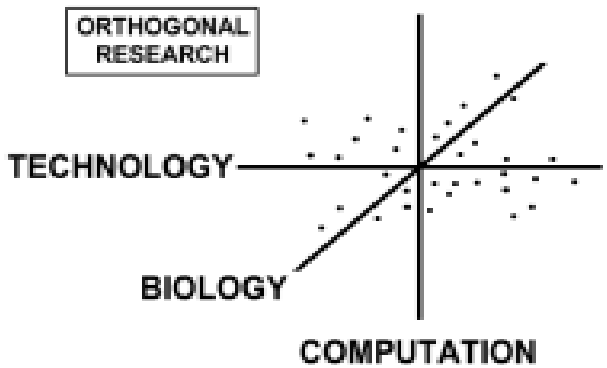
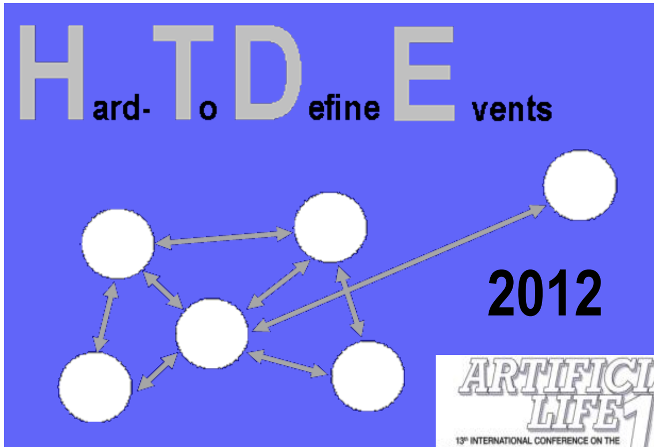
Multiscale Integration and Heuristics of Complex Physiological Phenomena



Presented at the Embryo Physics Course.
Silver Bog, Second Life

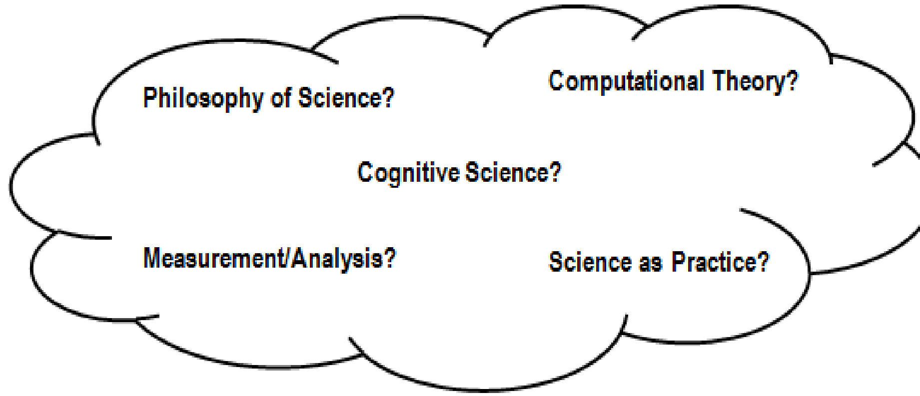
Bradly Alicea
Michigan State University
http://www.msu.edu/~aliceabr http://syntheticdaisies.blogspot.com

Artificial Life XIII Conference   East Lansing, MI   July, 2012



Recursive me! Giving this talk at HTDE 2012.

What is this Workshop About?



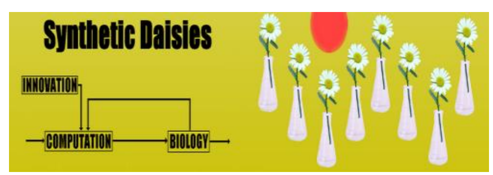
Inspired by a need to synthesize a methodology of getting at "what we least know"

* experimentation relies on observables.

* good theory relies on experimental verification.

What if we cannot define our problem scope or variables very well?

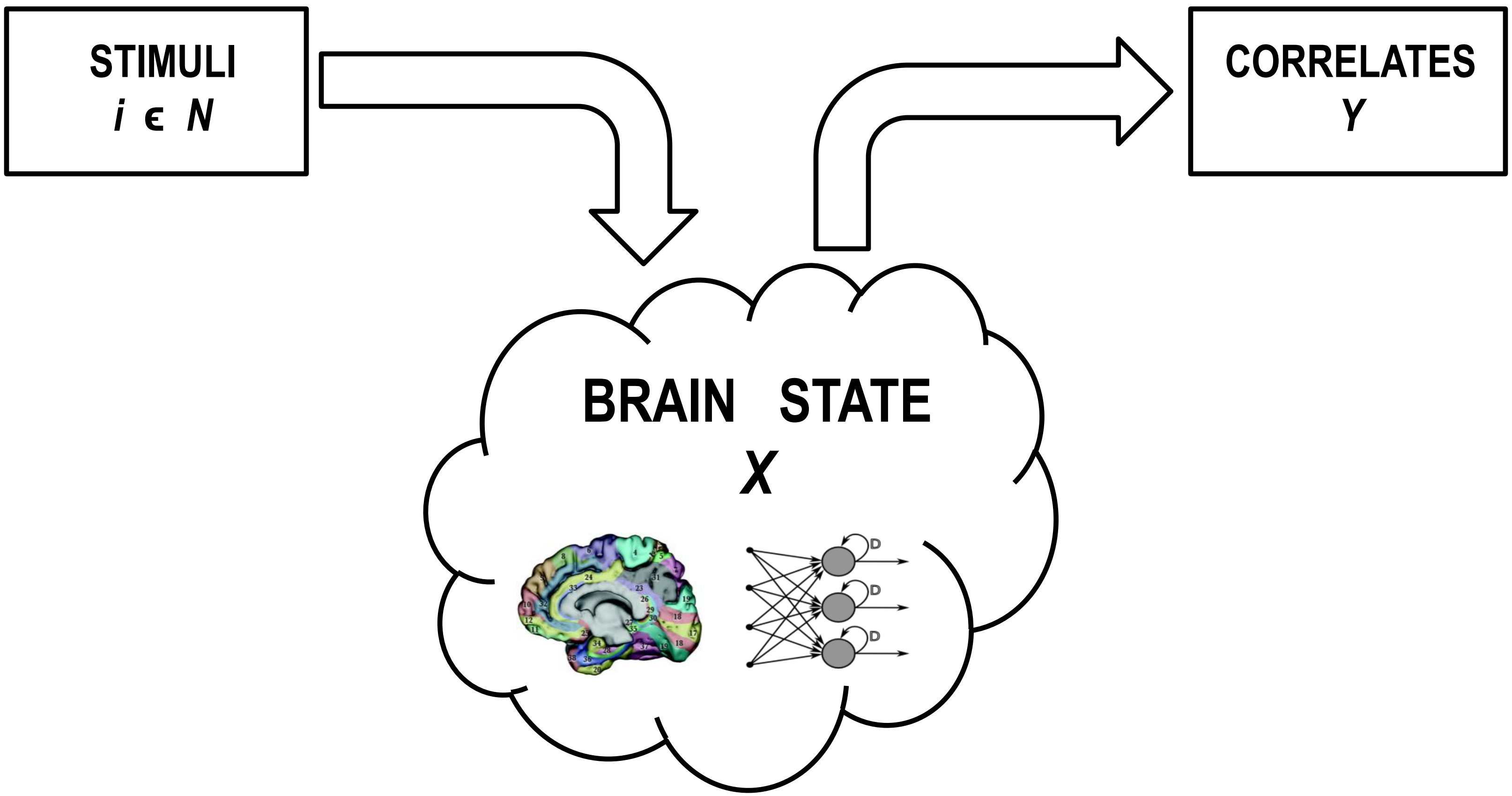
What if they are highly context-dependent?



vimeo

Residuals of the workshop hosted at Synthetic Daisies and Vimeo (videos).

Classic Empirical Example of a “Hard-to-Define” Event



Classic Empirical Example of a “Hard-to-Define” Event

STIMULI
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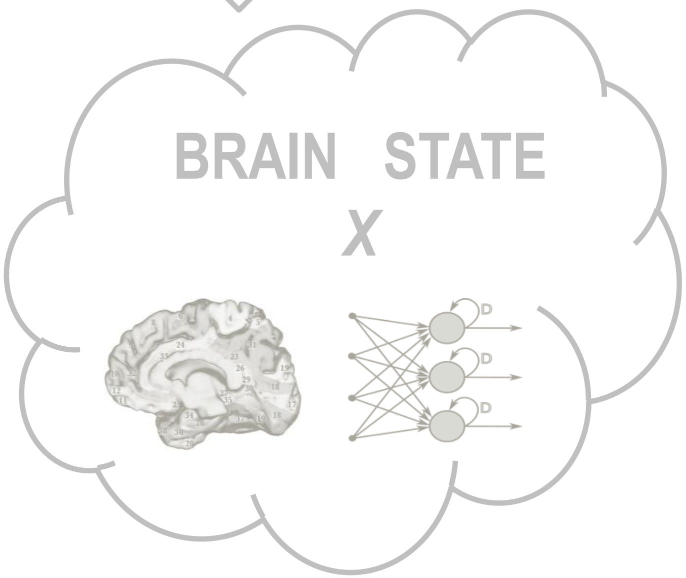
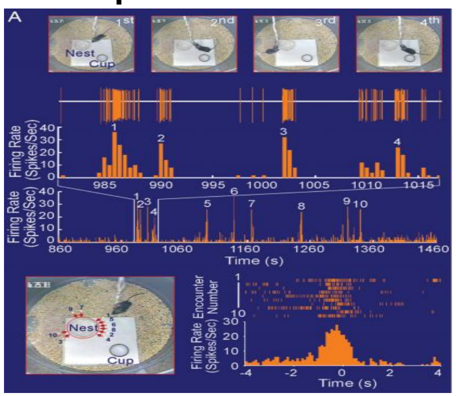
Y



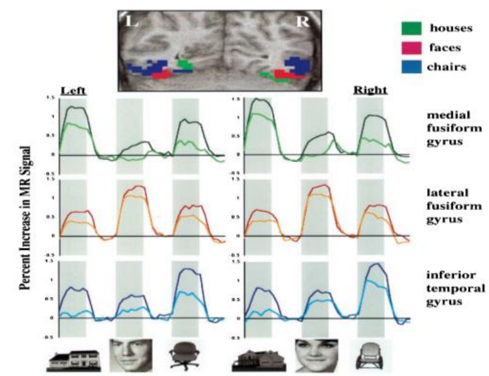
Concept of a Nest:



Lin et.al Neural encoding of the concept of nest in the mouse brain. PNAS, 104(14), 6066-6071 (2007).

Figure 1.A: transient “on” cells.

Distributed representations:



Ishai et.al Distributed representation of objects in the human ventral visual pathway. PNAS, 96, 9379-9384 (1999).

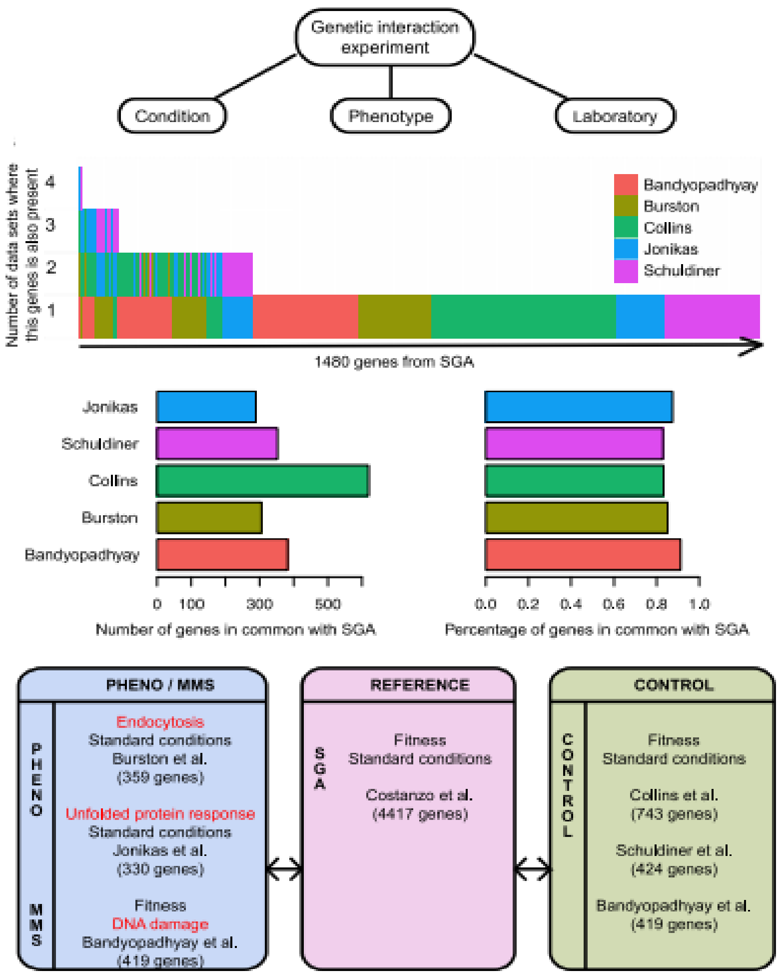
Figure 1.

What makes this “hard-to-define”?

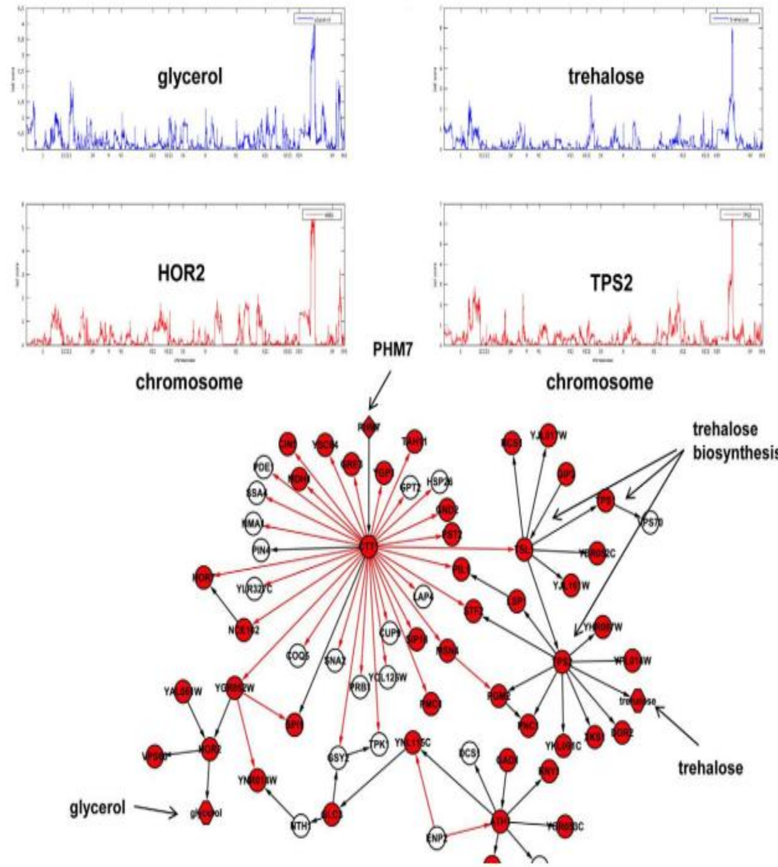
* lack of appropriate measures, analytical techniques?

* lack of context, understanding w.r.t. what results mean (synthesis)?

Does more data get us closer to an objective set of variables (empirically-speaking)?



COURTESY: Figure 7, PLoS Biology, 10(4), E1001301 (2012).

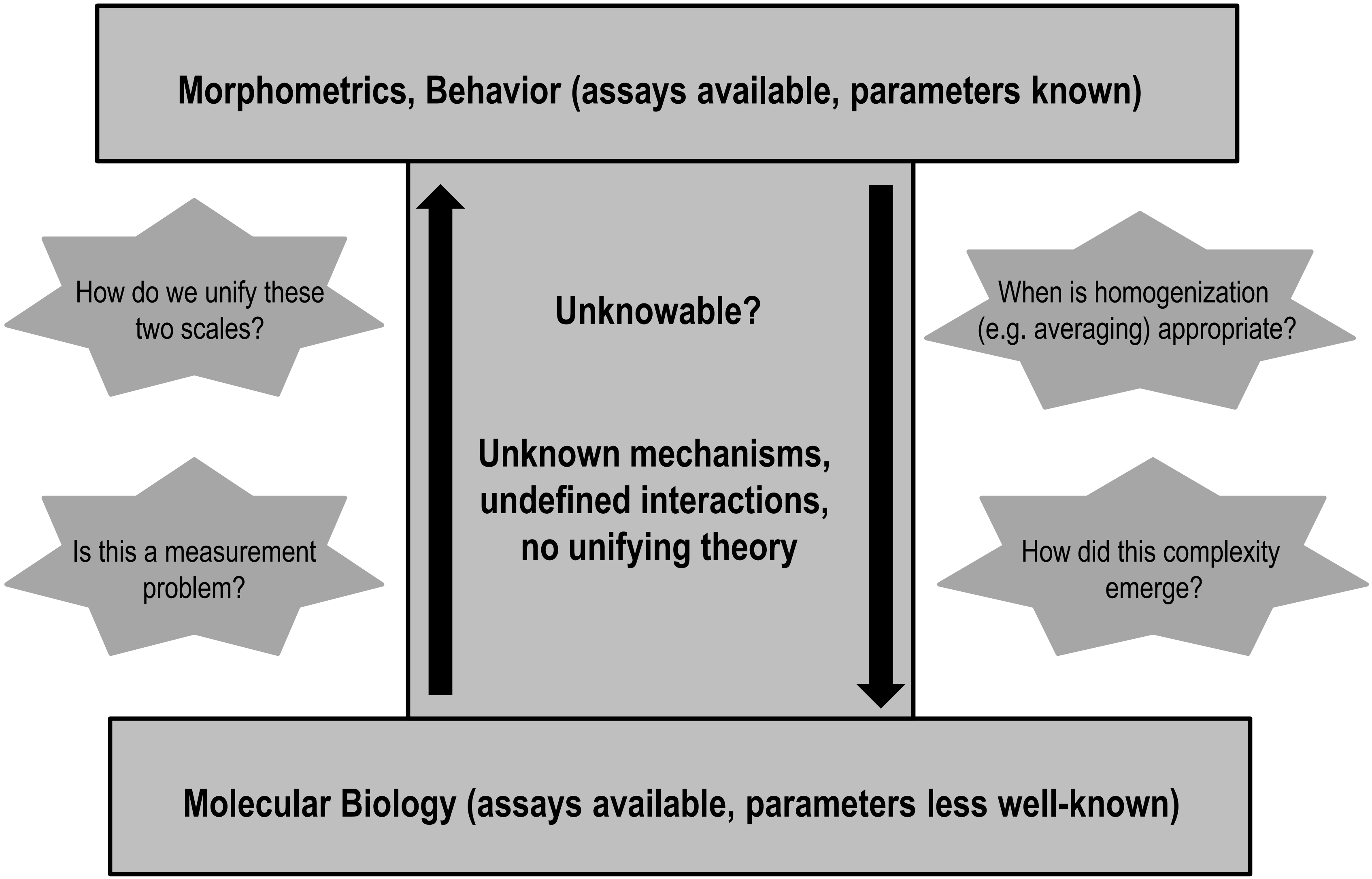


COURTESY: Figure 1, PLoS Computational Biology, 8(6), e1002559.

LEFT: Merging multiple types, sources of data.

ABOVE: Complementary information (gene-gene interactions).

“From Brain to Behavior” is a hard-to-define problem!



Different Types of Hierarchy: organizational and spatial (temporal will be ignored for now):

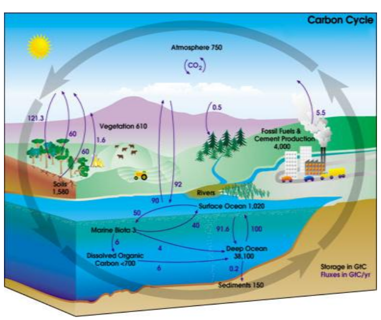
* Organizational (defined by specialization, role). Examples: social, ecological.

* Spatial (defined by features, lengths). Examples: cities, continents.

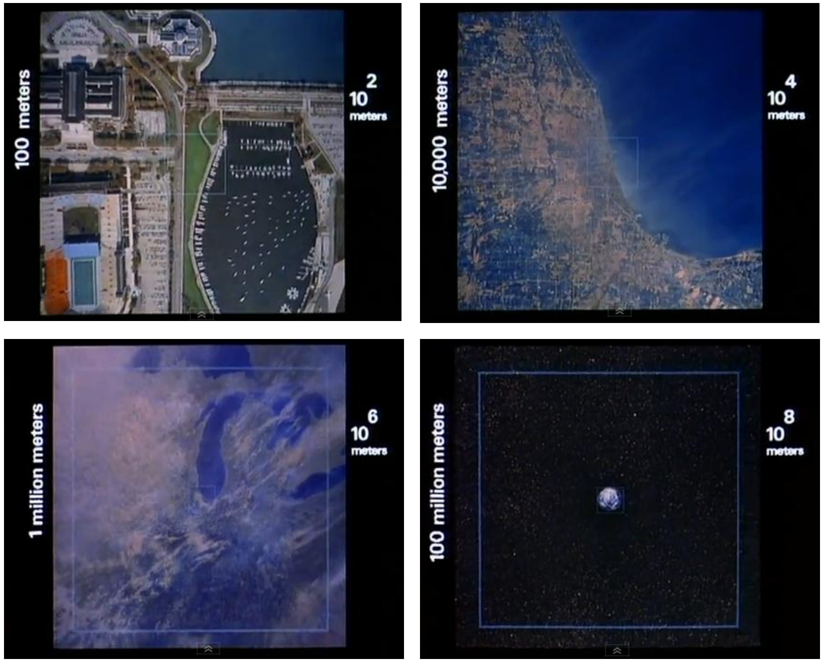
Physiological systems (e.g. animal body) are a combination of the two:

* cells can form organs, systems with specialized components (renal, circulatory).

Organizational



Spatial



COURTESY: Power of 10 (Eames, YouTube)

Example from Brain-machine Interfaces (BMIs):

BMI systems with two components (Carmena, IEEE Spectrum, March 2012).

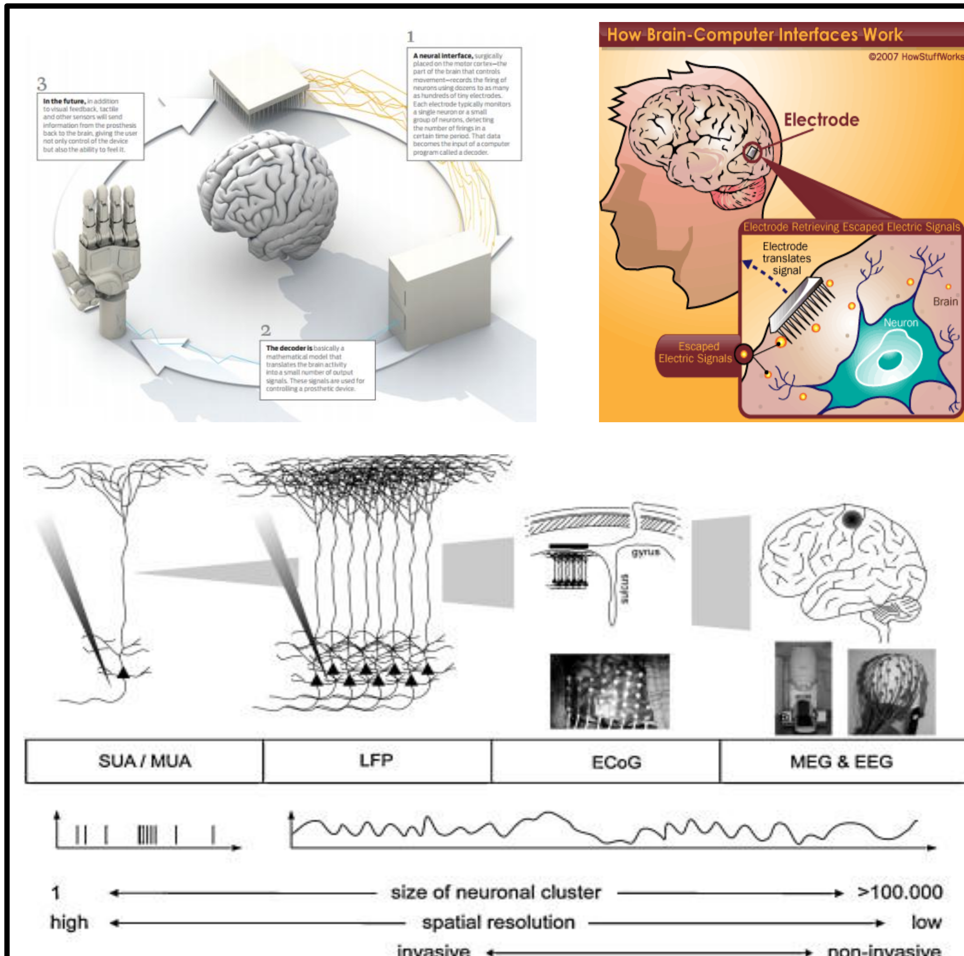
Two electrophysiological sources of information:

* high-frequency signals (single unit recordings).

* low-frequency signals (local field potentials).

How do these get fused together into a coherent control signal?

* multiscale problem, much mutual and independent information embedded in both scales



Waldert et.al, Journal of Neuroscience, 28(4), 1000–1008 (2008).

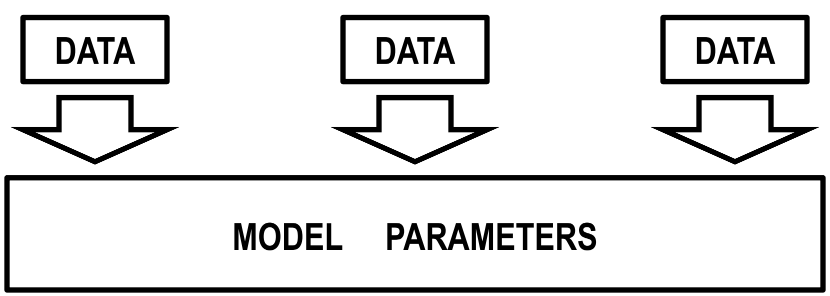
Scale (hierarchical level) Linking

Baeurle, S.A. (2009). Multiscale modeling of polymer materials using field-theoretic methodologies: a survey about recent developments. Journal of Mathematical Chemistry, 46, 363-426.

* using a single set of model parameters to describe data from multiple scales.

* multigrid techniques sometimes used for well-defined problems.

Infer model parameters from data (multiscalar data)



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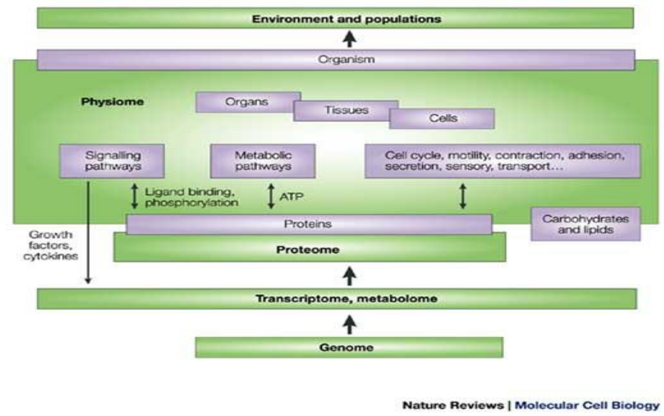
How do we link gene expression to cellular behavior? Cellular behavior to organismal behavior? Using a common currency?



Physiome project: Figure 1. Hunter and Borg, Nature Reviews Molecular Cell Biology, 4, 237-243 (2003)

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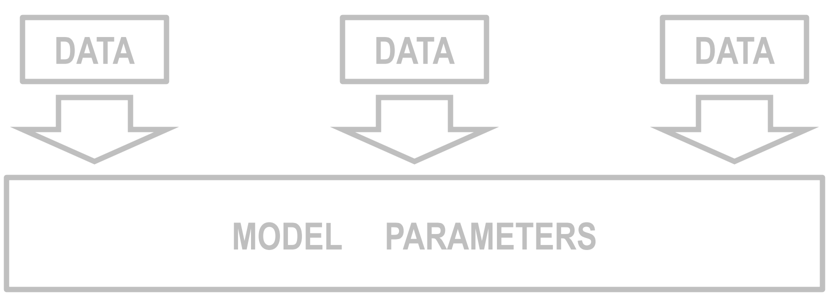
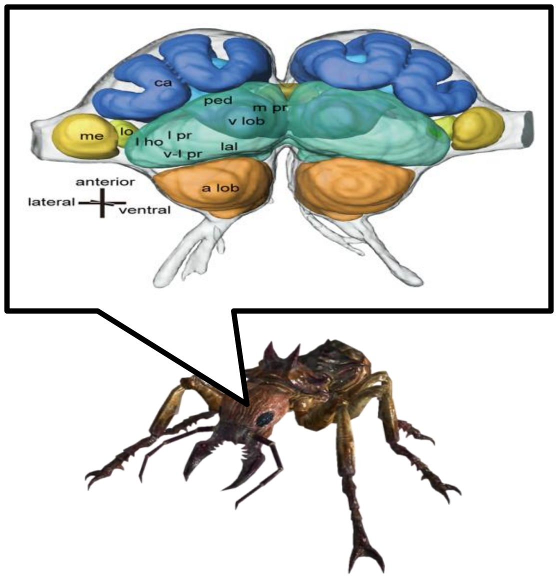


Figure 1. Frontiers in Behavioral Neuroscience, 4(28), 1-9 (2010).



Consequences of modeling averages and extremes:

Extremely local scale: intracellular millieu, neurons.

* **example:** behaviors can vary widely between cells in a population, result in a coherent macro-state (population vector coding).

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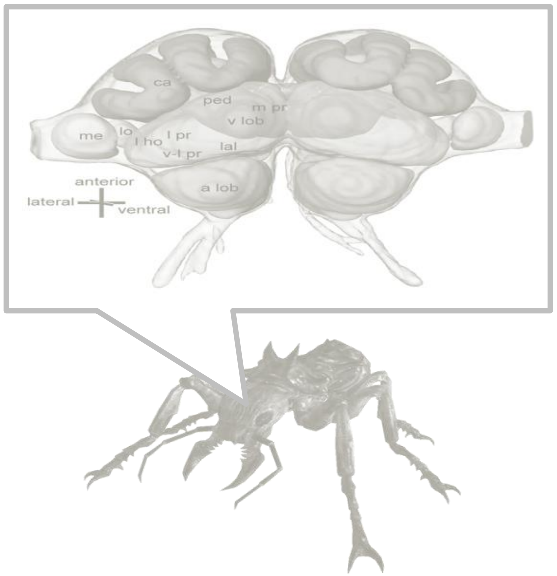


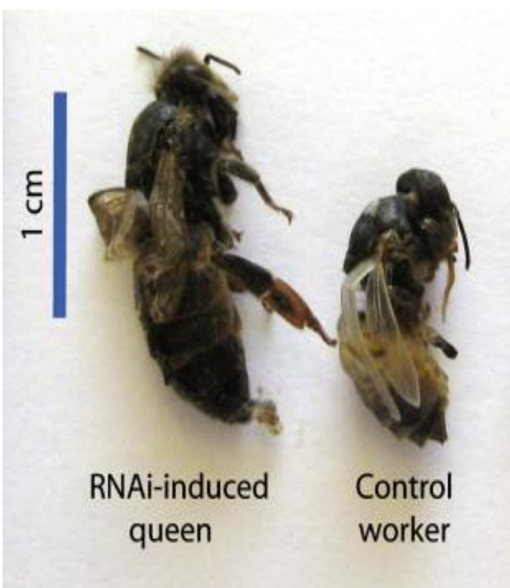


Figure 3. Hormones and Behavior, 59(3), 399–406 (2011).

Consequences of modeling averages and extremes:

Extremely local scale: intracellular millieu, neurons.

* **example:** behaviors can vary widely between cells in a population, result in a coherent macro-state (population vector coding).

Extreme averaging: model of brain regions, brain states.

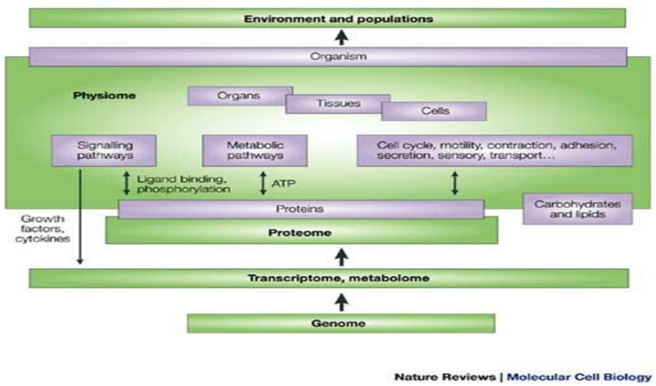
* **example:** a large number of electrophysiological, biochemical parameter values will result in an “emotion”.

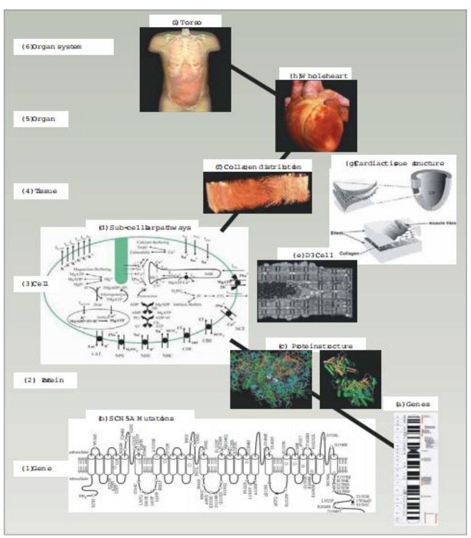
Will a “mean field model” work for scale linking? Average behavior at one scale may result from fluxes at another scale, different mechanisms at different scales.

* **example:** noise in gene expression can trigger changes in cellular state.

Computational-based approaches

Physiomic Modeling using CellML, SBML, and FieldML:





Hunter, IEEE Computer, 2006

Models are combined using ontologies (e.g. Bio PAX).

Challenge: complex models from separately-validated parts.

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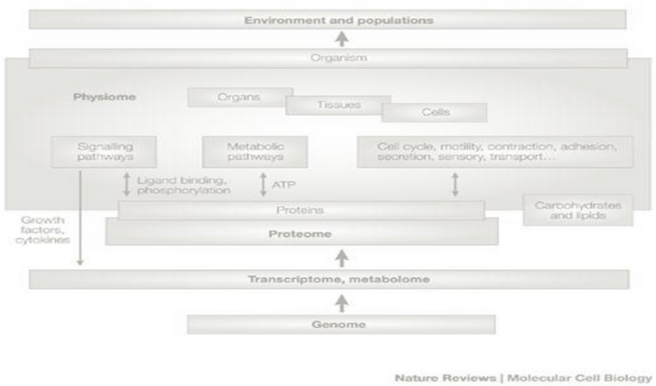

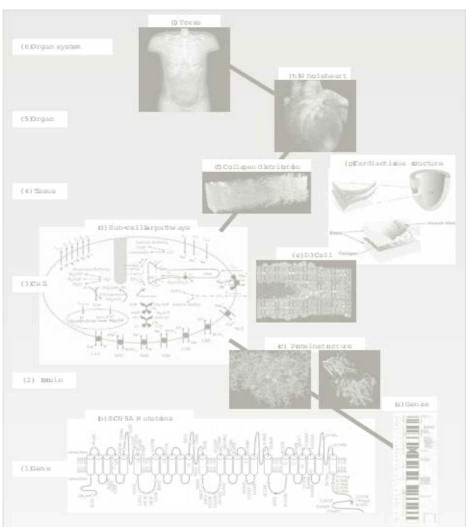

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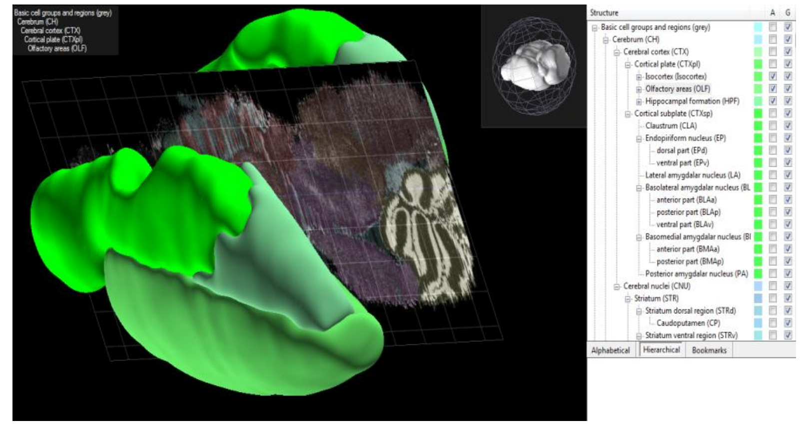
Allen Brain Atlas (merging anatomy and gene expression):



Anatomical and gene expression data combined using co-registration techniques.

* spatial hierarchy in the brain, organizational hierarchy based on connectivity and gene expression.

* no explicit model of temporal hierarchy.

Cellular Reprogramming as a Multiscale (temporal) Concept

Direct Reprogramming is a rare event:

1) cryptic populations: 1:10^6 cells, small number of cell can expand (genetic drift-like).

2) efficiencies (infection): 0.0002 to 29%.

3) number of genes required to "reprogram": 4 out of 29,000 (human).

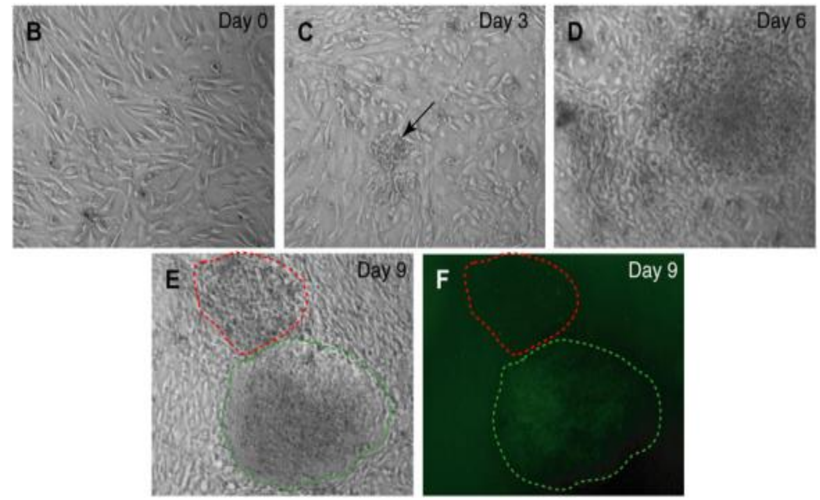
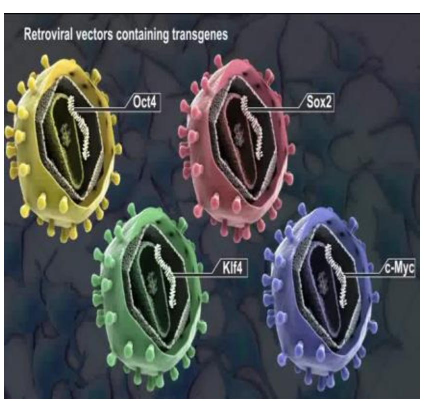
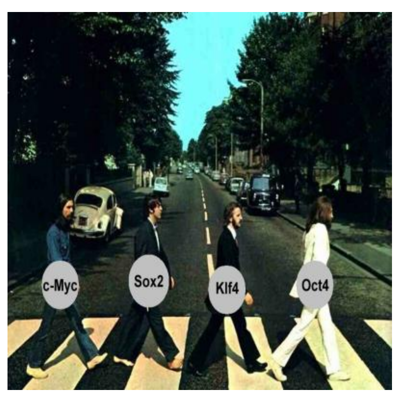
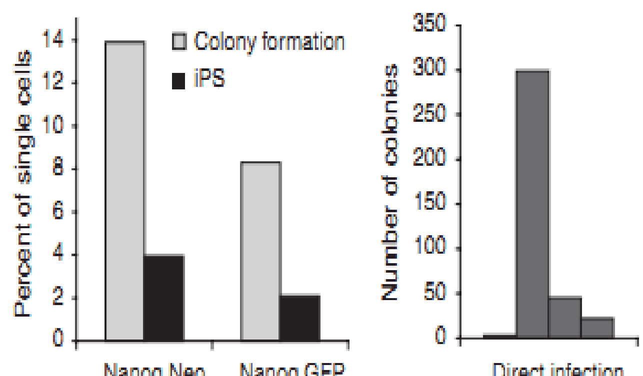


Figure 1, Stadfeld, M. et.al, Cell Stem Cell, 2, 230-240, (2008).



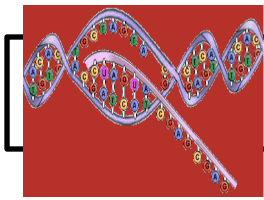


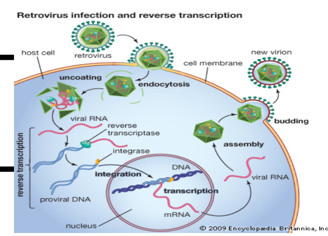
COURTESY: Stem Cell School (http://stemcellschool.com/)

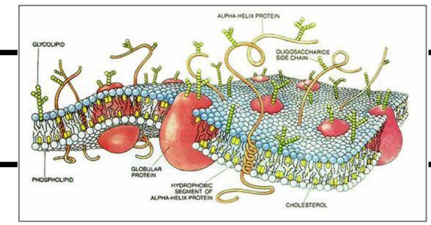


From Figure 2, Wernig et.al, Nature Biotechnology, 26(8), 916-924 (2008).

Temporal Hierarchies (e.g. slow kinetics of reprogramming)
vs.
Scope (when processes occur across spatial, organizational scales)







Transcription, Cell division (hours)	Plasmid incorporation (hours, days)	Structural Remodeling (days)	Stable, mature cell colonies (days, weeks)

Temporal Hierarchies (e.g. slow kinetics of reprogramming)
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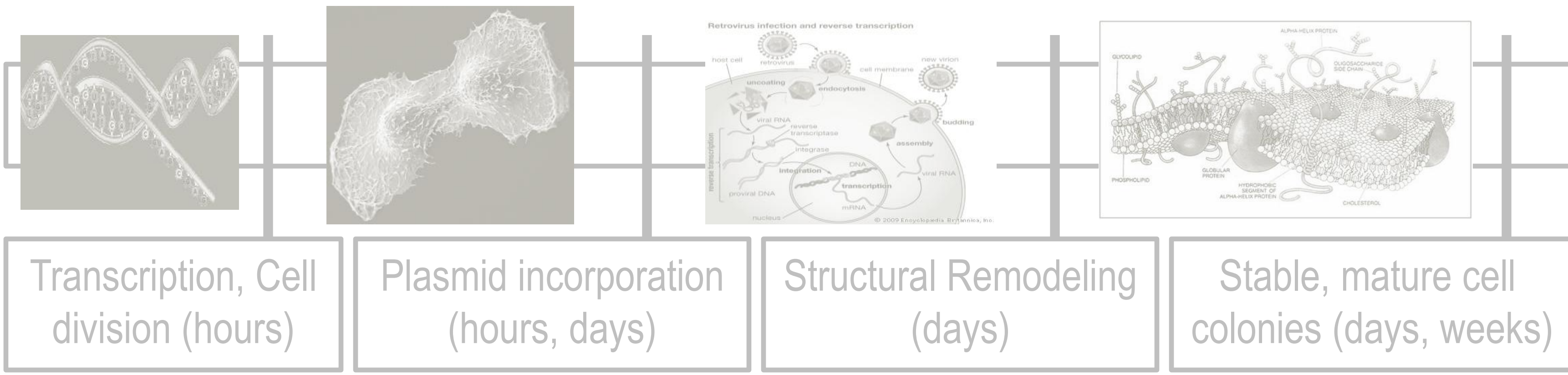
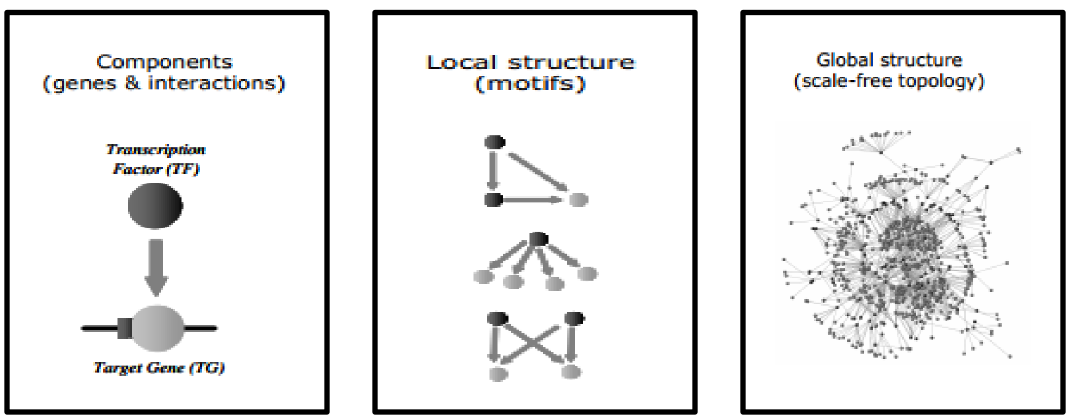


Scale (e.g. 10^1, 10^2, 10^3) vs. Scope (e.g. 2nd, 3rd, and 4th-order interactions).



Babu, Bio-Inspired Computing and Communication LNCS 5151, 162-171 (2008).

Scope (not spatial scale *per se*, but hierarchical):

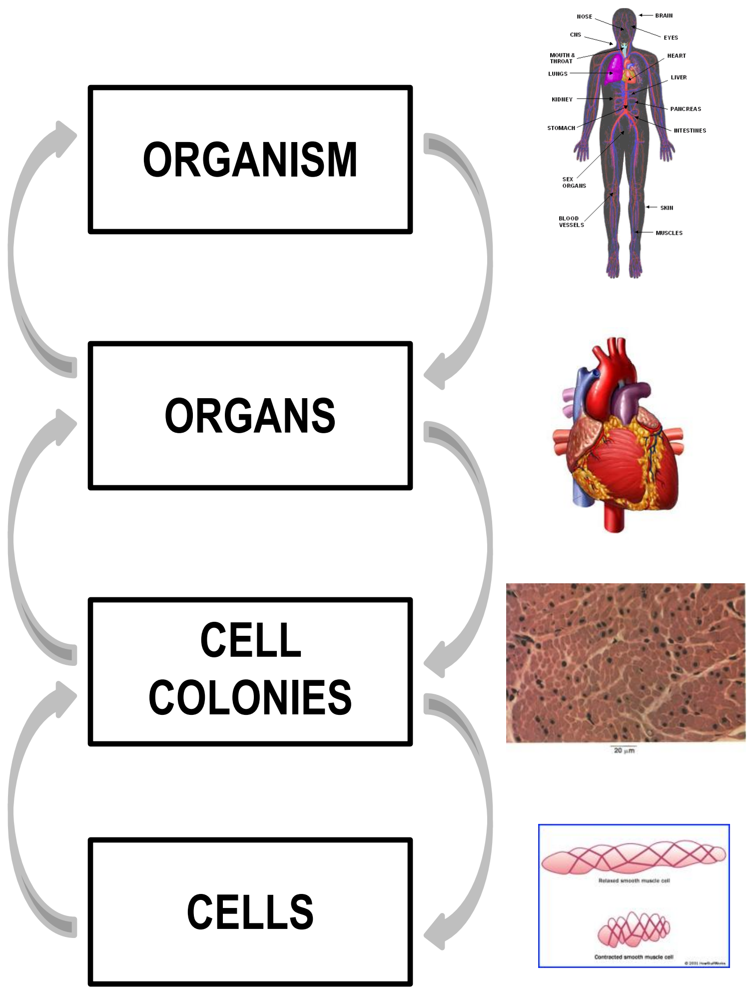
* expression of single gene can lead to a cascade.

* a cascade produces a gene expression network.

How to Model the Emergence of Biological "Scale": from trophic approaches to first-mover principles

Trophic Model

arXiv.org



Exchange of energy and information between scales (see Alicea, Hierarchies of Biocomplexity: modeling life's energetic complexity. arXiv:0810.4547):

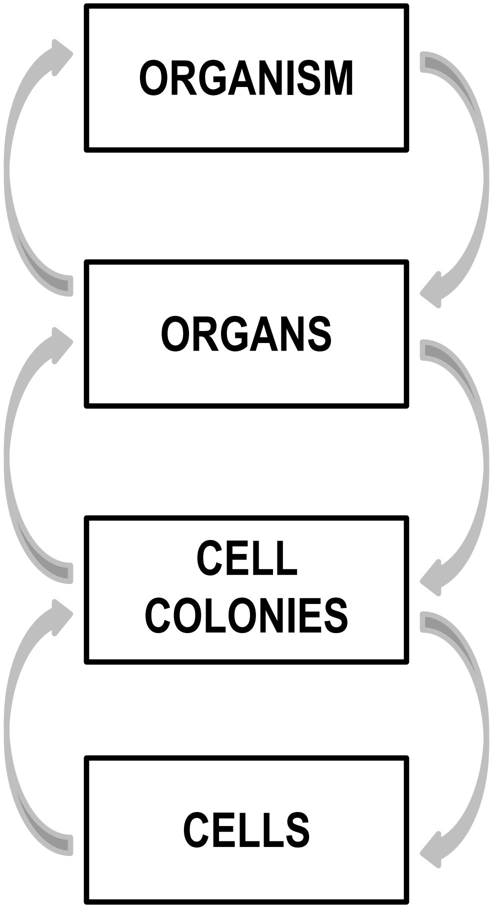
TOP-DOWN:

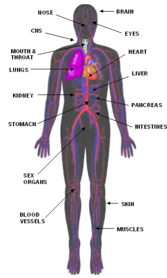
* constraint-based (information) interactions between scales.

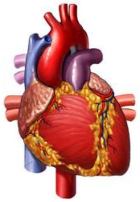
* enforces trophic dependency (food web, complex dynamics).

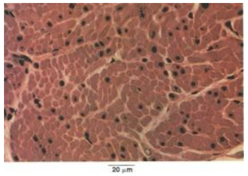
Trophic Model

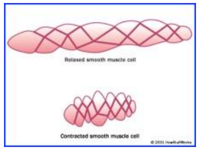
arXiv.org











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BOTTOM-UP:

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Trophic Model

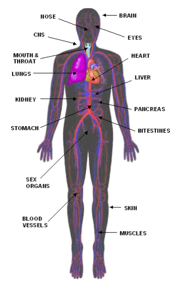
arXiv.org

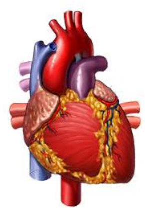
ORGANISM

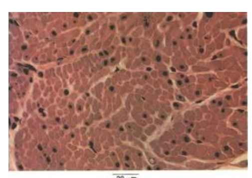
ORGANS

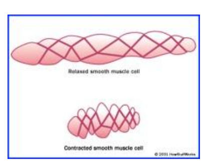
CELL COLONIES

CELLS









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PREDATOR-PREY-LIKE INTERACTIONS:

* coevolution (interdependence).

* extended to other systems (not explicitly consumptive).

Multiscale Decision-making Models (autonomous agents):

Wernz, C. and Deshmukh, A. (2010). Multiscale Decision-Making: Bridging Organizational Scales in Systems with Distributed Decision-Makers, European Journal of Operational Research, 202, 828-840.

Hierarchical Interaction of Agents:

* behaviors coupled (e.g. short-term to long-term, local-to-global).

Hierarchical Production Planning (Hax and Meal, 1975):

* higher levels "constrain" lower levels (organizational hierarchy).

* top-down and bottom-up interactions can be modeled as a two player game.

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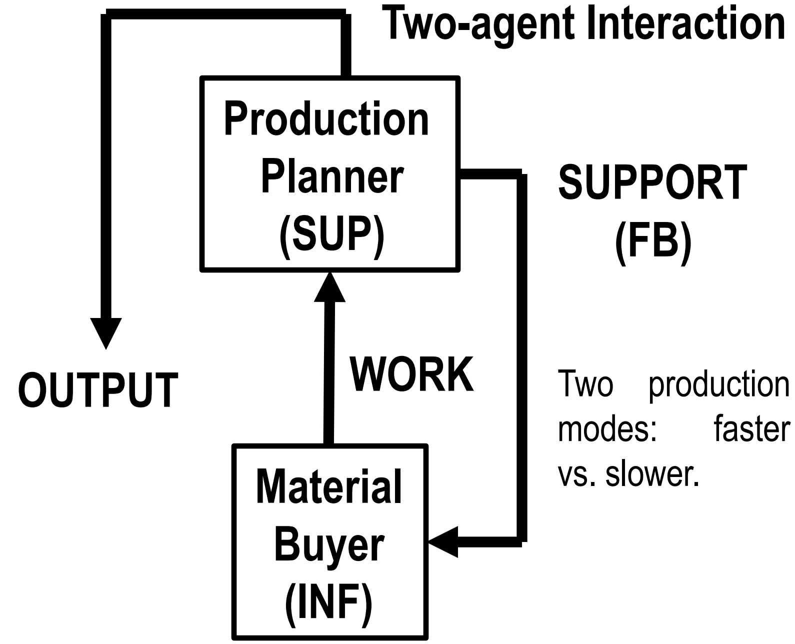
Two-agent Interaction



* magnitude of influence = state to which agent moves (faster vs. slower).

* reward and influence of other agent = state.

Multiobjective Fitness Approach:

* fitness (quasi-optimization) at multiple scales, according to multiple objectives.

* cells optimize their survivability in a microenvironment.

* tissues and organs (coupled to this) have separate objective (perform physiological function).

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Multiobjective Optimization: rather than single solution based on one criterion, find best trade-offs that satisfy constraints (g_1, g_2) at all scales (global optimum).

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Two-level problem (bi-level linear programming). Each level is a local optimum in bivariate space: x_1, x_2

Each partition (cells, f_1 and tissues, f_2) is a local optimization processes (P_1, P_2).

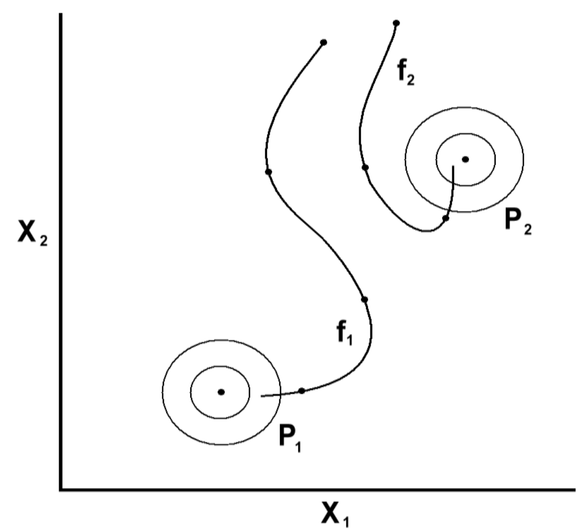
FORMALISM FROM: Migdalas, Parlados, and Varbrand Multilevel Optimization (1998).

$$[P_1] = \min_{x^1} f_1(x^1, x^2)$$

$$\text{subject to } g_1(x^1, x^2, \dots\dots, x^k) \leq 0$$

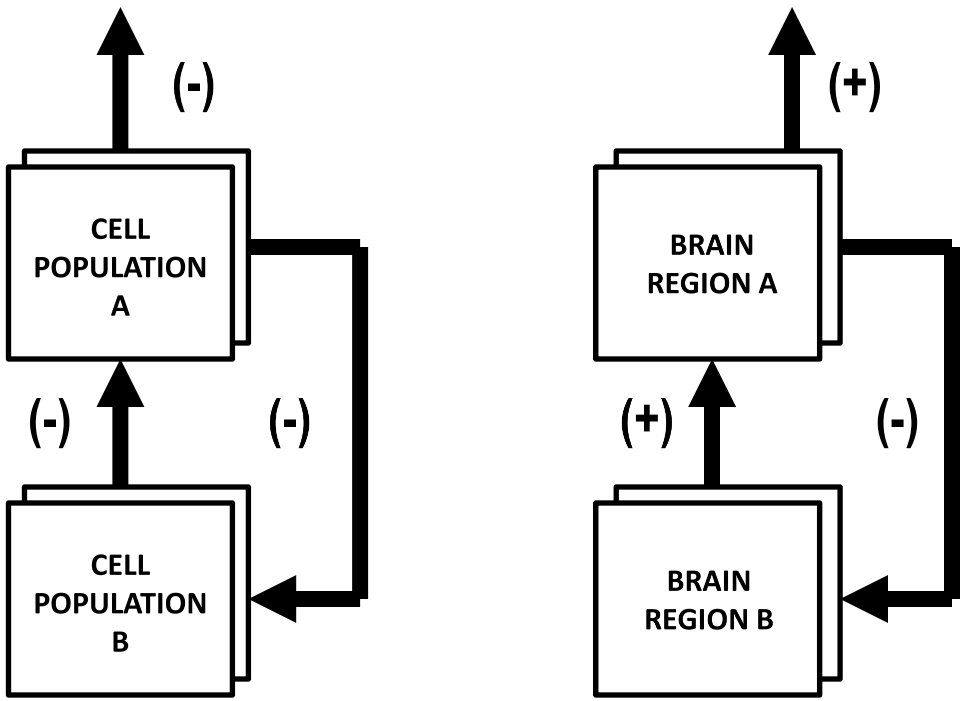
$$[P_2] = \min_{x^2} f_2(x^1, x^2)$$

$$\text{subject to } g_2(x^1, x^2, \dots\dots, x^k) \leq 0$$



Examples of control within and between hierarchical levels in the brain:

* in this case, we are interested in the emergence of scale (organizational).



CROSS-INHIBITION (leaderless)

Honeybee Worker Swarms: Seeley et.al (2012), Science, 335, 108-111.

FEEDBACK (leader emerges)

Industrial Production: Wernz and Deshmukh (2010), European Journal of Operational Research, 202, 828-840.

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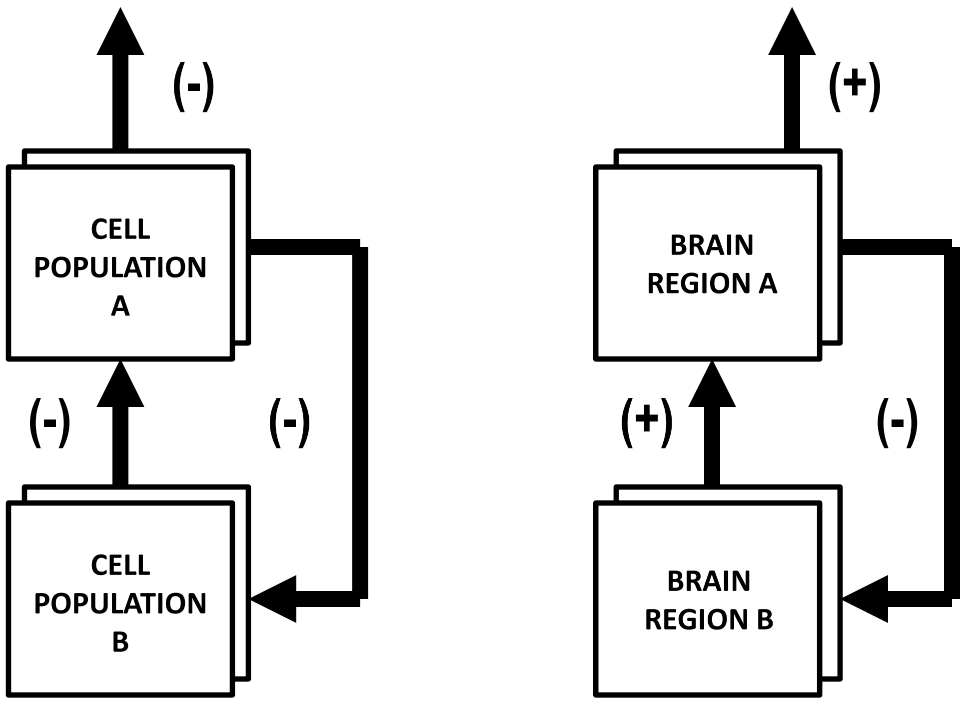
* in this case, we are interested in the emergence of scale (organizational).



CROSS-INHIBITION (leaderless)

Honeybee Worker Swarms: Seeley et.al (2012), Science, 335, 108-111.

FEEDBACK (leader emerges)

Industrial Production: Wernz and Deshmukh (2010), European Journal of Operational Research, 202, 828-840.

Cell populations A and B are countering each others' feedforward signals.

* populations counter each other (if signals are matched).

Brain Region A has taken on the role of coordinator in the network:

* becomes an autoregulatory loop.

$$[P_1] = \min_{x^1} \; f_1(x^1, x^2)$$

$$[P_2] = \min_{x^2} \; f_2(x^1, x^2)$$

$$[S_1] = \min_{s^1} \; f_1(x^1, x^2, x^3)$$

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Model multiobjective optimization process as a leader-follower (Stackleberg) game:

* given finite behaviors (strategies), payoff matrix determines outcomes.

* players (levels) will converge upon strategic equilibria.

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S_1

	f_1			
S_2 f_2		x_1	x_2	x_3
	x_1			
	x_2			
	x_3			

$$[L_1] = \min_{x^1} f_1(x^1(t_1, \ldots, t_n), x^2(t_1, \ldots, t_n))$$

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FORMALISM FROM: Migdalas, Parlados, and Varbrand Multilevel Optimization (1998).

Model multiobjective optimization process as a leader-follower (Stackleberg) game:

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Stackleberg (first-mover) equilibria:

LEADER chooses initial behavior and/or output level, moves towards P_1.

FOLLOWER constrained by behavior of leader, chooses behavior and/or output level that moves towards P_2.

S_1

S_2

	f_1			
f_2		x_1	x_2	x_3
	x_1			
	x_2			
	x_3			

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Biological Multiscale Complexity and Adaptation as "open-ended, first-mover evolution"

Open-ended Evolution:

1) Enabling conditions for "open-ended evolution". Biology and Philosophy, 23(1), 67-85 (2008).

2) Degeneracy: a link between evolvability, robustness and complexity in biological systems Theoretical Biology and Medical Modelling, 7, 1 (2010).

* optimization criteria are always changing.

* end product is not determined *a priori.* Remember, organism shaped by environment.

* enables degeneracy, which is a form of phenotypic robustness.

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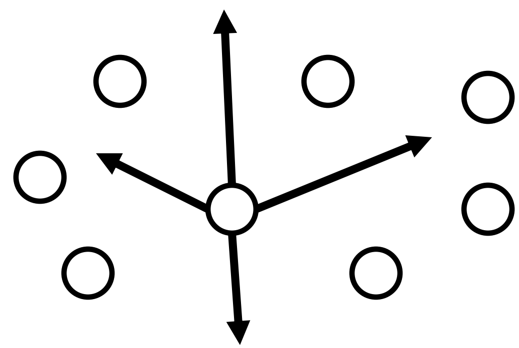

Performed by all cells in parallel

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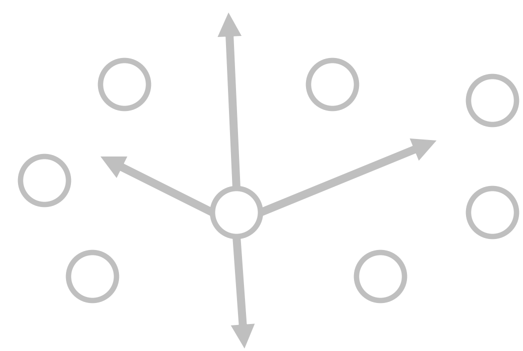

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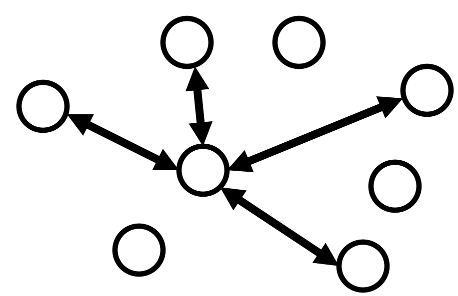
Collective Behavior: second-mover directed walk, responds to local interactions, global constraints.



Consequence of interactions

Spatial restriction → patterns and functional partitioning

Emergence From “First-mover” Principles:

Suppose all cells are greedy and make the first move (mass action)……

* some cells get closer to optimum than others, these are more likely to be first-movers in subsequent interactions.

OR

* outcome is averaged over all individuals in a subpopulation (niche), which serves as a collective signal to the second-mover cells.

Over time, this organizes cells into layers, patterns, and other higher-order structures. “Symbiosis”-like (happens gradually, as a series of transitions in evolution).

* rate-limiting (e.g. liver does not subsume EVERY cell it interacts with).

* fractal (cells organized under organs, organs organized under organisms) process.

Final thoughts: linking processes with hierarchy

Morphomechanical reactions (Beloussov, Chapter 2, 1998)

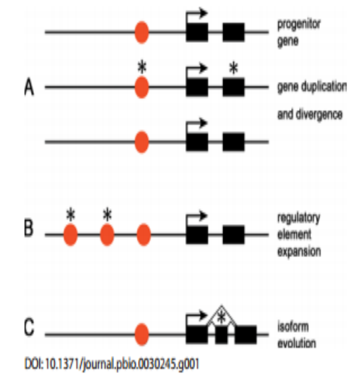
* instances of morphogenesis, multilevel hierarchy of responses.

Evolution at Two Levels: On Genes and Form

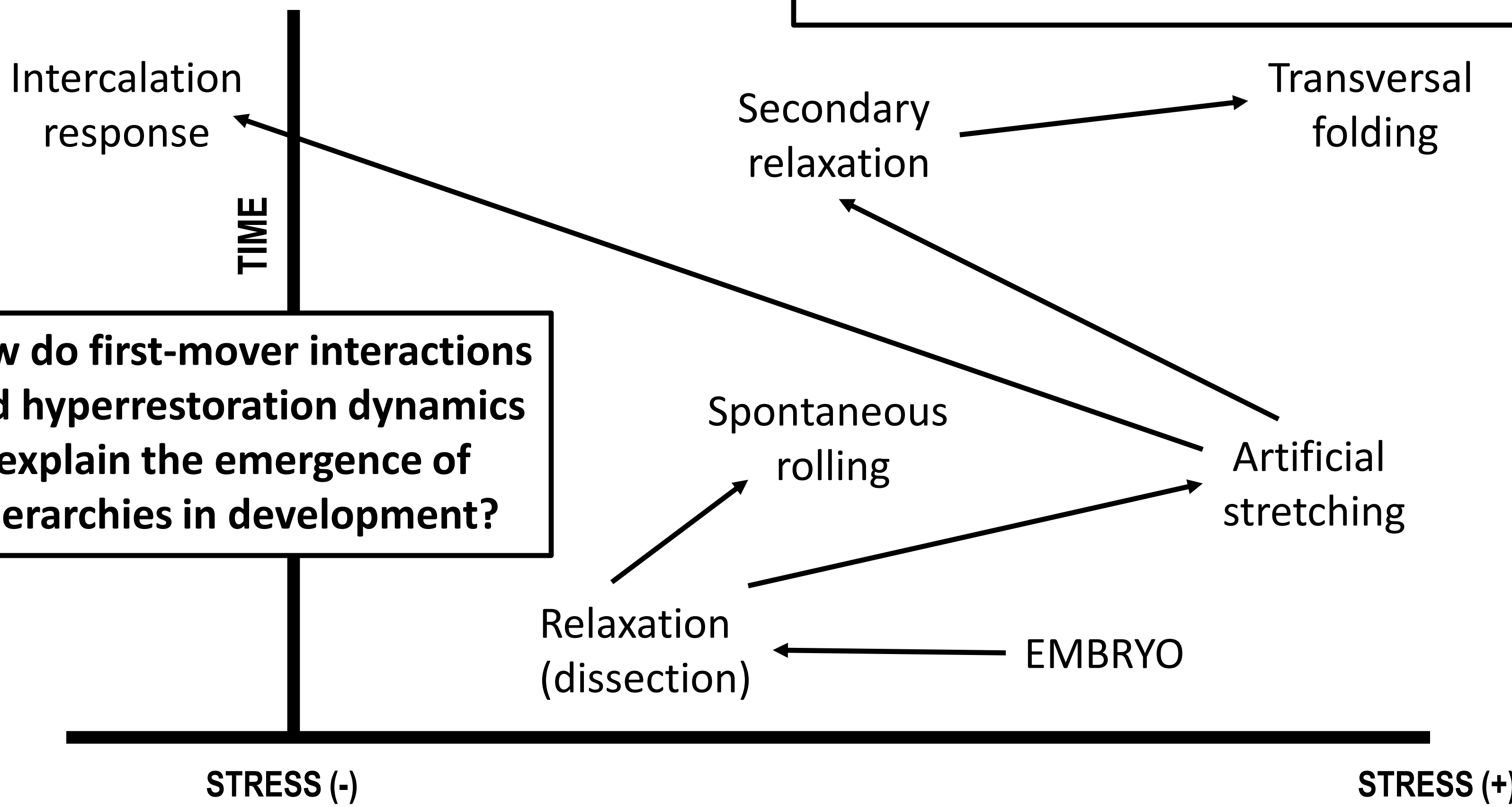
Sean B. Carroll

Sean Carroll's addendum to King and Wilson, 1975.

Genes and Phenotype



How do first-mover interactions and hyperrestoration dynamics explain the emergence of hierarchies in development?



Hyperrestoration rule:
* a cell or a piece of tissue is perturbed (abnormal stresses)

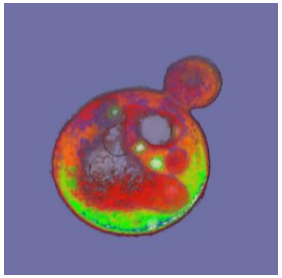
* develops an active mechanical response directed towards restoring the initial amount of stress.

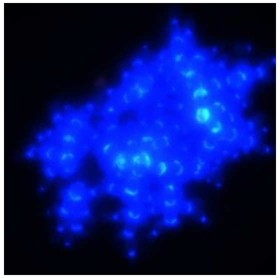
* performs this correction with overshoot (e.g. hysteretic response).

EXAMPLES: smooth sphericalization, edge curling (reactions to stretching at level of individual cells, but are tissue size- and shape-dependent).

Example where it does not explain the data:

Travisano et.al (2012, 2013): multicellularity in yeast.





Artificial + kin selection: pressure for "staying together" multicellularity among clonal (mother-daughter) cells.

Extension-Extension Positive feedback: new material intercalated in area perpendicular to stretching as a response to external stretching.

Contraction-Extension Positive feedback: movement of cells between poles of cell sheets as positive feedback (response to stretching forces).