

# Gene network drift and speciation

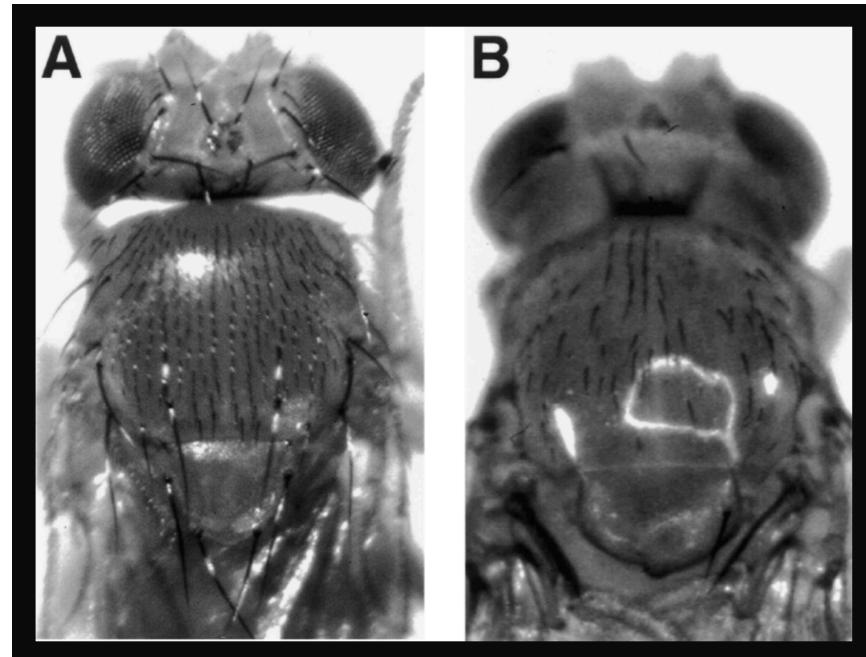
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# Developmental systems drift: many molecular pathways can produce the same phenotype

- *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

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

$A$ : 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  $t$

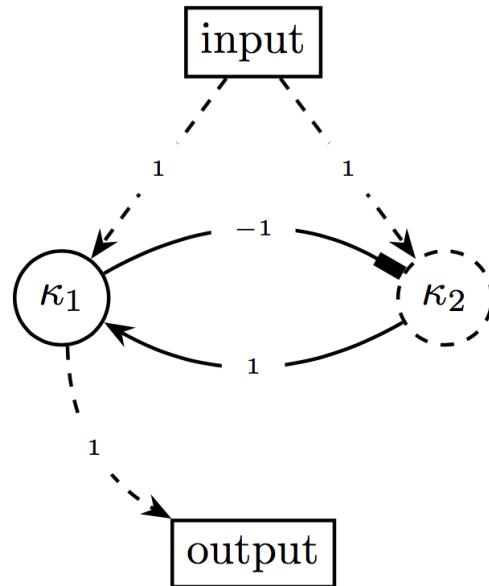
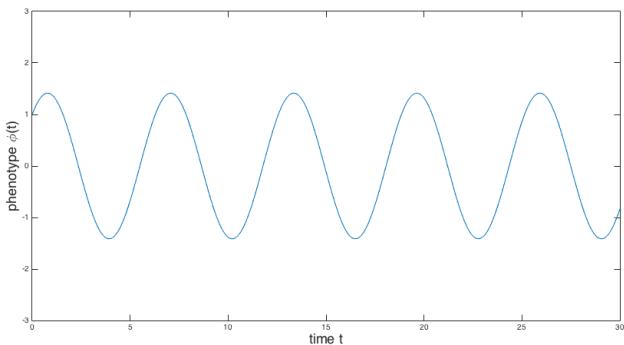
$\kappa(t)$ : **internal** molecular concentrations at time  $t$

$\phi(t)$ : **external** molecular concentrations at time  $t$  – phenotype

Example: consider an oscillating two-gene network

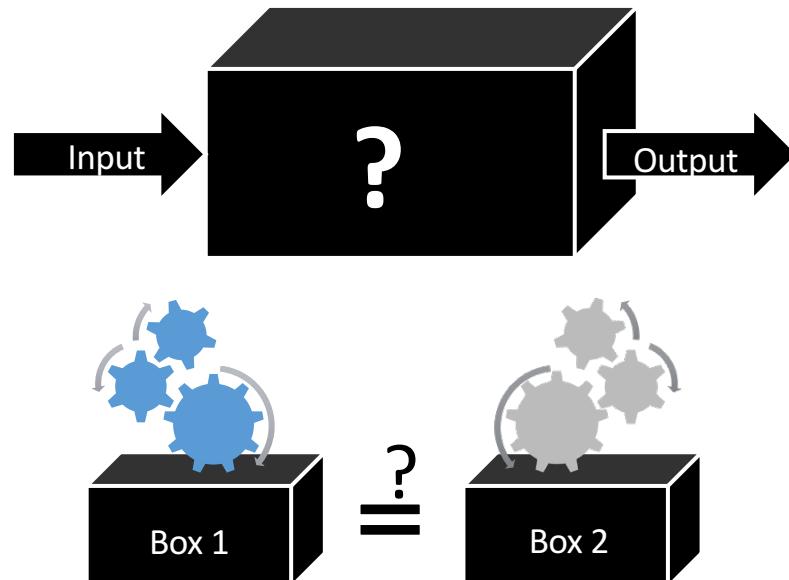
$$\Sigma = \begin{cases} \dot{\kappa}(t) &= A\kappa(t) + Bu(t) \\ \phi(t) &= C\kappa(t) \end{cases}$$

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



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

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

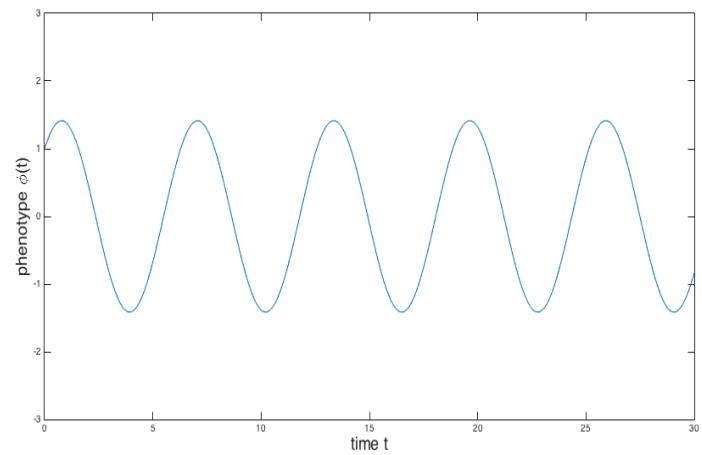


# Two different oscillator mechanisms with identical phenotypes

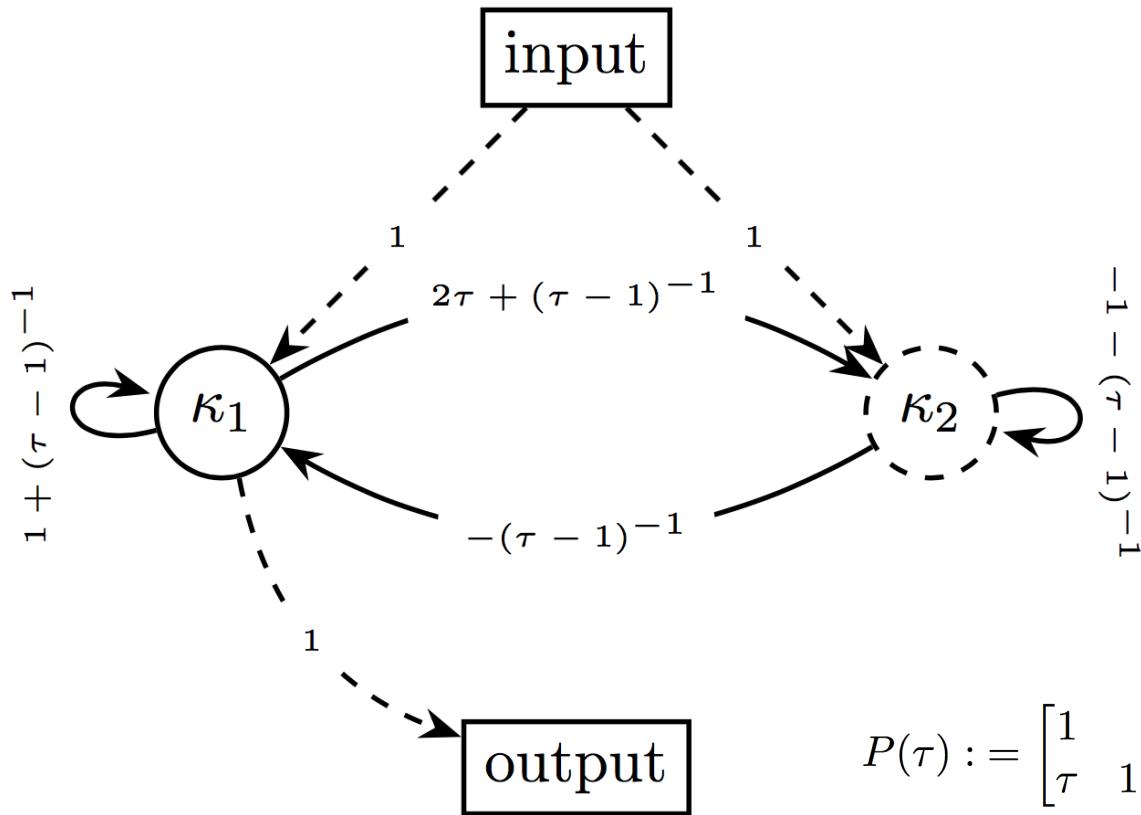
$$\Sigma = \begin{cases} \dot{\kappa}(t) &= \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \kappa(t) + \begin{bmatrix} 1 \\ 1 \end{bmatrix} u(t) \\ \phi(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \kappa(t) \end{cases}$$

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

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



# All phenotypically equivalent gene network oscillators



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

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

Under selective and environmental stasis, evolution explores equivalent networks.

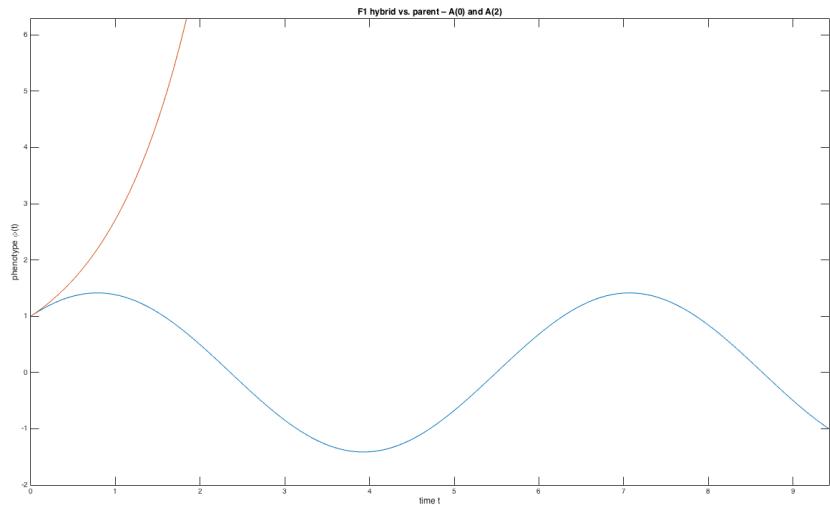
Phenotype is conserved however mechanism is not.

$$\phi(t) = \hat{\phi}(t) \text{ yet } A(\tau) \xrightarrow{T} A(\hat{\tau})$$

# 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.

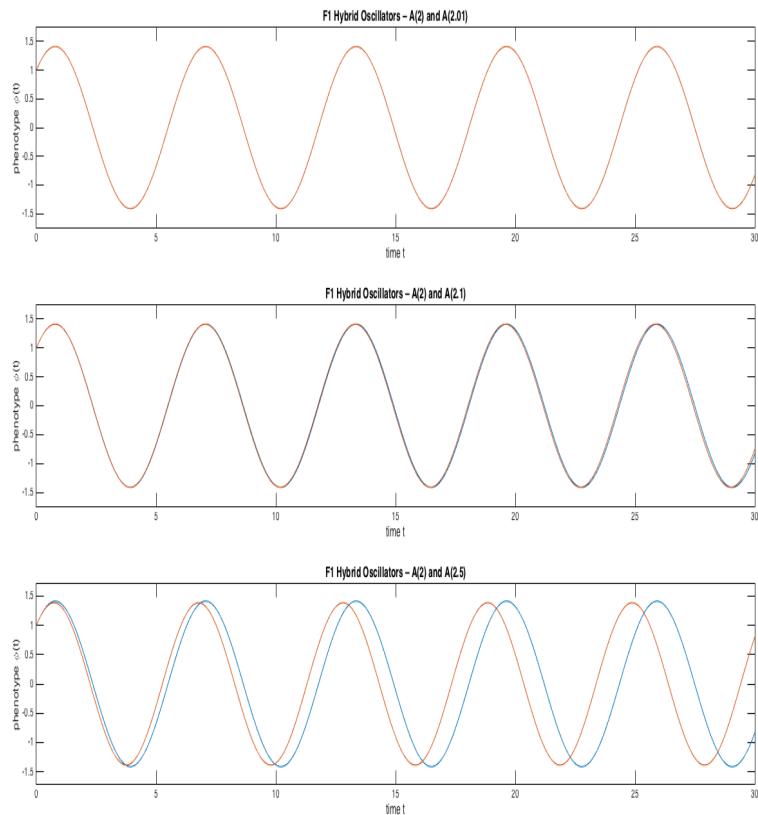
$$\mathcal{F}(\hat{\phi}(t)) = \exp \left\{ -\frac{1}{\sigma} \int_0^\infty \|\phi(t) - \hat{\phi}(t)\|^2 dt \right\}$$



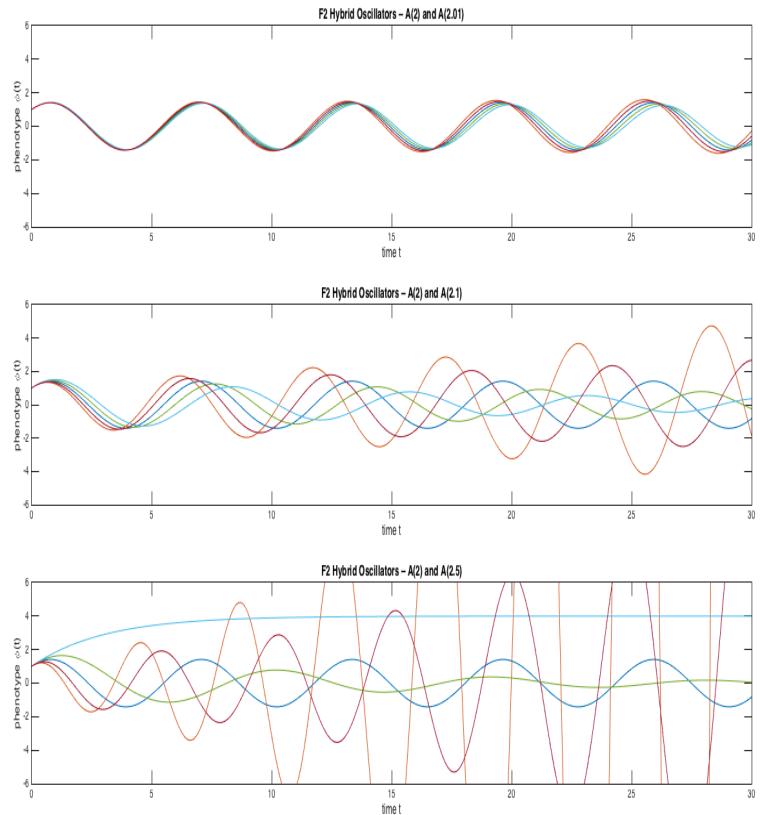
Oscillators  $A(0)$  and  $A(2)$   $F_1$ s  
 Parents (blue), hybrids (orange).  
 Hybrid  $\phi_{F_1}(t) = e^t$

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

$F_1$



$F_2$

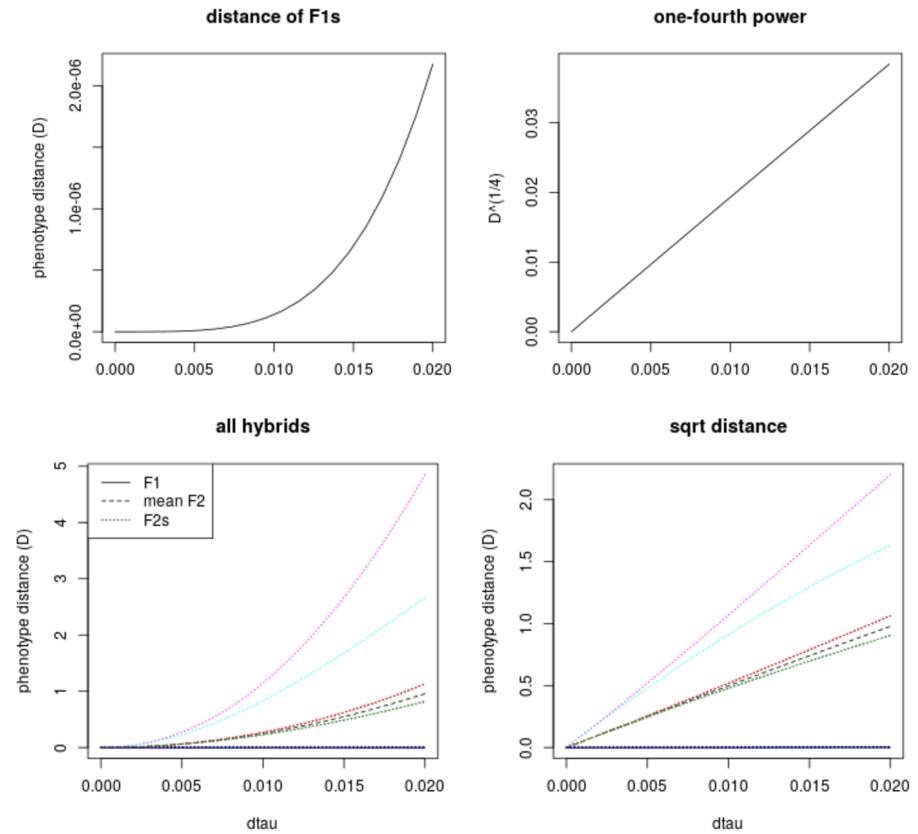
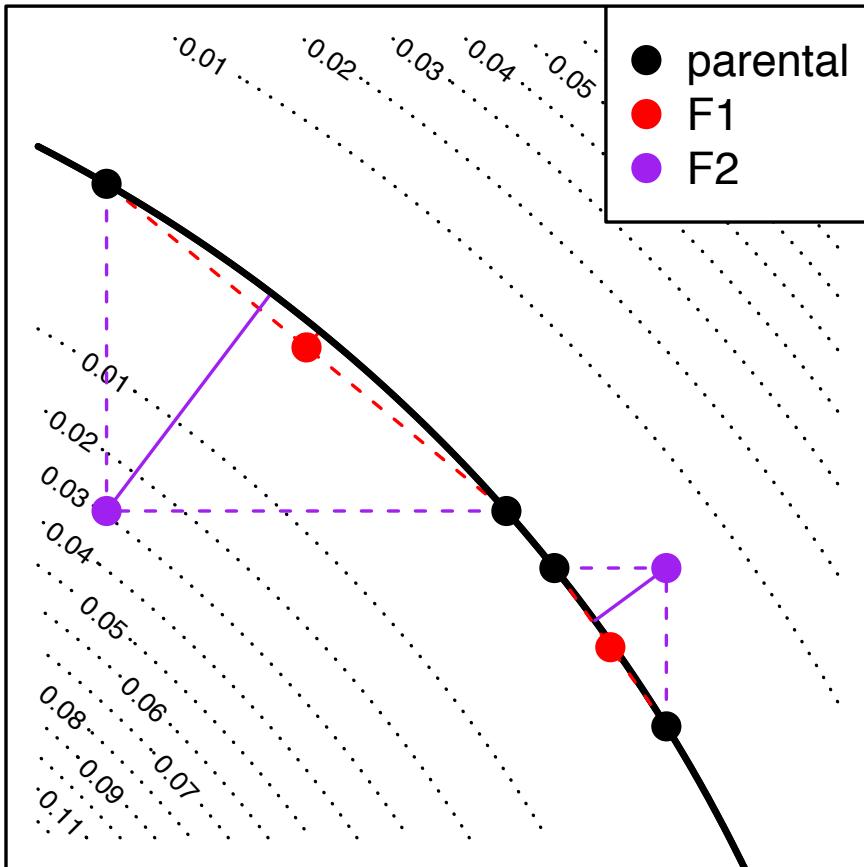


genetic distance

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  $F_1$ s (top) and at a quadratic rate in  $F_2$ s (bottom) as a function of  $\tau$ .



Note: this is general and not specific to oscillator network

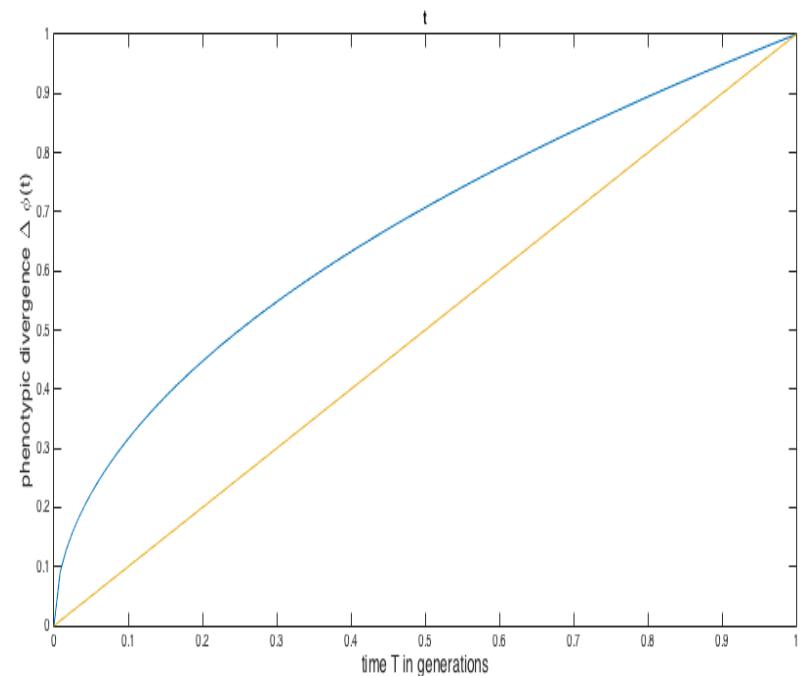
What rate do hybrid phenotypes diverge in allopatry under environmental and selective stasis?

Using a quantitative genetics model:

The phenotypic divergence will be (locally),

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

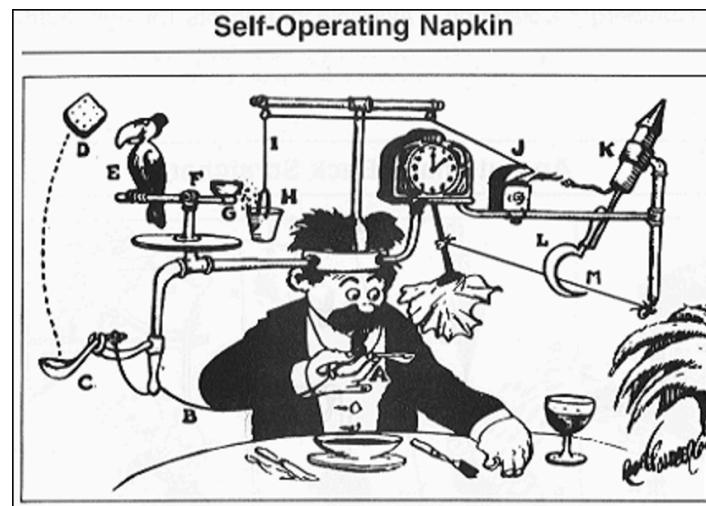
$$\Delta\phi_{F_2}(t) \approx c_2 \sqrt{\frac{T}{N}} \text{ in } F_2 \text{ (blue)}$$



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
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- Erik Lundgren
- Hossein Asgharian

