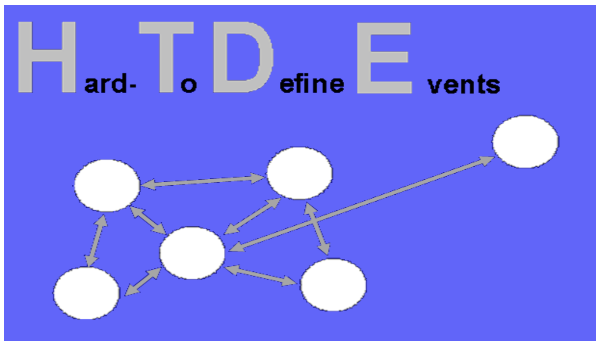
Multiscale and Rare Events in Physiology



ARTIFICIAL LIFE 13
13th INTERNATIONAL CONFERENCE ON THE SIMULATION & SYNTHESIS OF LIVING SYSTEMS

Presented at the HTDE (Hard-to-Define Events) Workshop 2012,
Artificial Life XIII, East Lansing, MI   USA

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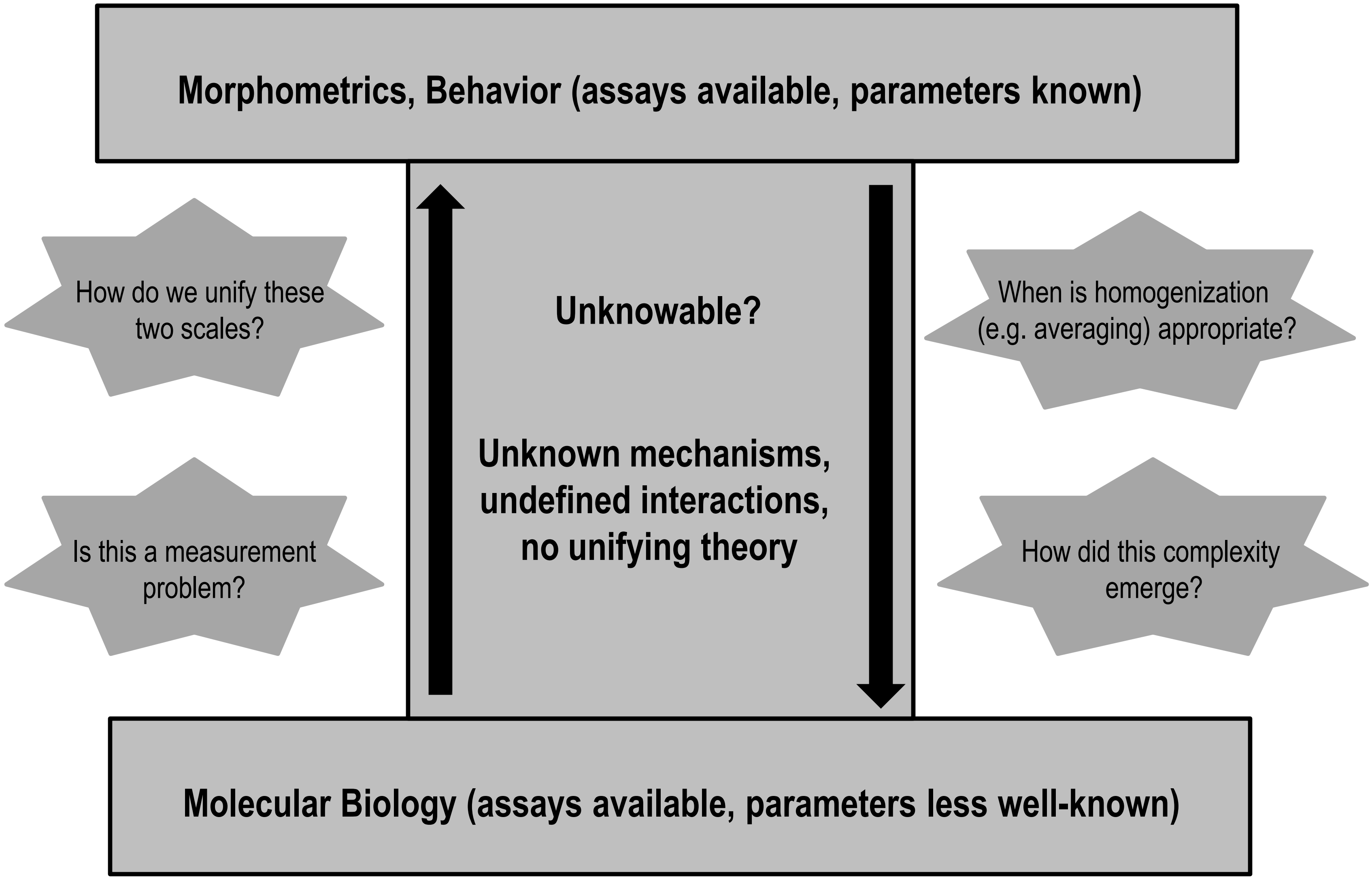
http://www.msu.edu/~aliceabr   http://syntheticdaisies.blogspot.com

“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.

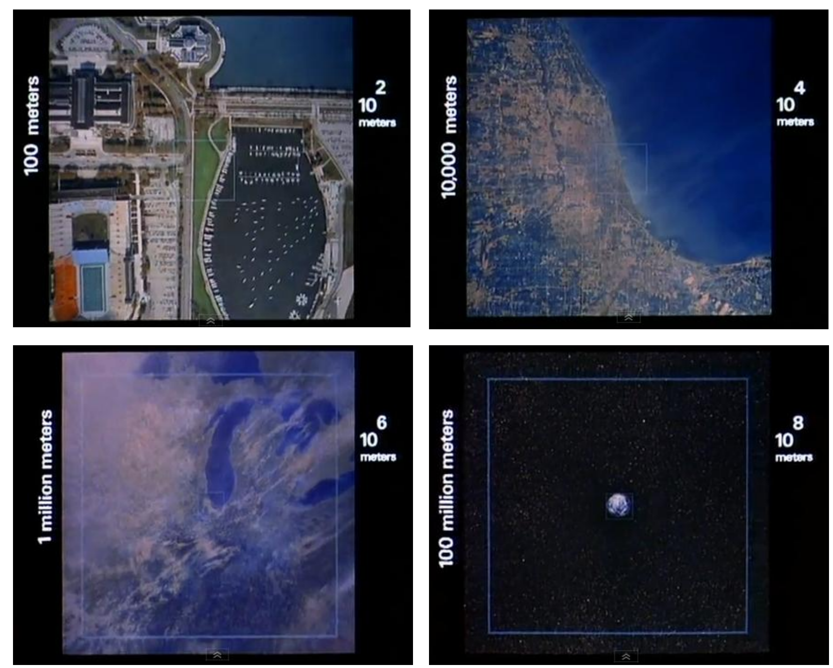
* Spatial (defined by features, lengths). Examples: cities, continents.

Physiological systems (e.g. animal body) is 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).

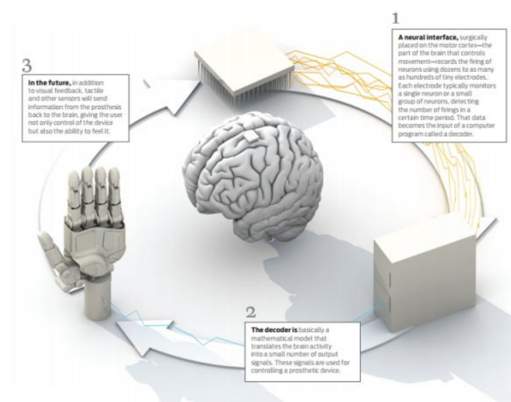
Two electrophysiological sources of information:

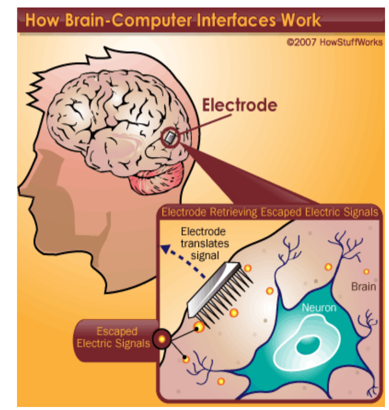
* high-frequency signals (single unit recordings).

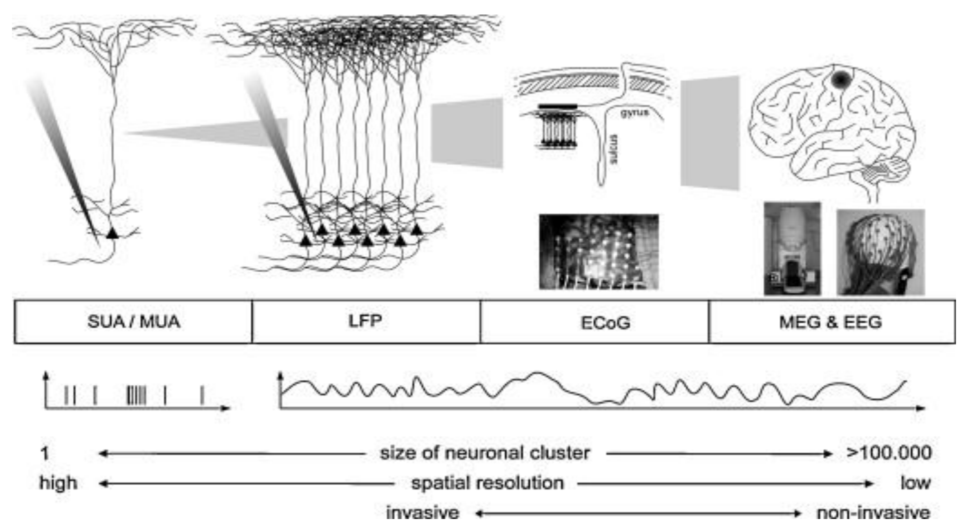
* low-frequency signals (local field potentials).

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).

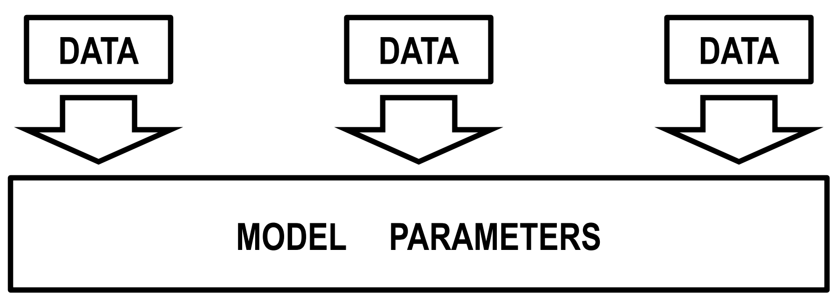
Scale (hierarchical level) Linking

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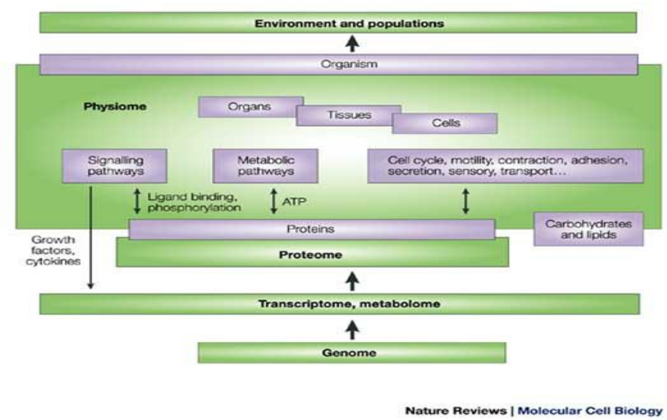
How do we link gene expression to cellular behavior? Cellular behavior to organismal behavior? Using a common currency?



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

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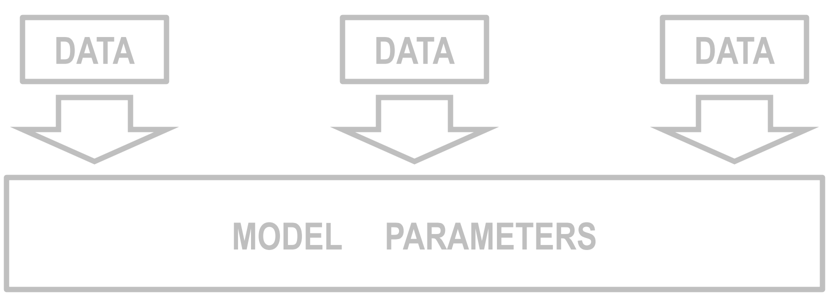
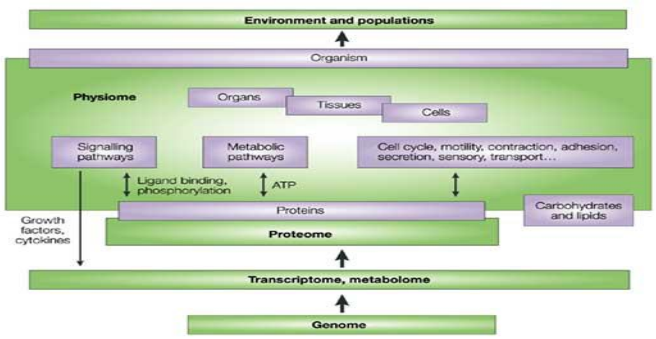
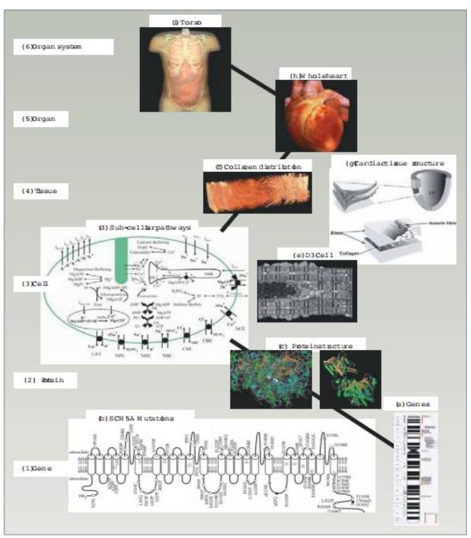


Computational-based approaches

Physiomic Modeling using CellML, SBML, and FieldML:



Nature Reviews | Molecular Cell Biology



Hunter, IEEE Computer, 2006

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

Challenge: complex models from separately-validated parts.

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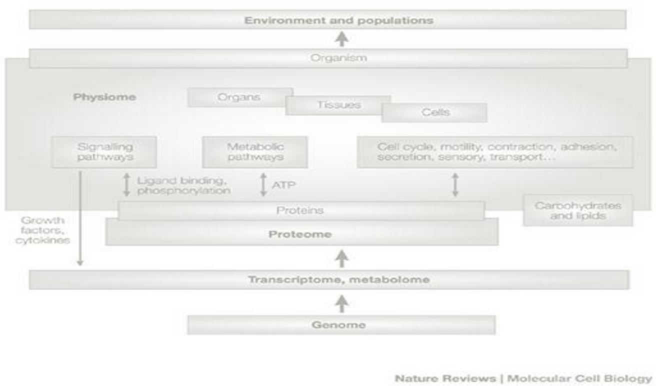

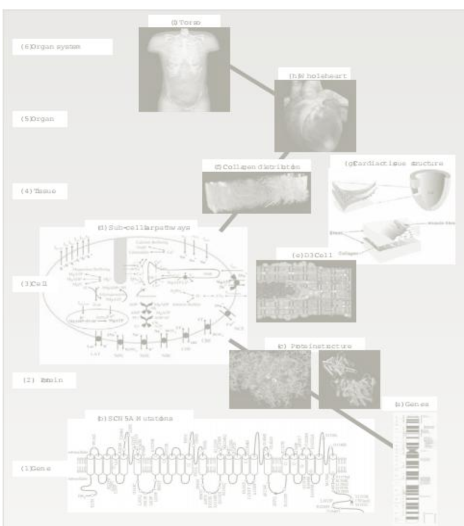

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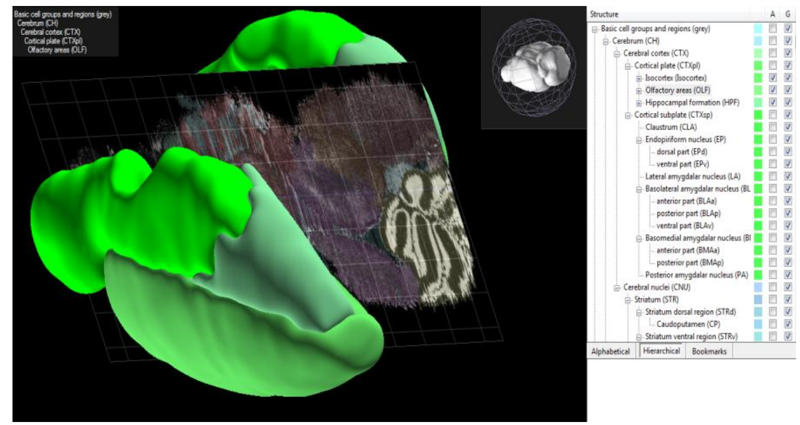
Allen Brain Atlas (merging anatomy and gene expression):

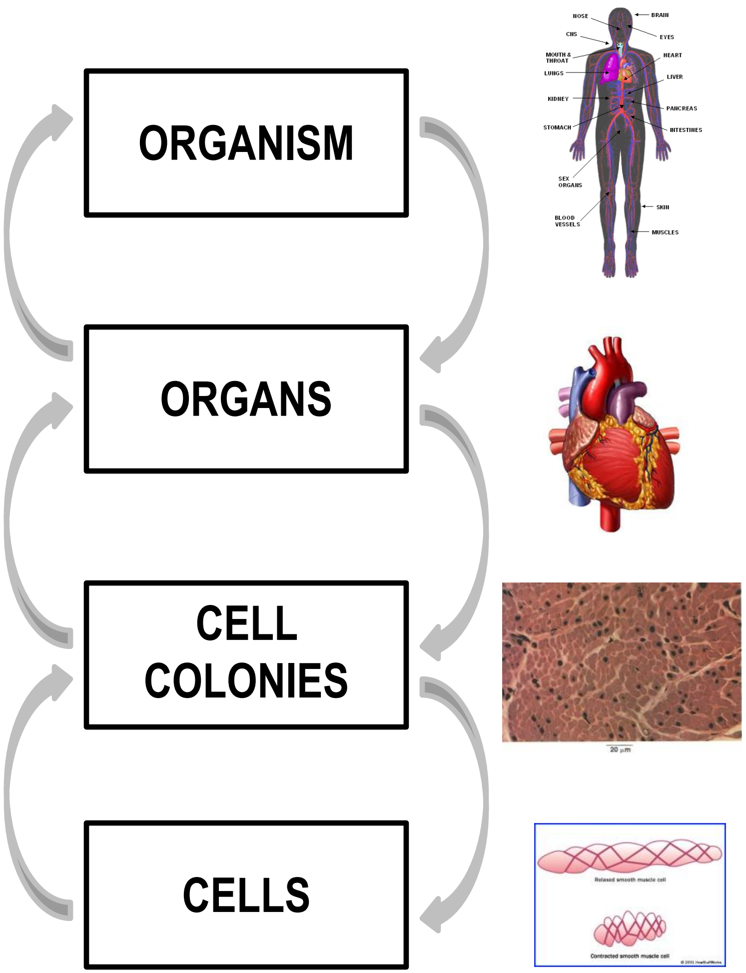


Anatomical and gene expression data combined using co-registration techniques.

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

* no explicit model of temporal hierarchy.

Trophic Model



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).

BOTTOM-UP:

* resource-based (energetic) interactions between scales.

* trophic relationship (discount between scales).

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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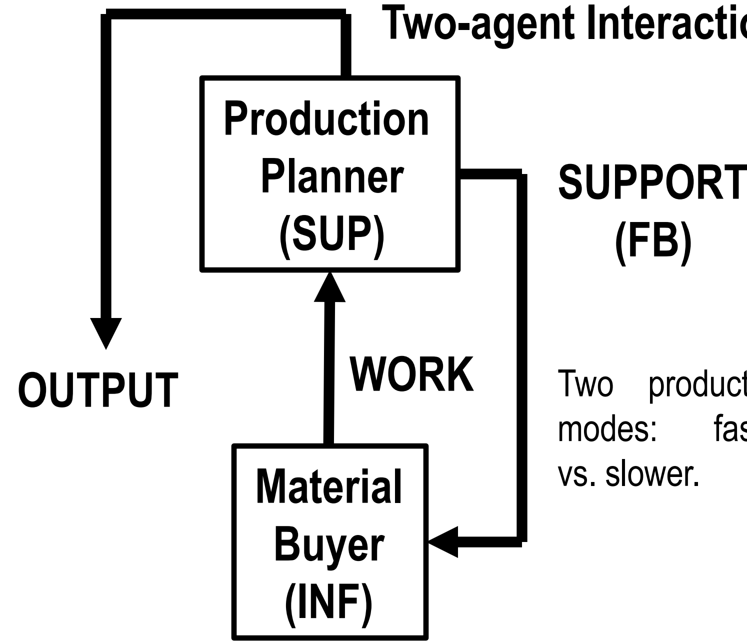
Two-agent Interaction



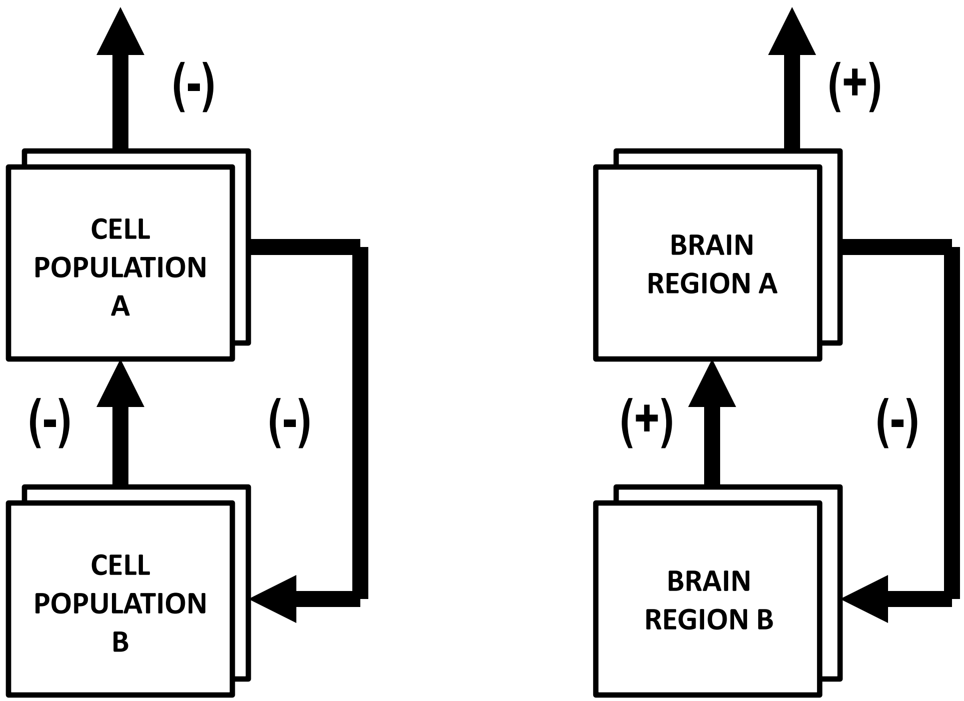
Two production modes: faster vs. slower.

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

* reward and influence of other agent = state.

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)

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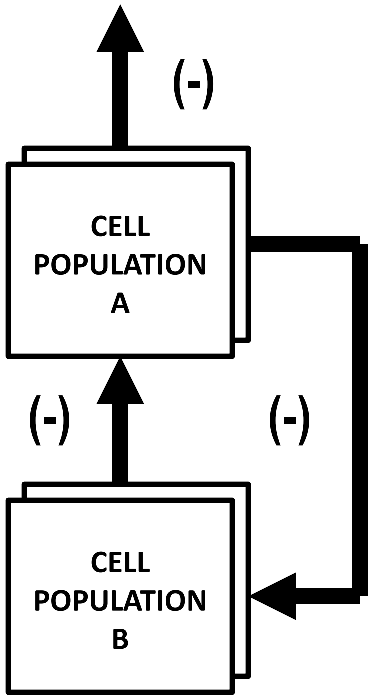

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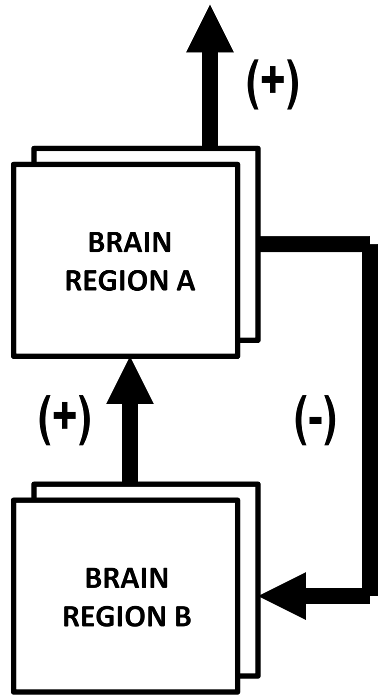

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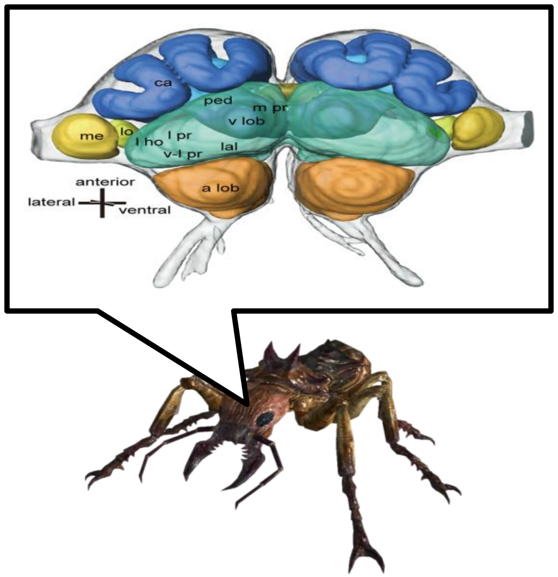
Cell populations A and B are countering each others' feedforward signals.

* 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.

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



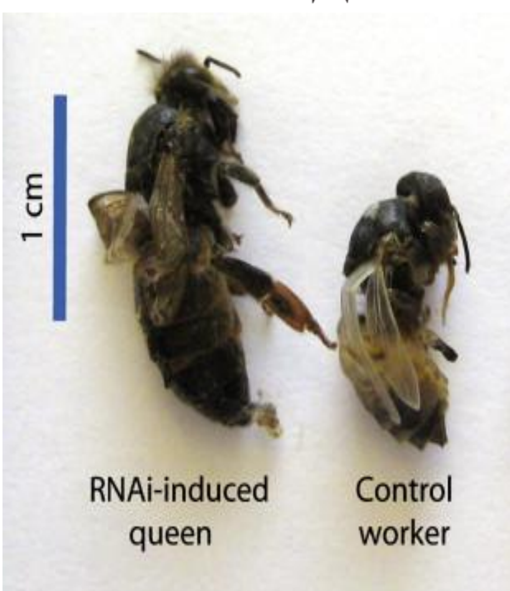


Figure 3. Hormones and Behavior, 59(3), 399–406 (2011).

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.

Cellular Reprogramming is a Rare Event (in conjunction with Dr. Steven Suhr)

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).

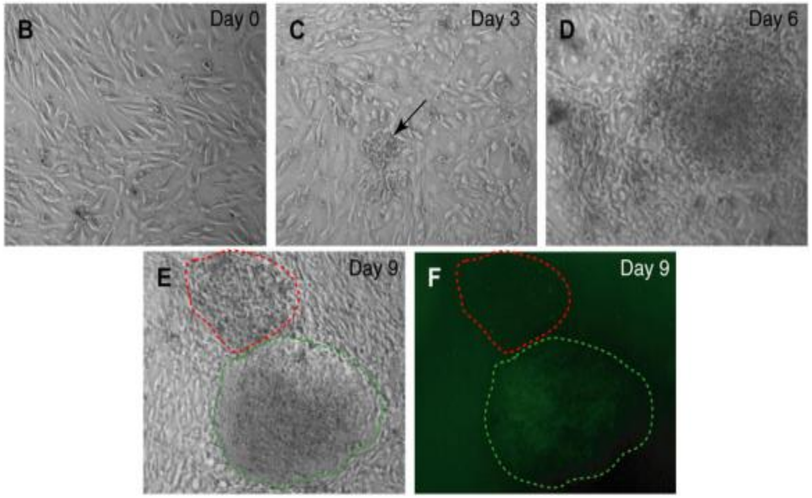
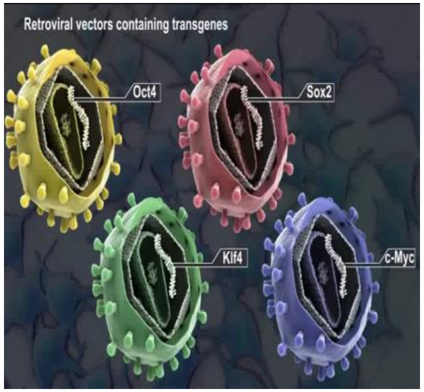
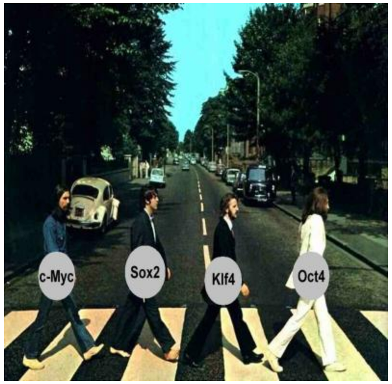
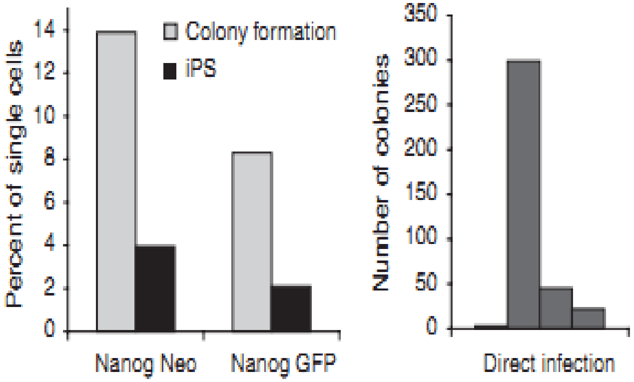


Figure 1, Stadfeld, M. et.al, Cell Stem Cell, 2, 230-240, (2008).



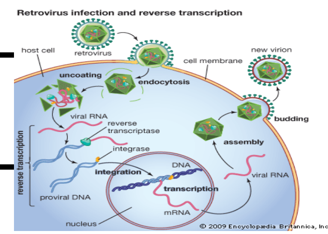


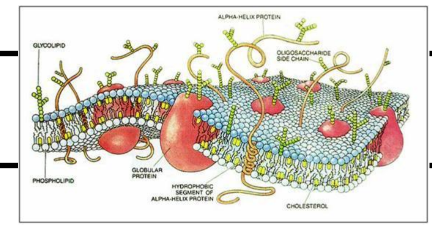
COURTESY: Stem Cell School (http://stemcellschool.com/)



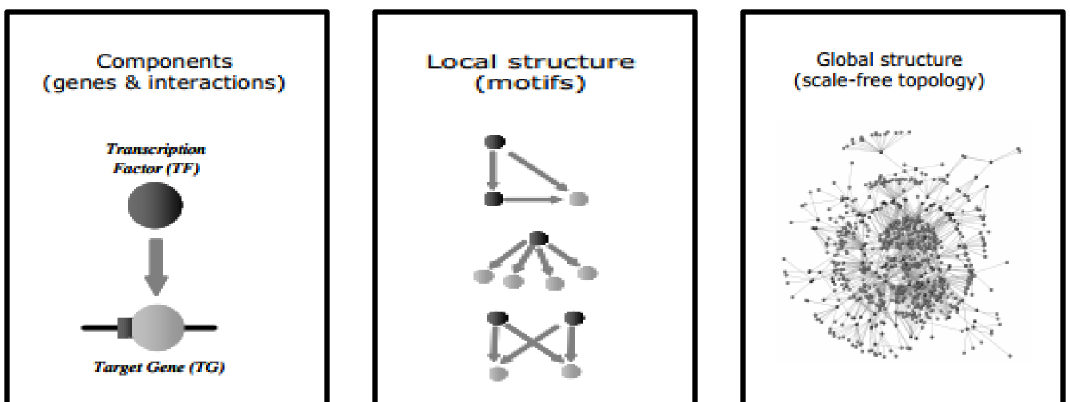
From Figure 2, Wernig et.al, Nature Biotechnology, 26(8), 916-924 (2008).

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)



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

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

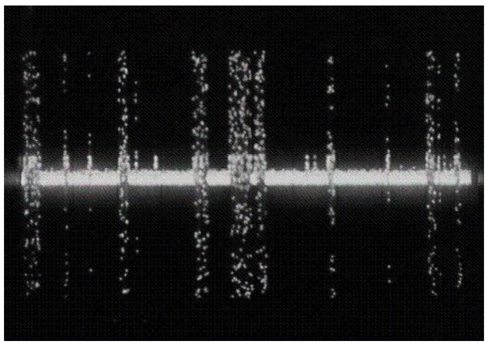
* expression of single gene can lead to a cascade.

* a cascade produces a gene expression network.

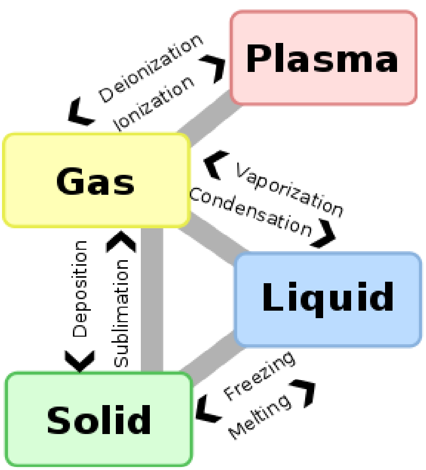
Direct Reprogramming as “Bursts” and “Phases”

“Bursty” behavior: large fluctuations randomly distributed in time (stochastic).

“Phasic” behavior: states which require major changes to initiate transitions.



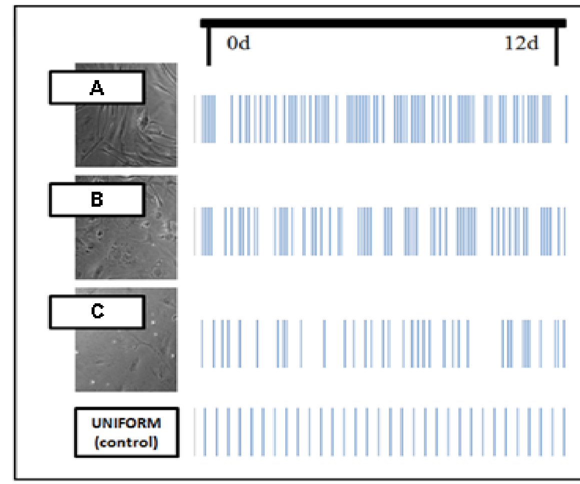
Bursty spectrum on a Local Area Network (LAN)



Phases and phase transitions for states of matter

Which model more completely describes direct reprogramming?

Can these models be merged?



Rate-based model *vs.* state space model