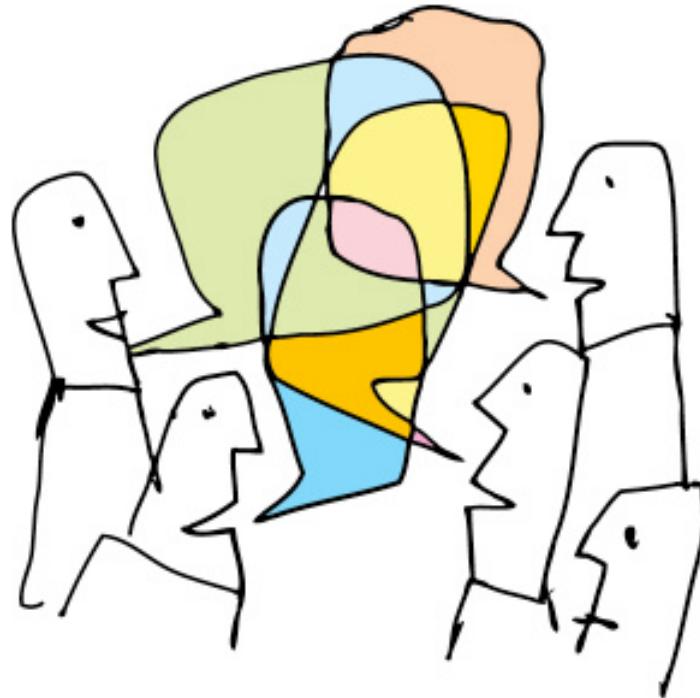
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The enforcer



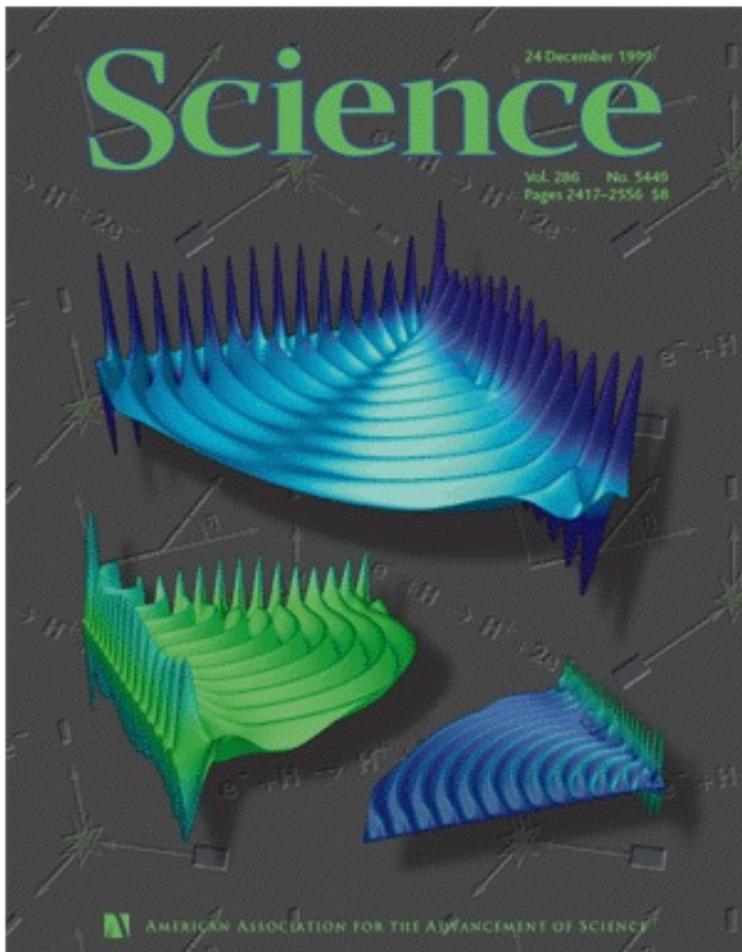
"What would happen if an innocent graduate student read this"

Where do we communicate?



“the medium is the message”

Scientific papers



Current System

- **Paper descriptions of models:**
 - Can't replicate based on methods
 - Can't review except phenomenologically
 - Figures often from different versions of the model
 - Models can't propagate / improve
 - No way to quantitatively measure progress in the field
- **Publish models after the fact in databases:**
 - Notoriously hard to re-use or understand
 - Often not the model that generated the paper
 - Without associated data
 - Without lineage
 - Motivation ??

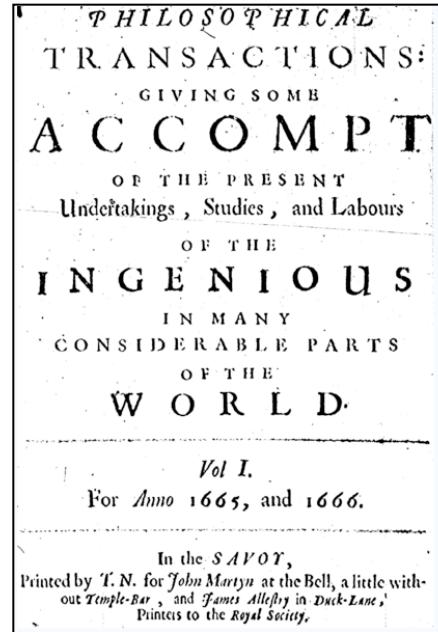
Printing Press



Why a scientific
Paper?

A Solution for Physics

350 years ago



“In the 1660s, the Royal Society’s founders met regularly to discuss scientific ideas and perform experiments; the outcomes of their experiments and discussions were recorded in the Society’s Transactions. These activities, pioneered by the Society, remain the accepted procedures whereby scientific ideas are criticized, refined and codified into publications that become part of ‘public knowledge’.

Martin Rees

“public knowledge”

(3075)

Numb. 80.

PHILOSOPHICAL TRANSACTIONS.

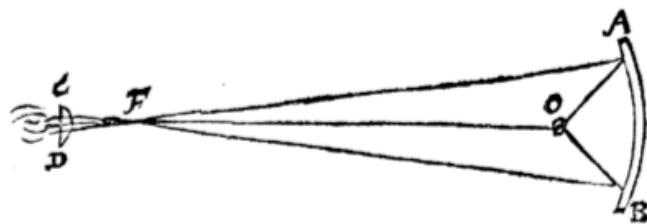
February 19. 1671.

C.

THE CONTENTS.

A Letter of Mr. Isaac Newton, Mathematick Professor in the University of Cambridge; containing his New Theory about Light and Colors: Where Light is declared to be not Similar or Homogeneal, but consisting of dissimil. rays, some of which are more refrangible than others: And Colors are affirm'd to be not Qualifications of Light, deriv'd from Refractions of natural Bodies, (as 'tis generally believed;) but Original and Connate properties, which in divers rays are divers: Where several Observations and Experiments are alledged to prove the said Theory. An Accomp't of some Books: I. A Description of the EAST-INDIAN COASTS, MALABAR, COROMANDEL, CEYLON, &c. in Dutch, by Phil. Baldæus. II. Antonii le Grand INSTITUTIO PHILOSOPHIÆ, secundum principia Renati Des-Cartes; novâ methodo adornata & explicata. III. An Essay to the Advancement of MUSICK; by Thomas Salmon M.A. Advertisement about Thæon Smyrnaeus. An Index for the Translations of the Year 1671.

A Letter of Mr. Isaac Newton, Professor of the Mathematicks in the University of Cambridge; containing his New Theory about Light and Colors: sent by the Author to the Publisher from Cambridge, Febr. 6. 1671; in order to be communicated to the R. Society.



Isaac Newton
1667

“public knowledge”

(3075)

Numb. 80.

PHILOSOPHICAL TRANSACTIONS.

February 19. 1671.

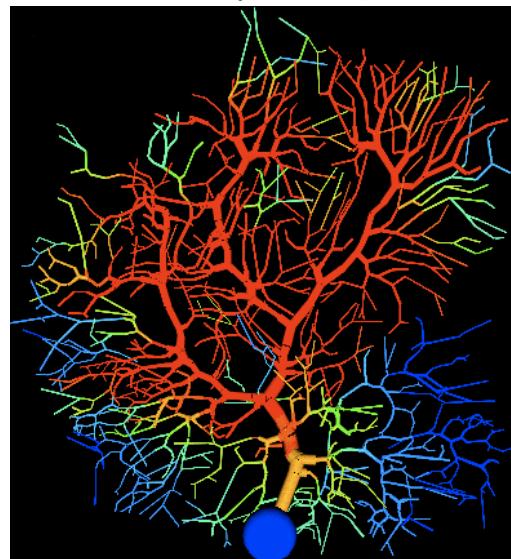
C.

THE CONTENTS.

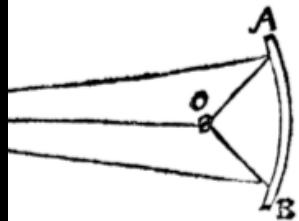
A Letter of Mr. Isaac Newton, Mathematick Professor in the University of Cambridge; containing his New Theory about Light and Colors: Where Light is declared to be not Similar or Homogeneal, but consisting of dissimil. rays, some of which are more refrangible than others: And Colors are affirm'd to be not Qualifications of Light, deriv'd from Refractions of natural Bodies, (as 'tis generally believed;) but Original and Connate properties, which in divers rays are divers: Where several Observations and Experiments are alledged to prove the said Theory. An Accomp't of some Books: I. A Description of the EAST-INDIAN COASTS, MALABAR, COROMANDEL, CEYLON, &c. in Dutch, by Phil. Baldæus. II. Antonii le Grand INSTITUTIO PHILOSOPHIÆ, secundum principia Renati Des-Cartes; novâ methodo adornata & explicata. III. An Essay to the Advancement of MUSICK; by Thomas Salmon M.A. Advertisement about Thæon Smyrnaeus. An Index for the Translations of the Year 1671.



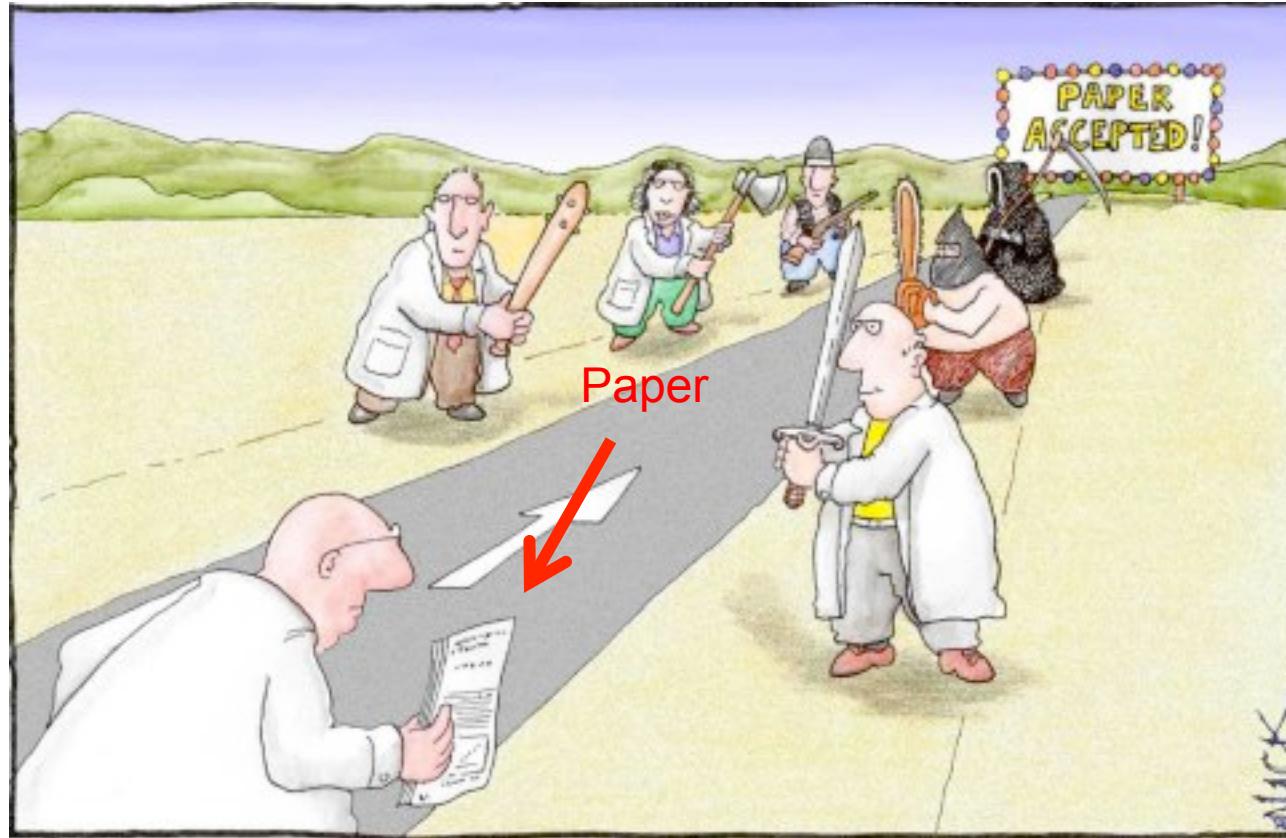
Isaac Newton
1667



Professor of the Mathematicks in the University of Cambridge; containing his New Theory about Light and Colors. Published from Cambridge, Febr. 6. 1671. Presented to the R. Society.



~~PROCESS~~

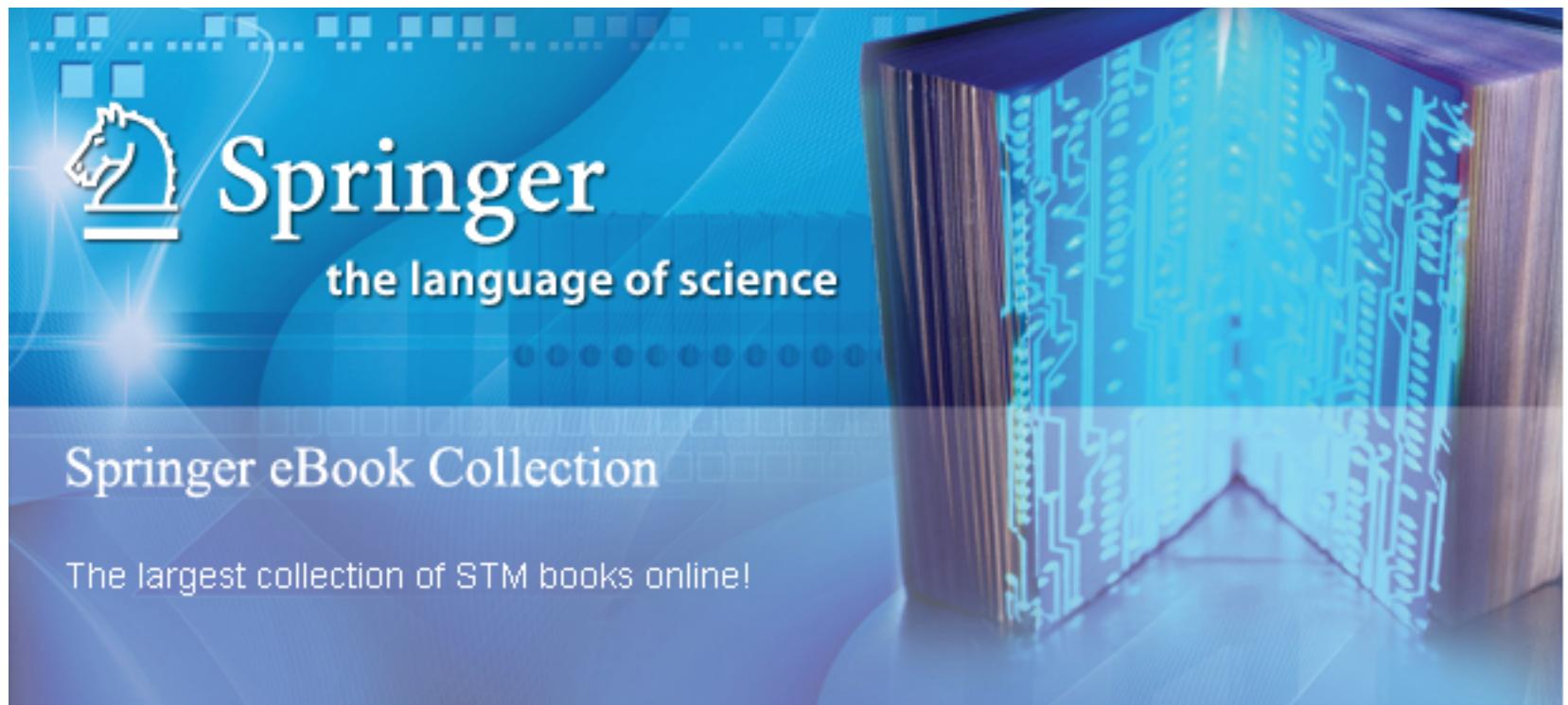


Completely inappropriate for biological models

Is there a solution?

Absolutely

THIS IS NOT THE SOLUTION

A promotional graphic for Springer's eBook Collection. On the left, the Springer logo (a chess knight icon) and the text "Springer" and "the language of science" are displayed against a blue background with abstract digital patterns. On the right, a large, open book is shown, where the pages are replaced by a dense grid of blue and white circuit board patterns, symbolizing digital content or e-books.

Springer
the language of science

Springer eBook Collection

The largest collection of STM books online!

Models are Digital Devices



The consequences of publishing models not paper

- **The review process:**

- Initial review is automatic
 - Model type determination
 - Parameter values in or out of range
 - Evaluate with respect to standards for that type of model
 - Measure of advancement over previous models
 - Parameter sensitivity
 - Only then is the paper peer reviewed

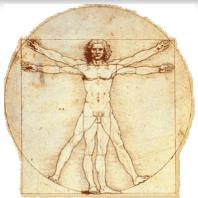
- **The consequences:**

- Actual model available in understandable form
 - Use in education
 - Can seed new connected research
 - Provide a basis for discussion and competition
 - Traceable (quantitative) “impact factor”
 - Link to NIH – funding priorities and policy

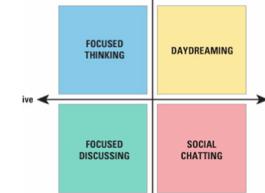
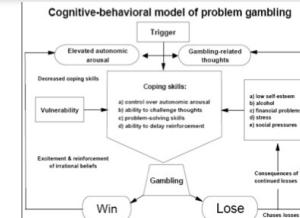
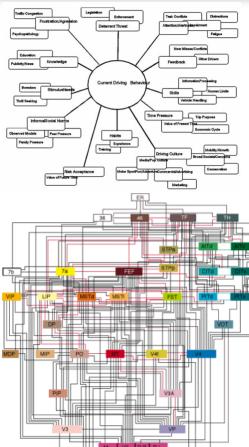
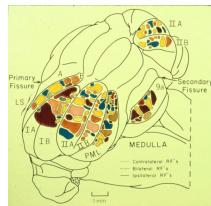
Value of Taxonomy

BIOLOGICAL SCALE

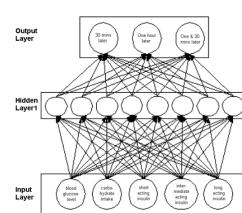
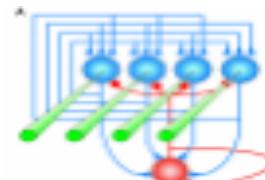
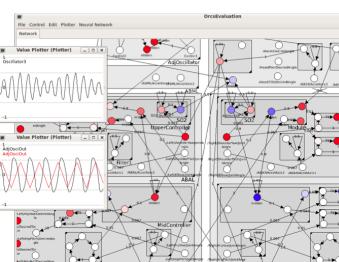
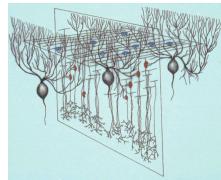
Behavior



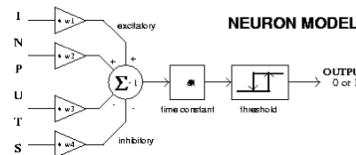
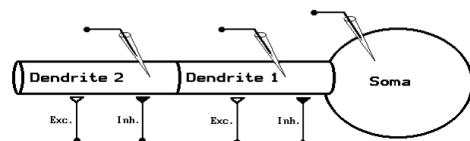
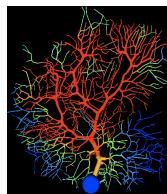
Systems



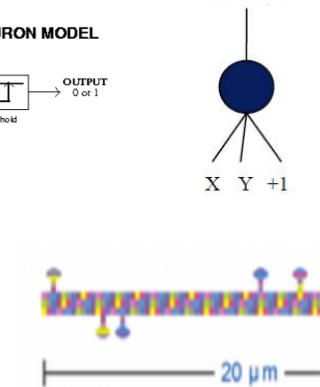
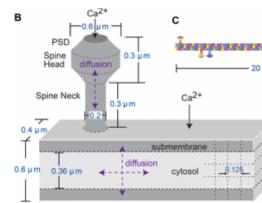
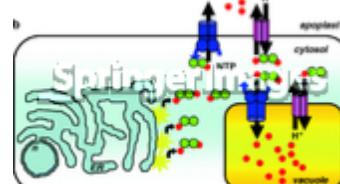
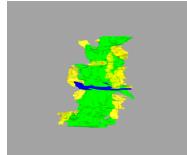
Network



Cellular



Subcellular

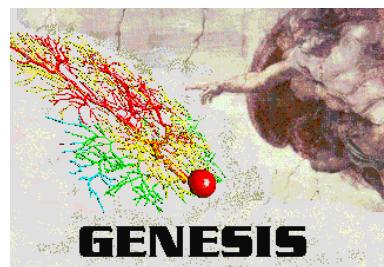


Is this possible

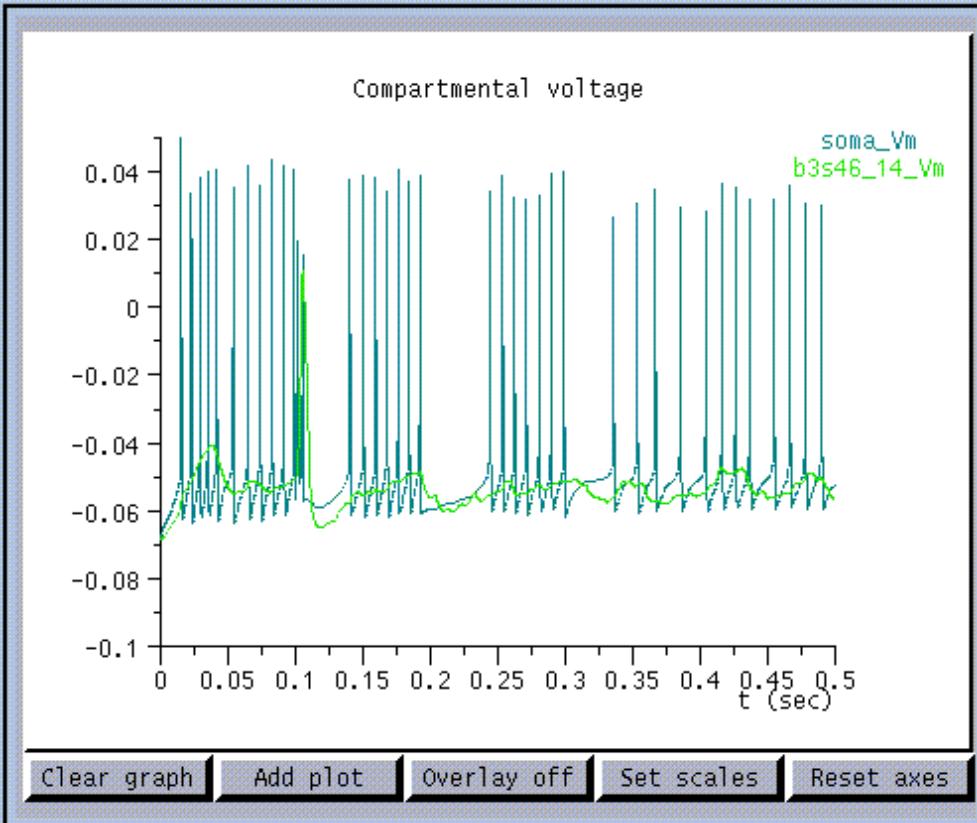
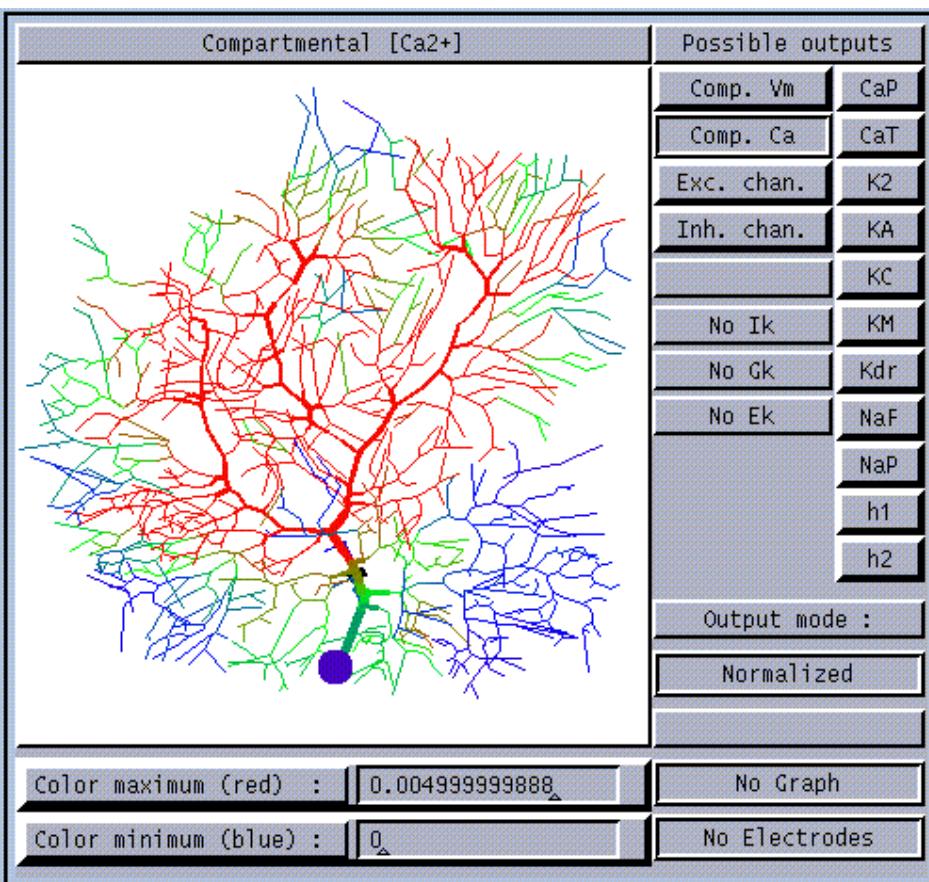
YES

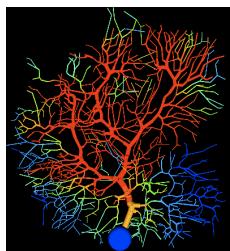
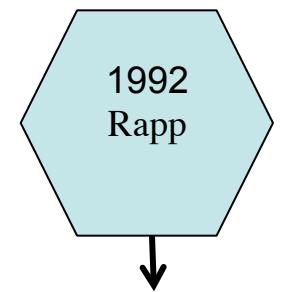
Tutorial of Purkinje cell model

E. De Schutter

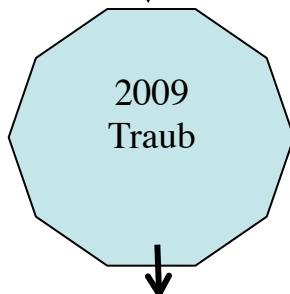
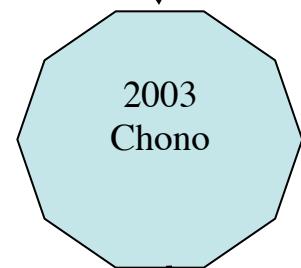
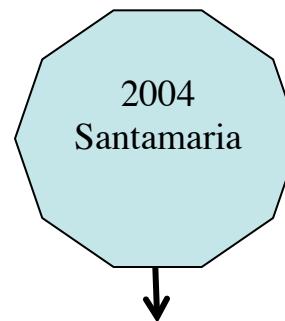
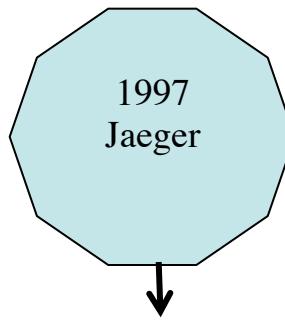
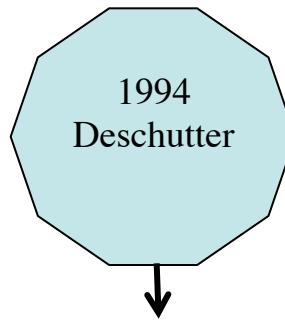


NEURON

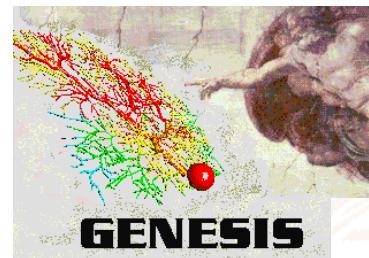
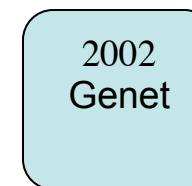
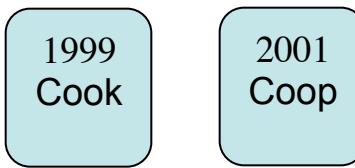




Consequences: A “community model”



Level of Biological Scale



NEURON

(Fortran 77: “code available”)

NIBIB MSM review panel meeting

Nov. 17, 2011

“Model Availability?”

Not without a modeling system

(Not necessarily with a modeling system)

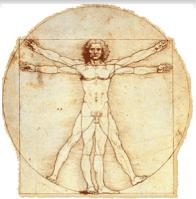
What will it take

- A simulation system designed to do this:
G-3
- Tutorial generator
- Education
- Pressure

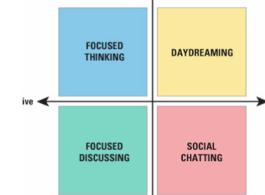
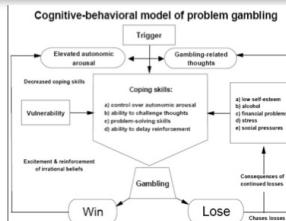
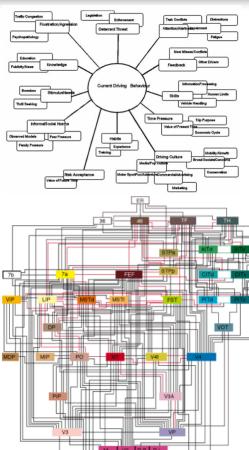
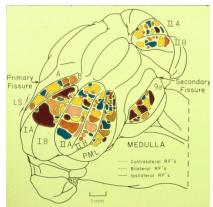
Further development of a Taxonomic structure

BIOLOGICAL SCALE

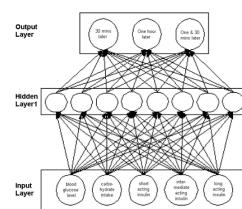
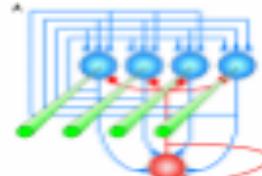
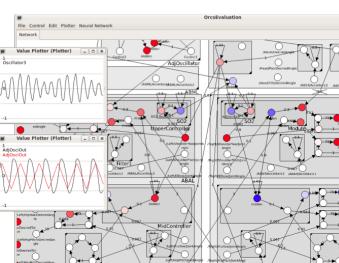
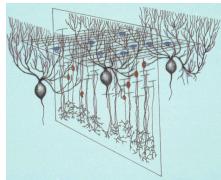
Behavior



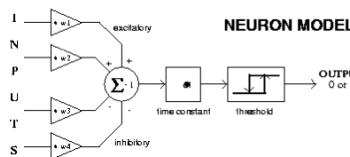
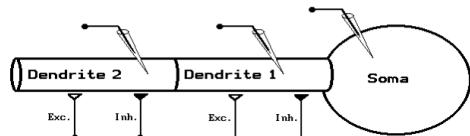
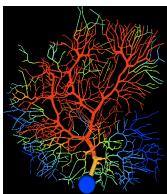
Systems



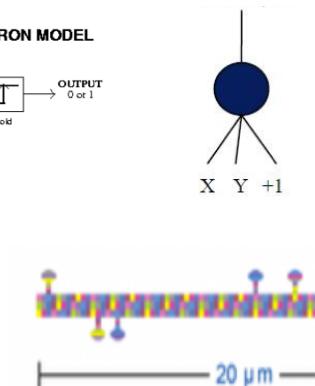
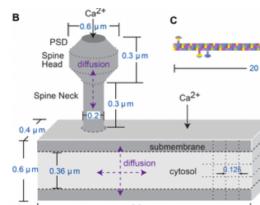
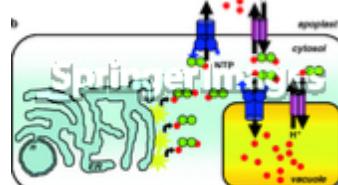
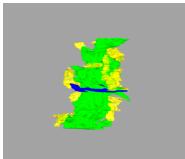
Network



Cellular



Subcellular



2nd IMAG Computational Neuroscience Working Group Workshop



FINALLY: How long will it take?



PHILOSOPHICAL
TRANSACTIONS:
GIVING SOME
ACCOMP'T
OF THE PRESENT
Undertakings, Studies, and Labours
OF THE
INGENIOUS
IN MANY
CONSIDERABLE PARTS
OF THE
WORLD.

Vol I.
For Anno 1665, and 1666.

In the SAVOY,
Printed by T. N. for John Martyn at the Bell, a little without Temple-Bar, and James Allestry in Duck-Lane,
Printers to the Royal Society.

1436

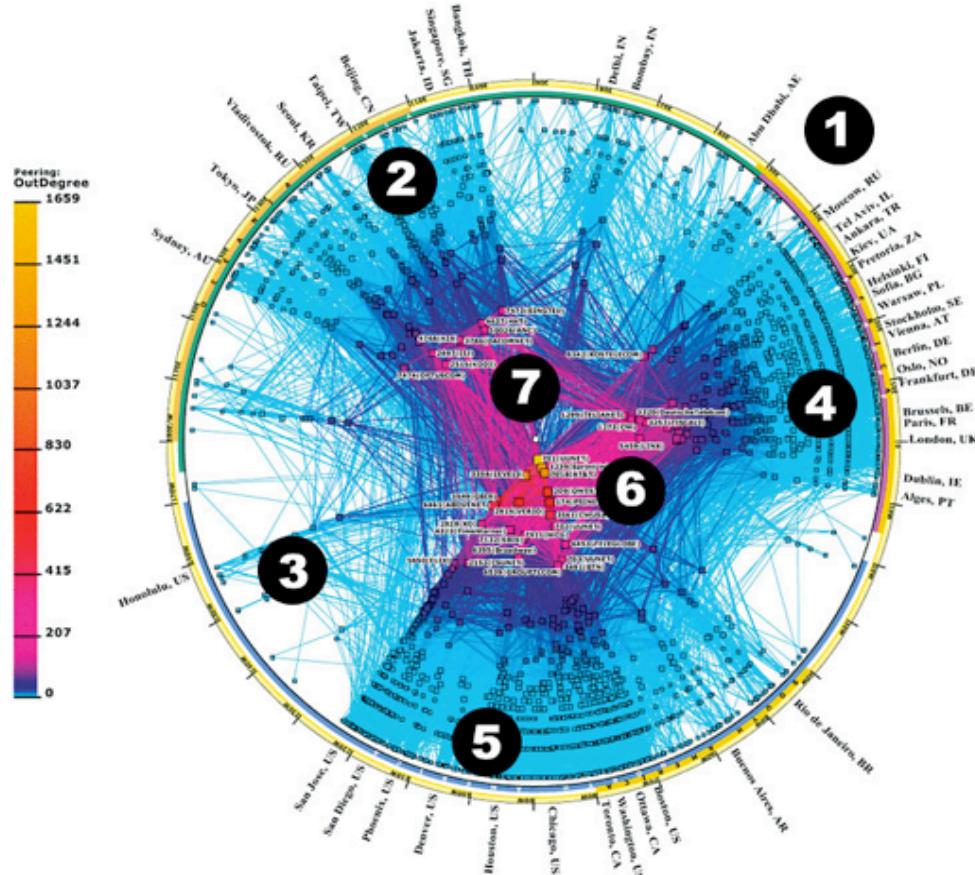


229 years



1665

Things are accelerating
“40% fortune 500 companies may not exist in 5 – 7 years”



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YOU CAN HELP