The Evolution of Phenotypically Invariant Gene Networks

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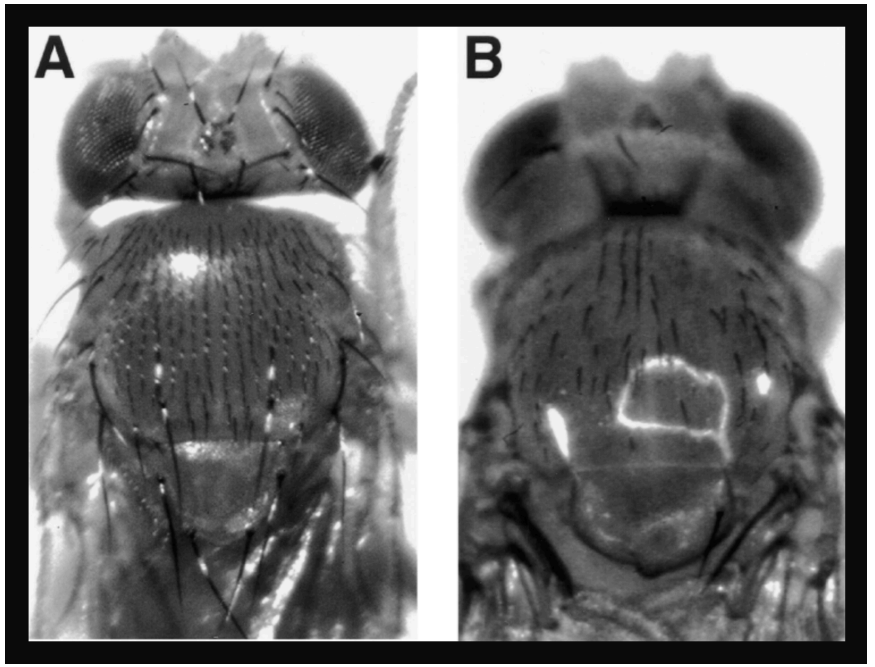
Developmental systems drift: many molecular pathways can produce the same phenotype

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



(A) parents and (B) hybrid

D. melanogaster and *simulans* vs. hybrid bristle patterns.

True and Haag, Evolution & Development, 2001.

Outline and motivating questions

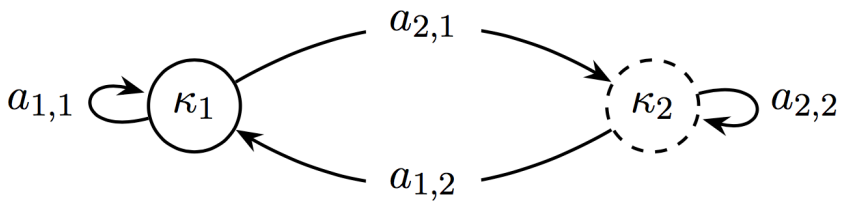
1. How to model the genotype-phenotype map as gene regulatory networks?
2. How many different gene networks can produce identical phenotypes?
3. At what rate does evolution explore phenotypically identical network organizations?
4. Can evolution along the phenotypically invariant landscape lead to speciation via reproductive incompatibility?
5. If so, at what rate?

How to model the genotype-phenotype map?

- A phenotype is defined as the time dynamics of molecules directly relevant to survival.
- Basically, the phenotype is the ***what***, ***when***, ***where,*** and ***amount*** of important molecules.
- These dynamics are the result of the interconnections of a **gene regulatory network** (*e.g.* transcription factors binding promoters), as well as environmental input.

Gene regulatory networks can be modelled as linear dynamical systems

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



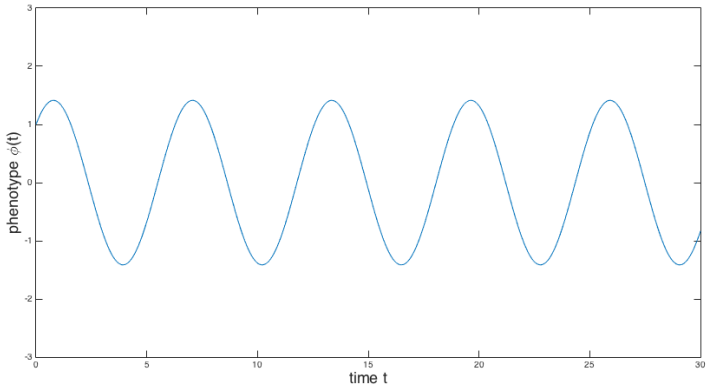
A is the gene network and each row is a promoter; B determines how the input is processed, and C filters only the dynamics relevant to survival – or what selection *observes*.

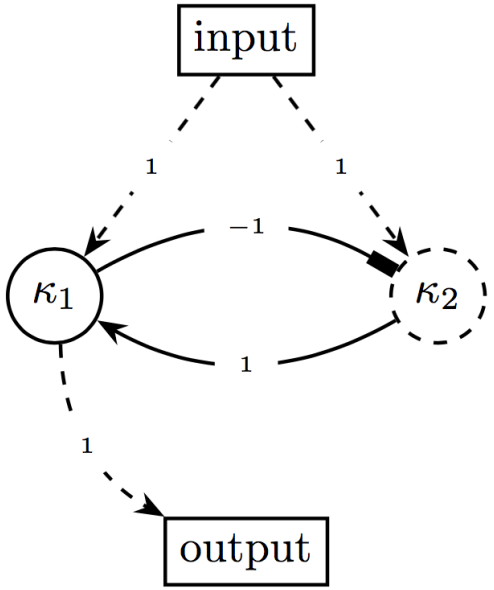
A is an $n \times n$ matrix, B is an $n \times l$ matrix, and C an $l \times n$ matrix. This approach is common electrical and control engineering.

Example: consider an oscillating two-gene network

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

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

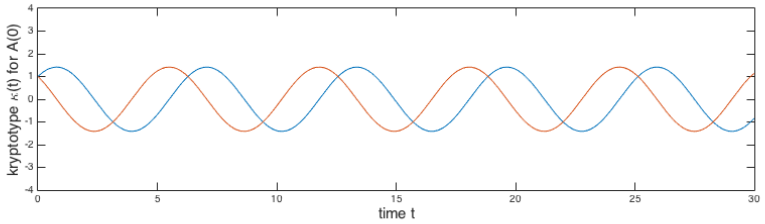




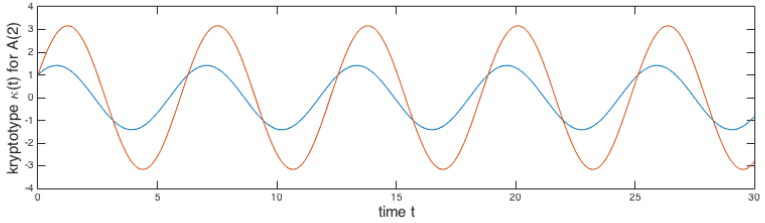
Note: $n = 2$ and $l = 1$.

Two **different** oscillator mechanisms with **identical** input-output dynamics and are indistinguishable under the same selection and environmental conditions.

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



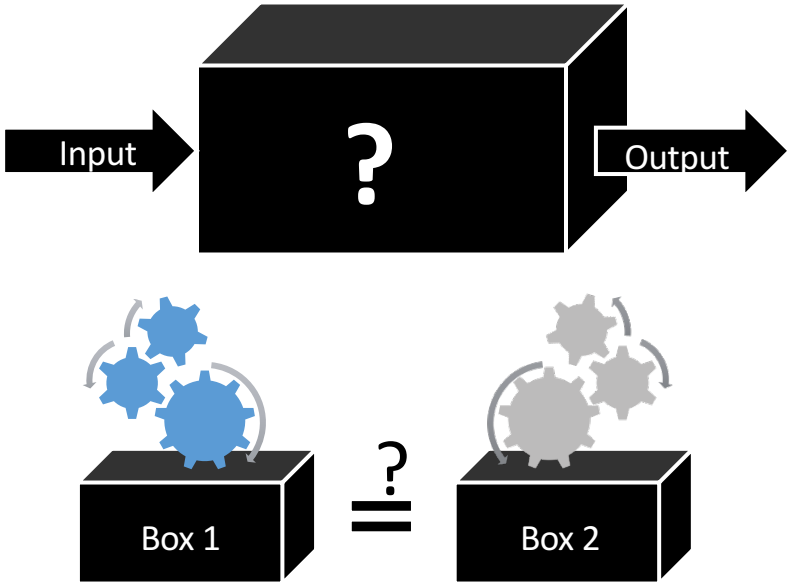
$$\widehat{\Sigma} = \begin{cases} \dot{\widehat{\kappa}}(t) &= \begin{bmatrix} 2 & -1 \\ 5 & -2 \end{bmatrix} \widehat{\kappa}(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u(t) \\ \widehat{\phi}(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \widehat{\kappa}(t) \end{cases}$$



$$\phi(t) = \widehat{\phi}(t) = \sin(t) + \cos(t)$$

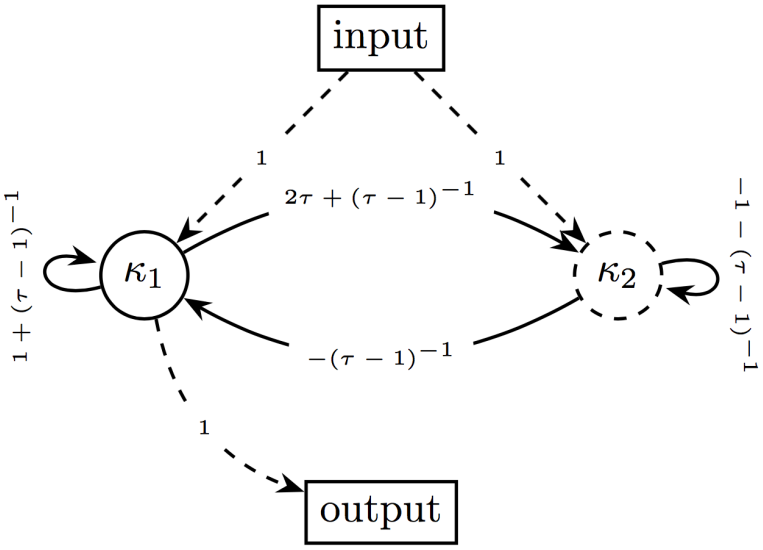
How many black boxes are input-output equivalent, yet have different internal mechanisms?

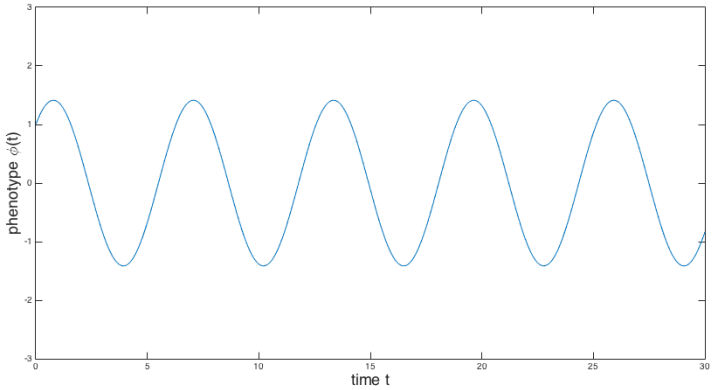
Typically the mechanism is **not unique**. An **infinite number of mechanisms** with an infinite number of components could theoretically be inside the box.



The set of all phenotypically equivalent gene networks

Example: all two gene oscillators are given by:





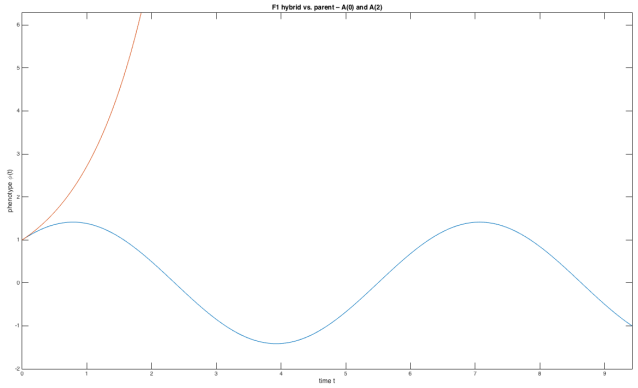
$$P(\tau) := \begin{bmatrix} 1 & 0 \\ \tau & 1-\tau \end{bmatrix} \qquad \tau \neq 1$$

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

- In a static environment and under stabilizing selection, evolution will explore the set of equivalent networks.
- Phenotype is conserved whereas mechanism is not.

Can evolution through the set of phenotypically invariant gene networks lead to Dobzhansky-Muller Incompatibilities?

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



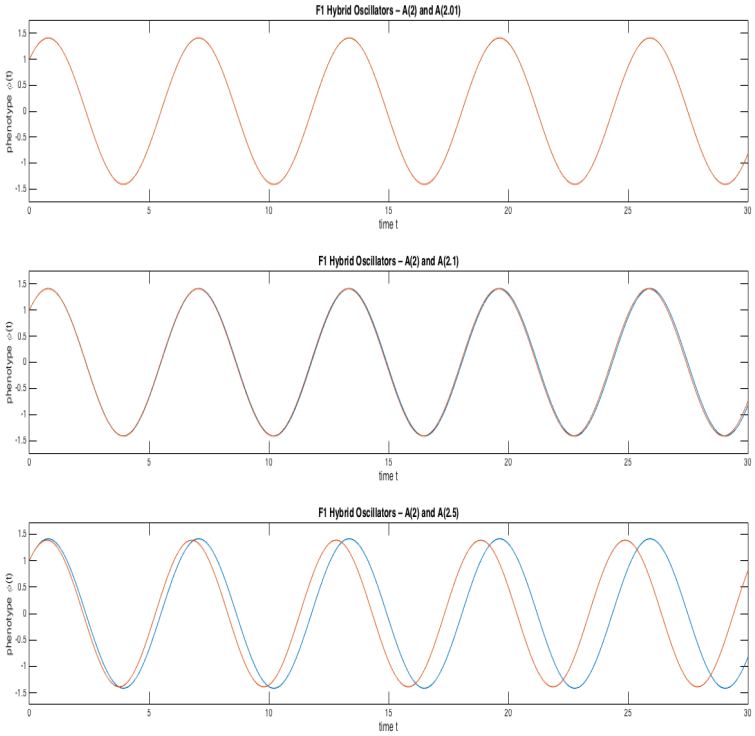
Oscillators $A(0)$ and $A(2)$ F_1s
Parents (blue), hybrids (orange).
Hybrid $\phi_{F_1}(t) = e^t$

$$\mathcal{F}\left(\widehat{\phi}(t)\right) = \exp\left\{-\frac{1}{\sigma}\int_0^\infty \left\|\phi(t) - \widehat{\phi}(t)\right\|^2 dt\right\}$$

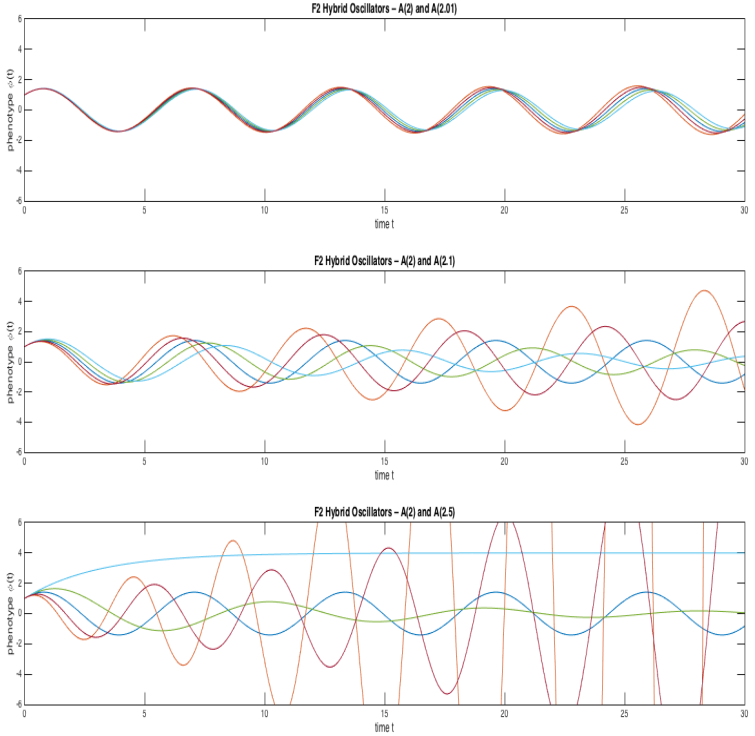
F_1(left) and F_2(right) Hybrids between $A(2)$ and $A(2.01)$ (top) , $A(2.1)$ (middle), and $A(2.5)$ (bottom).

F_1

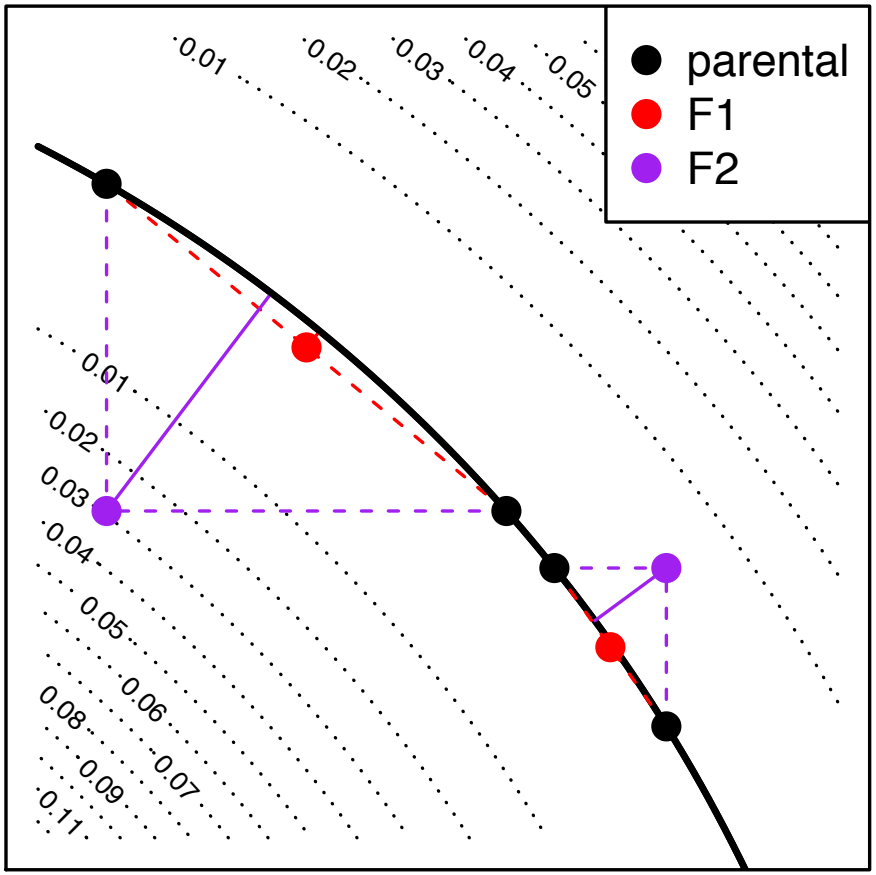
F_2

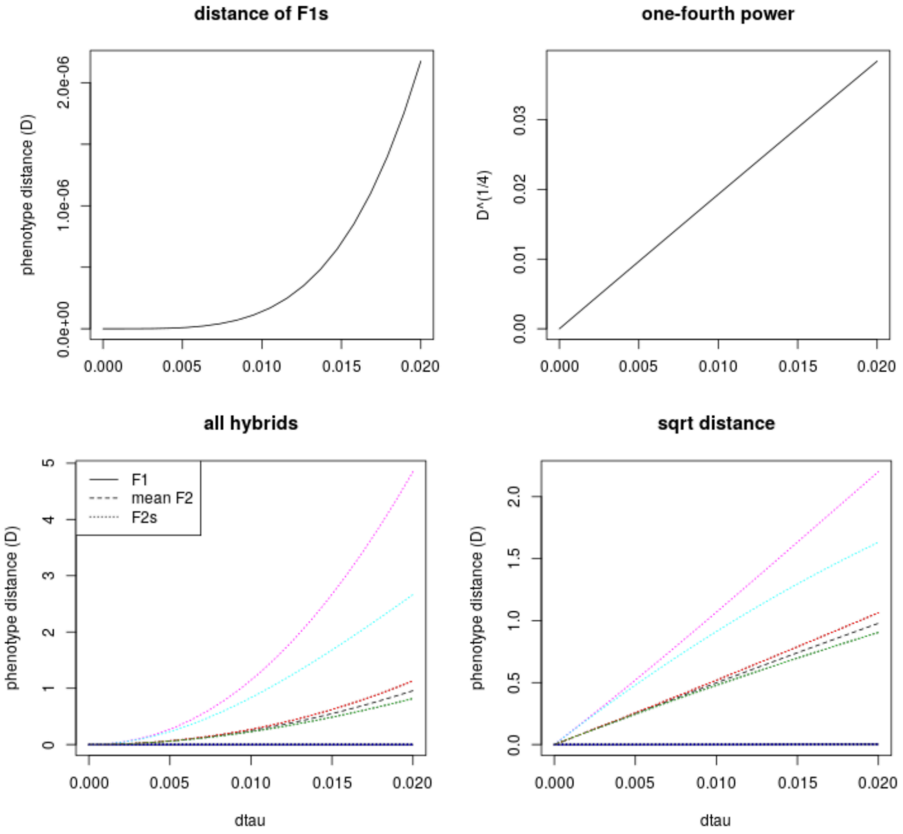


genetic dist.



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





Note: this is general and not specific to oscillator network

How fast does reproductive incompatibility occur in allopatry under environmental and selective stasis?

- Gene regulatory interaction strengths are treated as quantitative traits thus we use a quantitative genetics model.
- F_1 and F_2 phenotypes diverge quartically and quadratically, respectively.
- The phenotypic divergence will be,

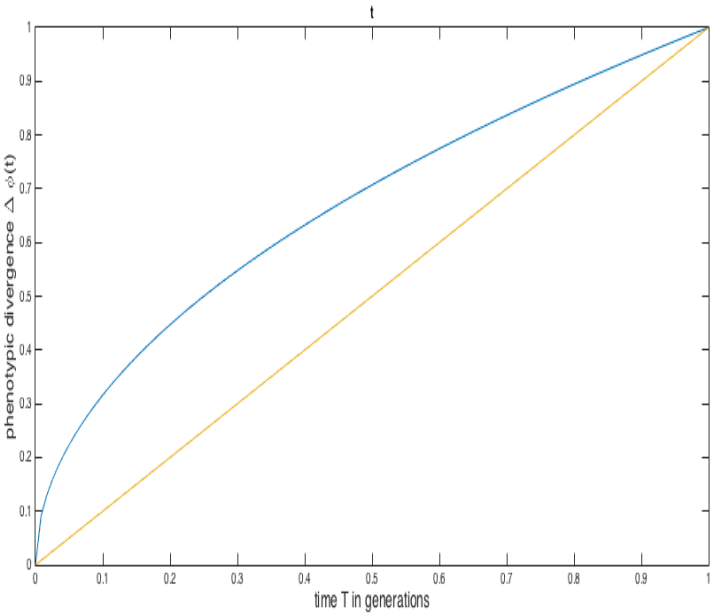
$$\Delta\phi_{F_1}(t) \approx c_1 \frac{T}{N} \text{ in } F_1\text{s (orange) and,}$$

$$\Delta\phi_{F_2}(t) \approx c_2 \sqrt{\frac{T}{N}} \text{ in } F_2\text{s (blue)}$$

formed by mating allopatric populations of size N isolated for T generations, where c_1 and c_2 are constants.

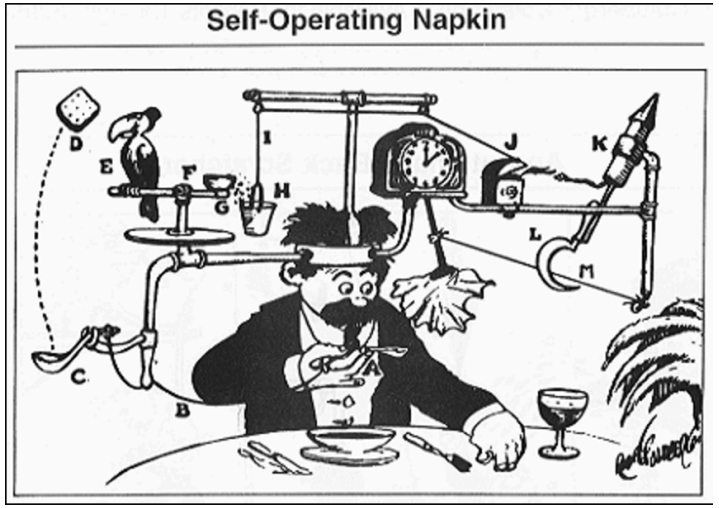
- Fitness is a Gaussian of phenotypic distance,

$$\mathcal{F} = \exp\left\{ -\left(\Delta\phi(t)\right)^2/\sigma \right\}$$



Ongoing work: a gene getwork ratchet – are gene networks molecular Rube Goldberg Machines?

- Up until this point networks above have been minimal or parsimonious – use the fewest components possible to achieve requisite phenotype dynamics.
- 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
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- Hossein Asgharian