Complexity and Hierarchies

In honor of George Stephanopoulos's 70th Birthday and Retirement from MIT

June 1, 2017





One must enjoy all seasons



The Architecture of Complexity (Herbert A. Simon, 1962)

- A complex system is made up of a large number of parts that interact in a non-simple way.
- Complex systems are less susceptible to external disturbances if they are hierarchically organised, decomposable systems.

- A hierarchy consists of a number of subsystems organized in a *functional* and *spatial* relationship to one another and, in their totality, possess the character of an integral whole.
- The hierarchical whole imparts new properties to its individual parts, which, in turn, fulfills previously non- existent functions.

George's prelude to process control literature

"Studies in the Synthesis of Control Structures for Chemical Processes. Part I: Process Decomposition, Optimizing Control Structures and the Selection of Secondary Measurements," *M. Morari, Y. Arkun and G. Stephanopoulos*, AIChE J., 26, p. 220 (1980).



Temporal Hieararchy

Spatial Hieararchy





Complexity and Hierarchies in Cellular Networks

Signal Transduction Pathways

MAPK (mitogen activated protein kinase) Pathway



MAPK Pathway Controls:

Cellular growth, proliferation, and differentiation.

hrs

min

Cell Cycle Control and ERK Signaling



Synthesis of Regulatory Cellular Feedback Structures



Synthesize:

- Sensor molecules;
- Actuator species;
- Reaction Network

How has evolutionary design done it?

Autocrine positive feedback

argos GF TACE EGI GI ERK argos ERK Grb2-SOS nucleus Ras Raf ERK MEK nucleus DUSP ERK

Cytoplasmic Negative Feedback Transcriptional Negative Feedback



Closed-Loop Dynamics of MAPK Pathway

A Hallmark of Cellular Dynamics: *Robust Bistability and Switching* Dynamics



Bistability and Feasible Regimes for ERK Signaling



Adaptive Feedback Topologies

MAPK's feedback topology/reaction network adapts to different external stimuli to generate different ERK dynamics and biological responses.



Analysis and Engineering of the Cellular Feedback Loops Hybrid Control





SOME CHALLENGES

- How complex should the models become? Logic based Boolean models vs continuous mechanistic models or a combination ?. A new paradigm?
- Complexity Reduction of the biochemical networks.
- Design of synthetic feedback networks (in vivo or in silico) for signal transduction pathways.
- Spatio-temporal control of multiple interacting signaling pathways.



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