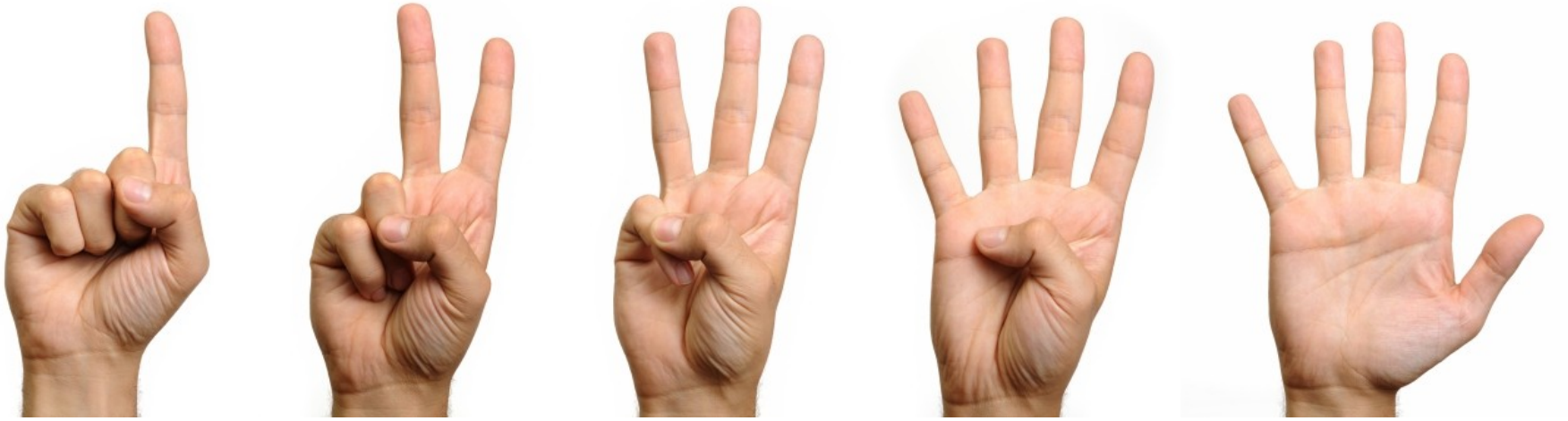
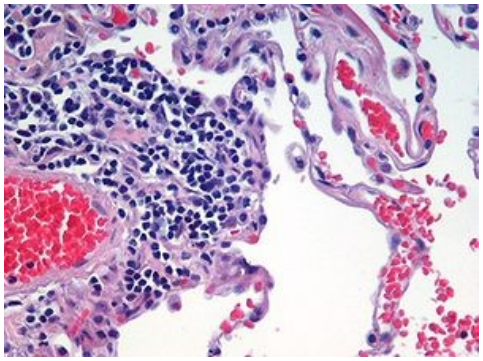
Natural numbers

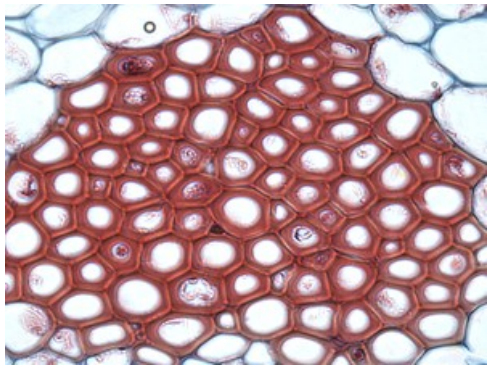


Mukund Thattai, NCBS/TIFR
ICTS Discussion Meeting
Dec 2011

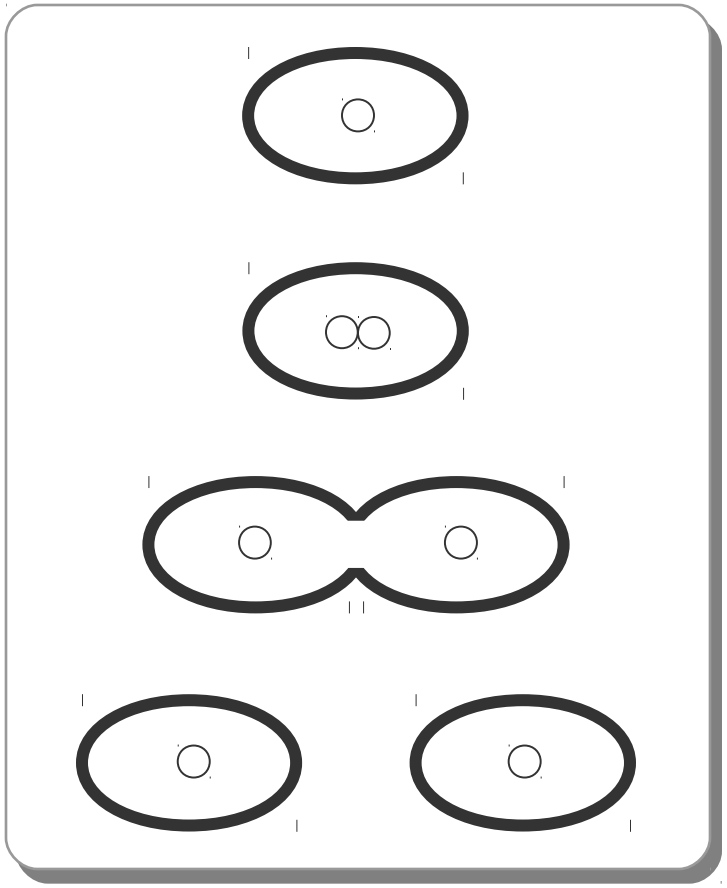

Life on earth is built from cells

Tissues, organs, animals and plants are interacting aggregates of cells



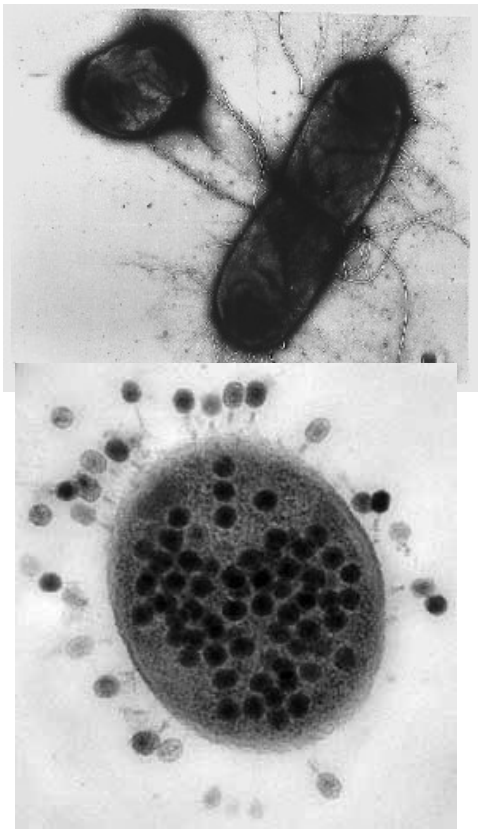


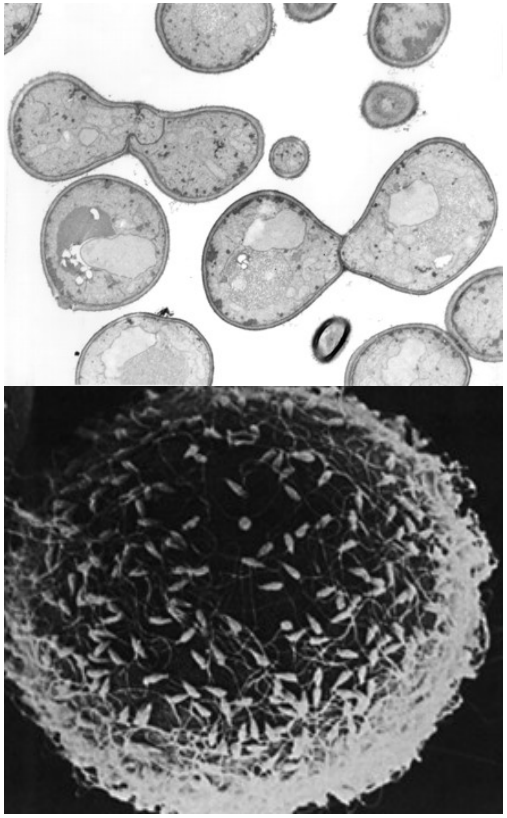
Cells grow and divide to make new cells...



... mirroring the replication of genetic material

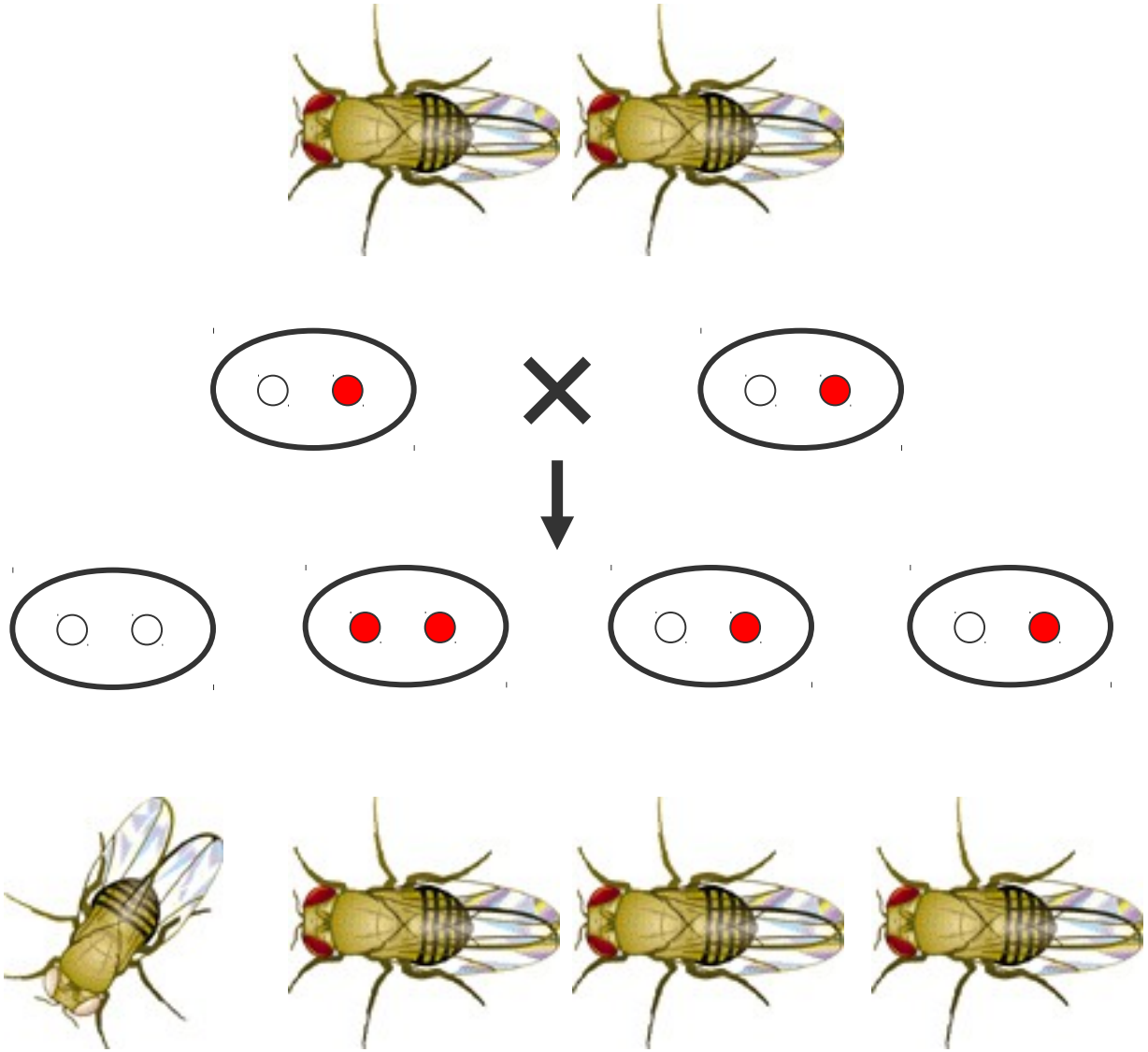
Since the origin of life, genetic material has been freely flowing between cells





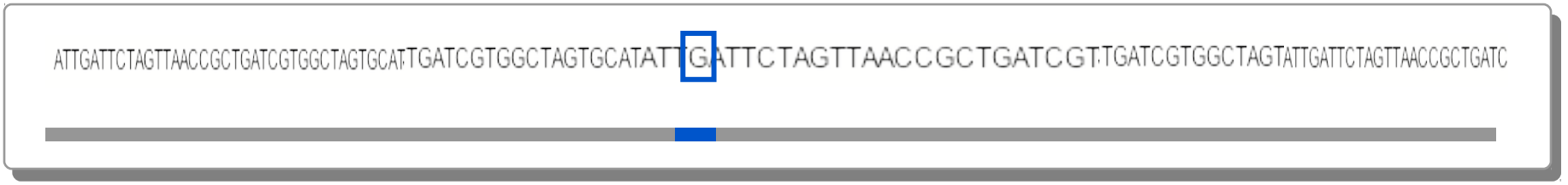
... leaving the genetic code unchanged for billions of years

Genes are ‘particles’ that underlie the heritability of phenotypes



We now know that genes are embodied as DNA sequences

We can think of them as single nucleotides....



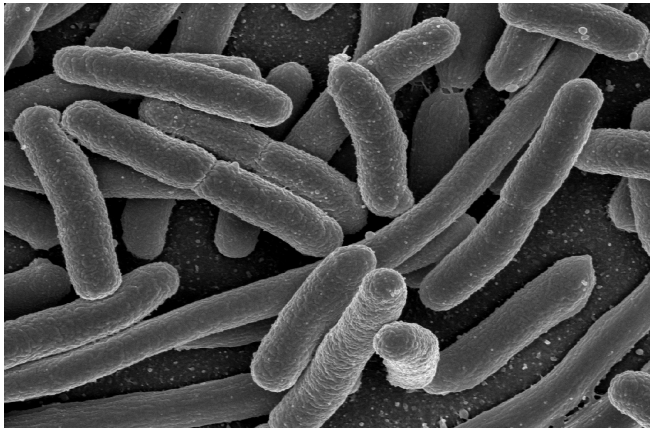
... or as long sequence stretches

They are discrete, replicated, vertically inherited, horizontally exchanged, and subject to mutation

- They can ‘code for’ proteins and RNA
- They can ‘regulate’ when and where proteins and RNA are produced
- They can regulate the 3D structure of chromosomes
- ...

Biological variability:
a map from protein numbers to phenotypes

Variability is a fundamental property of living matter at molecular scales...



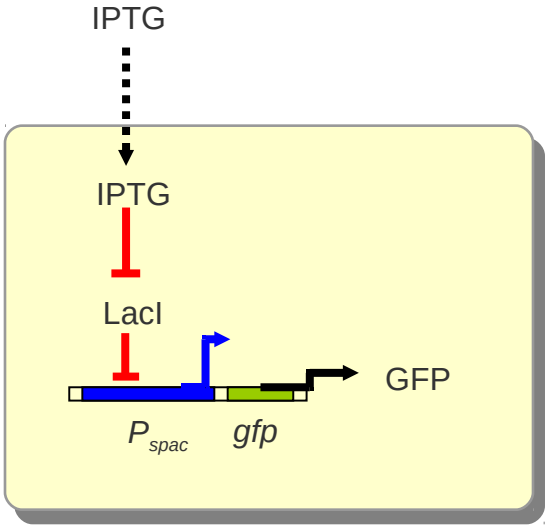
All life is made of cells

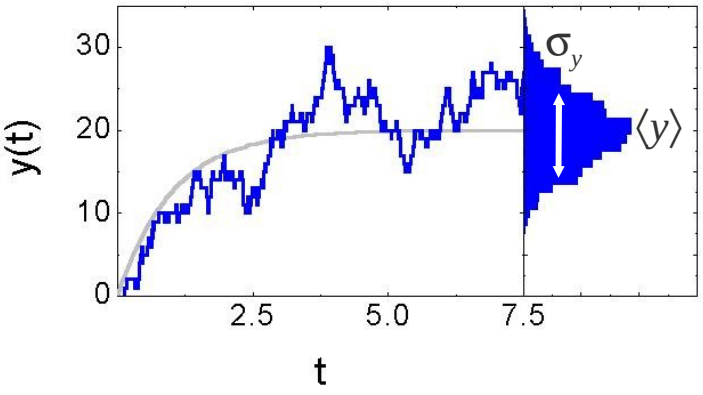
Cells are small

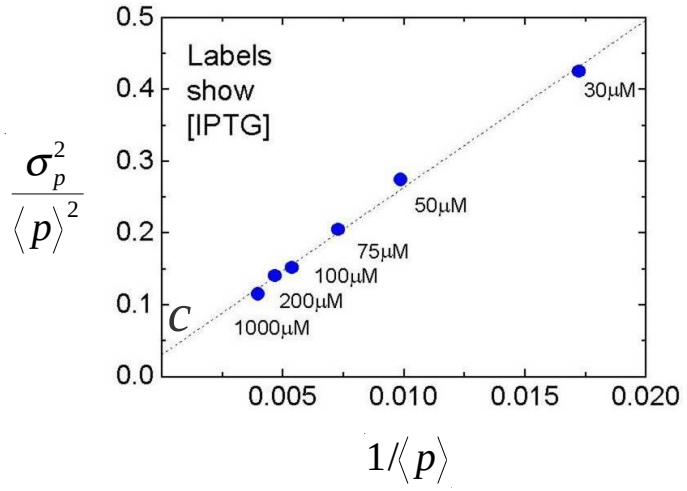
Small means noisy

... but macroscopic outcomes are precise

Protein and mRNA distributions show √n scaling

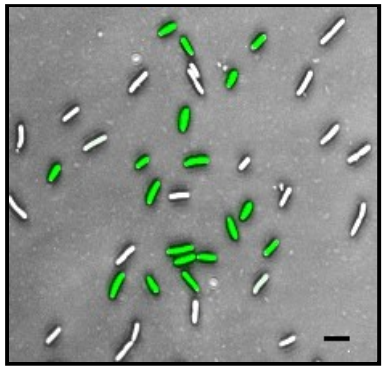


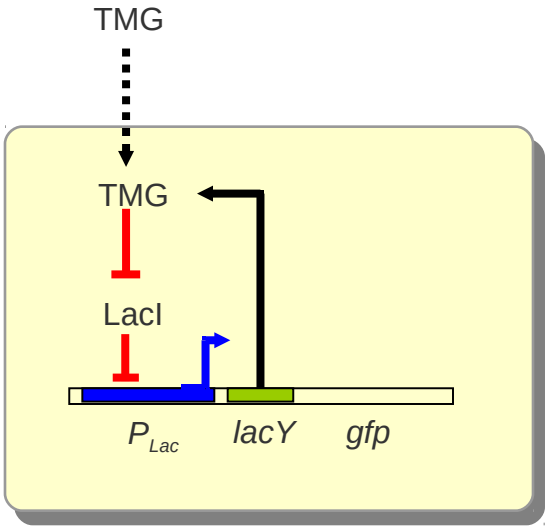


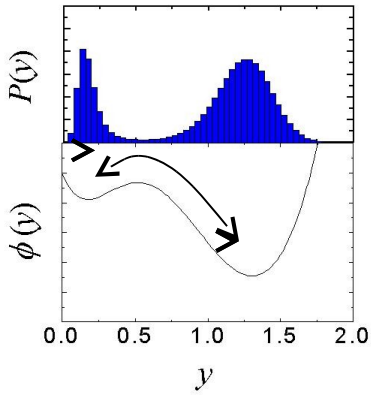


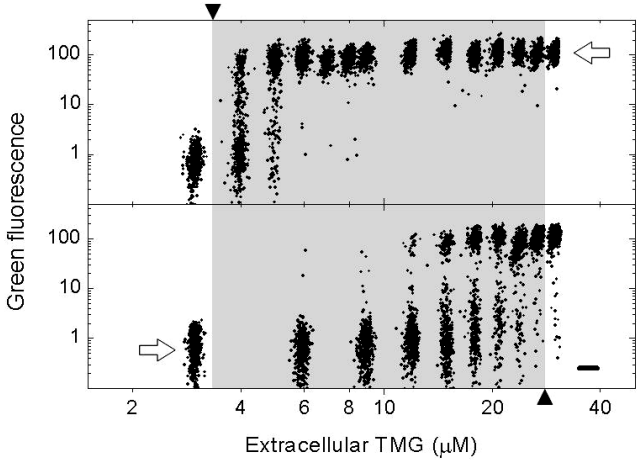
Thattai & van Oudenaarden, PNAS, 2001; Ozbudak et al., Nature Genet., 2002

Noise can flip a bistable switch





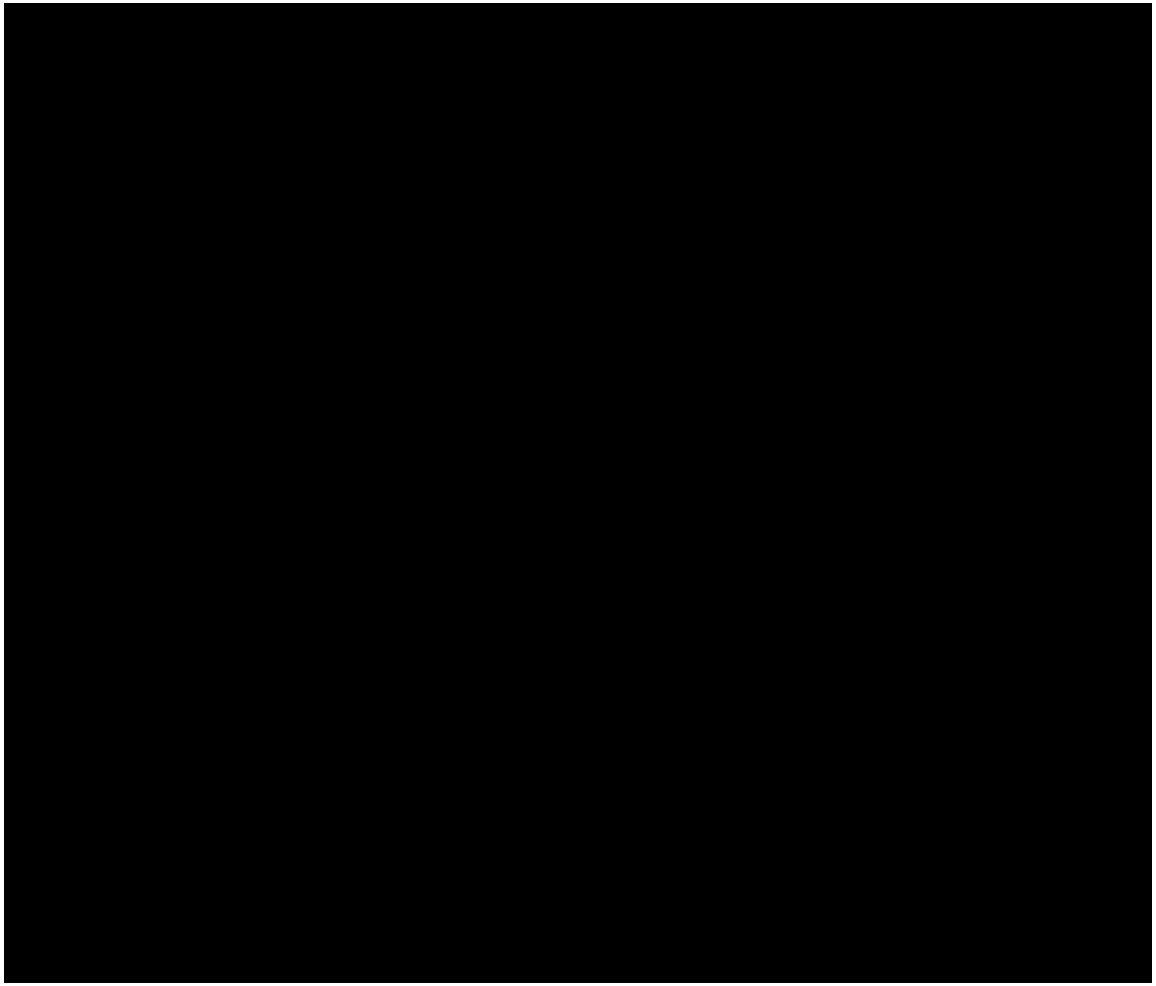




Ozbudak & Thattai et al., Nature, 2004

Single cells can ‘use’ noise to hedge bets

Cells switch between two states, each optimized to a different environment

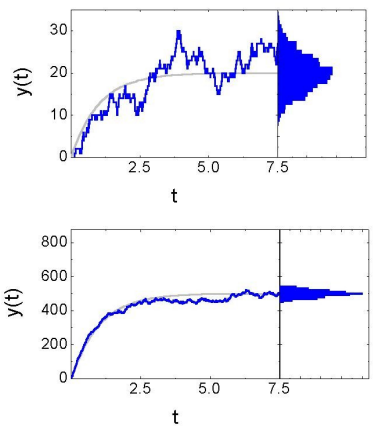


 Thattai & van Oudenaarden, Genetics, 2004; Acar, Mettetal & van Oudenaarden, Nature Genet., 2008; Kussell et al., 2005

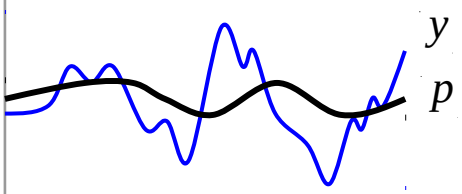
Controlling ‘noise’

$$\frac{\sigma_p^2}{\langle p \rangle^2} = \frac{1}{\langle p \rangle} + \frac{1}{\langle y \rangle} \frac{m}{1+m} \left| \frac{\partial \ln \langle p \rangle}{\partial \ln \langle y \rangle} \right|^2$$

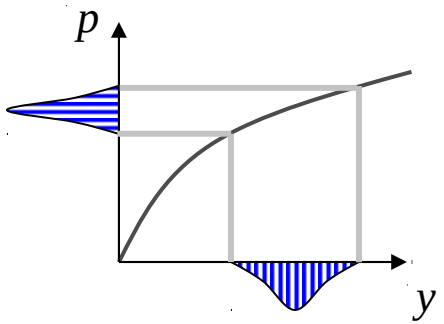
large numbers



time averaging

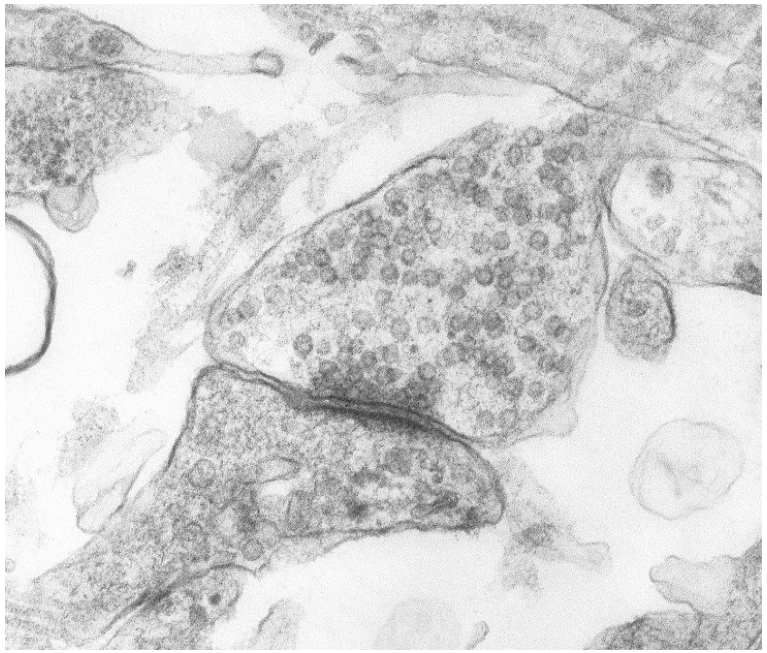


logarithmic gain



Thattai & van Oudenaarden PNAS ,2001

Molecular computation

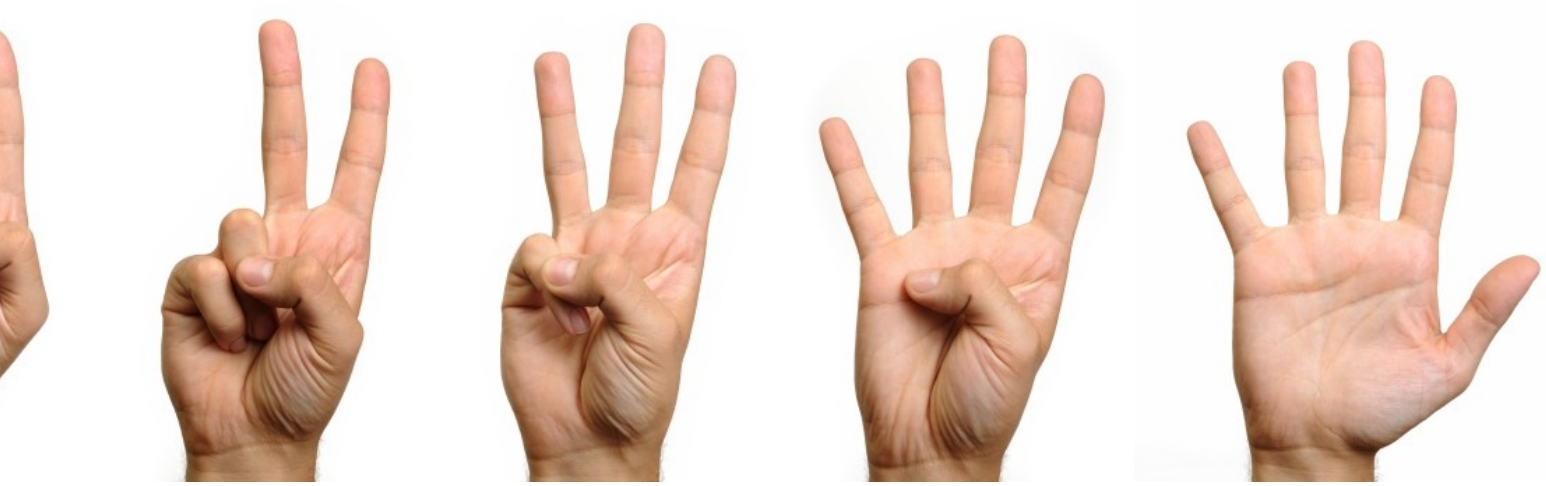


Open problems:

- fundamental theoretical limits on molecular control
- information processing by small numbers of molecules
- phenomenological theories of variability in complex systems

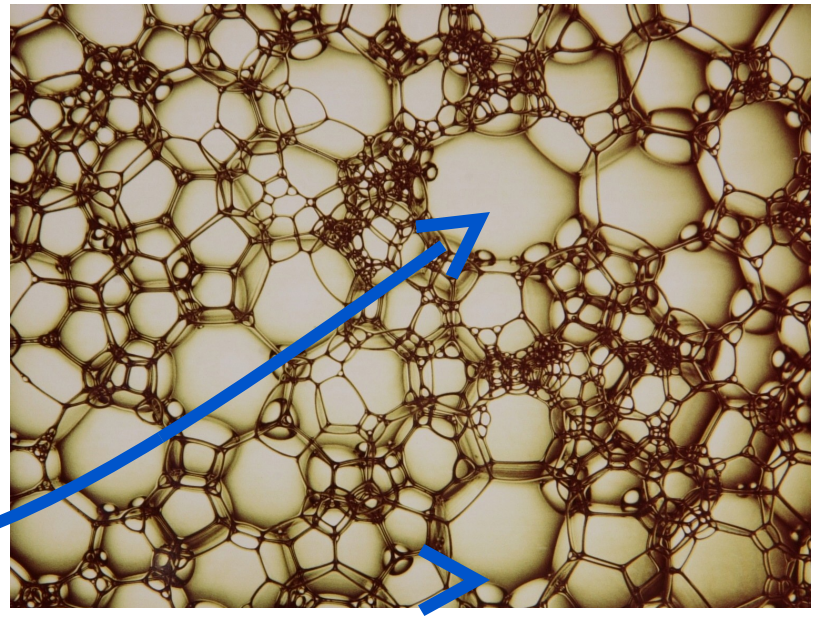
 Lestas et al., Nature, 2010

Development: A map from DNA elements to macroscopic features of animals



Animal development is an initial value problem

The genome defines the space of outcomes as a function of initial conditions



Existing cells interact with the environment to establish the initial conditions

Small web page Figure 1

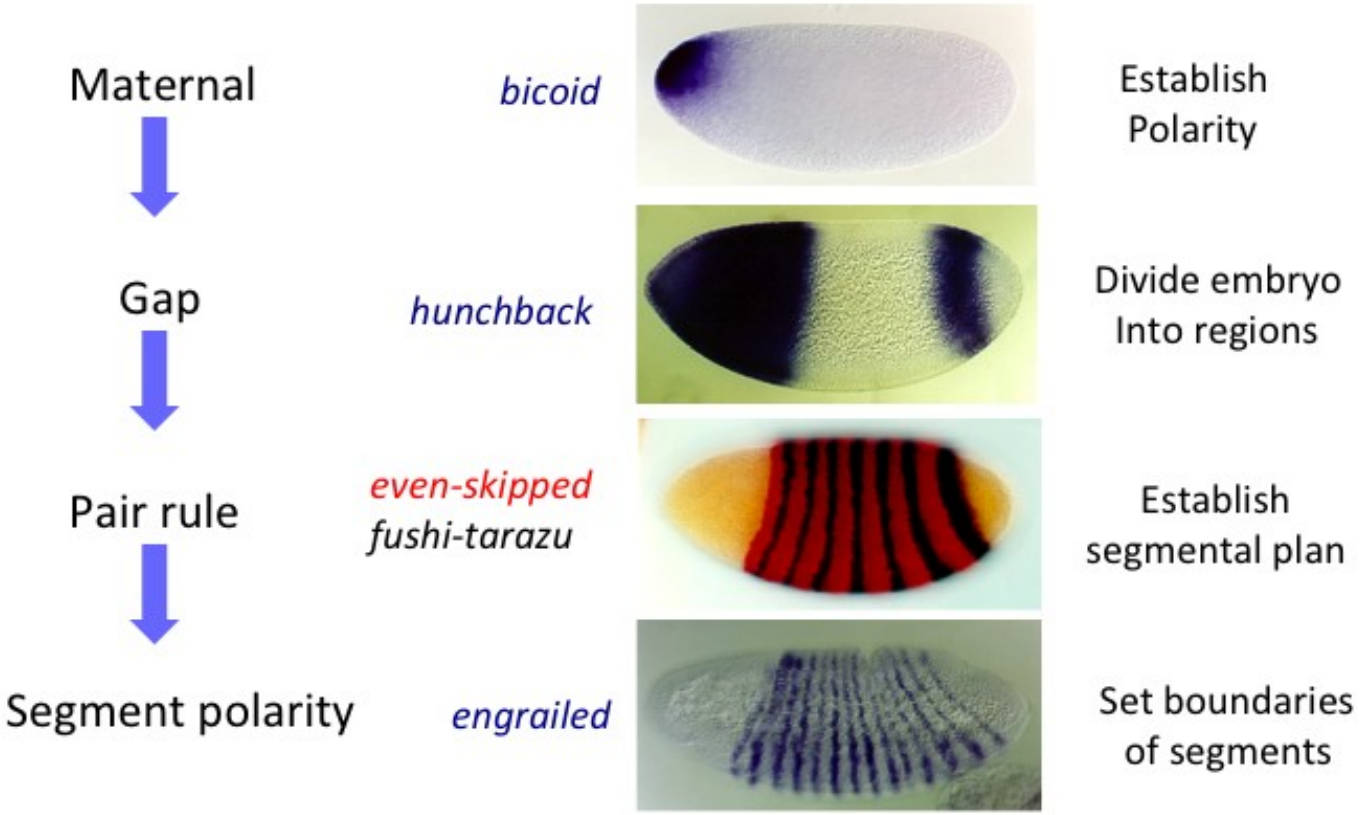


Figure 1: RNA expression patterns of selected genes in anterior posterior patterning. Anterior of each embryo is to the left.

Genes expressed at one timepoint turn on or off genes at subsequent timepoints, to form stripes

 Steven Small, NYU

Modular organization of the *eve* regulatory region

 Alberts et al., Molecular Biology of the Cell

Like stripes, digits develop idiosyncratically

Alligator limb

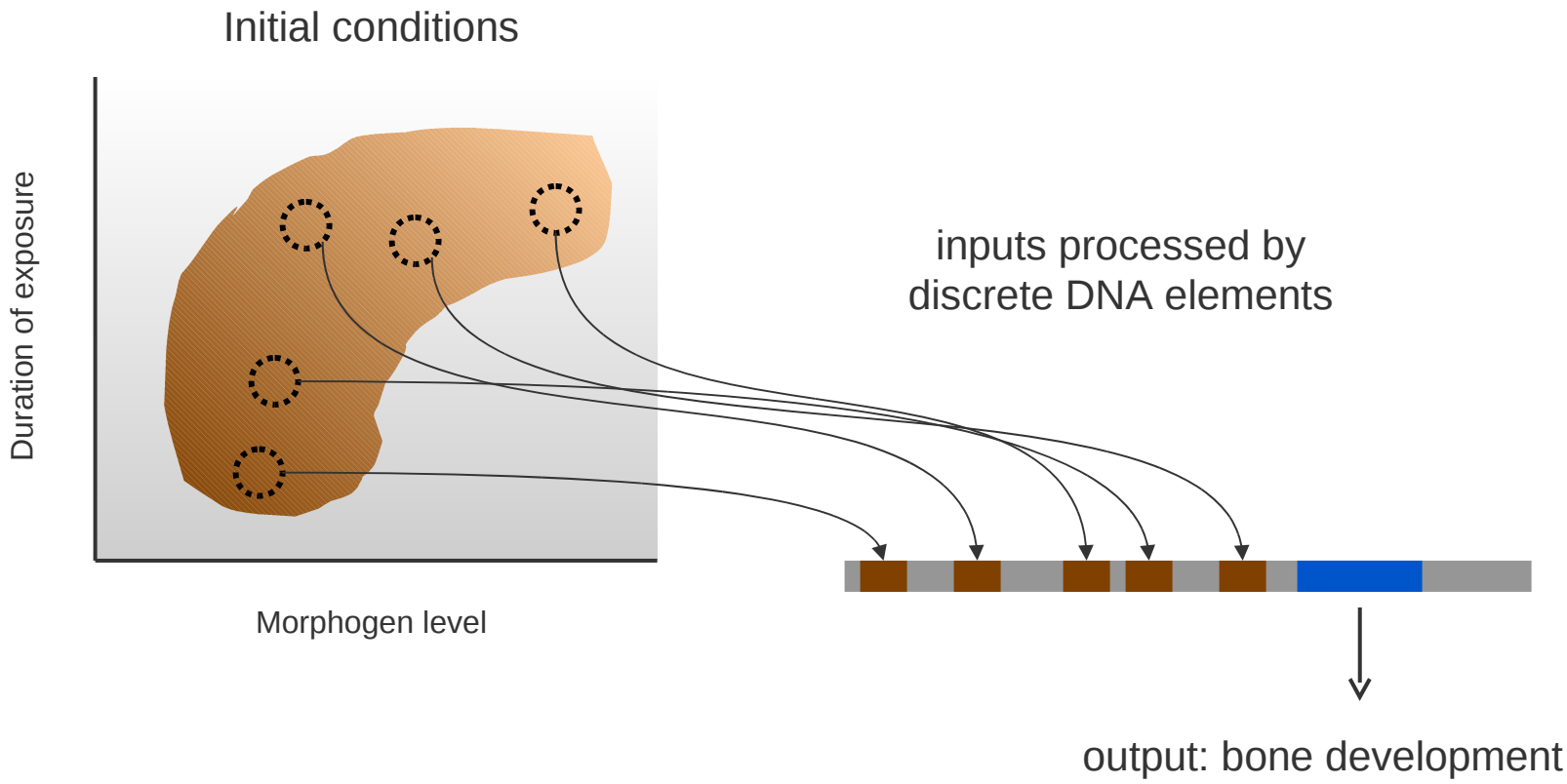
 Wagner & Gauthier, PNAS, 1999

Digit development is regulated by morphogens

Chick limb

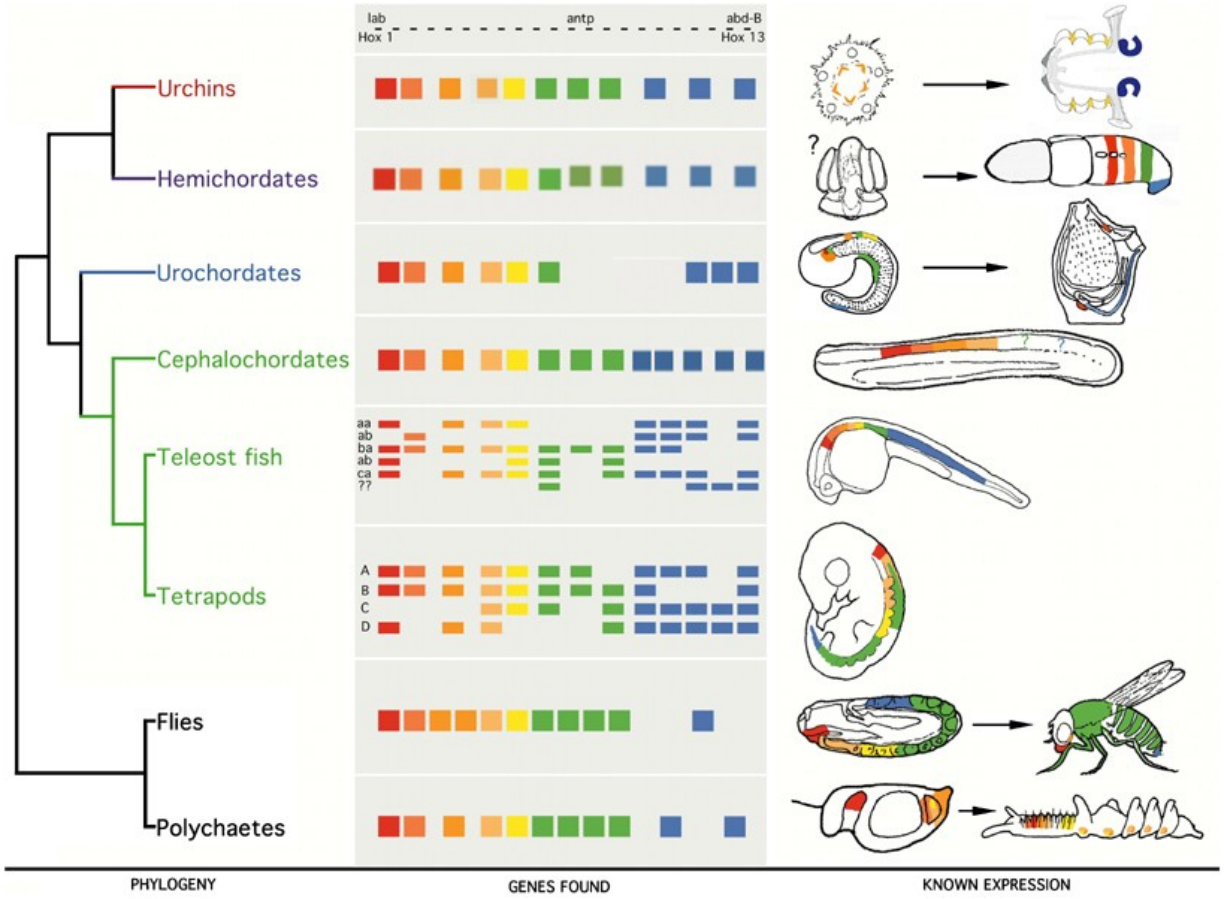
 Tickle, Nat Rev Mol Cell Biol, 2006

Each digit has a unique driver



So that’s where ‘5’ comes from. Why is this interesting to a theorist?

A remarkable map from DNA to body plans

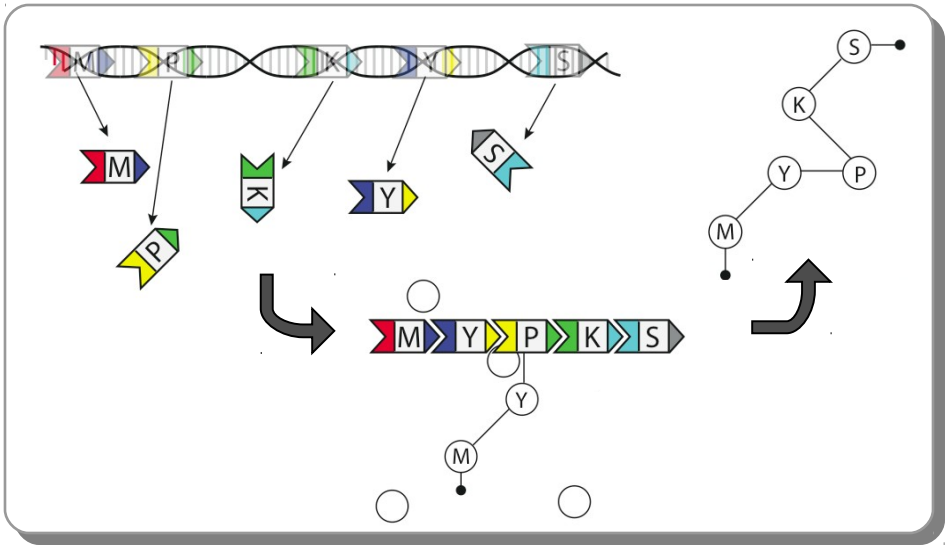


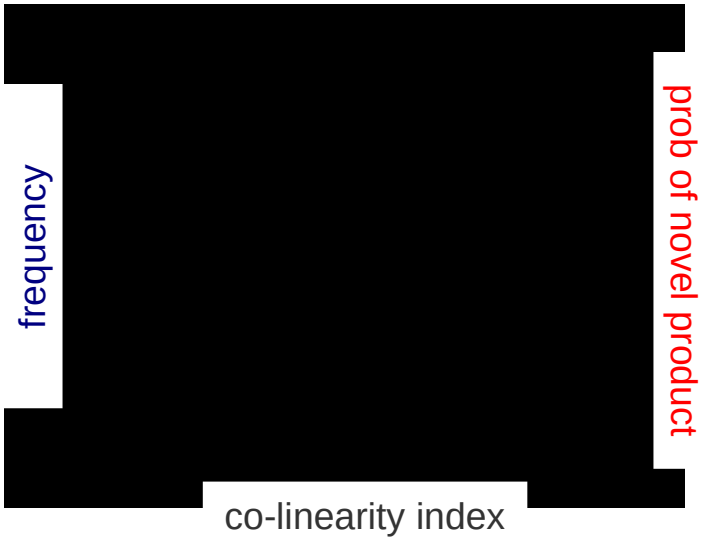
This *hox* gene cluster map might arise purely from evolutionary forces

 Swalla, Heredity, 2006

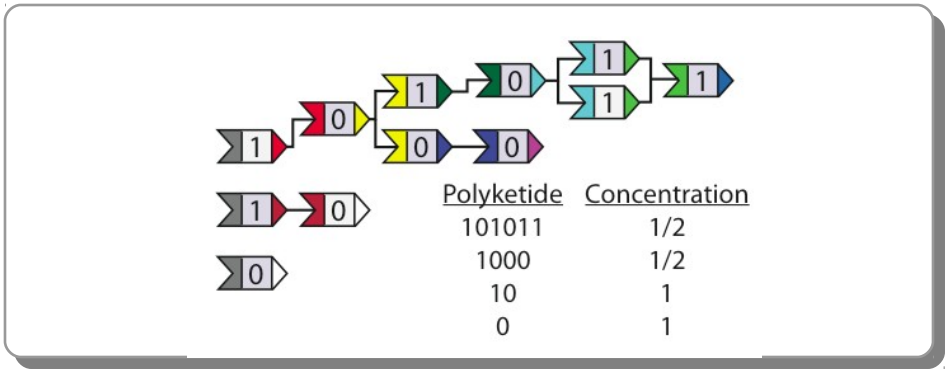
Gene order in a bacterial evolution model

Genes, proteins, polyketide products





Two types of catalytic domains;
Polyketide products are binary strings

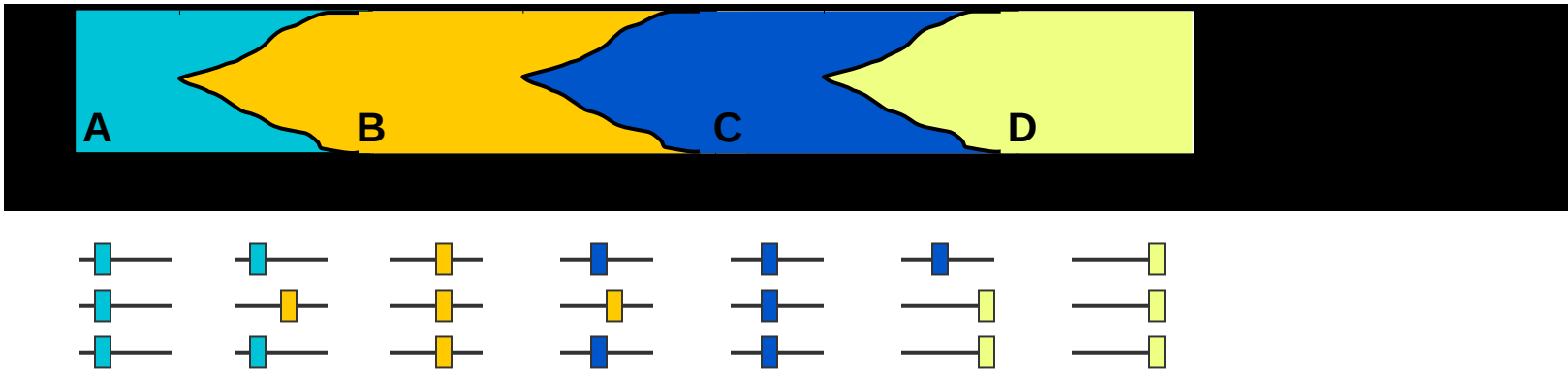


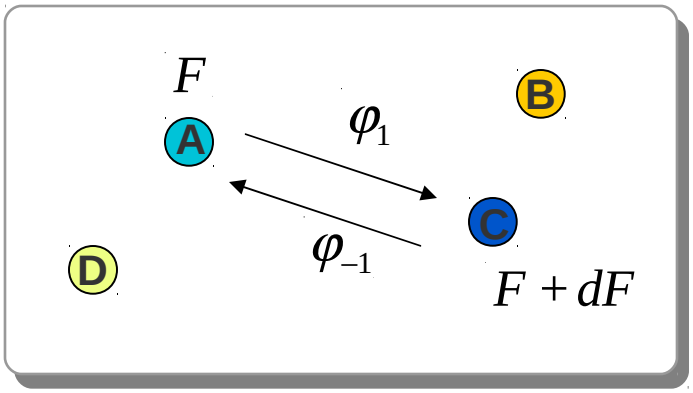
Competition, selection, and rampant gene swapping leads to gene ordering

Co-linear systems are more ‘evolvable’

Callahan et al., PNAS, 2010

Population genetics:
a map from mutations to populations





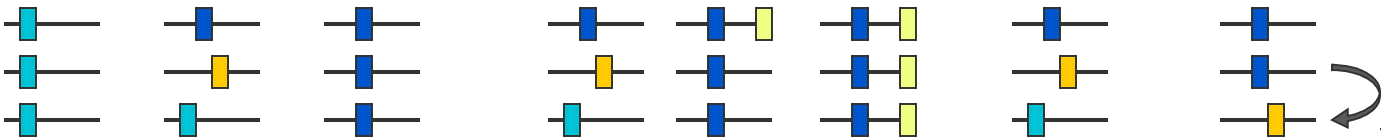
$$\frac{\varphi_1}{j_{-1}} = \exp(2(N-1)dF)$$

Nothing in biology makes sense except in light of evolution [Dobzhansky]

And nothing in evolution makes sense except in light of population genetics [Lynch]

 Khatri et al., PNAS, 2009

Real population genetics are rich in phenomena, but poorly understood



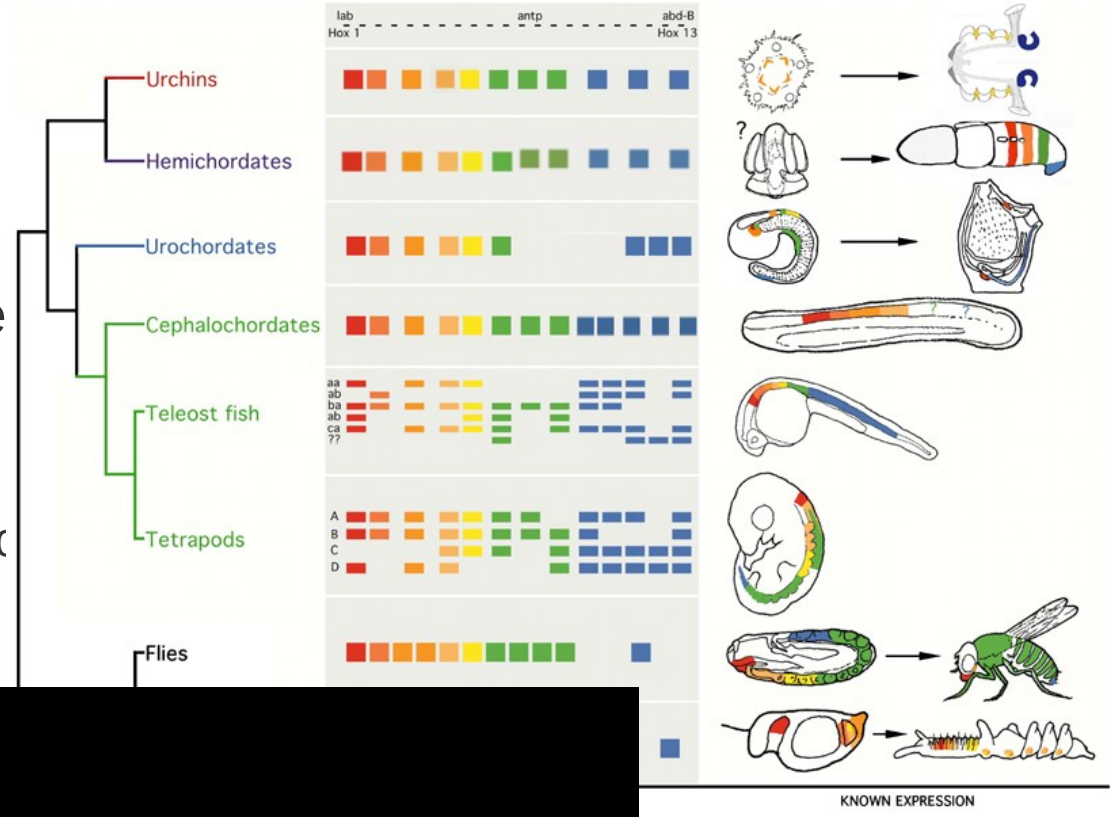
Open problems:

- populations in which multiple mutations coexist
- genomes with multiple mutations
- interactions between individuals
- analysis of experimental data

 Lang et al., Genetics, 2011

Protein numbe

DNA elements t



thattai@ncbs.res.in