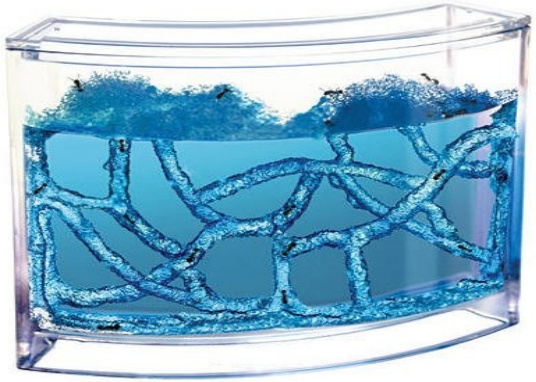
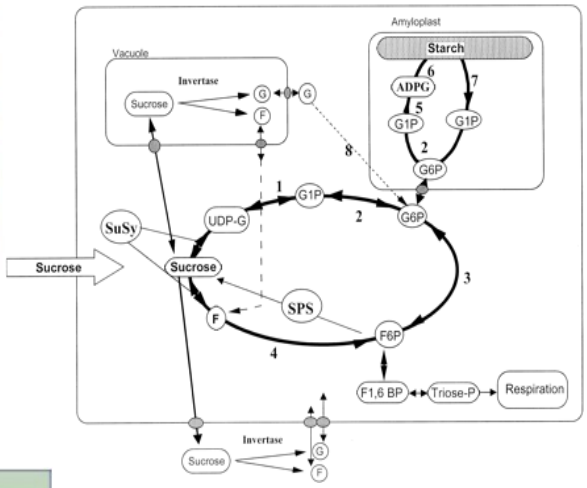
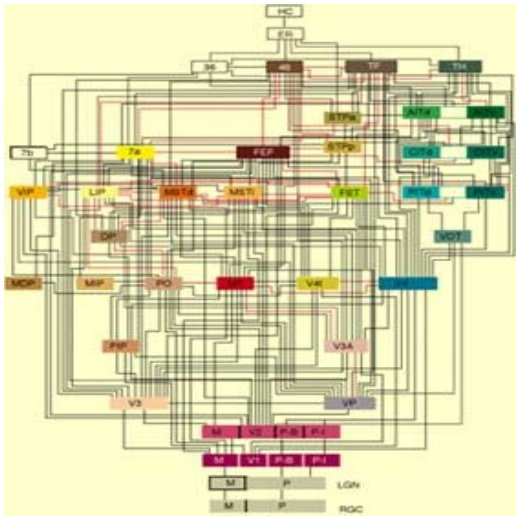
Formal Systems Architectures for Biology



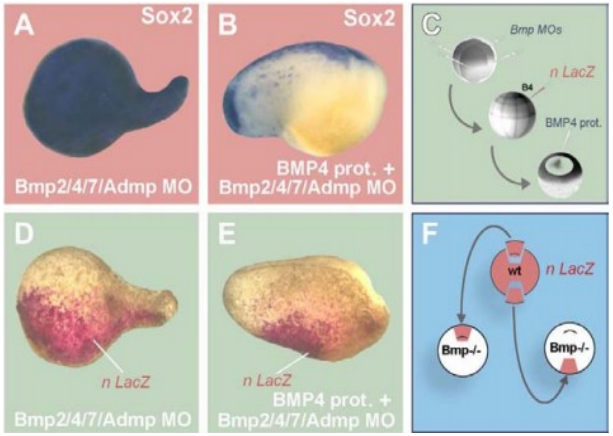
Ant Farm, self-contained example of traffic flow regulation



Futile cycles in sucrose pathway of tomatoes, J. Exp. Botany, 52(358), 881-889.

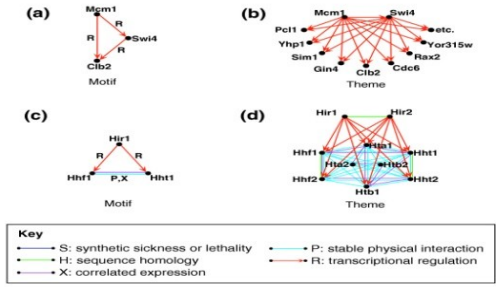


Connectivity network in Macaque brain. Cold Spring Harbor Symp Quant Biol, 55, 679-696 (1990).



Morphogenetic Fields in Early Embryo. Cell, 123, 1147-1160 (2005).

Feedforward Transcription Networks in Yeast. J. Biology, 4(2), 4 (2005).



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Formal Architectures: where to start?

Motif #1: Dominoes and Clocks

* how can we describe the function of cellular oscillations in cell cycle (dominoes) and embryogenesis (clocks)?

Motif#2: Futile Cycles

* what is the function and origin of futile cycles, and what is there effect on the broader biological system?

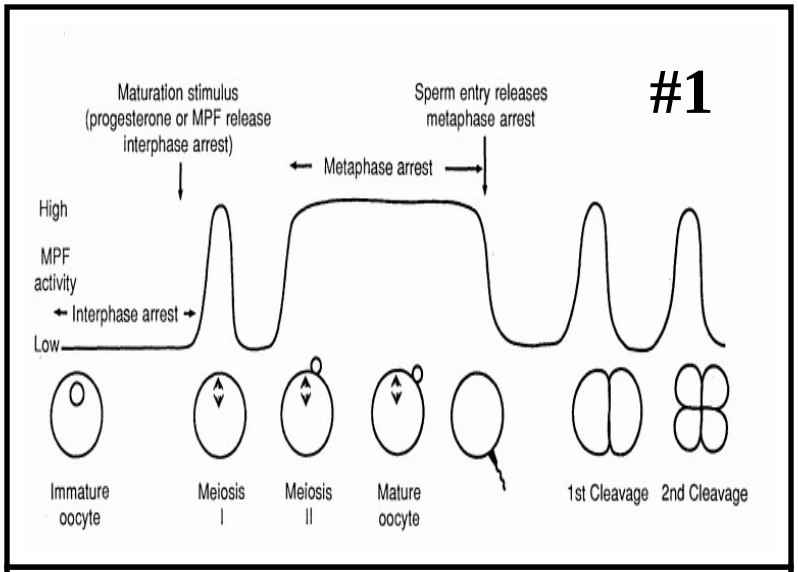
Motif #3: Complex Feedforward

* what are the dynamics of control without feedback, and how does this drive observed complexity?

Additional Feedback, Feedforward Mechanisms

* interconnected futile cycles, networks of flows, controllability of evolvability.

Linear and Recursive Architectures



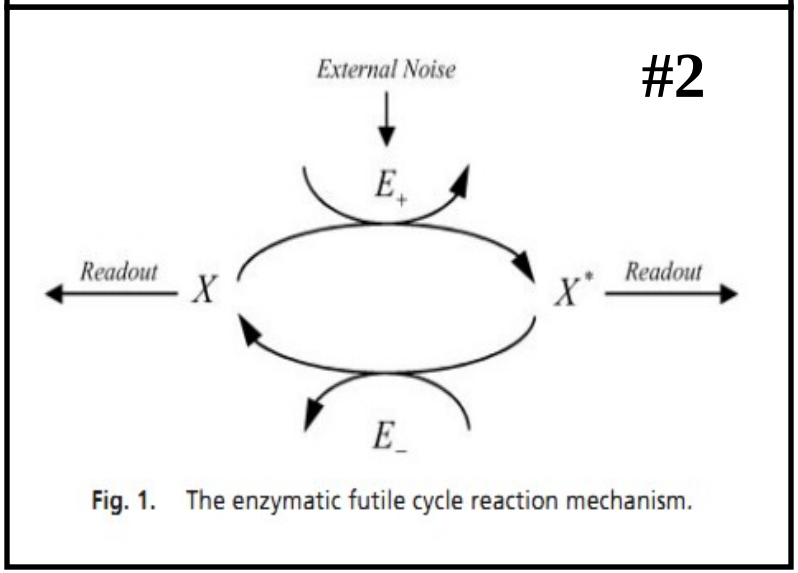
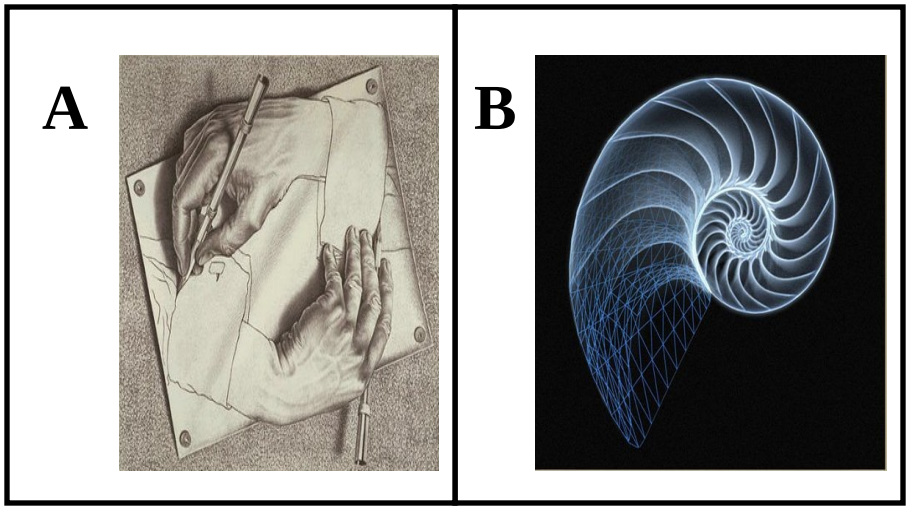


Fig. 1. The enzymatic futile cycle reaction mechanism.



#1. Clock model, Embryogenesis:
Murray, A.W. & Kirschner, M.W (1989). Dominoes and Clocks: The Union of Two Views of the Cell Cycle. *Science*, 246(4930), 614-621.

#2. Futile Cycle, enzymatic pathway:
Samoilov, M., Plyasunov, S., & Arkin, A.P. (2005). Stochastic amplification and signaling in enzymatic futile cycles through noise-induced bistability with oscillations. *PNAS USA*, 102(7), 2310-2315.

Linear and Recursive Architectures

#1. Cell cycle (domino model)

* example: path-dependent. Signaling pathways.

* example: circular. Cell cycle (mitosis).

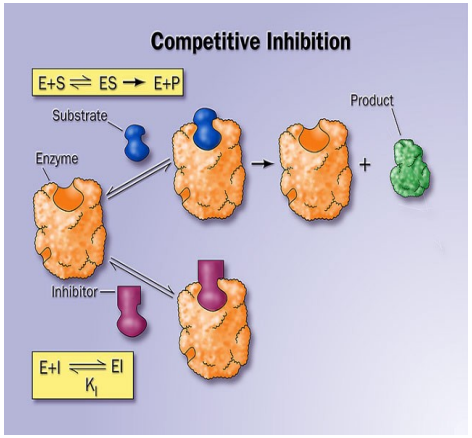
Path-dependent

Circular

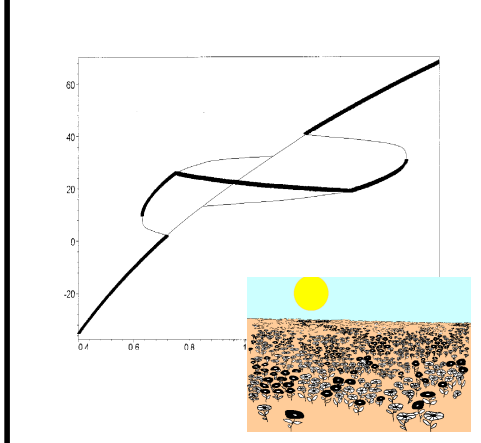
#3. Complex Feedforward

* example: competitive inhibition. Two enzymes binding to the same product.

* example: Daisyworld. Evolution/regulation of the biosphere.



Competitive Inhibition



Daisyworld

Motif #1: Dominoes and Clocks

Cell cycle: set of events responsible for the duplication of the cell.

* geneticists (G, mutations that arrest cell cycle) and embryologists/physiologists (E/P, arrest/facilitation of cell cycle) have provided two different perspectives.

* G approach has done well at describing linear, path-dependent processes.

* E/P approach has done well at describing oscillating processes.

Study of mutants:

* how individual cell cycle steps are coordinated so that things occur in the right order.

* each step is dependent on the previous one.

* explains coordinated cell size regulation (doubling time and number of steps involved can be decoupled).

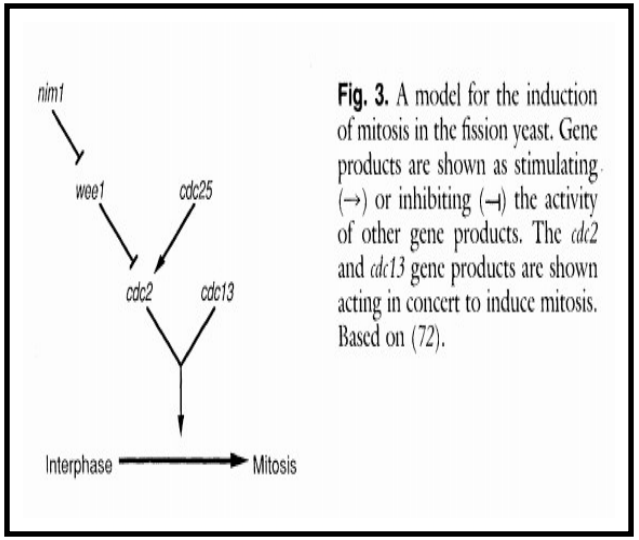
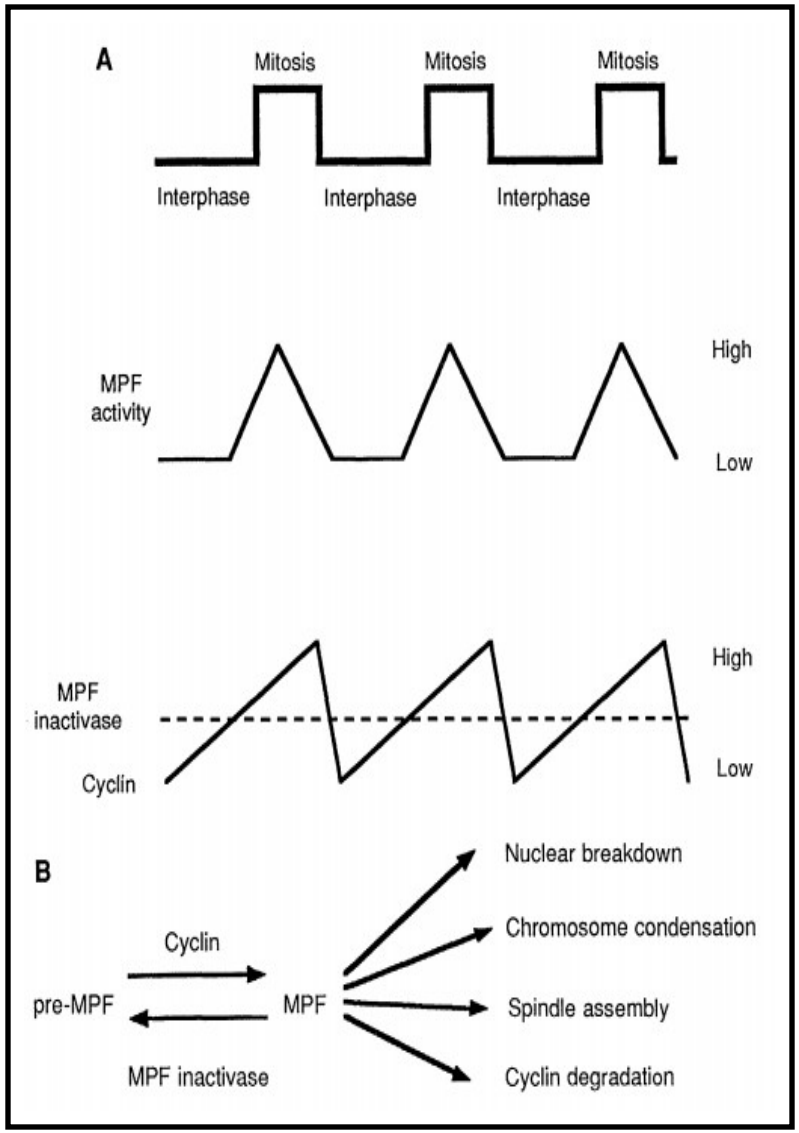


Fig. 3. A model for the induction of mitosis in the fission yeast. Gene products are shown as stimulating (→) or inhibiting (⊣) the activity of other gene products. The *cdc2* and *cdc13* gene products are shown acting in concert to induce mitosis. Based on (72).

Motif #1: Dominoes and Clocks



Cyclin is stable in cells that are arrested in meiosis or mitosis:

* cyclin degradation required to exit cell cycle.

* synthesis of cyclin required for activation of MPF in mitosis/meiosis.

* cyclin protein accumulates until rate of MPF activation by cyclin exceeds rate of MPF inactivation by enzyme, leading to overall MPF activation.

* MPF is a kinase, phosphorylates proteins involved in cell morphology and posttranslational modifications, lead to cyclin degradation.

* cyclin lost, MPF also deactivated via inactivase.

* no MPF activity turns off cyclin degradation, resets cyclin accumulation.

Motif #1: Dominoes and Clocks

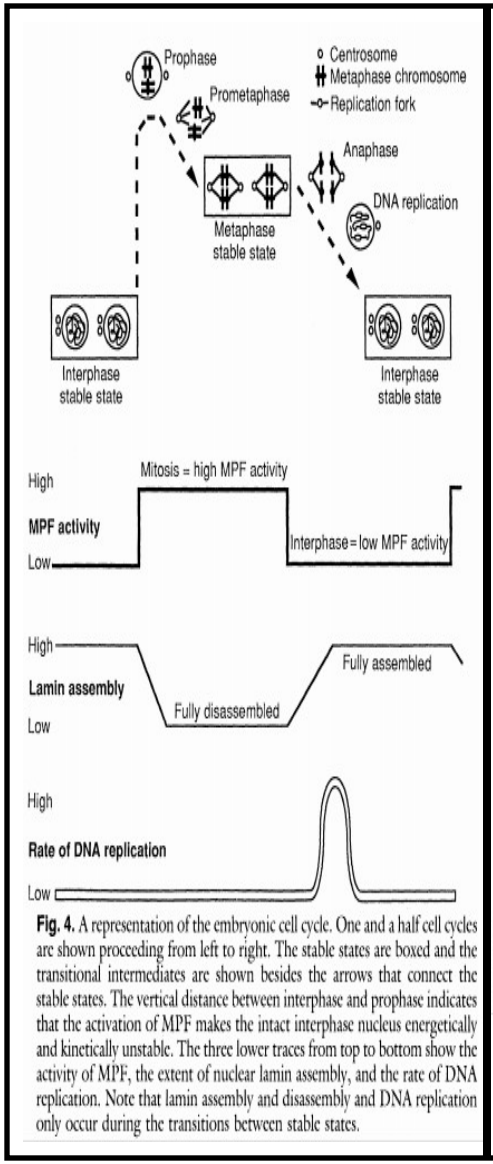


Fig. 4. A representation of the embryonic cell cycle. One and a half cell cycles are shown proceeding from left to right. The stable states are boxed and the transitional intermediates are shown besides the arrows that connect the stable states. The vertical distance between interphase and prophase indicates that the activation of MPF makes the intact interphase nucleus energetically and kinetically unstable. The three lower traces from top to bottom show the activity of MPF, the extent of nuclear lamin assembly, and the rate of DNA replication. Note that lamin assembly and disassembly and DNA replication only occur during the transitions between stable states.

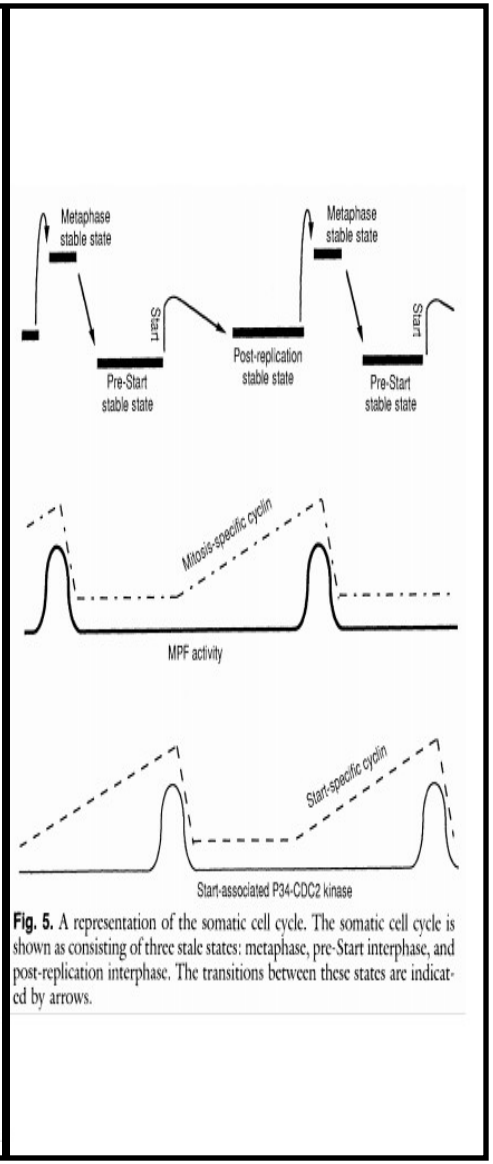
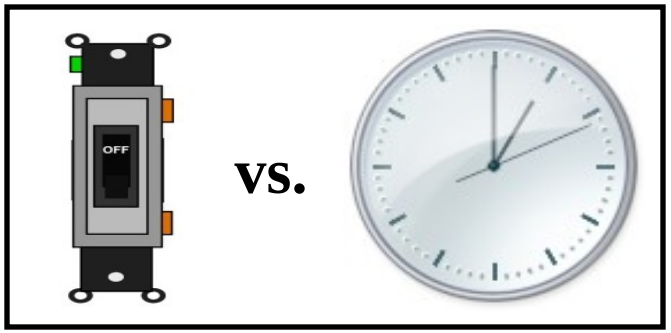


Fig. 5. A representation of the somatic cell cycle. The somatic cell cycle is shown as consisting of three stale states: metaphase, pre-Start interphase, and post-replication interphase. The transitions between these states are indicated by arrows.

Left: switch-like mechanism of the embryonic cell cycle.

* activity of MFP oscillates between high and low (switch-like) across cell cycle phases.



Right: clock-like mechanism of the somatic cell cycle.

* activity of MPF oscillates with specific spikes (analog-like) across cell cycle phases.

Motif #1: Dominoes and Clocks

Evolutionary Perspective:

* cell cycle as a set of dependent reactions. Therefore, cell cycle should be evolutionarily conserved, both between oocyte and somatic cells, and across species.

* compare the evolvability of cell cycle (highly constrained) with the evolvability of *Hox* genes and phenotypic modularity (highly constrained).

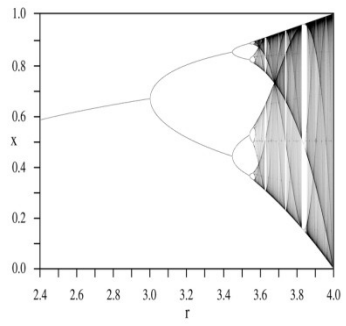
* cell cycle as set of dominoes. Process highly (historical) contingent on previous step.

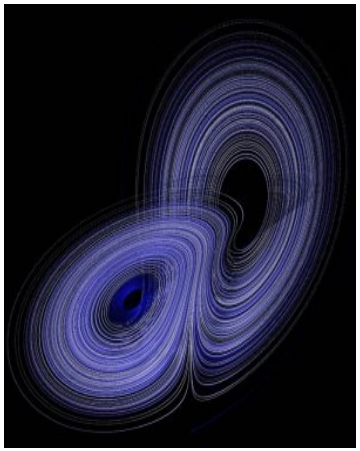
Noise Perspective:

* cell cycle as a clock-like process (time-dependent). Clocks are deterministic, is there room for stochastic processes?

* chaotic systems are oscillatory (attractors sensitive to initial condition).

Lorentz Attractor and Logistic Map





Motif #1: dominoes and clocks

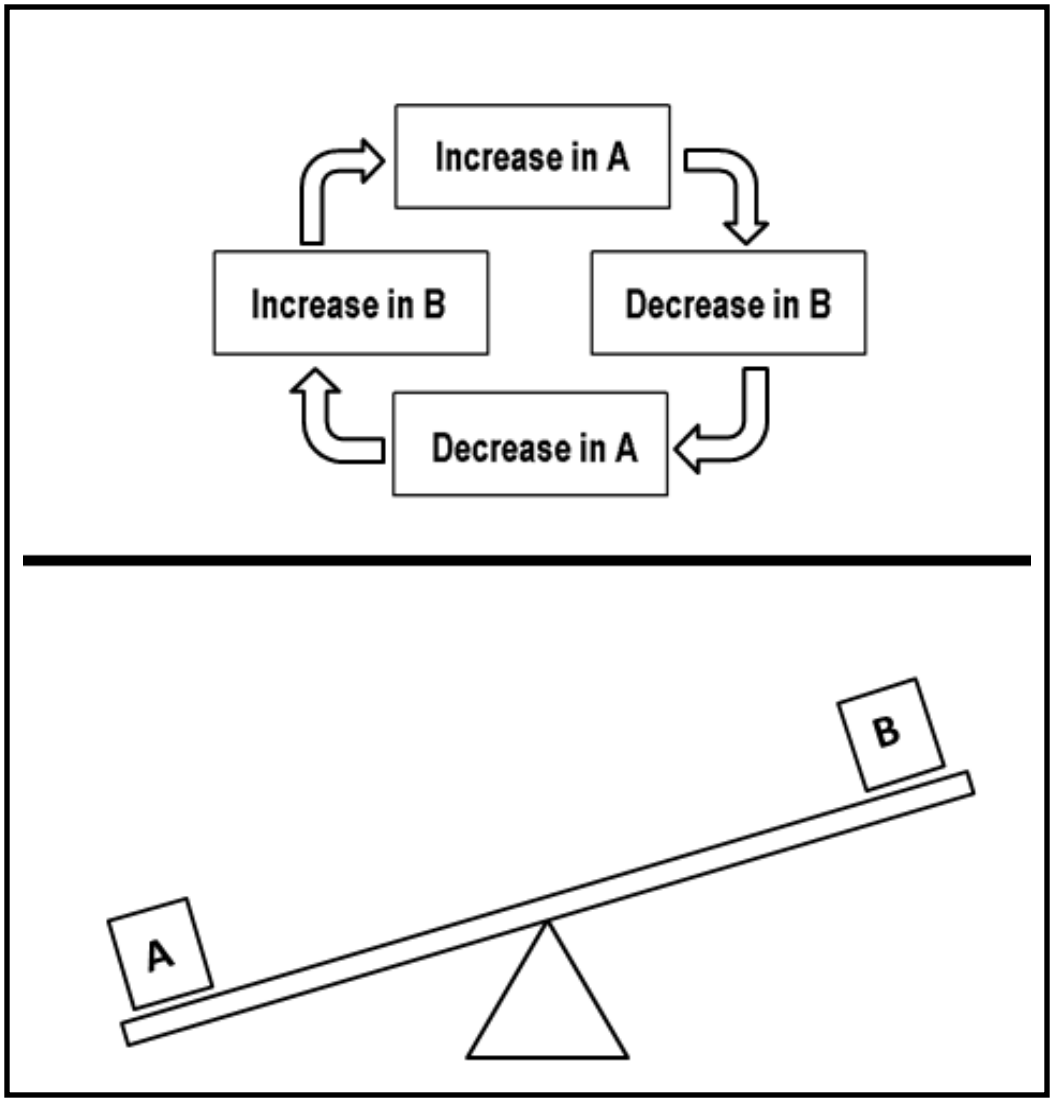
One outstanding problem remains: path-dependent phenomena that occur in a loop (top).

Recursion that enforces balance between two entities (seesaw model, bottom).

* does this resemble futility? Running in place?

* does this resemble autoregulation? Homeostasis?

Perhaps there are elements of both…….



Motif #2: futile cycles

Futile cycles: two processes running at the same time in opposite directions, and have no output product other than entropy and heat energy.

Samoilov, Plysunov, and Arkin (2005). *PNAS USA*, 102(7), 2310-2315.

* also observed in signal transduction, metabolism, MAPK cascades, GTPase cycles, produces bimodal output.

* alternative explanation for Menten-Michaelis (linear) kinetics with feedbacks.

* authors propose analytical framework using Langevin SDEs governed by M-M kinetics and driven by noise.

Two effects: 1) stochastic signal amplification and 2) mechanism for multistability (dynamic switching between states).

Technological futile cycles? Top: biomechanical energy harvester, Bottom: human batteries

Motif #2: futile cycles

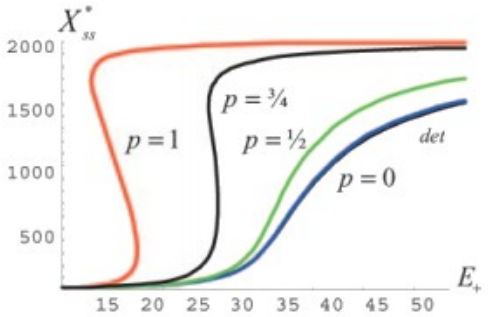


Fig. 2. The analytical stationary-state response curves, $R_{N(p)}$, for the enzymatic futile cycle (Fig. 1 with parameters of Fig. 3), obtained by using Eqs. 1, 3, and 6 with $\sigma_- = 0.2$ and various values of p (includes the deterministic curve, which largely overlaps).

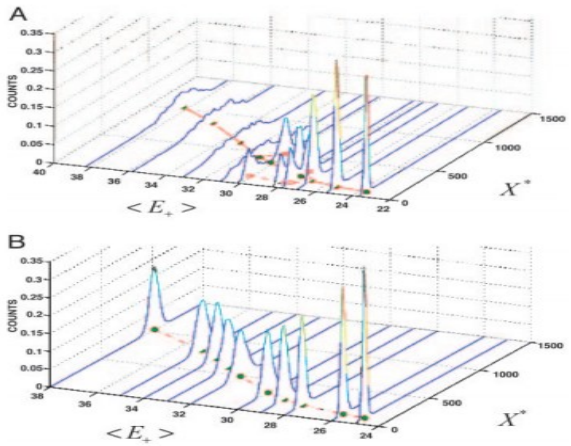


Fig. 4. Signal response histograms for the simulated futile cycle (Expressions 7 and 8) (● represents positions of the average, whereas □ represents positions of the stationary states where different). (*A*) Molecular count histogram of X^* vs. different values of the average enzyme input, $\langle E_-(t) \rangle$, generated by the noise driver given in Expression 8. The evolution of the probability distributions of X^* with increase in $\langle E_-(t) \rangle$ demonstrates the noise-induced bistability effect. (*B*) If no external driver is applied, bistable behavior is not observed (uncertainty is due purely to the internal noise).

Top Left: stationary state response curves for a range of values (p). Ranges from p=0 (deterministic, sigmoidal) to p = 1 (maximum noise, S-curve).

Bottom Left: signal response histograms (x, y axes = top left. Evolution of PDF (points and contours):

* external noise introduced (graph A) = induced bistability (bimodal distribution on axis z).

* internal noise only (graph B) = no induced bistability.

Real-world example: Control and Regulatory Mechanisms Associated with Thermogenesis in Flying Insects and Birds. *Bioscience Reports*, 25(3/4), 2005.

***** facultative thermogenesis: ability to generate body heat on demand -- product of futile cycle reactions in fat pads.

Motif #2: futile cycles

Qian and Beard, IEE Proc. Systems Biology, 153(4), 192-200 (2006).

Main idea: understand steady-state concentrations of c_1, c_2 (intermediates) w.r.t. net flux J at fixed enzyme activities.

* how can we increase/reduce stochiometric sensitivity of c_1 (regulator/control agent of process x) w.r.t. J?

c_0, J at steady state

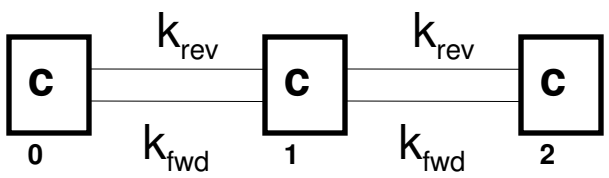
Stochiometric sensitivity coefficients (η)

$$c_1 = \frac{k_1}{k_{-1}} c_0 - \frac{1}{k_{-1}} J \qquad (2)$$

$$c_2 = \frac{k_1 k_2}{k_{-1} k_{-2}} c_0 - \frac{k_2 + k_{-1}}{k_{-1} k_{-2}} J \qquad (3)$$

$$\eta_1 = \left| \frac{\partial \ln c_1}{\partial \ln J} \right| = \frac{J}{k_{-1} c_1} \qquad (4)$$

$$\eta_2 = \left| \frac{\partial \ln c_2}{\partial \ln J} \right| = \frac{(k_2 + k_{-1}) J}{k_{-1} k_{-2} c_2} \qquad (5)$$



High grade chemical energy converted to low grade heat energy (but does it retain information content?)

Motif #2: futile cycles

$$e^{\Delta\hat{G}^{\circ}/RT} = \frac{k_{-1} + \hat{k}_3}{k_1 + \hat{k}_{-3}} = e^{\Delta G^{\circ}/RT}\left(\frac{1 + \sigma e^{\Delta G_{DE}/RT}}{1 + \sigma}\right) \quad (11)$$

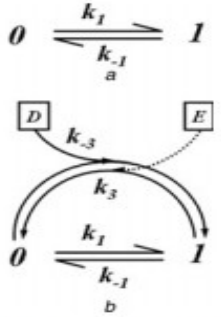


Fig. 2 *Futile cycle attached to the reaction 0 ⇌ 1*

a Biochemical reaction between species 0 and 1 in isolated system reaches its equilibrium with concentrations $c_1^{eq}/c_0^{eq} = k_1/k_{-1} = e^{-\Delta G^{\circ}/RT}$ Enzyme can change the rate constants, but not the free energy difference ΔG°. However, if this reaction is coupled to other reactions in an open biochemical network as shown in Fig. 2*b*, a futile cycle is able to shift the population ratio c_1/c_0 to be greater (or less) than the equilibrium value k_1/k_{-1}
b Additional reactions involve species *D* and *E*. There is now a futile cycle involving species 0 and 1
Equilibrium between *D* and *E* is $c_D^{eq}/c_E^{eq} = c_1^{eq}k_3/(c_0^{eq}k_{-3}) = k_1k_3/(k_{-1}k_{-3})$. If the concentrations of *D* and *E* are not at their equilibrium, then $\ln(c_Ek_1k_3/(c_Dk_{-1}k_{-3})) = \Delta G_{DE} \neq 0$, which is the active energy source (e.g. nucleotide hydrolysis) that pumps the futile cycle. In a steady state this energy is dissipated as heat. Same mechanism is behind the nuclear Overhauser effect in magnetic resonance, kinetic proofreading in biosynthesis [6], and catalytic wheel [9]

Interesting findings:

* sensitivity increases as one moves downstream (c0 → c2).

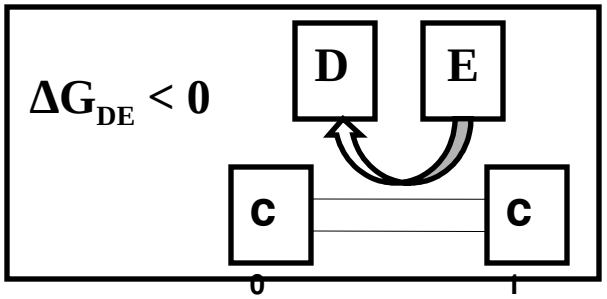
* change in Gibbs free energy ($\Delta G_{DE,}$ free energy = concentration) with increased sensitivity means less backward flux (when backward flux > J).

Observations for ΔG_{DE}:

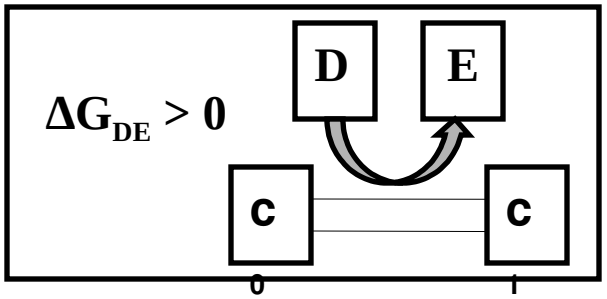
* at equilibrium, $\Delta G_{DE} = 0$.

* for $\Delta G_{DE} > 0$, futile cycle driven in clockwise direction. Reaction driven away from equilibrium.

* for $\Delta G_{DE} < 0$, futile cycle driven in counterclockwise direction. Reaction driven away from equilibrium.



D, E are coupled to reaction between C0, C1, creates a directional futile cycle that can be driven to edge of chaos.



Motif #2: futile cycles

Common Form of Motif #2: multisite phosphorylation-dephosphorylation cycle: Wang and Sontag, *J. Mathematical Biology*, 57, 29-52 (2008).

* can generate several dynamic behaviors (bistability, ultrasensitivity).

* futile cycles = enzymatic interconversions.

MAPK cascades (see Biophysical Journal, 92, 1–9, 2007) = three tiers of similar structures with multiple feedbacks.

* each level is a futile cycle.

Steady states in futile cycles:

* futile cycles are sequential, not random.

* futile cycle is processive (kinase facilitates 2+ phosphorylations).

* dual phosphorylation/dephosphorylation in MAPK are distributive (kinase facilitates 1 phosphorylation).

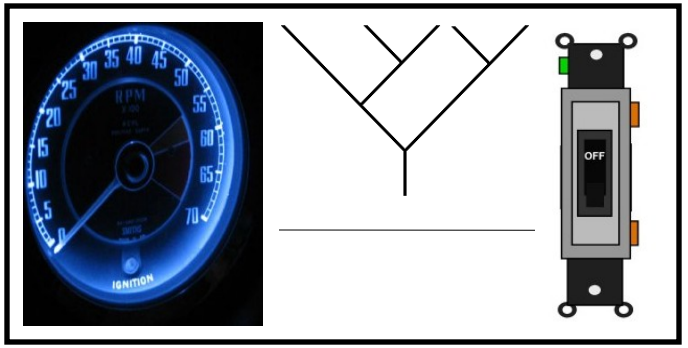
* dual phosphorylation/dephosphorylation in futile cycles are distributive, otherwise they exhibit a unique steady state (does not = experiment).

Motif #2: futile cycles

Evolutionary perspective:
Natural selection favors switches (discrete dynamics) over dials (analog dynamics).

* evolution of a novel control system in cell.

* noise "filtering" as a form of regulation.



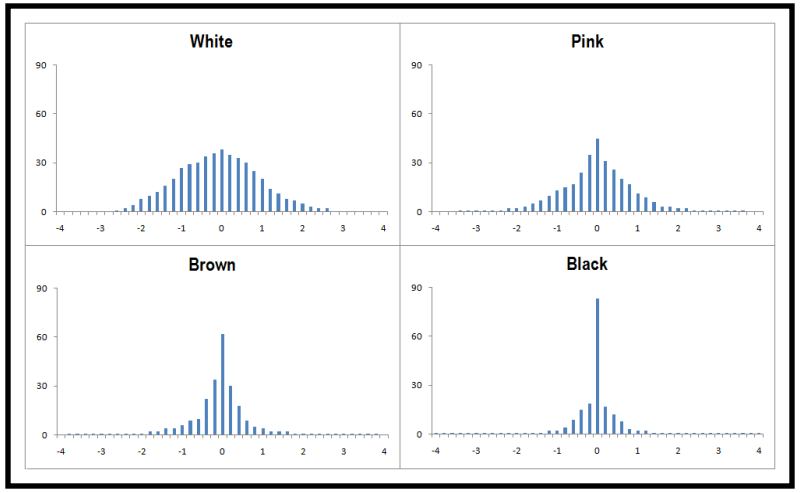
$1/x^{\gamma}$ noise – larger value for γ, PDF has longer tail, less support, and higher kurtosis

"Noise" perspective:
Noise-induced bistability is possible (switch case).

* two parameters influence stochastically-driven enzymatic cycles:

* strength of external driving (magnitude).

* exact distribution of noise (e.g. 1/f varieties- white, pink, brown, black).



Motif #3: complex feedforward

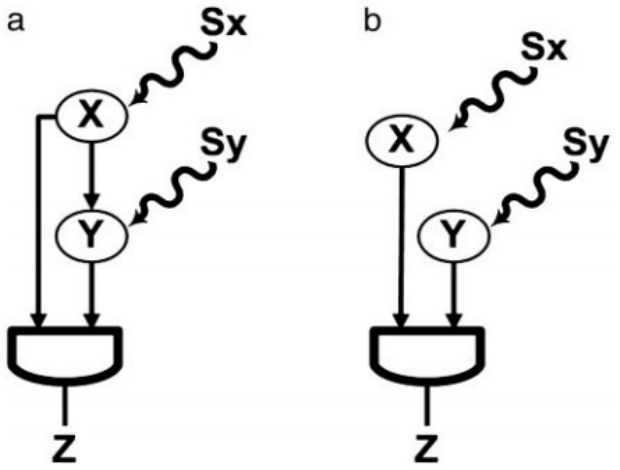


Fig. 1. (*a*) FFL. Transcription factor X regulates transcription factor Y, and both jointly regulate Z. Sx and Sy are the inducers of X and Y, respectively. The action of X and Y is integrated at the Z promoter with a cis-regulatory input function (7, 14), such as AND or OR logic. (*b*) Simple regulation of Z by X and Y.

* sign-sensitivity: (+) is acceleration, (-) is delay w.r.t. stimulus input at discrete steps.

* X and Y are transcription factors, S_x, S_y are binding proteins, cofactors, etc.

Mangan and Alon. *PNAS USA*, 100(21), 11980-11985 (2003).

* feedforward control mechanism found in *E.coli* and yeast.

* tested eight (8) FF network configurations (using Boolean rules).

Table 1. Structure and function of the coherent FFL types, with AND- and OR- gates at the Z promoter

	Coherent type 1		Coherent type 2		Coherent type 3		Coherent type 4	
Species	Structure	Abundance	Structure	Abundance	Structure	Abundance	Structure	Abundance
E. coli	X → Y → Z	28	X ⊣ Y → Z	2	Y → Y ⊣ Z	4	X ⊣ Y ⊣ Z	1
S. cerevisiae		26		5		0		0
Z Logic→	AND	OR	AND	OR	AND	OR	AND	OR
Steady-state Z(Sx,Sy)	$S_x \wedge S_y$	S_x	$\bar{S}_x \wedge S_y$	$\bar{S}_x$	$\bar{S}_x$	$\bar{S}_x \wedge \bar{S}_y$	S_x	$S_x \vee \bar{S}_y$
Response delay								
Sx on step	Delay	—	—	Delay	—	—	Delay	Delay
Sx off step	—	Delay	Delay	—	Delay	Delay	—	—
Inverted out	No	No	Yes	Yes	Yes	Yes	No	No

Coherent FFL types and their abundance in transcription databases of *E. coli* and *S. cerevisiae* (6, 11). Z(Sx,Sy): Steady-state Z expression of coherent FFLs for the four combinations of Sx and Sy on and off levels ($\wedge$,$\vee$,¯ represent AND, OR, NOT). Response: Response delay of coherent FFLs to on and off S_x steps in the presence of Sy. —, not delayed. Inverted out means that Z goes off in response to Sx on step.

Motif #3: complex feedforward

Table 2. Structure and function of the incoherent FFL types, with AND-gates at the Z promoter

	Incoherent type 1		Incoherent type 2		Incoherent type 3		Incoherent type 4	
Species	Structure	Abundance	Structure	Abundance	Structure	Abundance	Structure	Abundance
E. coli	X → Y → Z, X → Z	5	X ⊣ Y ⊣ Z, X ⊣ Z	0	X → Y → Z, X → Z	1	X ⊣ Y → Z, X → Z	1
S. cerevisiae		21		3		1		0
Z logic →	AND		AND		AND		AND	
Steady-state								
Z(Sx,Sy)	$S_x \wedge \bar{S}_y$		$\bar{S}_x \wedge \bar{S}_y$		0		0	
Pulse								
Sx on step	Weak		—		—		Strong	
Sx off step	—		Weak		Strong		—	
Sy effect	Destroy		Destroy		Enable		Enable	
Response acceleration								
Sx on step	Accelerate		—		—		Accelerate	
Sx off step	—		Accelerate		Accelerate		—	

Incoherent FFL types and their abundance in transcription databases (6, 11). Z(Sx,Sy): Steady-state Z expression of incoherent FFL with no basal level of Y (∨, ¯ represent AND, NOT). Pulse: Response to steps of Sx, in the presence of Sy, in FFLs with no basal activity, Sy effect on pulse: Enable, no pulse is created when Sy is off; Destroy, Z output is a low pulse when Sy is on, but is high and steady when Sy is off (Fig. 3). Response acceleration: Acceleration of response of and steady-state values of incoherent FFL with basal activity to on and off steps in the presence of Sy. —, not accelerated.

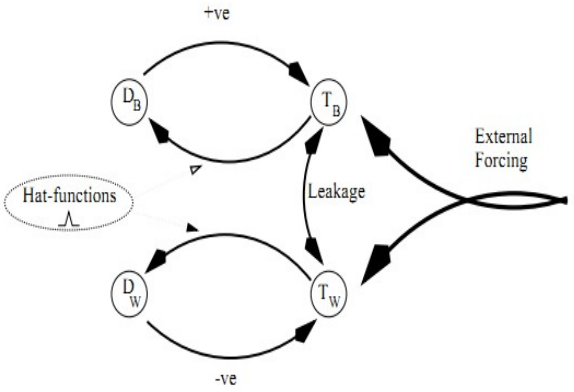


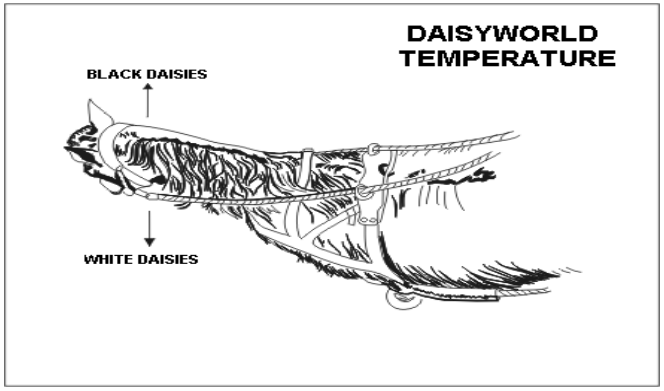
Figure 2. Interactions in the cut-down model: a black daisybed above, separate white one below. Both receive external forcing from the sun, and the only interaction between them is by 'leakage' or heat conductance.

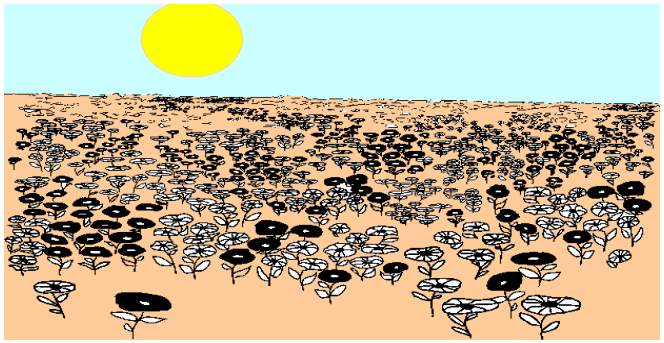
Incoherent FF systems: signs on the direct (e.g. Y-Z) and indirect (e.g. X-Z) pathways are opposite.

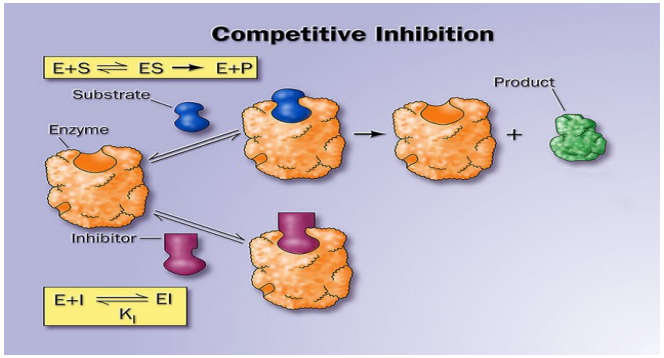
Harvey, Homeostasis and Rein Control. *Artificial Life 9*.

* "cut-down" model: external source independently drives each state (e.g. rein control), which keeps proportions of each state in the system stable.

Motif #3: complex feedforward







Saunders, Koeslag, Wessels. Integral Rein Control in Physiology. *J. Theoretical Biology*, 194, 163-173 (1998).

* rein control: two inputs directly provide an input – competition/coordination between the two results in control (e.g. achieving equilibrium).

1) Competitive binding: two enzymes that compete for binding sites on a substrate

* produces an equilibrium through inhibition of one input.

2) Daisyworld: two inputs (black and white daisies that absorb/reflect sunlight)

* proportion of each population determines properties of atmosphere (e.g. temperature).

Additional Feedback, Feedforward Mechanisms

Del Vecchio and Sontag. Engineering Principles in Biomolecular Systems. *European Journal of Control*, vol. 15 (3-4), 2009

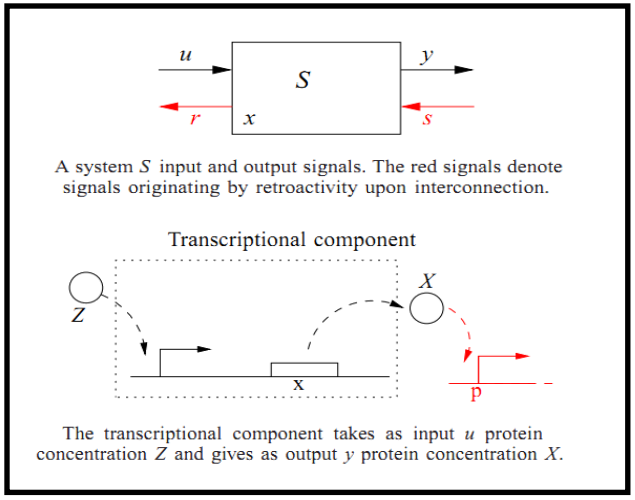
What is the relationship between modularity and feedback (in synthetic biology)?

* **interconnected systems:** behavior of an upstream component is affected by presence of downstream component (counter to idea of mutually exclusive modules).

* **retroactivity example:** oscillator as a source that synchronizes several downstream transcriptional processes, but oscillator dynamics affects by downstream elements using up its product.

* conventional control theory = inputs, outputs, and states (internal and mutually exclusive).

* with retroactivity, two additional components: retroactivity to input, retroactivity to output.

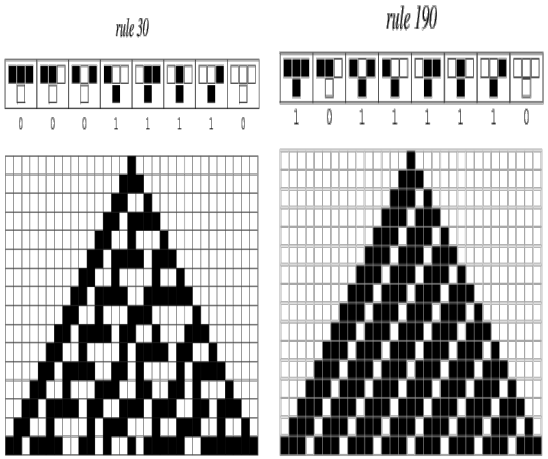


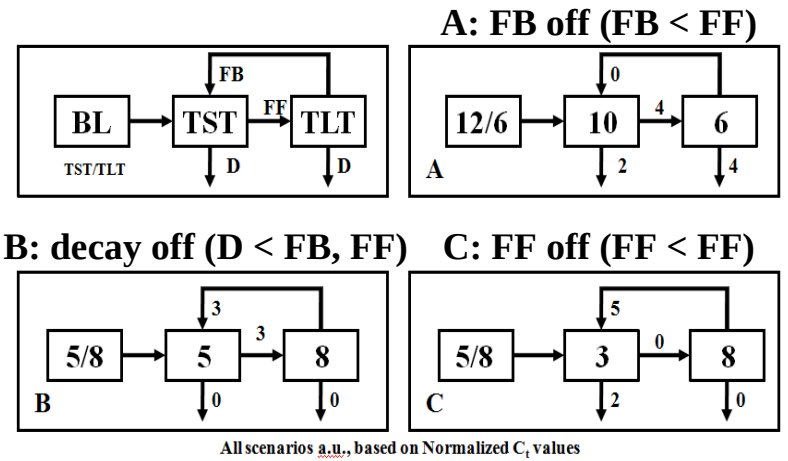
Nature Precedings : doi:10.1038/npre.2011.6369.2 : Posted 20 Sep 2011

Additional Feedback, Feedforward Mechanisms

Discrete dynamics (emergent, right):
* simple rules + intrinsic randomness = complex patterns.

* combine rules, can we "control" very complex self-assembly processes?





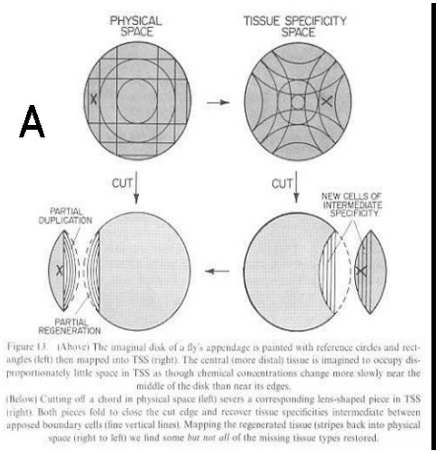


Figure 13. (Above) The imaginal disk of a fly's appendage is painted with reference circles and rectangles (left) then mapped into TSS (right). The central (more distal) tissue is imagined to occupy disproportionately little space in TSS as though chemical concentrations change more slowly near the middle of the disk than near its edges.
(Below) Cutting off a chord in physical space (left) severs a corresponding lens-shaped piece in TSS (right). Both pieces fold to close the cut edge and recover tissue specificities intermediate between apposed boundary cells (fine vertical lines). Mapping the regenerated tissue (stripes back into physical space (right to left) we find some *but not all* of the missing tissue types restored.

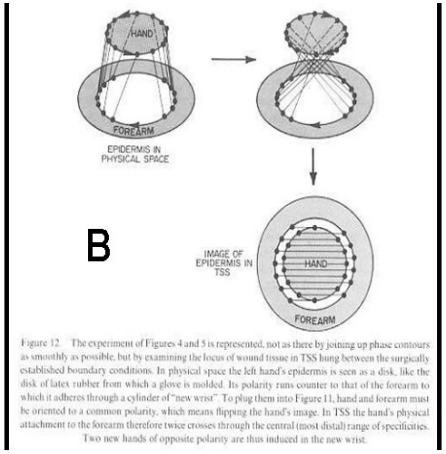


Figure 12. The experiment of Figures 4 and 5 is represented, not as there by joining up phase contours as smoothly as possible, but by examining the locus of wound tissue in TSS hung between the surgically established boundary conditions. In physical space the left hand's epidermis is seen as a disk, like the disk of latex rubber from which a glove is molded. Its polarity runs counter to that of the forearm to which it adheres through a cylinder of "new wrist". To plug them into Figure 11, hand and forearm must be oriented to a common polarity, which means flipping the hand's image. In TSS the hand's physical attachment to the forearm therefore twice crosses through the central (most distal) range of specificities. Two new hands of opposite polarity are thus induced in the new wrist.

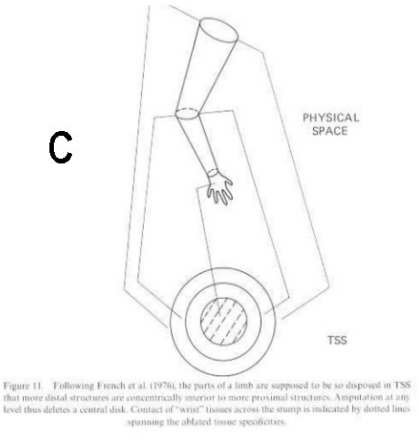


Figure 11. Following French et al. (1976), the parts of a limb are supposed to be so disposed in TSS that more distal structures are concentrically interior to more proximal structures. Amputation at any level thus deletes a central disk. Contact of "wrist" tissues across the stump is indicated by dotted lines spanning the ablated tissue specificities.

Discrete dynamics (regulation, above):
BL = baseline (control value).

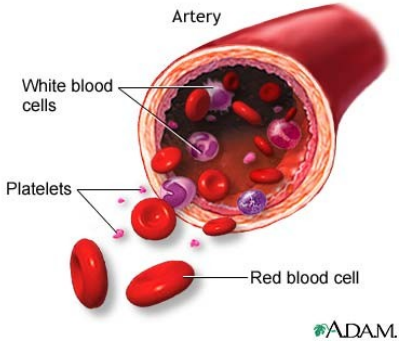
BL → TST, BL → TLT: 0d → *n*d.

TLT → TST: *n* + 1d.

Discrete dynamics (geometric) in development and regeneration
COURTESY: Winfree (1980). Geometry of Biological Time.

Additional Feedback, Feedforward Mechanisms

Traffic flow and regulation in networks:



Flows consist of particles (cars, ants, platelets). Particles follow pathways of variable width, number at variable velocities.

Multiple FB and FF mechanisms: velocity of particles relative to other particles (FB), autonomous velocity (FF), cycles in network (FB), outbound paths (FF).

Jamming parameter: when threshold is reached (.75), phase transition occurs (from free-flowing to solid).

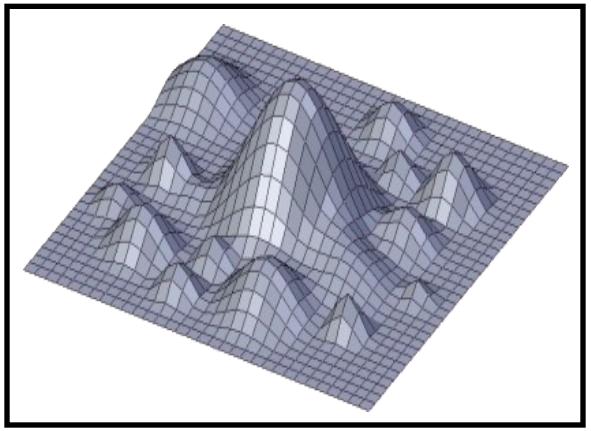
Flow control:

* how does FF component get regulated (by FB, initial inputs, connectivity)?

* what are the collective (aggregate) effects of particle behavior on flow dynamics?

Future Directions

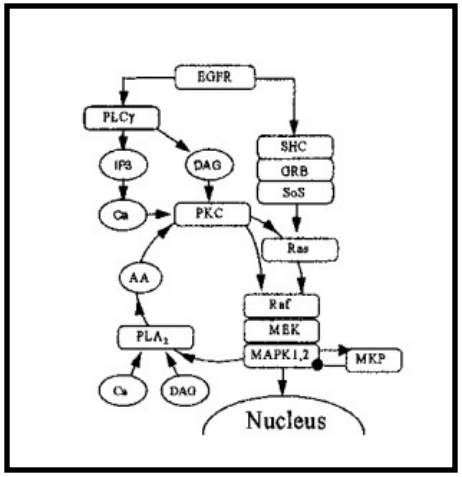
How do “top-down” control mechanisms constrain the function of “bottom-up” emergent structures?



Evolutionary systems are not goal-oriented (only respond to fitness constraints locally in time).

* one aspect of evolvability = exploratory behavior (relaxed linkage of parts). Parts = motifs.

Signaling pathways are “emergent” structures -- Bhalla and Iyengar, Science, 381, 283 (1999). Decoupling FB and aggregations within pathways = altered function.

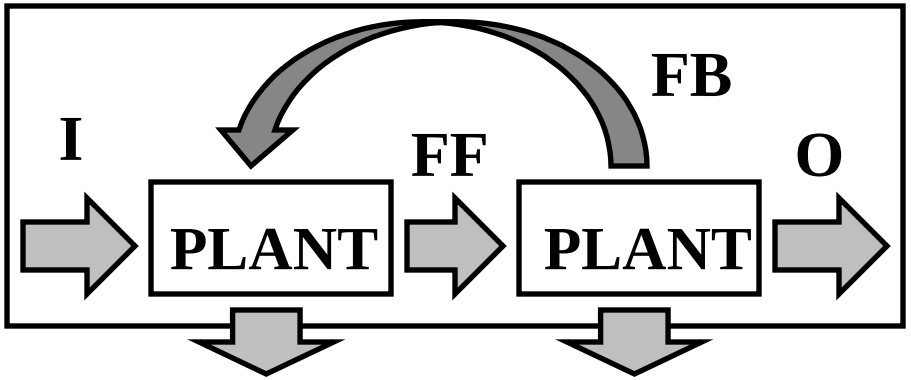


Controllability: ability to move system around entire configuration space (ergodic) using finite repertoire.

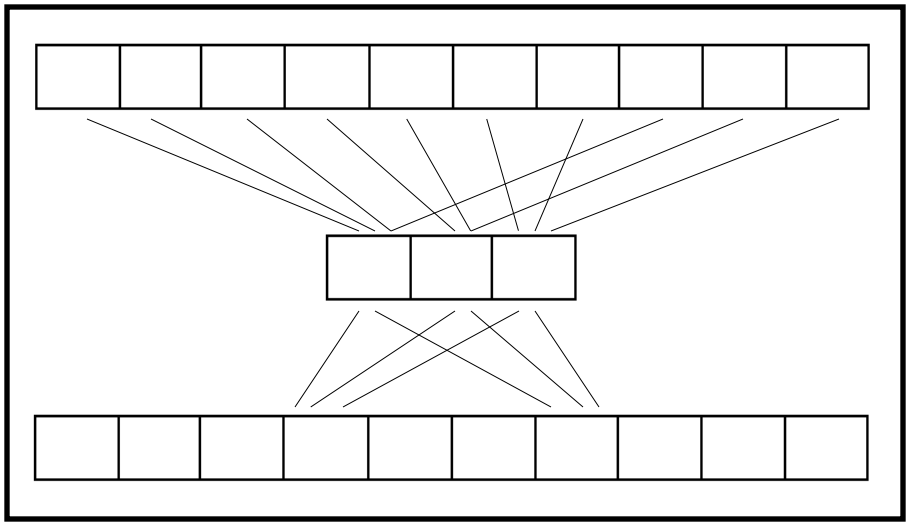
* can controllability act to “push” individuals towards fitness maxima (fitness landscape, upper left)?

* do diffusive (neutral) processes contribute to observed natural diversity in pathways?

Future Directions



Feedback control with feedforward, decay



Gather transformation, CUDA programming

The system at left has two plants and a SISO (single input, single output) architecture.

* input and feedback serves as convergent input on first plant – how do we parse this effect?

* what about MIMO (multiple input, multiple output) systems?

Parallel architectures are needed (CUDA example, feedforward).

* way to better model polygenic systems, pleiotropic effects (one gene, many products)?

* what about the effects of, interactions between scale (e.g. multiscalar systems)?