The Evolution of Phenotypically Invariant Gene Networks

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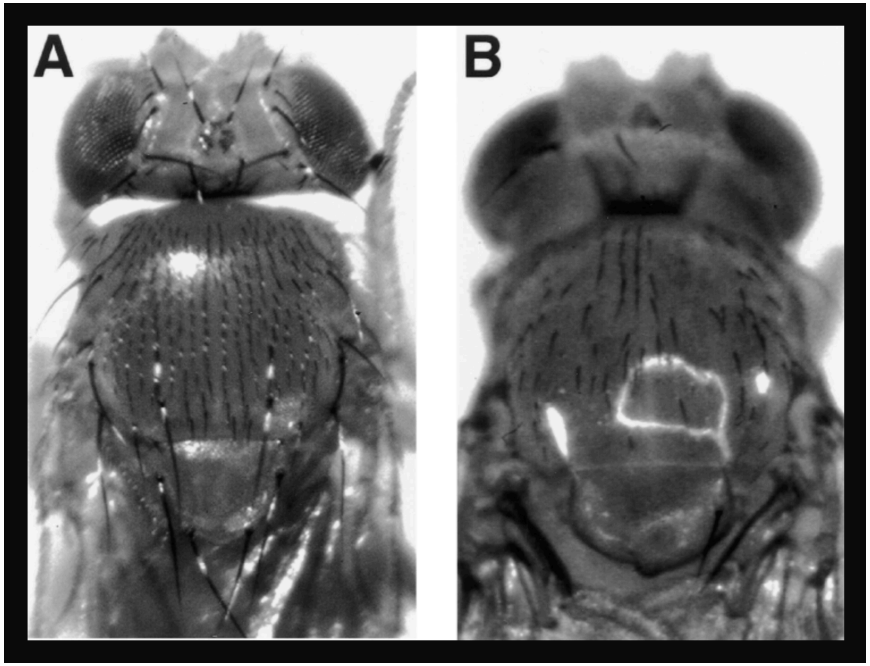
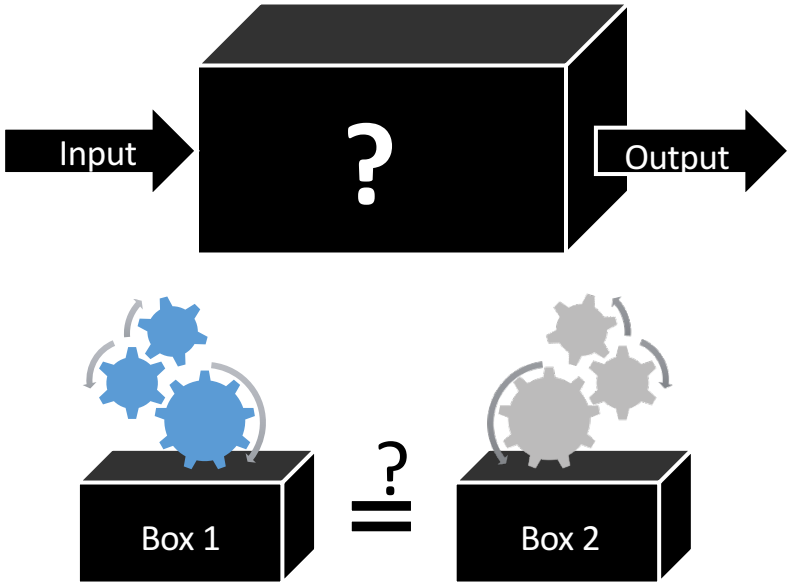
Developmental systems drift: many molecular pathways can produce the same phenotype

Drosophila hybrid bristle patterning (True and Haag 2001), yeast gal regulon, cell cycle control (Kearsey and Cotterill, 2003), circadian clock (Sancar, 2008), and the *Drosophila* gap gene network.



How many black boxes are input-output equivalent, yet have different internal mechanisms?

Typically the mechanism is **not unique**. An **infinite number of mechanisms** with an infinite number of components could theoretically be inside the box.

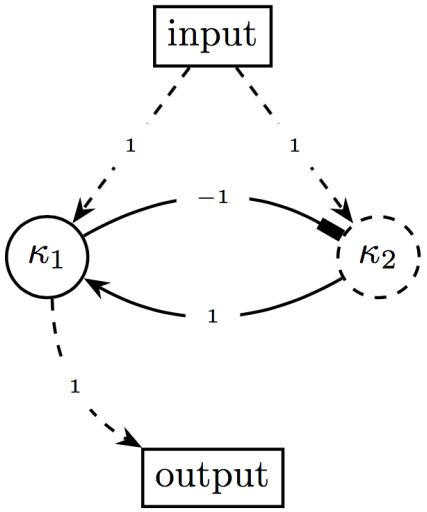


Gene regulatory networks can be modelled as linear dynamical systems

$$\Sigma = \begin{cases} \dot{\kappa}(t) &= A\kappa(t) + Bu(t) \\ \phi(t) &= C\kappa(t) \end{cases}$$

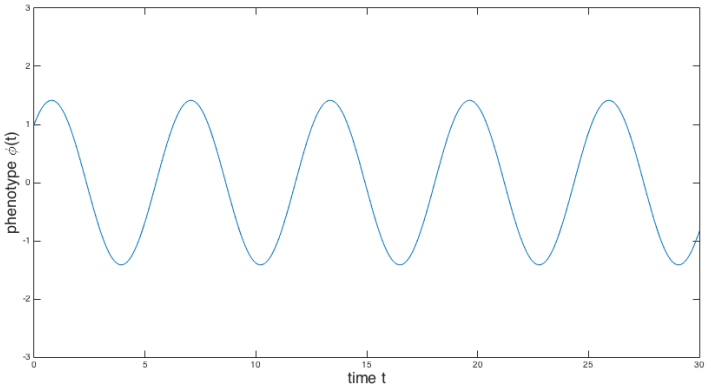
A is an $n \times n$ matrix, B is an $n \times l$ matrix, and C an $l \times n$ matrix.

A is the gene network and each row is a promoter; B determines how the input is processed, and C filters only the dynamics relevant to survival – or what selection *observes*.



$$\Sigma = \begin{cases} \dot{\kappa}(t) &= \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \kappa(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u \\ \phi(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \kappa(t) \end{cases}$$

$$\phi(t) = \sin(t) + \cos(t)$$



Consider a two gene network with oscillating expression dynamics of gene-1 ($n = 2$ and $l = 1$).

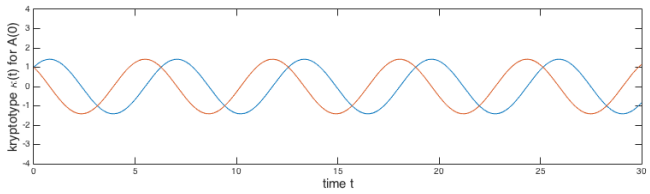
Different gene network architectures can produce identical phenotypes

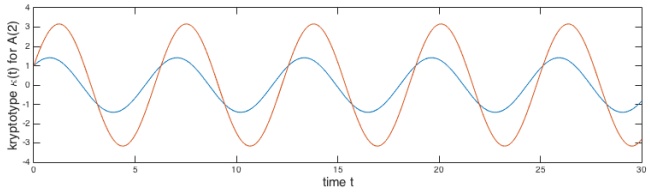
Example: two **different** oscillator mechanisms with **identical** input-output dynamics.
Indistinguishable under the same selection and environmental conditions.

$$\Sigma = \begin{cases} \dot{\kappa}(t) &= \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \kappa(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u(t) \\ \phi(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \kappa(t) \end{cases}$$

$$\widehat{\Sigma} = \begin{cases} \dot{\kappa}(t) &= \begin{bmatrix} 2 & -1 \\ 5 & -2 \end{bmatrix} \kappa(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u(t) \\ \phi(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \kappa(t) \end{cases}$$

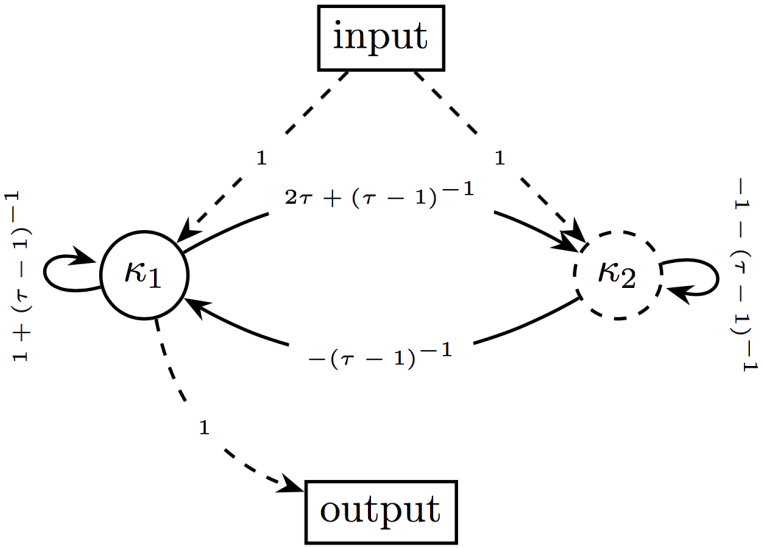
$$\phi(t) = \sin(t) + \cos(t)$$

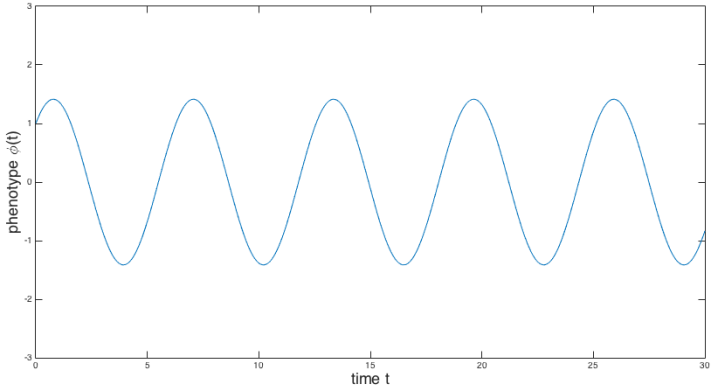




Analytically describe all phenotypically invariant gene networks

Example: all two gene oscillators are given by:



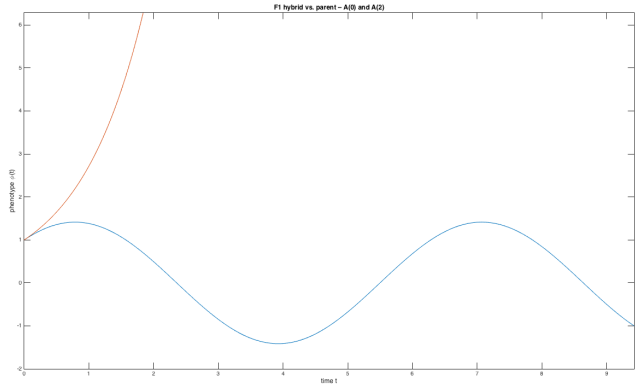


$$P(\tau) := \begin{bmatrix} 1 & 0 \\ \tau & 1-\tau \end{bmatrix} \qquad \tau \neq 1$$

$$A(\tau) := P(\tau) A P^{-1}(\tau)$$

Dobzhansky-Muller Incompatibilities between phenotypically identical gene networks.

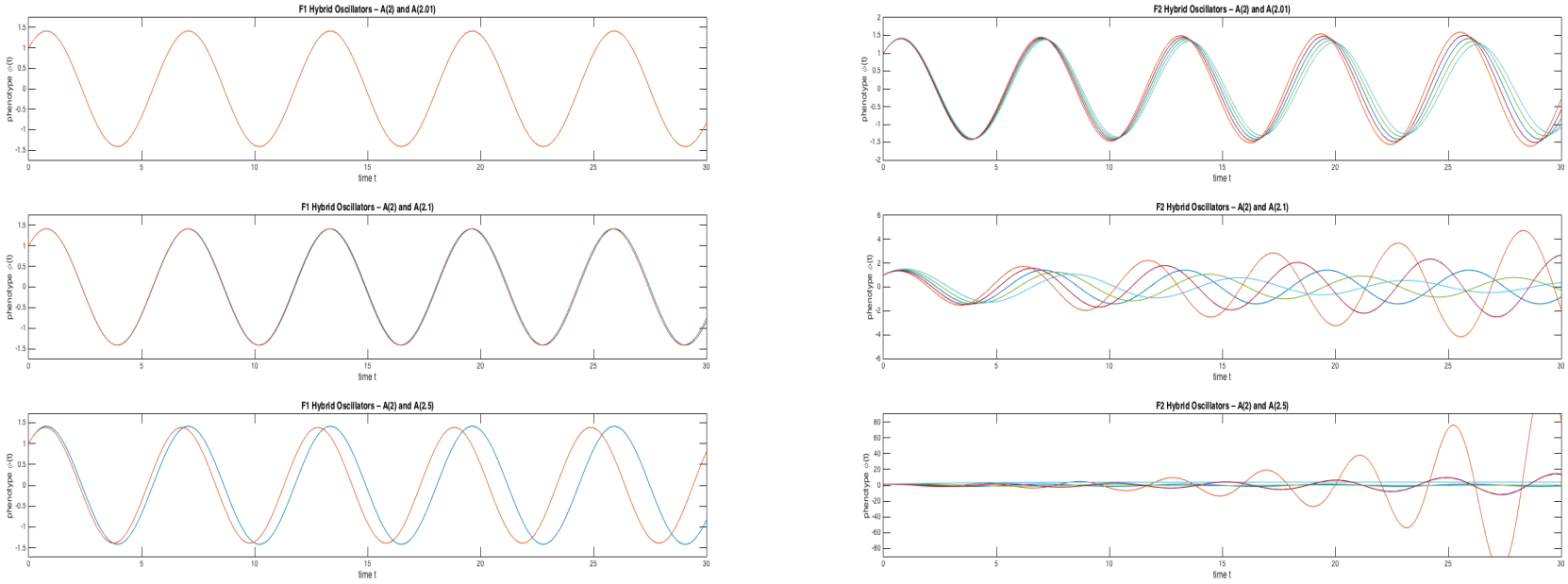
- F_1 hybrids are formed by averaging the two parental gene networks A and A'.
- F_2 hybrids are formed by recombining genes (swapping rows between A and A'), then two gametes are chosen and averaged.
- Fitness can be scored as a function of phenotypic distance.



Oscillators $A(0)$ and $A(2)$ F_1s
Parents (blue), hybrids (orange).

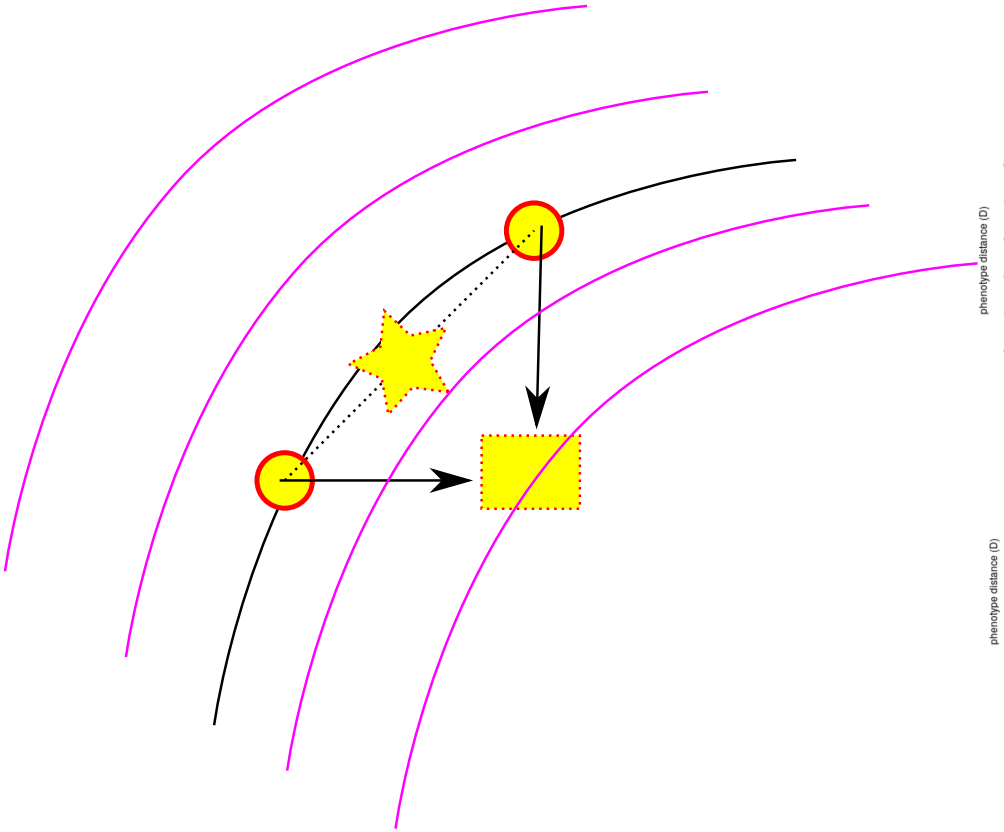
$$\mathcal{F}\left(\widehat{\phi}(t)\right) = \exp\left\{-\int_0^\infty \left\|\phi(t) - \widehat{\phi}(t)\right\| dt\right\}$$

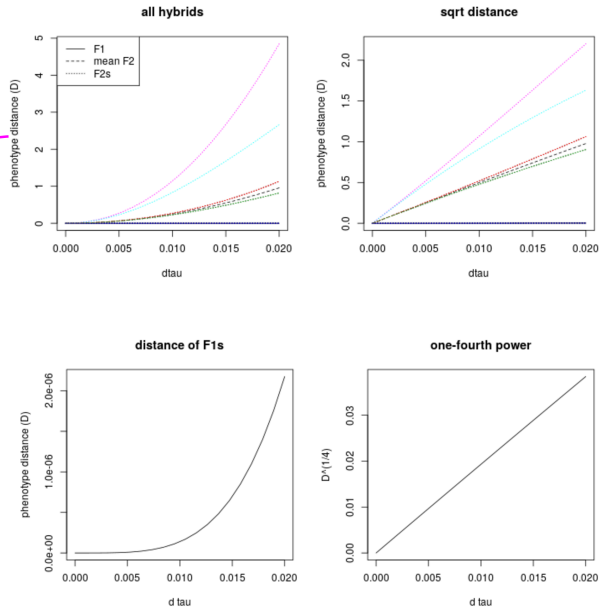
F_1(left) and F_2(right) Hybrids between $A(2)$ and $A(2.01)$ (top) , $A(2.1)$ (middle), and $A(2.5)$ (bottom).



F_1s diverge quartically; F_2s diverge quadratically.

Phenotypes diverge at a quartic rate in F_1s (top) and at a quadratic rate in F_2s (bottom) as a function of τ.





Star is F_1s, rectangle is F_2s, and circles are parents.

How fast does reproductive incompatibility occur in allopatry?

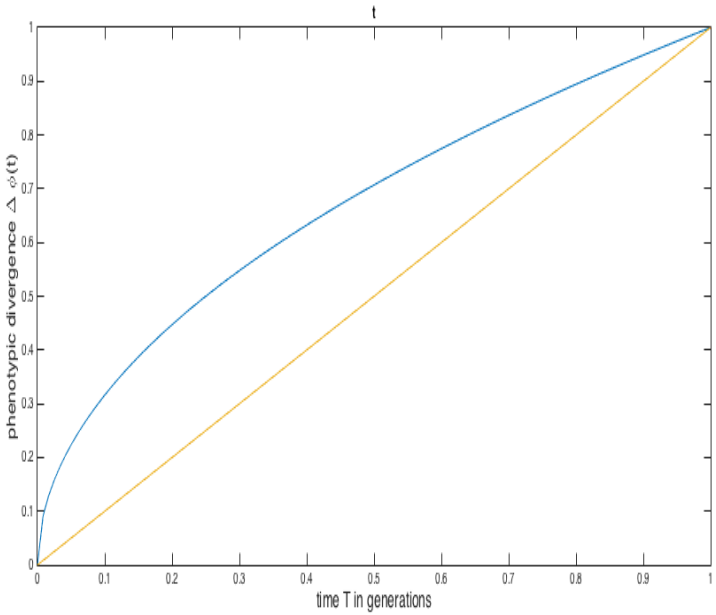
- Gene regulatory strengths are quantitative traits thus we use a quantitative genetics model.
- F1 and F2 phenotypes diverge quartically and quadratically, respectively.
- The reproductive incompatibility will be,

  $\sim \exp\left(-2\left(\frac{T}{N}\right)c_2\right)$ in F2s (blue)

  and

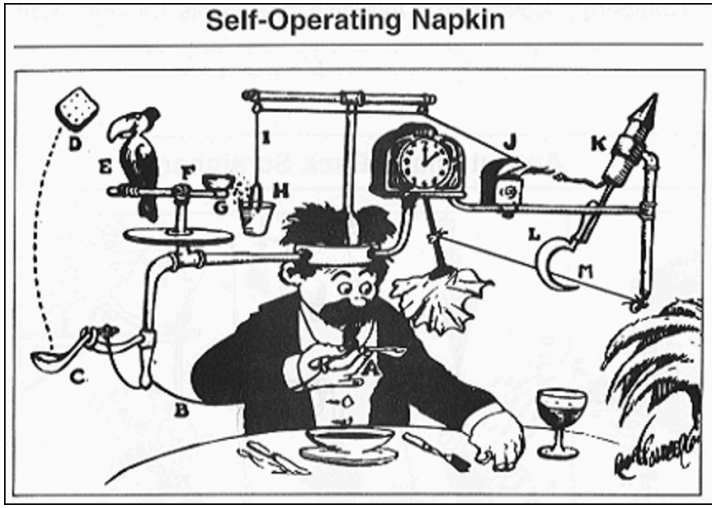
  $\sim \exp\left(-2\left(\frac{c_1 T}{N}\right)^2\right)$ in F1s (orange)

  formed by mating allopatric populations of size N isolated for T generations.



Gene Network Ratchet – Are Gene Networks Rube Goldberg Machines?

- How often will a gene network grow or diminish in size?
- If network growth is far more likely than reduction, will we observe a “ratchet?”
- Maybe like bureaucracy
- Is there an equilibrium network size?
- Why are some networks observed to be like Rube Goldberg machines and others not? (e.g. circadian clock in cyanobacteria vs. mammals [Sancar, 2008]).



Thank You!

- Peter Ralph
- Sergey Nuzhdin
- Erik Lundgren
- Hossein Asgharian