NetSciReg Satellite Session
Monday, June 19, 2017
Indianapolis, Indiana, USA

Cybernetic Representations of Suboptimal Regulatory Systems

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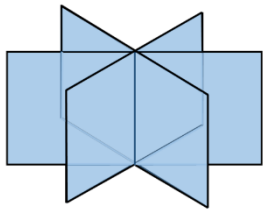
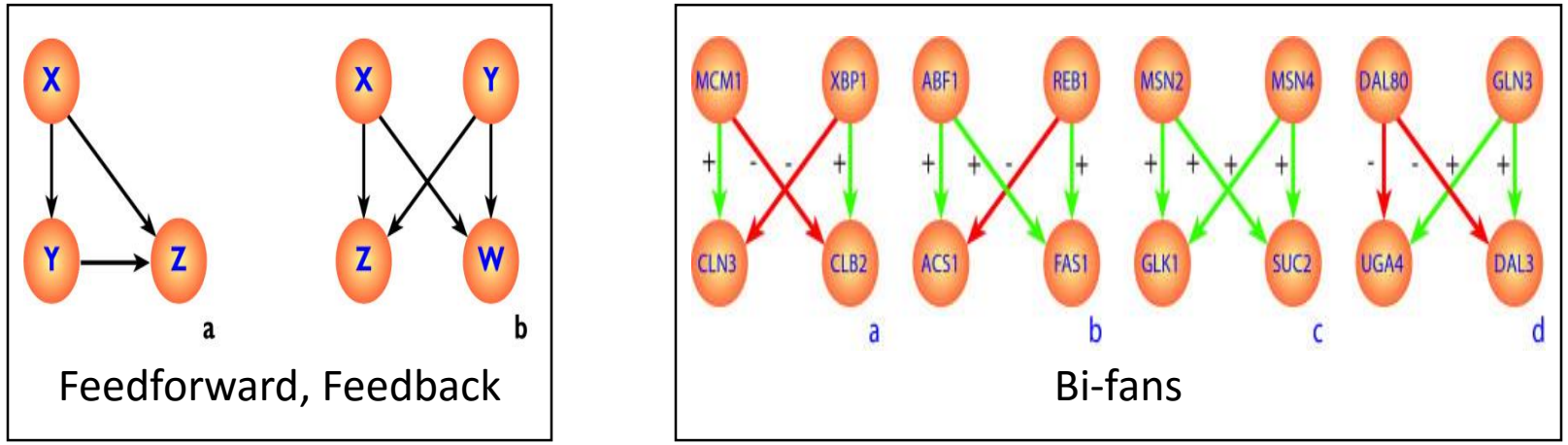
OpenWorm Foundation, Orthogonal Research



How do we understand holistic regulation (not just gene networks) in biological systems?

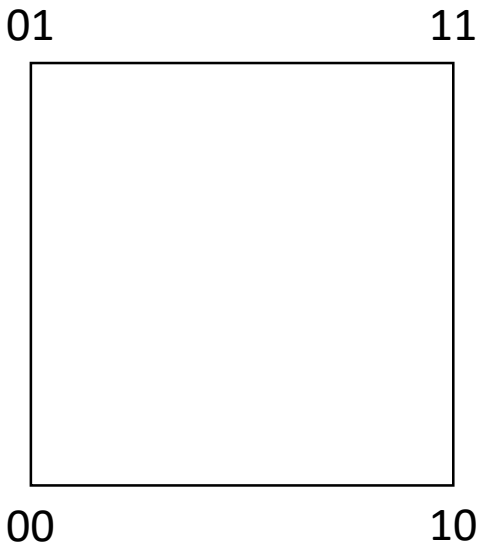
1) Motif Approach: simple, recurring mechanisms (e.g. switches, feedback loops, bi-fans).

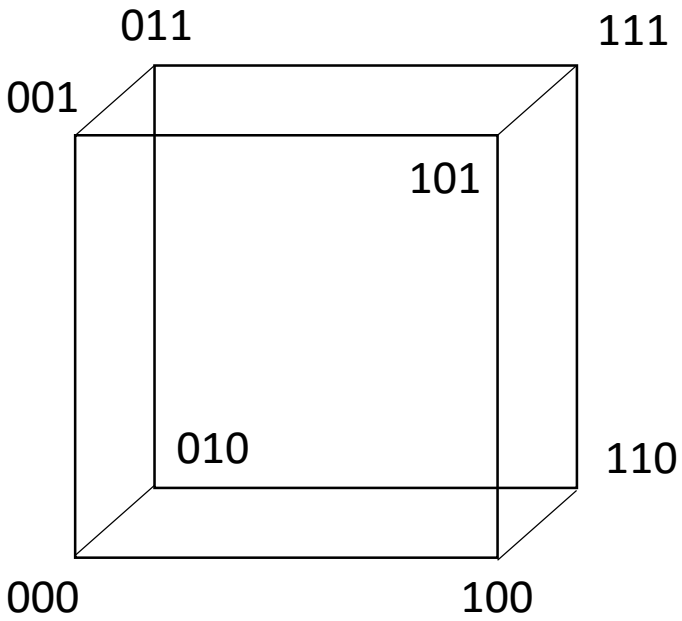
COURTESY: BMC Genomics, 7, 108 (2006).

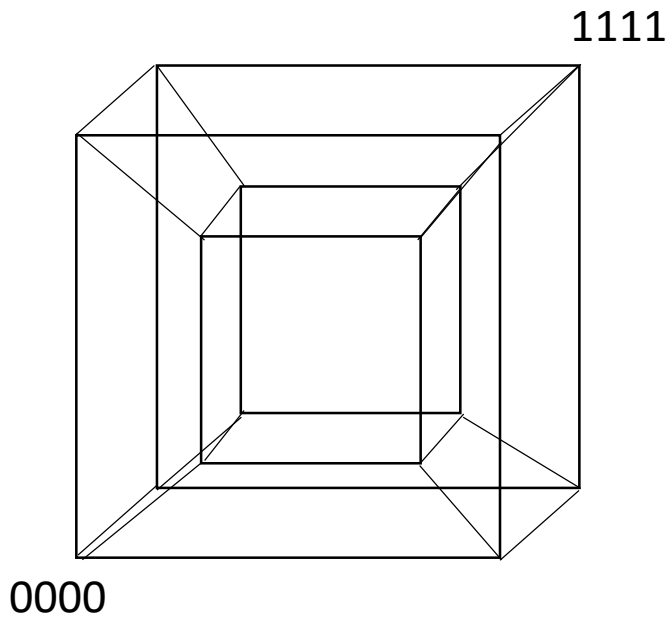


* reductionist approach to structure, merely descriptive and does not relate structure to function.

2) Stepwise Model: a discrete system of potential phenotypes, steps represent the number of steps required to change from one phenotype to another.



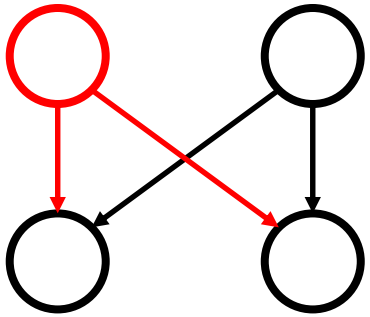




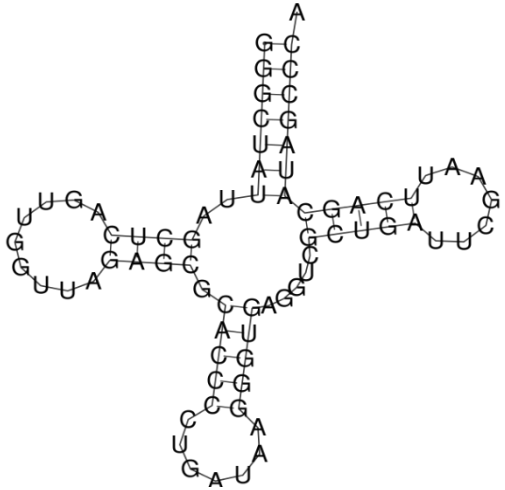
* based on simple, discrete phenotypes (e.g. RNA). Description length (number of bits) scales with complexity (number of steps required to go from one homogeneous phenotypic state (e.g. 000) to another (e.g. 111).

Change in structure = local change in function (switch to bi-fan)

Motif Change

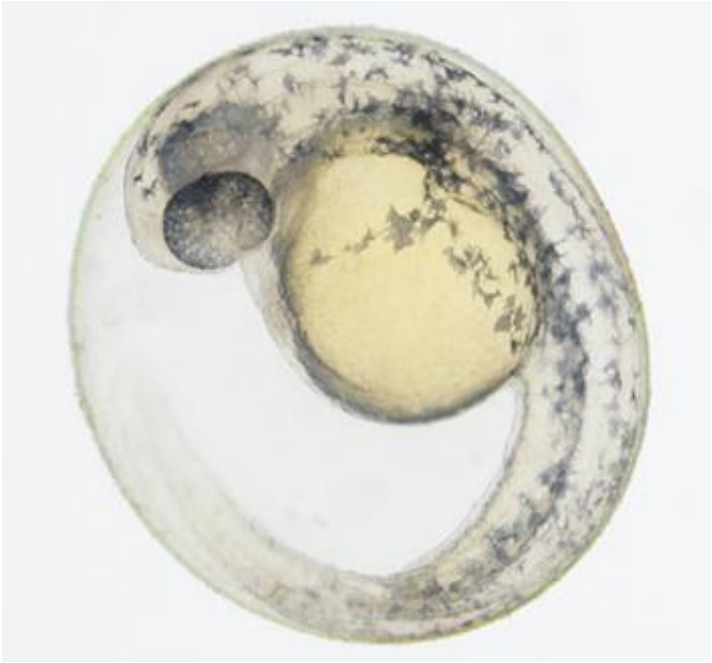


Stepwise Change



Stepwise model describes discrete structural or functional changes (RNA phenotype)

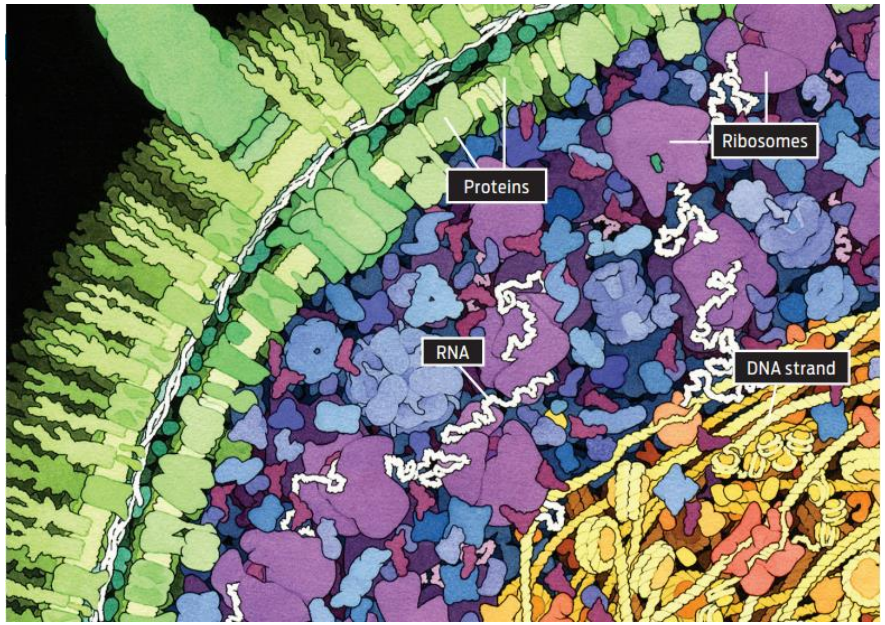
Regulatory Change



Cybernetic model describes changes in function and geometric structure (e.g. Zebrafish embryo) as the stepwise addition of regulatory motifs.

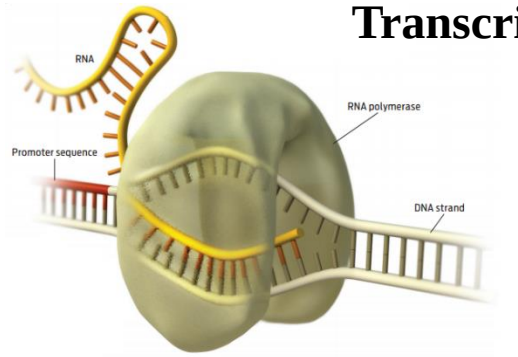
Cybernetic regulation can be seen in a regulatory model of mRNA production in mammalian cells.

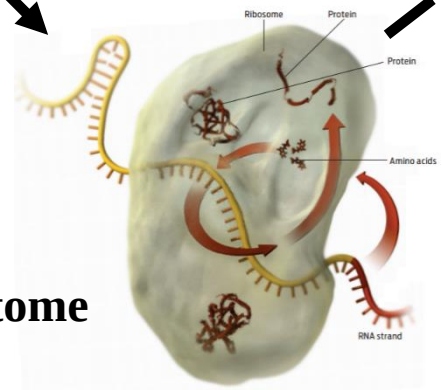
Images from: IEEE Spectrum, March 2011, 38-43.



Modeling Cellular Information Processing Using a Dynamical Approximation of Cellular mRNA. bioRxiv, doi:10.1101/006775.

Transcriptome





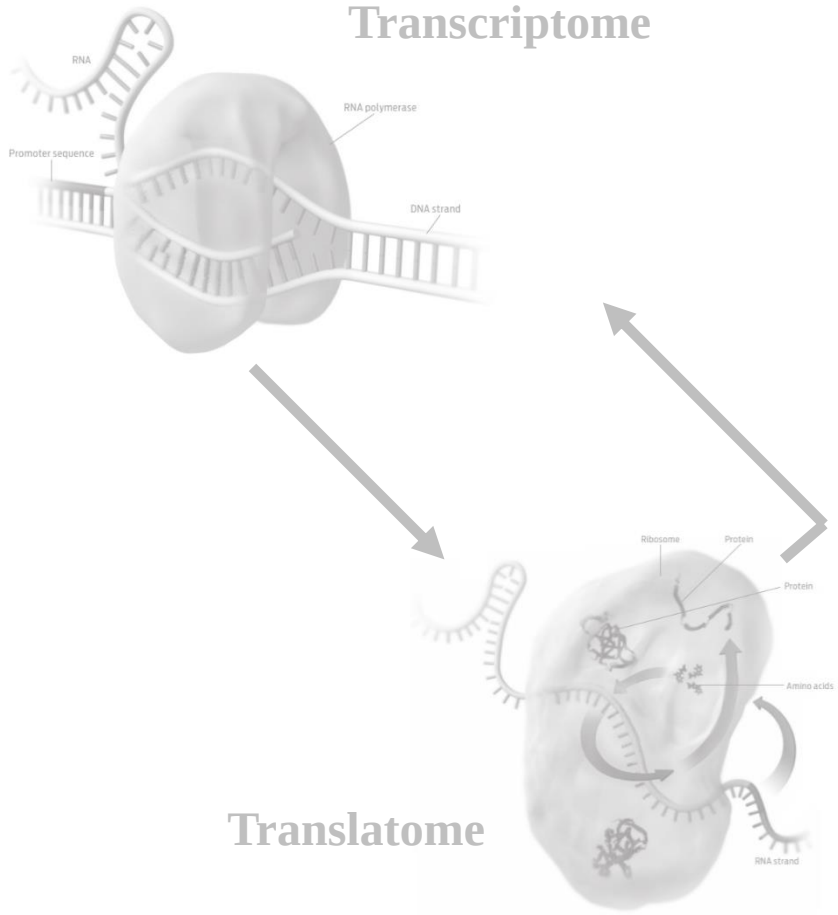
Translatome

Cybernetic regulation can be seen in a regulatory model of mRNA production in mammalian cells.

First-order delay differential equation can be used to describe production and decay of mRNA.

$$\frac{dy}{dt} = f[x(t-\tau)]$$

$$\tau = \begin{cases} -ax^2 + ax + b, & \text{aggregation} \\ ax^2 + ax - b, & \text{nonlinear decay} \\ -ax + b, & \text{decay} \end{cases}$$

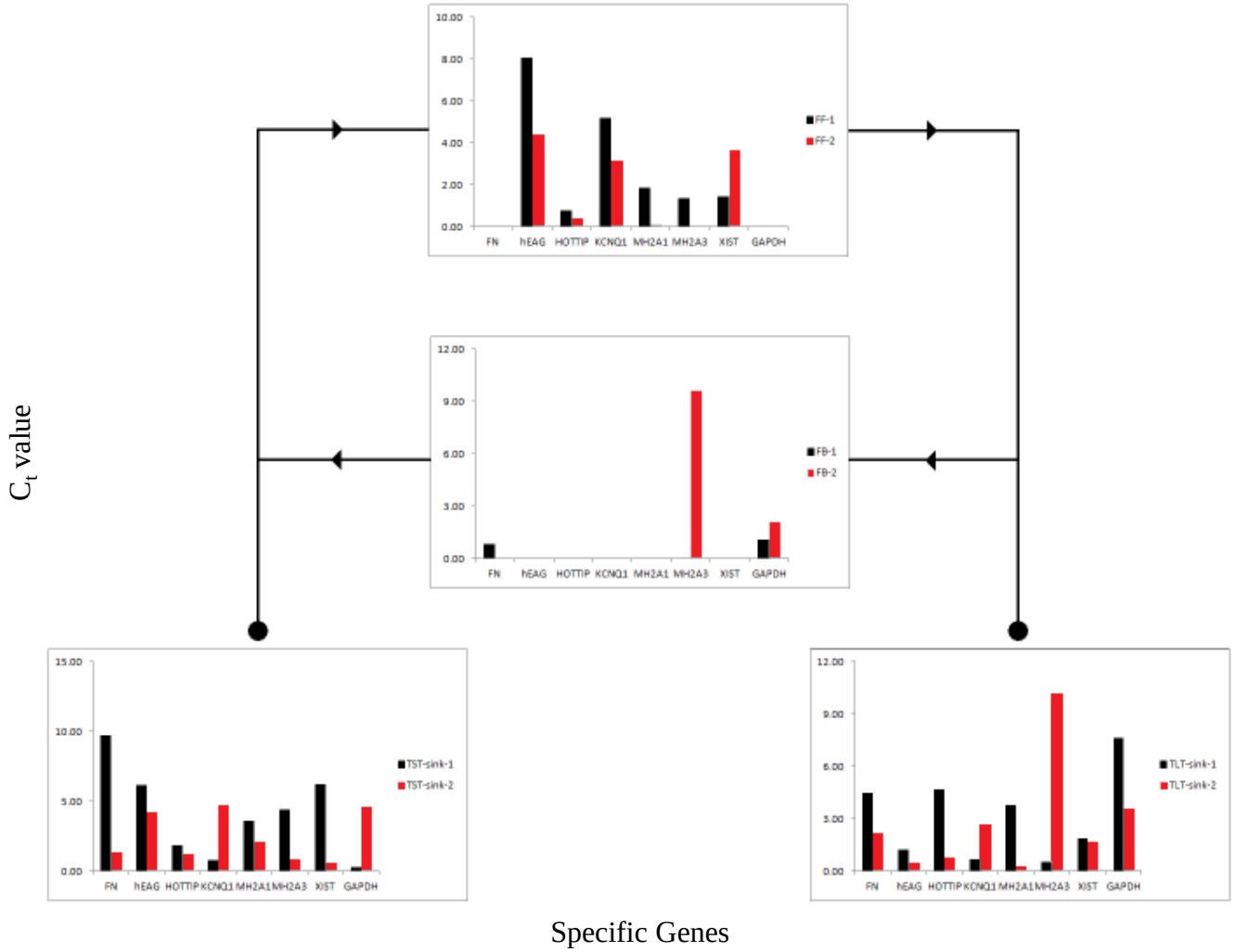


In a cybernetic/DDE hybrid model, a first-order feedback loop can be used to identify specific systems-level behaviors.

$$\frac{dy}{dt} = f[x(t-\tau)]$$

Aggregation, nonlinear decay are second-order (e.g. polynomial) effects

$$\tau = \begin{cases} -ax^2 + ax + b, & \text{aggregation} \\ ax^2 + ax - b, & \text{nonlinear decay} \\ -ax + b, & \text{decay} \end{cases}$$

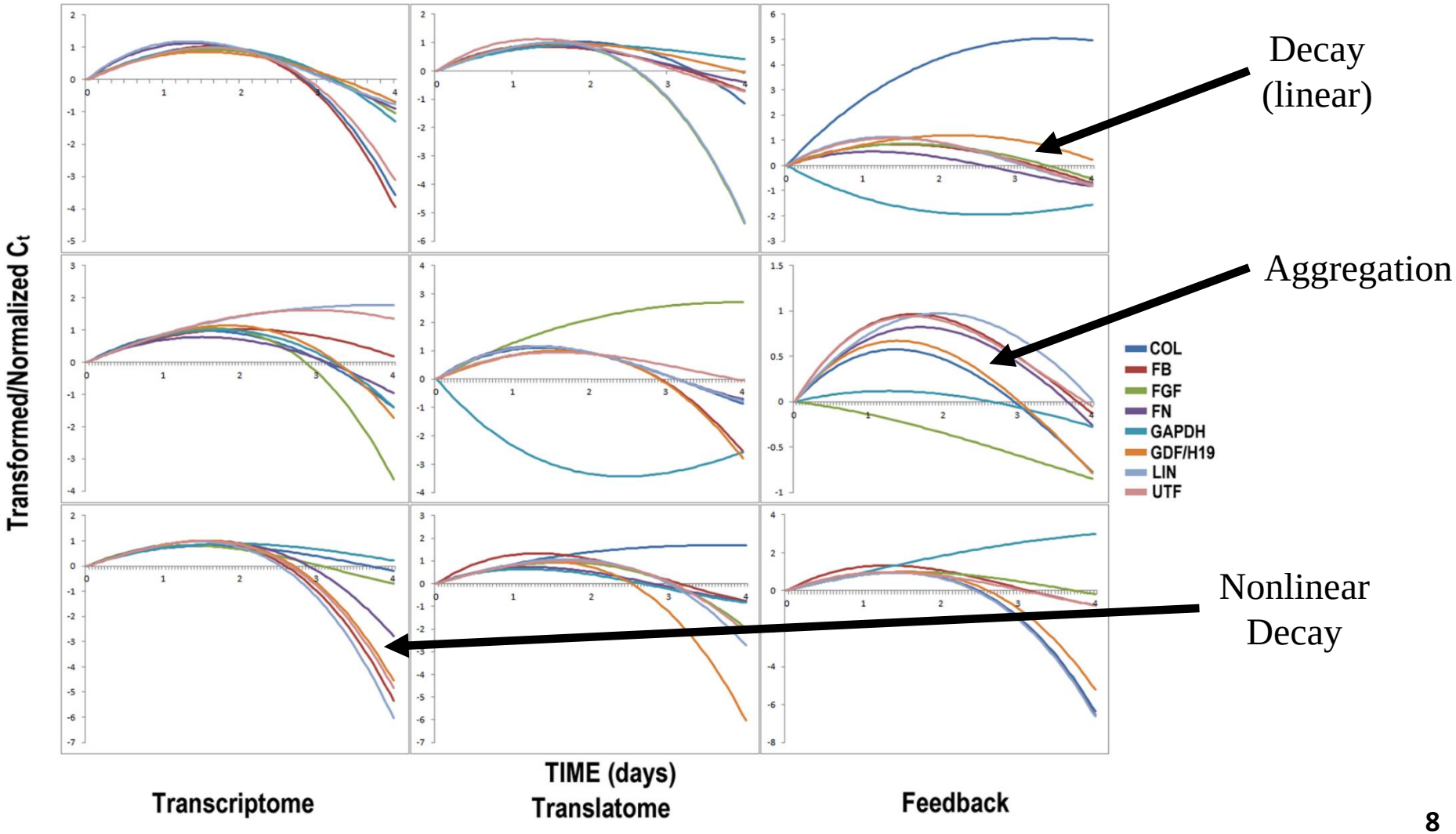


Regulation of mRNA over 4 day period (smoothed time-series data) results in characteristic system-level behaviors

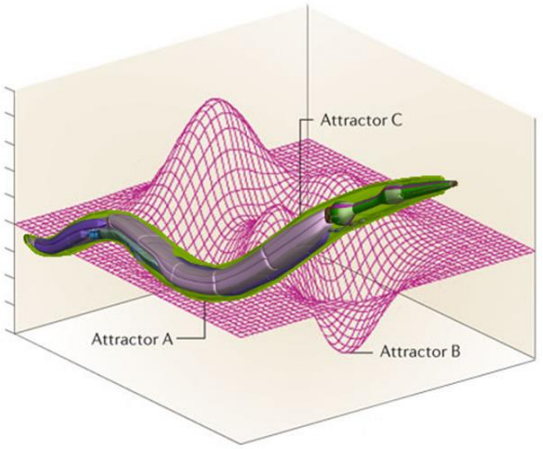
Translation Suspended with Saporin

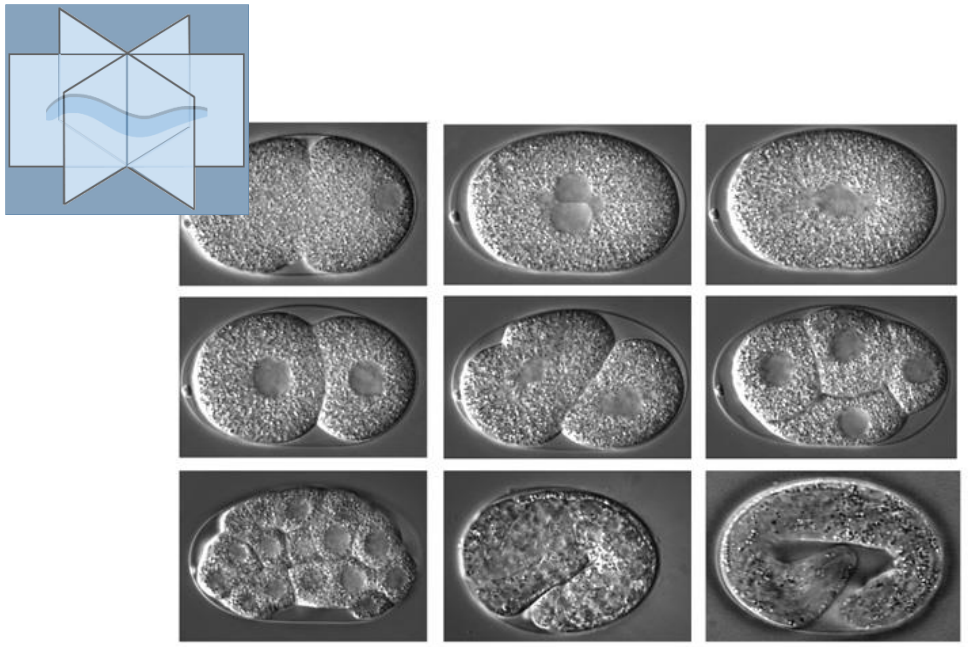
Transcription Suspended with Actinomycin D

Transcription and Translation Suspended with Mitomycin C



DevoWorm





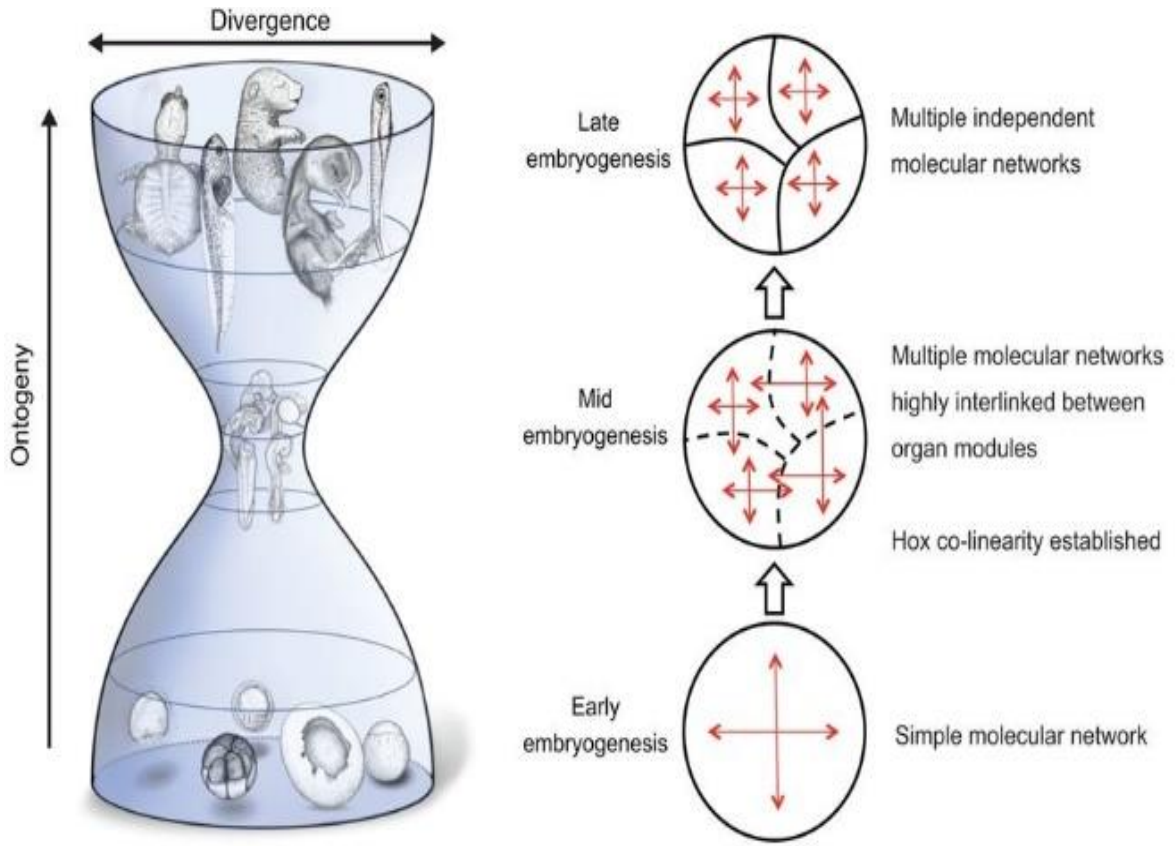
Our current model system is development (embryogenesis).

What is the architecture for a cybernetic model of regulatory change?

At the molecular level, the independence of network modules in development is an important determinant of output variation:

* phylotypic phase: molecular networks between phenotypic modules interact.

* late embryogenesis: molecular networks become independent.



COURTESY: Development, 141, 4649-4655 (2014). doi: 10.1242/dev.107318.

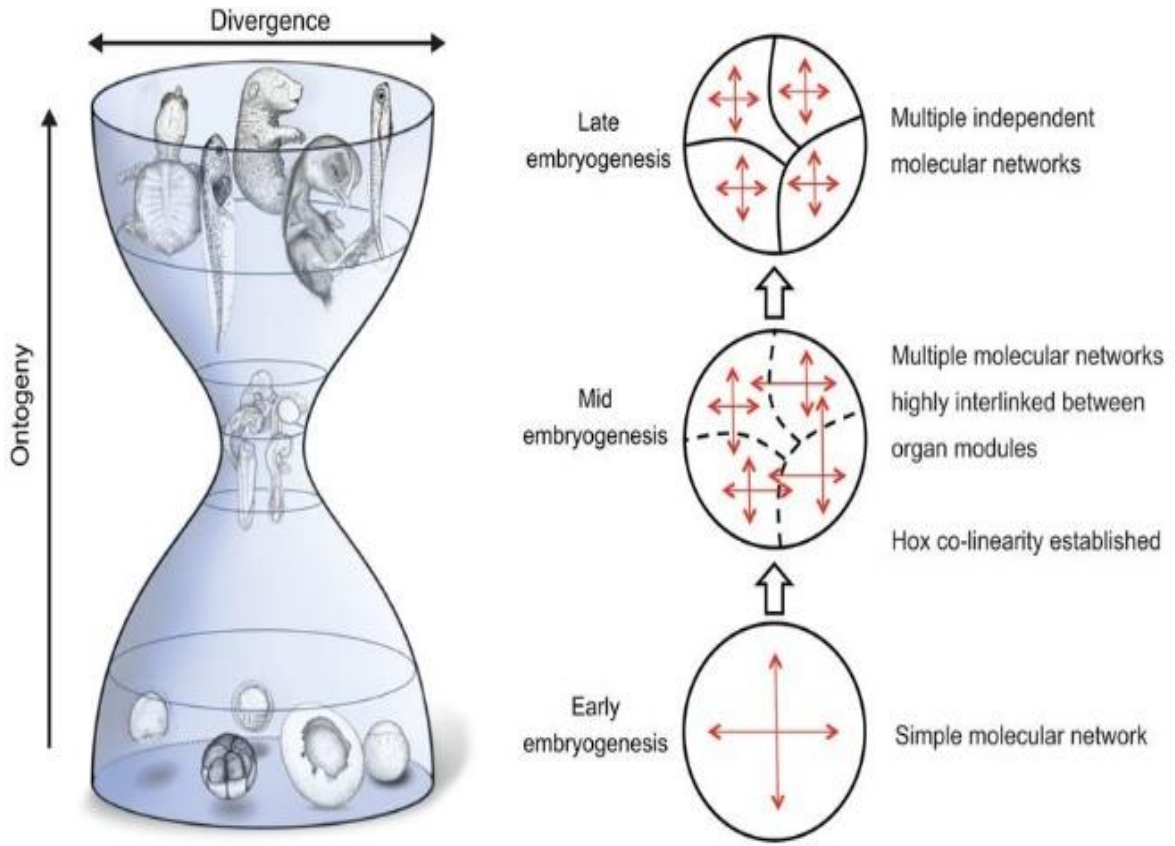
At the molecular level, the independence of network modules in development is an important determinant of output variation:

* phylotypic phase: molecular networks between phenotypic modules interact.

* late embryogenesis: molecular networks become independent.

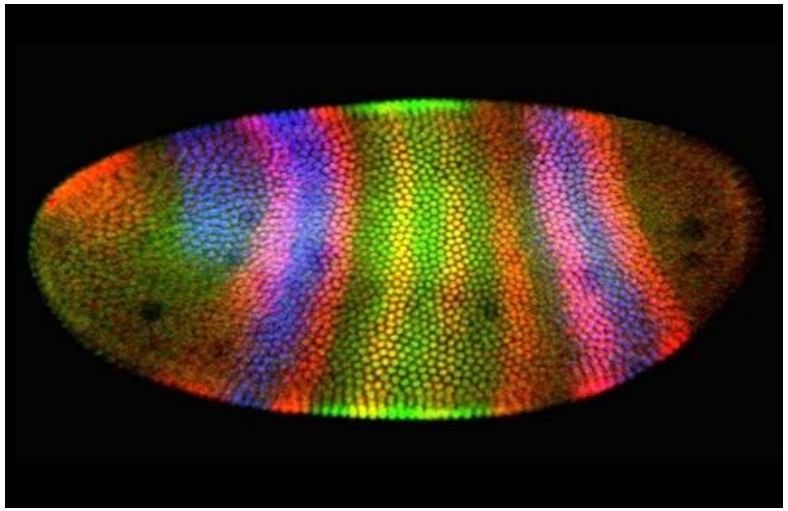
In molecular networks, it is both complexity AND modularity that drive highly variable output.

But how do regulatory network structures emerge and act as maps of more general biological change?

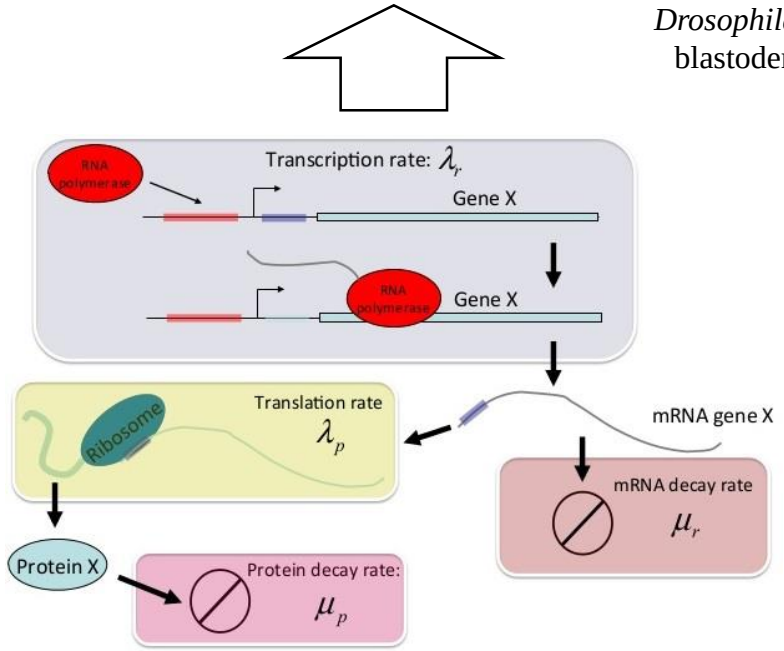


COURTESY: Development, 141, 4649-4655 (2014). doi: 10.1242/dev.107318.

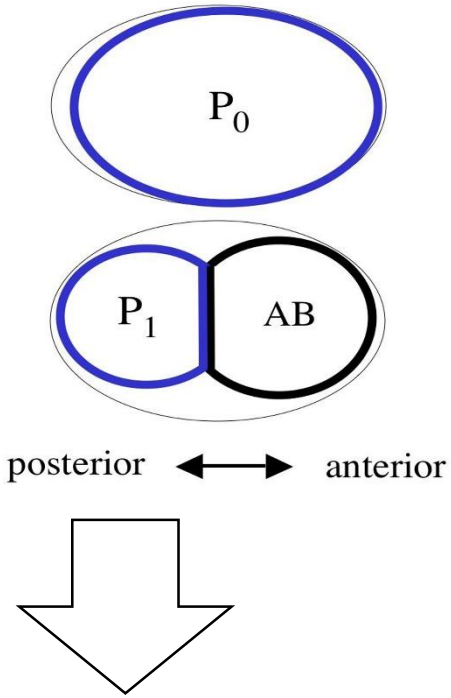
Fundamental Unit of Regulation (moving from molecules to phenotype)



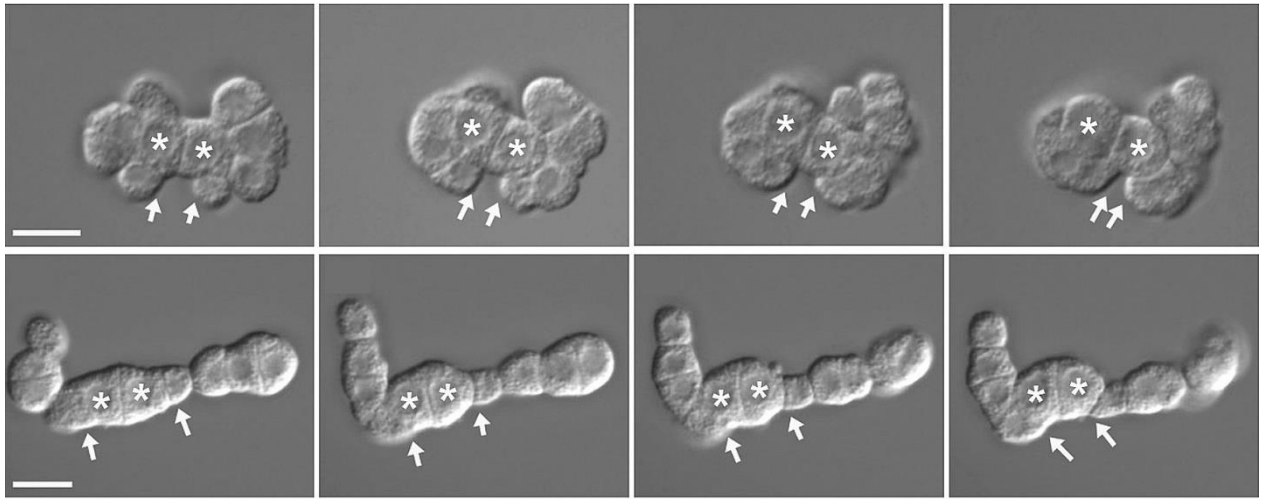
Drosophila embryo, blastoderm stage



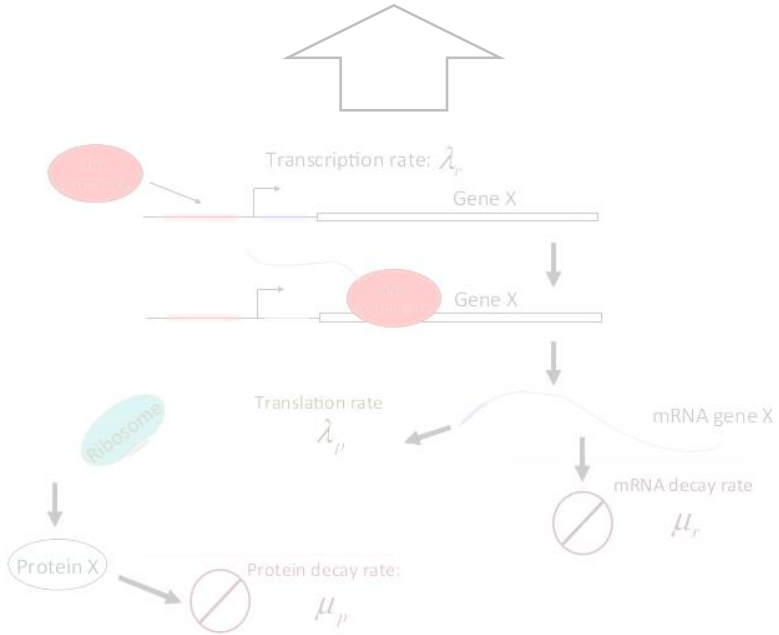
COURTESY: Erik van Nimwegen, "Gene Expression Noise, Regulation, and Noise Propagation", Slideshare.



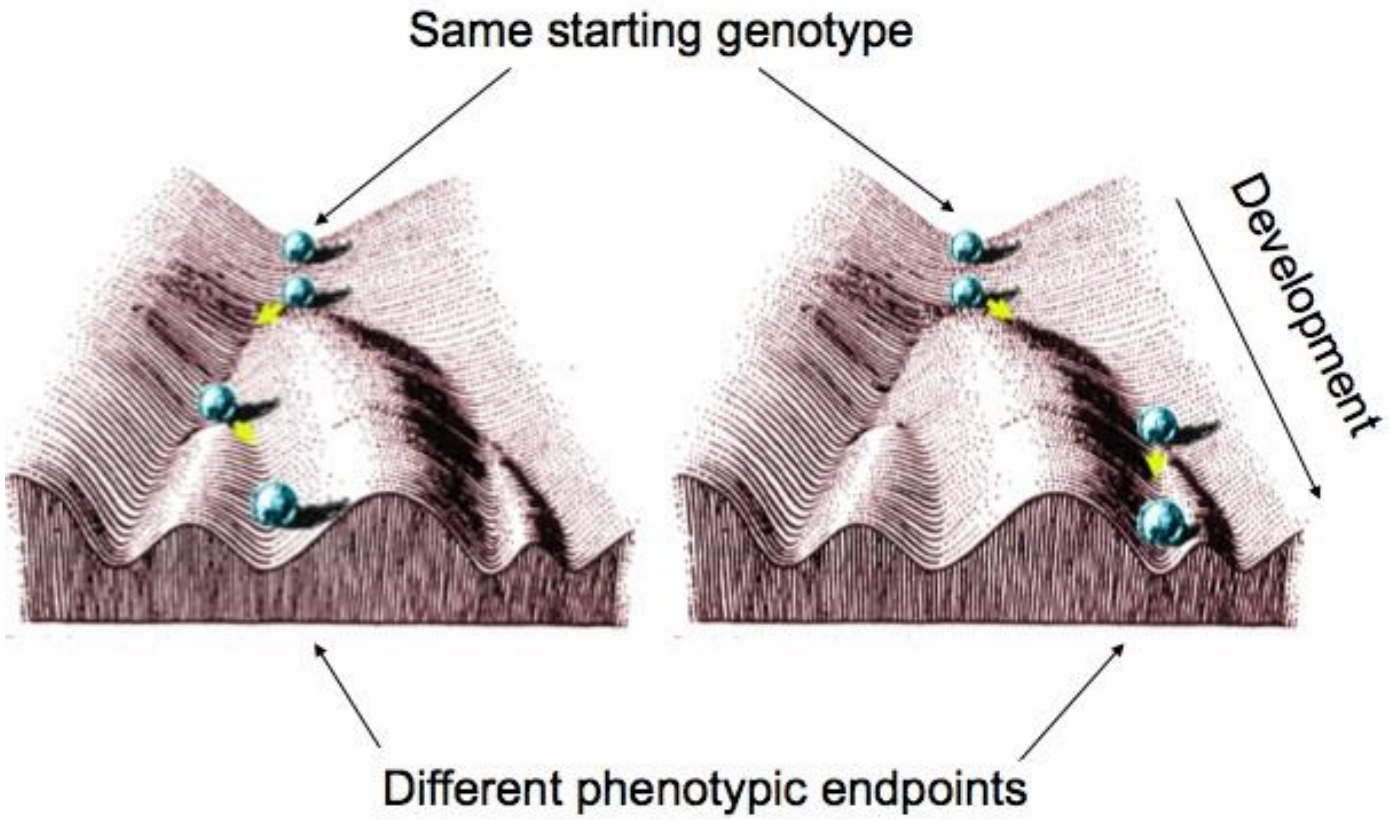
Cellular-level behaviors of P1 sublineage (*C. elegans*): isolated from whole embryo, forms characteristic division patterns.



Nance, Lee, and Goldstein, "Gastrulation in *C. elegans*". WormBook.

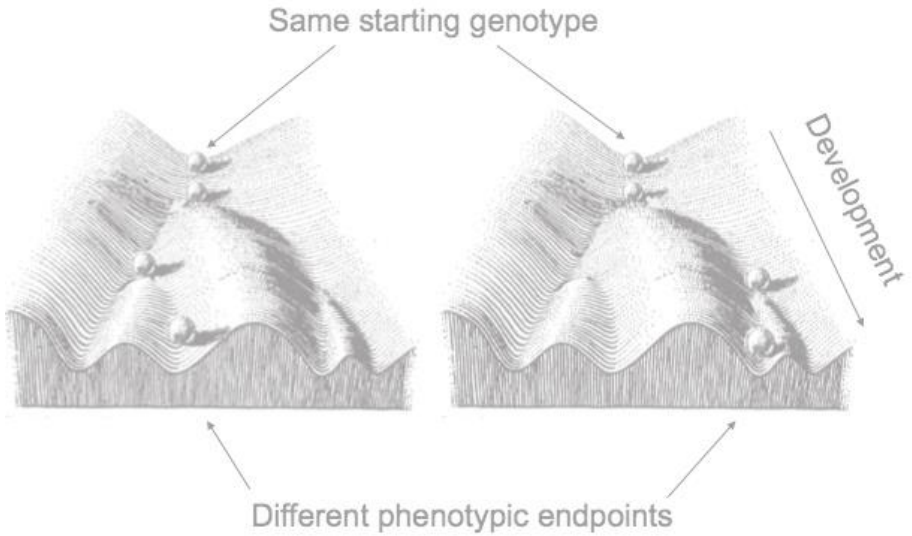


Two sources of developmental trajectory variation



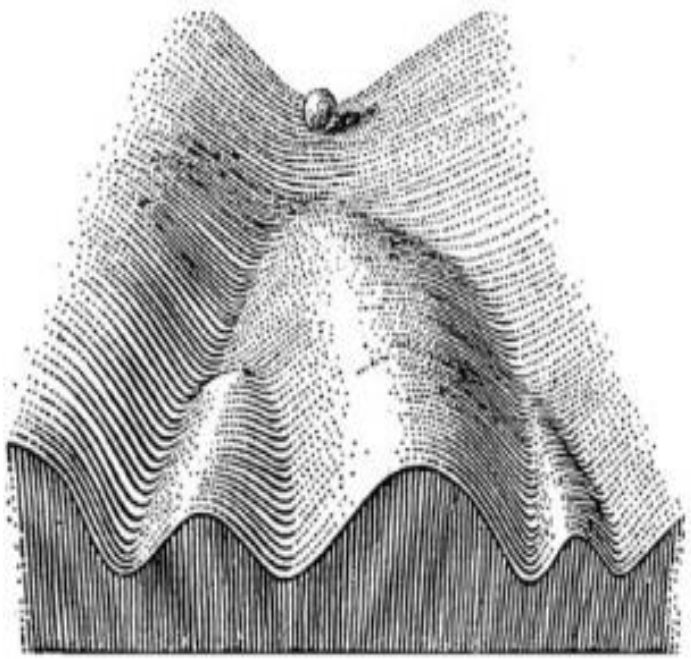
1) Intrinsic Developmental Variation: (noise in gene expression, RNA translation, protein kinetics)

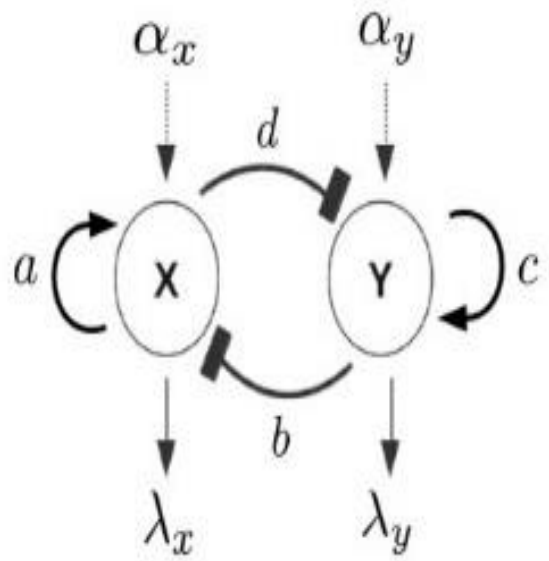
COURTESY: Mitchell, K. Genetics of Emergent Phenotypes. Wiring the Brain blog, March 21 (2013). http://www.wiringthebrain.com/2013/03/the-genetics-of-emergent-phenotypes.html



Intrinsic Developmental Variation (noise in gene expression, RNA translation, protein kinetics)

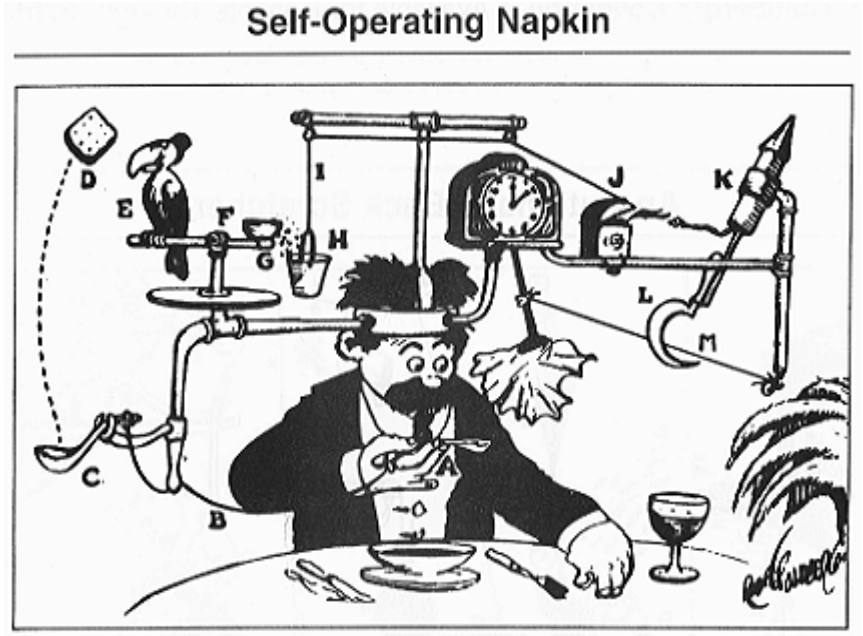
COURTESY: Verd et.al (2014). Classification of transient behaviours in a time-dependent toggle switch model. BMC Systems Biology. 8(1), 43.



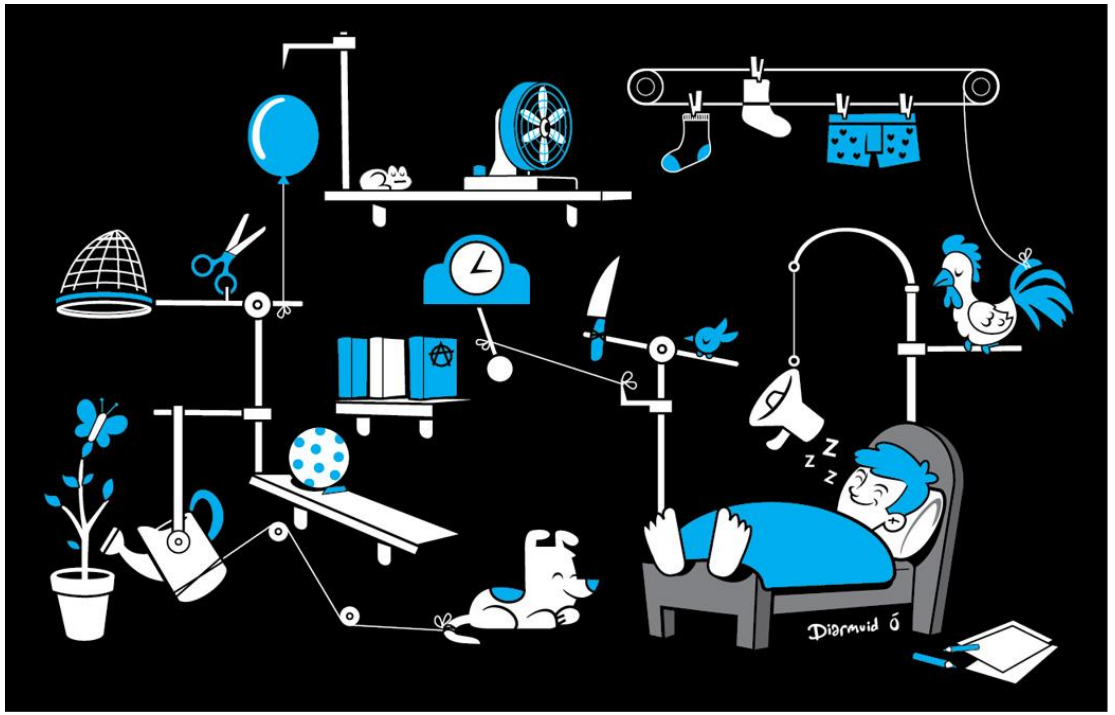


Developmental Switching (control developmental trajectory)

2) Functional Sub-optimization: based on the emergence of a regulatory network built upon a series of intermediary states or co-opted components.



Professor Butts and the Self-Operating Napkin (Rube Goldberg, 1931)

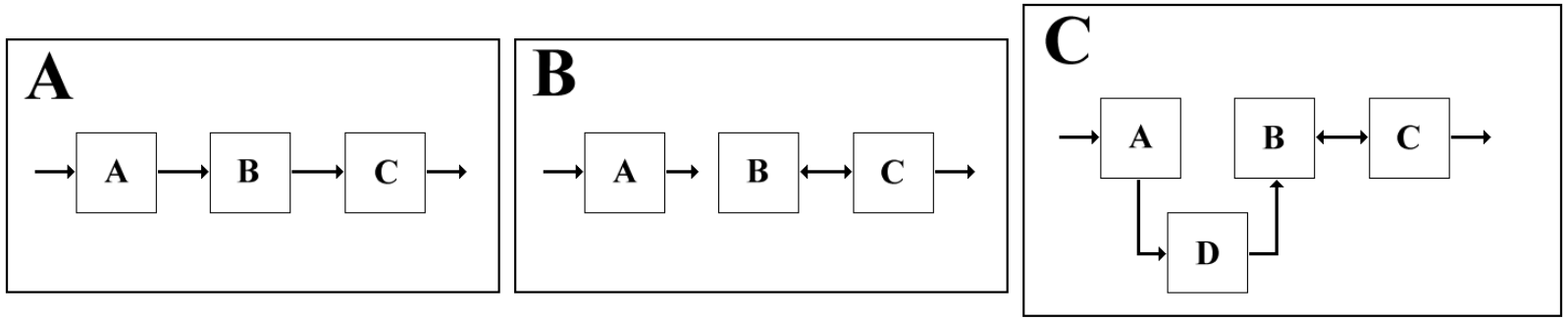


Rube Goldberg Machine (RGM is stepwise, discrete).

Find out more in: The 'Machinery' of Biocomplexity: understanding non-optimal architectures in biological systems. arXiv, 1104.3559.

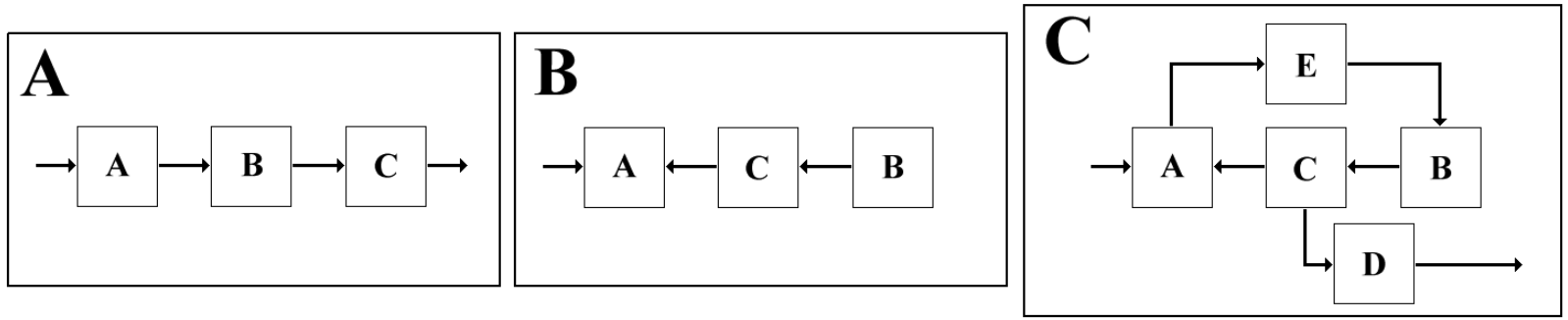
Convolution Architecture: suboptimal structure mapped to regulatory phenotype

Scenario #1: Mutation/Co-option



Mutation:
Small-scale changes
(stepwise)

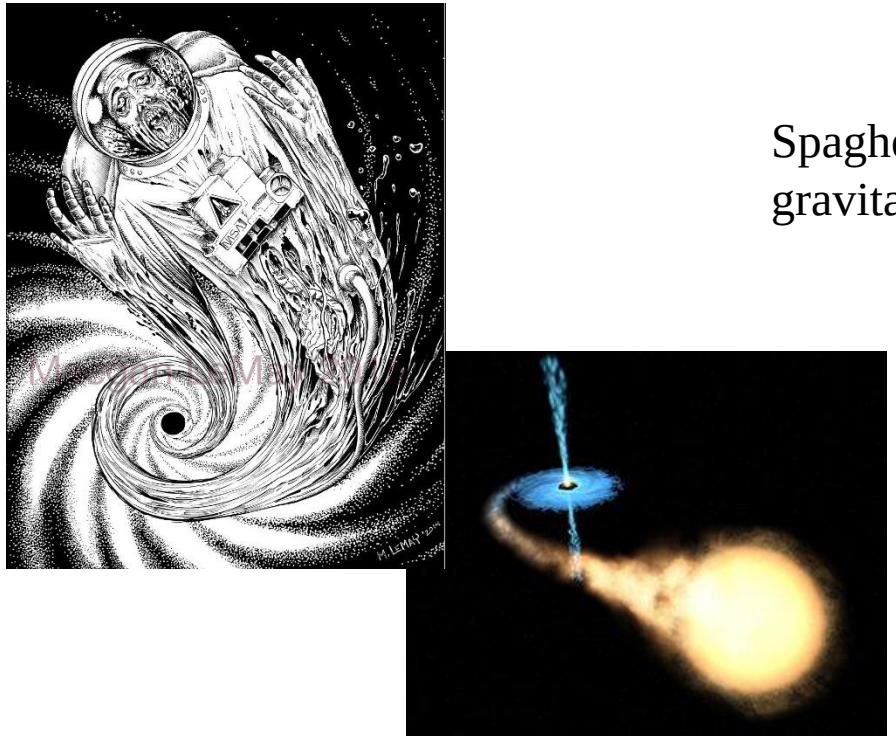
Scenario #2: Inversion



Inversion:
Large-scale changes
(motifs)

Convolution architectures will “spaghettify” as they increase in length.

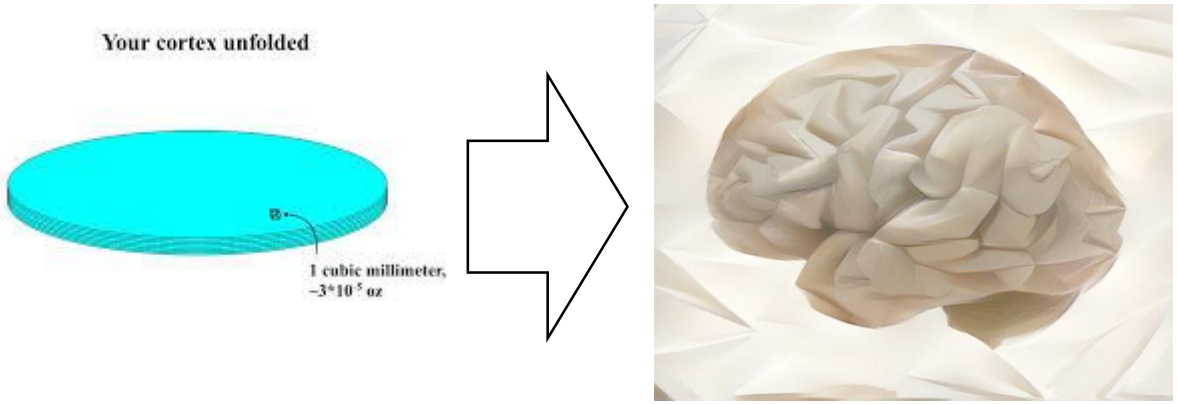
* output is increasingly variational (greater number of equivalent outputs), more diverse dynamical behavior overall.



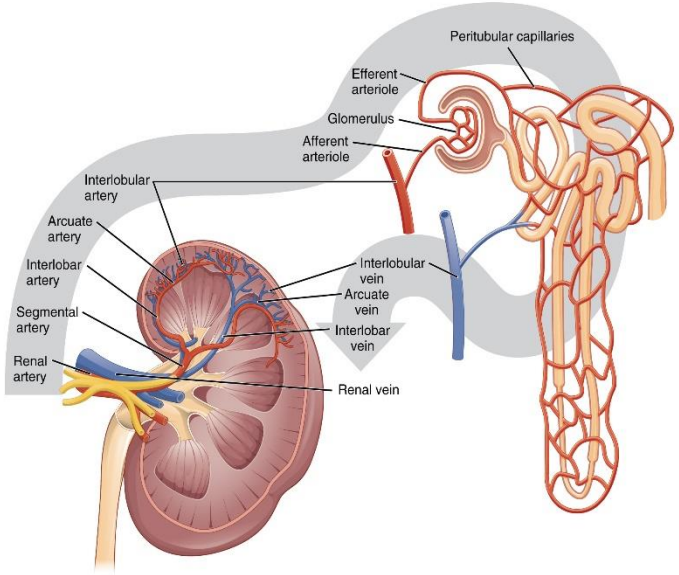
Spaghettification in physics: action of a very high gravitational force on matter entering a black hole.

Convolution architectures will “spaghettify” as they increase in length.

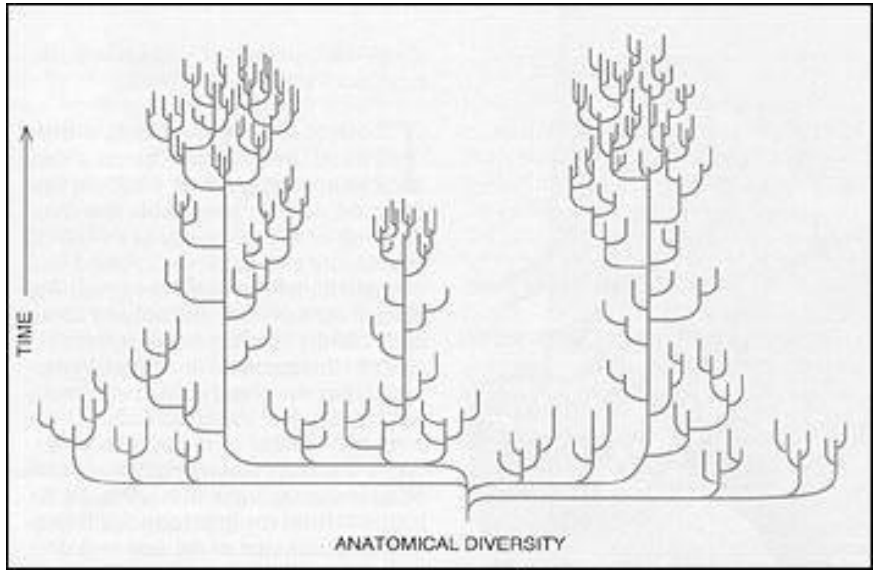
* output is increasingly variational (greater number of equivalent outputs), more diverse dynamical behavior overall.



Spaghettification in biology: action of selective forces on cells and tissues to create and regulate structures of high complexity.



Cybernetic Regulation can also serve as the underlying enabler of a stepwise model

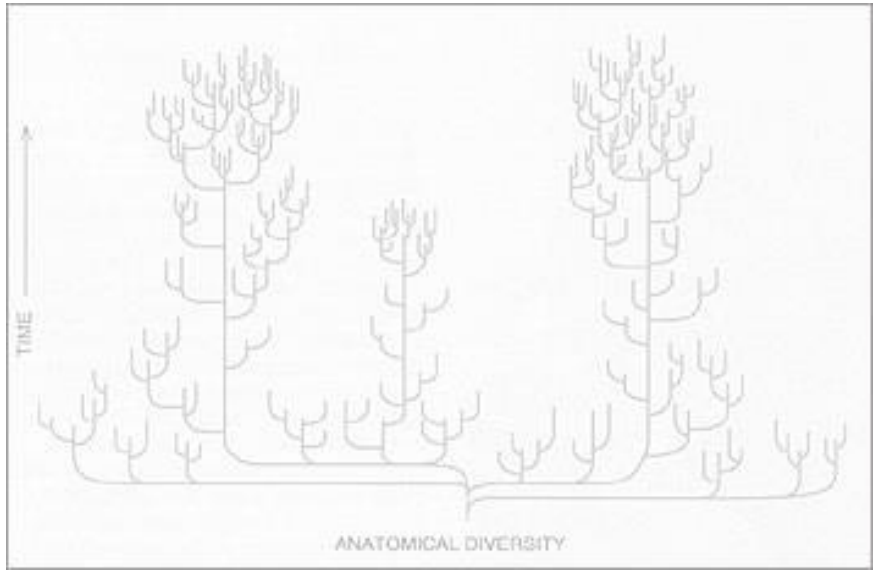


Cybernetic Convolution Architecture (CCA):

* combination of automata (black boxes with flexible identities) and connections.

* addition of regulatory modules to an existing scaffold.

Cybernetic Regulation can also serve as the underlying enabler of a stepwise model



Cybernetic Convolution Architecture (CCA):

* combination of automata (black boxes with flexible identities) and connections.

* addition of regulatory modules to an existing scaffold.

Attachment rule: attach motifs with an equal or lesser descriptive complexity.

* greater convolution occurs through locally minimizing complexity, but maximizing nonlinearity through long-range feedbacks.

CCA relies upon three regularities

1) Law of Requisite Variety:
* the controller always exhibits more variation than the controlled.

* rules for attachment: sets of elements cannot attach to main pathway until main pathway exhibits more combinatorial complexity than the newly-incorporated set of elements.

2) Law of Open-ended Evolution:
* as network spaghettifies: very large space of possible configurations produced, continual growth in complexity.

* mapped from the genotype (binary representation) to the phenotype (cybernetic model).

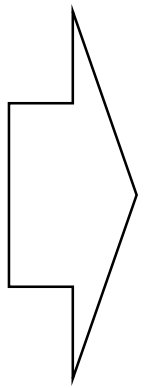
3) Every Good Regulator Theorem (EGRT):
* every well-regulated system has access to a model of that system (e.g. internal model).

* selection mechanism (semi-independent of genotype) for addition (and removal) of nodes and arcs.

Defining the CCA Network as a Biological System

* CCAs would be constructed through the discovery of hypotheses from multiple systems and levels of analysis.

* CCA is a meta-biological network that drives the regulation of phenotype from multiple sources of variation.



Metabiological

Nodes and arcs do not represent specific biological objects.

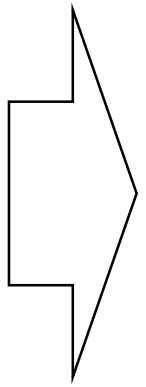
Defining the CCA Network as a Biological System

* CCAs would be constructed through the discovery of hypotheses from multiple systems and levels of analysis.

* CCA is a meta-biological network that drives the regulation of phenotype from multiple sources of variation.

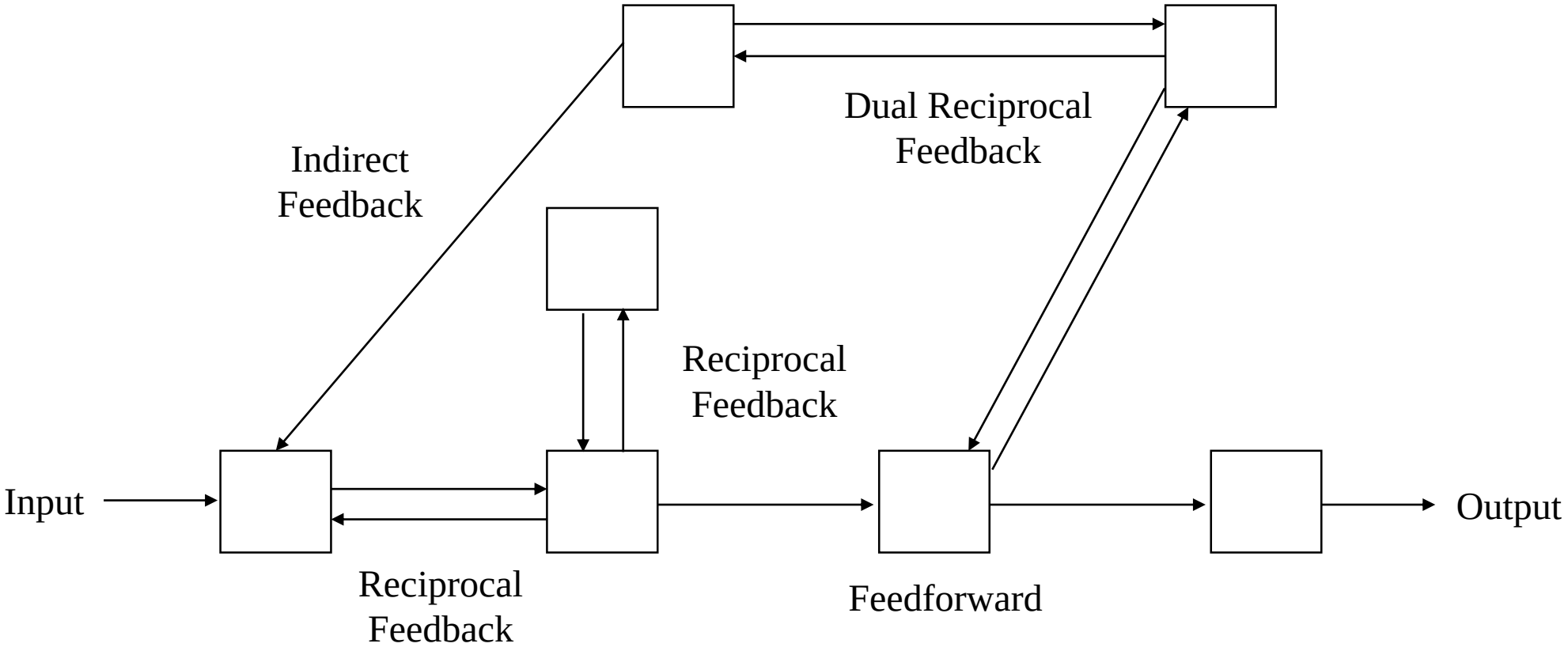
* growth of CCA networks from simple to complex demonstrate how CCA emerge in evolution and are (recapitulated) in development.

* growth results in network spaghettification. Spaghettification is exemplified by the number of alternate pathways in the network (and is equivalent to variety).



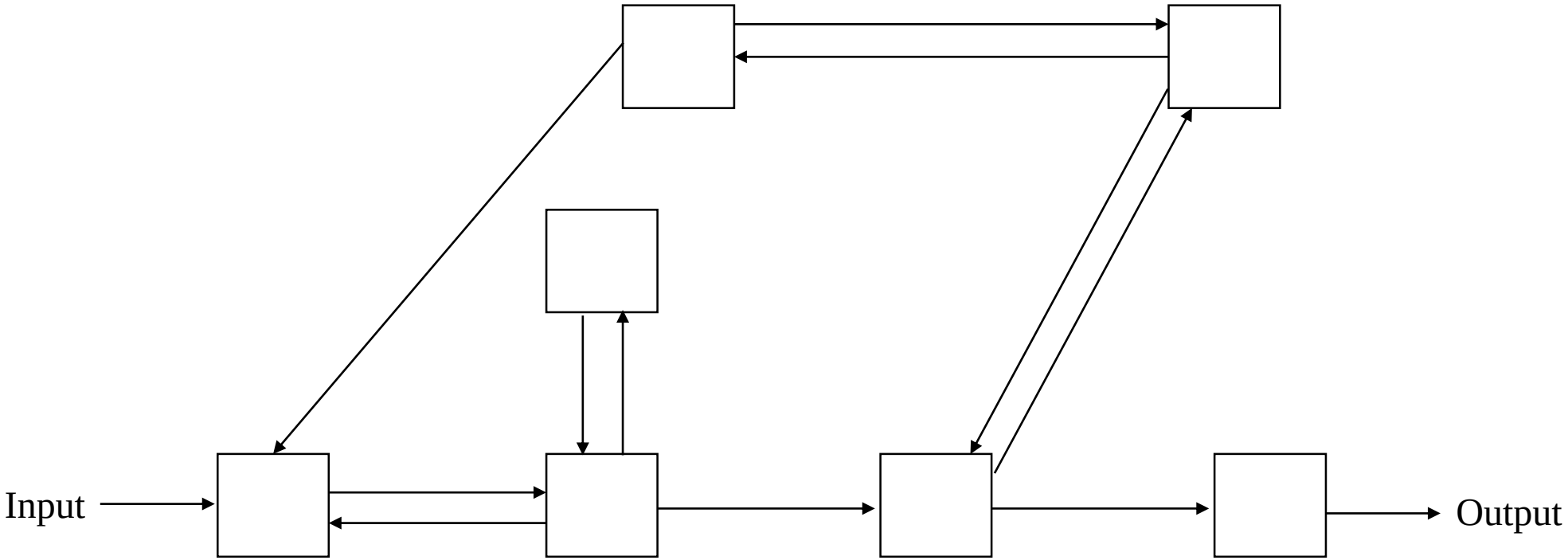
Spaghettification
Controlled growth in variation through a dynamic process

CCA as a simple network (nonlinear outputs)



Input = initial phenotype (e.g. 1-cell embryo).

Output = evolved/developed phenotype (e.g. 256-cell embryo).



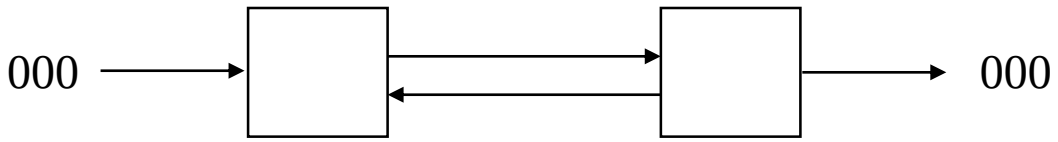
Based on phenotypes that result from regulatory mechanisms. Description length of I/O phenotypes **do not** scale with complexity of network.

A fully-descriptive (or optimal) regulatory network involves finding deeper principles than specific gene expression, cell divisions, or cell movements (although CCA is meant to capture all of these elements).

Origins of Spaghettification in Action

Attachment rule: only motifs of equal or less complexity than the existing linear network can be added onto the regulatory structure (law of requisite variety)

Complexity rule: shortest path defined by feedforward path only, longest path requires all feedforward and feedback elements to be explored.



Step 0: begin with an input and a reciprocal feedback mechanism.

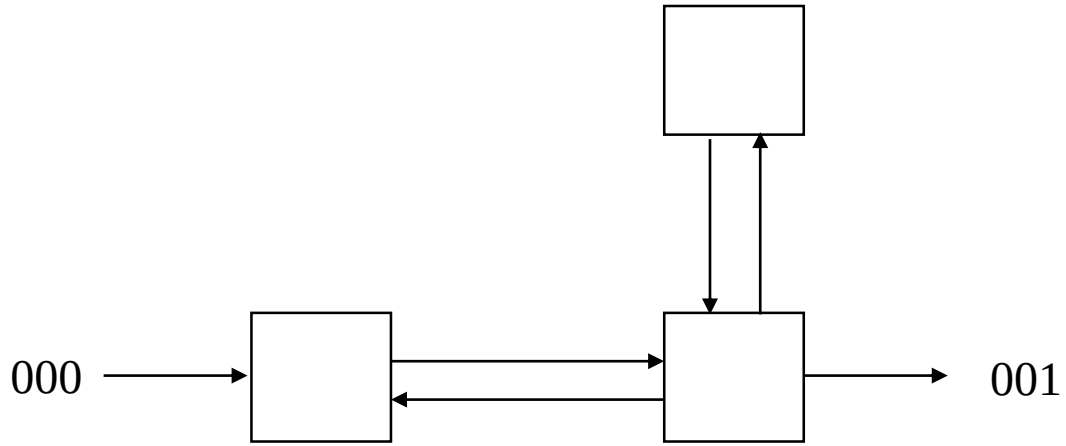
Initial genotype (e.g. 000).

Shortest path = 3, Longest path = 5

Step 1: add a reciprocal feedback motif onto a reciprocal feedback motif.

Results in a single flipped bit (e.g. 001).

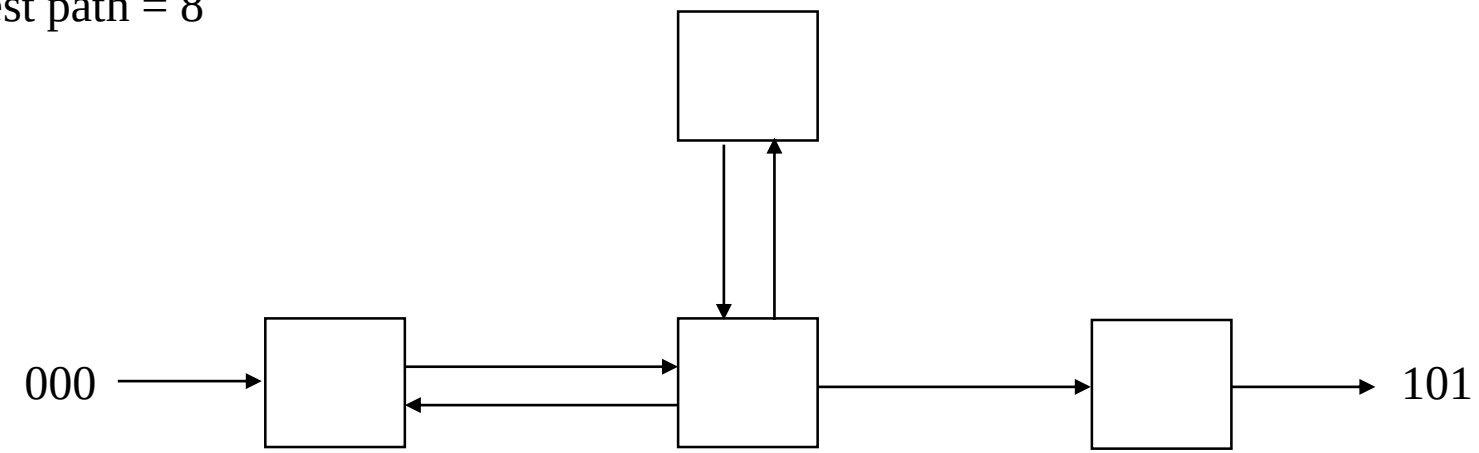
Shortest path = 3, Longest path = 7



Step 2: add a single feedforward motif to a dual reciprocal feedback motif.

Results in a single flipped bit (e.g. 101).

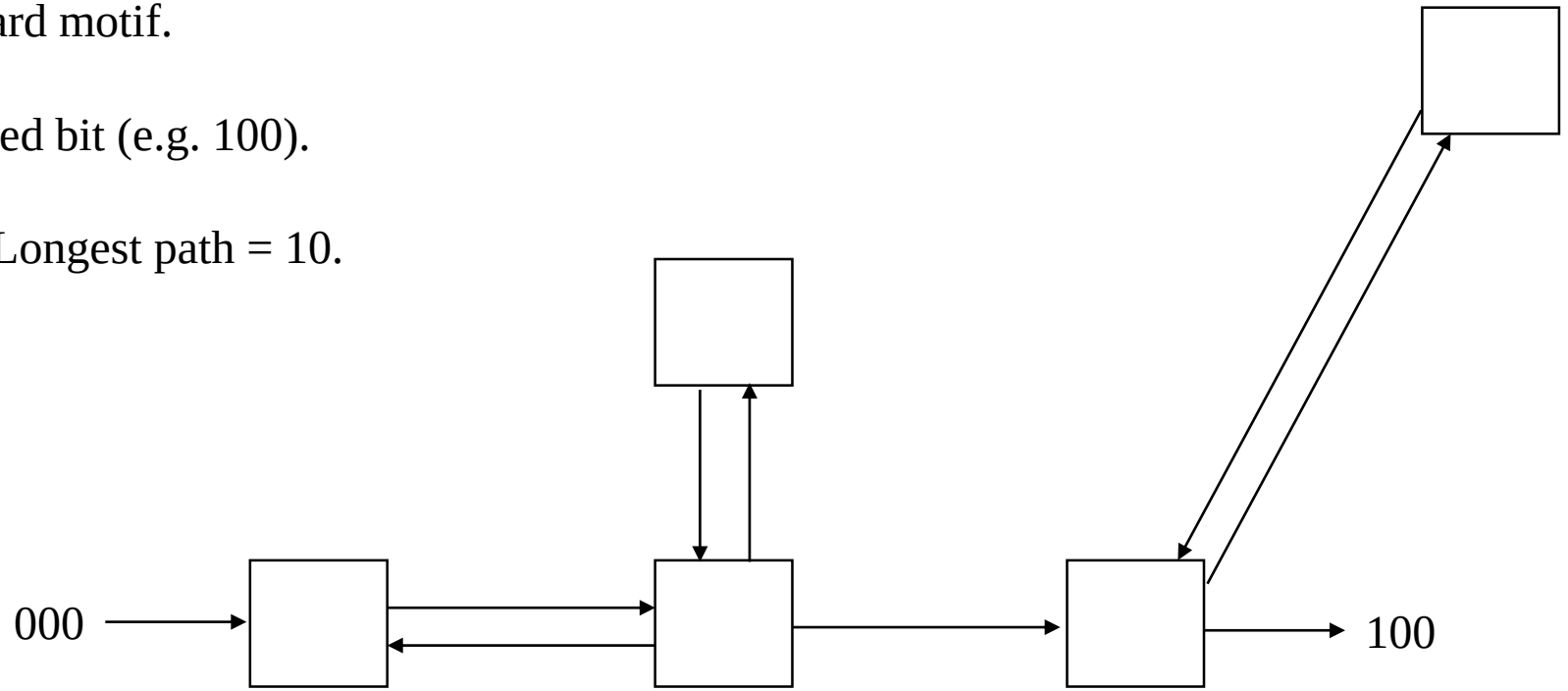
Shortest path = 4, longest path = 8



Step 3: add a reciprocal feedback motif to dual reciprocal feedback and single feedforward motif.

Results in a flipped bit (e.g. 100).

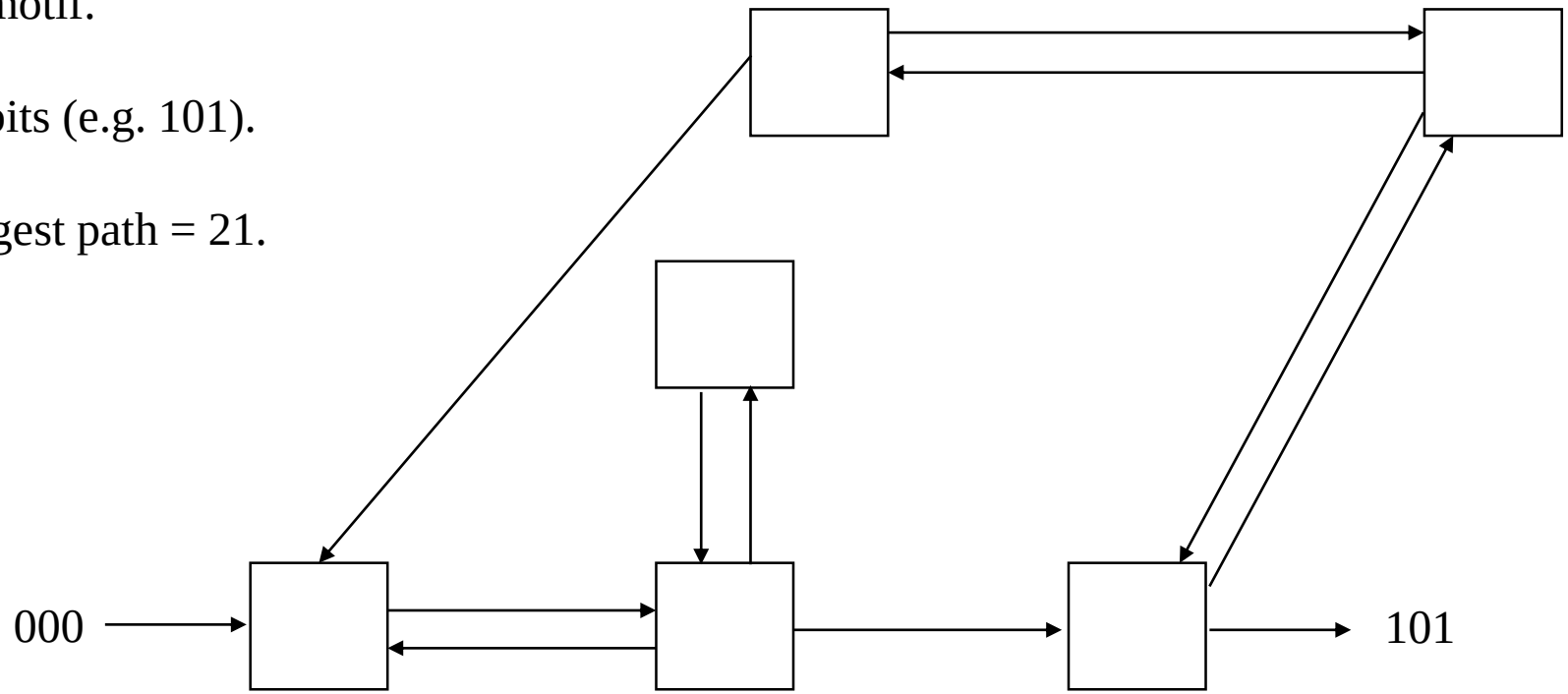
Shortest path = 4, Longest path = 10.



Step 4: add a dual reciprocal feedback motif to dual reciprocal feedback and single feedforward motif.

Results in no flipped bits (e.g. 101).

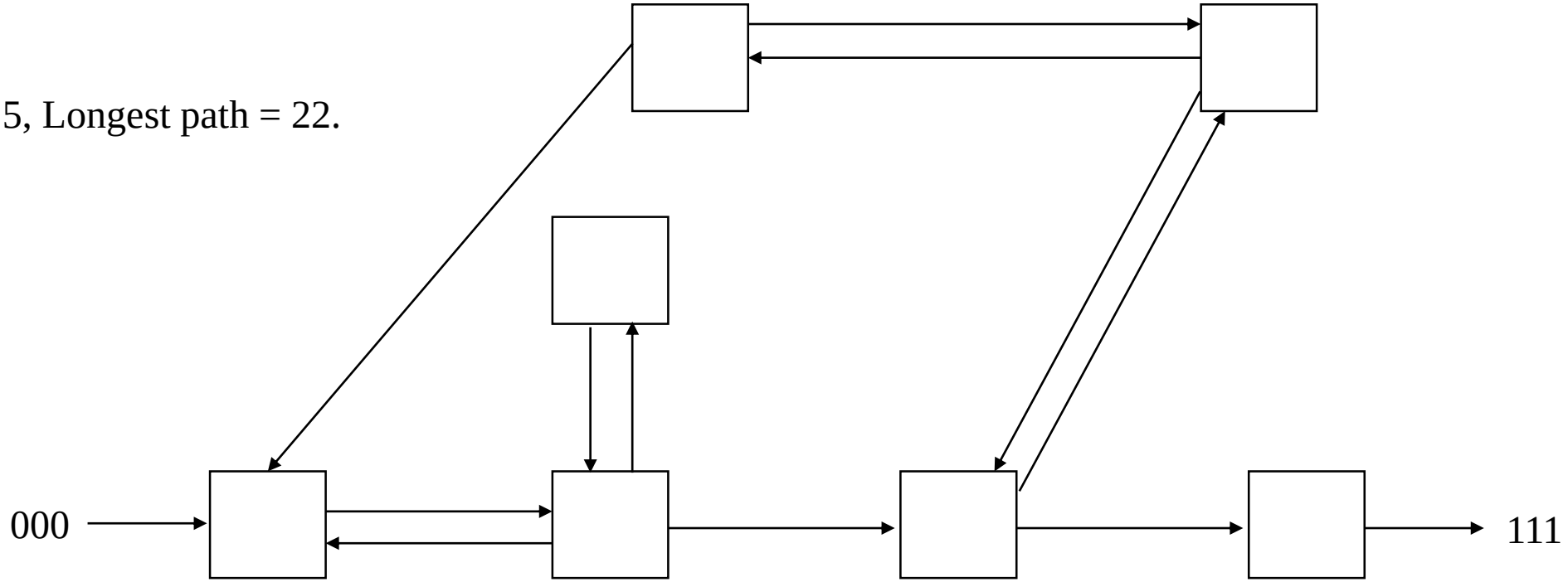
Shortest path = 4, Longest path = 21.



Step 5: add a indirect feedback and a feedforward motif.

Results in a single flipped bit (e.g. 111).

Shortest path = 5, Longest path = 22.



Assessing Pathway Information (con't)

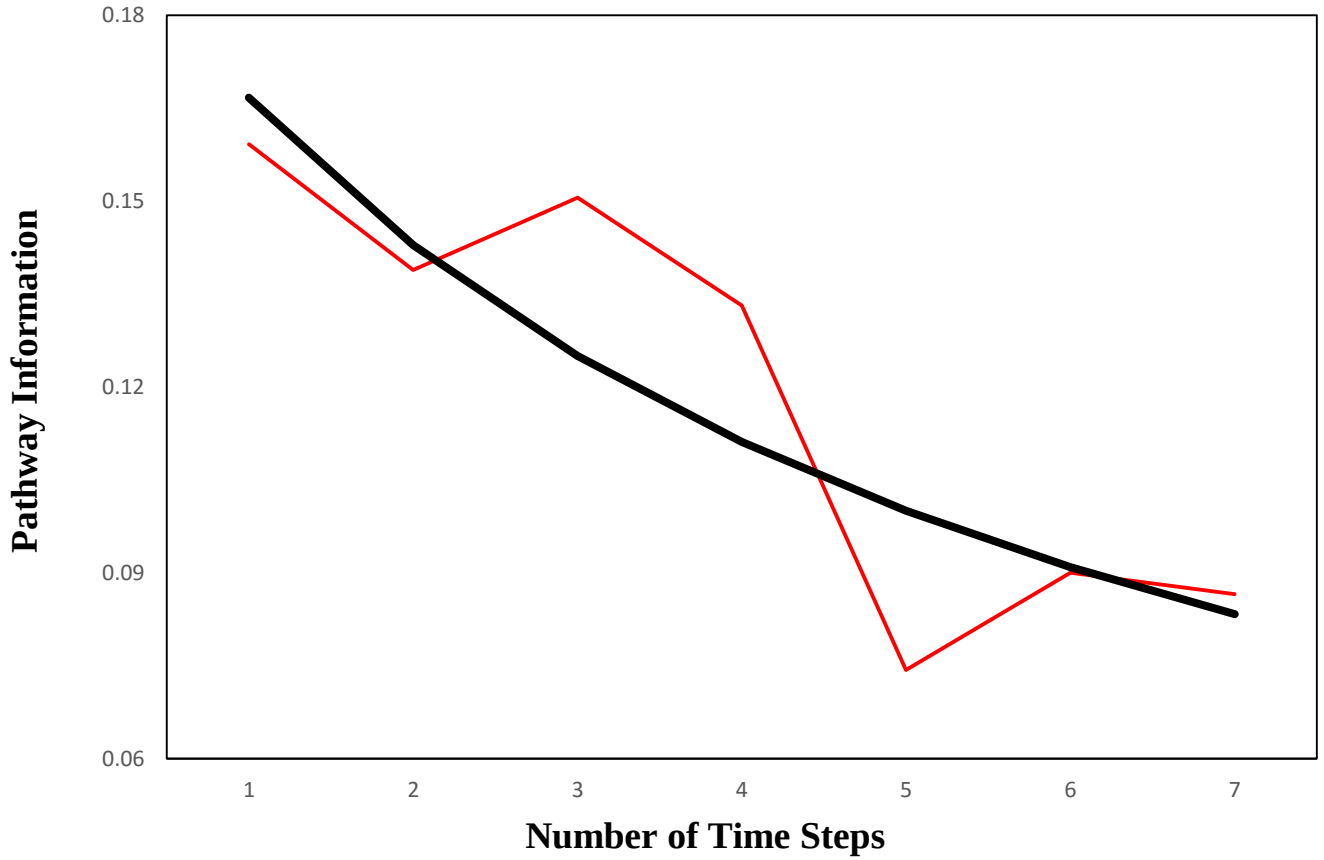
$$P(x_t) = 1 - \left(\frac{Shortest\ Path}{Longest\ Path}\right)$$

$$H(x_t) = -P(x_t)\log P(x_t)$$

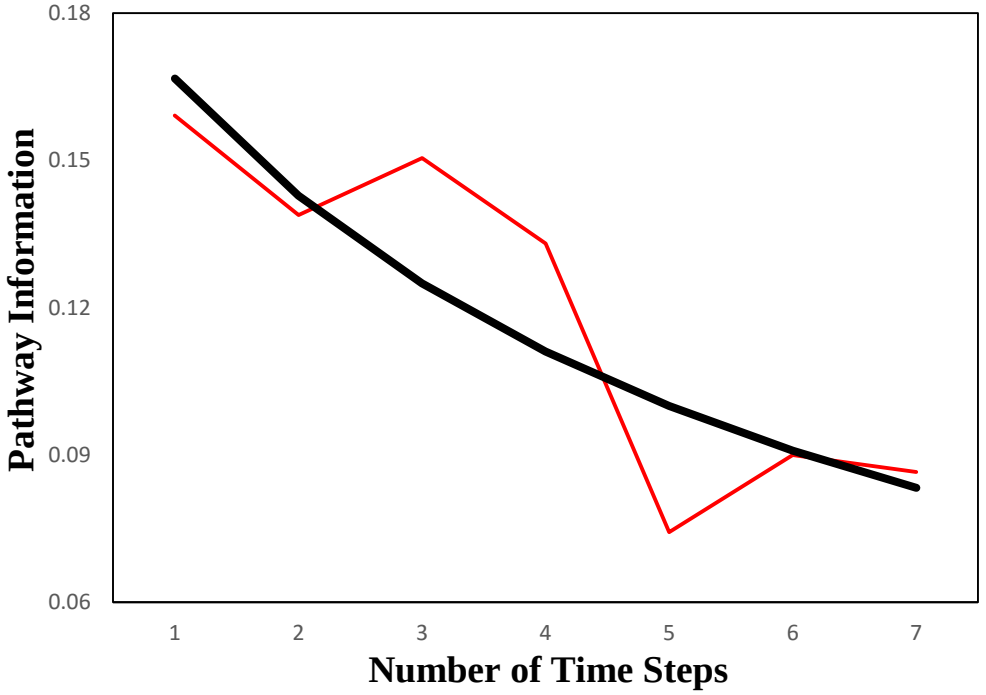
BLACK: Idealized asymptotic function.

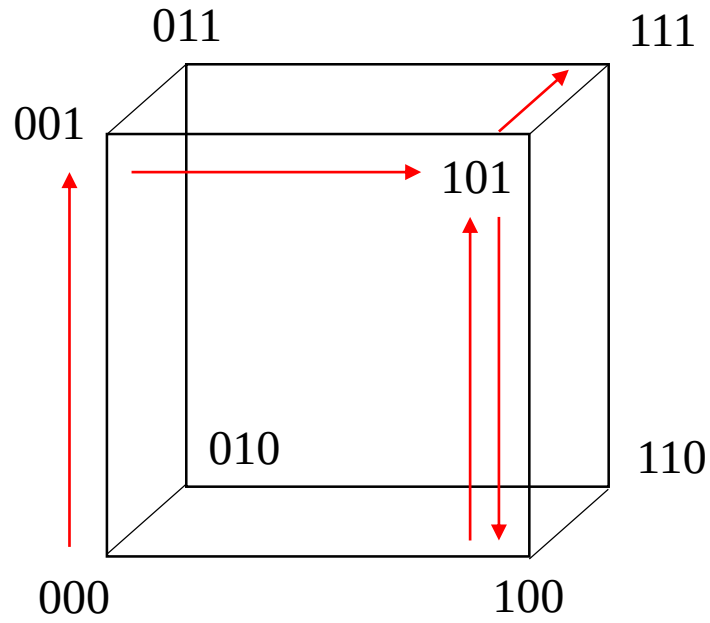
RED: Pathway Information (decrease with time).

* greater opportunity for sub-optimal networks to emerge from convolution.

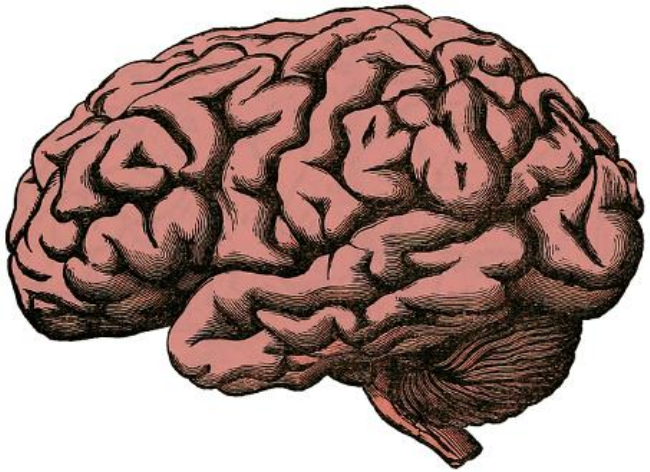


Comparison to Mutational Model

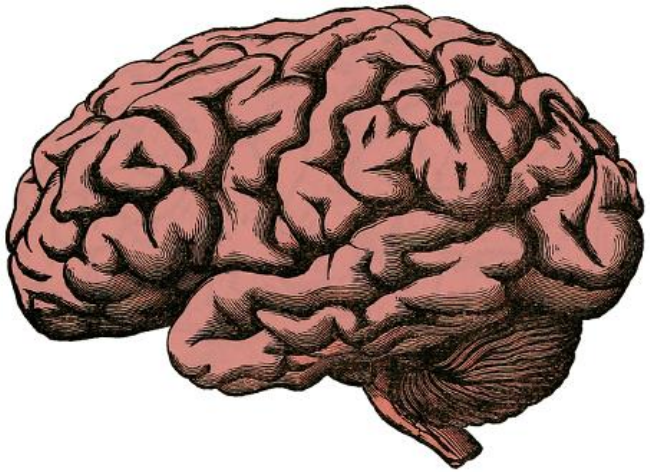




SUB-OPTIMIZATION: Regulatory needs will select for greater than optimal number of steps.



Biological Convolution: folding of neocortex in human brain. As sheet of cells grows, it folds up to conserve space, with previously non-contiguous regions in close proximity.



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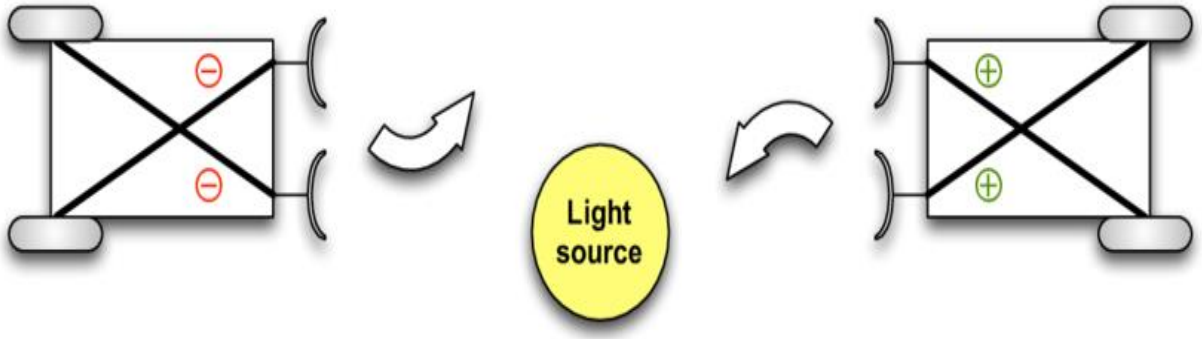
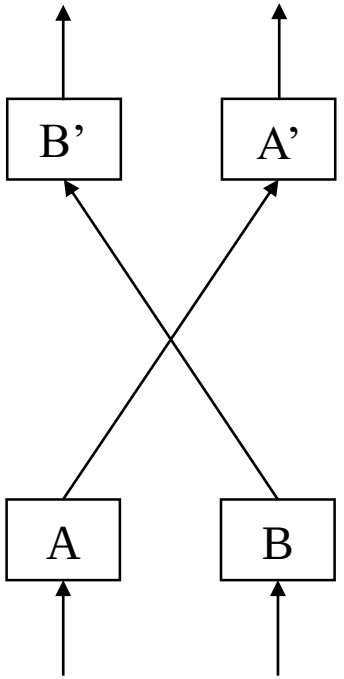


Image from: Zahedi and Ay, Quantifying Morphological Computation. Entropy, 15, 1887-1915 (2013).

Biologically-inspired Convolution: the nervous system of a Braitenberg vehicle, which produces complex behaviors from a simple internal structure.

Convolution in nature: simple regulatory pathways come into juxtaposition in the course of evolutionary change (e.g. bigger brains, new sensory organs and effectors).



Cross-talk motif: two intersecting feedforward pathways.

Produces four outputs (combinatorial complexity), which increases the available information but decreases specificity.

* requires the addition of feedbacks and intermediary elements, which in turn requires new elements to "close the loop".

Spaghettification: network rewiring model that retains all (or selected) previous connections.

Outputs provide support for a complex phenotype:

* chaotic dynamics, higher-order motifs, production of large-scale, far-from-equilibrium events (e.g. Dragon Kings, cascades).

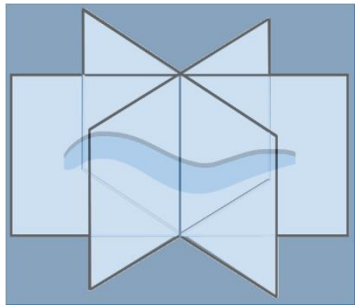
Thanks for Your Attention!

Network Frontier Workshop

NICO

January, 2013: Comments and Discussion

I post preprints



The ‘Machinery’ of Biocomplexity: understanding non-optimal architectures in biological systems. arXiv, 1104.3559.

Modeling Cellular Information Processing Using a Dynamical Approximation of Cellular mRNA. bioRxiv, doi:10.1101/006775.

Robert Stone, Dr. Thomas Portegys
Origins of the Embryo: self-organization through cybernetic regulation. http://tiny.cc/origins-embryo