Gene network drift and speciation

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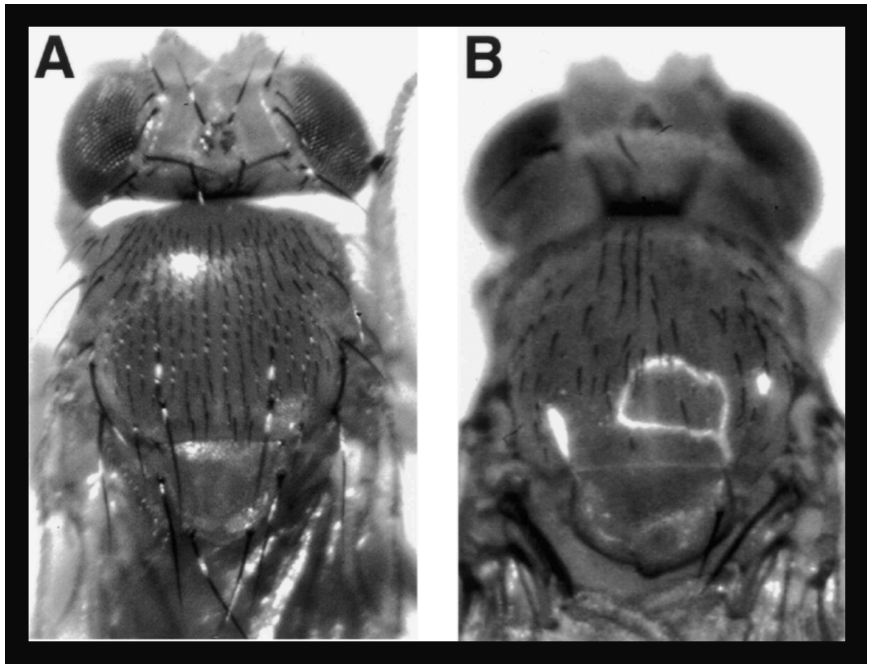
Developmental systems drift: many molecular pathways can produce the same phenotype

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



(A) parents and (B) hybrid

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

True and Haag, Evolution & Development, 2001.

Can systems drift lead to speciation?

We approach this with a simple mathematical model of transcriptional regulatory networks.

How to model the genotype-phenotype map?

- Phenotype is defined as the molecular time dynamics relevant to survival.

- 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 as linear dynamical systems

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

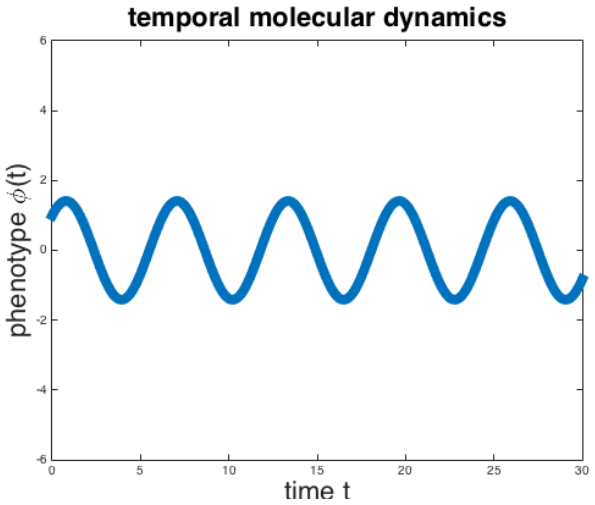
A: regulatory network ($n \times n$ matrix); rows are promoters
B: processes input ($n \times l$ matrix)
C: filters dynamics relevant to survival ($l \times n$ matrix)

$u(t)$: input at time t
$\kappa(t)$: all molecular concentrations at time t
$\phi(t)$: relevant molecular concentrations at time t – **phenotype**

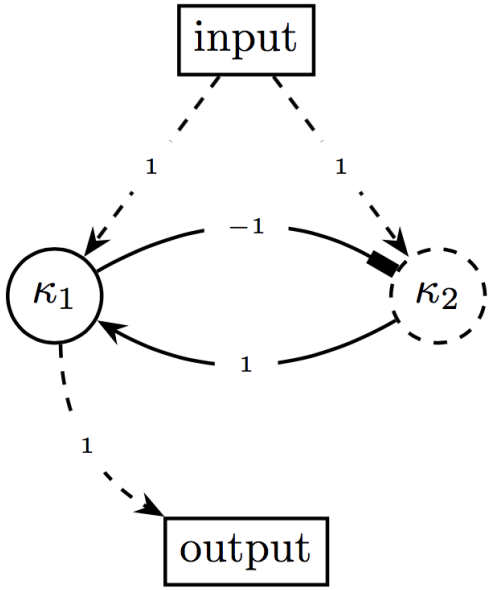
Example: consider an oscillating two-gene network

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

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

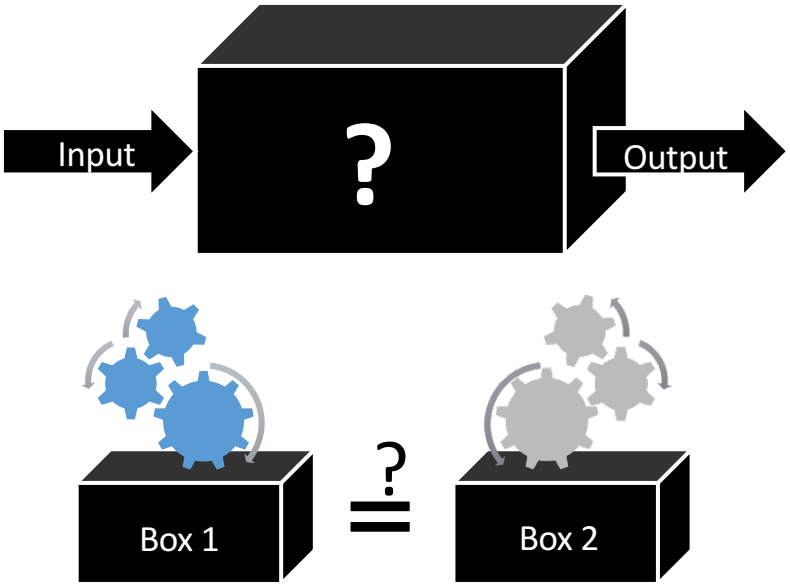


$$\phi(t) = \sin(t) + \cos(t)$$



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

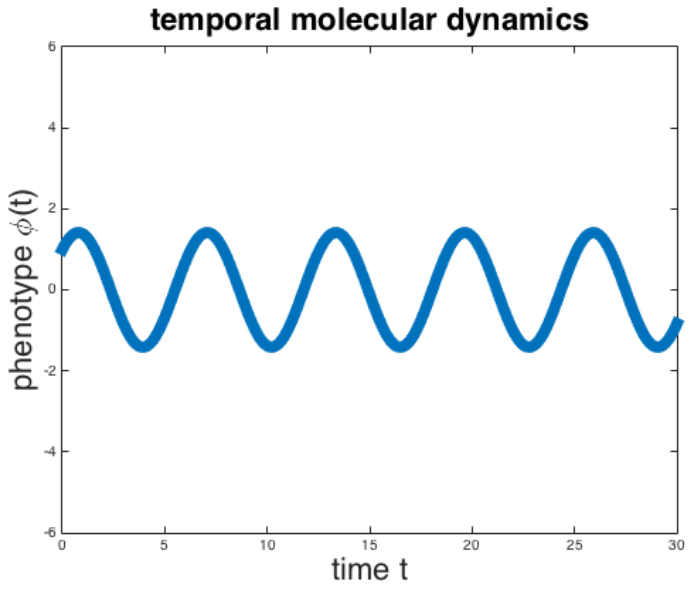
How many black boxes are input-output equivalent, yet have different internal mechanisms?



Two **different** oscillator mechanisms with **identical** phenotypes

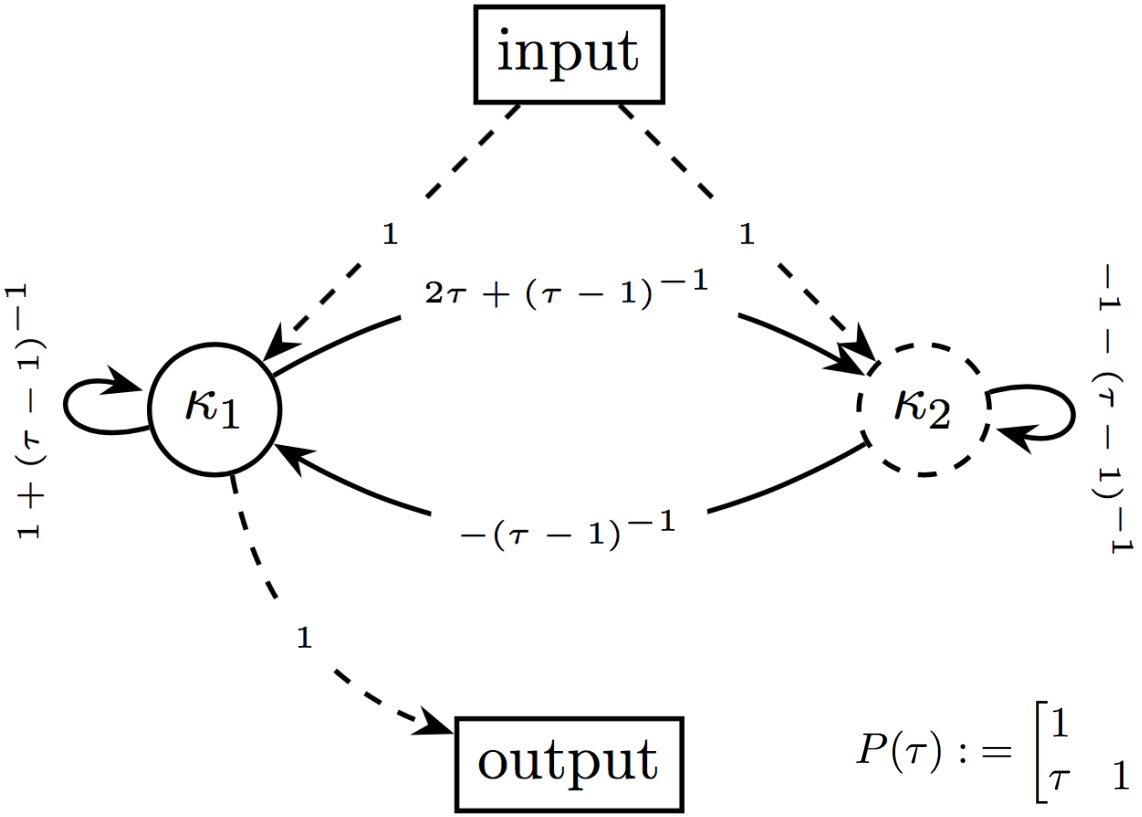
$$\begin{aligned}\dot{\kappa}(t) &= \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \kappa(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u(t) \\ \phi(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \kappa(t)\end{aligned}$$

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



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

All phenotypically equivalent gene network oscillators



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

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

Under selective and environmental stasis, evolution explores equivalent networks.

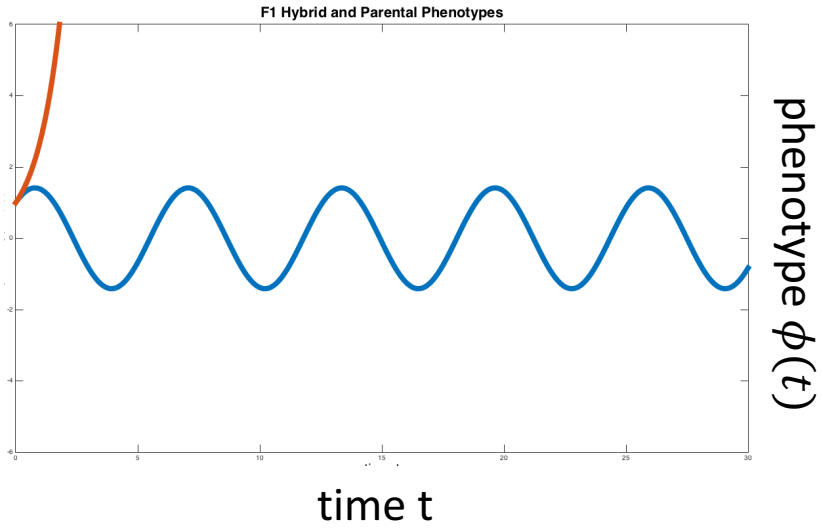
Phenotype is conserved however mechanism is not.

$\phi(t) = \hat{\phi}(t)$ yet $A(\tau) \overset{T}{\rightarrow} A(\hat{\tau})$

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

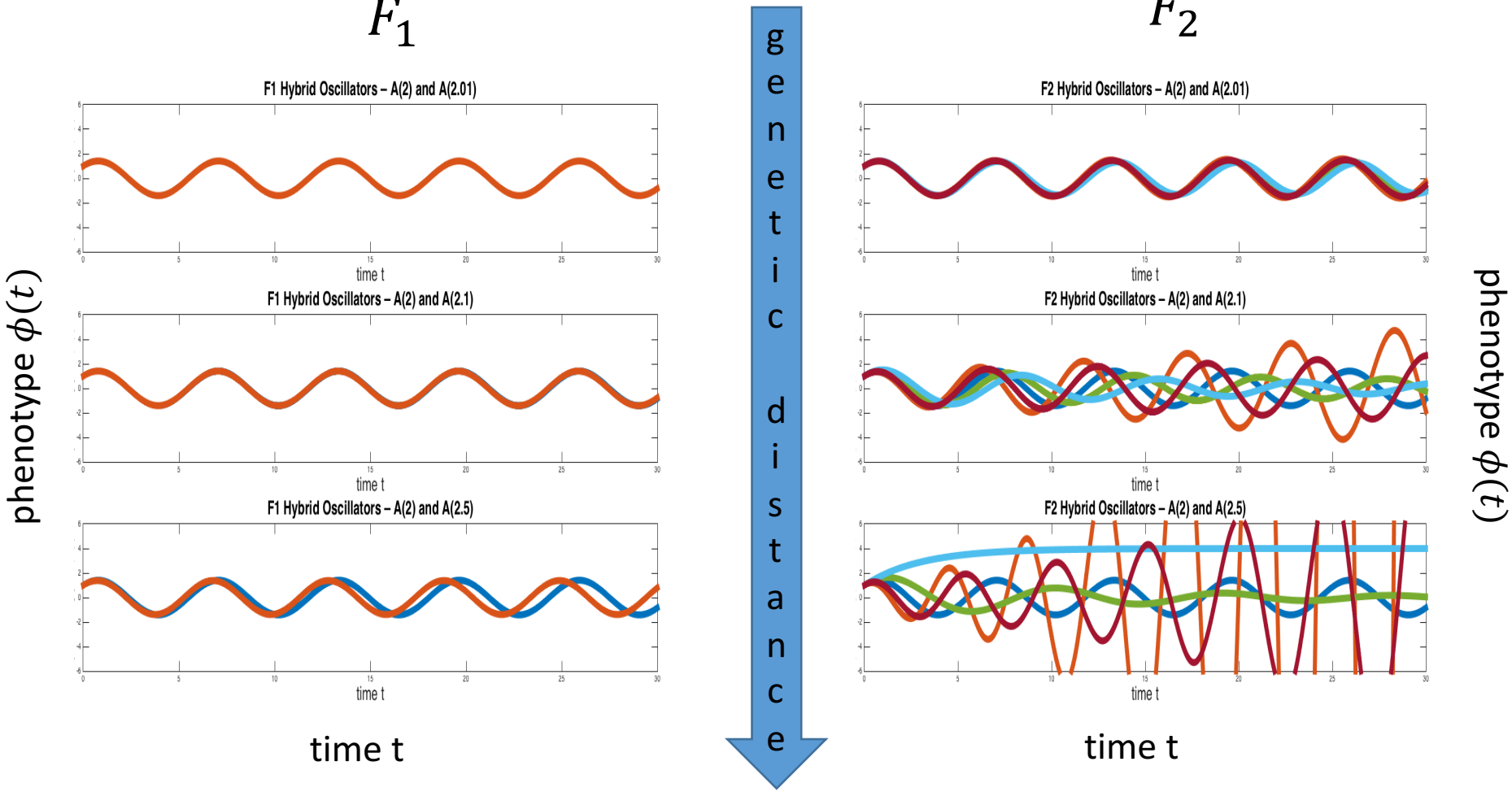
- Diploid F_1 hybrids are formed by averaging the two parental gene networks A and A'.
- F_2 hybrids are formed by first recombining genes (swapping rows between A and A'), then next, two gametes are chosen and averaged.
- Fitness can be scored as a function of phenotypic distance.

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



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

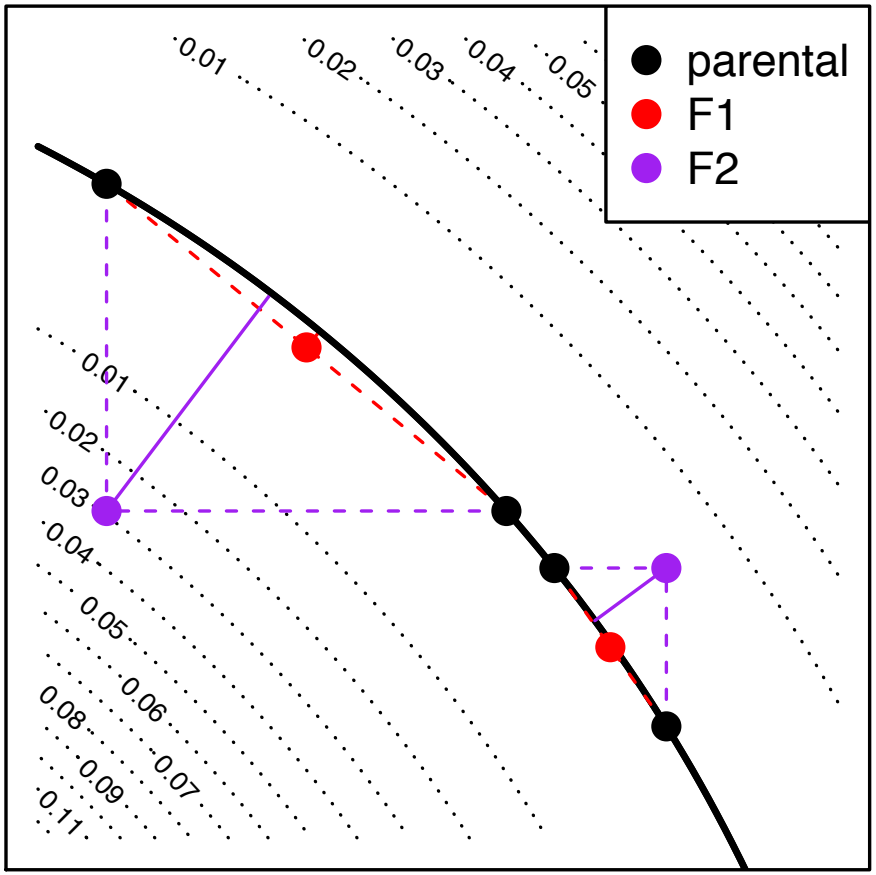
F_1(left) and F_2(right) Hybrids between $A(2)$ and $A(2.01)$ (top) , $A(2.1)$ (middle), and $A(2.5)$ (bottom).

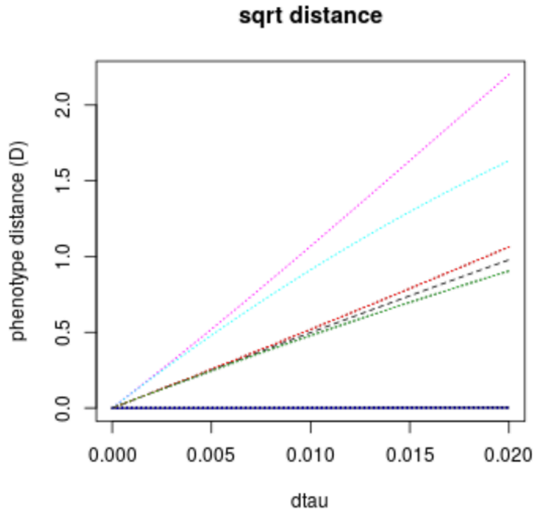


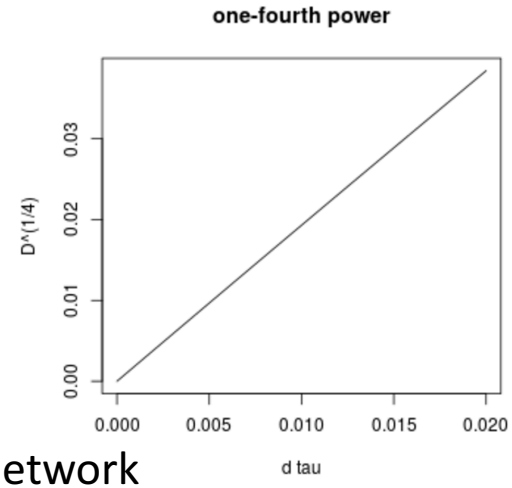
In general, how fast do incompatibilities appear?

All gene networks can neutrally drift – usually in many directions. There is always more than one possible network architecture per phenotype – and we have an analytical description of them using the Kalman decomposition.

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

What rate do hybrid phenotypes diverge in allopatry under environmental and selective stasis?

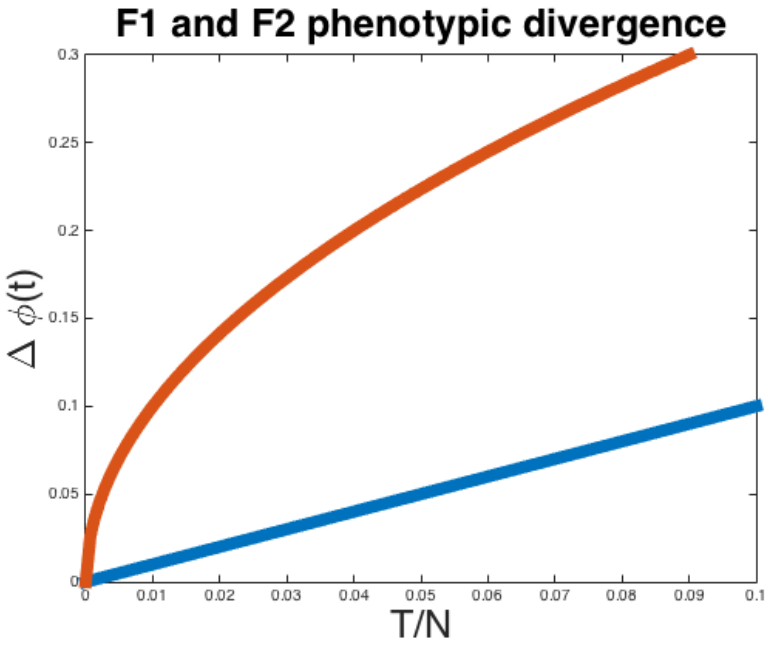
Using a quantitative genetics model:

The phenotypic divergence will be (locally),

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

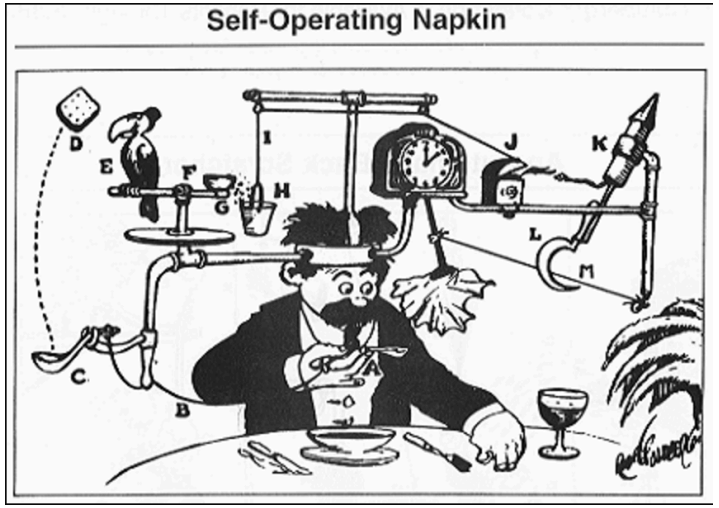
$$\Delta\phi_{F_2}(t) \approx c_2 \sqrt{\frac{T}{N}} \text{ in } F_2 \text{ (blue)}$$

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



Future work: a gene network 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]).



In conclusion:

*There is more than one way to **skin** a cat.*

Here we argue: there is also more than one way to **develop** a cat.

Evolution explores this space, leading to Dobzhansky-Muller Incompatibilities.

Thank You!

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