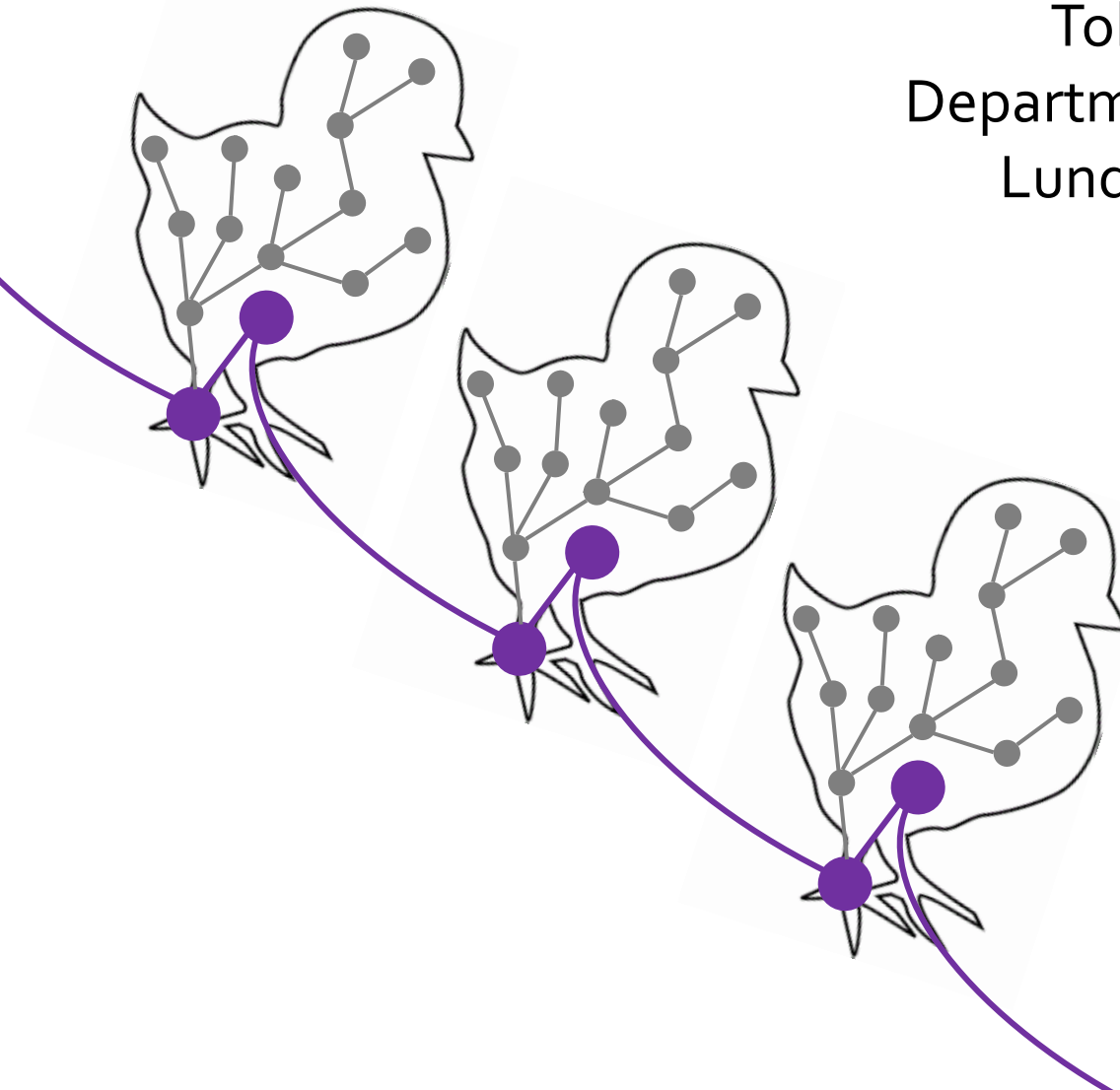


Epigenetics in Ecology and Evolution

Tobias Uller
Department of Biology
Lund University



Today's topics

- What is epigenetics?
- Epigenetics in ecology and evolution
- Developmental plasticity
 - Evolution of polyphenism
 - Long-term effects of early life conditions
- Transgenerational epigenetic inheritance
 - Some examples
 - A bit of theory (about when it is adaptive)
- Population epigenetics

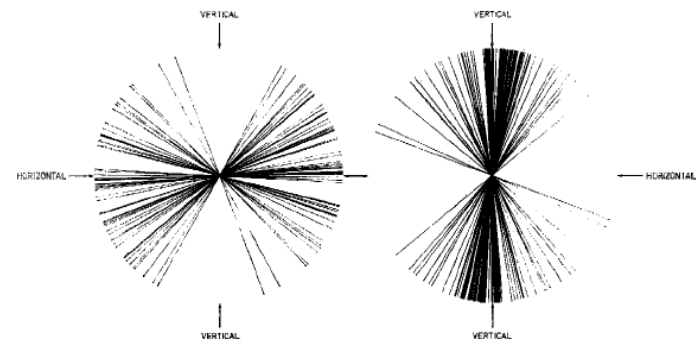
What is epigenetics?



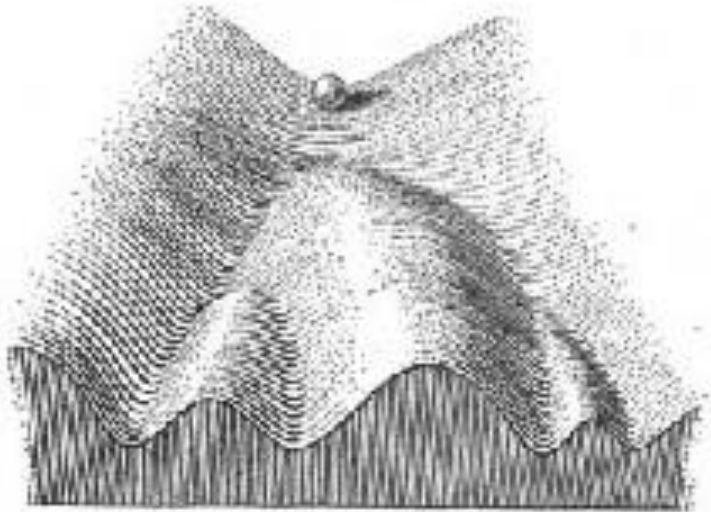


Courtesy of Dag Åhrén



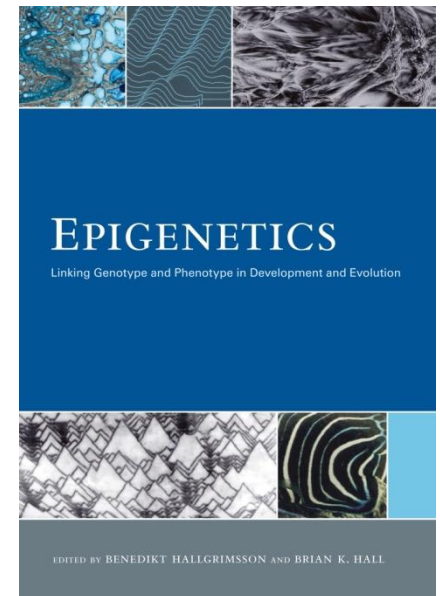
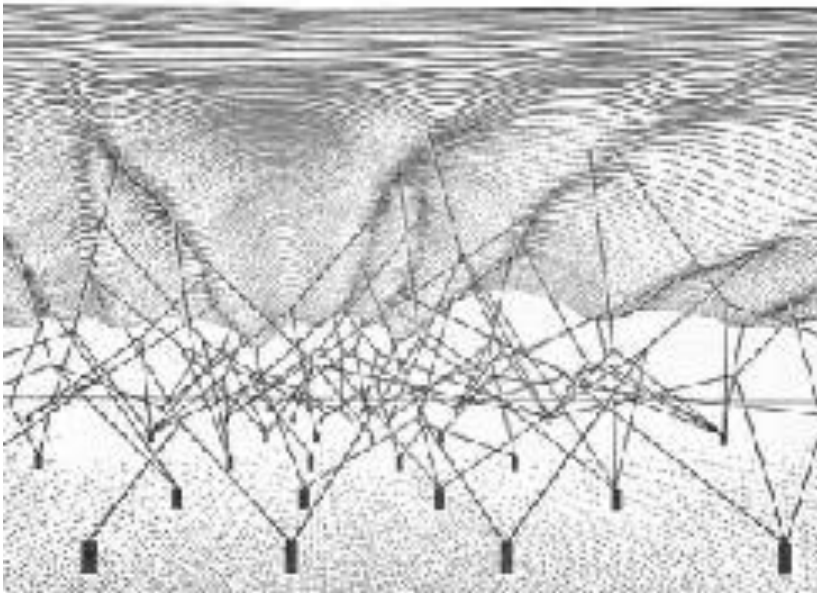


"...the visual cortex may adjust itself during maturation to the nature of its visual experience."



“the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being”

Waddington 1942



Nanney's cellular control systems

Genetic – “a library of specificities”

Epigenetic – “auxiliary mechanisms [...] determining which specificities are to be expressed in any particular cell”

Nanney 1958



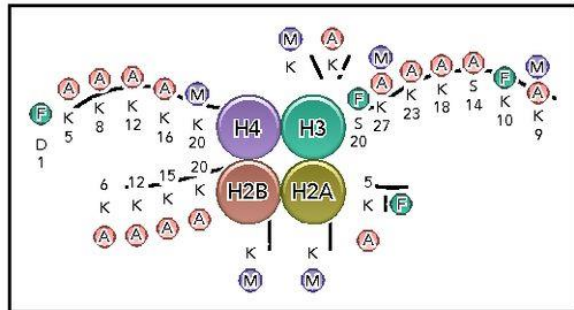
Example of contemporary definition

Epigenetics is “the study of phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression that are not dependent on changes to DNA sequence”

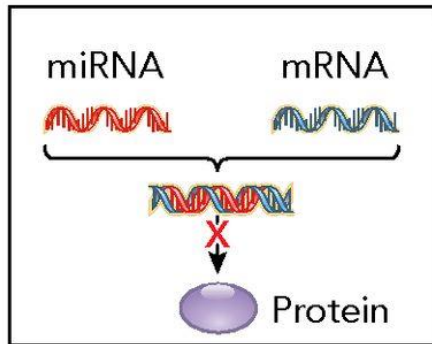
Deans & Maggert 2015

Chromosome {

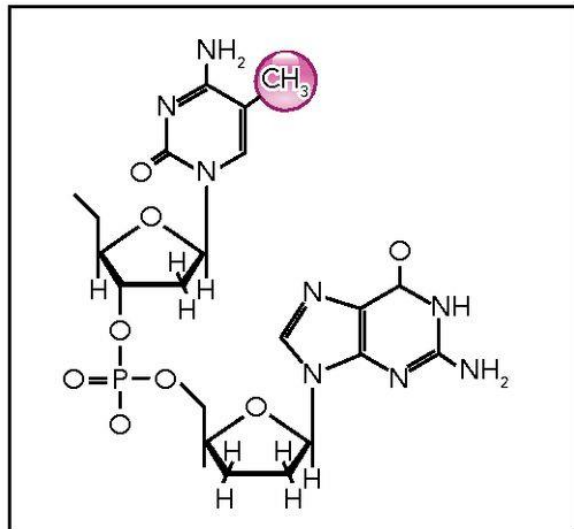
Histone
modification



RNA
interference



DNA
methylation

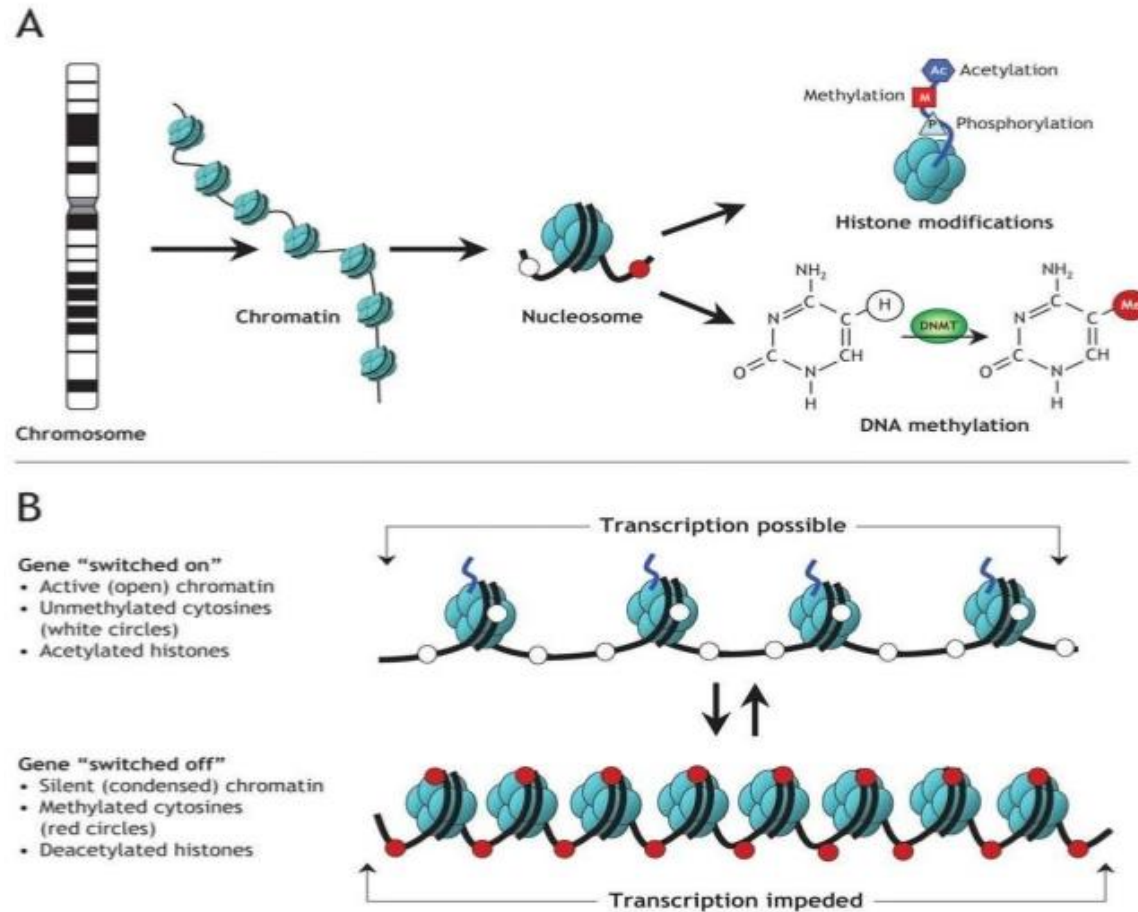


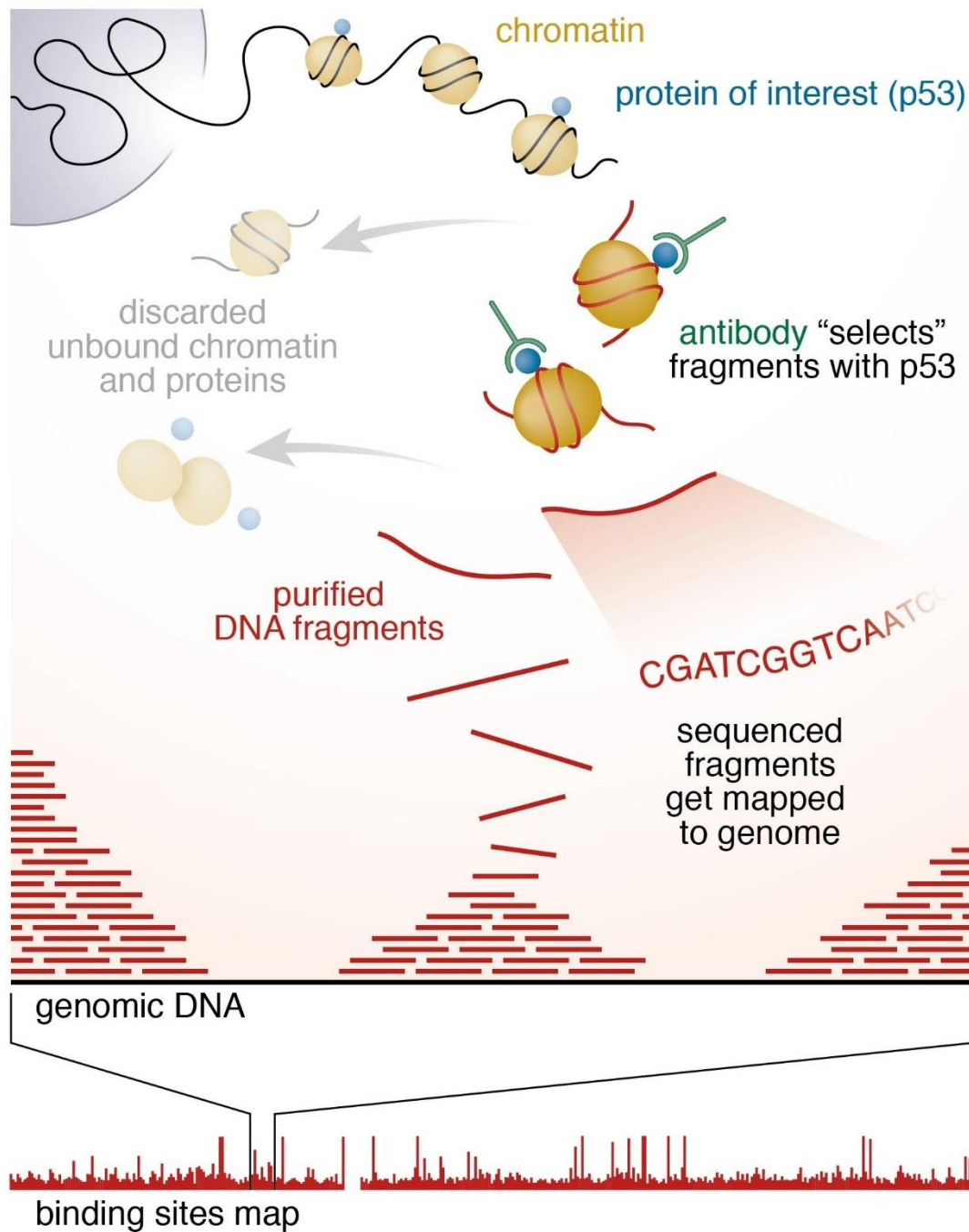
mRNA

Nucleosome



So what do the epigenetic modifications do?



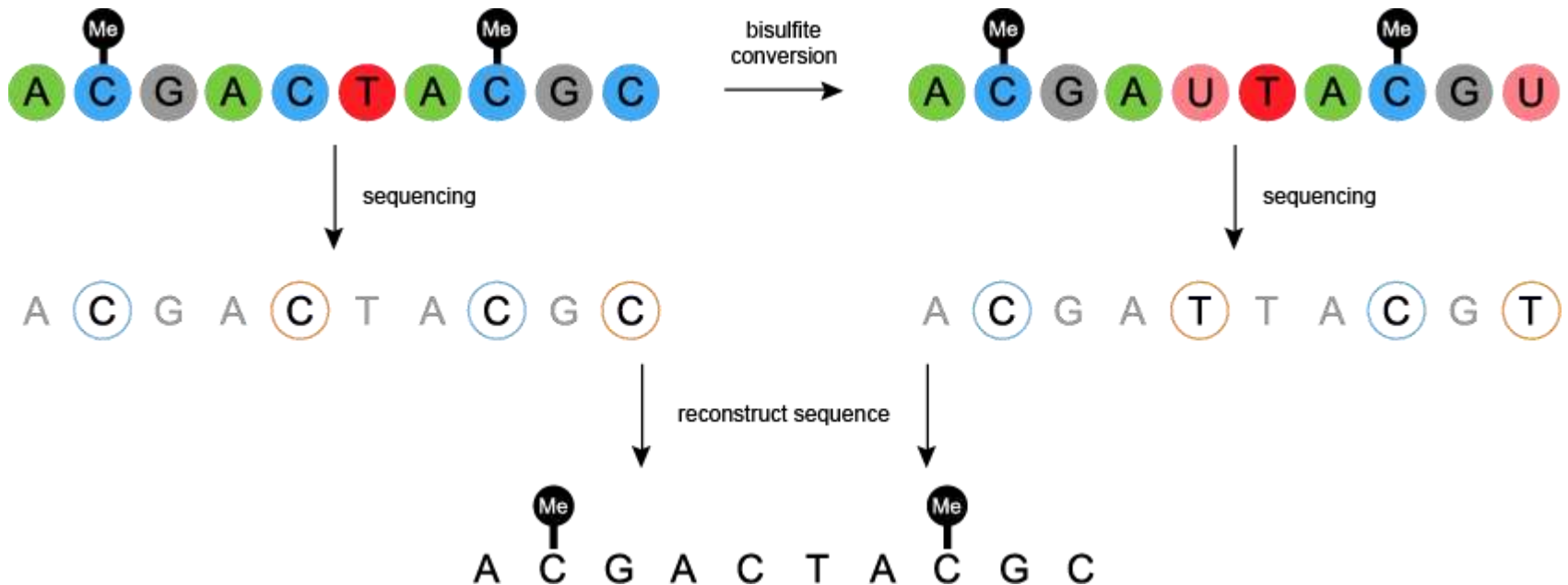


Characterizing histone-DNA interactions

- - ChIPSeq

Characterizing DNA methylation – bisulfite sequencing

- Whole Genome Bisulfite Sequencing
- Reduced Representation Bisulfite Sequencing
- Bisulfite RADseq



Epigenetics in ecology & evolution

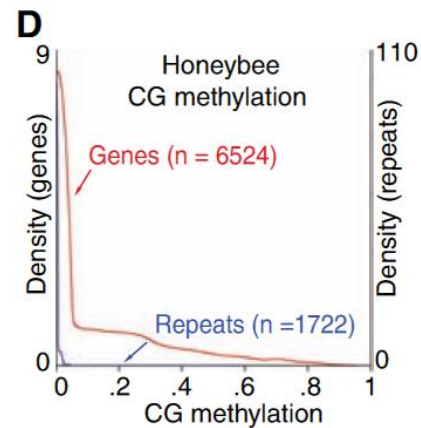
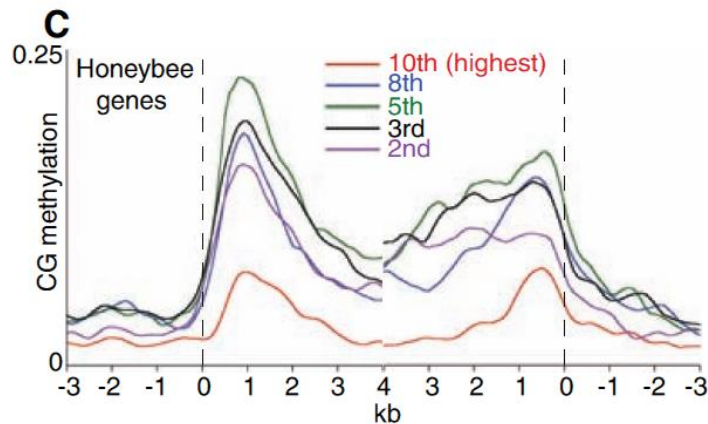
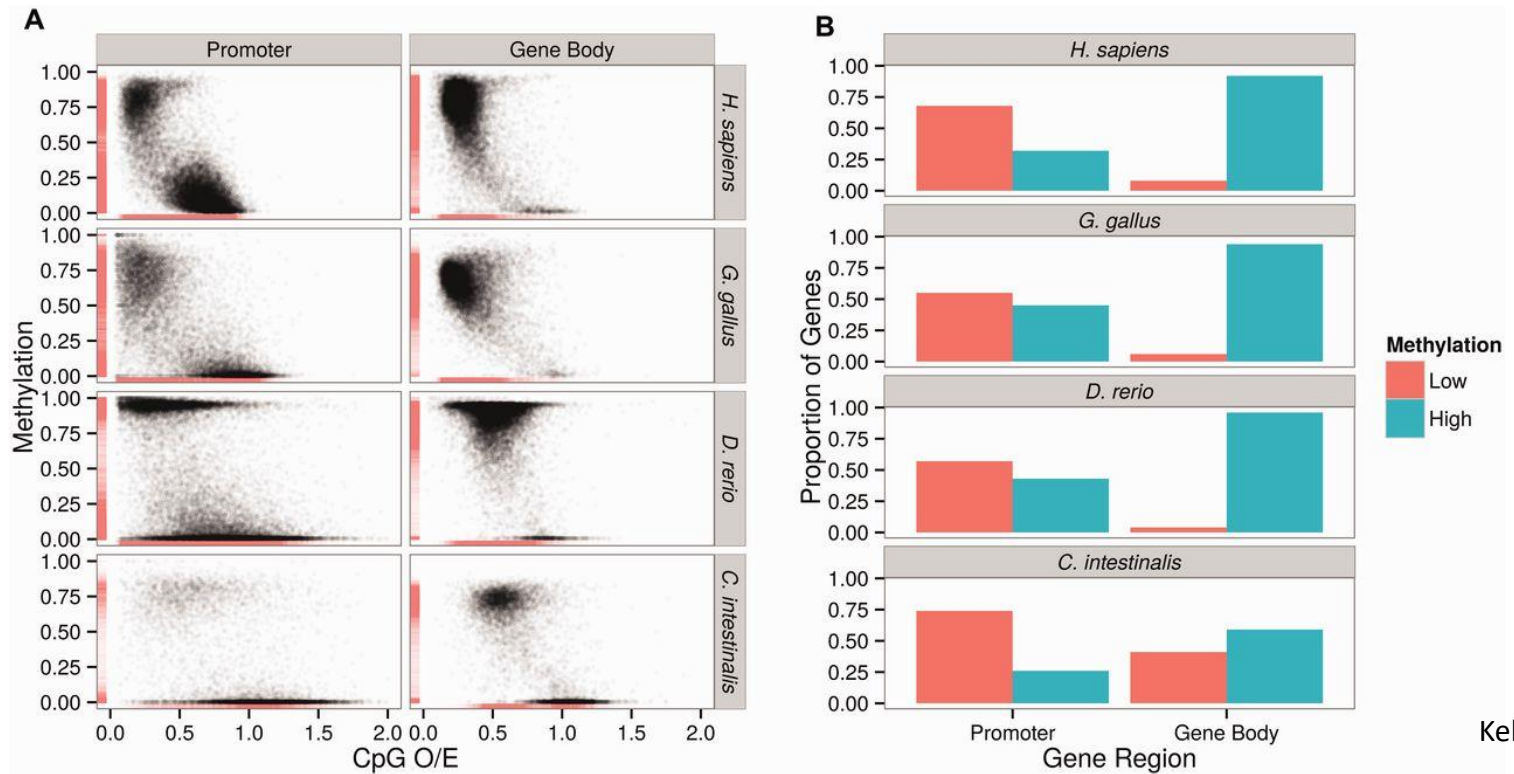


Object – ask questions about its properties

Tool – use it to improve performance on a task

Scaffold – use it to get a different vantage point

Differences in DNA methylation patterns in vertebrates and invertebrates

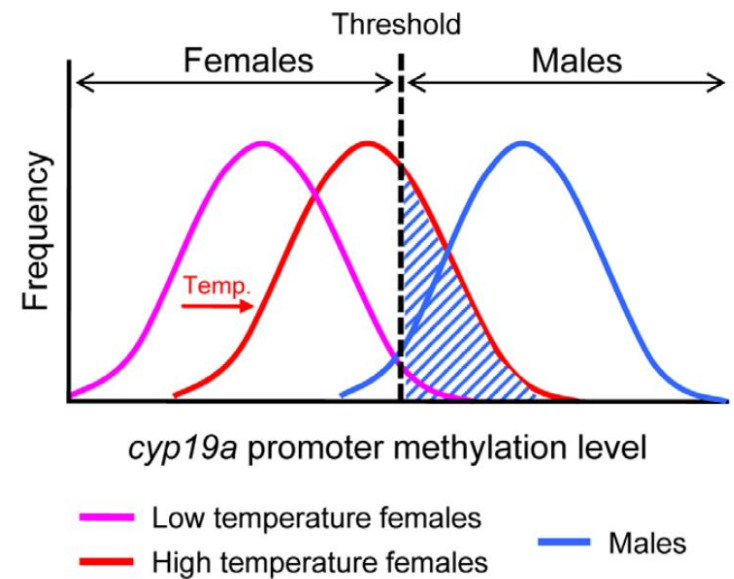
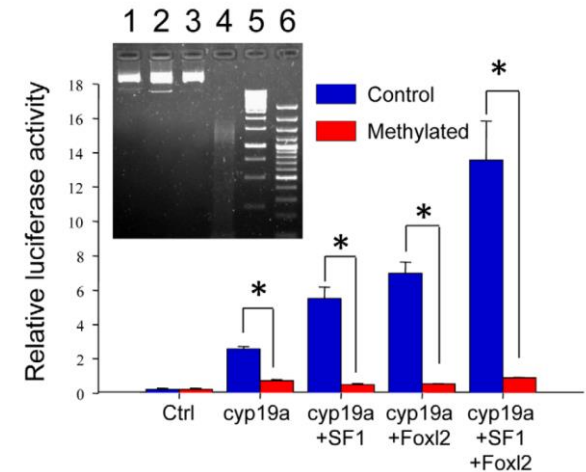
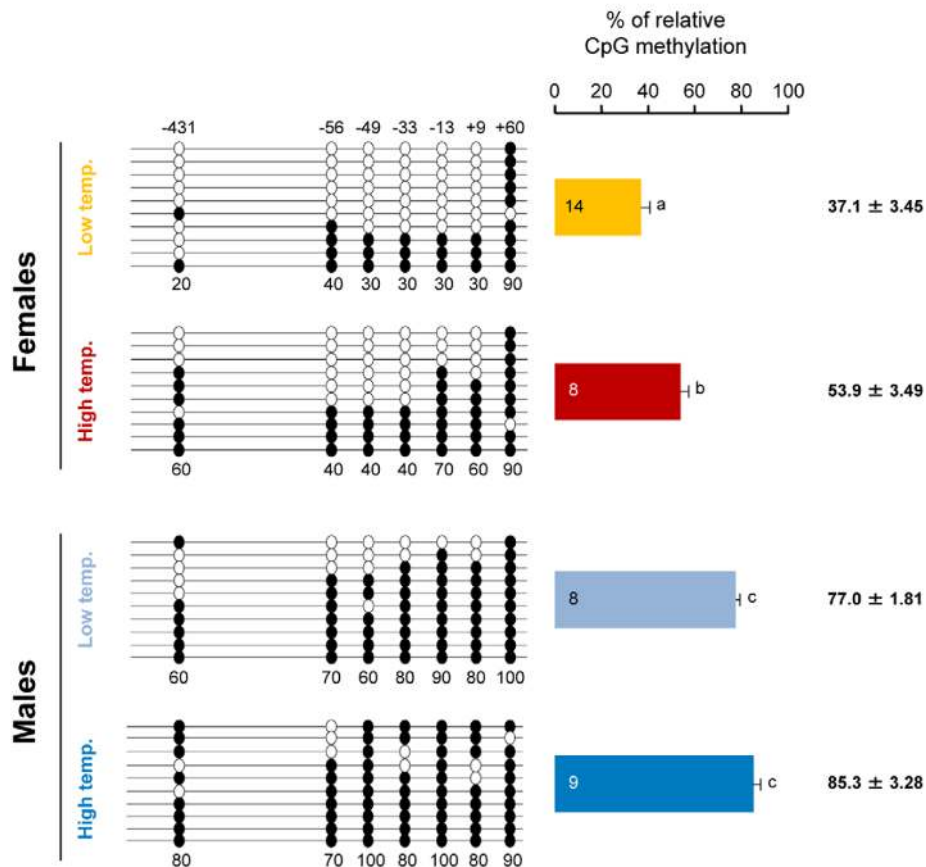


Zemach et al. 2010

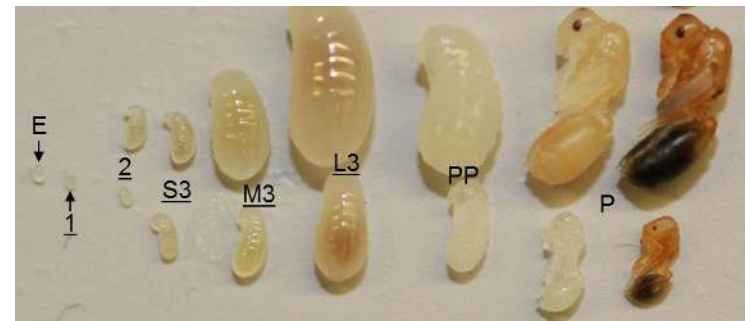
Developmental plasticity



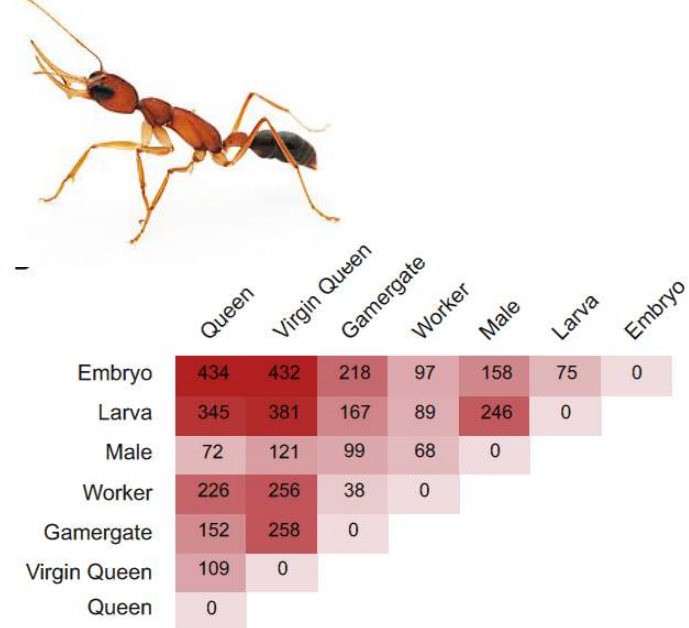
cyp19a methylation and sex determination in sea bass





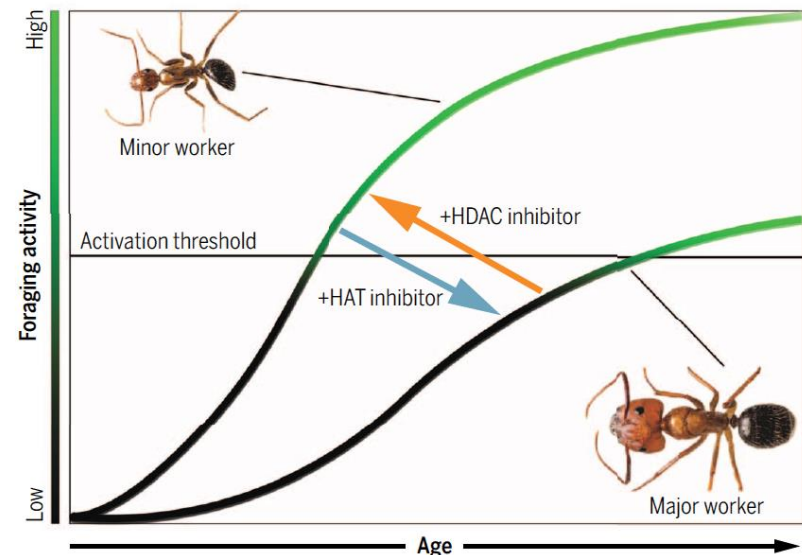
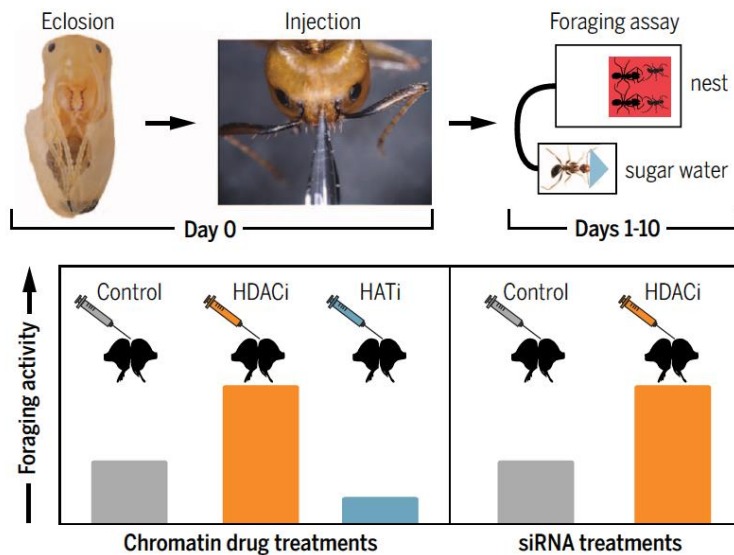


Methylation may drive caste differentiation in ants....

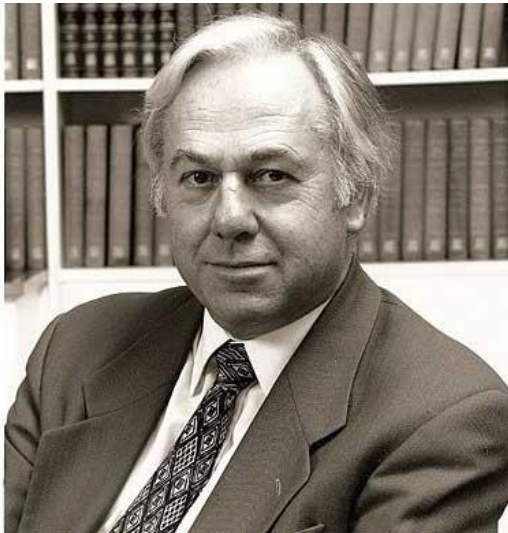


Bonasio et al. 2012. Curr Biol

... or maybe histone modifications... (behavioural differences)

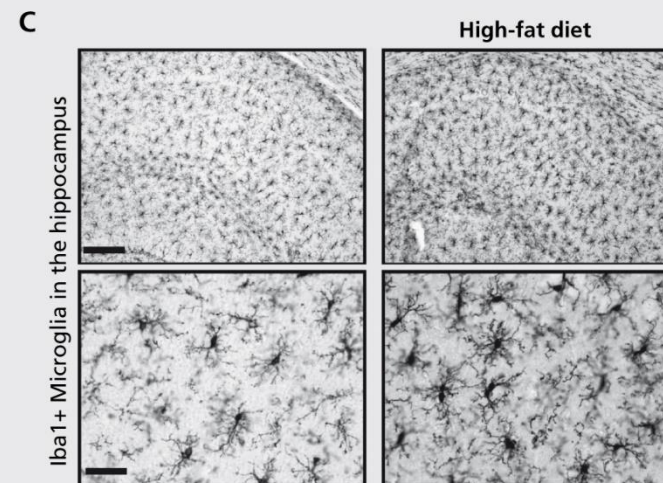
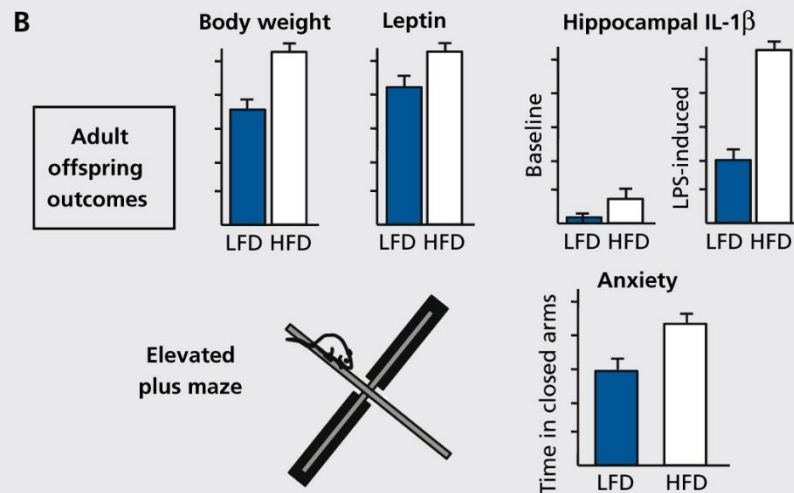
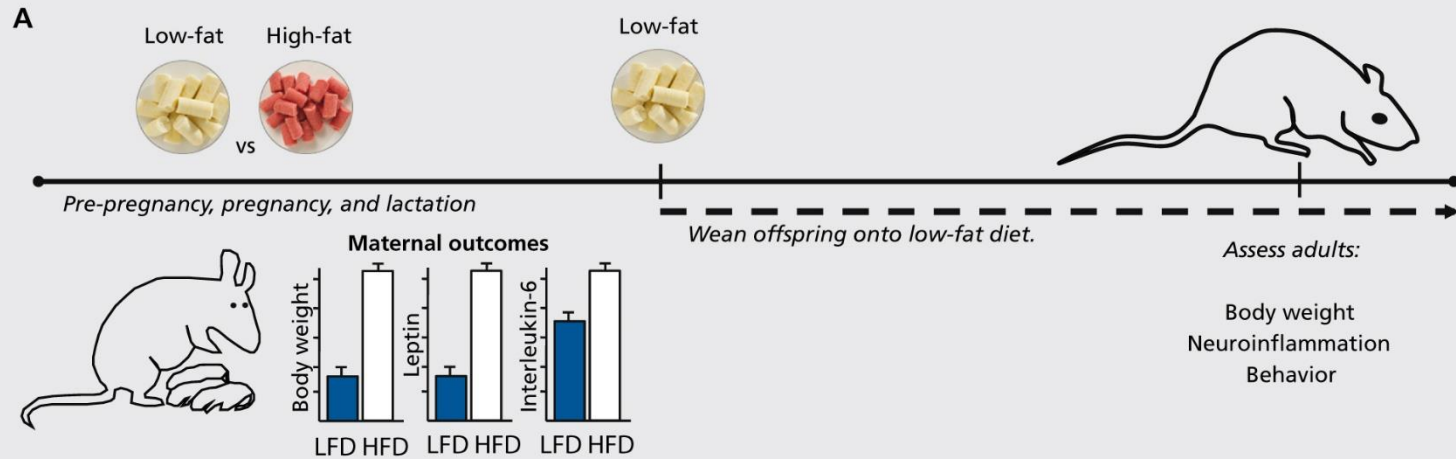


Simola et al. 2016. Science

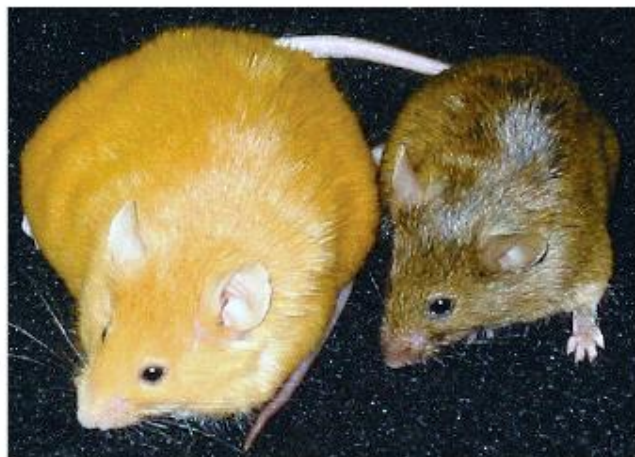


The Barker Hypothesis

“Recent findings suggest that human fetuses adapt to a limited supply of nutrients and in doing so permanently change their physiology and metabolisms. These “programmed” changes may be the origins of disease in later life, including coronary heart disease and the related disorders stroke, diabetes, and hypertension”



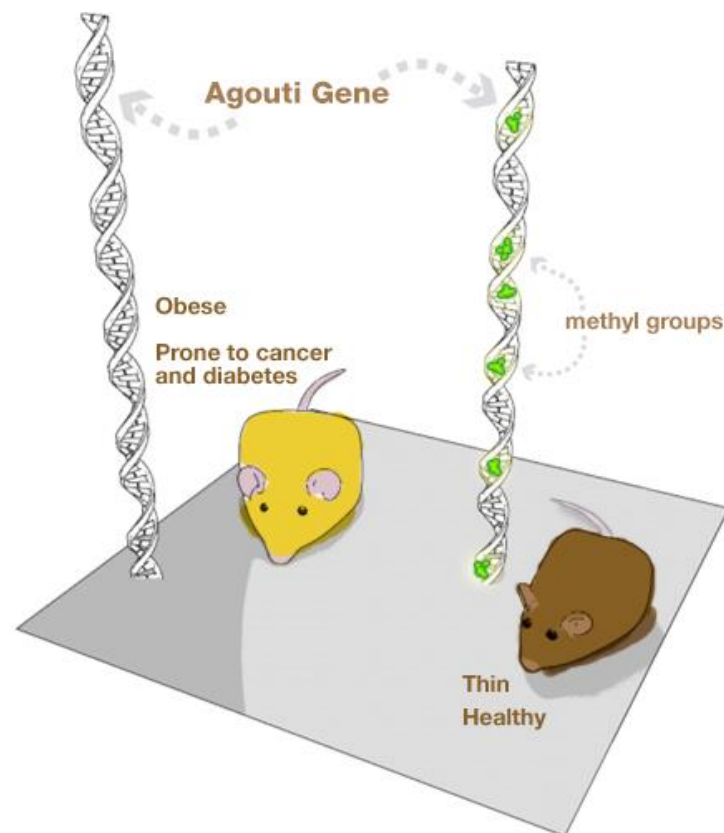
These Two Mice are Genetically Identical and the Same Age



While pregnant, both of their mothers were fed Bisphenol A (BPA) but DIFFERENT DIETS:

The mother of this mouse received a **normal mouse diet**

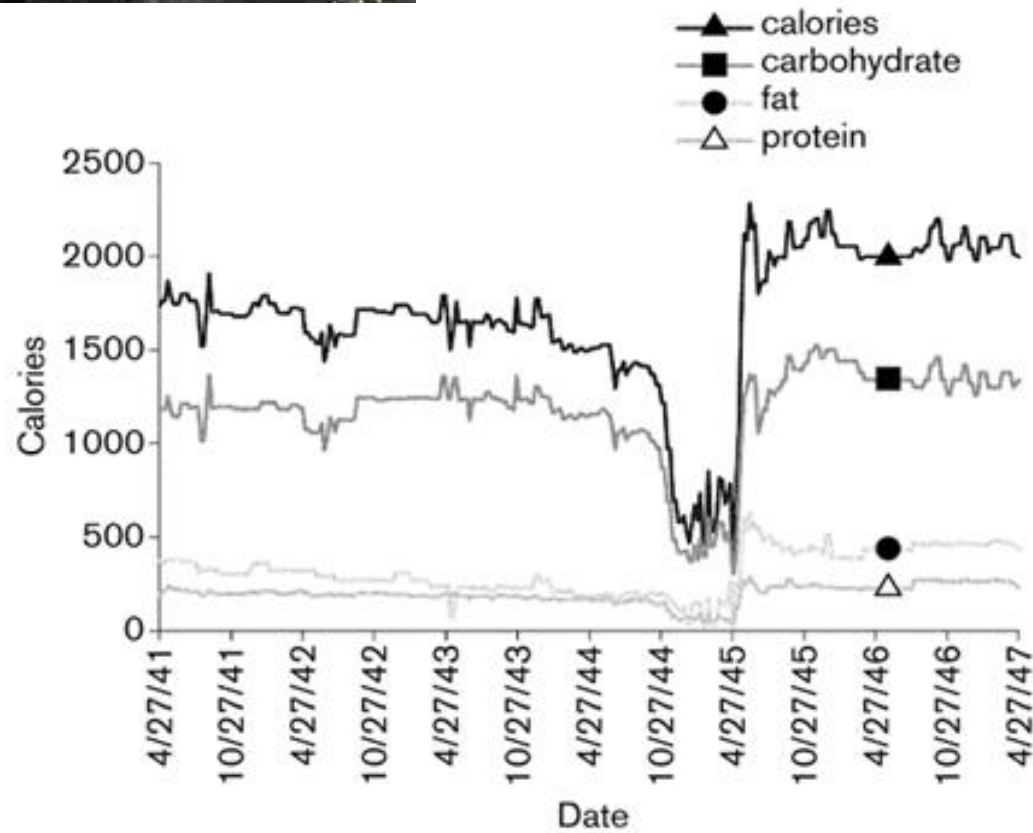
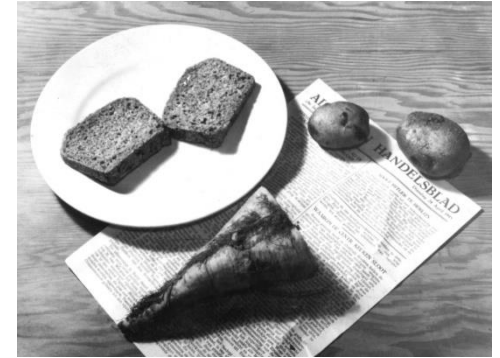
The mother of this mouse received a diet **supplemented** with choline, folic acid, betaine and vitamin B12

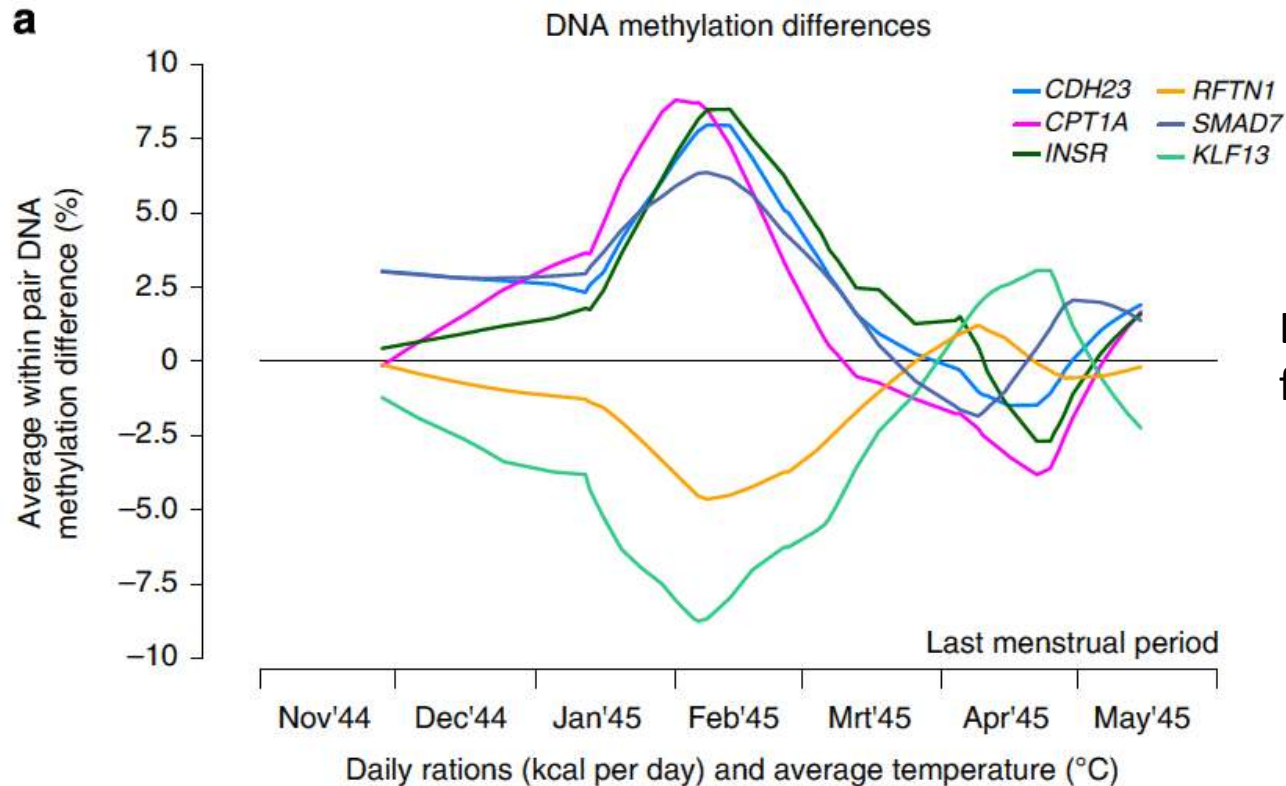


Supplement $\xrightarrow{\beta=0.19 \text{ (} p=0.008 \text{)}} \text{Coat Color}$

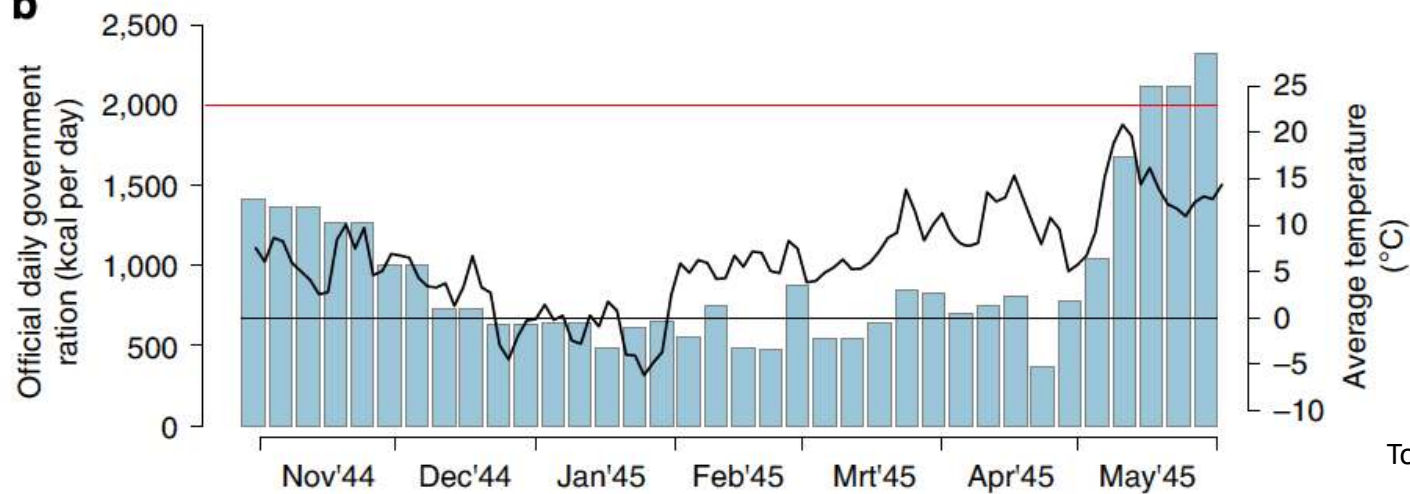
$\beta=0.36 \text{ (} p=0.005 \text{)}$ $\nearrow$ **A^{VY} Methylation** $\searrow$ $\beta=0.41 \text{ (} p=0.001 \text{)}$
 Supplement $\xrightarrow{\text{X}} \text{Coat Color}$
 $\beta=0.04 \text{ (} p=0.49 \text{)}$

The Dutch Hunger Winter cohort

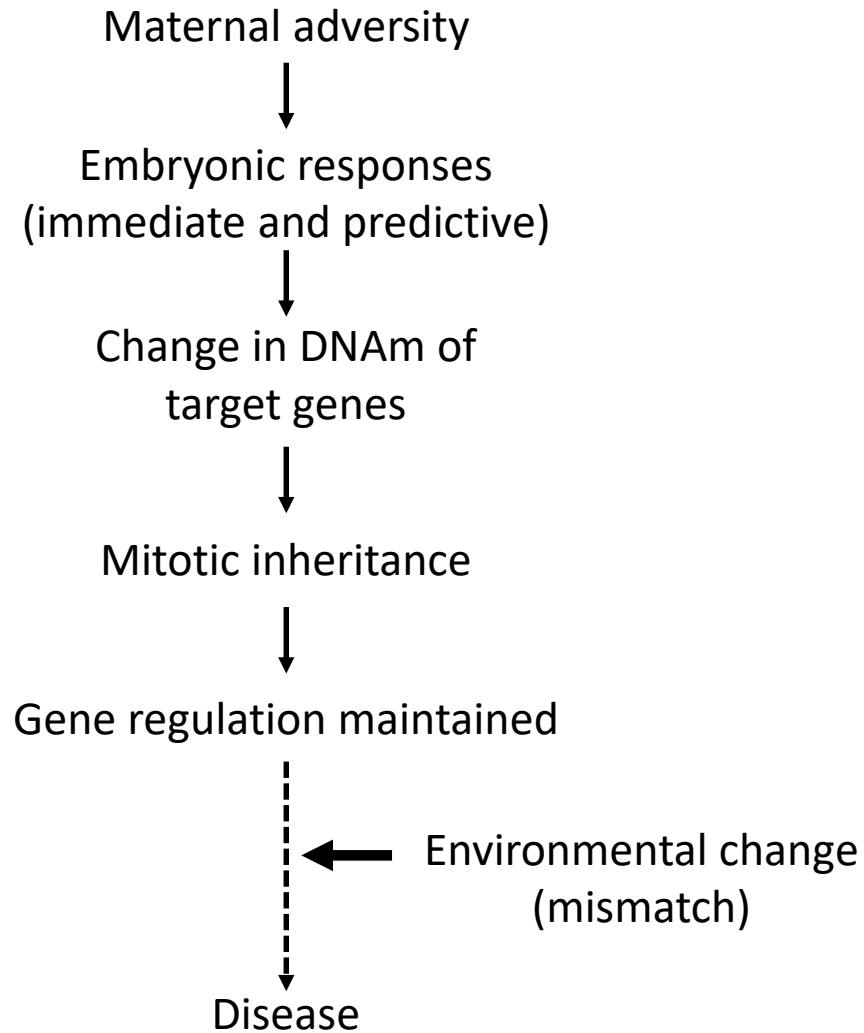


a

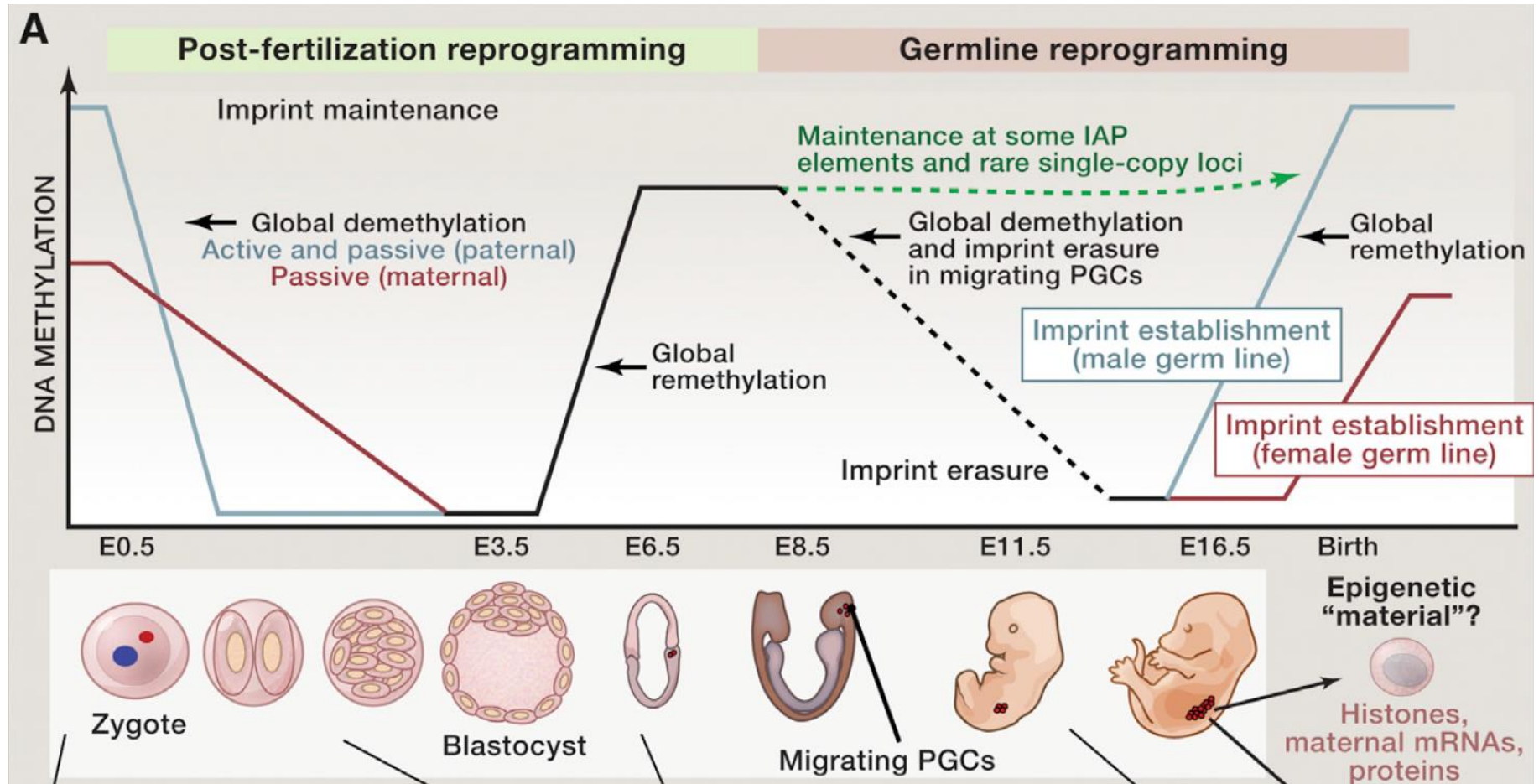
Largest difference for first trimester exposure

b

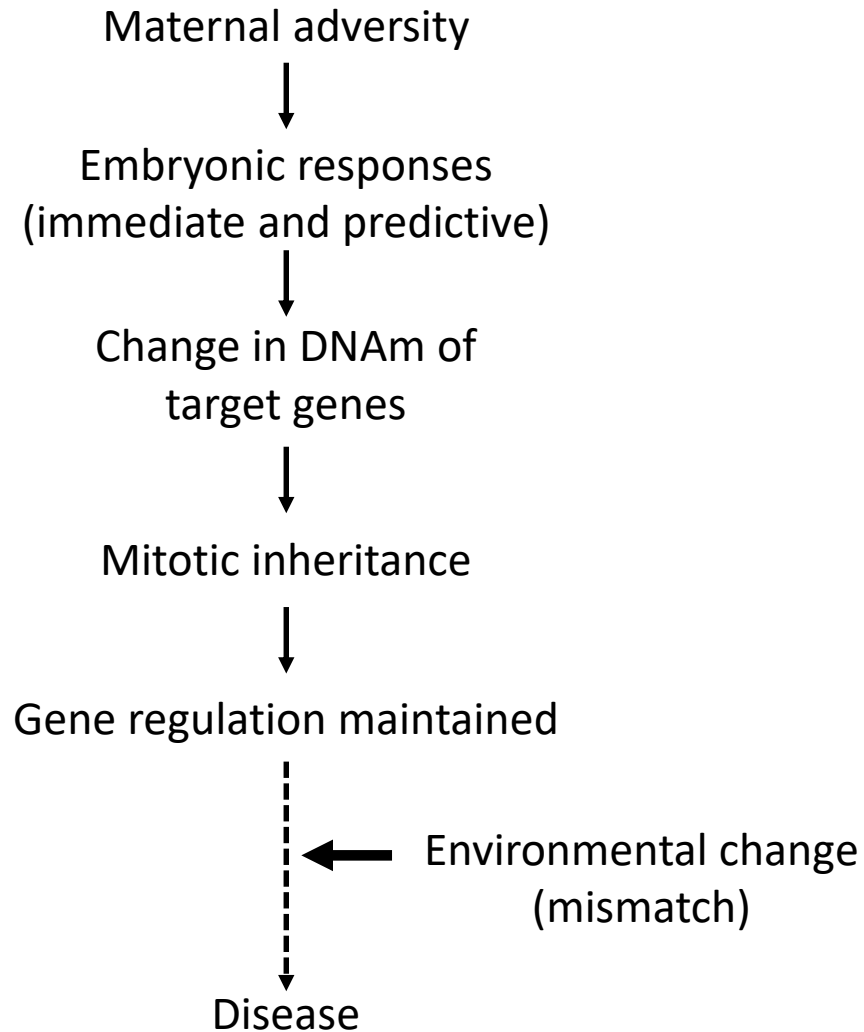
Adaptive plasticity



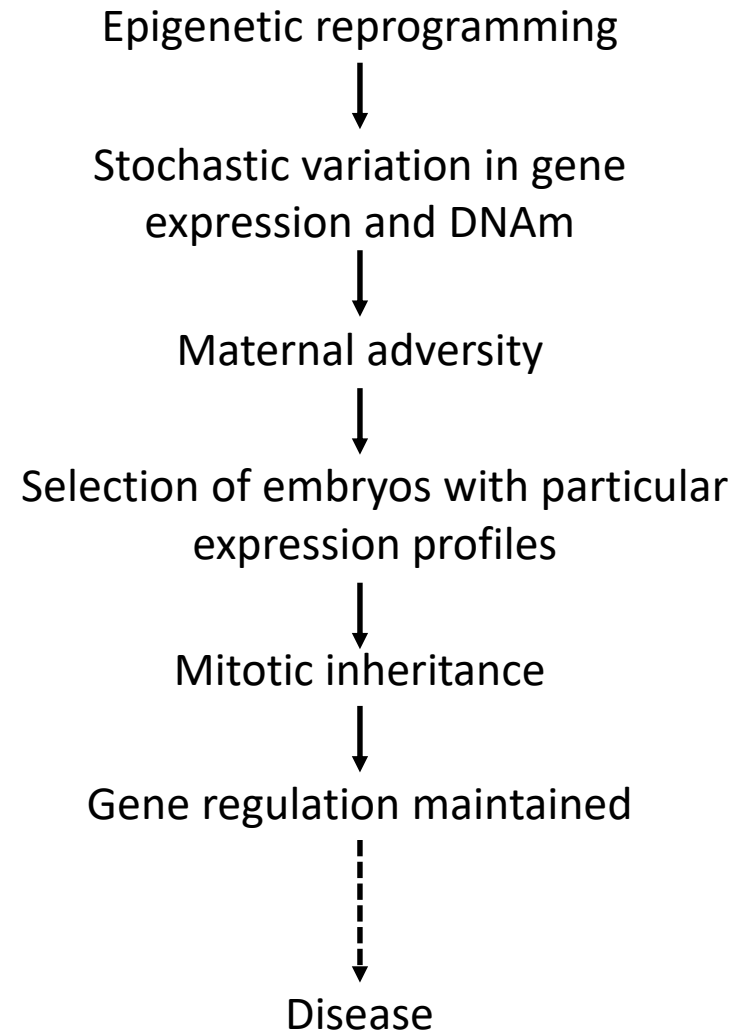
Epigenetic reprogramming in mammals – twice



Adaptive plasticity

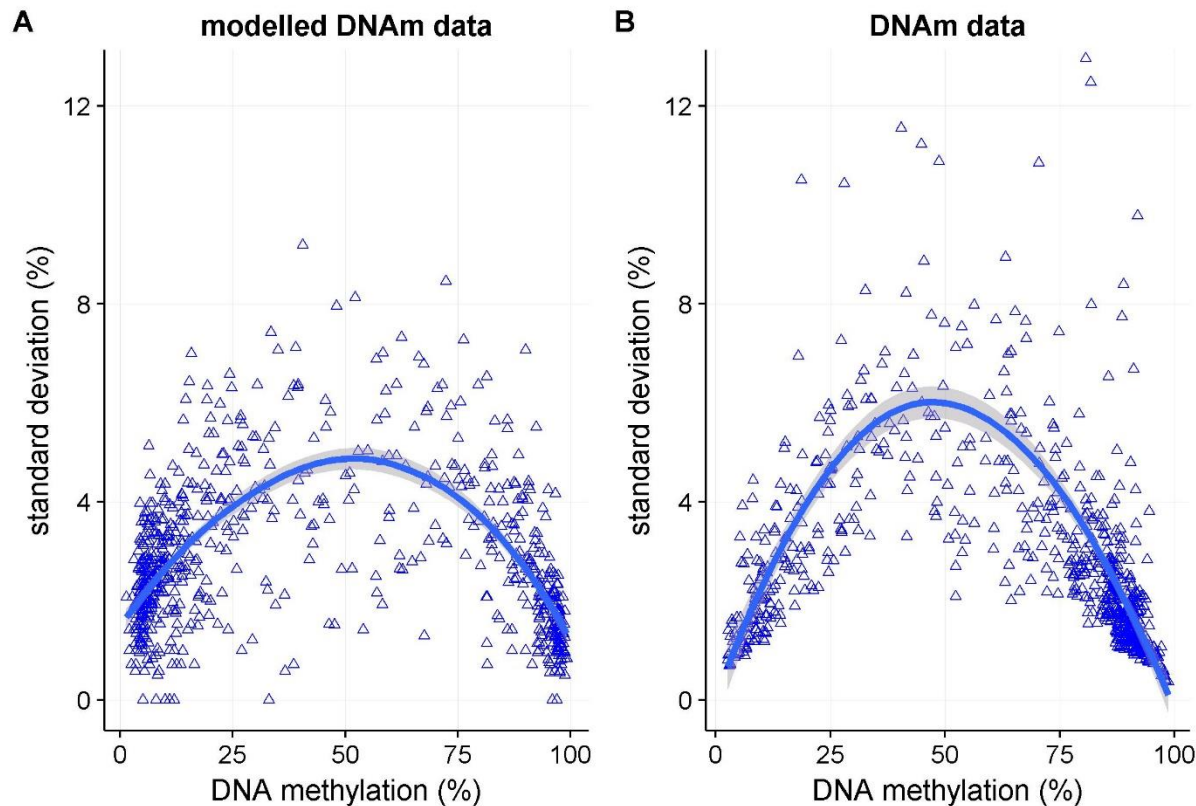


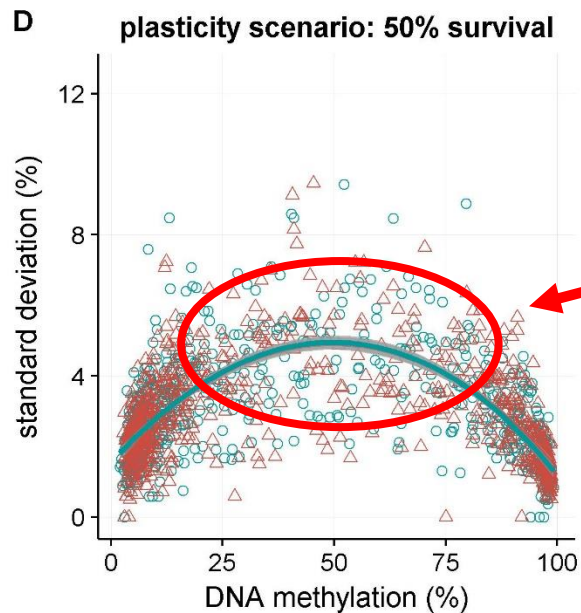
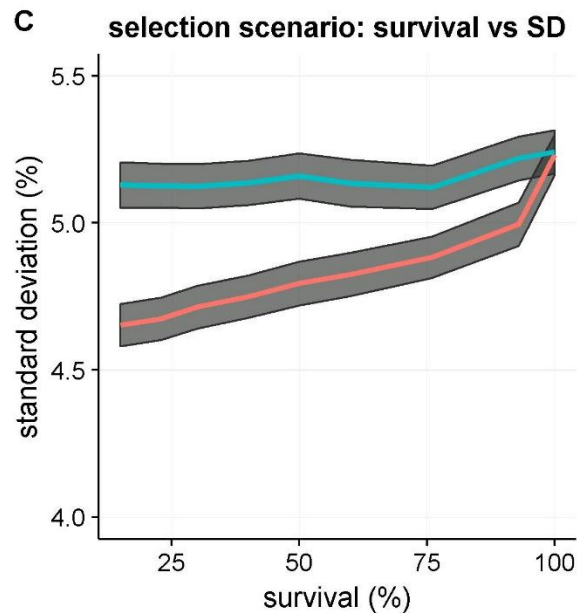
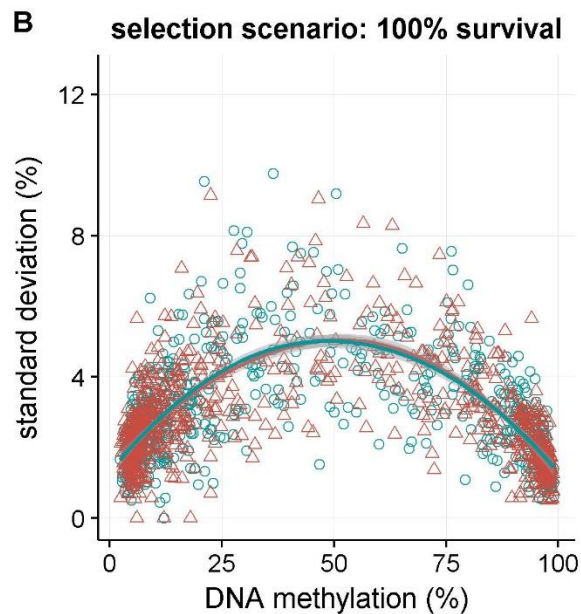
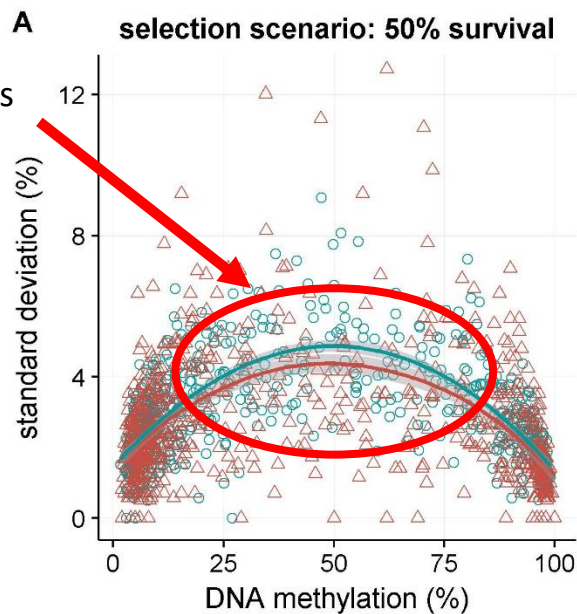
Epigenetic selection



Mechanistic modelling of epigenetic reprogramming

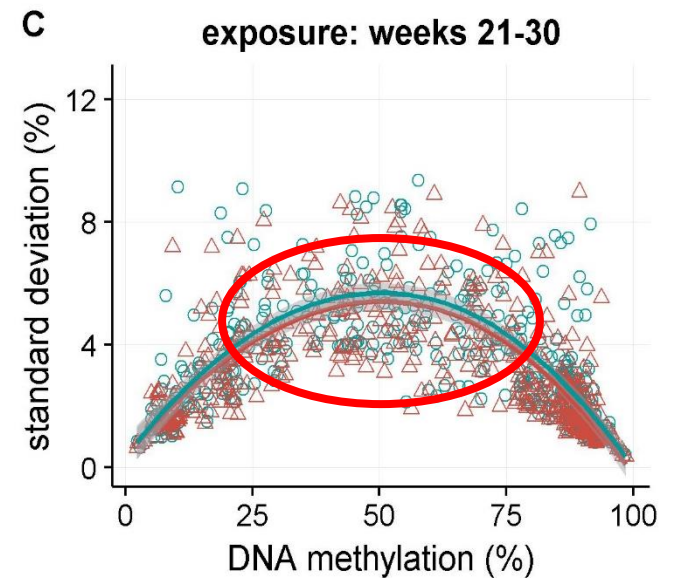
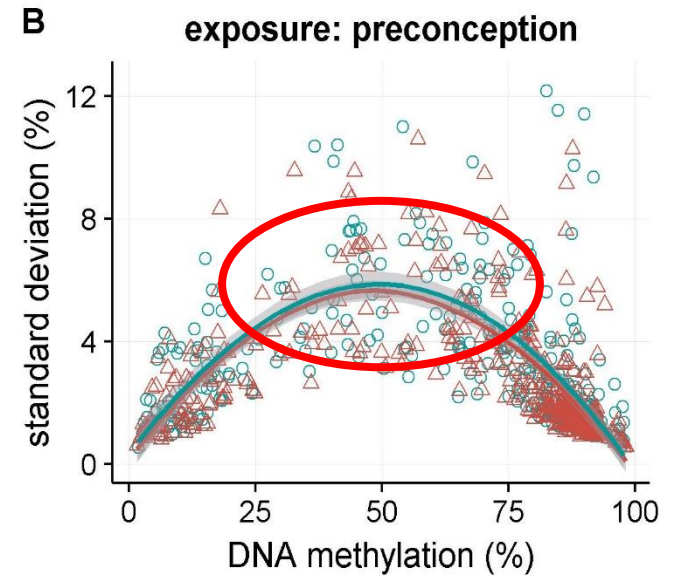
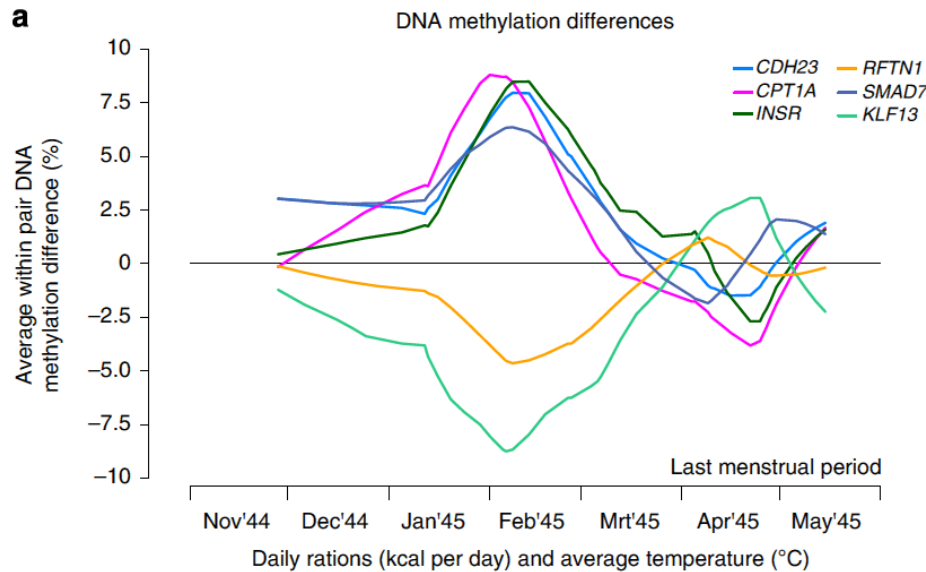
- Interaction between TF and DNAm
- Allowing for environmental effects





exposed control

Empirical pattern of DNA methylation in the Dutch Hunger Winter Cohort suggest that epigenetic selection has taken place



exposed control



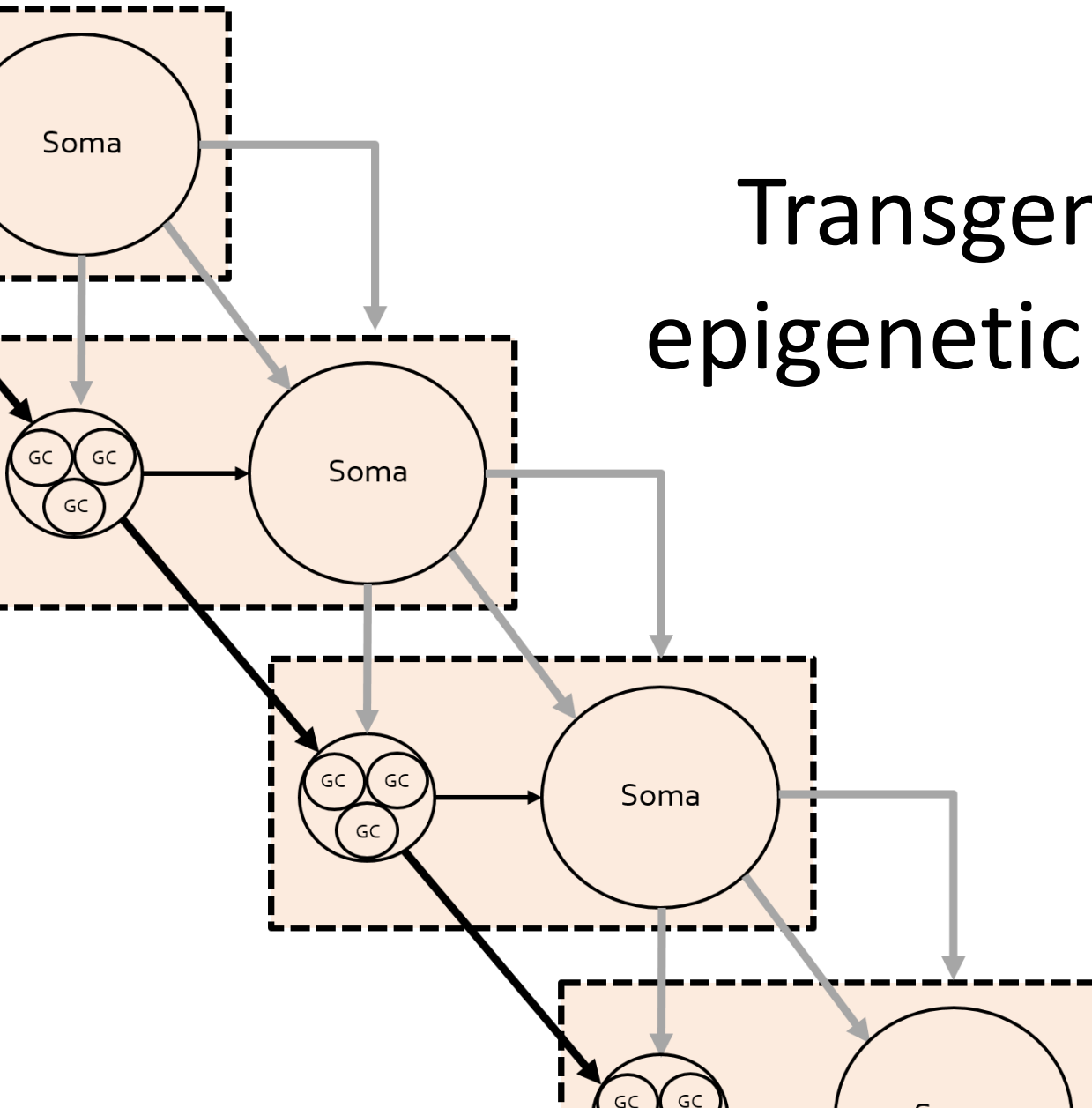
Don't blame the mothers

Careless discussion of epigenetic research on how early life affects health across generations could harm women, warn **Sarah S. Richardson** and colleagues.

Causation matters for scientific, medical, and legal reasons....



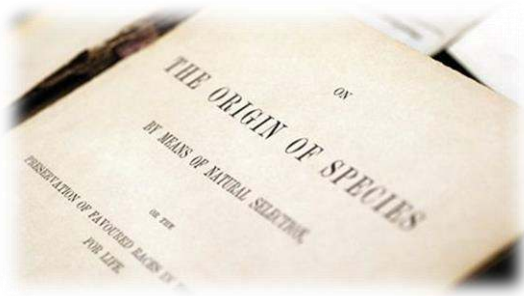
Transgenerational epigenetic inheritance



"These laws, taken in the largest sense, being Growth with Reproduction; Inheritance which is almost implied by reproduction; Variability from the indirect and direct action of the external conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a Struggle for Life, and as a consequence Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms."

Darwin 1859

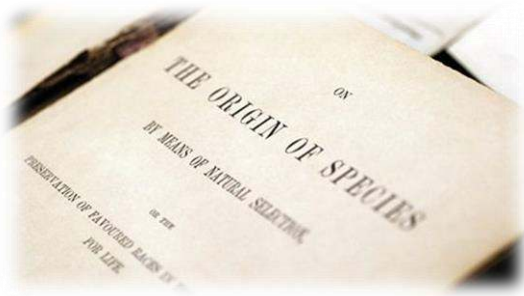
THE ORIGIN OF SPECIES
BY MEANS OF NATURAL SELECTION
AS THE
CAUSE OF THE



"These laws, taken in the largest sense, being Growth with Reproduction; Inheritance which is almost implied by reproduction; Variability from the indirect and direct action of the external conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a Struggle for Life, and as a consequence Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms."

Darwin 1859

The Principles of Evolution by Natural Selection



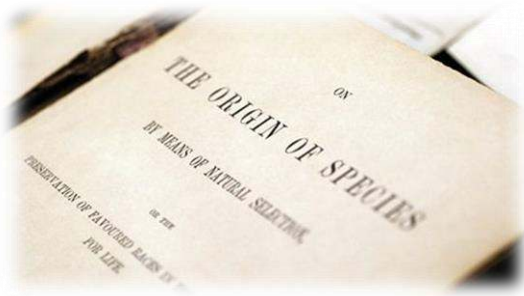
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Darwin 1859

The Principles of Evolution by Natural Selection



Variation in traits among members of a species



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Darwin 1859

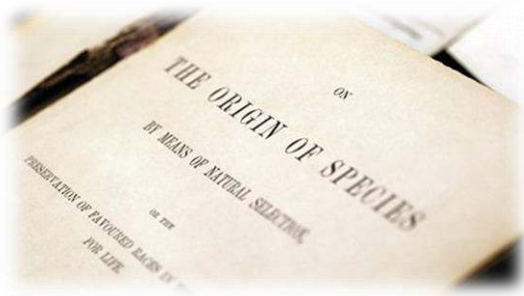
The Principles of Evolution by Natural Selection



Variation in traits among members of a species



Different variants leave different numbers of offspring



"These laws, taken in the largest sense, being **Growth with Reproduction**; Inheritance which is almost implied by reproduction; **Variability from the indirect and direct action of the external conditions of life, and from use and disuse**; **a Ratio of Increase so high as to lead to a Struggle for Life**, and as a consequence Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms."

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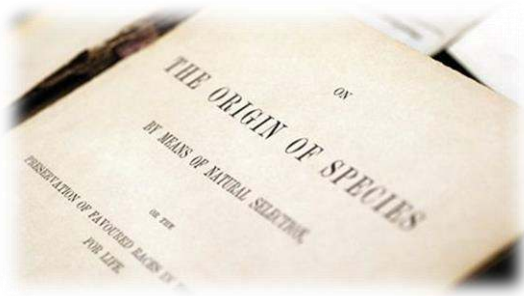
Variation in traits among members of a species



Different variants leave different numbers of offspring



Variation is heritable, so that offspring resemble their parents



"These laws, taken in the largest sense, being **Growth with Reproduction**; **Inheritance which is almost implied by reproduction**; **Variability from the indirect and direct action of the external conditions of life, and from use and disuse**; **a Ratio of Increase so high as to lead to a Struggle for Life**, and as a consequence Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms."

Darwin 1859

The Principles of Evolution by Natural Selection



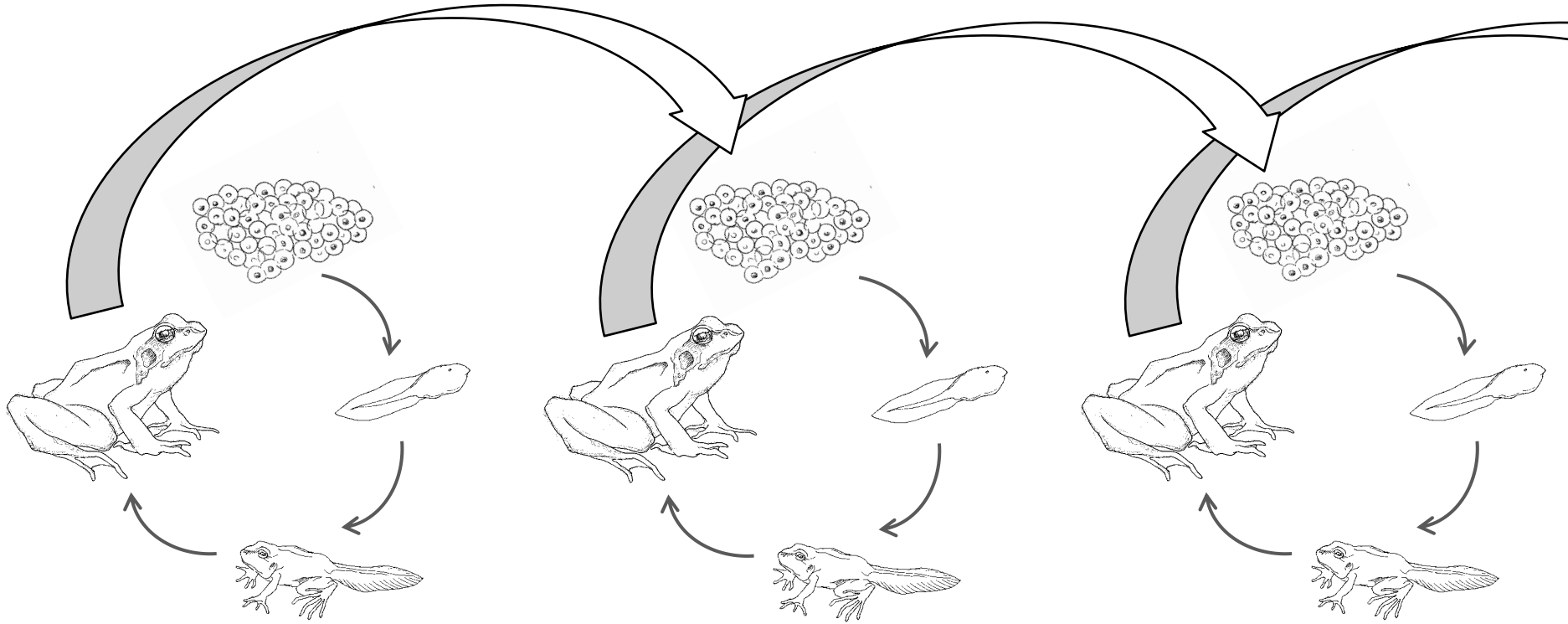
Variation in traits among members of a species



Different variants leave different numbers of offspring



Variation is heritable, so that offspring resemble their parents



"Heredity is not a peculiar or unique principle for it is only similarity of growth and differentiation in successive generations.... The causes of heredity are thus reduced to the causes of successive differentiation of development, and the mechanisms of heredity are merely the mechanisms of differentiation."

Conklin 1908. Science

"We have come to look upon the problem of heredity as identical with the problem of development."

Morgan 1910. Am Nat



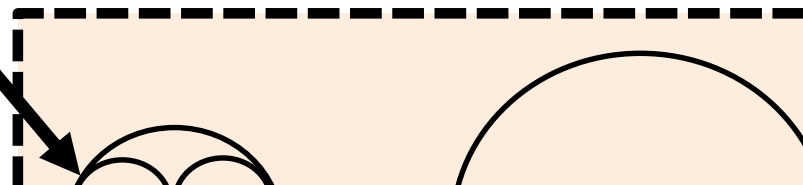
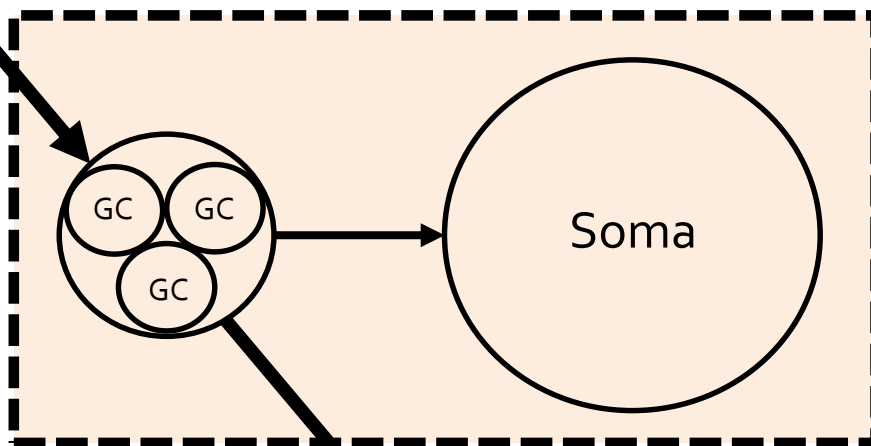
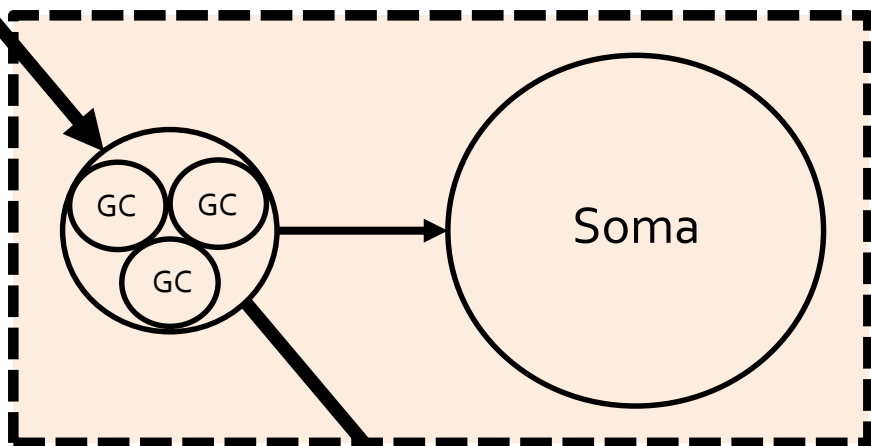
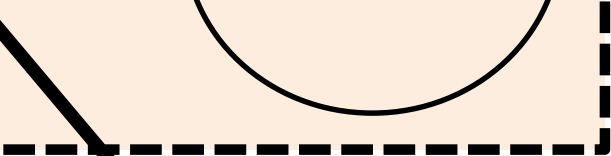
T.H. Morgan

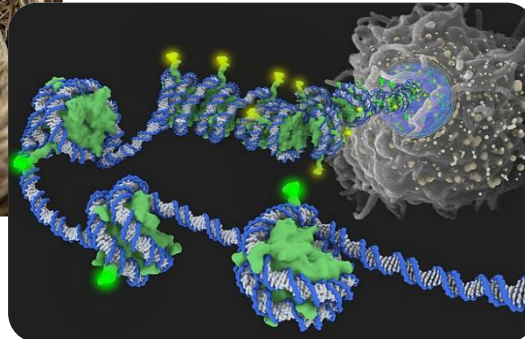
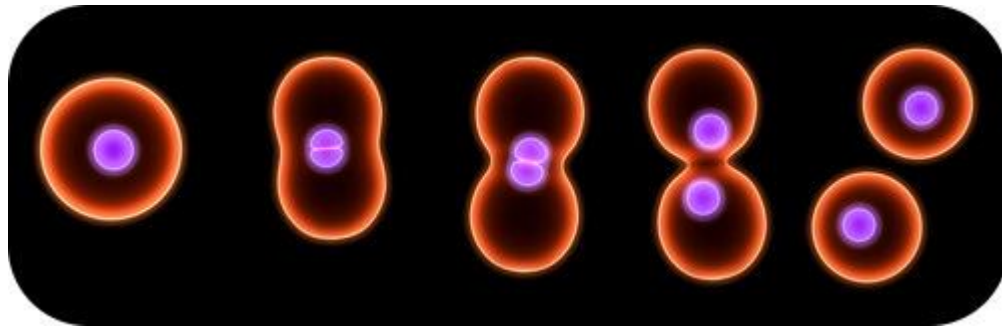


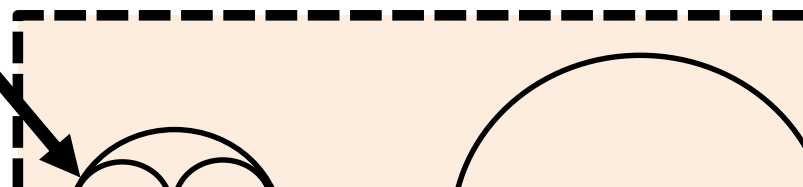
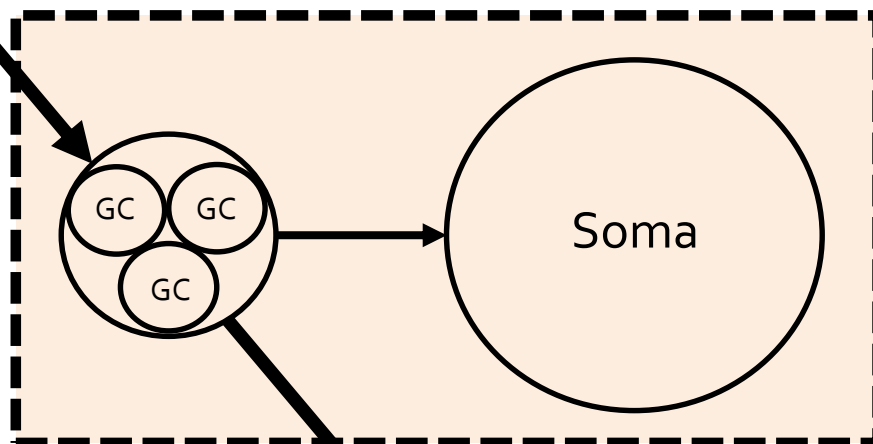
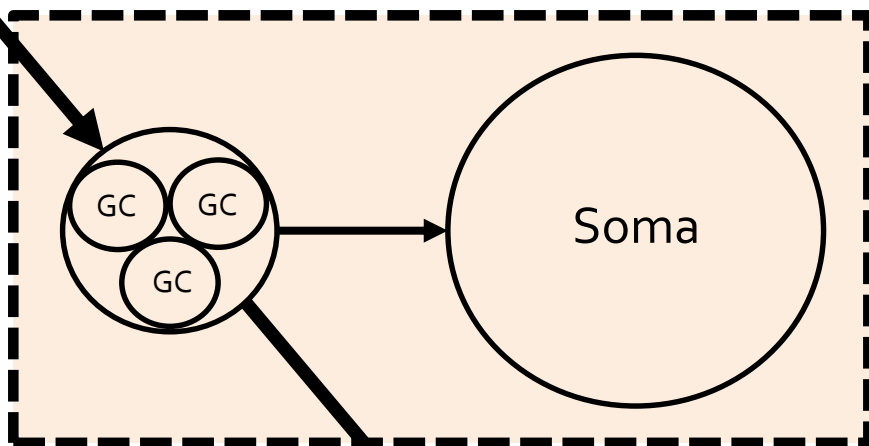
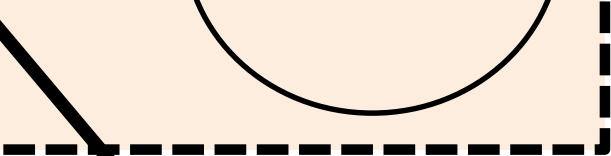
Calvin Bridges in the Fly Room, ca 1926

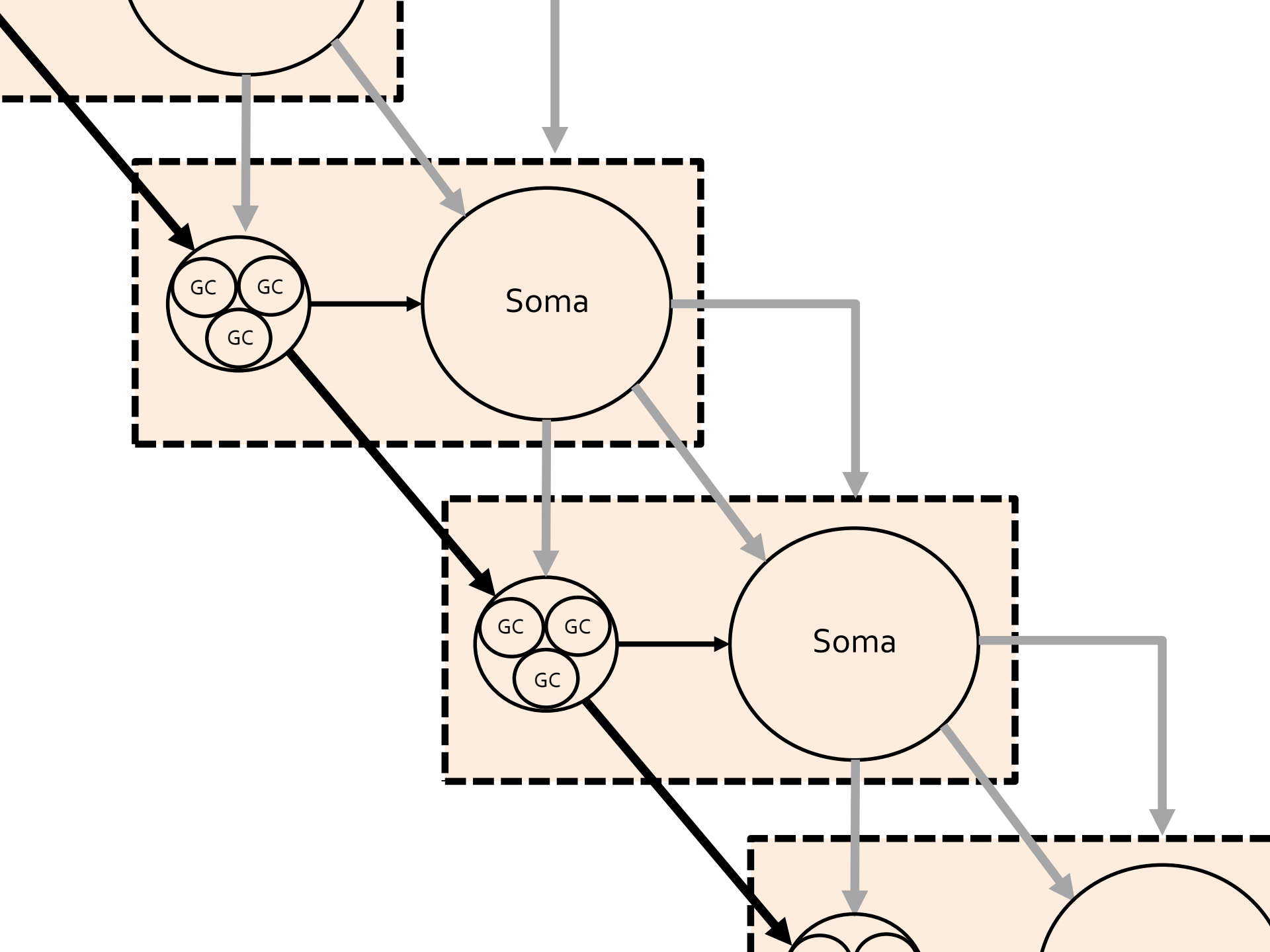
"....we may say that a particular factor (p) is the cause of pink [eye colour], for we use cause here in the sense in which science always uses this expression, namely, to mean that a particular system differs from another system only in one special factor.... Although Mendel's law does not explain the phenomena of development, and does not pretend to explain them, it stands as a scientific explanation of heredity, because it fulfils all of the requirements of any causal explanation."

Morgan et al. 1915. The mechanisms of Mendelian heredity



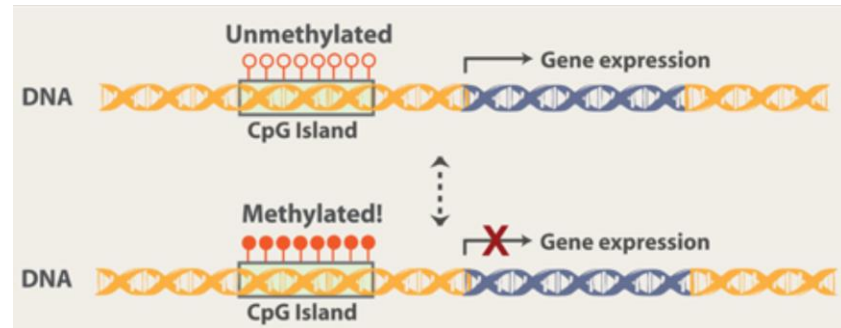




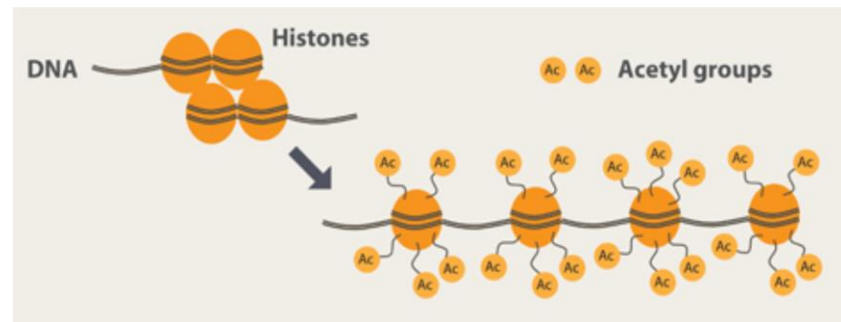


How do epigenetic mechanisms fit?

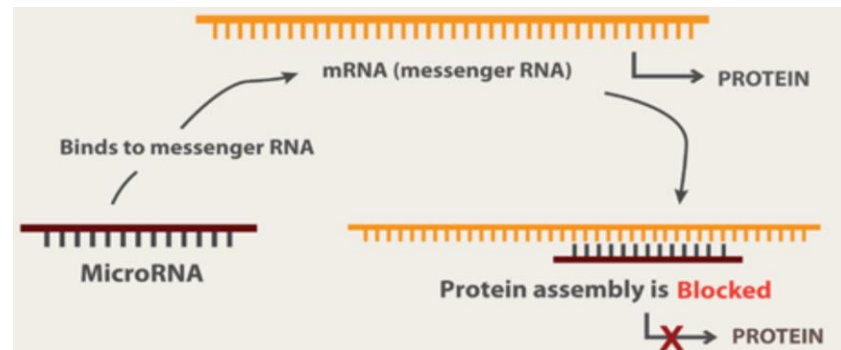
- **DNA methylation**



- **Histone modification**



- **MicroRNA action**

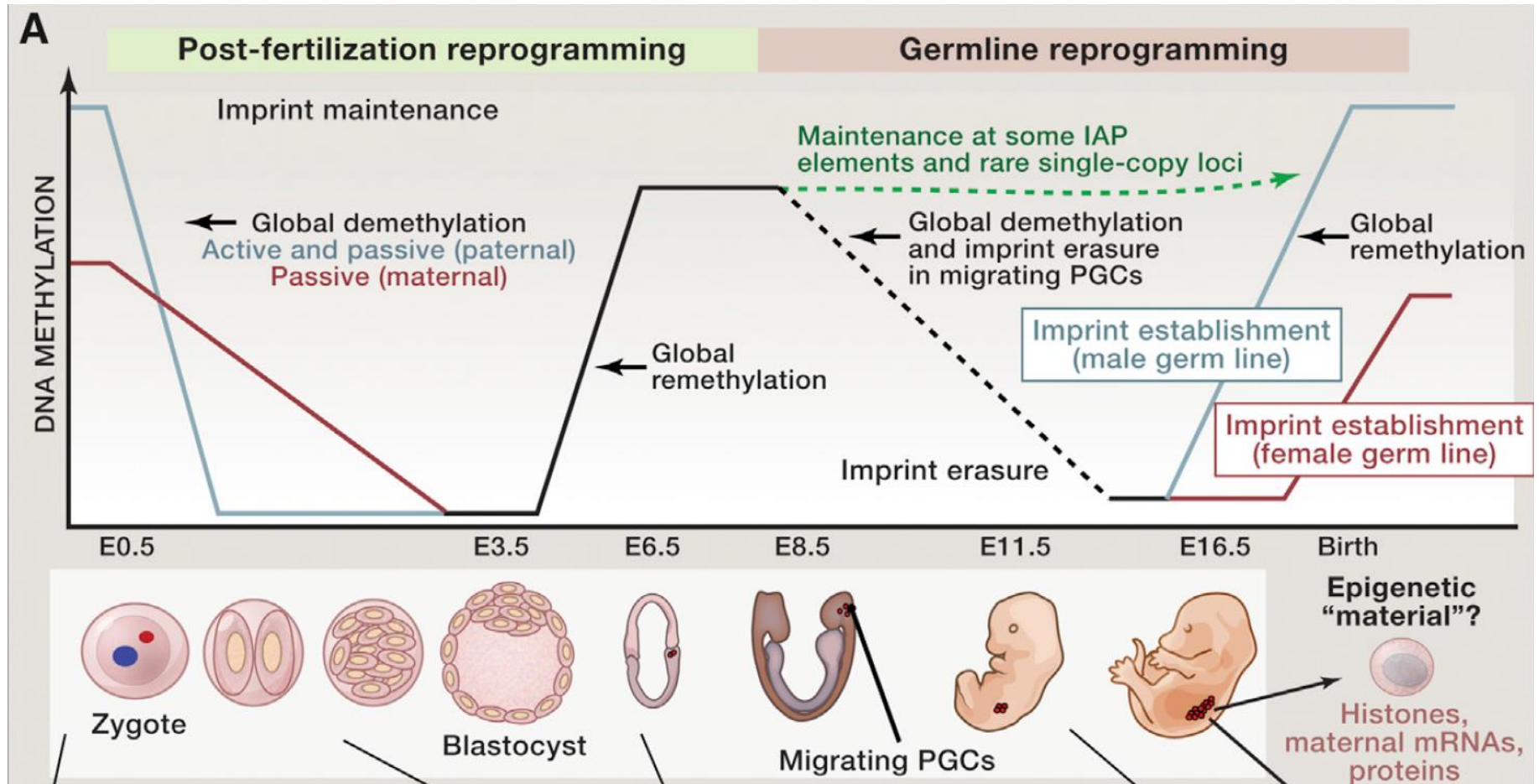


<http://knowingneurons.com/2013/06/13/your-brain-on-epigenetics/>

- **Epigenetic “marks” usually reset between generations!**

Transgenerational epigenetic inheritance

■ Limited scope in mammals: double resetting

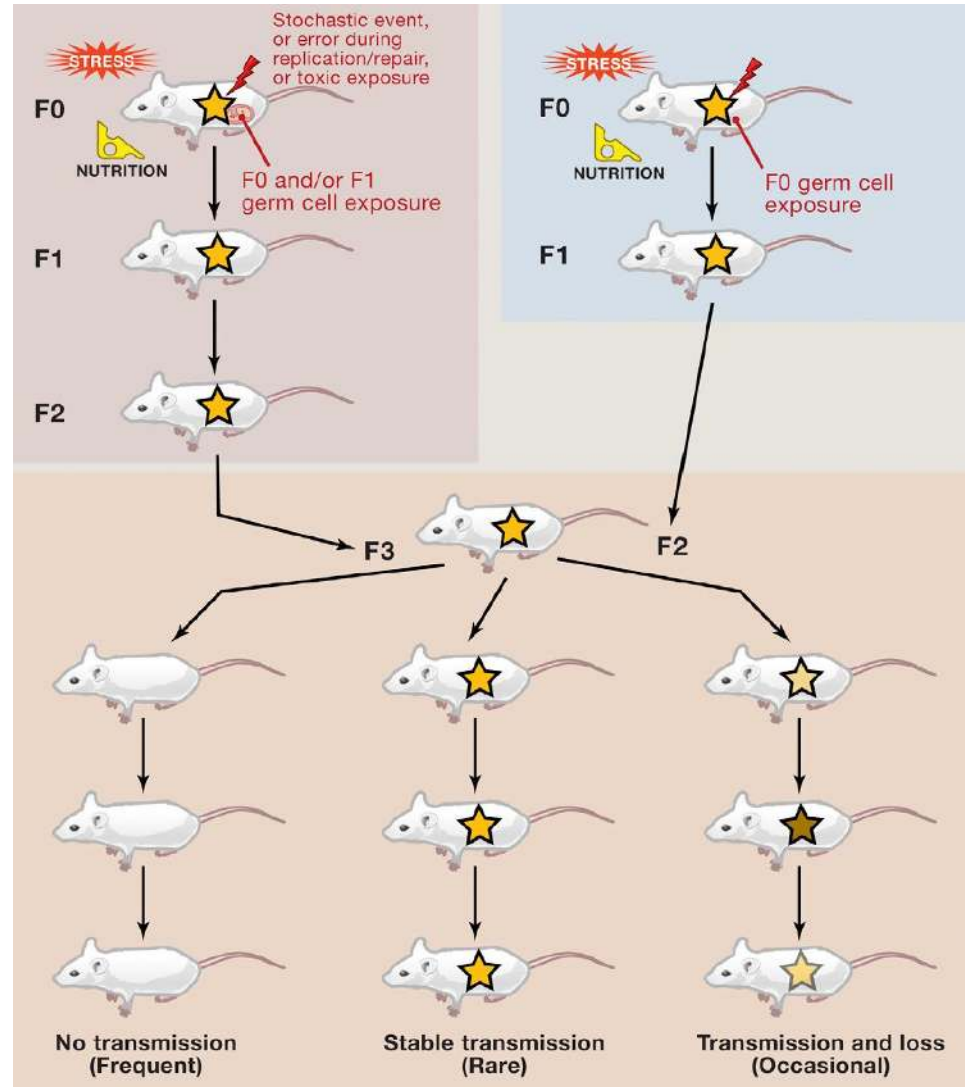


Between-generation epigenetic inheritance

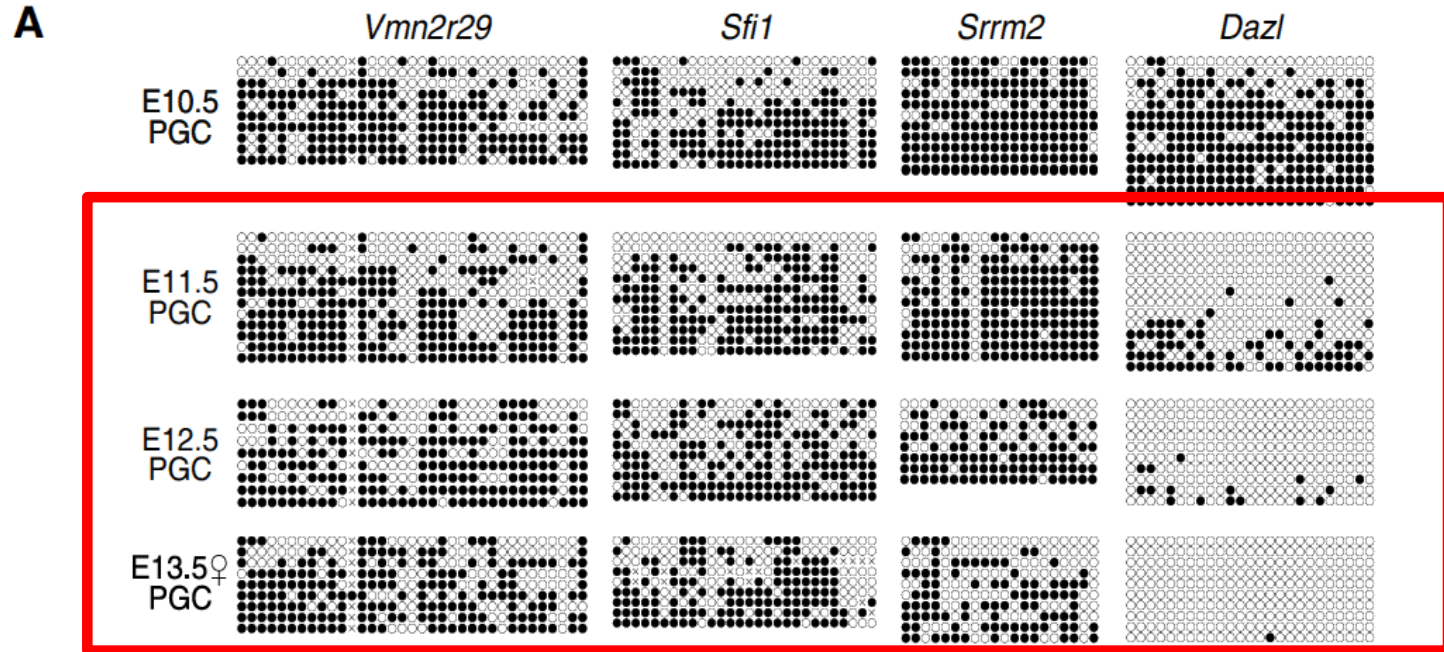
Intergenerational
(e.g. parental effects)

Transgenerational

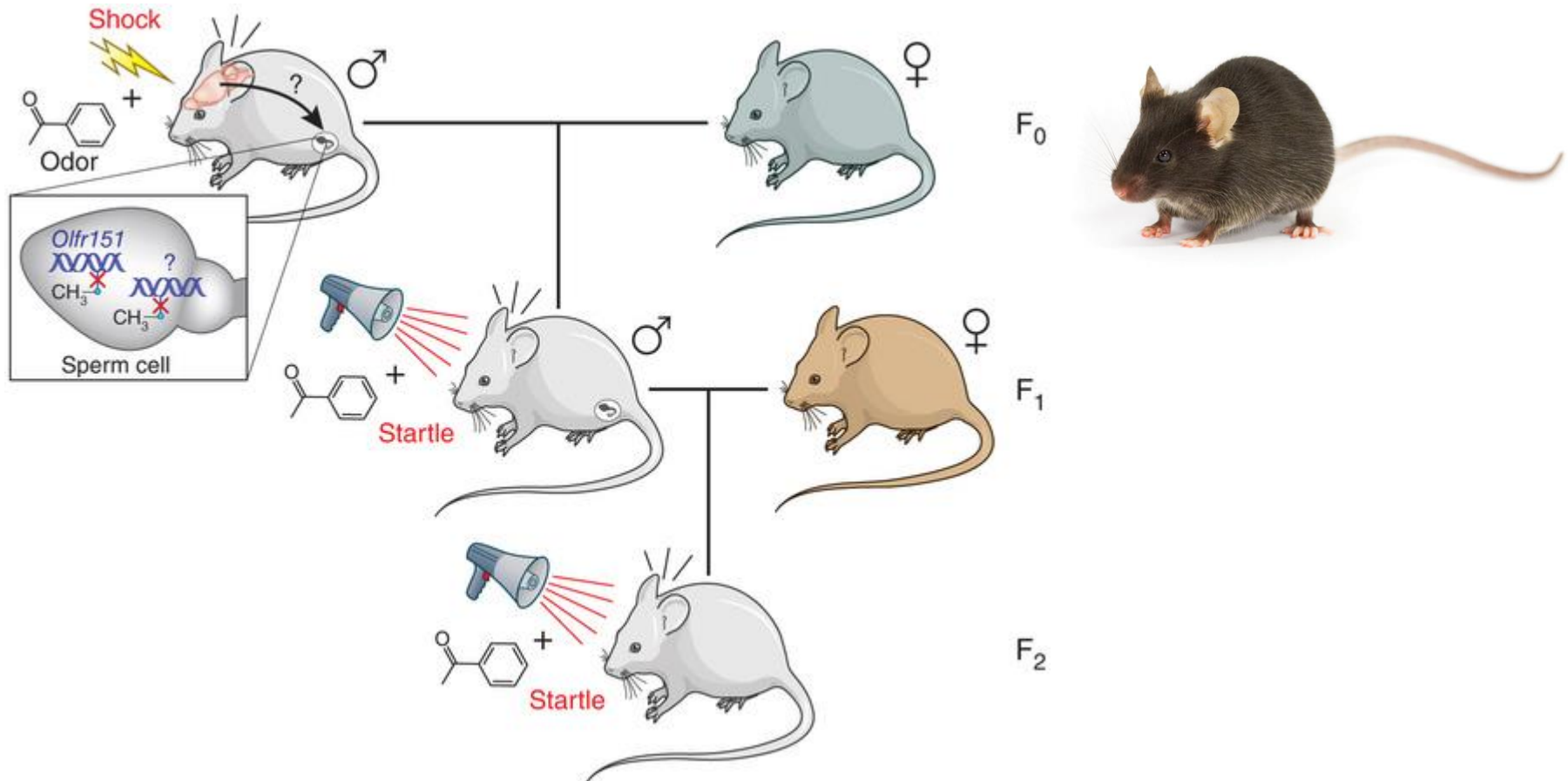
Resistance against
resetting,
partial resetting,
incomplete resetting



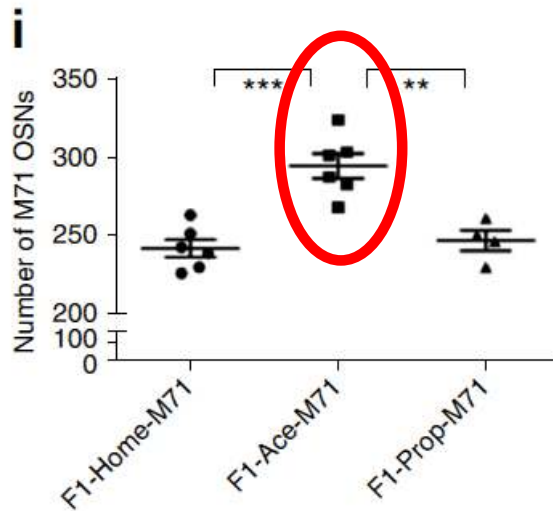
Methylation can escape reprogramming in the primordial germ cells



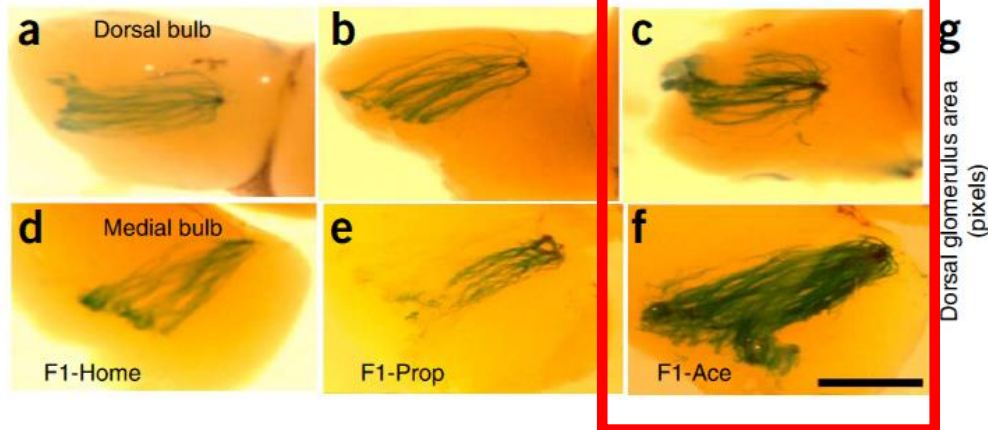
Directional trans-generational plasticity in mice

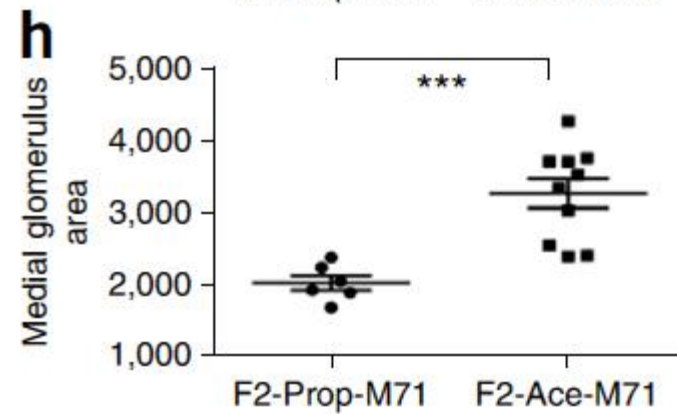
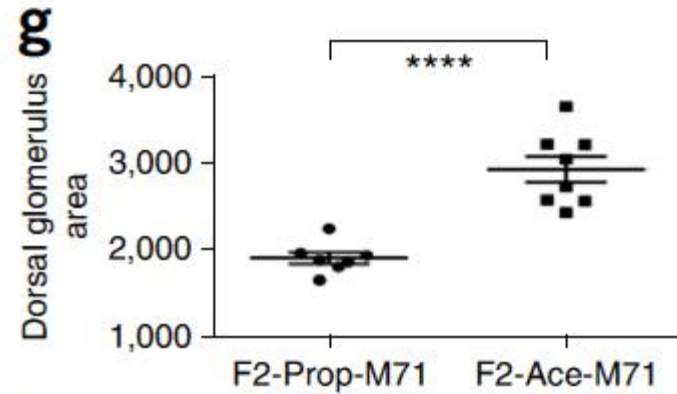
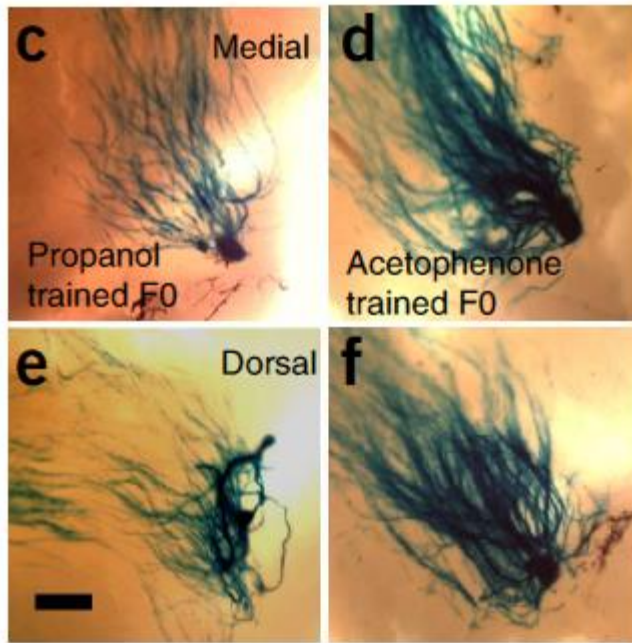
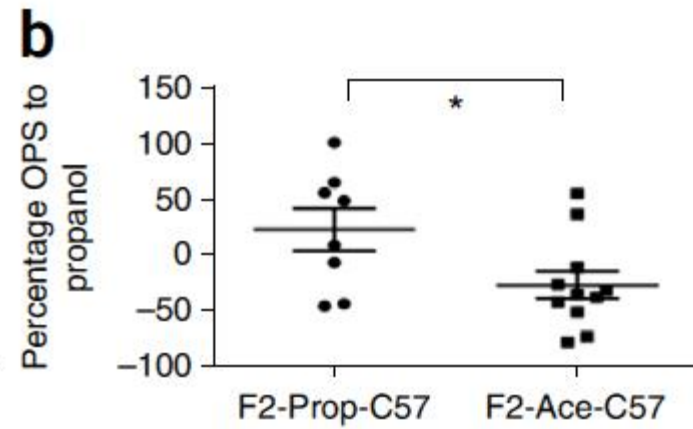
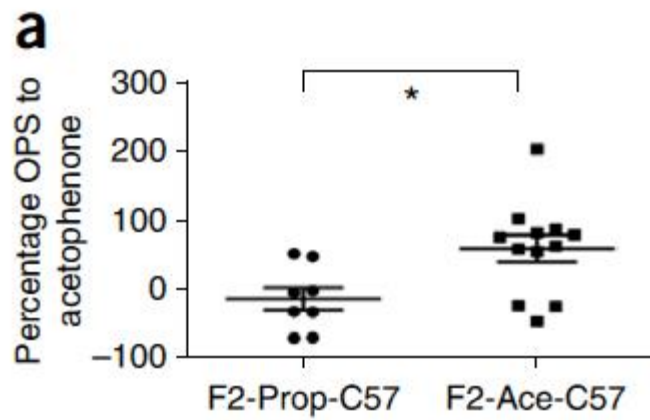


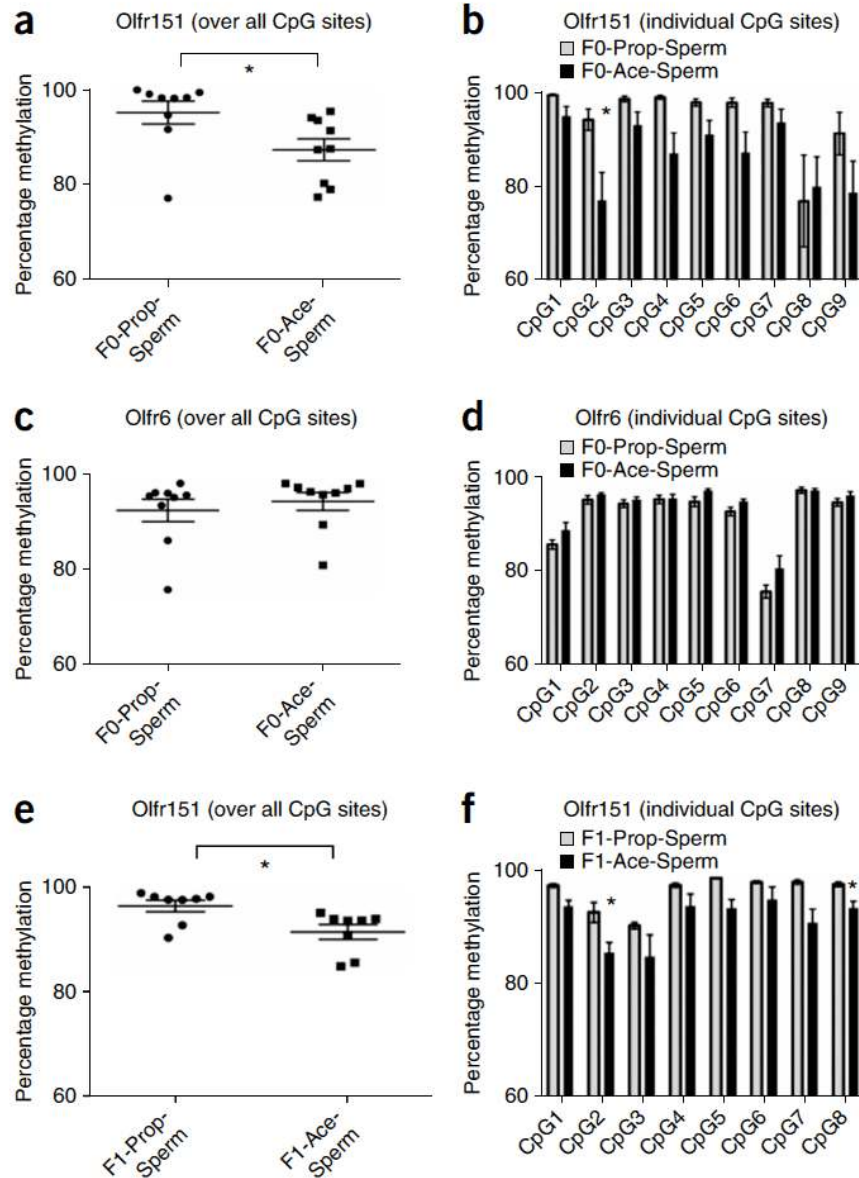
Directional trans-generational plasticity in mice



Offspring of male mice exposed to acetophenone have heightened sensitivity and larger glomeruli in the corresponding olfactory bulb





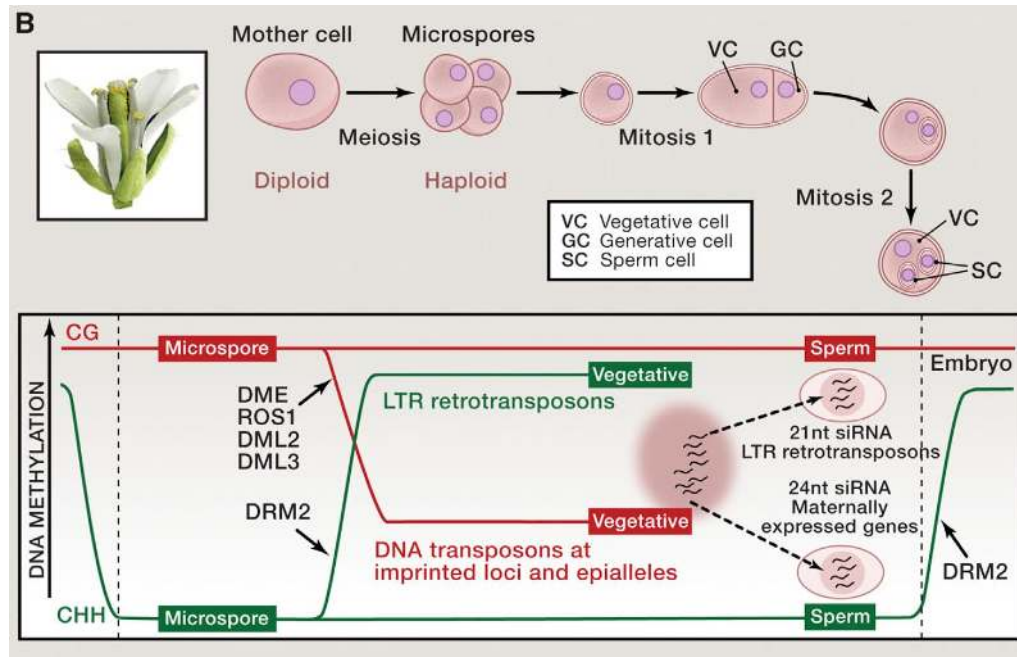


Summary

- Odour fear conditioning results in anatomical, epigenetic, and behavioural responses in F1 and F2
- These changes are specific and targeted such that responses to (grand)paternally conditioned odour are heightened
- The mechanisms are accompanied by epigenetic modification of an olfactory receptor, which is passed on through sperm

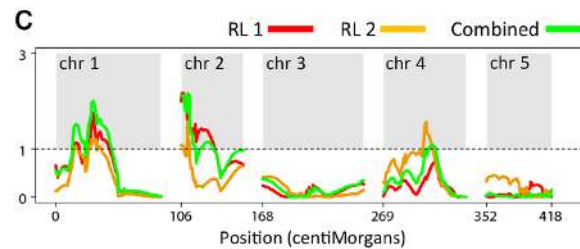
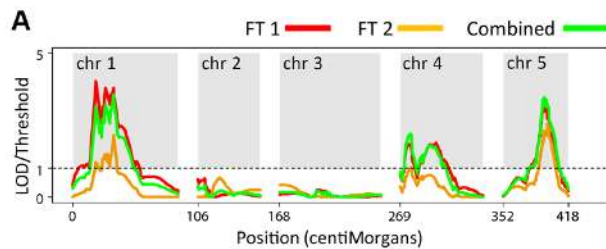
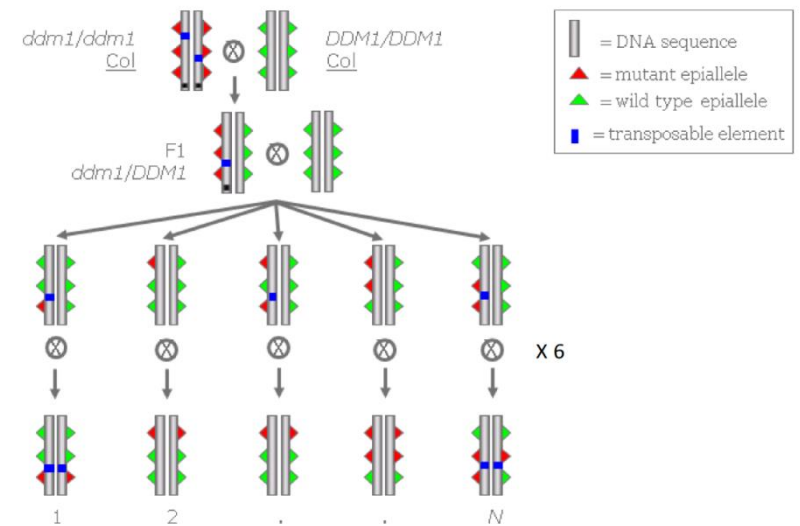
Transgenerational epigenetic inheritance

- More likely in plants: less extensive resetting

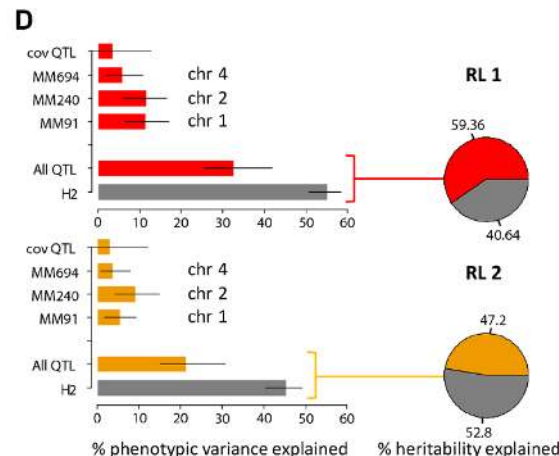
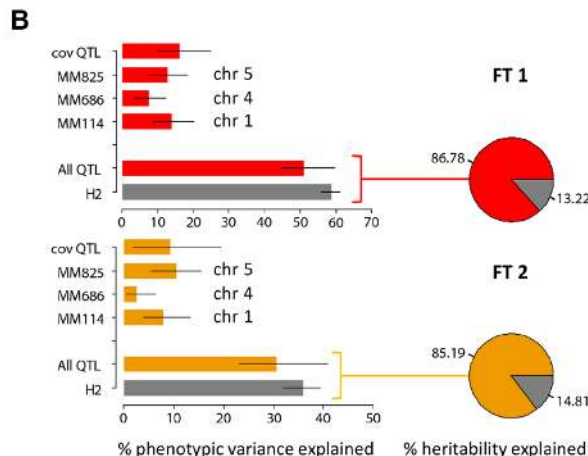


- Epigenetic states inherited 10s of generations

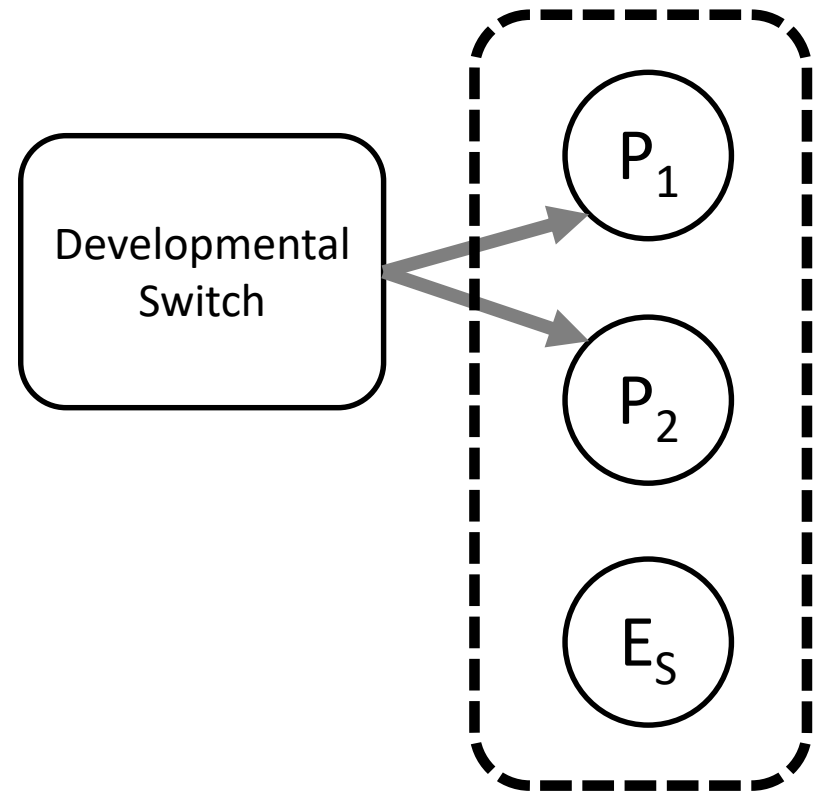
Stable epigenetic inheritance in Arabidopsis



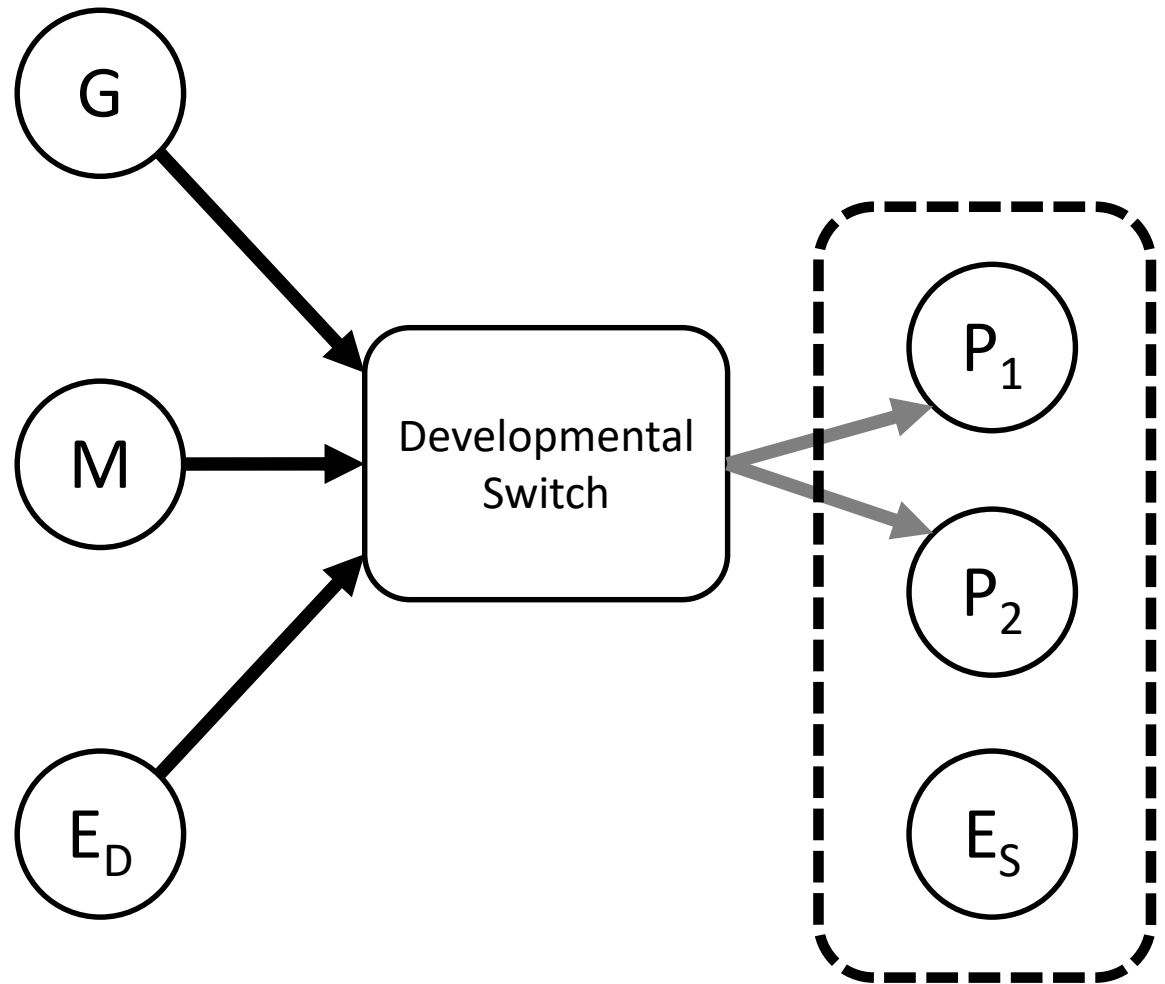
QTL mapping and percent variance explained in flowering time (left) and root length (right)



Can incomplete resetting
be adaptive?

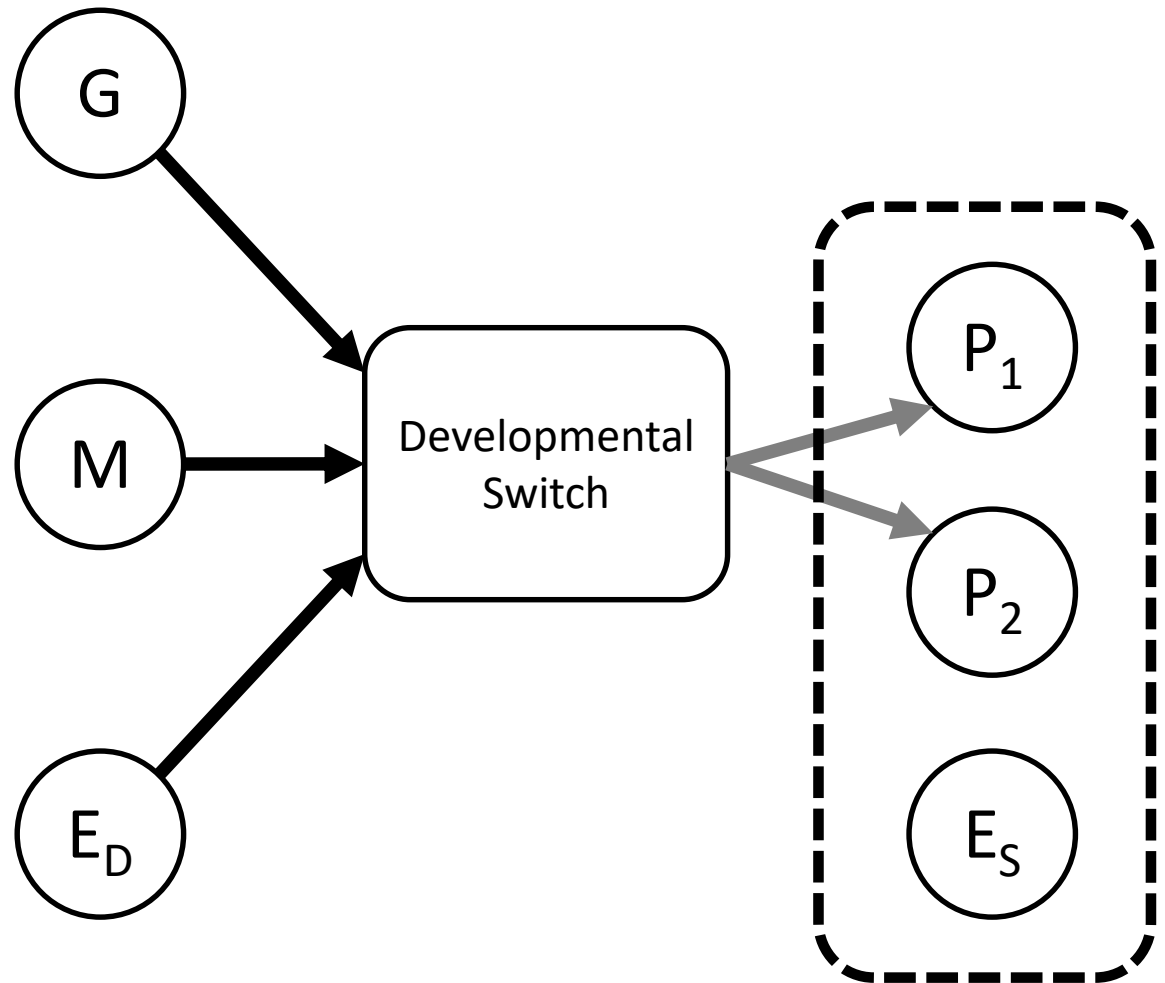


Phenotypic output
and selection



Response to input

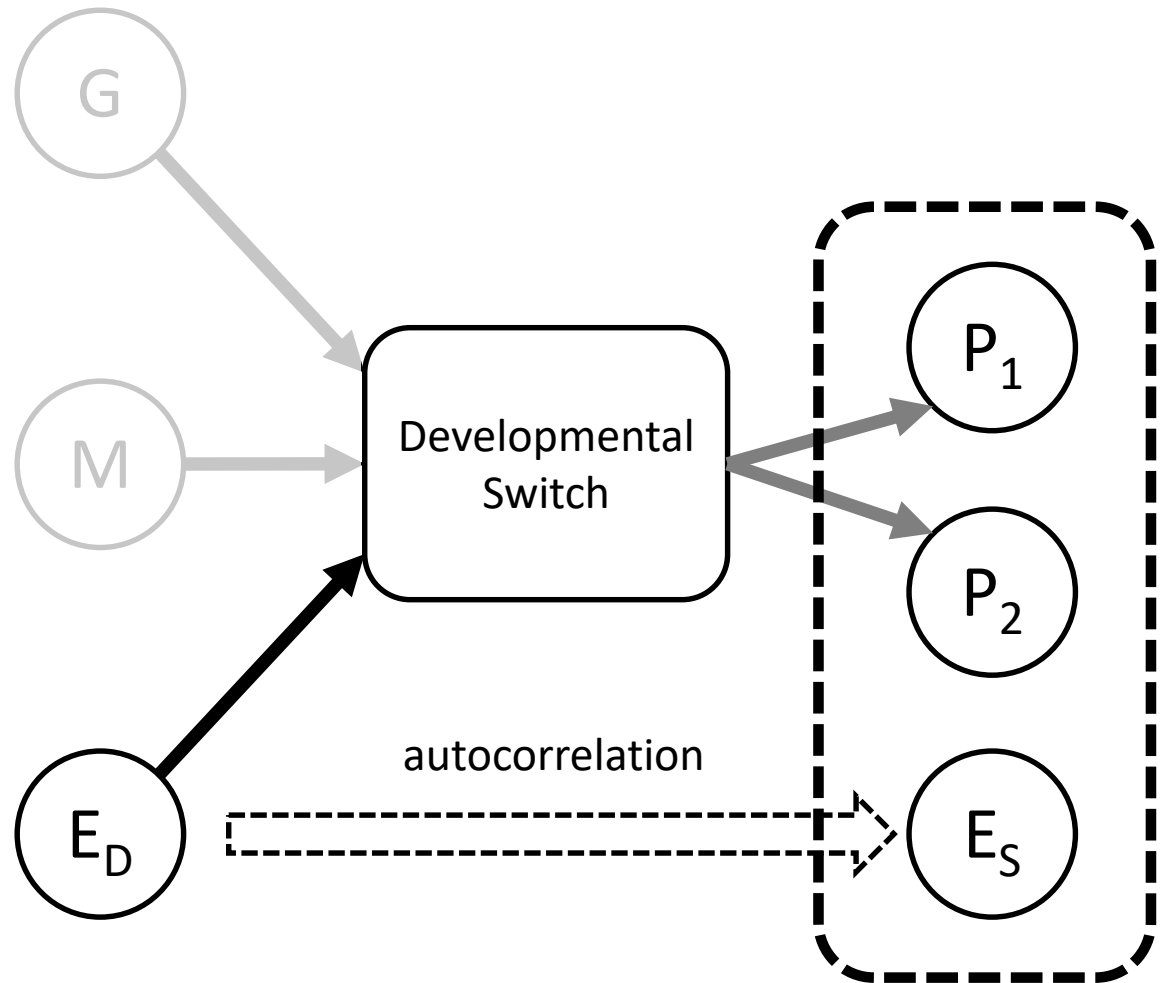
Phenotypic output
and selection



Information-generating processes

Response to input

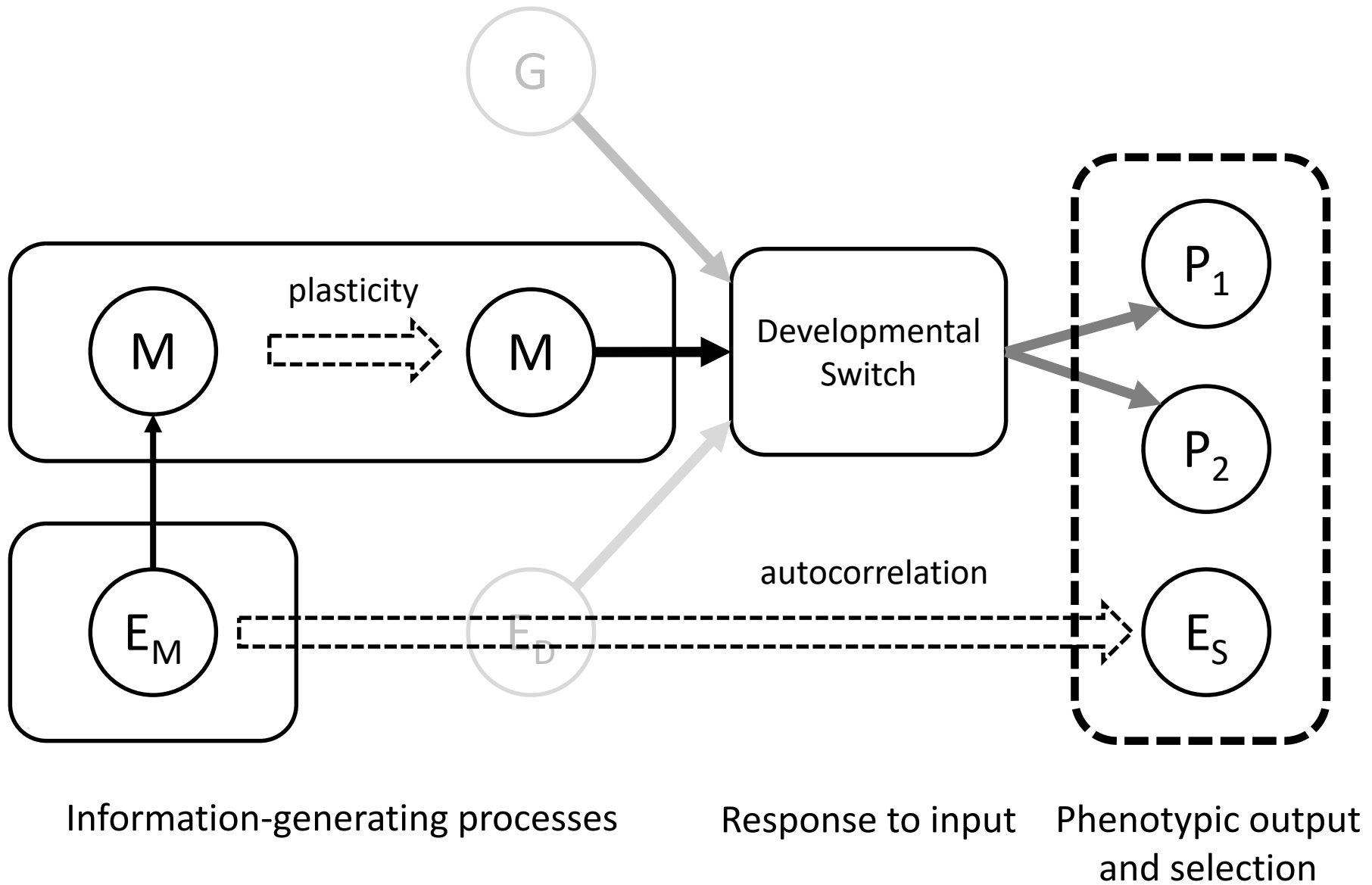
Phenotypic output
and selection

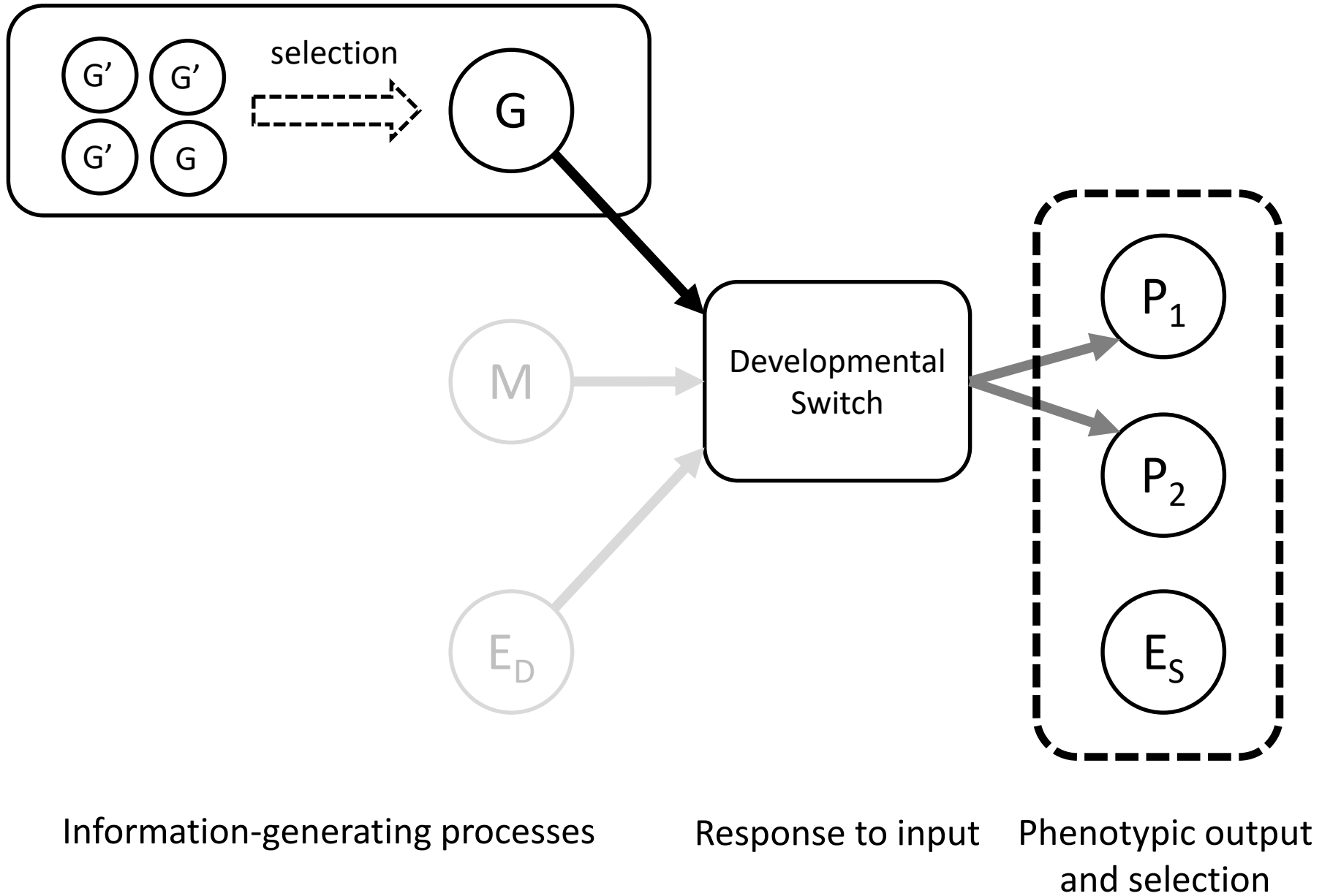


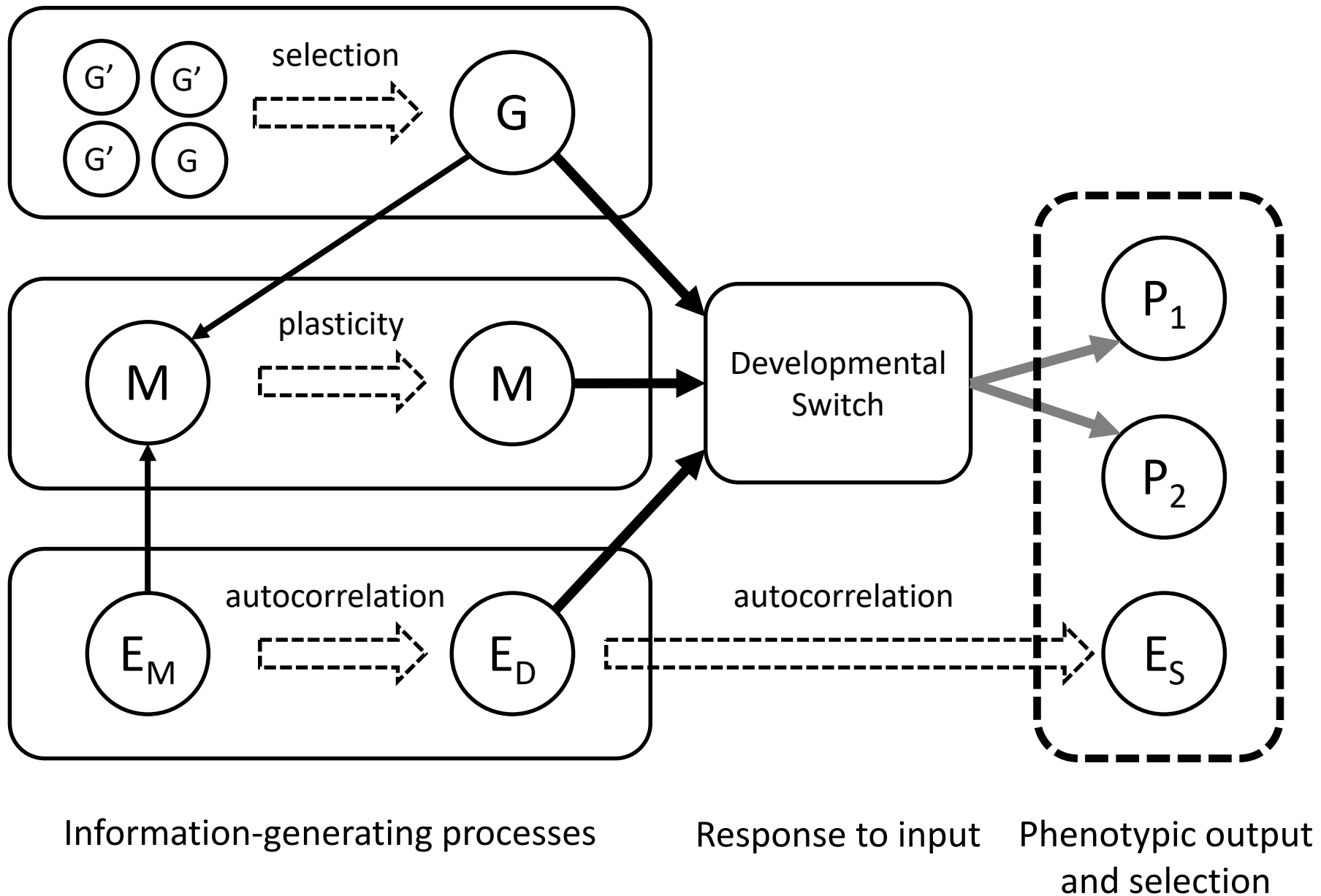
Information-generating processes

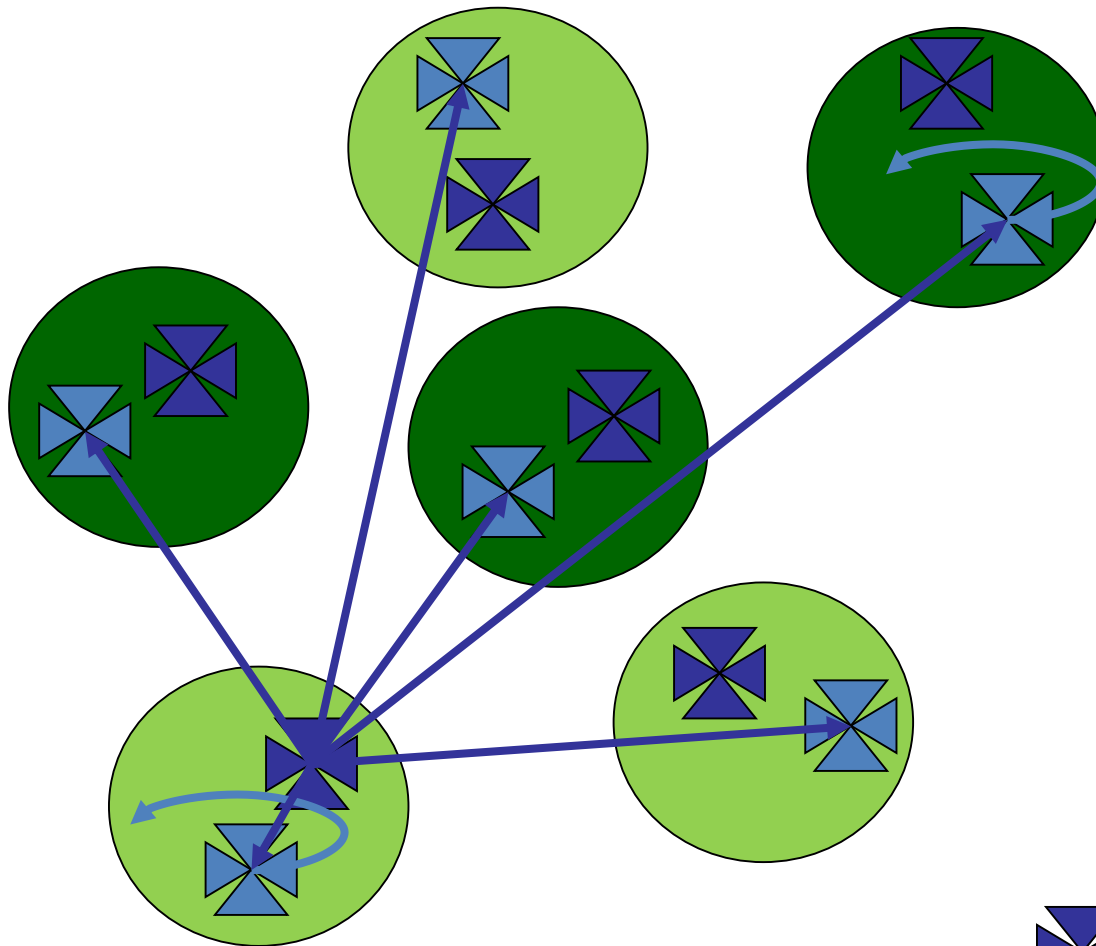
Response to input

Phenotypic output
and selection





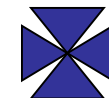




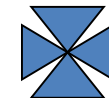
TRENDS in Ecology & Evolution

C. americanum

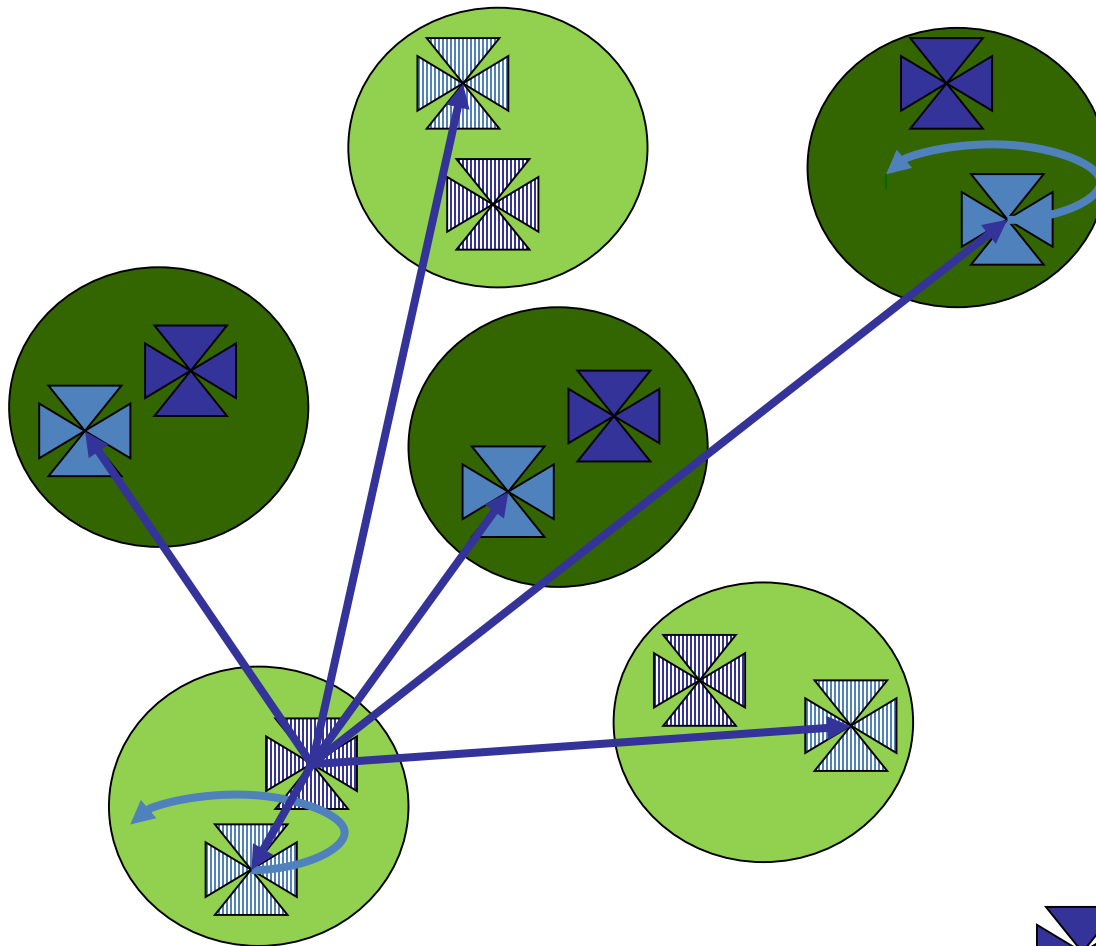
Galloway & Etterson 2007. Science



MALE FLOWER

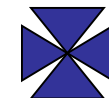


FEMALE FLOWER

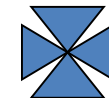


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Galloway & Etterson 2007. Science

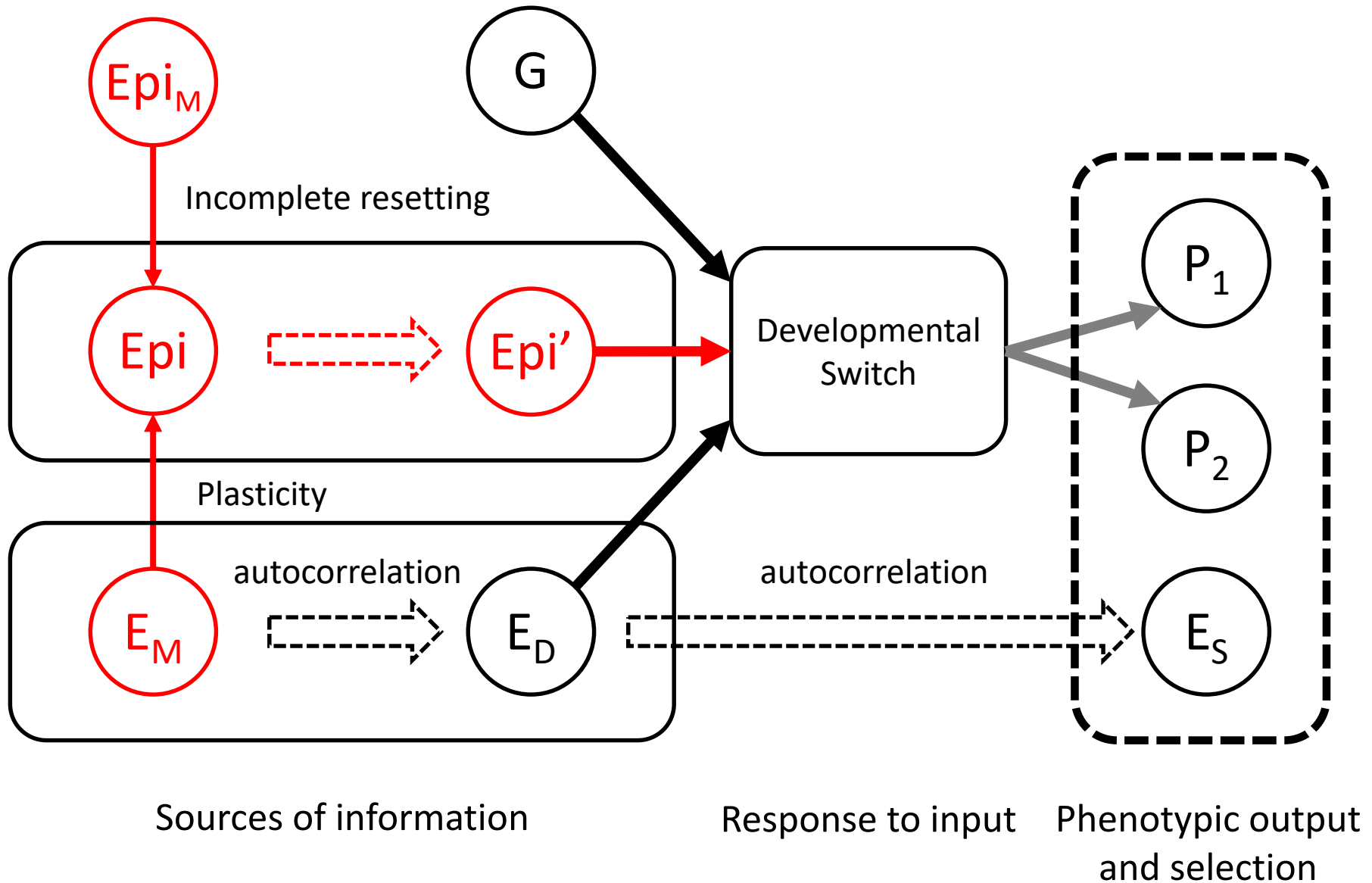


MALE FLOWER



FEMALE FLOWER

Transgenerational epigenetic inheritance





Analytical model ingredients

- Fluctuating environment x_t
- Discrete non-overlapping generations
- Quantitative epigenetic mark y_t
 - partial resetting $h \begin{cases} h = 0 & \text{total erasure} \\ h = 1 & \text{no resetting (max heritable)} \end{cases}$
 - maternal effect: linear reaction norm $m_0 + m_1 x_{t-1}$
 - developmental noise d_t
- Fitness depends on match between y_t and x_t



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 - developmental noise d_t
- Fitness depends on match between y_t and x_t
- Evolution of 3 parameters

Fluctuating environment

- First order autoregressive process (AR1)

$$x_{t+1} = r x_t + (1 - r)\mu_x + e_t$$

Fluctuating environment

- First order autoregressive process (AR1)

$$x_{t+1} = r x_t + (1 - r) \mu_x + e_t$$

r (auto)correlation between x_{t+1} and x_t

$r = 0$ no correlation

$r = 1$ perfect correlation

Fluctuating environment

- First order autoregressive process (AR1)

$$x_{t+1} = r x_t + (1 - r) \mu_x + e_t$$

r autocorrelation between x_{t+1} and x_t

μ_x long-term average of x

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r autocorrelation between x_{t+1} and x_t

μ_x long-term average of x

e_t **noise** fluctuations $\square$ $\text{normal}(0, \sigma_e^2)$

Dynamics epigenetic marks

- Changes in individual offspring:

$$y_{t+1} = h y_t + m_t + d_t$$

Dynamics epigenetic marks

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h degree of resetting (0 = complete, 1 = none)

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m_t maternal effect

Linear reaction norm: $m_t = m_0 + m_1(x_t + \varepsilon)$

Maternal error: $\varepsilon \sim \text{normal}(0, \sigma_\varepsilon^2)$

Dynamics epigenetic marks

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m_t maternal effect

Linear reaction norm: $m_t = m_0 + m_1(x_t + \varepsilon)$

Maternal error: $\varepsilon \sim \text{normal}(0, \sigma_\varepsilon^2)$

d_t developmental noise $\sim \text{normal}(0, \sigma_d^2)$

Main results

Natural selection on (m_0, m_1, h) favors incomplete resetting ($h > 0$) when

$$r^2 \sigma_\varepsilon^2 > \sigma_e^2 - \sigma_w^2 - \sigma_d^2$$

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- Environmental stochasticity

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- + Maternal inaccuracy
- Environmental stochasticity
- **Strength of selection**

Main results

Natural selection favors
incomplete resetting ($h > 0$) when

$$r^2 \sigma_{\varepsilon}^2 > \sigma_e^2 - \sigma_w^2 - \sigma_d^2$$

- + Autocorrelation (stability) environment
- + Maternal inaccuracy
- Environmental stochasticity
- Strength of selection
- + Developmental noise

Main results

Natural selection favors
incomplete resetting ($h > 0$) when

$$r^2 \sigma_{\varepsilon}^2 > \sigma_e^2 - \sigma_w^2 - \sigma_d^2$$

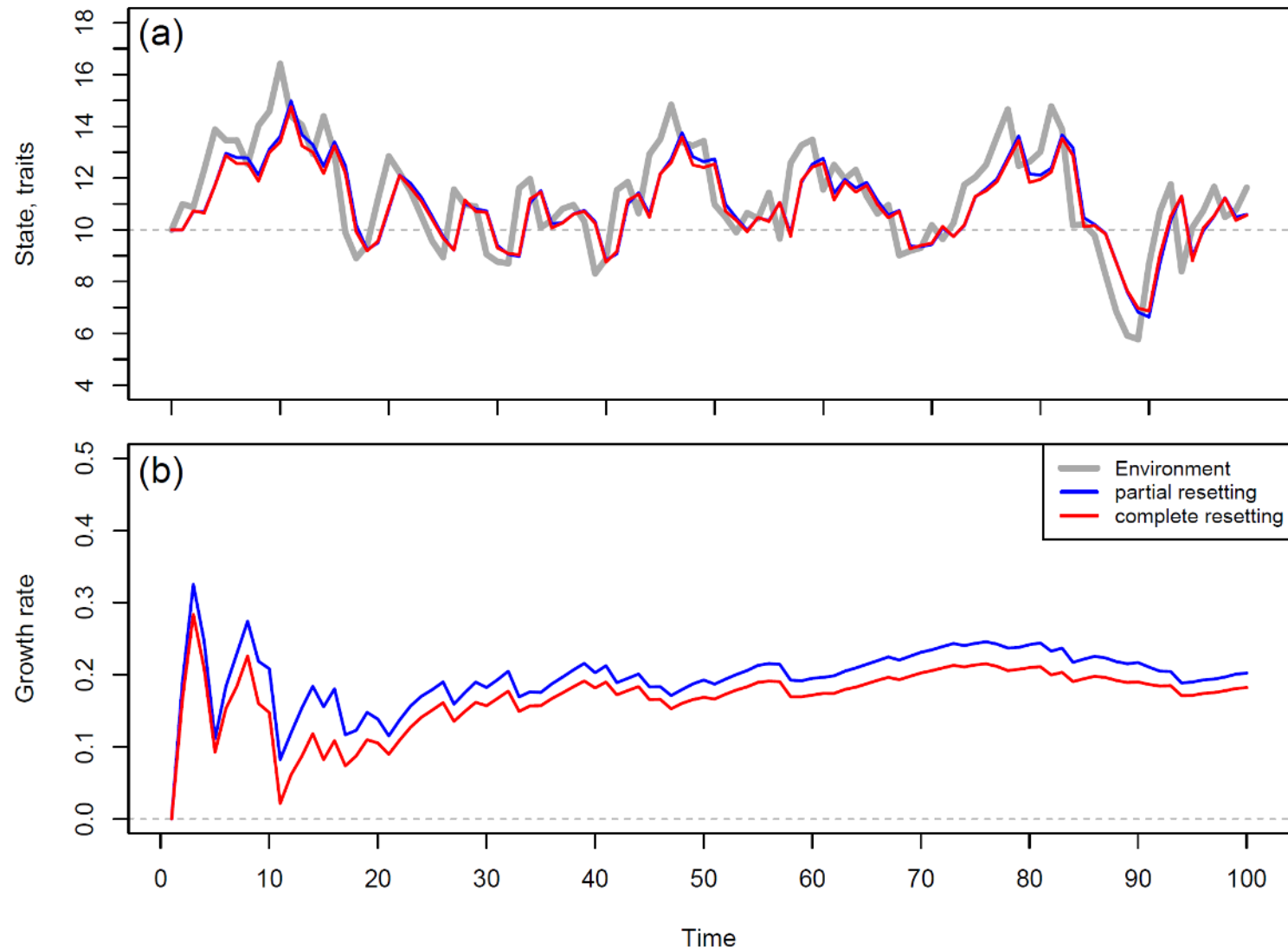
In other words: incomplete resetting



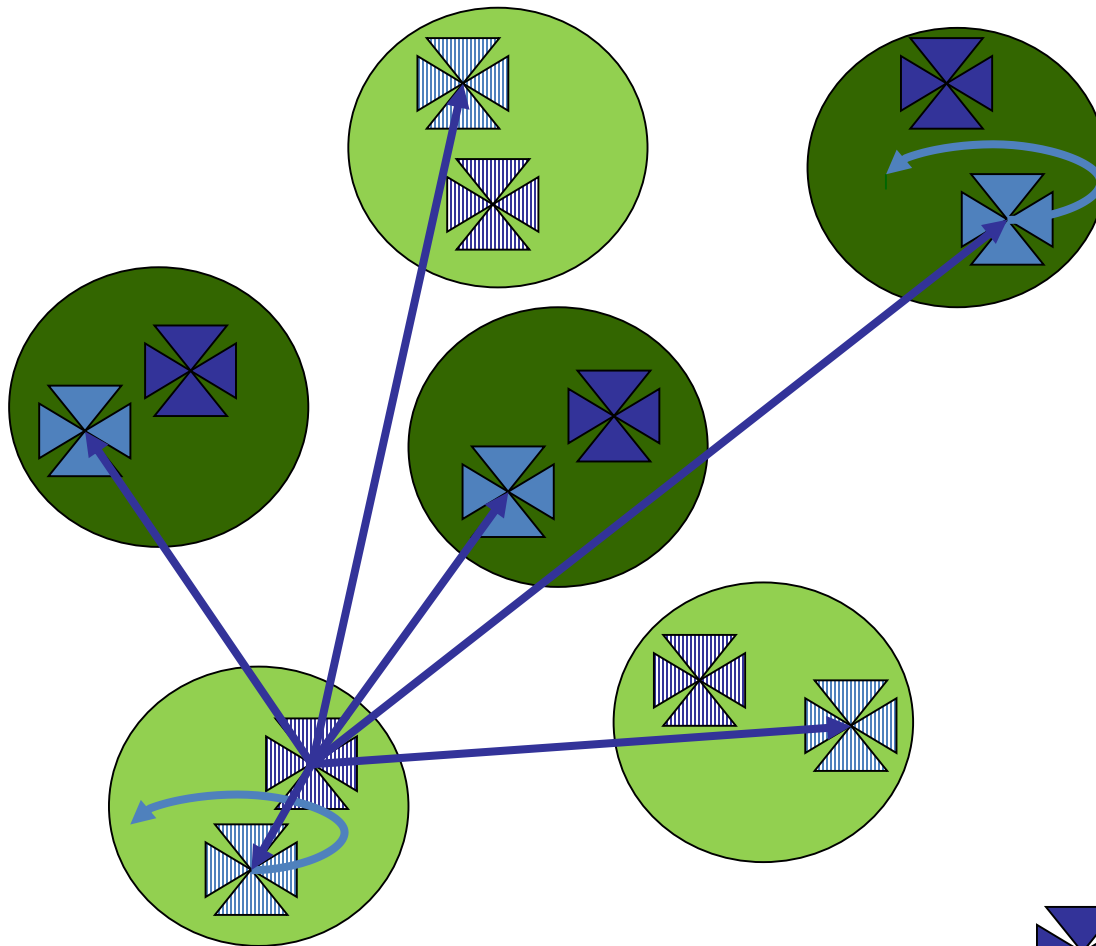
+ Protects against maternal & developmental
“errors” in stable environment

– Slows down adaptation to changing environment

Numerical example

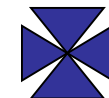


$$r = 0.8, \sigma_{\varepsilon}^2 = 2.0, \sigma_e^2 = 2.0, \sigma_w^2 = 1.0, \sigma_d^2 = 0.5$$

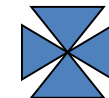


C. americanum

Galloway & Etterson 2007. Science



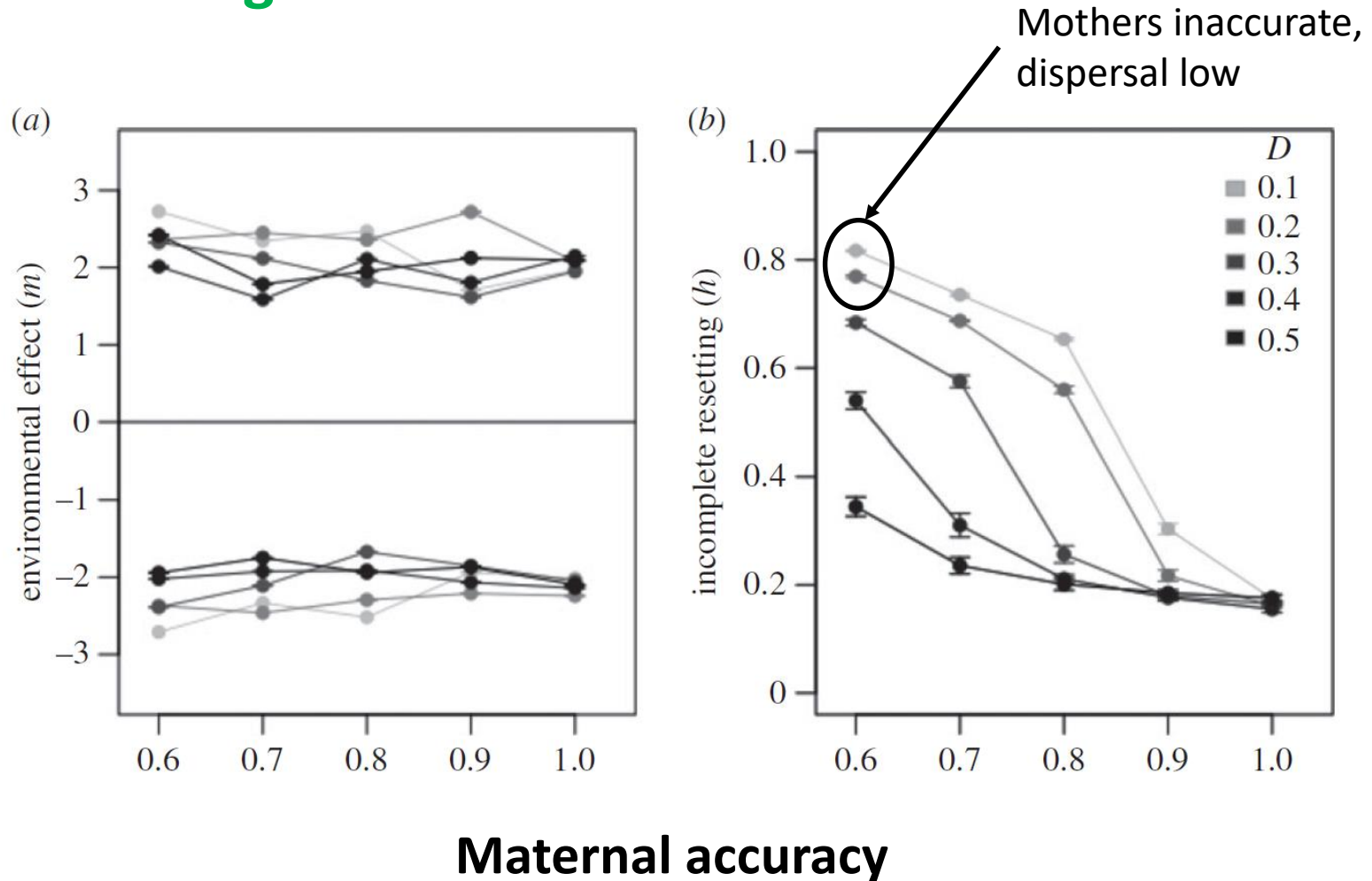
MALE FLOWER



FEMALE FLOWER

Individual-based simulations

- Qualitative results carry over to spatially heterogeneous environments

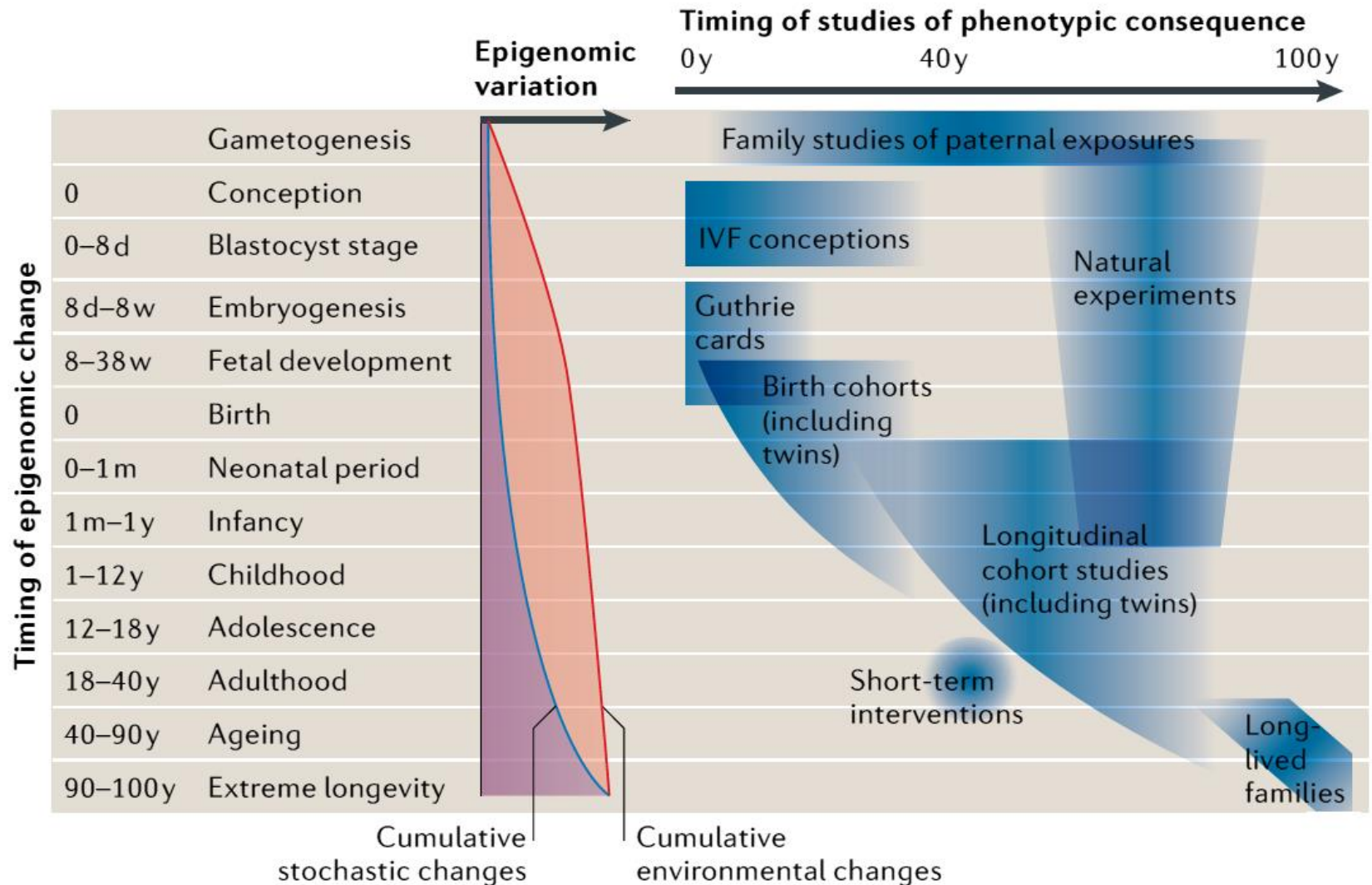


Population epigenetics

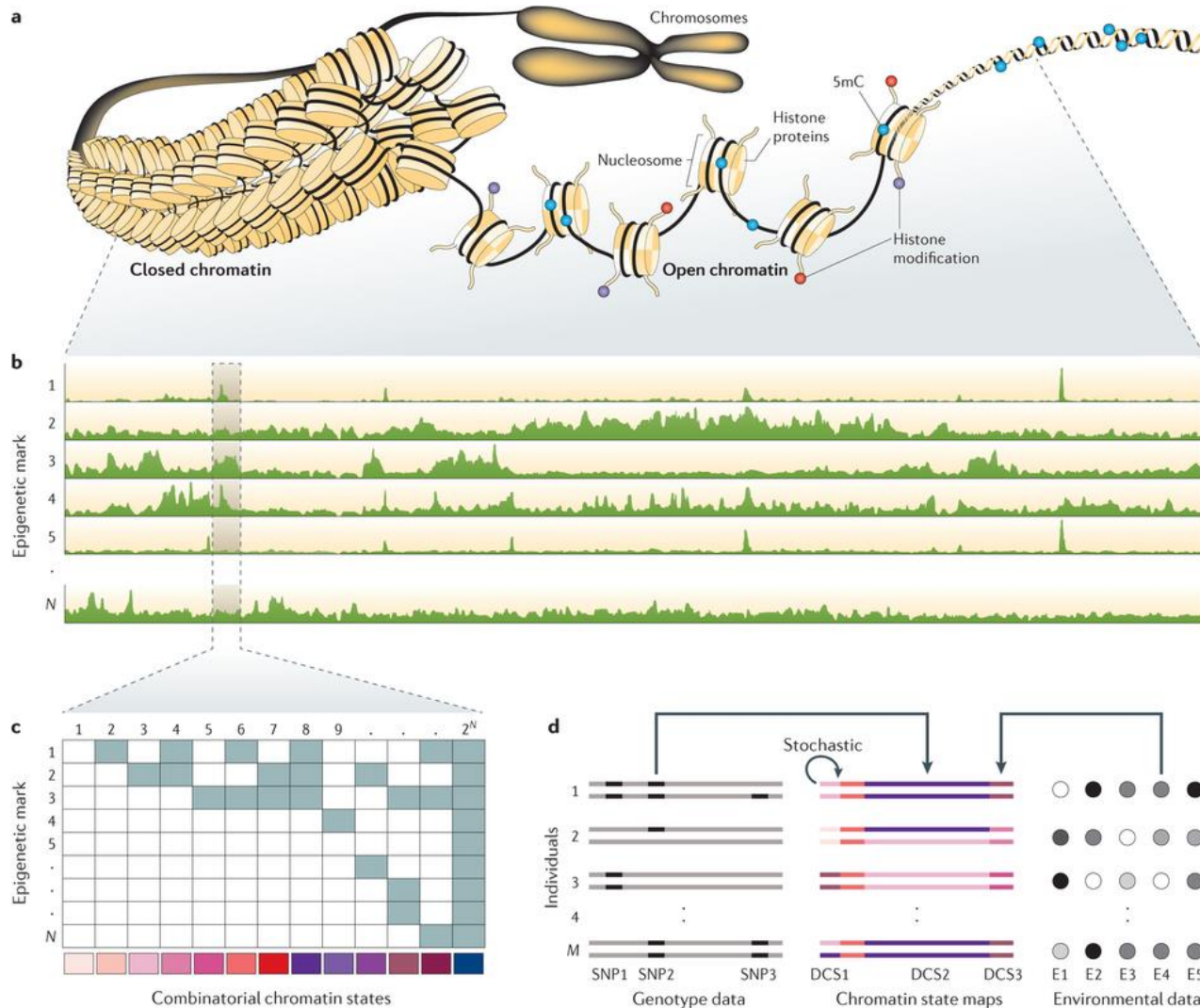
Why population epigenetics?

- Identify associations with phenotypic, environmental and genetic factors
- Test for transgenerational inheritance
- Role of epigenetic variation (inherited or not) in adaptive evolution

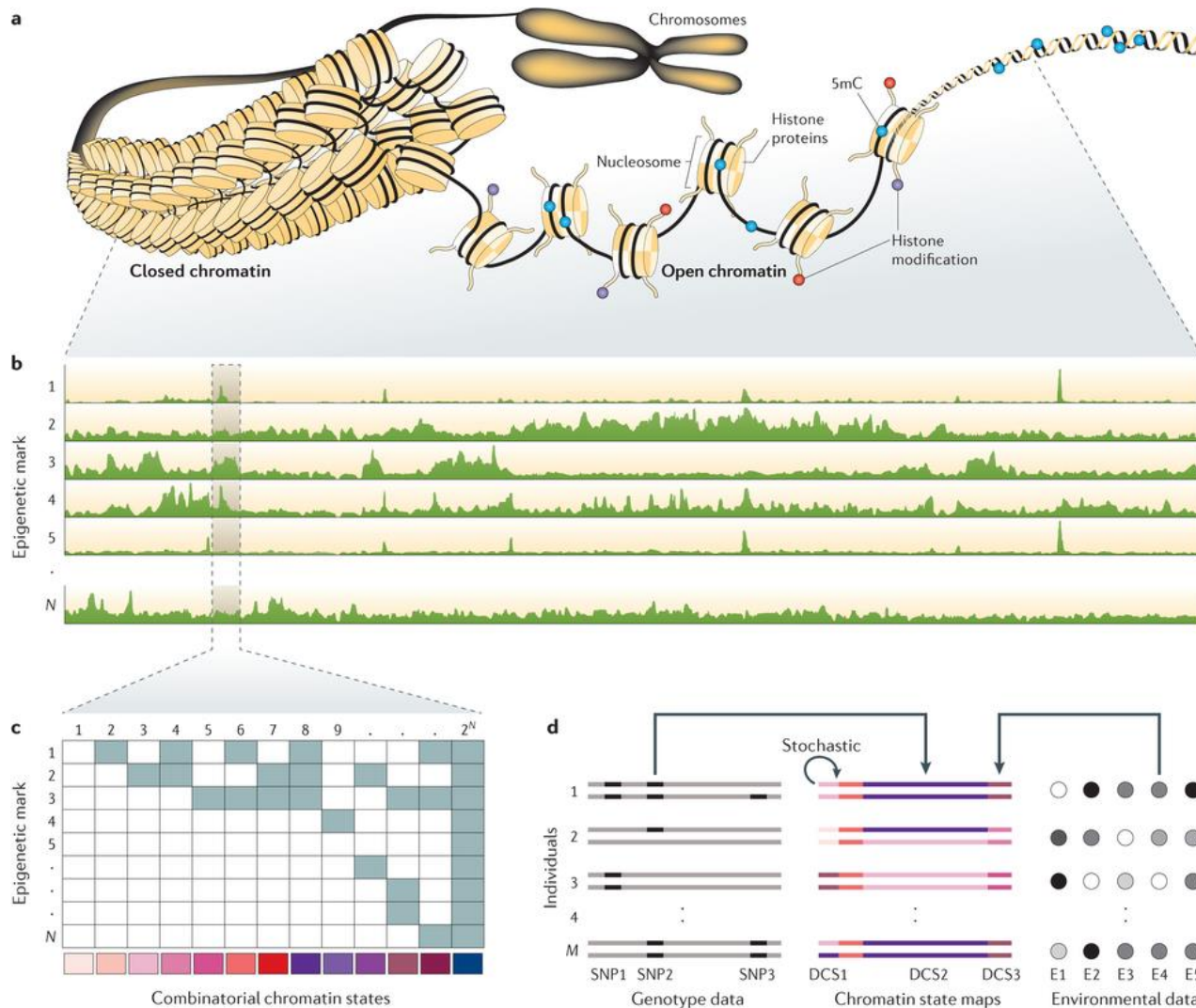
Study designs for studying epigenetic variation in human populations



Population epigenetic data - workflow

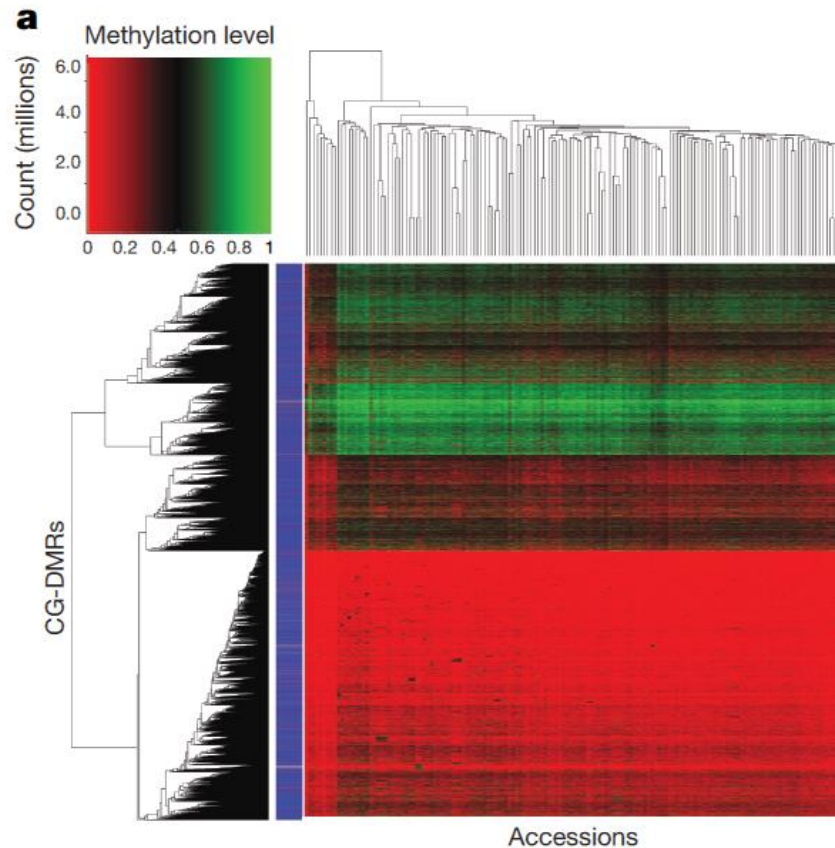


"The statistical challenge is to try to identify these causal factors from millions of measured SNPs and a large number of environmental factors"



Columns are genotypes

Population epigenetics I. Genomic patterns



Rows are differentially
methylated regions (DMRs)



Transposons

Genes

Average methylation

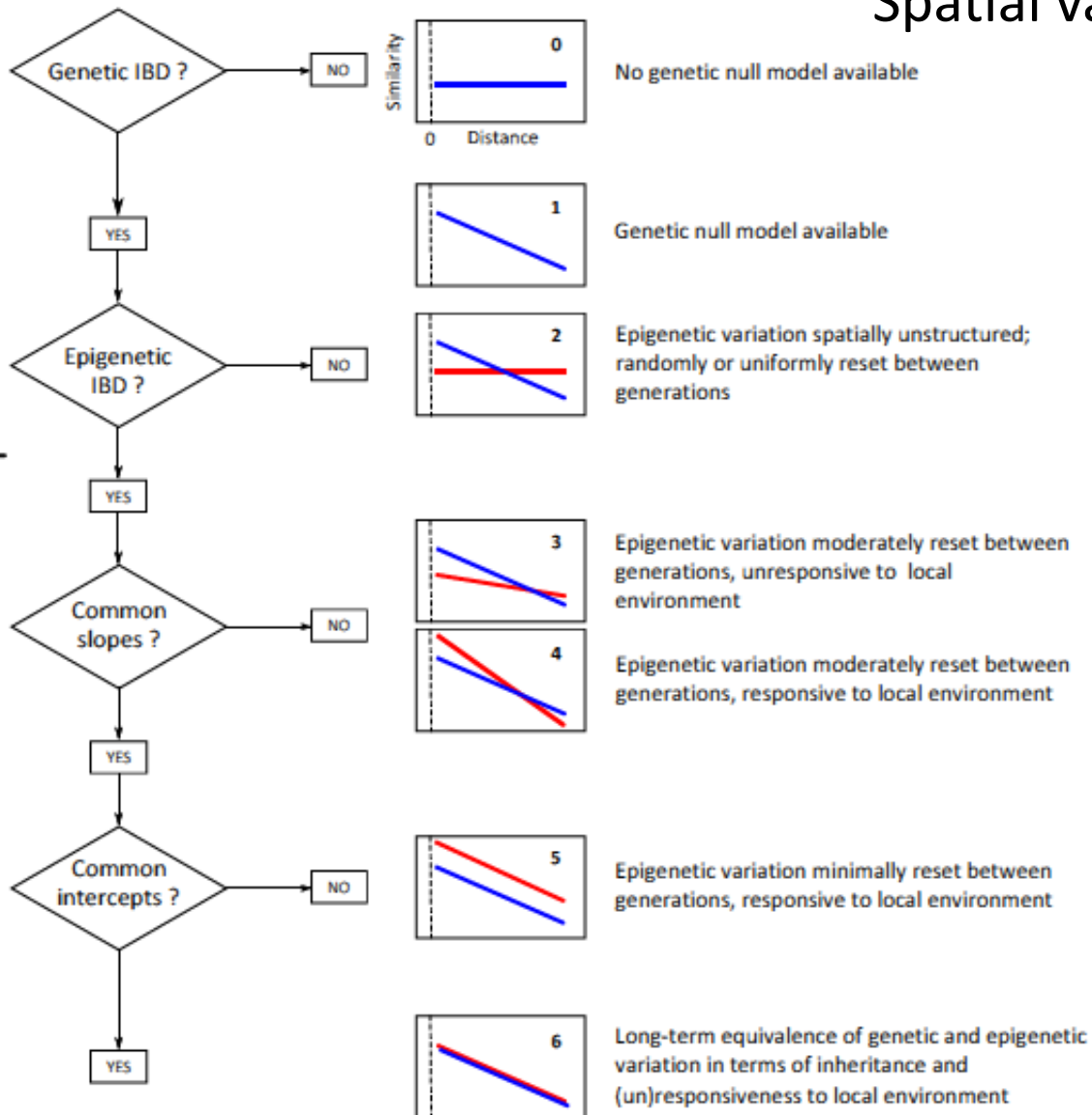


Population epigenetics II. Spatial variation

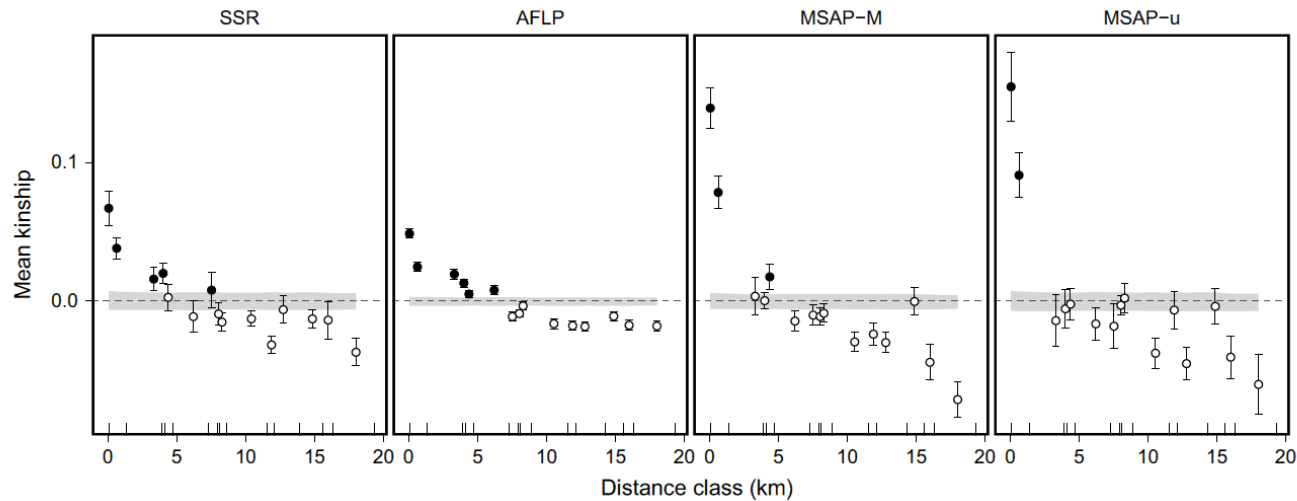
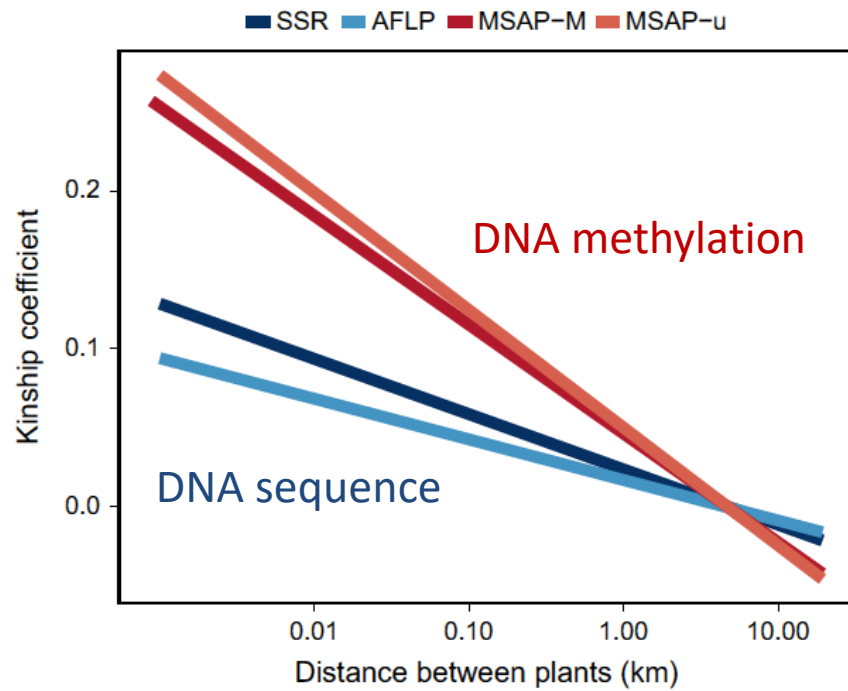
— Genetic similarity
— Epigenetic similarity

Genetic variation spatially structured

Epigenetic variation spatially structured

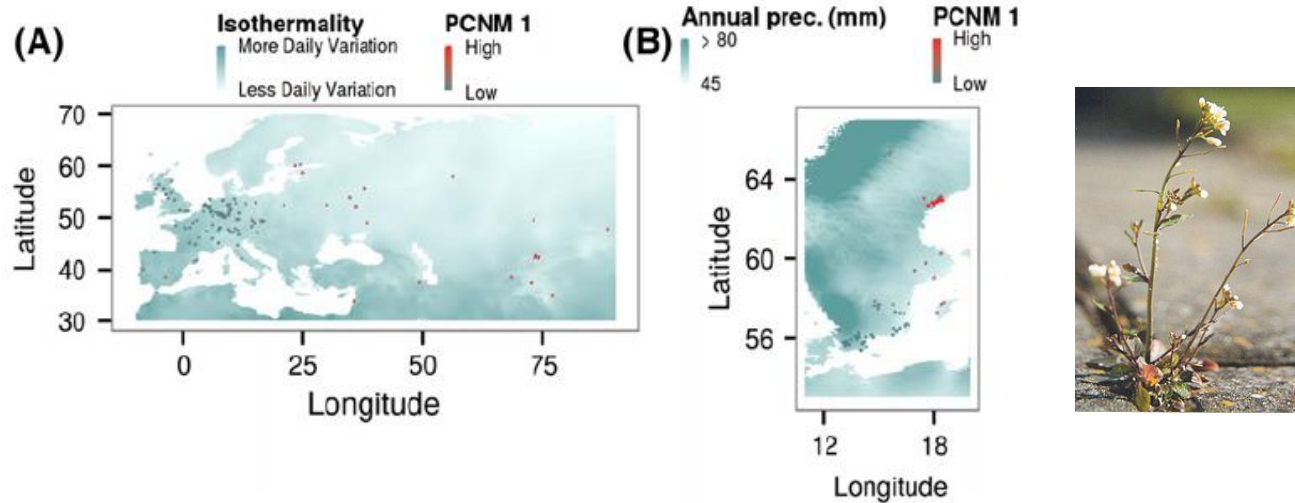


Population epigenetics II. Spatial variation



Population epigenetics III.

Association with climate



Data sets	Response variables	Full Model		Space-adjusted Model	
		(Climate + Space)			
		Adj. R^2	P -value	Adj. R^2	P -value
Eurasian panel	C-DMRs	0.07	0.002	0.03	0.182
Schmitz <i>et al.</i> (2013)	CG-DMRs	0.05	0.010	0.03	0.170
Swedish panel	C-DMRs	0.16	0.001	0.09	0.001
Dubin <i>et al.</i> (2015)	CG-DMRs	0.18	0.001	0.09	0.001

Remember this guy?



Let us stay sober...

- Technology and bioinformatics
- The cell heterogeneity problem
- Evolutionary relevance
 - From correlation to causation
 - *The relevance of epigenetics to evolution is not primarily that it adds discrete units to our inheritance. It is that it encourages us to rethink what we mean by inheritance.*

Tobias Uller, just now

Acknowledgements

Dutch Hunger Winter

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Models and stuff

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Sinead English

Nick Shea

Heikki Helanterä

Miranda Waggoner

[www.ullergroup.se](http://www ullergroup.se)

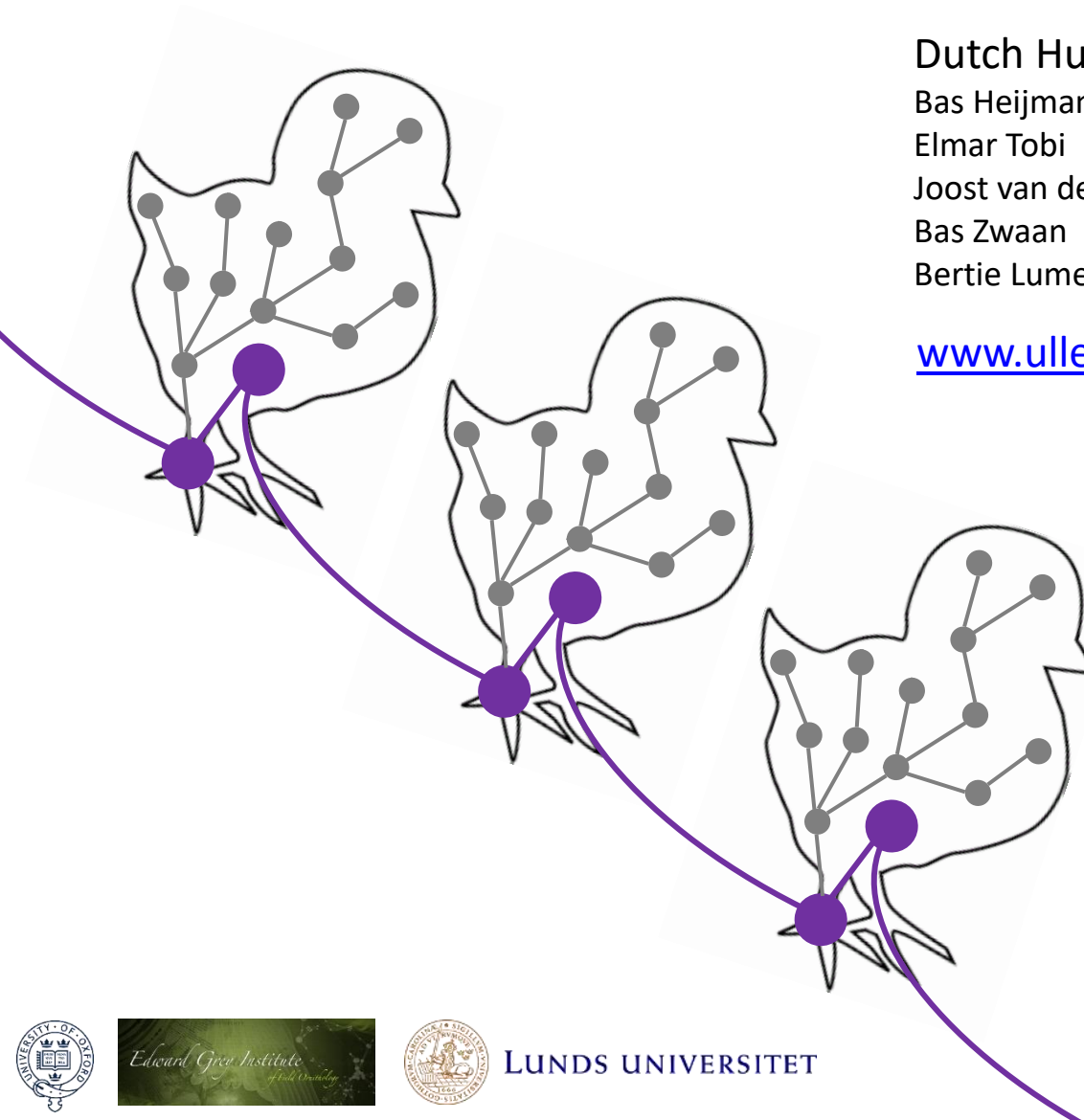
*Knut och Alice
Wallenbergs
Stiftelse*



THE ROYAL
SOCIETY



John
Templeton
Foundation



LUNDS UNIVERSITET