8. Modeling the full cellular regulatory system 1

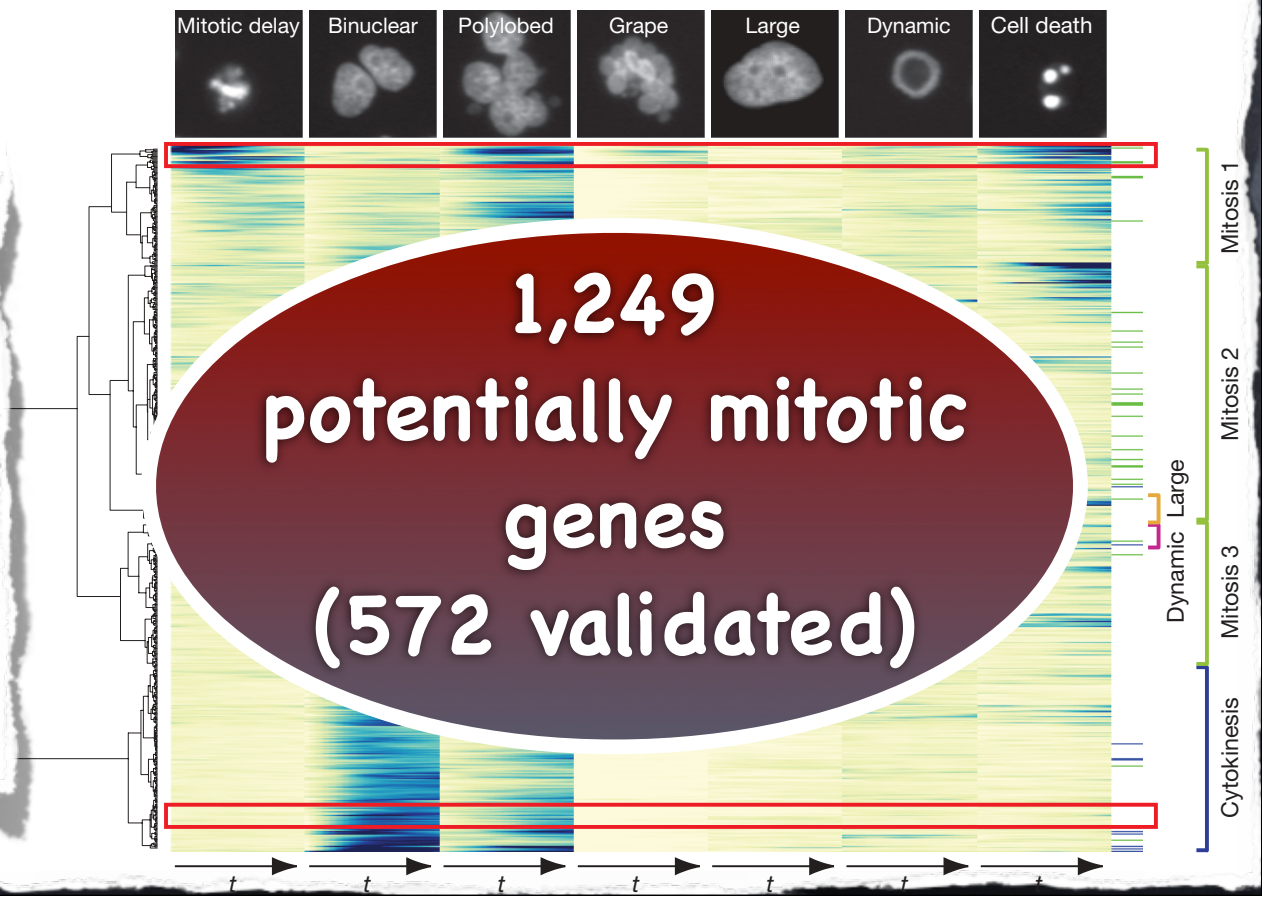
Warning: Statistical physics.
It only works on average.

http://regan.med.harvard.edu/CVBR-course.php

Gap between genes and phenotypes

- Functional annotation
  - works well for structural proteins: ribosome, cytoskeleton
  - regulatory processes & complex phenotypes: trouble
  - "gene is involved in ..." problem

- An example: cell cycle
  - siRNA for ~ 21,000 genes
  - automatic time-lapse microscopy
  - automatic scoring of aberrant cell cycle



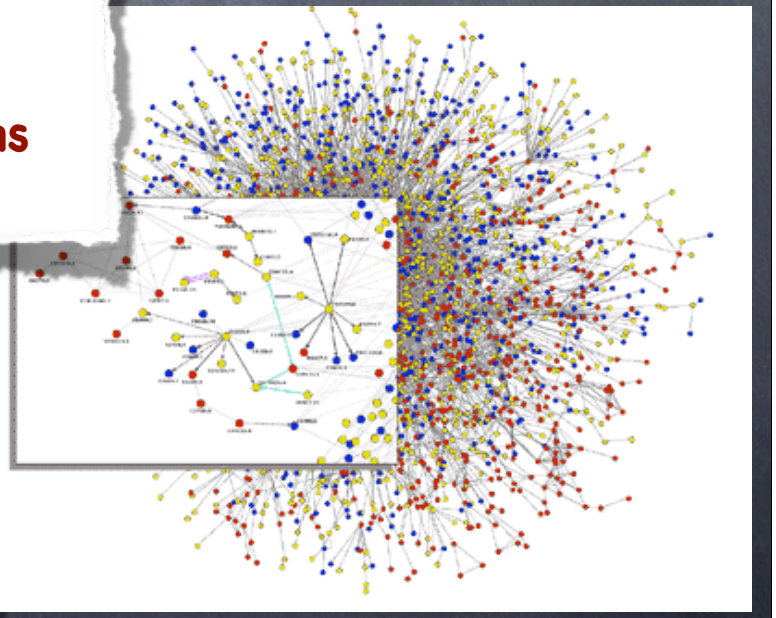
What is missing?

ZOOM

Great assays for phenotype

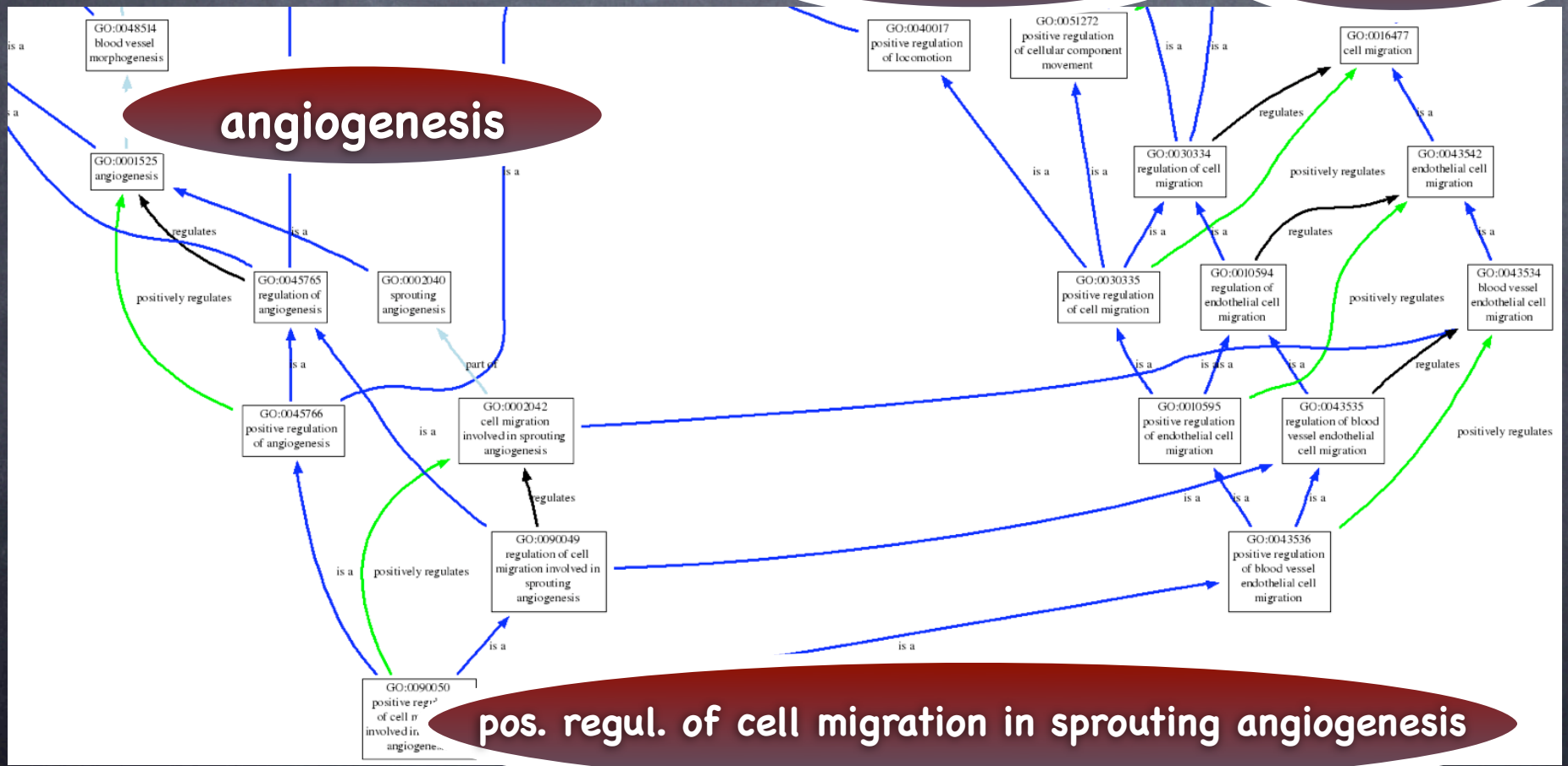
Great assays for genes

- Connections matter
  - cell-wide interaction networks are becoming available
  - TROUBLE: "small world" means the WHOLE CELL is within a few interactions of almost any gene!



- KEGG pathways:
  - great with metabolism
  - OK with signaling cascade START, no detail of what happens at the level of transcription!

- Gene Ontology
  - hierarchically organized (ZOOM ?)
  - guided by human mind dictated principles, probably different from the way function is organized in the cell!



What is function, anywhay?

- Something the cell DOES (for a biological purpose)
  - most definitions are evolutionary
  - only useful for human categorizations

- Functional gene ontologies described in an abstract of a review:

  "GO represents function from the gene's eye view, in relation to a large and growing context of biological knowledge at all levels."

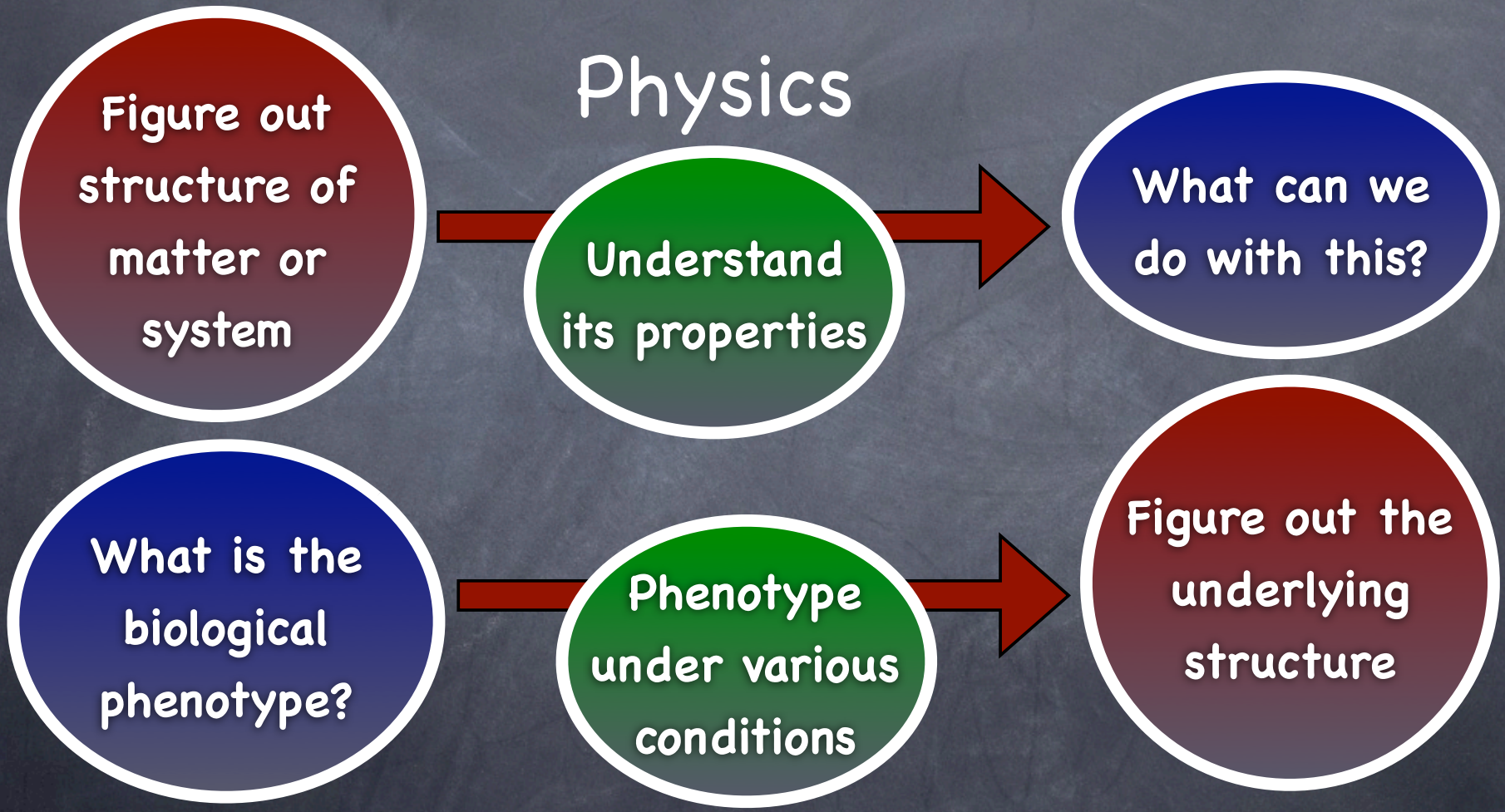
  "Pathway ontologies represent function from the point of view of biochemical reactions and interactions, which are ordered into networks and causal cascades."

nodes

links

Organization (strcuture, dynamics) of the network?

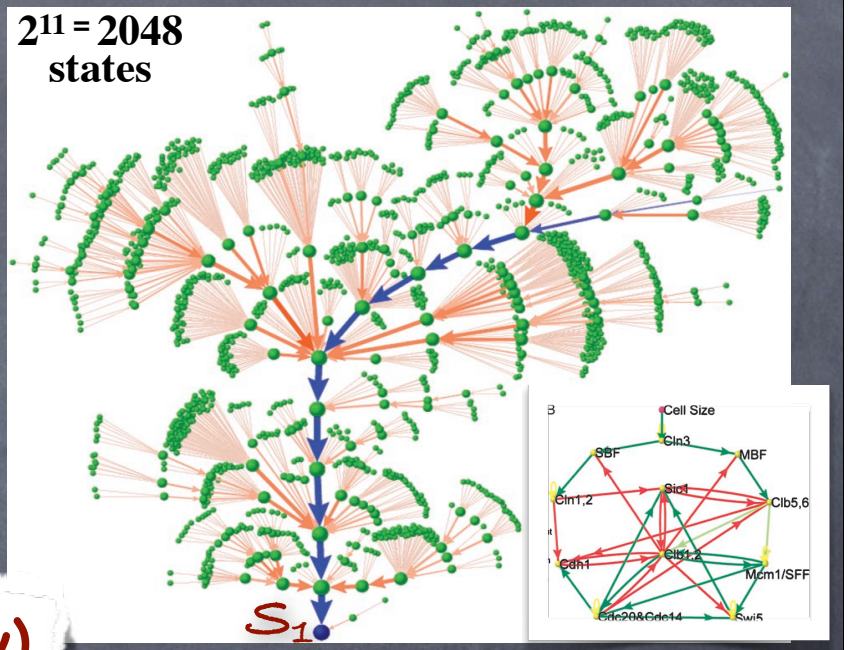
What is function? Physics is not accostumed to this concept...



Some mandatory properties of function

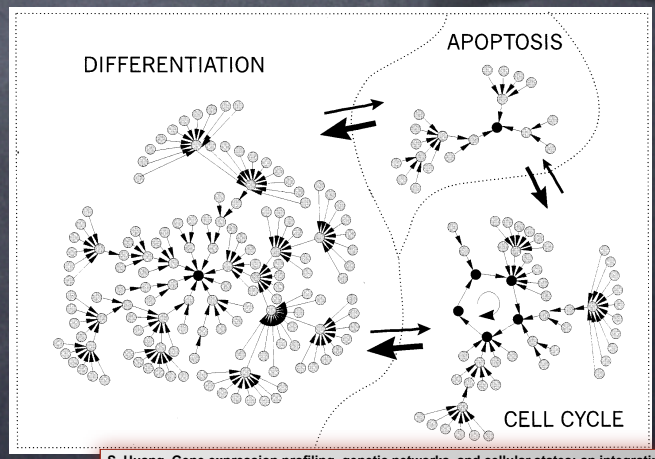
1. A robust state or behavior
   - Environmental variability (noise)
   - Recognizable within different contexts

   Examples:
   - cell types
   - cell cycle, apoptosis



2. A choice in function (multistability)
   - Functions need to be controlled: turned ON - OFF, modulated
   - Responsiveness to specific stimuli

   Examples:
   - cell type to turn into
   - cell cycle or apoptosis



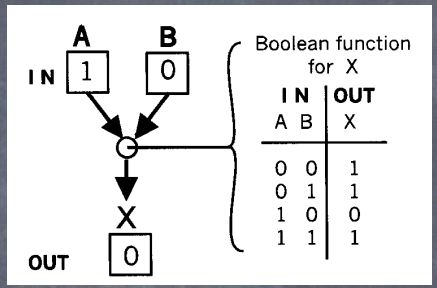
S. Huang. Gene expression profiling, genetic networks, and cellular states: an integrating concept for tumorigenesis and drug discovery. J. Mol. Med, 77(6):469–480, 1999.

A minimal model: Boolean networks

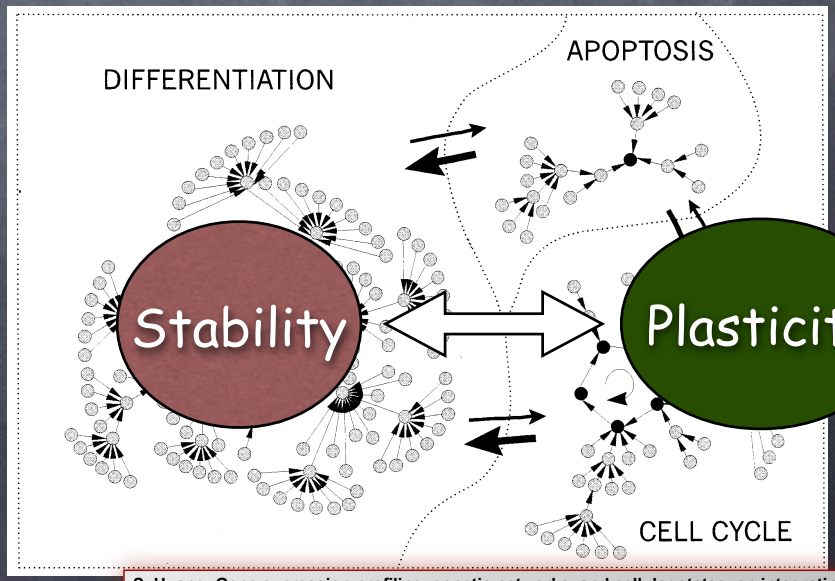
- Random network
- State of the system, or gene activity profile: (0,1,1,0,0,1,1,1,0,...,0)
- Random Boolean rules
  - ➡ p - prob. output value 1

Kauffman, S, Homeostasis and differentiation in random genetic control networks, Nature 224, pp 177, 1969

(NOT A) OR B



- State changes in time: trajectory in nD space
- Structure of state space determines all possible dynamics



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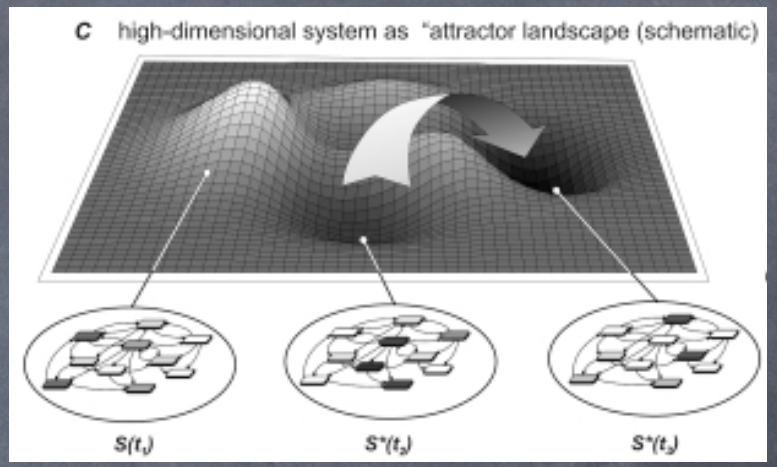
Random Boolean networks have an ordered regime

- Only a small fraction of all cell states are **stable**
- The system does not visit all possible states
- **Attractors**:
  - Fixed points: a state in which all Boolean rules are satisfied
  - Limit cycles: a finite number of states through which the system cycles
- **Attractor basins**



Function = mutually exclusive attractor states:

- **stable cell types**
- **stable phenotypes**
- **stable paths**

Power of the conceptual framework

- All nonlinear dynamical systems have attractor states and basins, they can also have multistable but non-chaotic dynamics
- Most conclusions from Boolean systems apply regardless of system details!

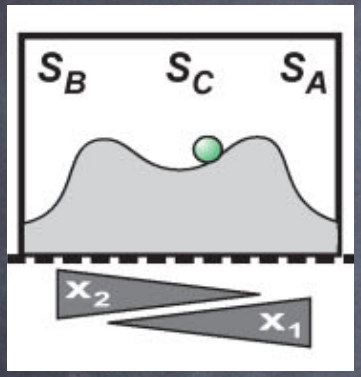
Homeostasis

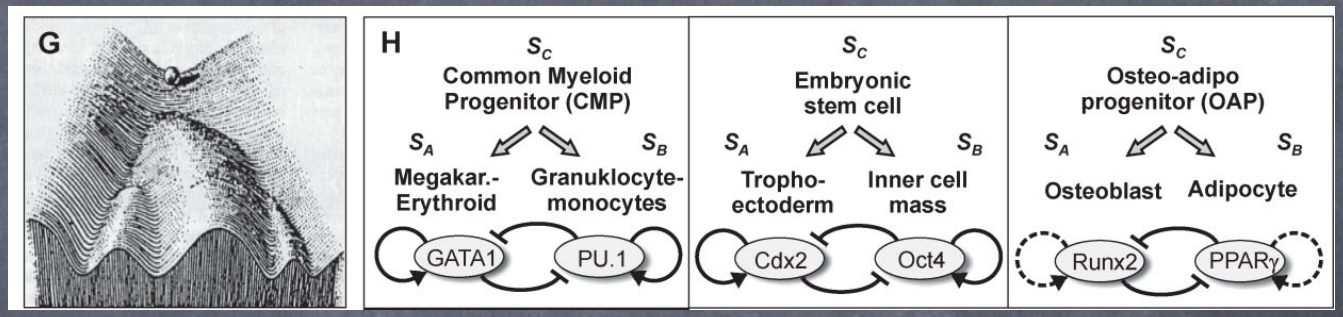
- Robustness to environmental fluctuations, variability
- Large basin size -> stable functional state
- In oscillation, not juggling multiple parallel signals during the same cycle

Power of the conceptual framework

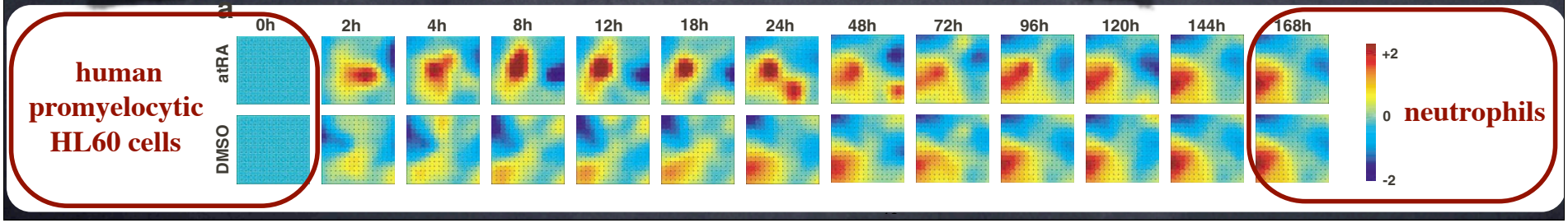
Functional choices

- Multi-stability: more than one stable attractor
- Flexibility: specific stimuli can trigger attractor change





- Change of function does not require exquisite control of signaling -> basin change
- Multiple converging routes to 1 phenotype



Power of the conceptual framework

Epigenetics

- Dynamical systems have "memory"
- Inheritance of a phenotype does not mean exact inheritance of the entire cell state!
- Daughter cells ONLY need to inherit a state within the same attractor basin!
- Role of epigenetic DNA modification:
  - LESS PRONE TO CELLULAR NOISE?
  - guarantee the choice of attractor basin!

Power of the conceptual framework

The microenvironment

- Some cells are only "themselves" within their tissue micro-environment
- Translation to dyn. systems: state of a few nodes in the network are fixed by this environment
  1. cannot dynamically change due to internal dynamics
     - this is akin to rewiring the network!
     - new "pseudo-attractors" can arise, only seen if the microenvironment is right
  2. OR: microenvironment can be seen as setting the input to the already existing network, allowing it to choose appropriately

Power of the conceptual framework

Disease

- Environment
  - for the dynamical system this is the same as microenvironment
    - forcing the system into a "pseuso-attractor" (i.e. the cell is in a non-physiological state)
    - giving the wrong instruction for functional choice (i.e. the cell is in a wrong physiological state)
- Mutation
  - reshuffling of the attractor landscape
  - new disease-attractors may arise
  - stability of not desired functional states may increase

Cancer as an example

Huang and Ingber. A non-genetic basis for cancer progression and metastasis: self-organizing attractors in cell regulatory networks. Breast Disease (2006): 26, 27-54.

- Uncontrolled cell growth
- progressive disruption of tissue architecture
- Metastasis
  - ECM breakdown
  - epithelial to mesenchymal transition (EMT)

This is a physiological state!

- Standard models of cancer progression
  - Multi-step progression
    - random mutations + DNA modifications
    - selection pressure
    - => rare metastatic population
    - selection of all genetic alterations ONE BY ONE would be required (~90 in cancer cells)
    - not clear where the pressure comes from

Orchestrated switch of large part of genome!

- Direct challenge
  - expression of metastatic tumors MORE SIMILAR to primary tumor than to metastatic tumor in other patients...
  - not a separate genetic phenotype, selected for by competition!

- Intrinsic metastasis model:
  - primary tumor has (or does not have) the genetic signature predictive of metastasis

But how?

- Metastatic dissemination:
  - tumor cells found in bone marrow BEFORE primary tumor apparent
  - these cells may start independent tumors on their own with mutli-step progression
  - these cells sometimes have epithelial phenotype at the new site, at least for a while

- Cancer as a trans-differentiation event
  - not entirely the business of the transforming cell
  - cytokines, ECM influence transformations
    - TGFb in carcinoma cells -> ETM
  - Question:
    - why is this transformation so robust
    - why do carcinoma cells react to TGFb by undergoing EMT, instead of cell cycle arrest, as normal epithelial cells?

Fundamental chanhe in view from mutation

- Reactivation of "embryonic programs"
  - how can this happen so readily and still allow embryonic development to be a robust process?

The attractors of cancer

One genome, one landscape

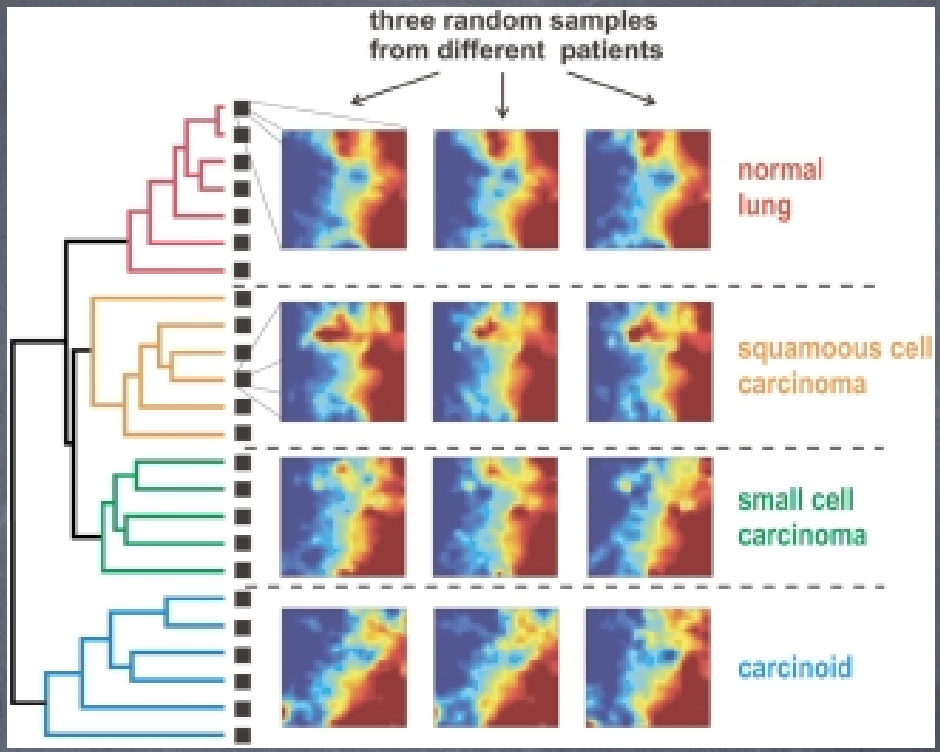
- The genome of an organism and all possible interactions define the dynamical system
- There is ONE large space of states and ONE set of attractors
  - Difference in cell type: difference in WHERE the cell sits in the landscape
  - => "embryonic attractors" are present but not used in the dynamical system of adult cells

Some attractors are hard to get to

- Far away in state space
- Large "epigenetic" barriers (i.e. quite a few things have to change at the same time to place the system in another attractor basin)
  - 4 transcription factors that make iPS cells
  - normal tissue environment never facilitates these types of changes

Cancer states are attractor states

- Discrete subtypes
- Large number of different underlying mutation
- no continuum of phenotypes!



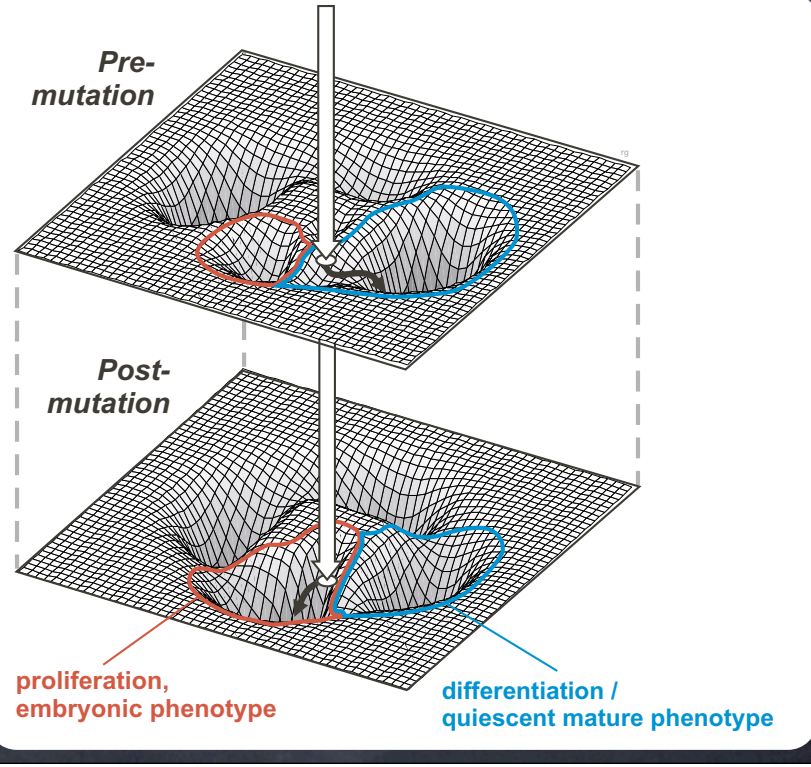
What do mutations do?

- Permanent rewiring of the regulatory network
- Ordered random networks are ROBUST to limited rewiring
  - attractor landscape will shift, or change LOCALLY => basic cell funcitonality stays the same, except in a few places
  - basin sizes change
  - barrier hights change

- Allow access to embryonic attractors from an adult expression profile (Huang)
  - external stimuly may be needed for switch, even after mutations => role of environment
  - NOT de-differentiation, but similarity to embryonic states!
  - EMT: change into the mesenchymal attractor
    - multiple stimuli can robustly achieve it with cancer cells
    - "normal" epithelial cells cannot easily cross the barrier

Cancerous mutations

Increase of embryonic basin



The attractor landscape offers an integrative framework for different ideas

- Multi-step progression with selection
  - initial reshuffling of landscape may make proliferation accessible but less robust (NOT de-differentiation!)
    - early tumor cells are often apoptotic, further mutation and selection is likely to play a role

- Intrinsic metastasis model & metastatic dissemination
  - original reshuffling of landscape can allow access to proliferation AND mesenchymal attractors (both accessible to ES cells)

- De-differentiation
  - not quite: a cancer cell is an altered dynamical system, but NOT entirely new
  - embryonic-type programs are re-activated, very similar to ES cells

9. Modeling the full cellular regulatory system 2

- Modularity and Hierarchy -

September 28
12 PM