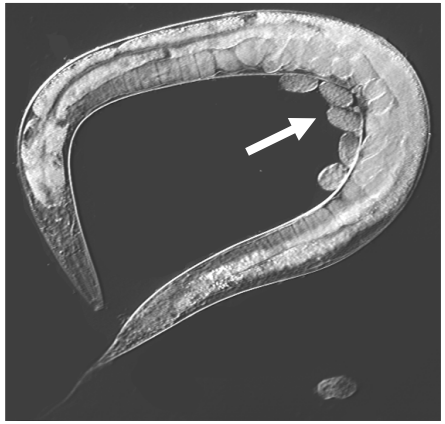
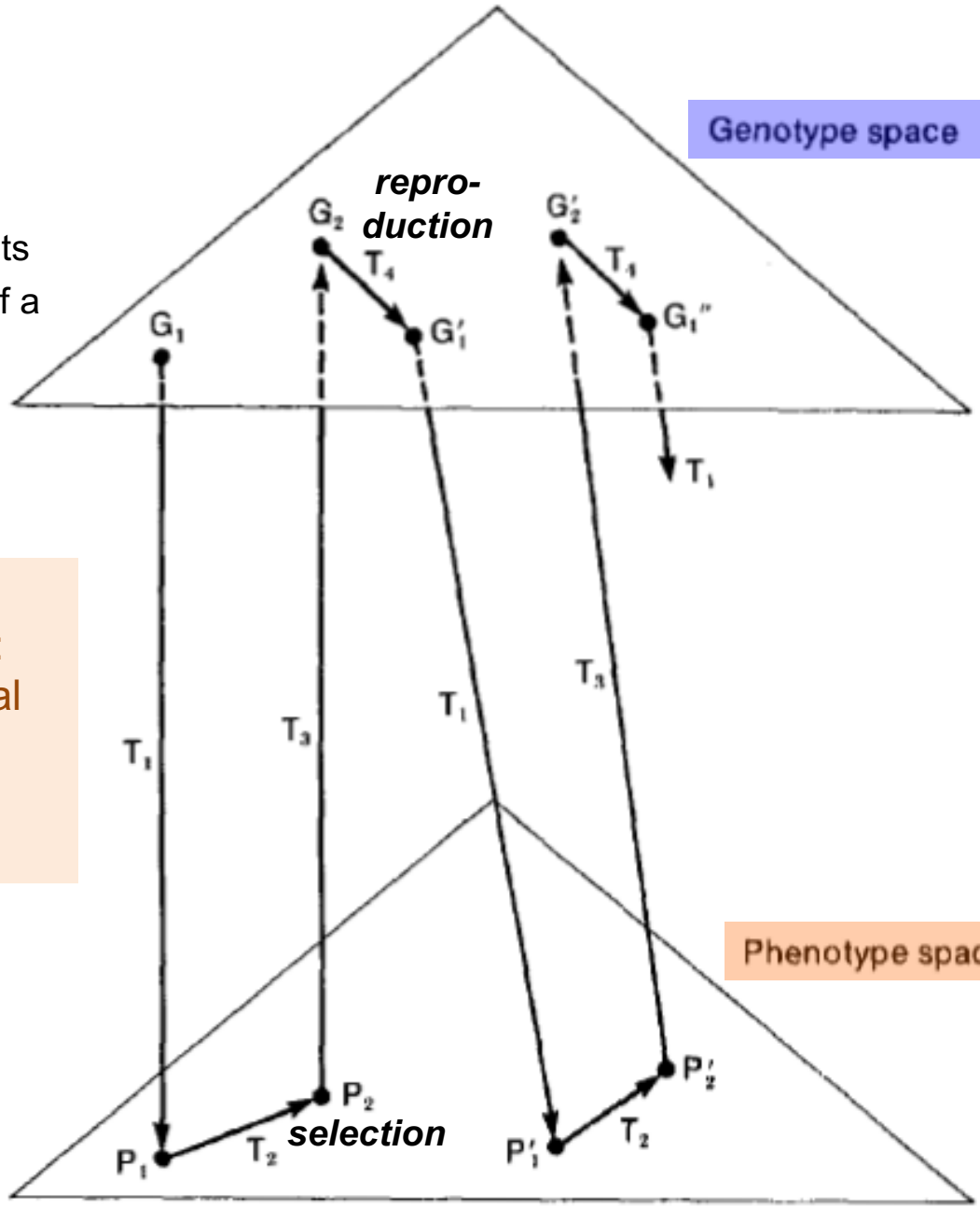
Relation génotype-phénotype dans les destinées développementales de six cellules chez *Caenorhabditis elegans*



Marie-Anne Félix
ENS Paris

Lewontin's depiction of evolution on a genotype-phenotype map

Lewontin 1974



Here . represents the mean state of a **population**

Population genetics: stochastic processes and selection coefficient

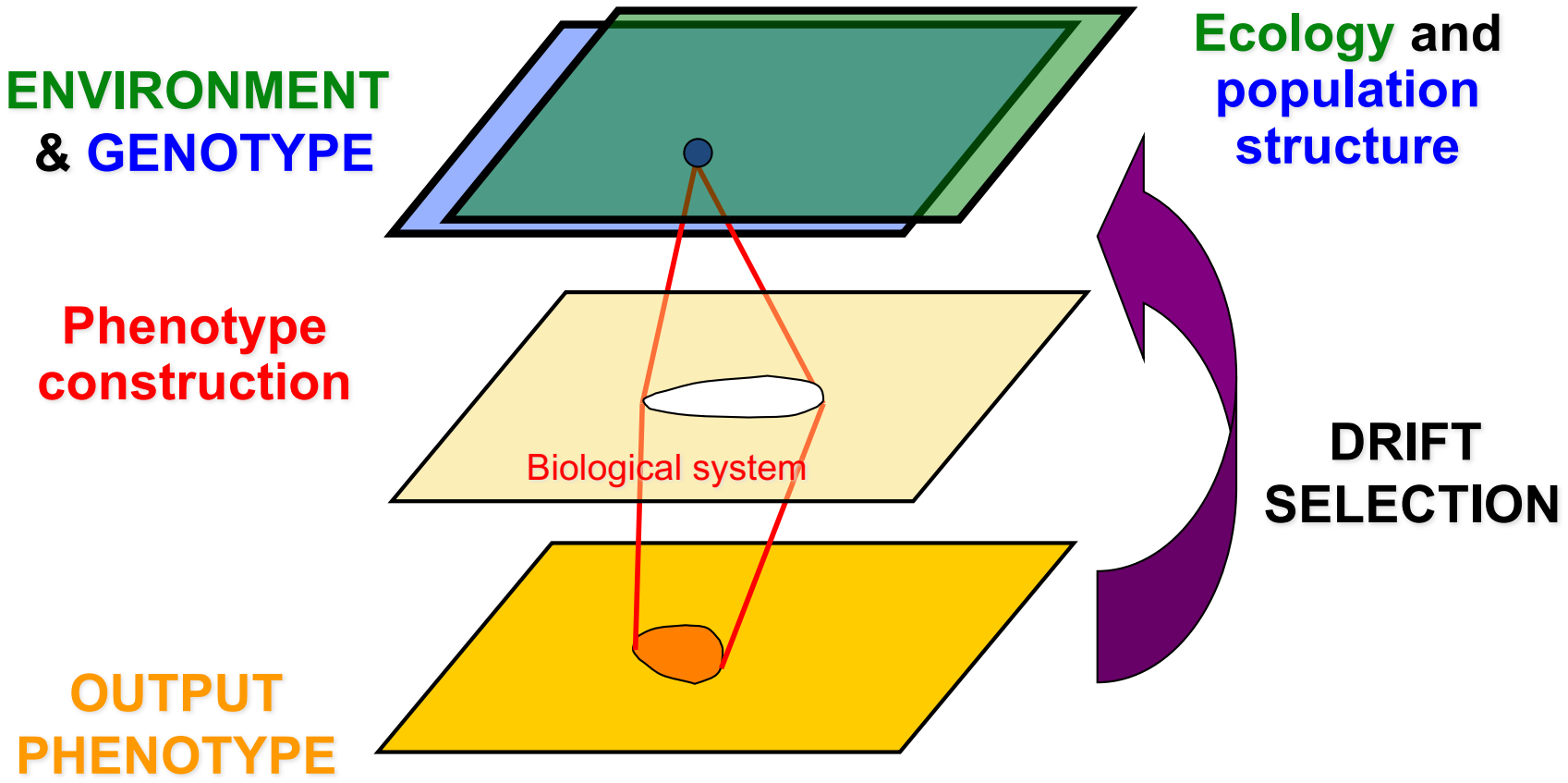
Phenotype construction: developmental and cellular biology physiology

Quantitative genetics: heritability of phenotypes

Evolutionary biology of phenotypes, evolutionary ecology

Adding environment and phenotype construction

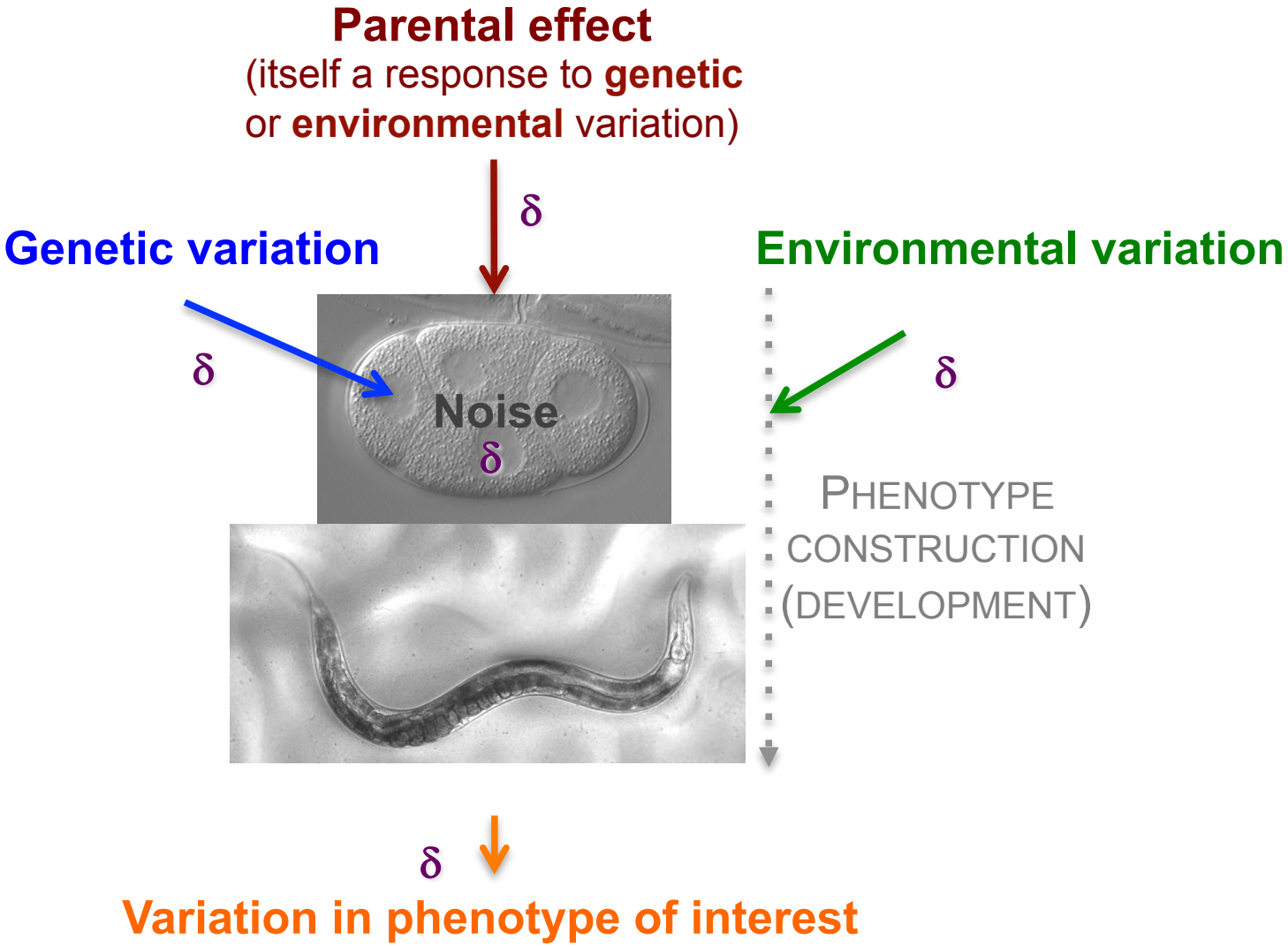
Here ● represents an individual or isogenic population and corresponding probability distributions



Genotype-Environment / Phenotype

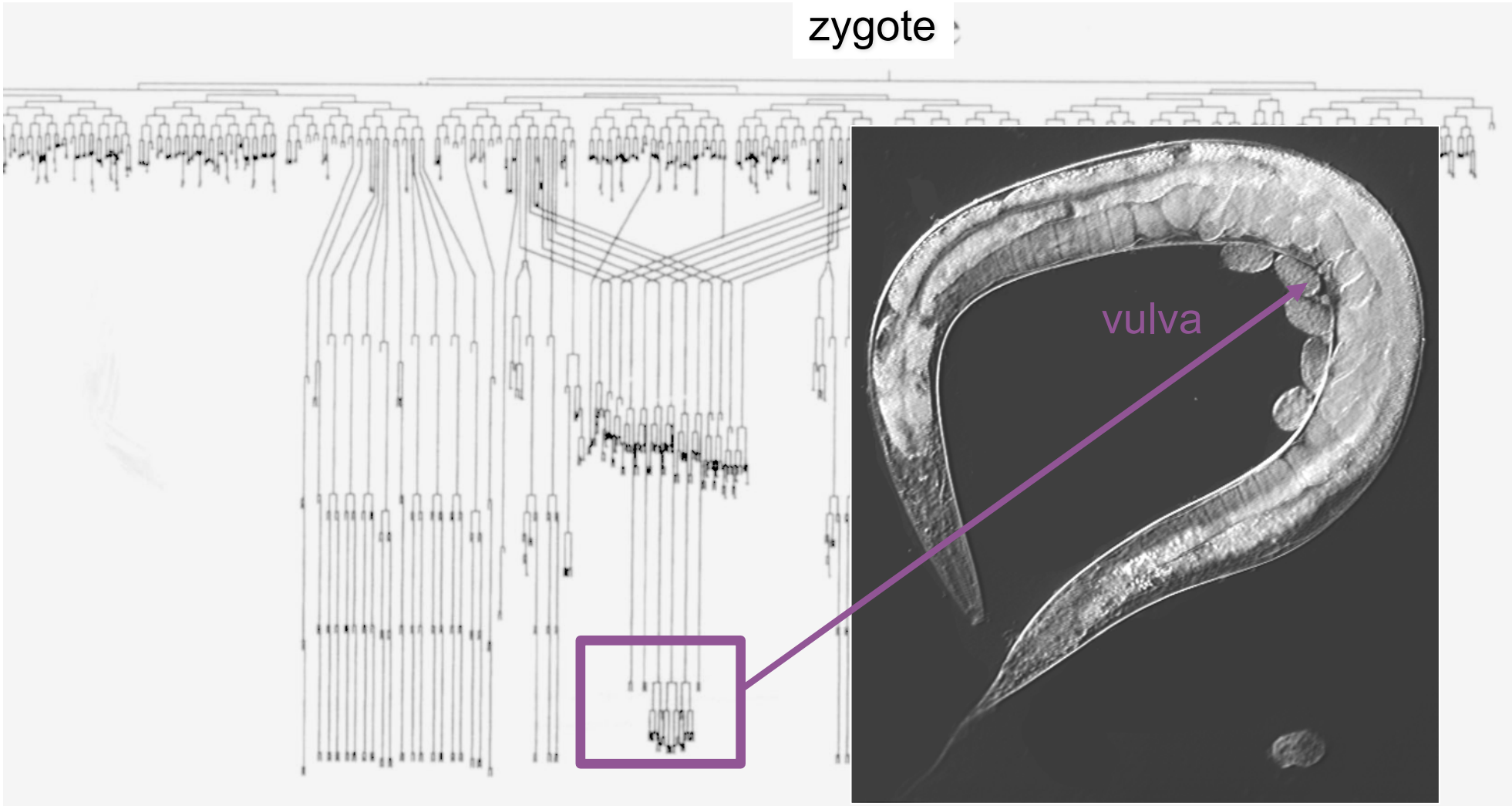
Variational relationship

in experimental biology and in evolution



C. elegans cell lineage

J. Sulston et al. 1977-83

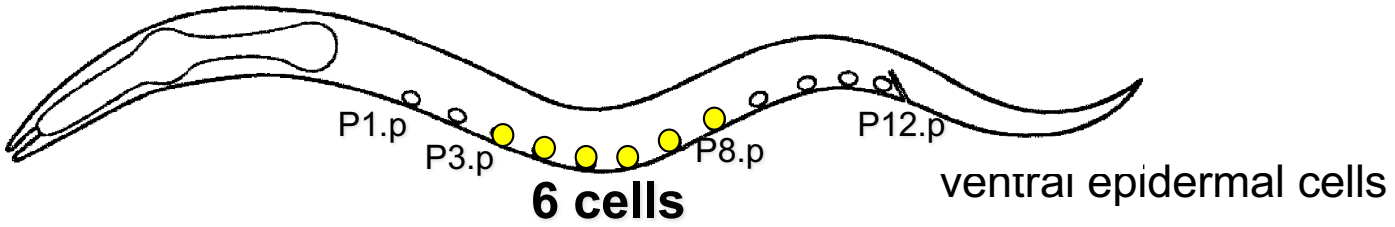


Adult hermaphrodite: 959 somatic cells

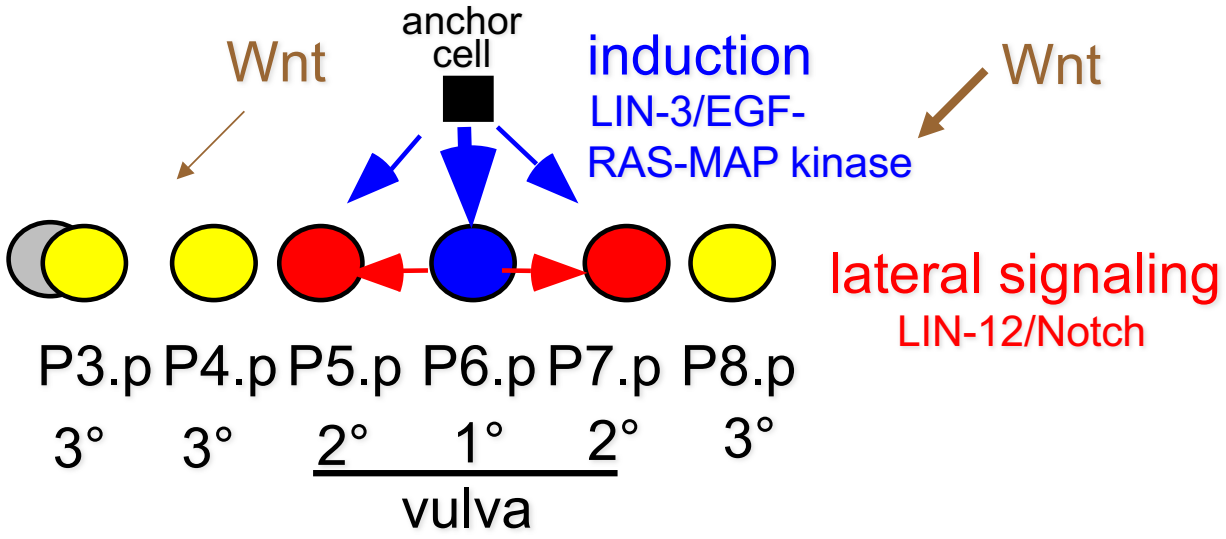
XX Hermaphrodites (+ X0 males) Isogenic lines

C. elegans vulval precursor cell fate patterning

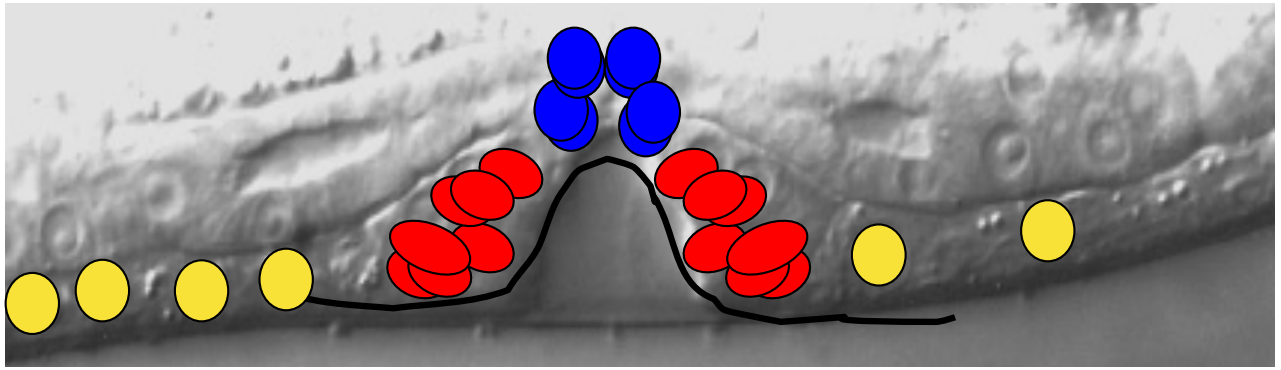
L1 stage
Pn.p cell birth



Early-mid L3 stage
Vulva cell fate patterning

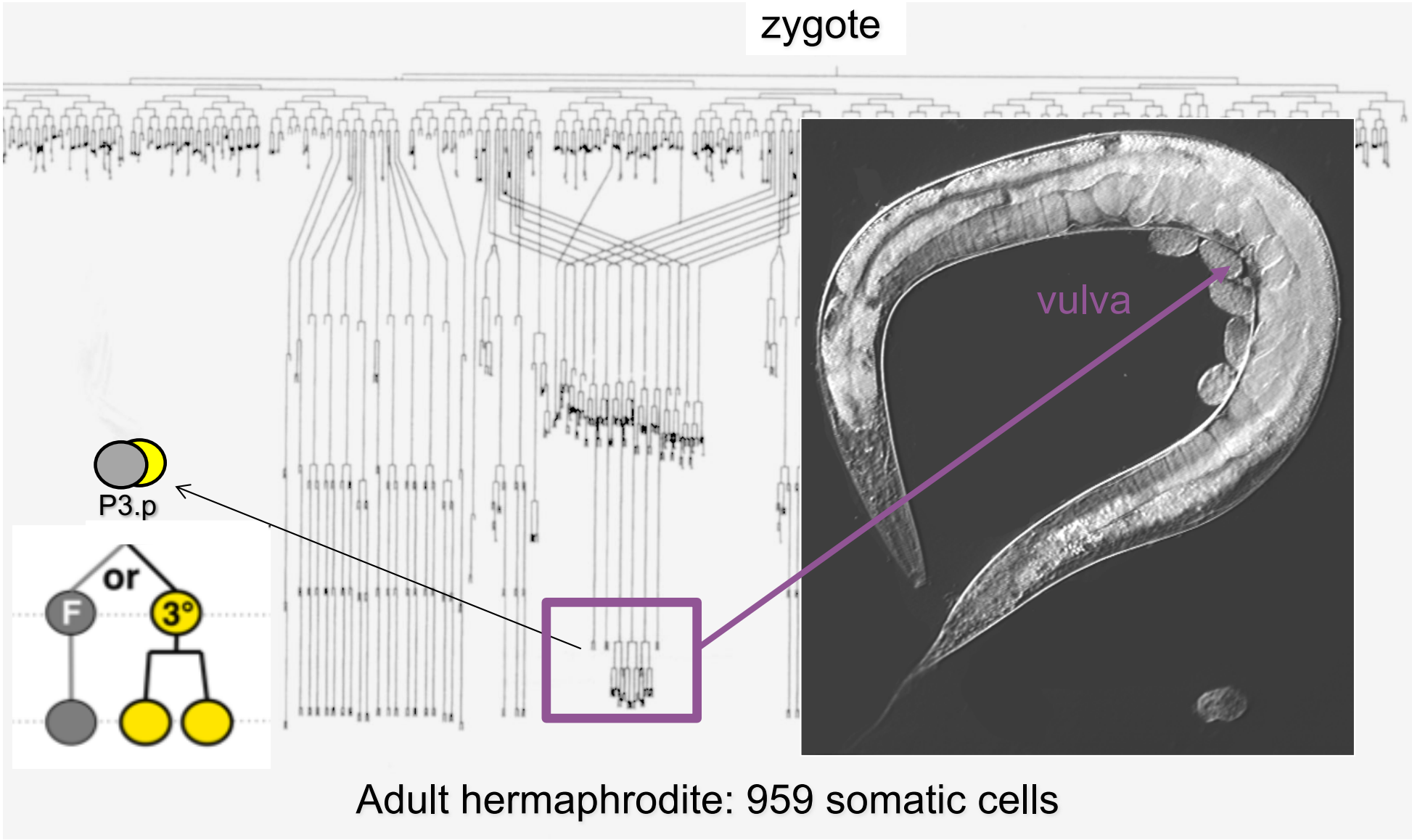


Late L3-early L4 stage
Vulva divisions



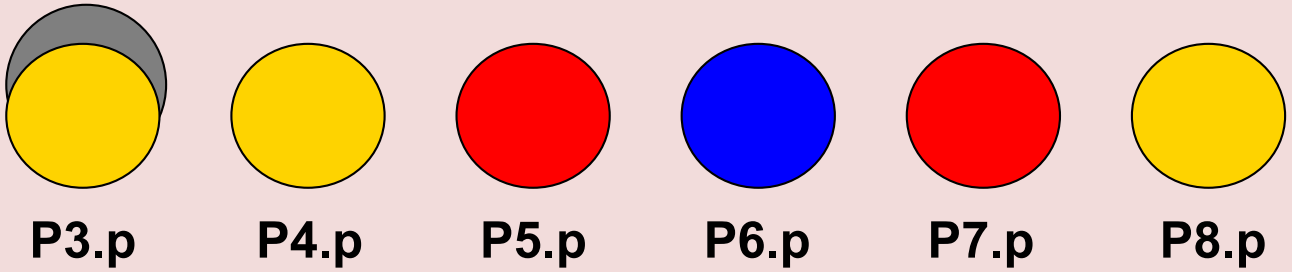
Quasi-invariant *C. elegans* cell lineage

J. Sulston et al. 1977-83



Adult hermaphrodite: 959 somatic cells

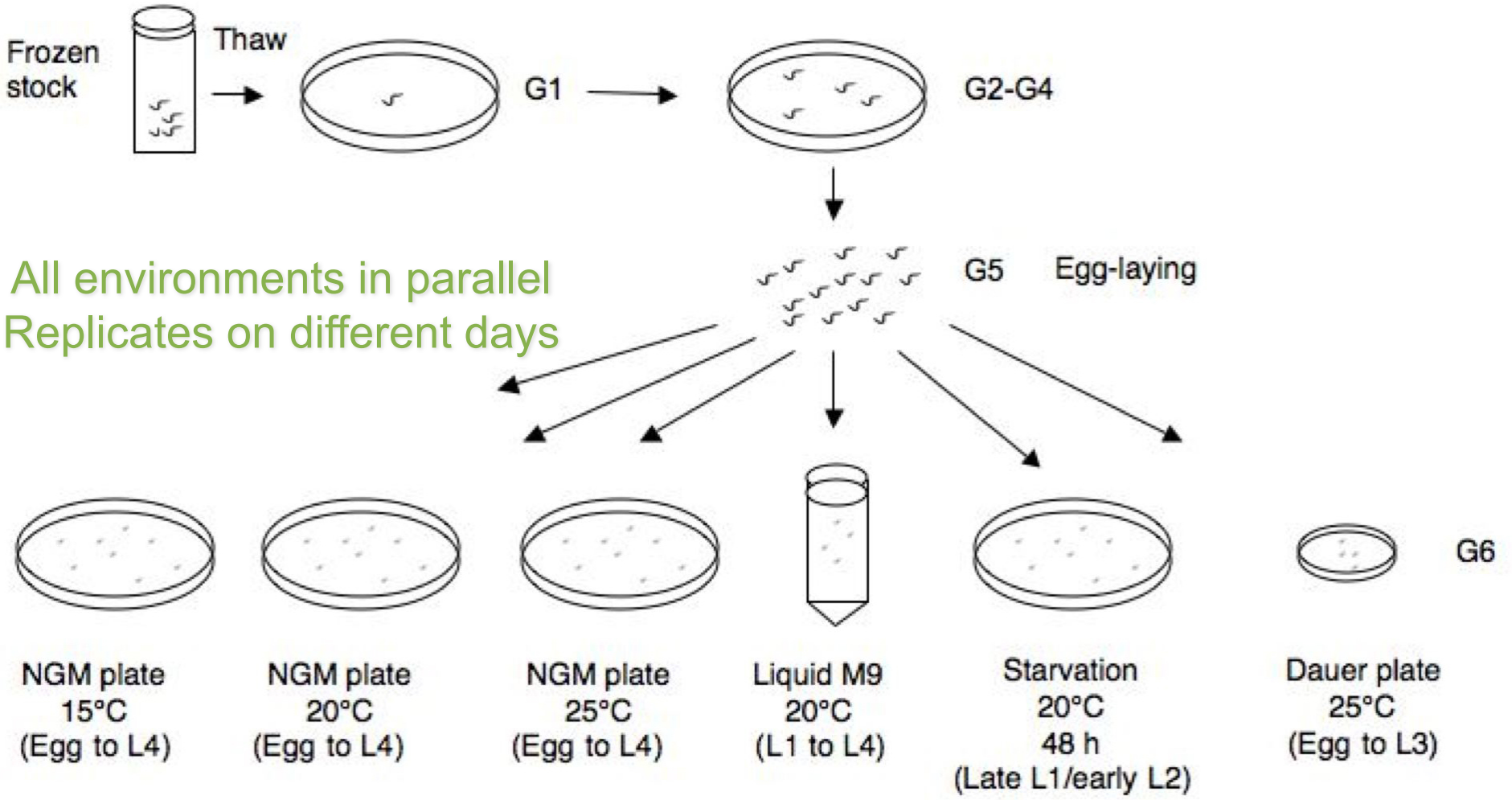
.. or 958



- **Sensitivity to noise and environmental variation**
- **Evolution in *C. elegans* and *Caenorhabditis* genus**
- **Sensitivity to random mutation**
- **Sensitivity to variation in signaling pathways**

Robustness of the vulva system in different environments

Experimental environments

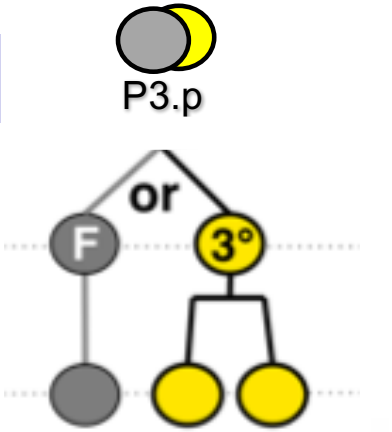


Abbreviations
G: Generation
NGM: Nematode Growth Medium

Braendle & Félix *Dev. Cell*, 2008

The fate of only one of the six cells, P3.p, is highly sensitive to **stochastic** and **environmental** variation

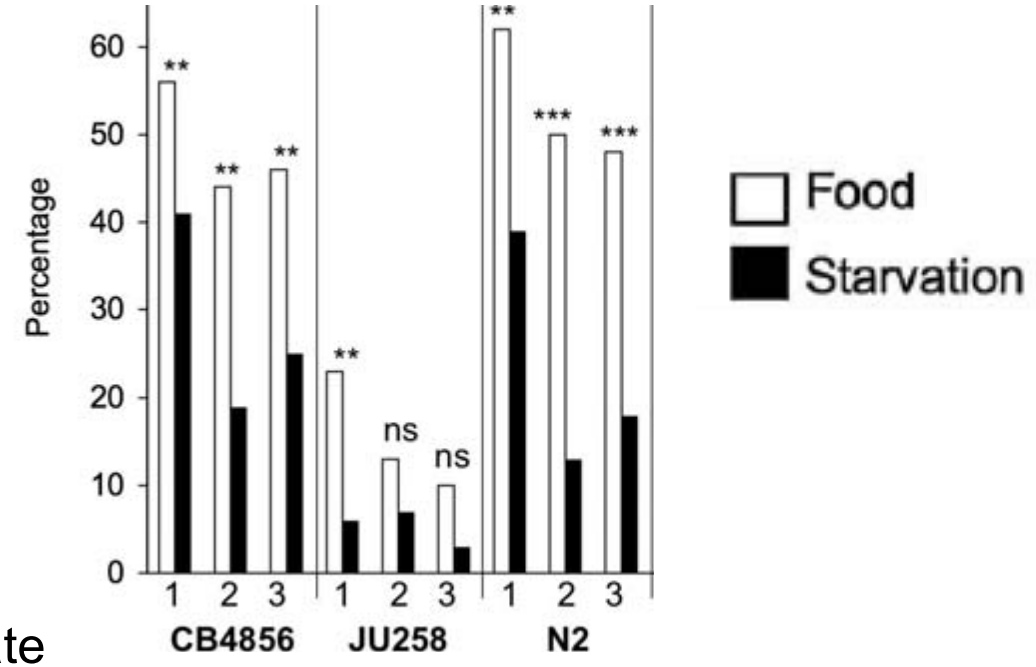
Sensitivity to noise



C. elegans N2
Isogenic reference line
in standard environment:
ca. 45% division

Environmental effect

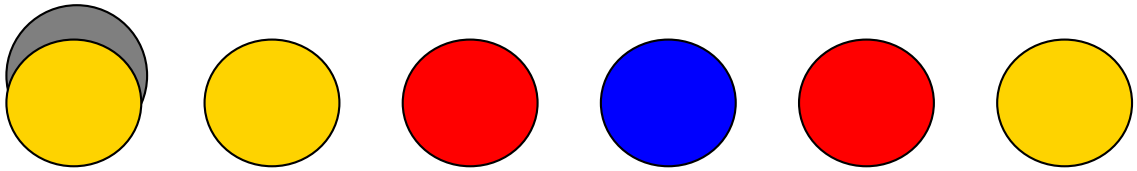
P3.p division frequency



C. elegans isolate

Braendle & Félix *Dev. Cell*, 2008

Sensitivity to stochastic and environmental variation in different vulva traits



decreasing sensitivity to environmental variation

Class

D C B A

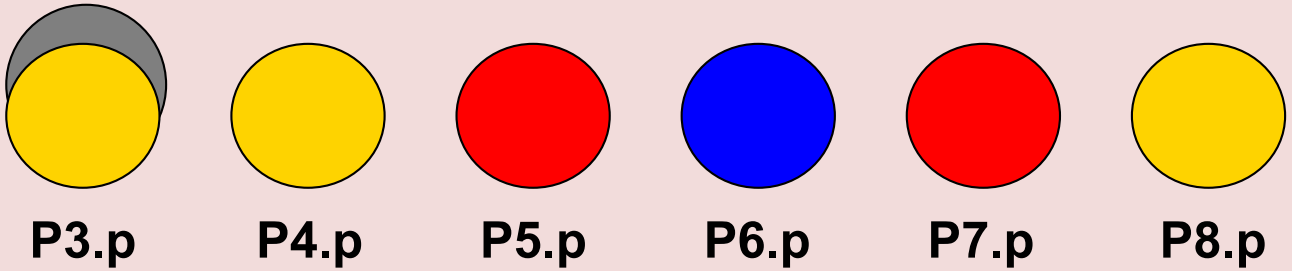
P3.p fate

P4.p/P8.p fate

central fate on P5.p or P7.p complete vulva

incomplete vulva

Braendle & Félix *Dev. Cell*, 2008

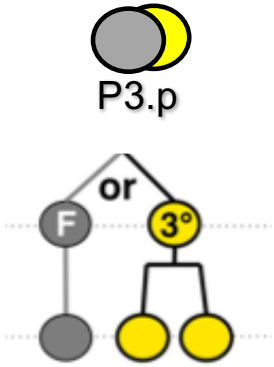


- Sensitivity to noise and environmental variation
- **Evolution in *C. elegans* and *Caenorhabditis* genus**
- Sensitivity to random mutation
- Sensitivity to variation in signaling pathways

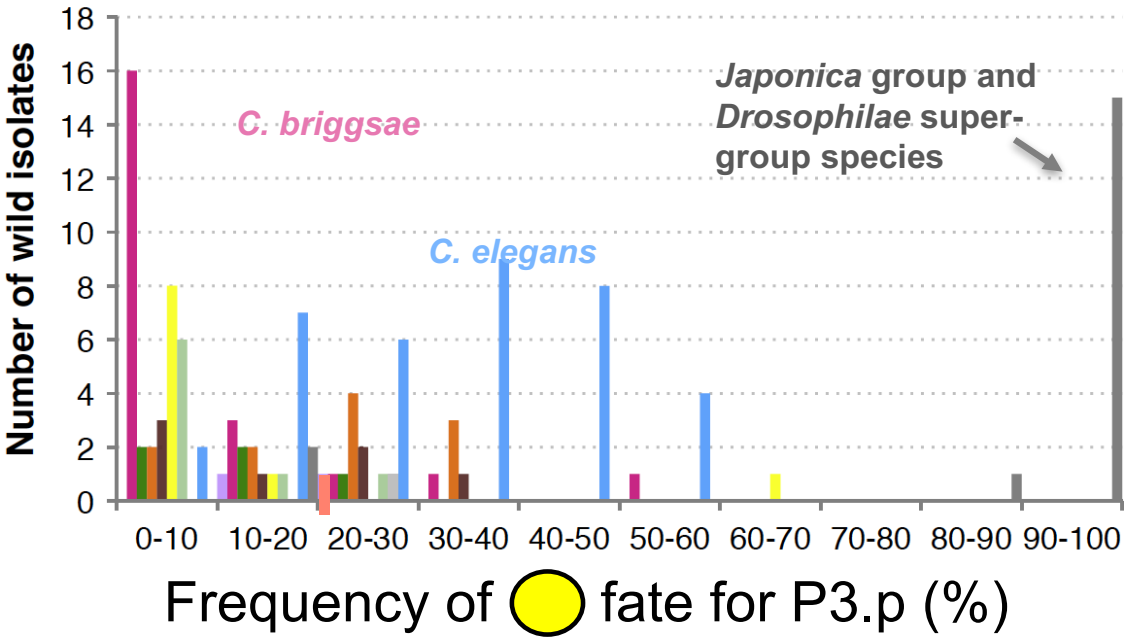
Evolution in the *Caenorhabditis* genus

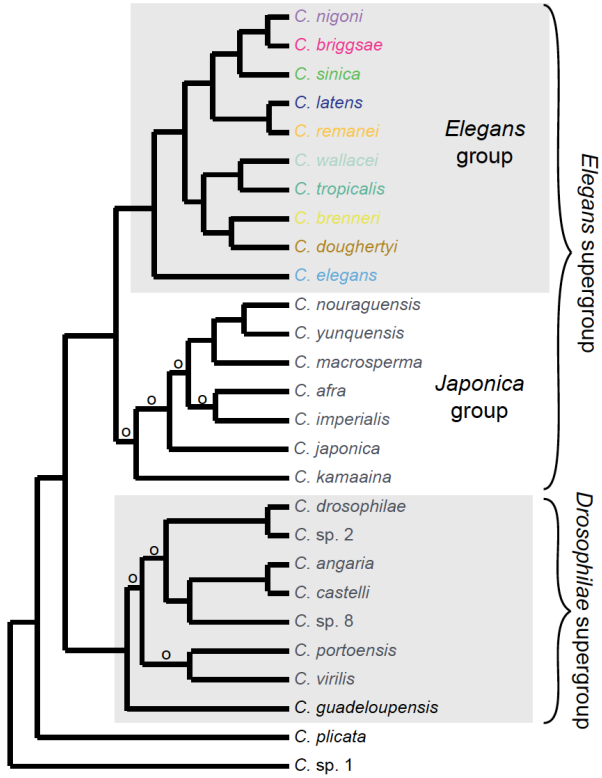
Evolutionary labile
- intra-specific
- inter-specific

especially in *Elegans* group



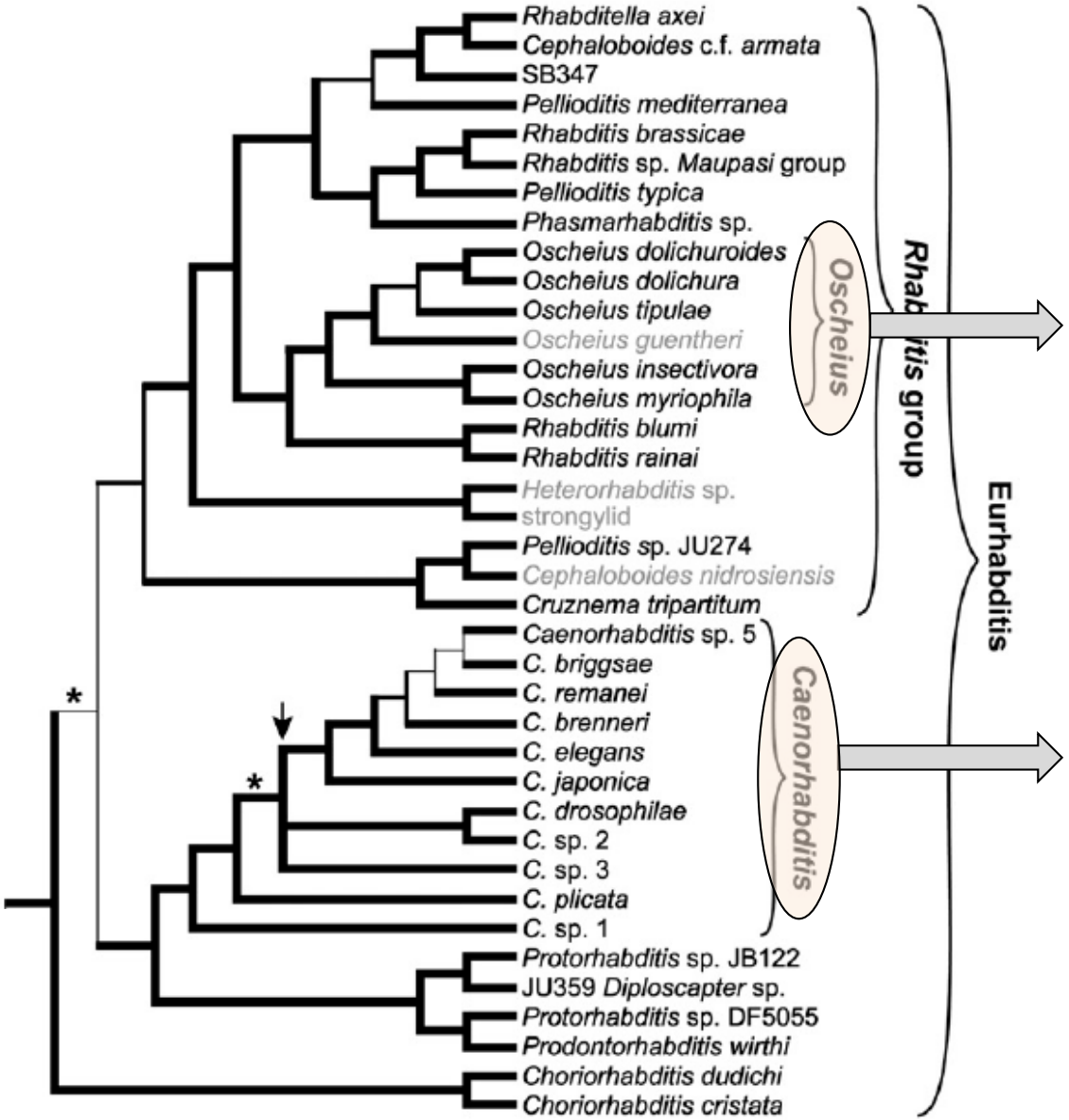
Evolutionary invariant
whole genus





Pénigault & Félix, Dev Biol 2011

Evolutionary trends in vulval traits



P3.p invariant
P4.p and P8.p vary

EMS mutagenesis

P3.p varies
P4.p and P8.p invariant

Mutation accumulation lines

Phylogeny: Kiontke et al. 2007

Delattre & Félix, 2001
Pénigault & Félix, 2011

Phenotypic evolution

Respective roles of
natural selection,
historical contingency,
and
developmental bias?

Developmental constraint / bias

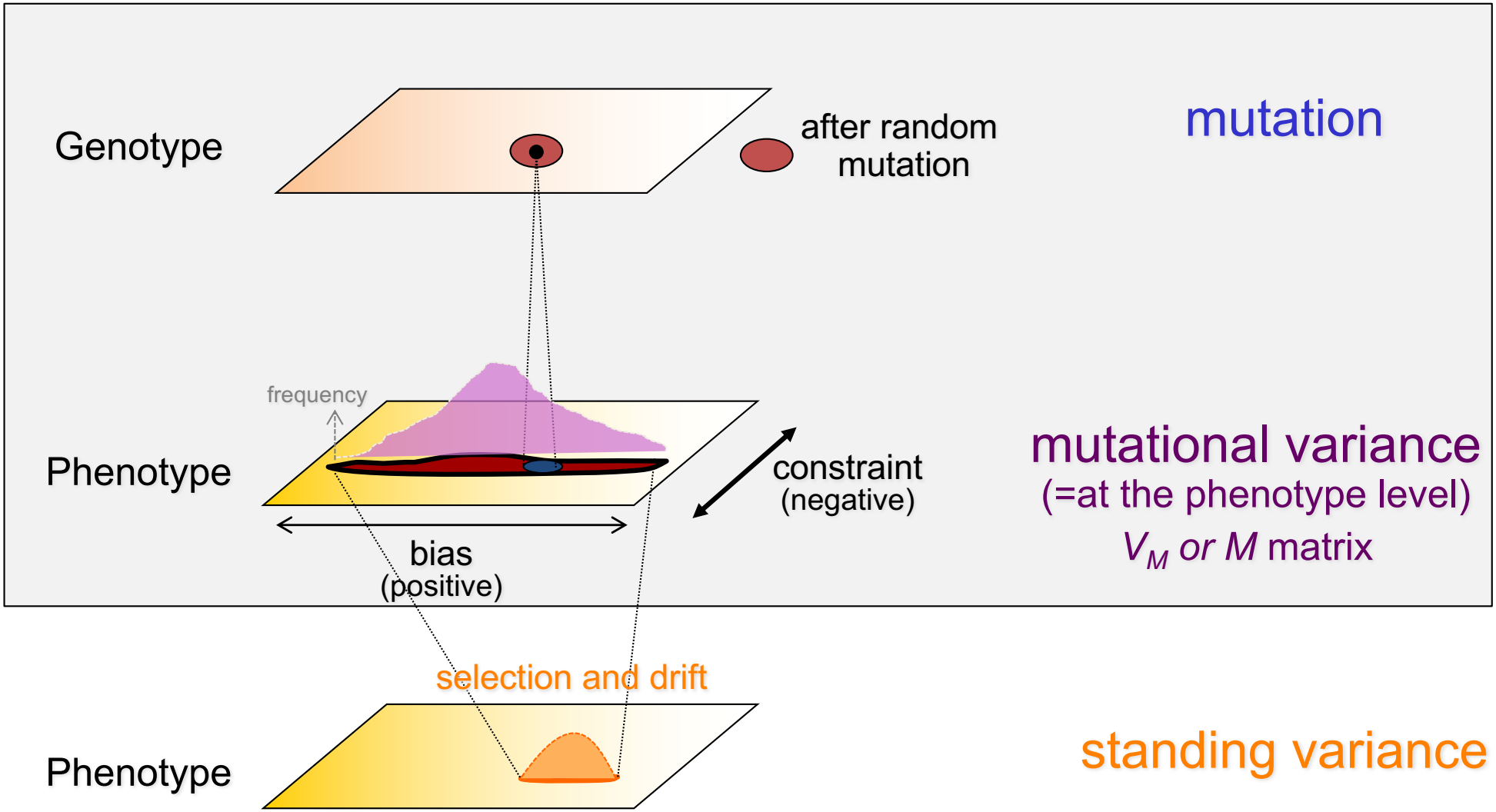
Analogy with the Spandrels of San Marco
S. J. Gould and R. Lewontin, 1985

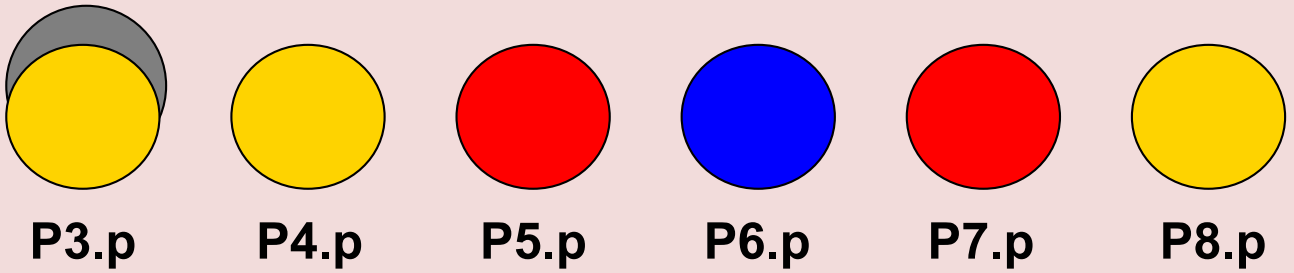
Contrast:

1. The spandrels were designed to fit the four evangelists

2. The spandrels are the necessary geometric consequence of a dome on arches

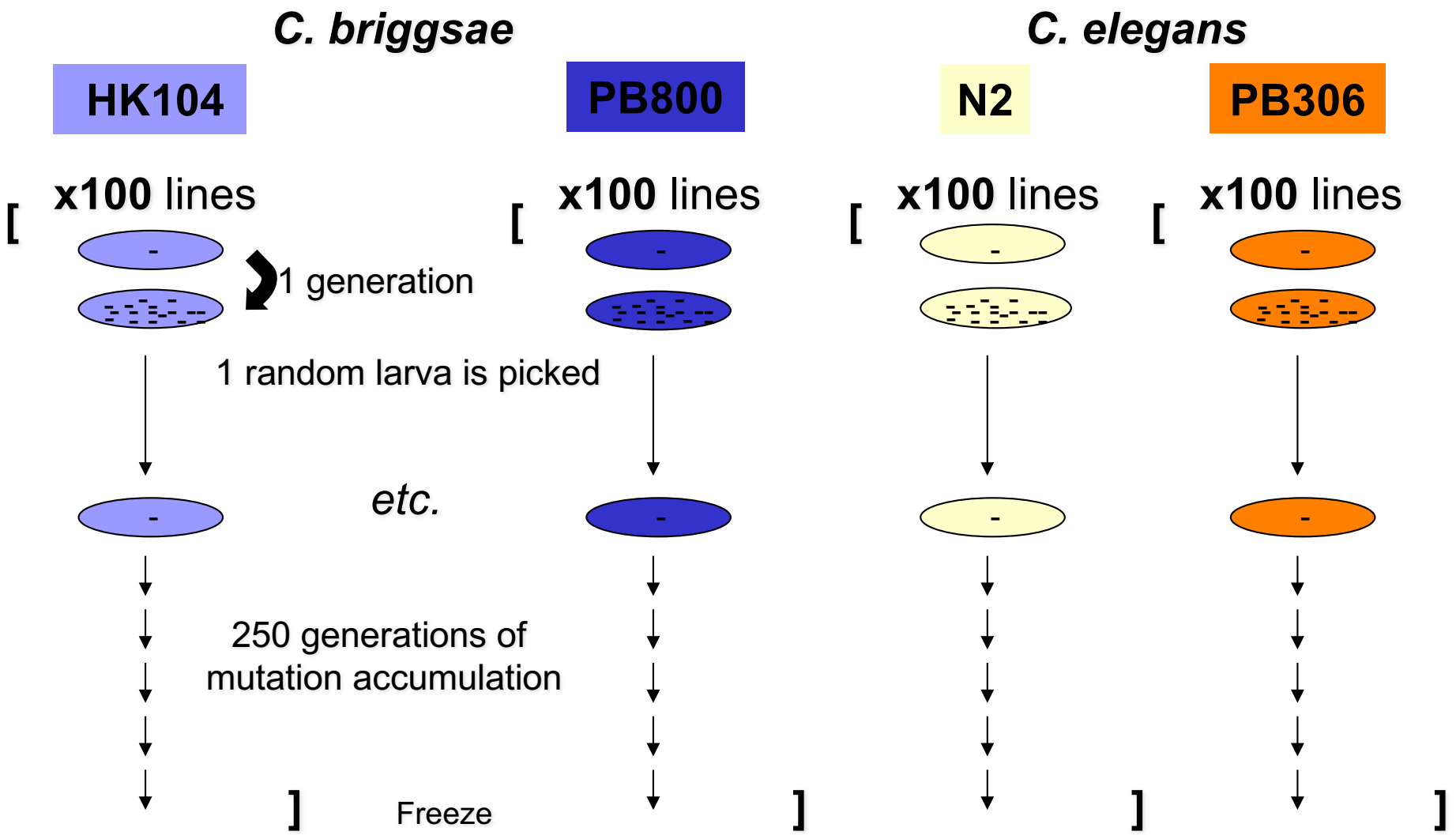
Developmental constraint / bias





- Sensitivity to noise and environmental variation
- Evolution in *C. elegans* and *Caenorhabditis* genus
- **Sensitivity to random mutation**
- Sensitivity to variation in signaling pathways

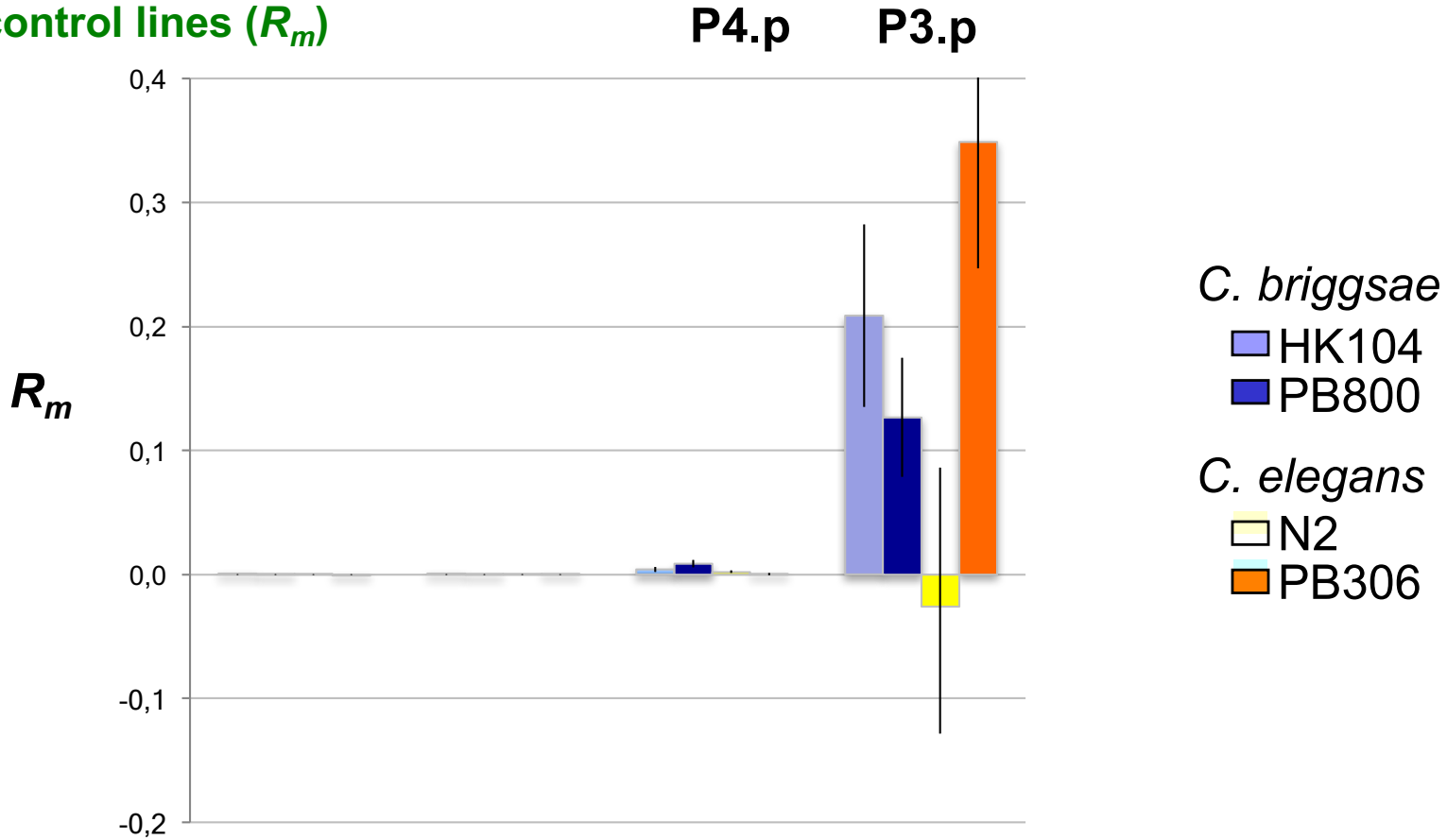
Mutation accumulation lines
4 starting wild genotypes



C. Baer & M. Lynch

Rate of directional evolutionary change of different vulva variant types

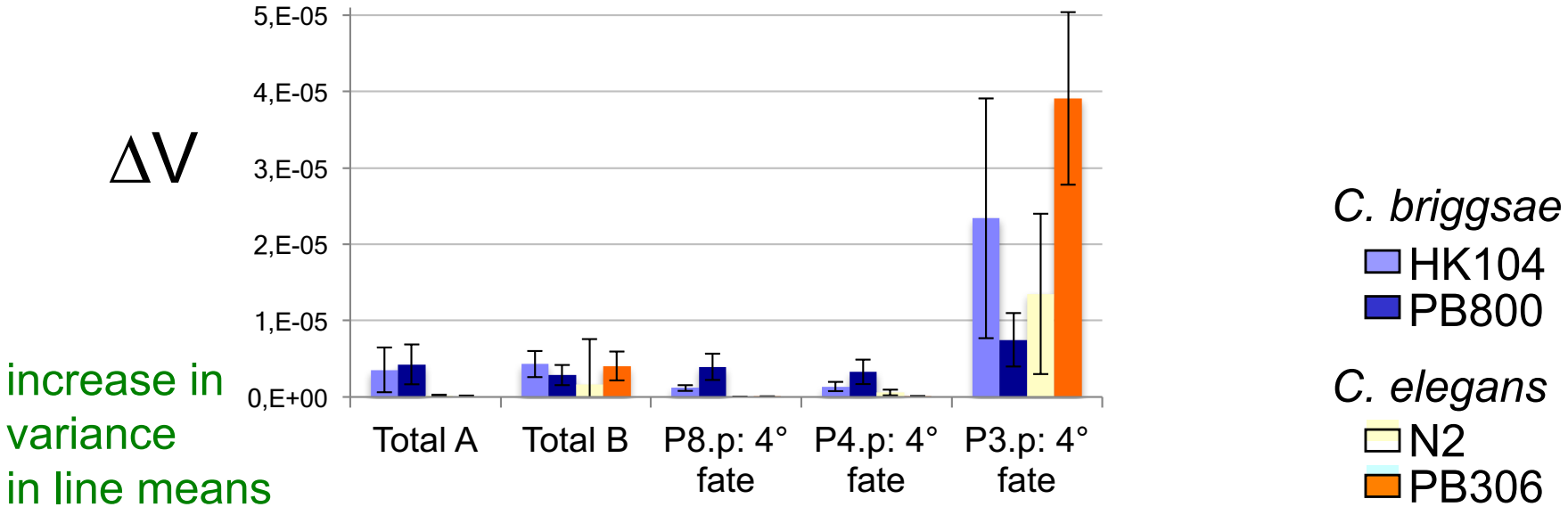
Per generation change in variant phenotype frequency compared to control lines (R_m)



P3.p fate varies upon mutation much more than P4.p (and P4.p/P8.p more than other cell fate changes)

Braendle, Baer and Félix *PLoS Genetics* 2010

Mutational variance of different vulva variant types



increase in variance in line means

(frequency trait: variance in the binomial parameter p_j, where p_j is the frequency of variant phenotypes in line j)

P3.p fate varies upon mutation much more than P4.p (and P4.p/P8.p more than other cell fate changes)

Braendle, Baer and Félix *PLoS Genetics* 2010

Conclusion

Mutational impact on Vulva Development

- Different vulva traits vary at different rates upon mutation

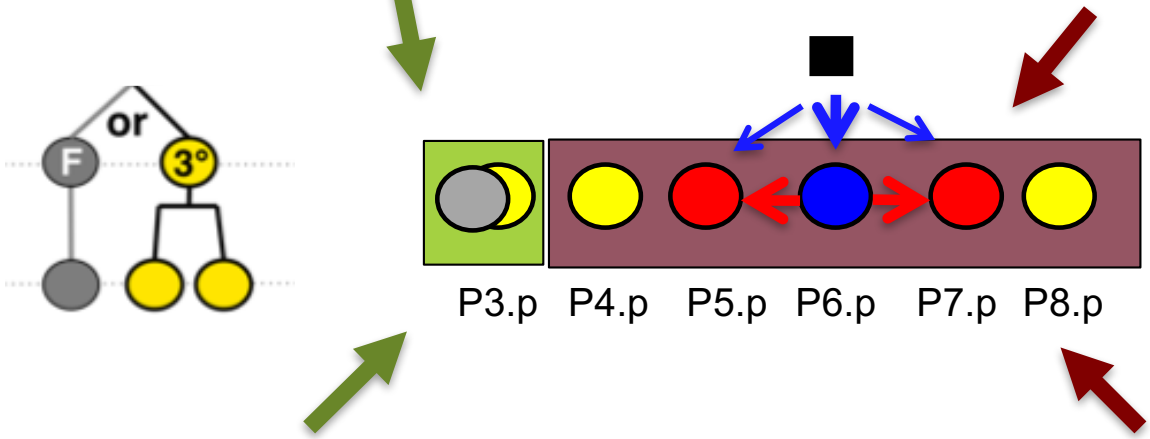
- The system is under stabilizing selection
  (it degrades in mutation accumulation lines)

- This relative mutational variance evolves:
  => may partially explain evolutionary trends.

Contrast:

P3.p
Sensitive
to noise, environmental variation
and random mutation

P(4-8).p
Relatively robust
to noise, environmental variation
and random mutation



Cryptic variation
accumulates

Evolutionary variation
in *C. elegans*
and the *Caenorhabditis* genus

Neutral???

Evolutionary stasis in
the *Caenorhabditis* genus

Stabilizing selection
(comparison mutation accumulation
vs. wild isolate variation)

What causes the difference in mutational variance among Pn.p cells?

- A highly mutable locus (e.g. microsatellite repeats) affecting P3.p?

Molecular origins of rapid and continuous morphological evolution *PNAS* 2010

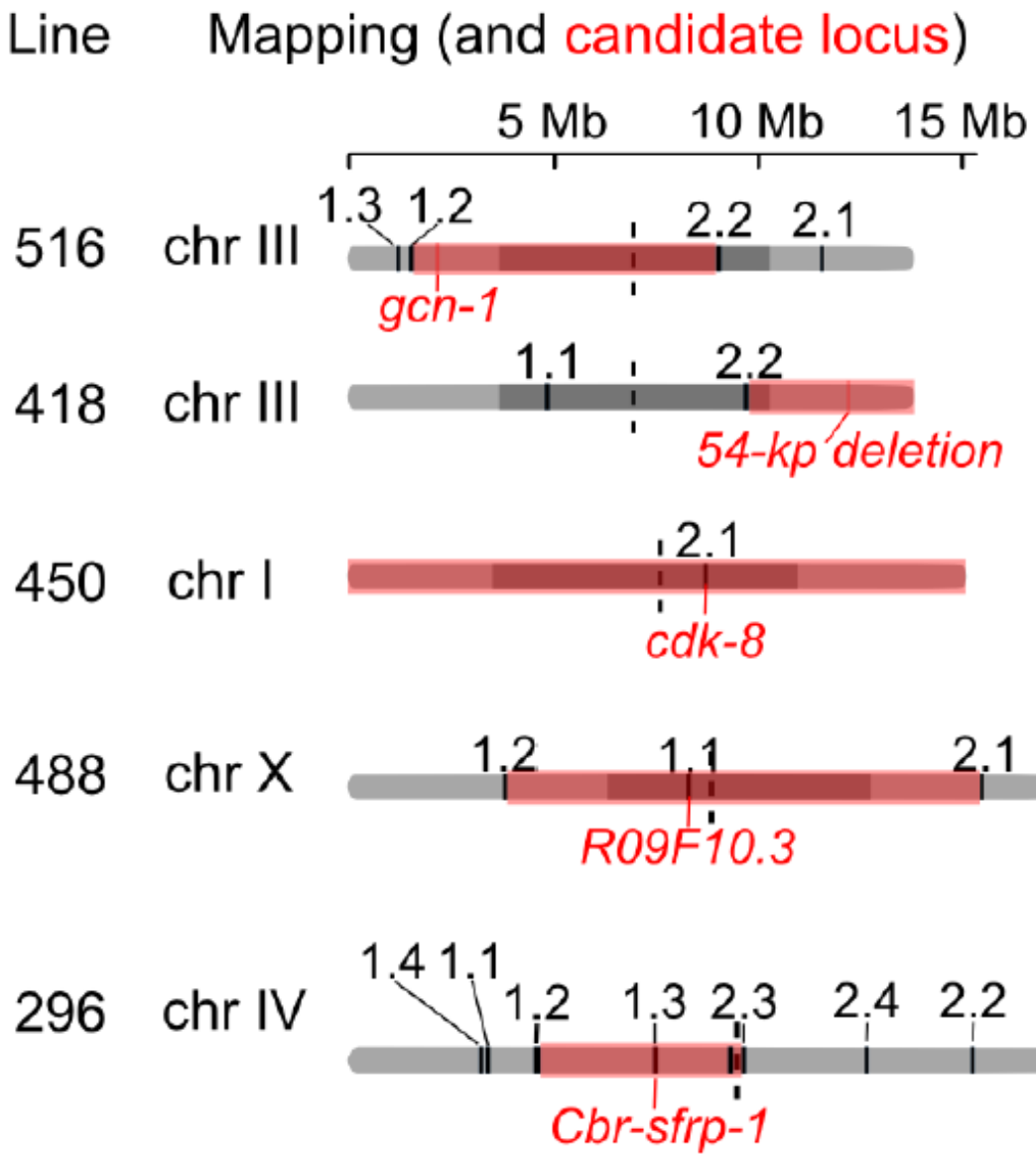
John W. Fondon III* and Harold R. Garner

Runx2 with microsatellite length variation
correlation with morphology in dogs

- A large mutational target affecting P3.p?
  many loci with a phenotype

Each mutation maps to a different genomic region

4/5 are not in genes known to be involved in P3.p fate specification



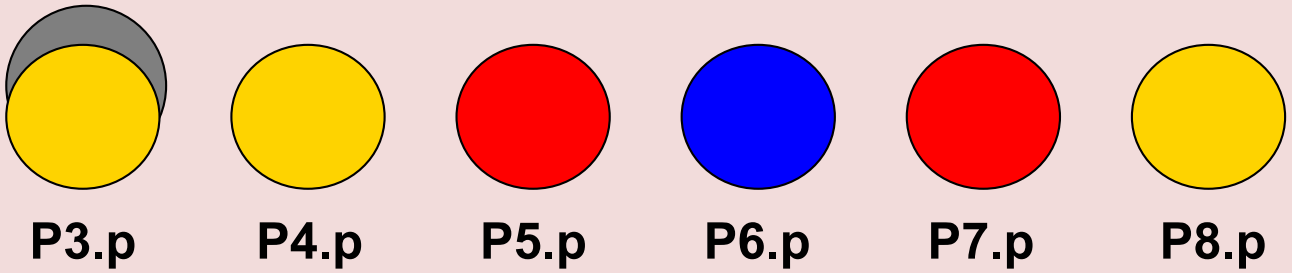
Size	Back-Cross depth	#Lines
7.5	2X	20
4.1	4X	35
15	3X	20
11.6	1X	20
4.7	3X	49

Fabrice Besnard

A large mutational target for P3.p

- A highly mutable locus (e.g. microsatellite repeats) affecting P3.p?

- **A large mutational target affecting P3.p**
  many genetic loci with a phenotype



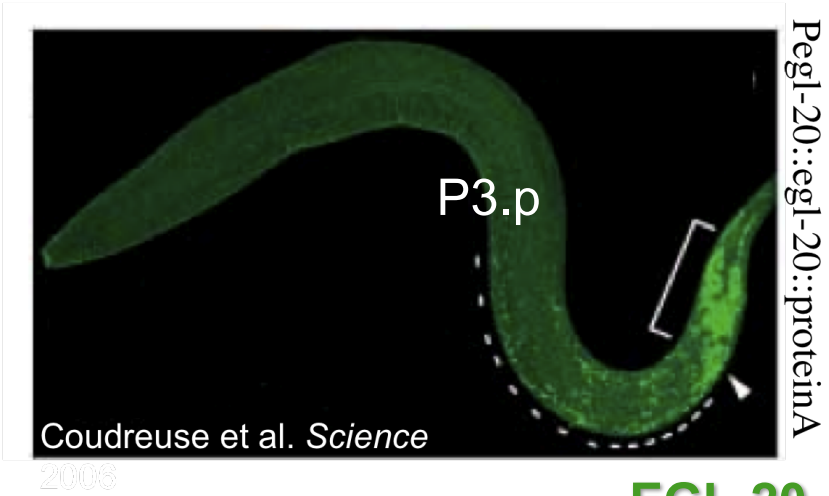
- Sensitivity to noise and environmental variation
- Evolution in *C. elegans* and *Caenorhabditis* genus
- Sensitivity to random mutation

- **Sensitivity to variation in signaling pathways:**

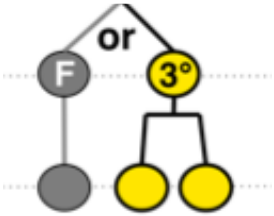
Explaining the degree of sensitivity to random mutation

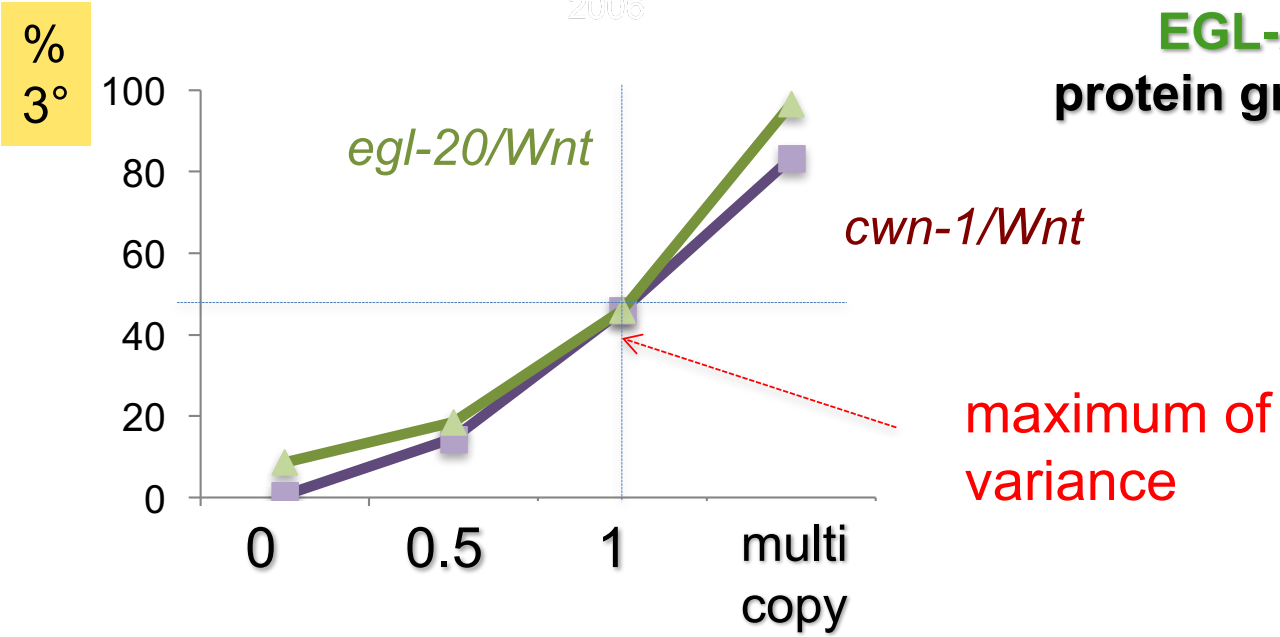
Experimental modulation of *Wnts*

egl-20* and *cwn-1 /wnts



EGL-20
protein gradient





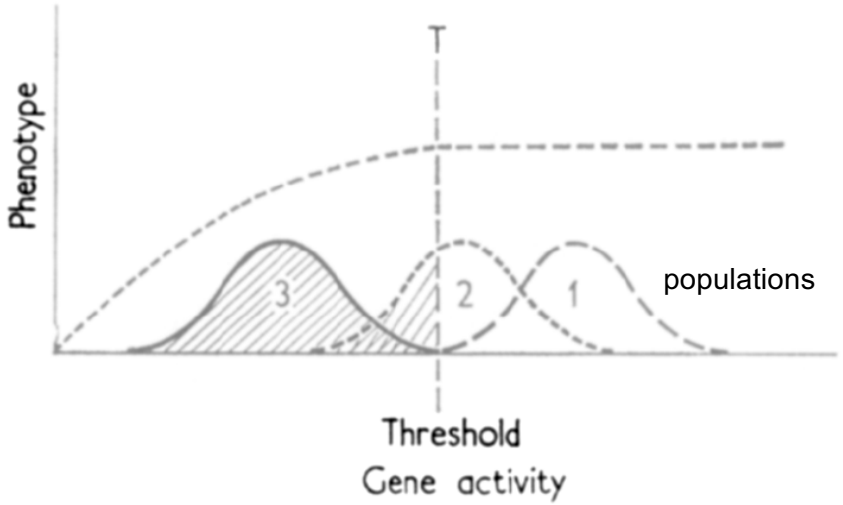
Pénigault & Félix, 2011

Non-linearity in

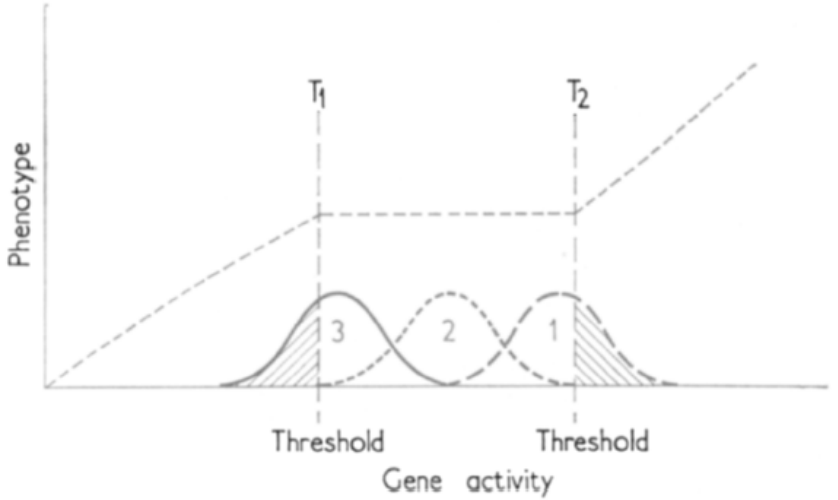
The Relationship Between Gene and Phenotype

J. M. RENDEL *J. Theoret. Biol.* (1962) **2**, 296–308

Simple threshold
dominance

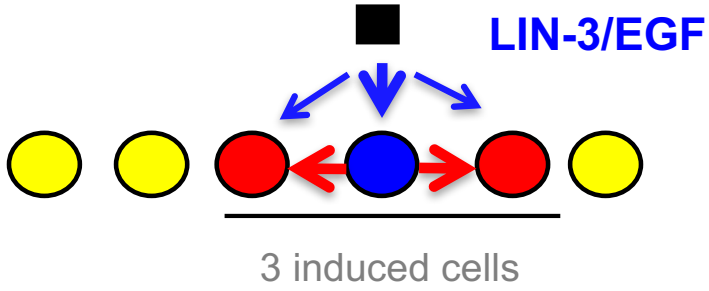


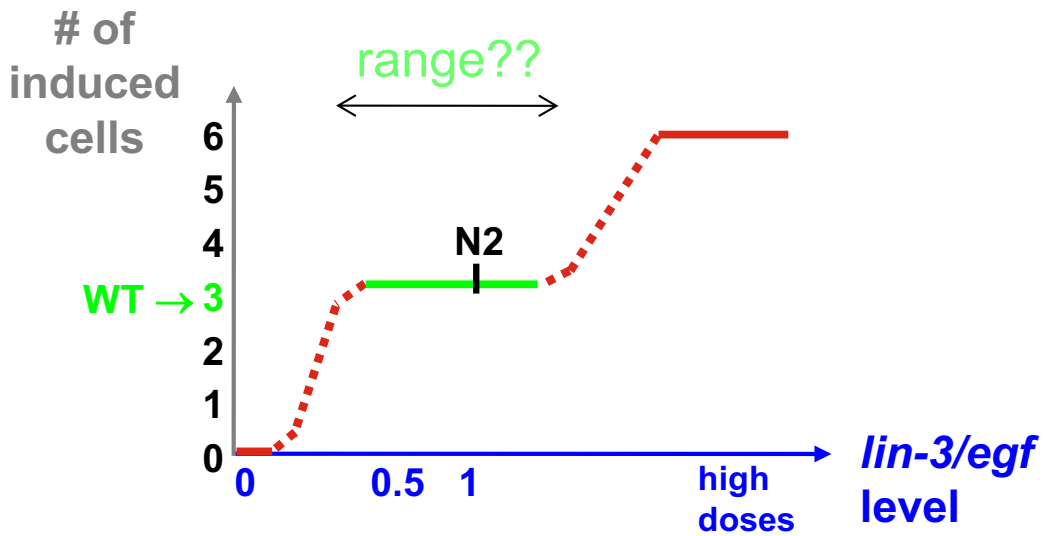
Intermediate plateau
canalization / robustness Waddington



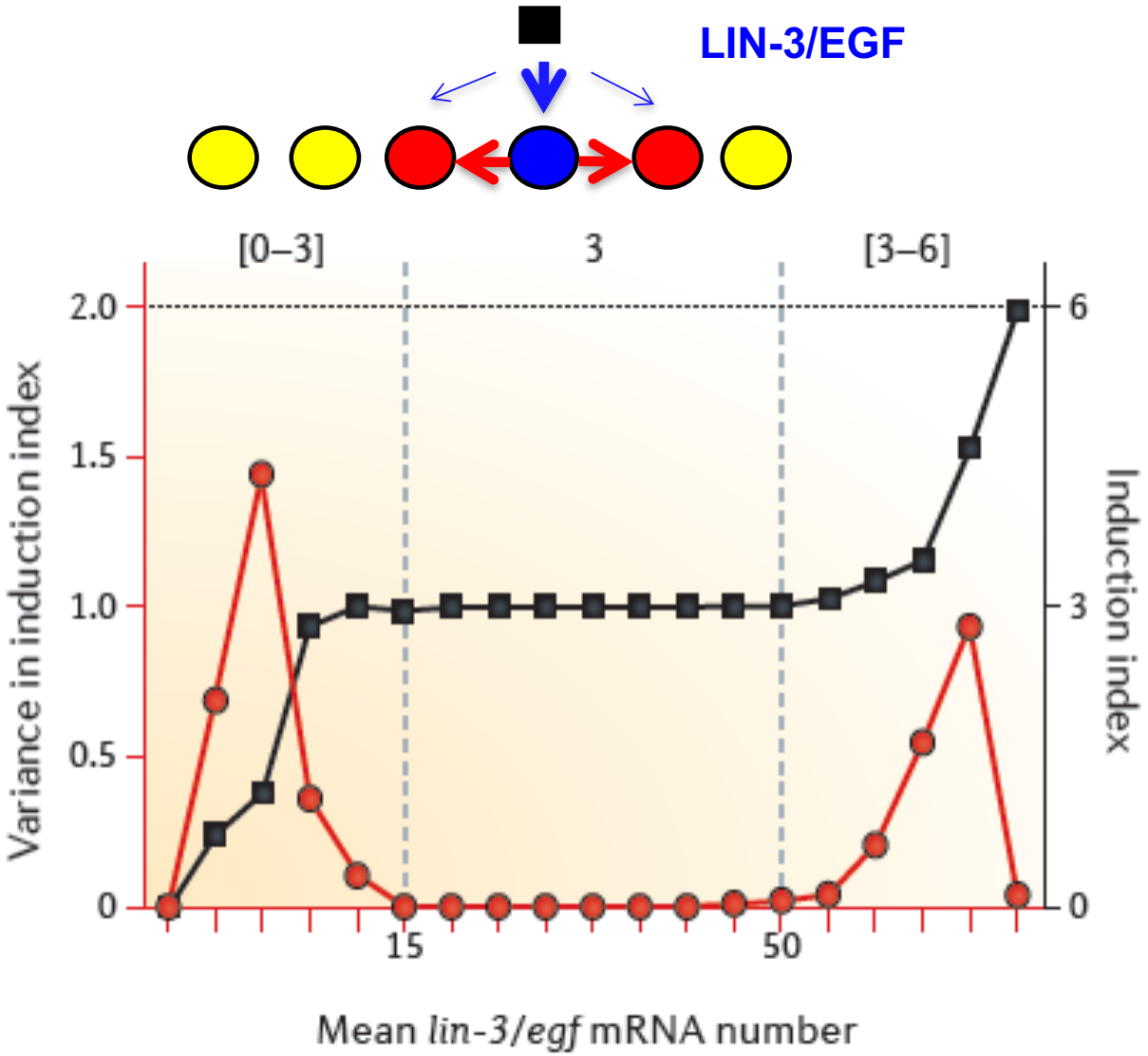
x axis was not measurable
⇒ Rendel uses a replotting of the *y* axis phenotypic scale
based on the phenotypic distribution (probit)
= "MAKE" value
meant to represent an intermediate substance activity

How robust is the system to variation in gene dosage of the upstream inducer (LIN-3/EGF)?





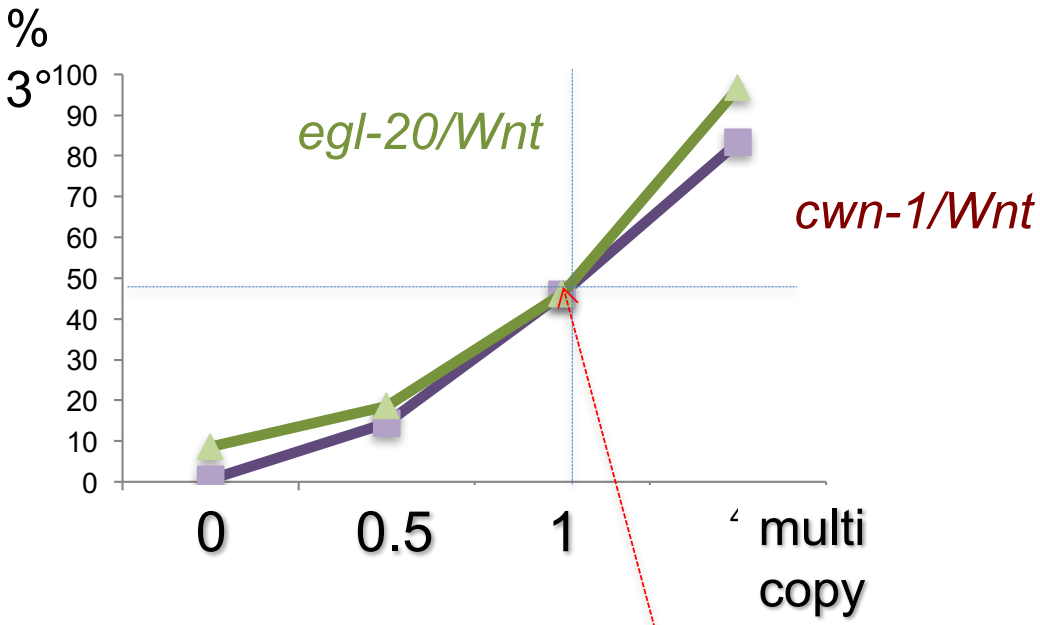
The vulva system is robust to a 4-fold variation in mean *lin-3* mRNA level



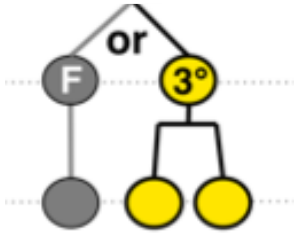
The **variance** increases
outside the zone where **mean index = 3**

Barkoulas et al. *Dev Cell* 2013

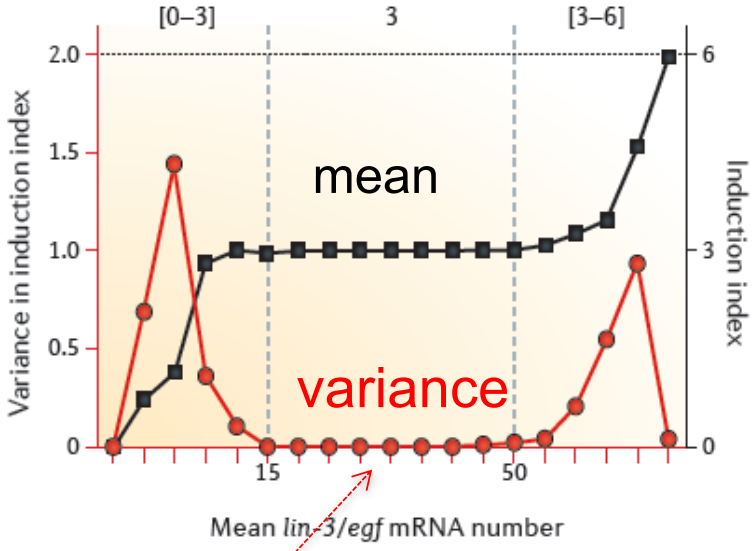
P3.p in a dose-sensitive region of the Wnt gradients



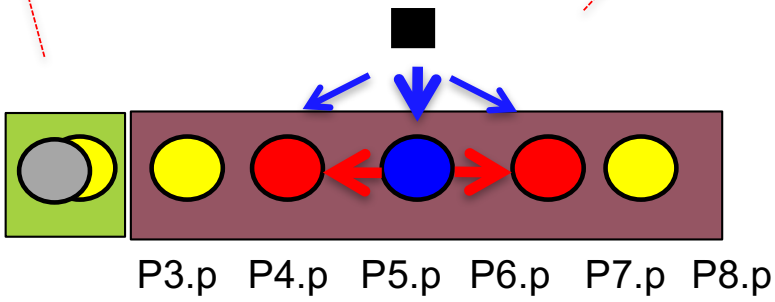
maximum of variance



P(4-8).p in a dose-insensitive region of the LIN-3 gradient



variance ~ 0



Knowledge of the developmental system
helps understand
the sensitivity to various input variations,
including random mutation.

The mutational variance matches
the evolutionary trend in Pn.p cell fate evolution.

Many thanks!

Marie Delattre
P3.p natural variation
2001

Christian Braendle
Environment
2008
MA lines
2010

Jean-Baptiste Pénigault
Wnt sensitivity
2011

Michalis Barkoulas
EGF
dose-response
2013

Fabrice Besnard
MA line genomics and genetics
To be written

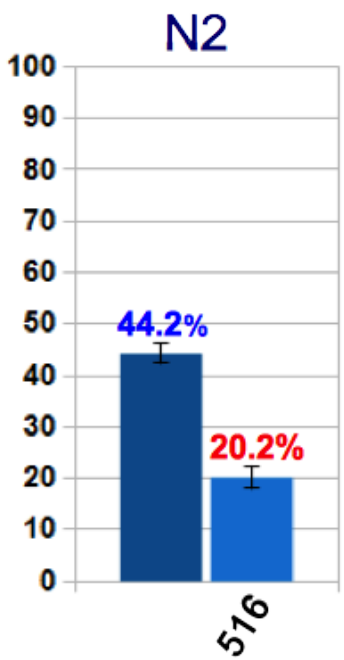
Mutation accumulation lines

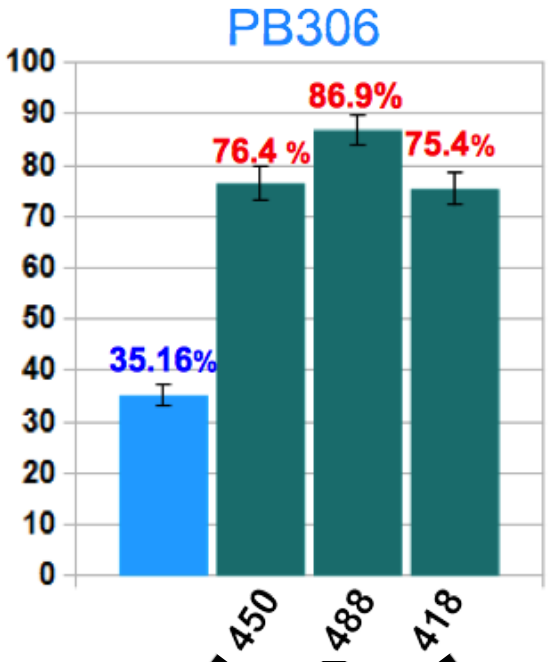
C. Baer & M. Lynch, U. Florida & Indiana

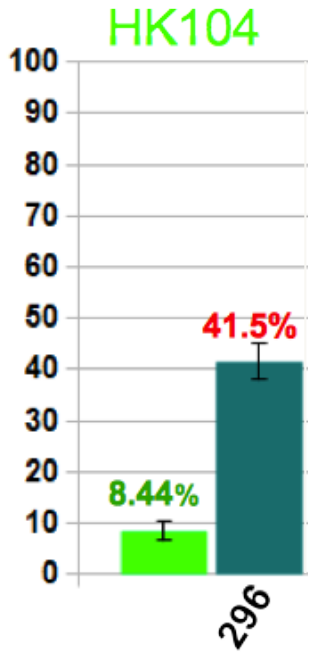
Worm natural collection and phylogeny

K. Kiontke & D. Fitch, NYU
M. Ailion, U. Wash
M. Rockman, NYU
C. Braendle, CNRS-Nice,
and many other samplers

The high mutational variance of P3.p is not due to a highly mutable locus but to mutations in a variety of loci







gcn-1 III L	*cdk-8 I*	*R09F10.3 X*	*III R*	*sfrp-1 IV*
1382 bp deletion	missense	frameshift 16 bp deletion	54 kb deletion	missense
mutant confirmation ✓	✓	✓		✓
translation	transcription Mediator	dystroglycan / Med27 domain	?	Wnt inhibitor

Fabrice Besnard

Trait plasticity versus invariance at different levels of the genotype-phenotype map