Epigenetics in Ecology and Evolution

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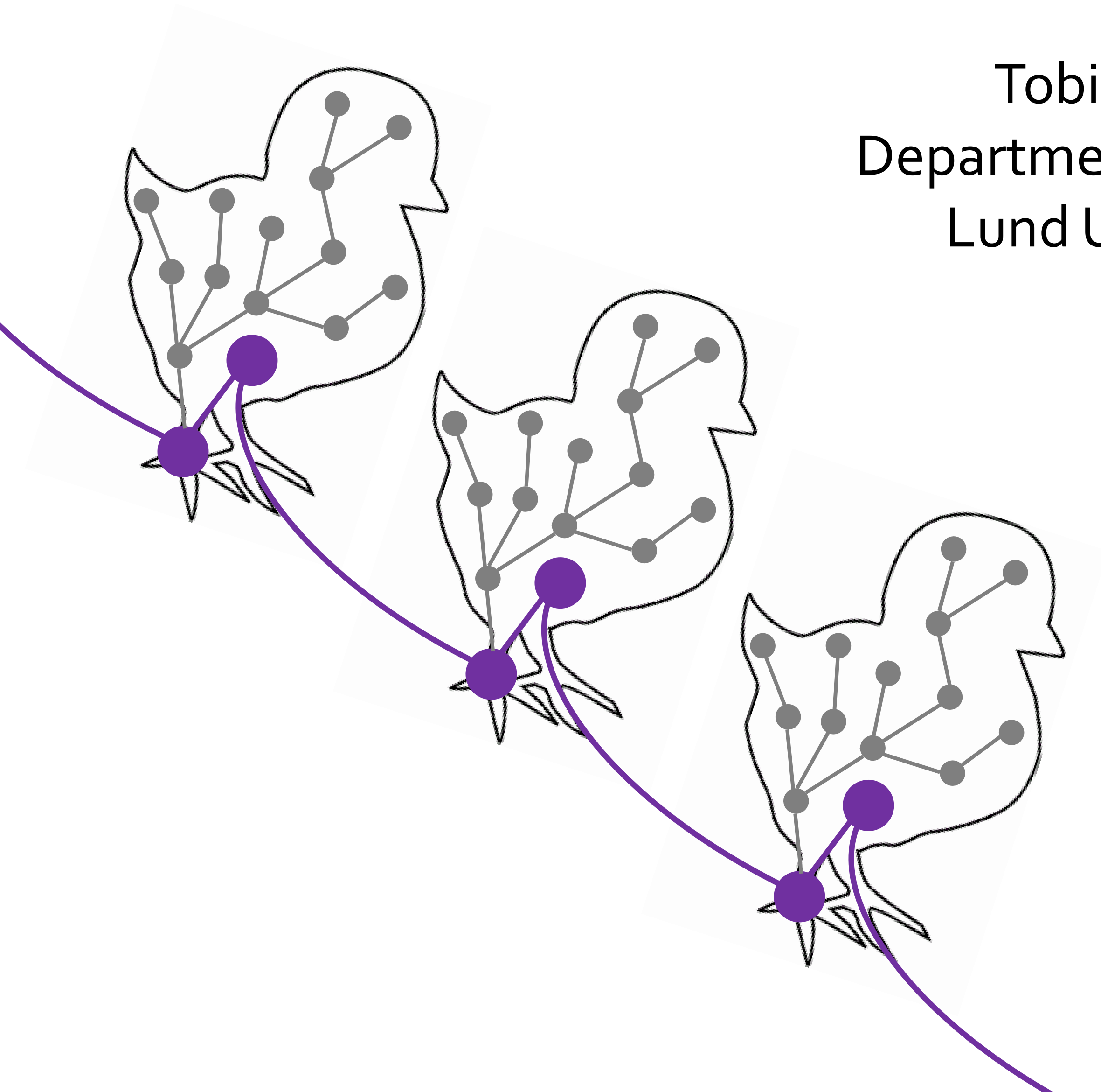
Lund University

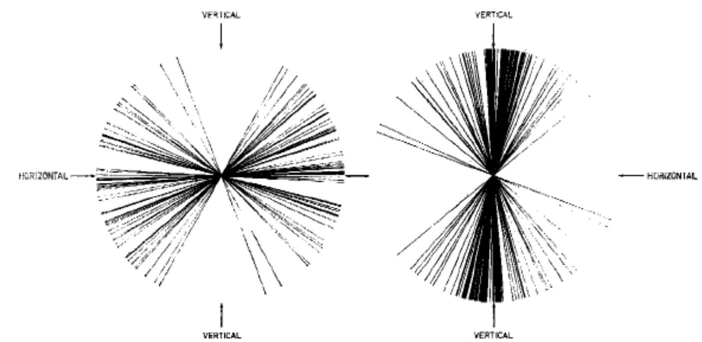


Today's topics

- 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

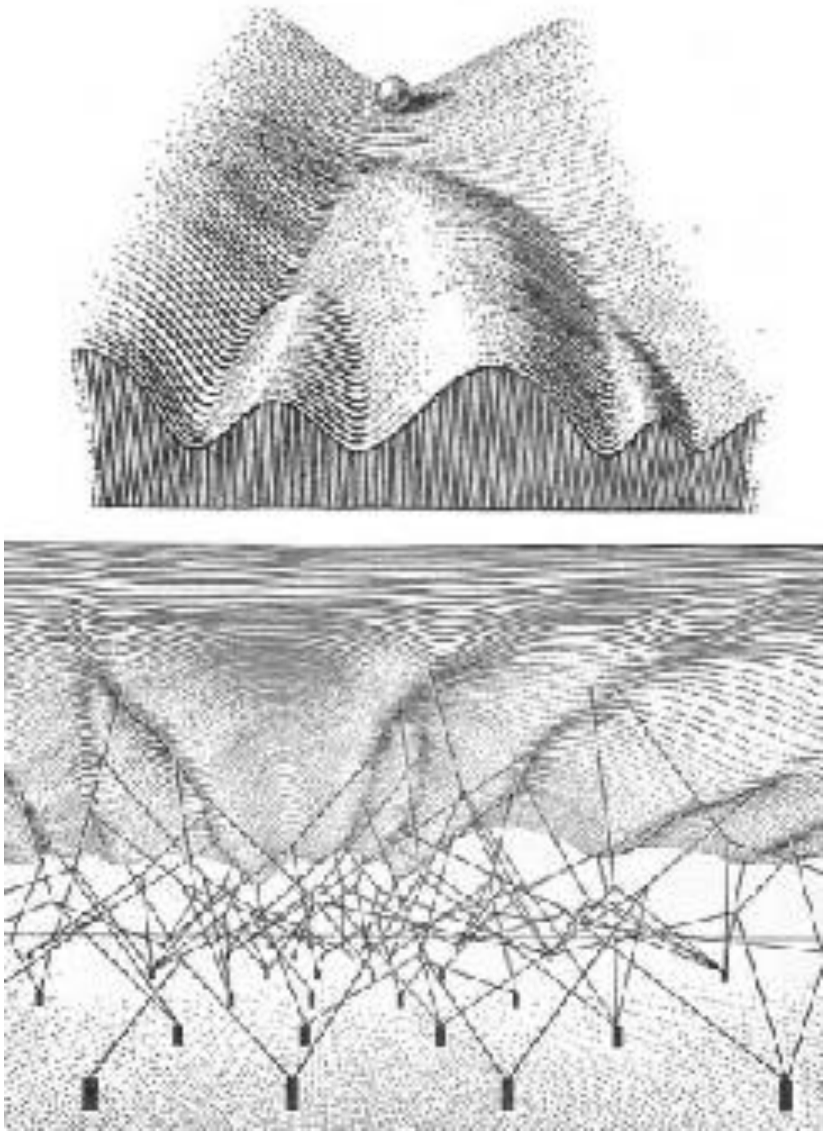
What is epigenetics?

Courtesy of Dag Ahrén



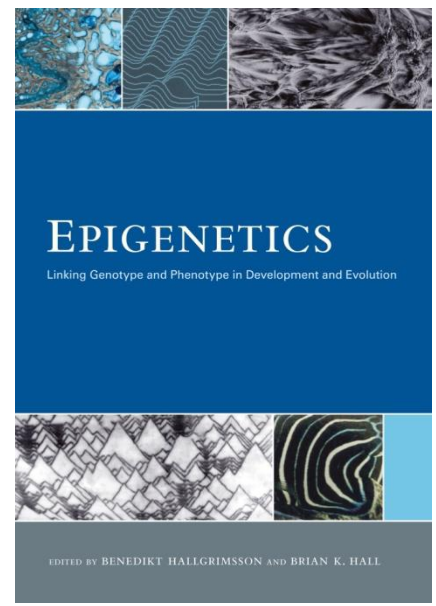
”…the visual cortex may adjust itself during maturation to the nature of its visual experience.”

Blakemore & Cooper 1970



"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"

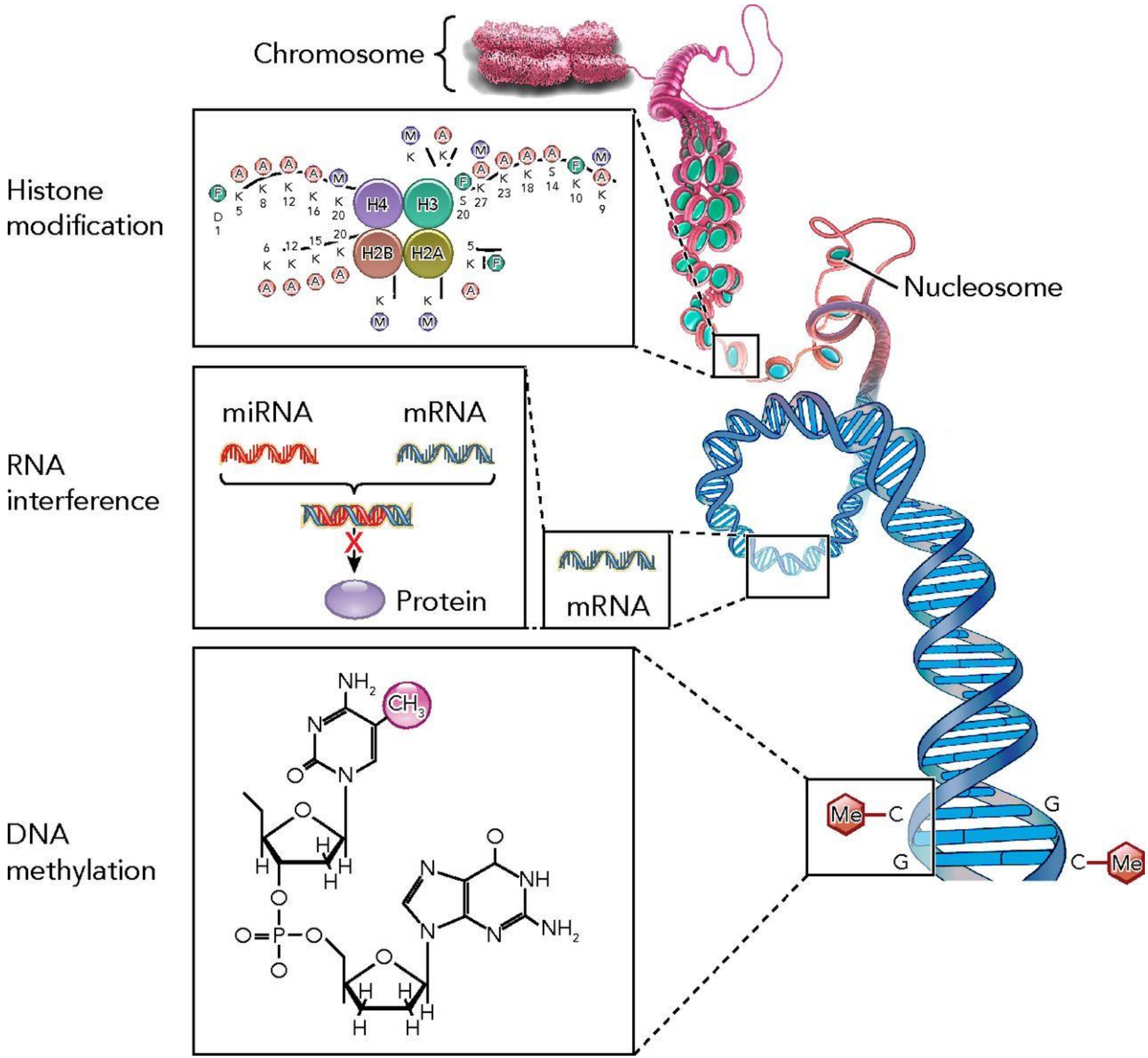
Epigenetic – "auxiliary mechanisms [...] determining which specificities are to be expressed in any particular cell"

Nanney 1958

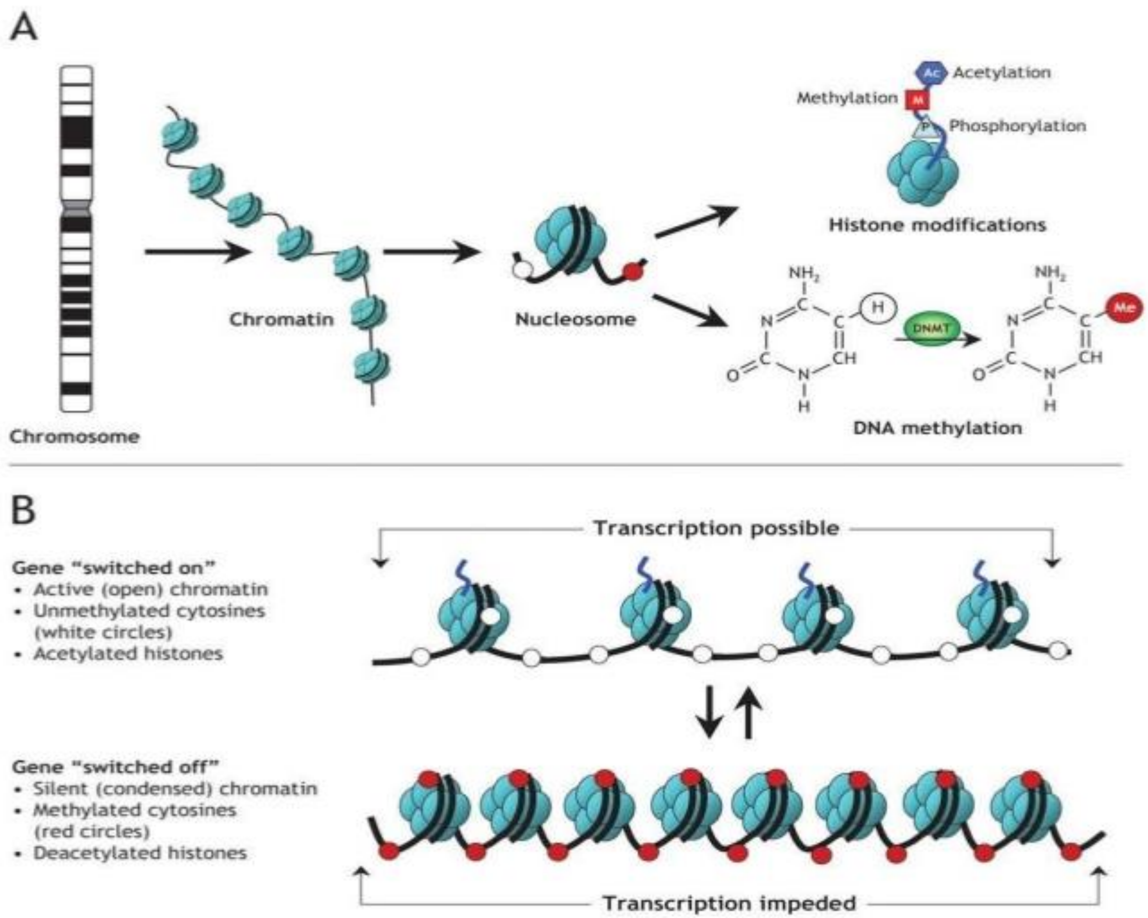
Example of contemporary definition

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"

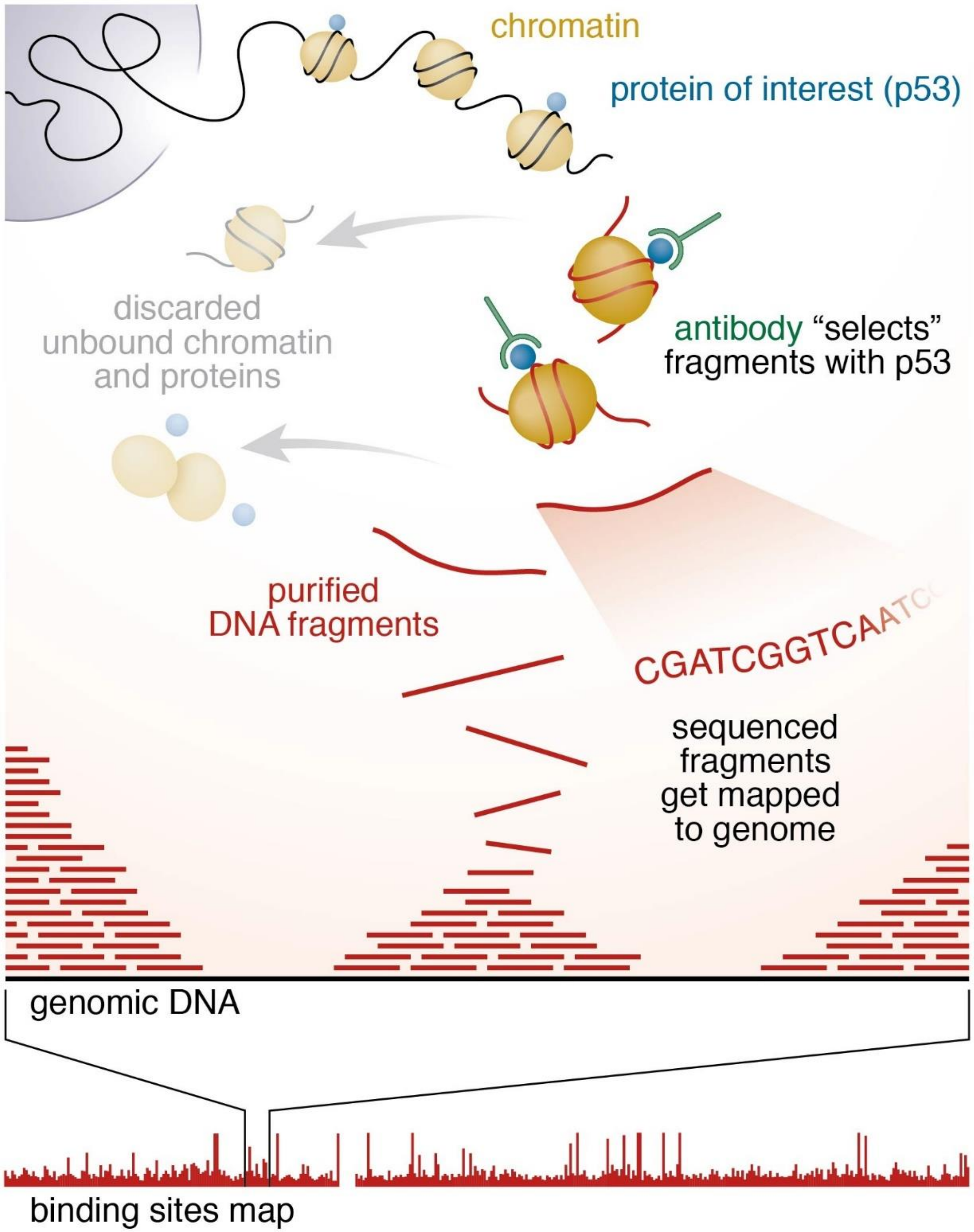
Deans & Maggert 2015


Chromosome
Histone modification
H4
H3
H2B
H2A
Nucleosome
RNA interference
miRNA
mRNA
Protein
mRNA
DNA methylation
Me
C
G

So what do the epigenetic modifications do?



http://pt.slideshare.net/SushmaMarla/dna-methylation

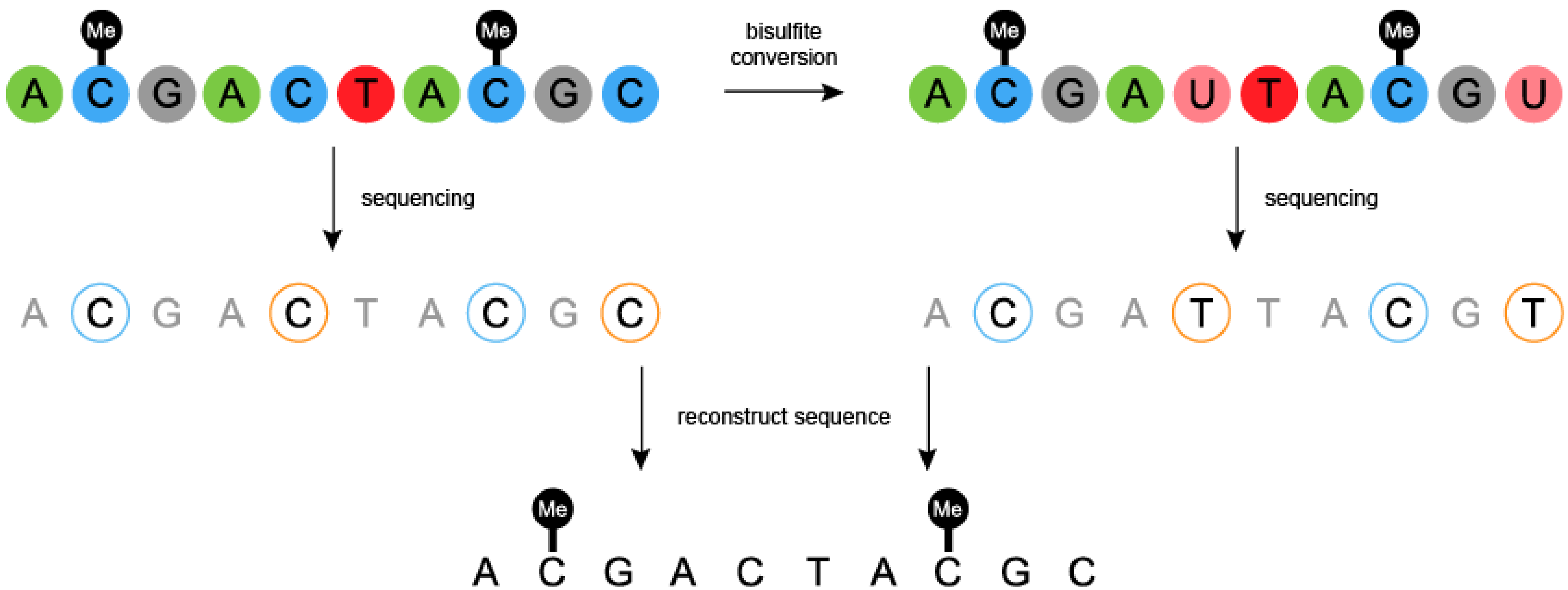


Characterizing histone-DNA interactions

- - ChIPSeq

Characterizing DNA methylation – bisulfite sequencing

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



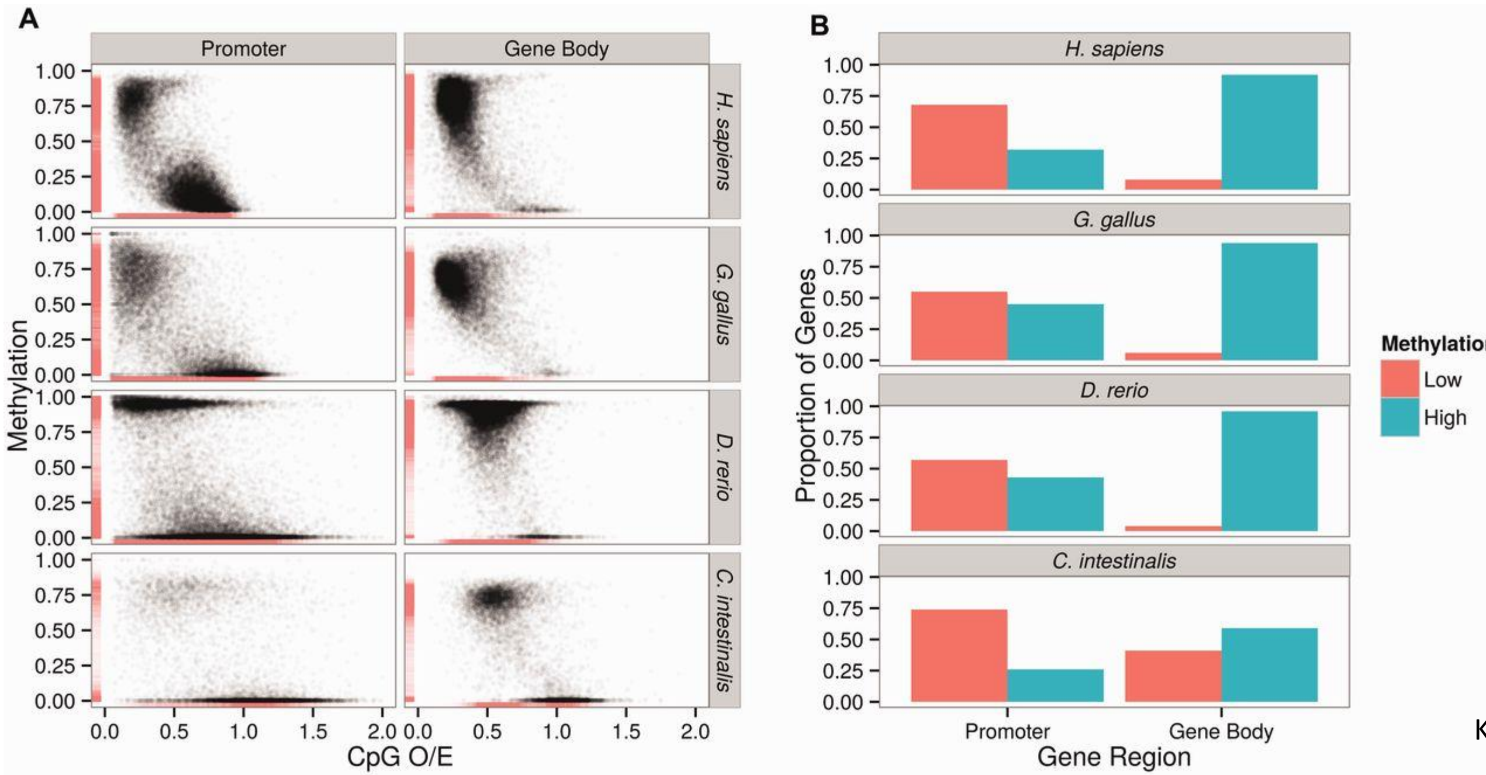
Epigenetics in ecology & evolution

Object – ask questions about its properties

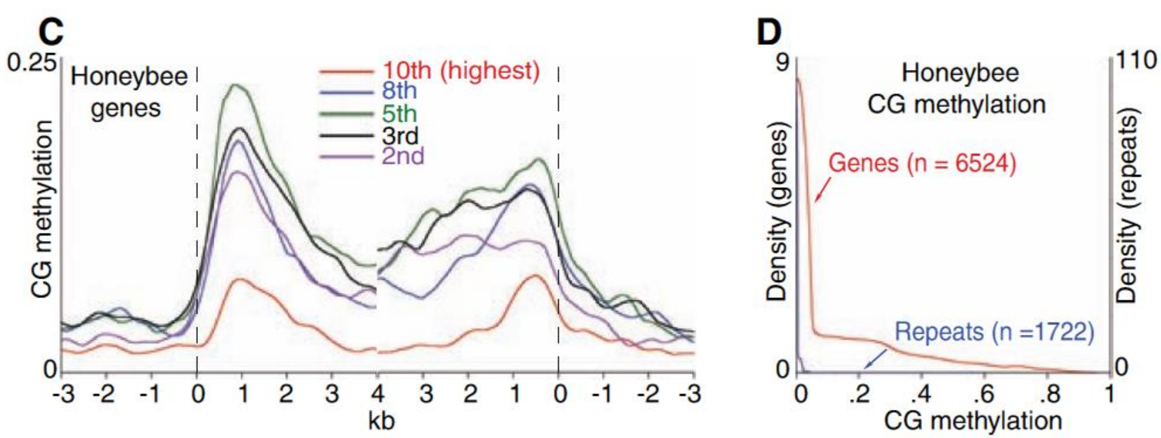
Tool – use it to improve performance on a task

Scaffold – use it to get a different vantage point

Differences in DNA methylation patterns in vertebrates and invertebrates



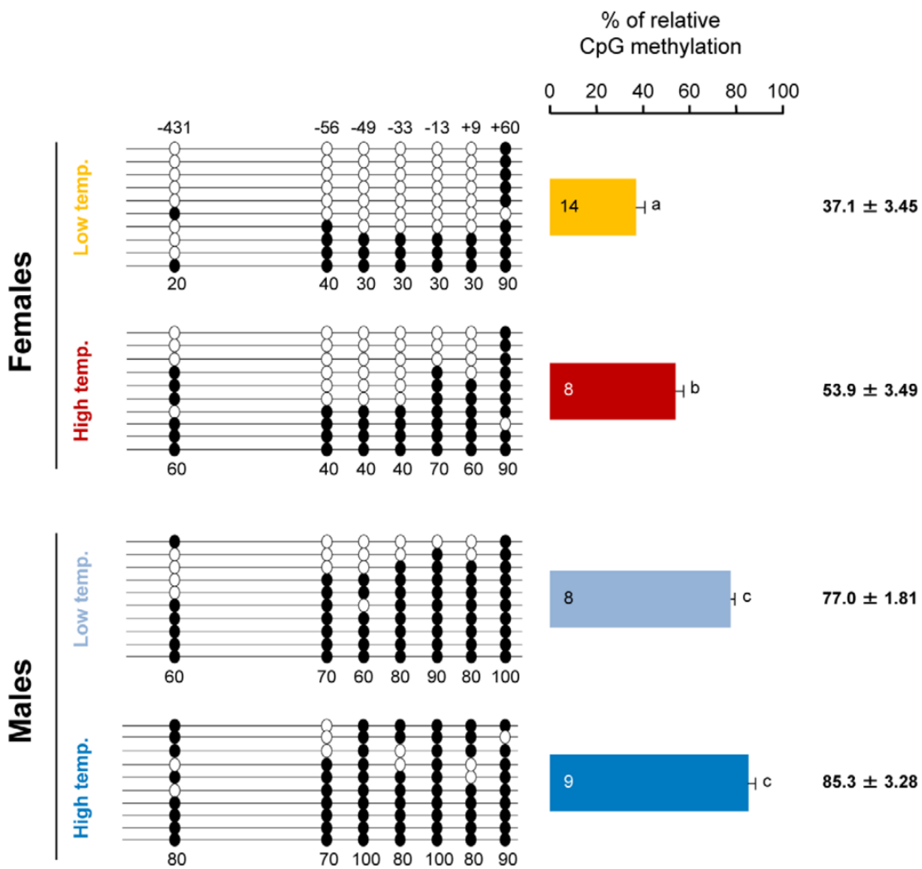
Keller et al. 2016

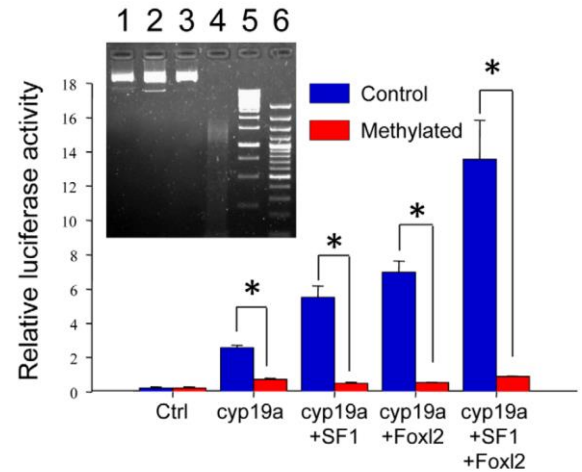


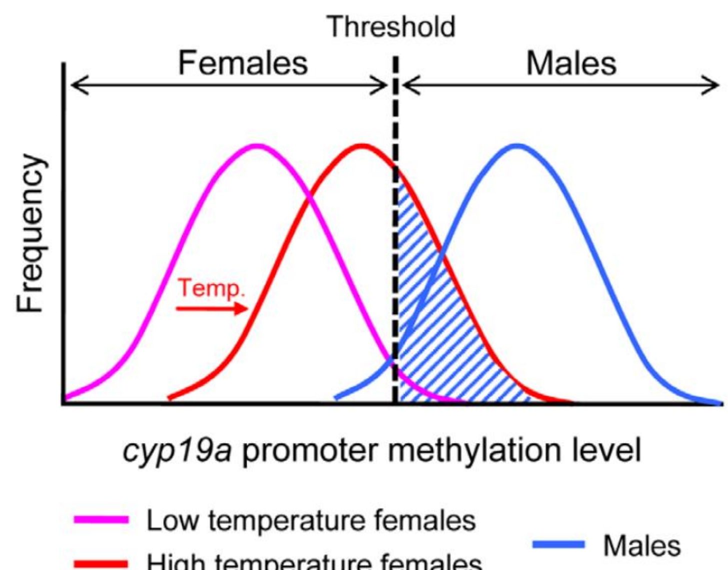
Zemach et al. 2010

Developmental plasticity

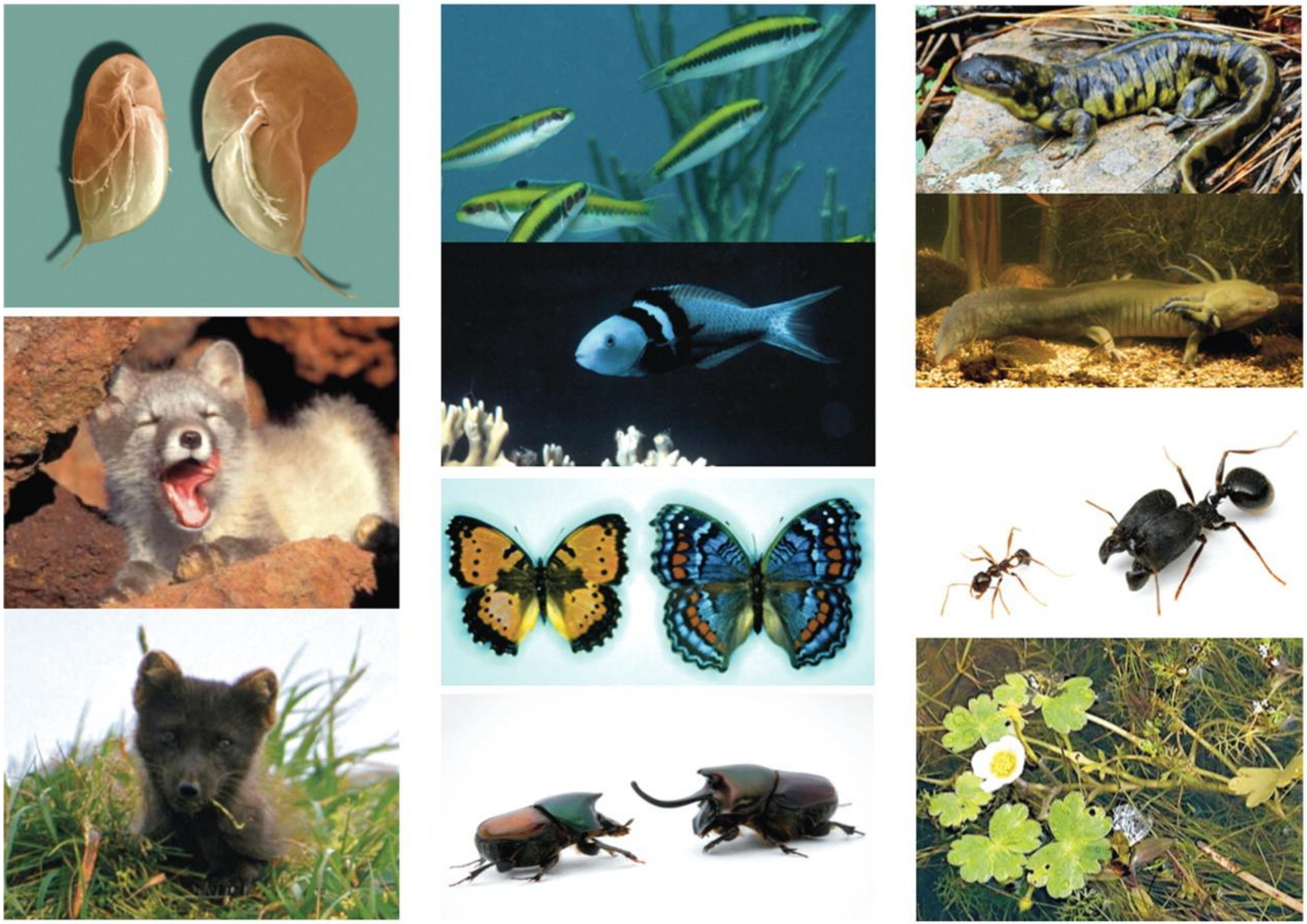
cyp19a methylation and sex determination in sea bass







Navarra-Martin et al. 2011. PLoS Biol

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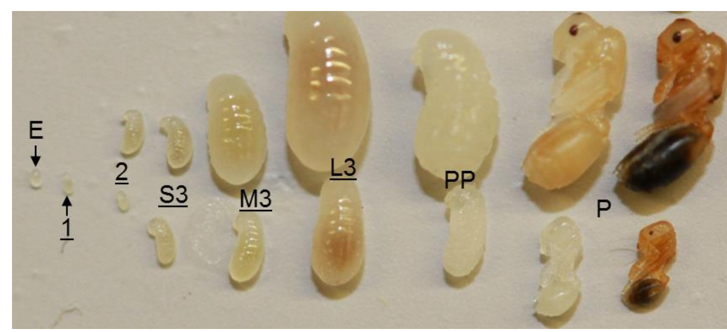

E
1
2
S3
M3
L3
PP
P

Methylation may drive caste differentiation in ants….

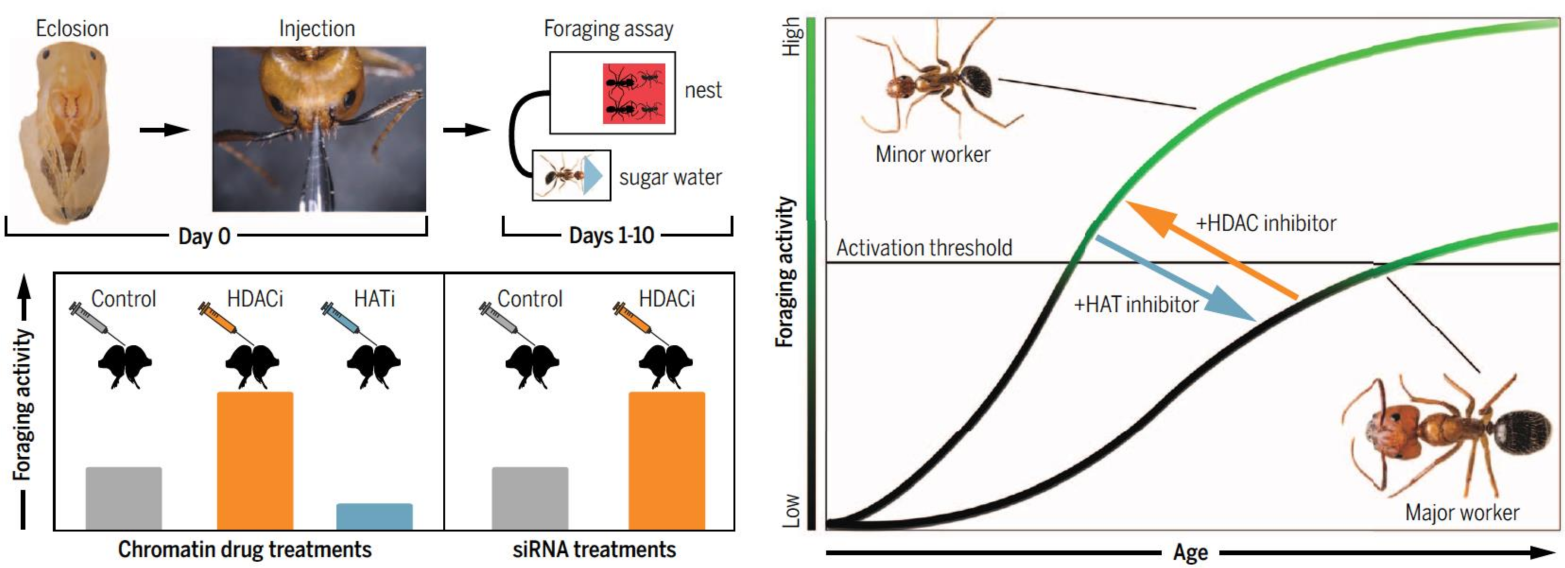
C

	Queen	Virgin Queen	Major	Minor	Male	Larva	Embryo
Embryo	846	1370	529	602	1493	263	0
Larva	460	573	46	47	1132	0	
Male	580	501	1230	1276	0		
Minor	530	488	9	0			
Major	401	481	0				
Virgin Queen	167	0					
Queen	0						

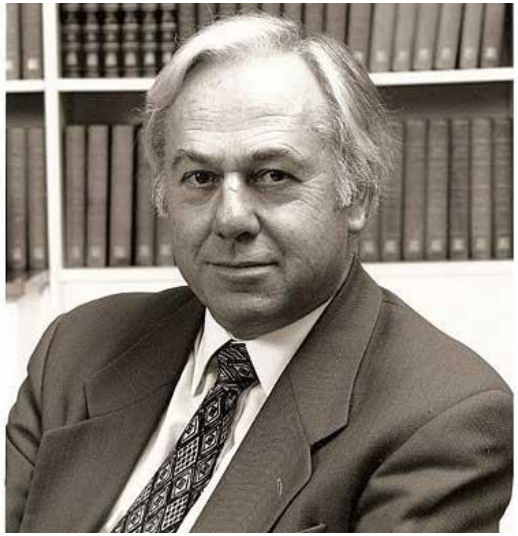
	Queen	Virgin Queen	Gamergate	Worker	Male	Larva	Embryo
Embryo	434	432	218	97	158	75	0
Larva	345	381	167	89	246	0	
Male	72	121	99	68	0		
Worker	226	256	38	0			
Gamergate	152	258	0				
Virgin Queen	109	0					
Queen	0						

Bonasio et al. 2012. Curr Biol

… or maybe histone modifications… (behavioural differences)

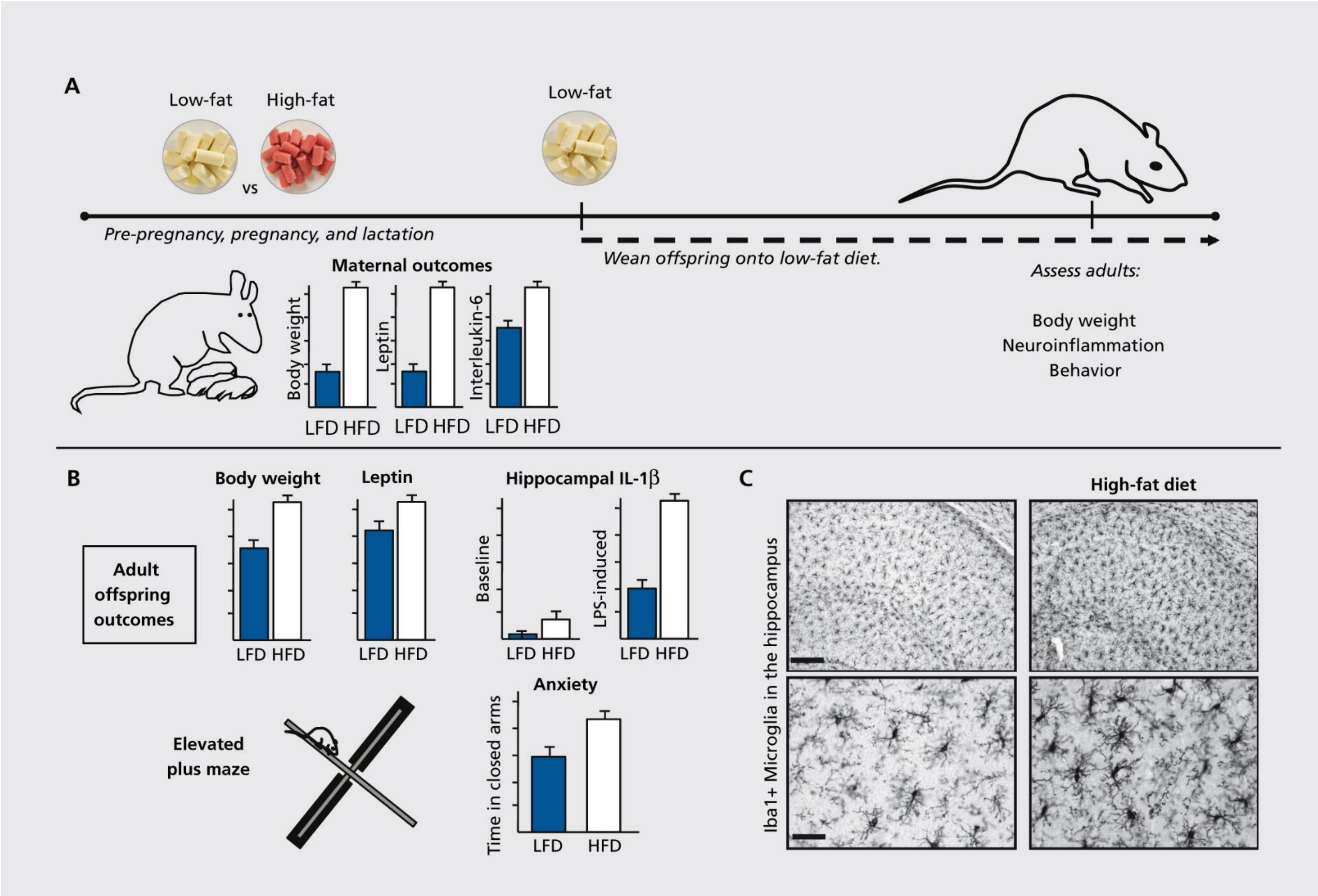


Simola et al. 2016. Science

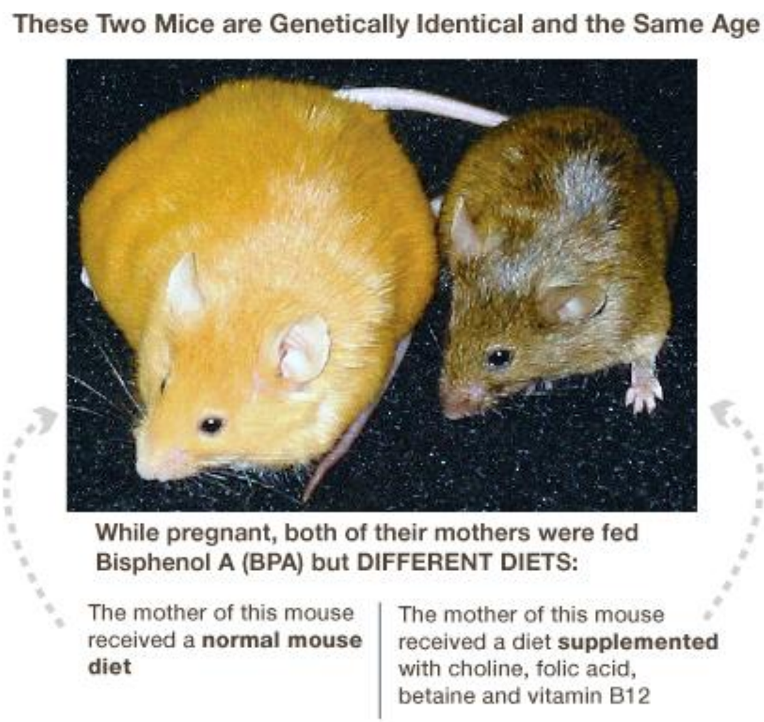


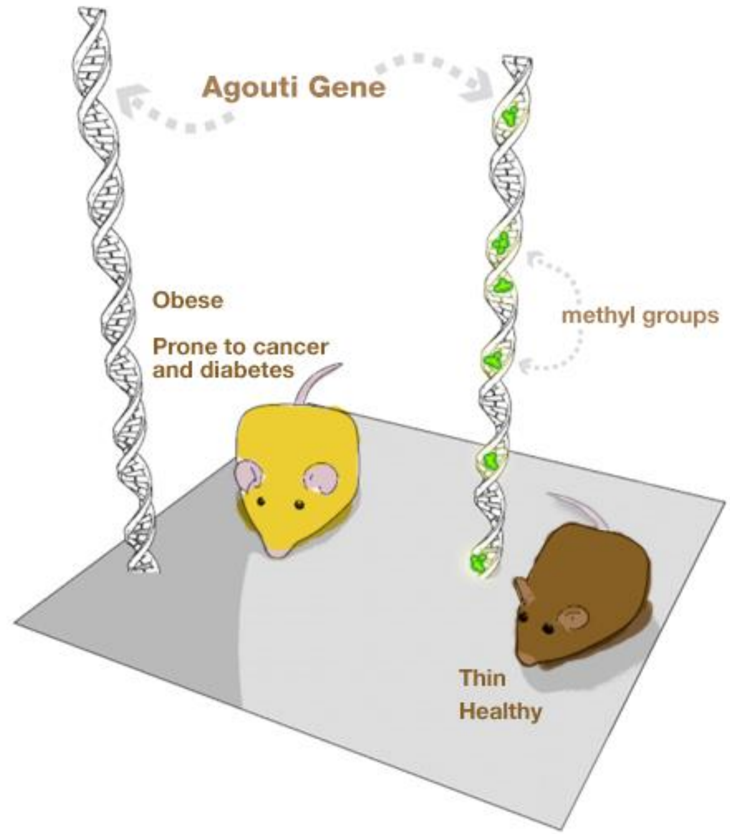
The Barker Hypothesis

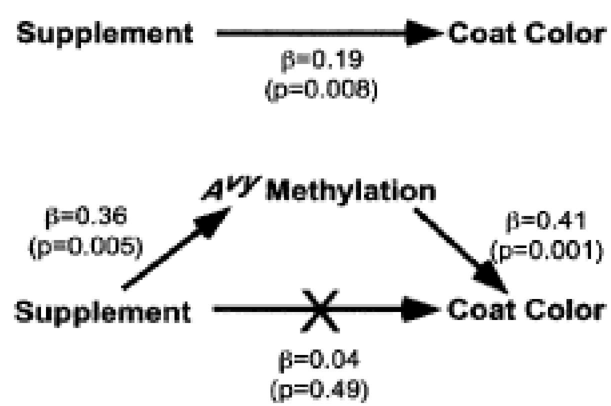
”Recent findings suggest that human fetuses adapt to a limited supply of nutrients and in doing so permanently change their physiology and metabolims. These ”programmed” changes may be the origins of disease in later life, including coronary heart disease and the ralated disorders stroke, diabetes, and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



Bilbo & Tsang 2010

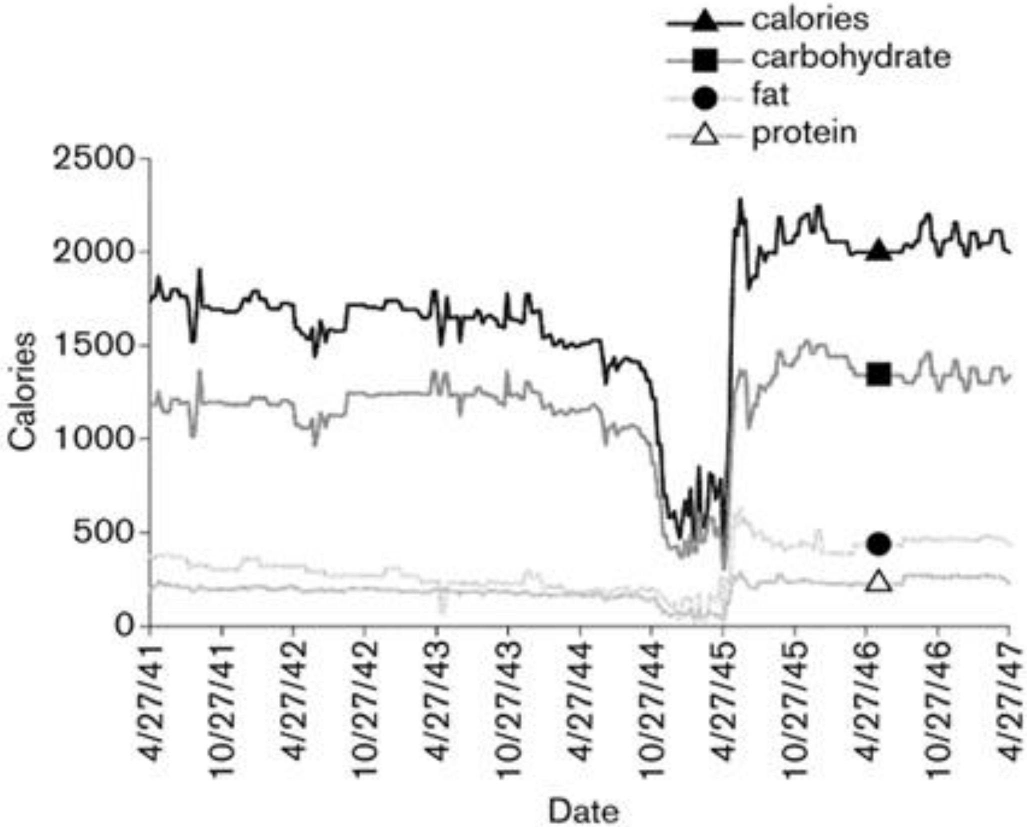




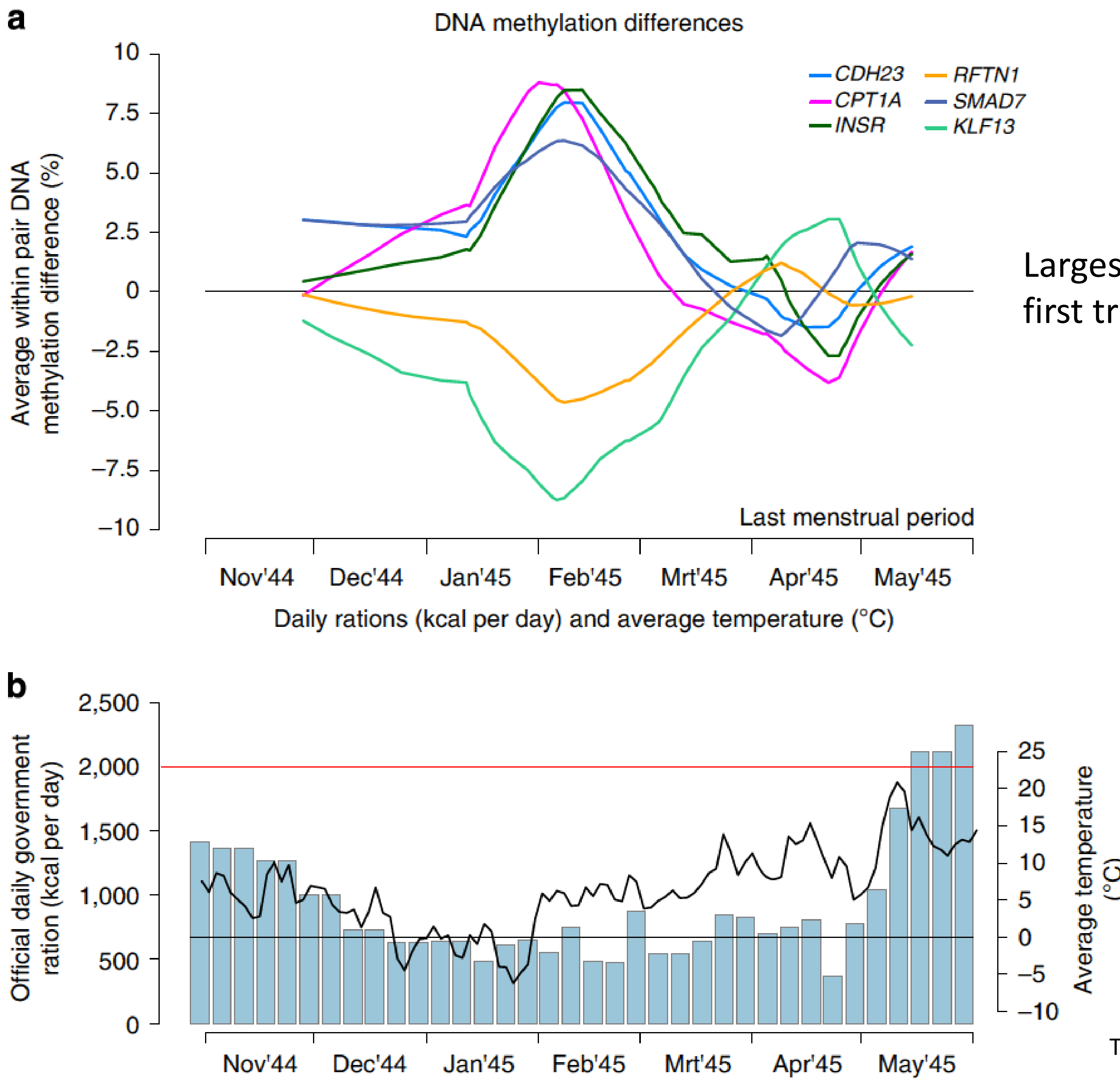


Waterland & Jirtle 2003

The Dutch Hunger Winter cohort

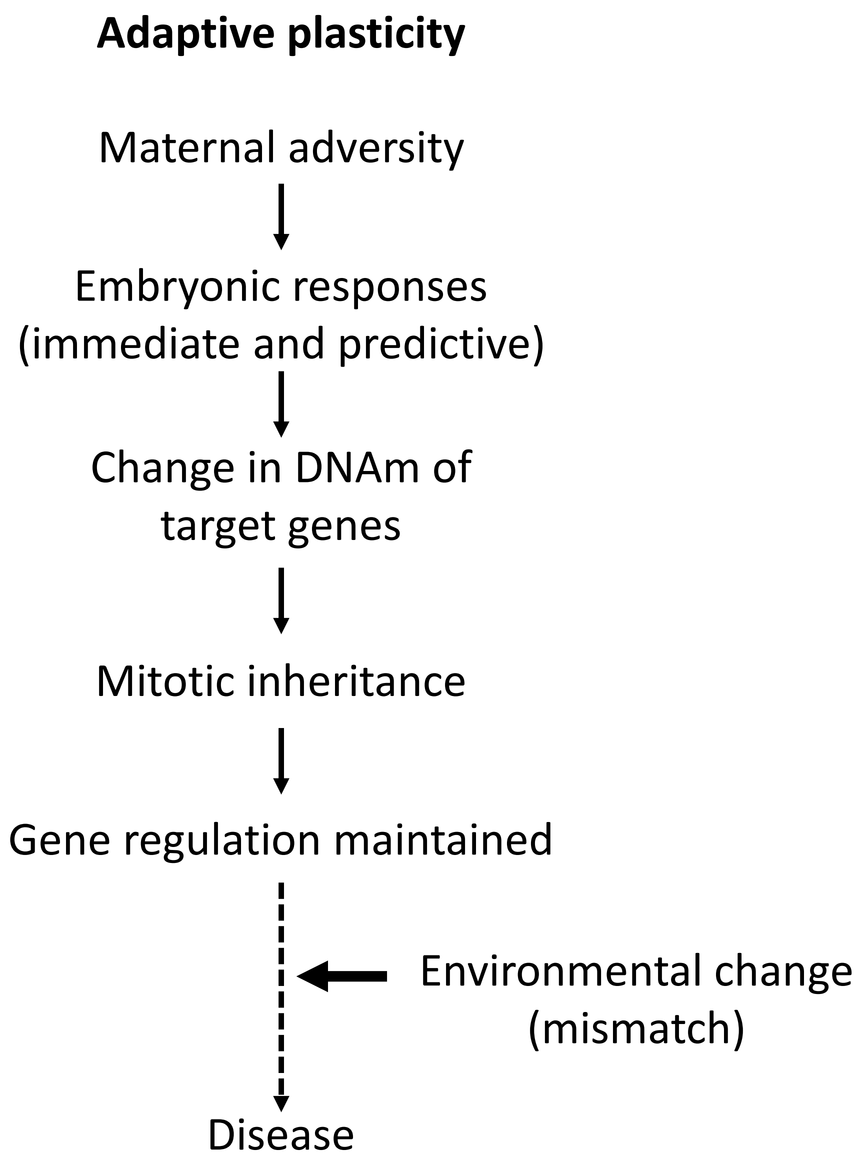


Lumey et al. 2007

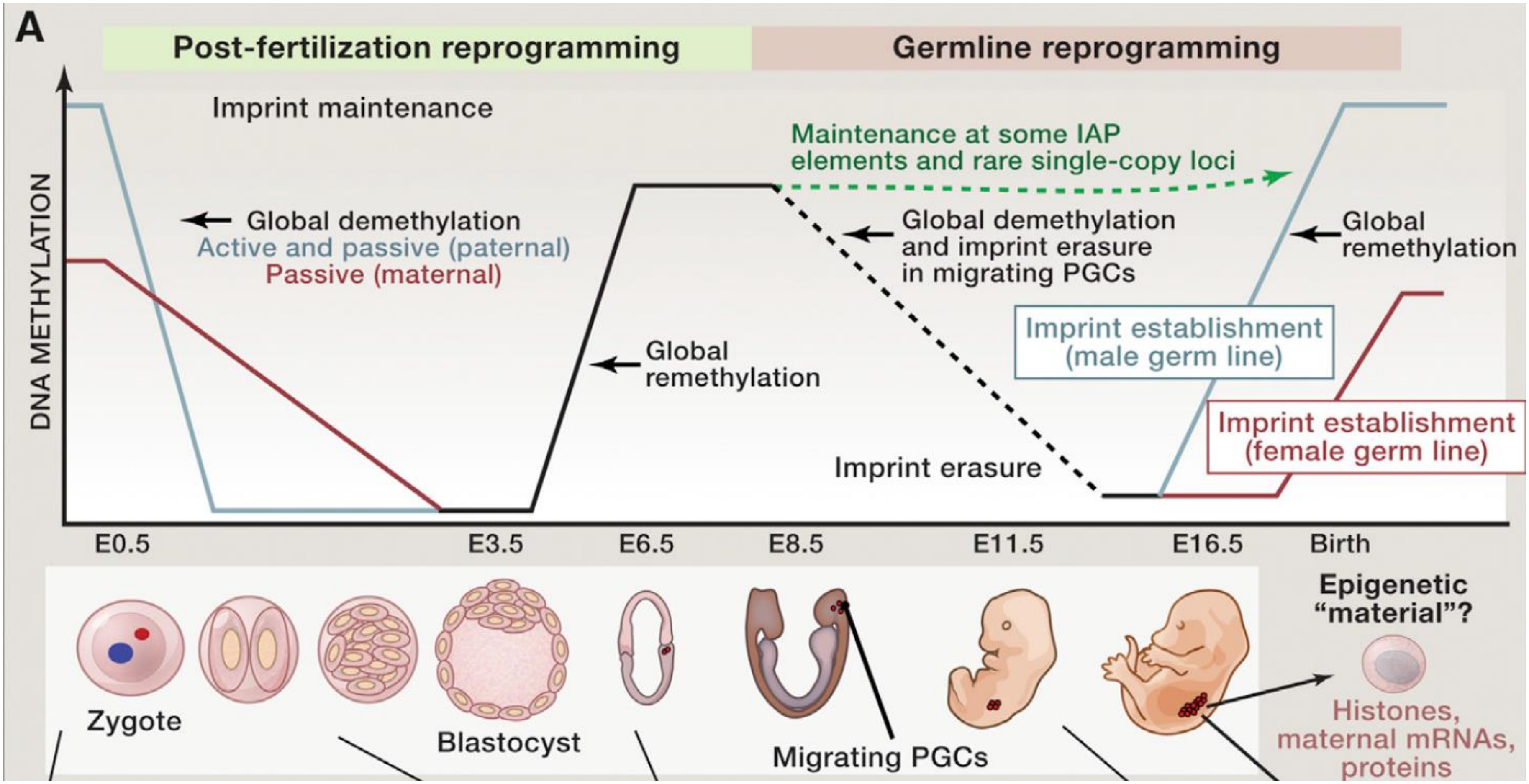


Largest difference for first trimester exposure

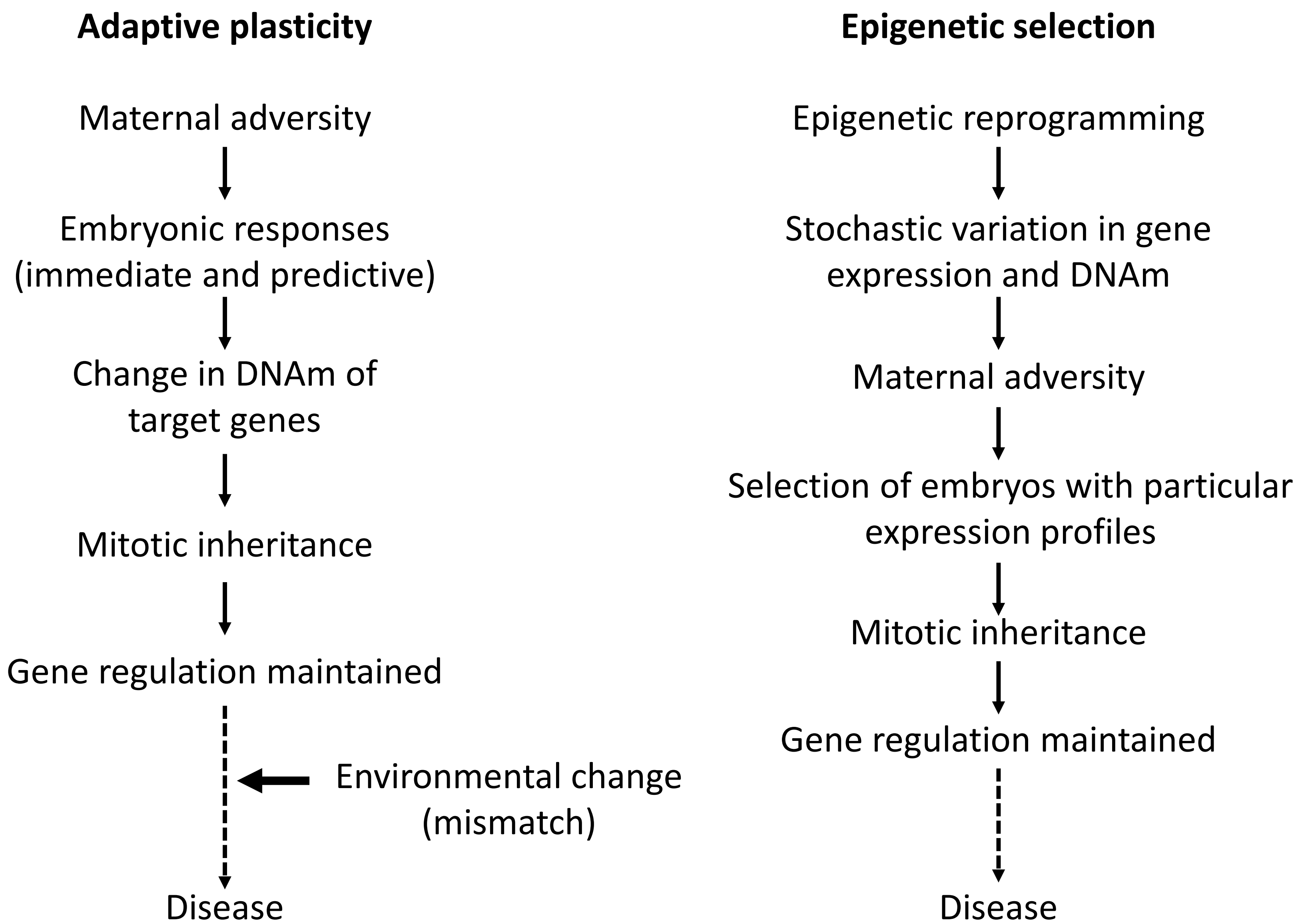
Tobi et al. 2014. Nat Comm


Adaptive plasticity
Maternal adversity
Embryonic responses (immediate and predictive)
Change in DNAm of target genes
Mitotic inheritance
Gene regulation maintained
Environmental change (mismatch)
Disease

Epigenetic reprogramming in mammals – twice

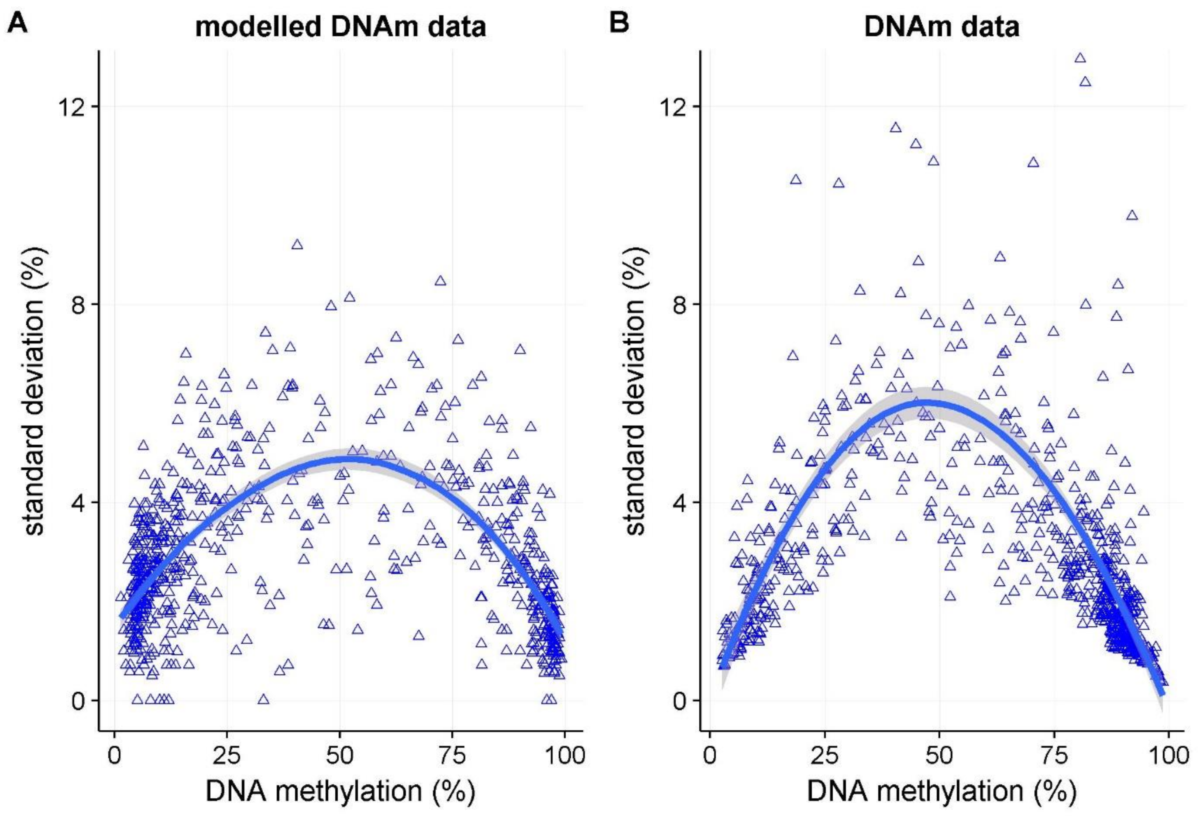


Heard & Martiensson 2014. Cell

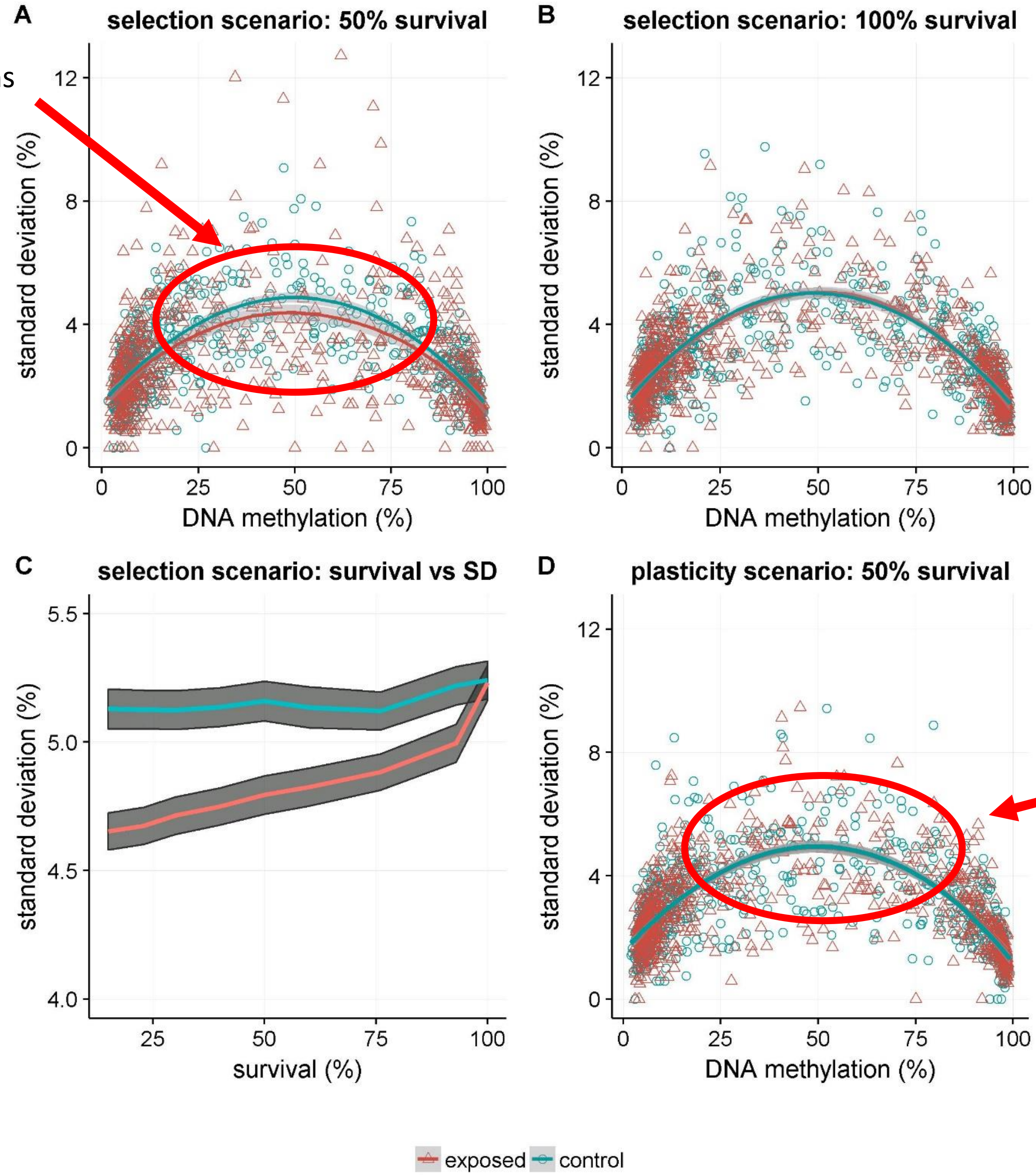

Adaptive plasticity
Maternal adversity
Embryonic responses
(immediate and predictive)
Change in DNAm of
target genes
Mitotic inheritance
Gene regulation maintained
Environmental change
(mismatch)
Disease
Epigenetic selection
Epigenetic reprogramming
Stochastic variation in gene
expression and DNAm
Maternal adversity
Selection of embryos with particular
expression profiles
Mitotic inheritance
Gene regulation maintained
Disease

Mechanistic modelling of epigenetic reprogramming

- Interaction between TF and DNAm
- Allowing for environmental effects

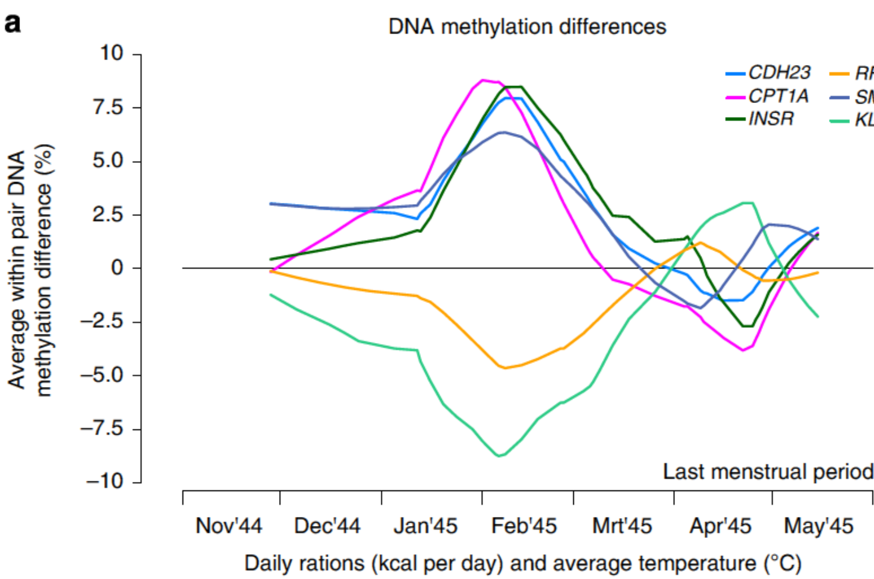


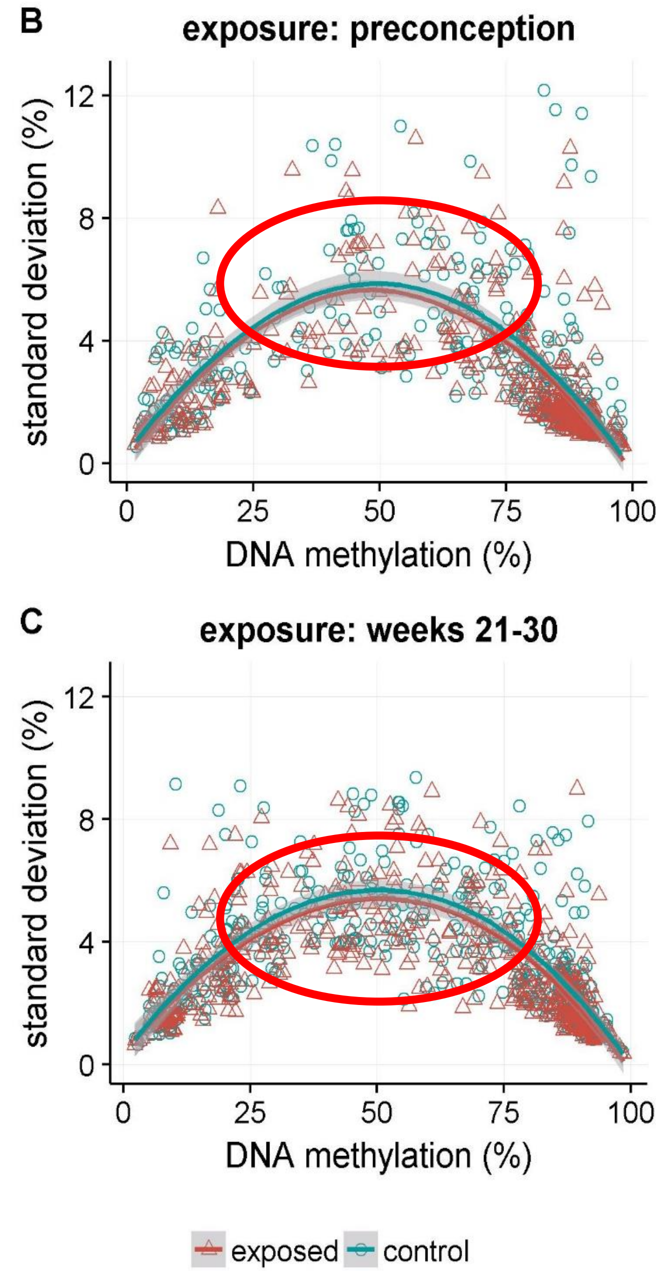
- Different means
- Reduced variance



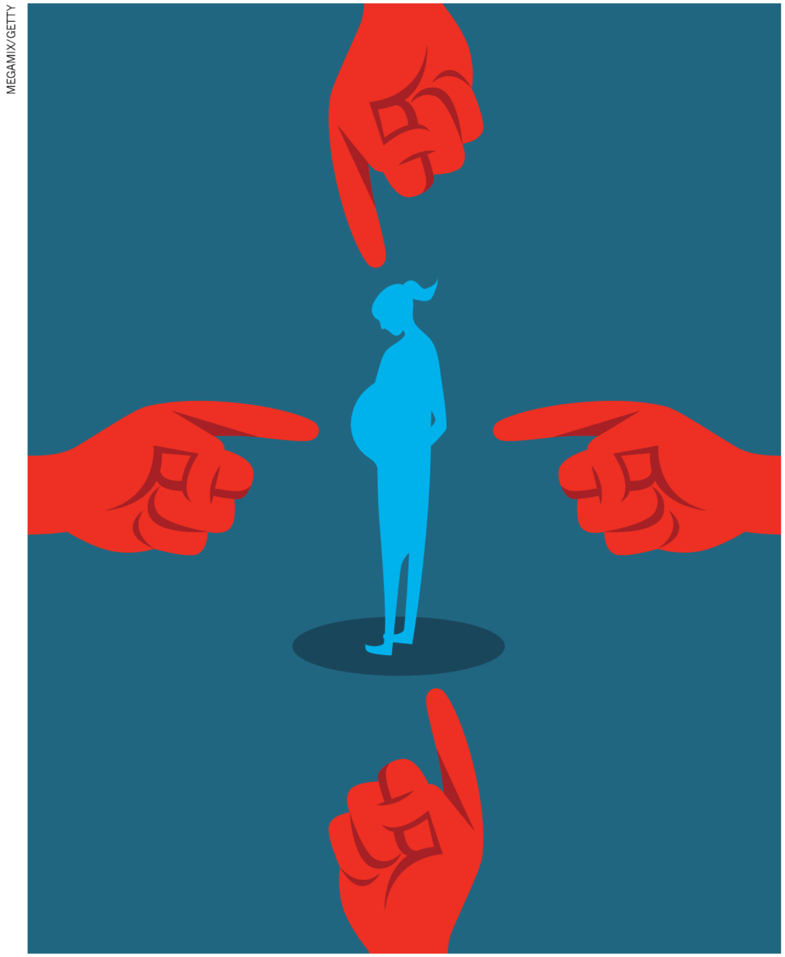
- Different means
- Same variance

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





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



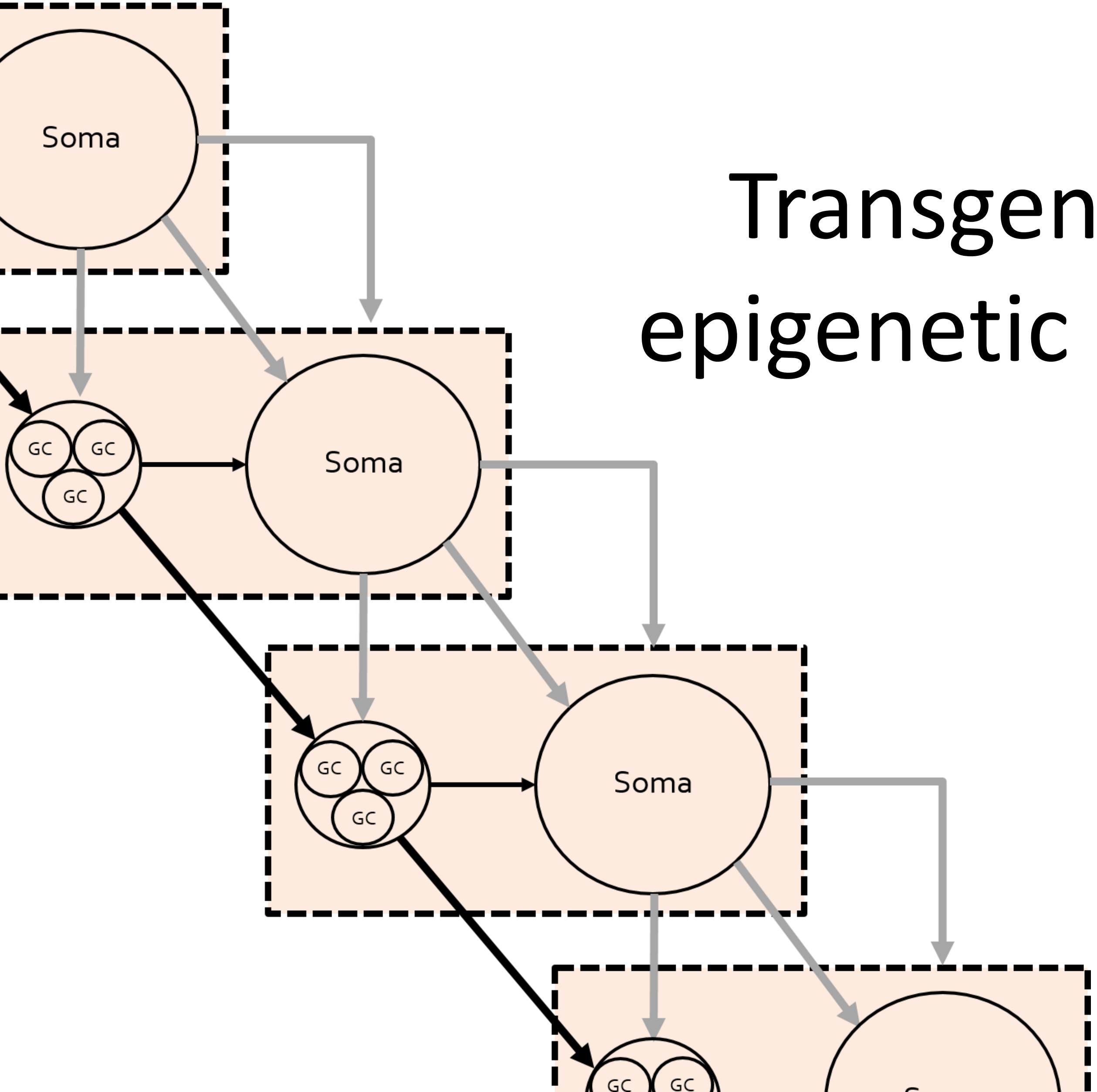
Don’t blame the mothers

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

Richardson et al. 2014. Nature

Waggoner & Uller 2014. New Genet Soc

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

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Darwin 1859

The Principles of Evolution by Natural Selection

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Darwin 1859

The Principles of Evolution by Natural Selection

variation

Variation in traits among members of a species

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Darwin 1859

The Principles of Evolution by Natural Selection

variation — Variation in traits among members of a species

selection — Different variants leave different numbers of offspring

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Darwin 1859

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selection — Different variants leave different numbers of offspring

heredity — Variation is heritable, so that offspring resemble their parents

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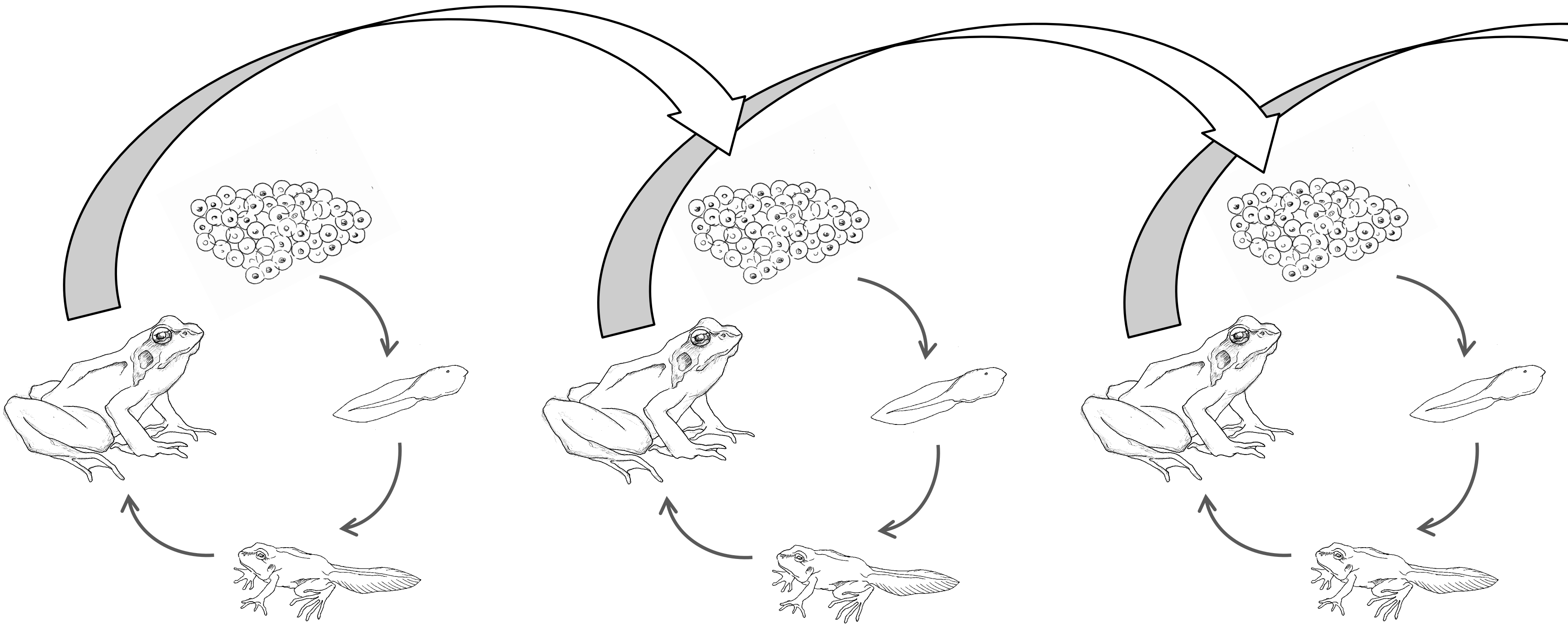


"Heredity is not a peculiar or unique principle for it is only similarity of growth and differentiation in successive generations…. The causes of heredity are thus reduced to the causes of successive differentiation of development, and the mechanisms of heredity are merely the mechanisms of differentiation."

Conklin 1908. Science

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

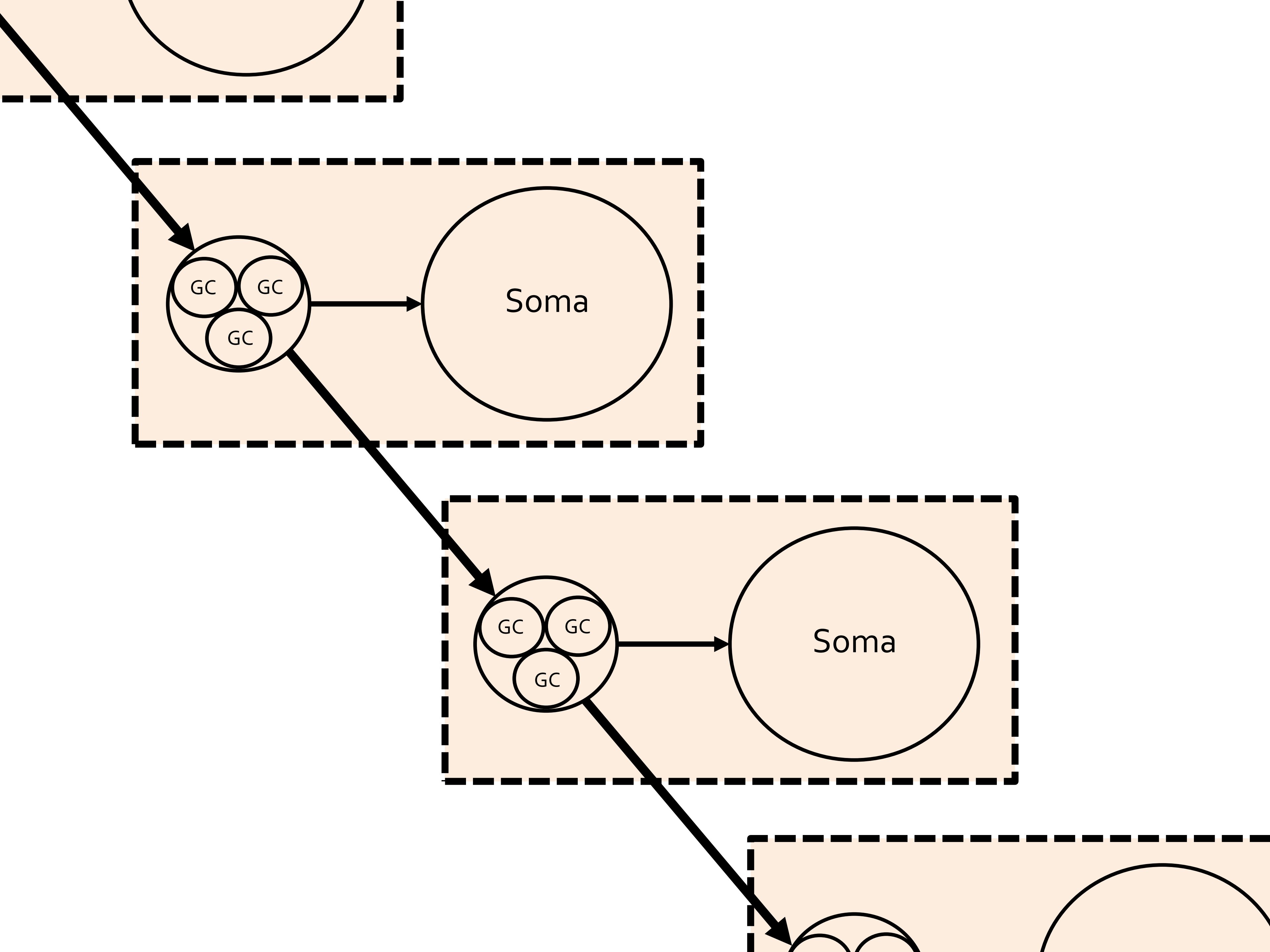
Morgan 1910. Am Nat

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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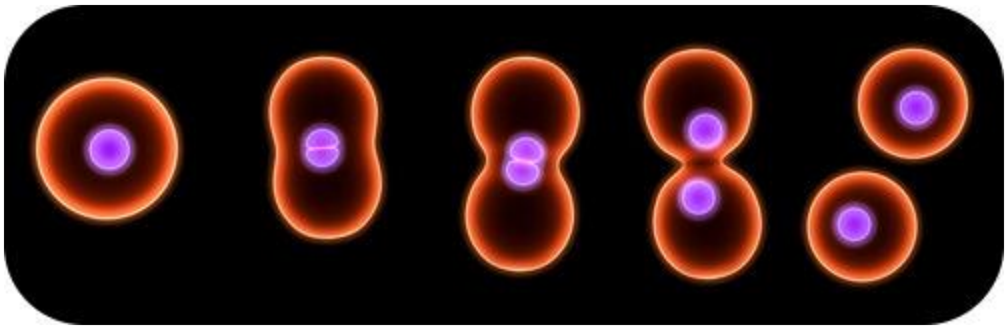

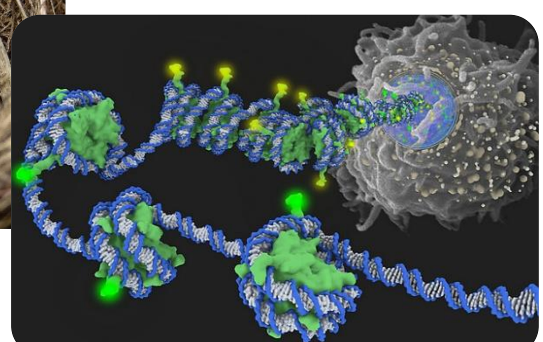

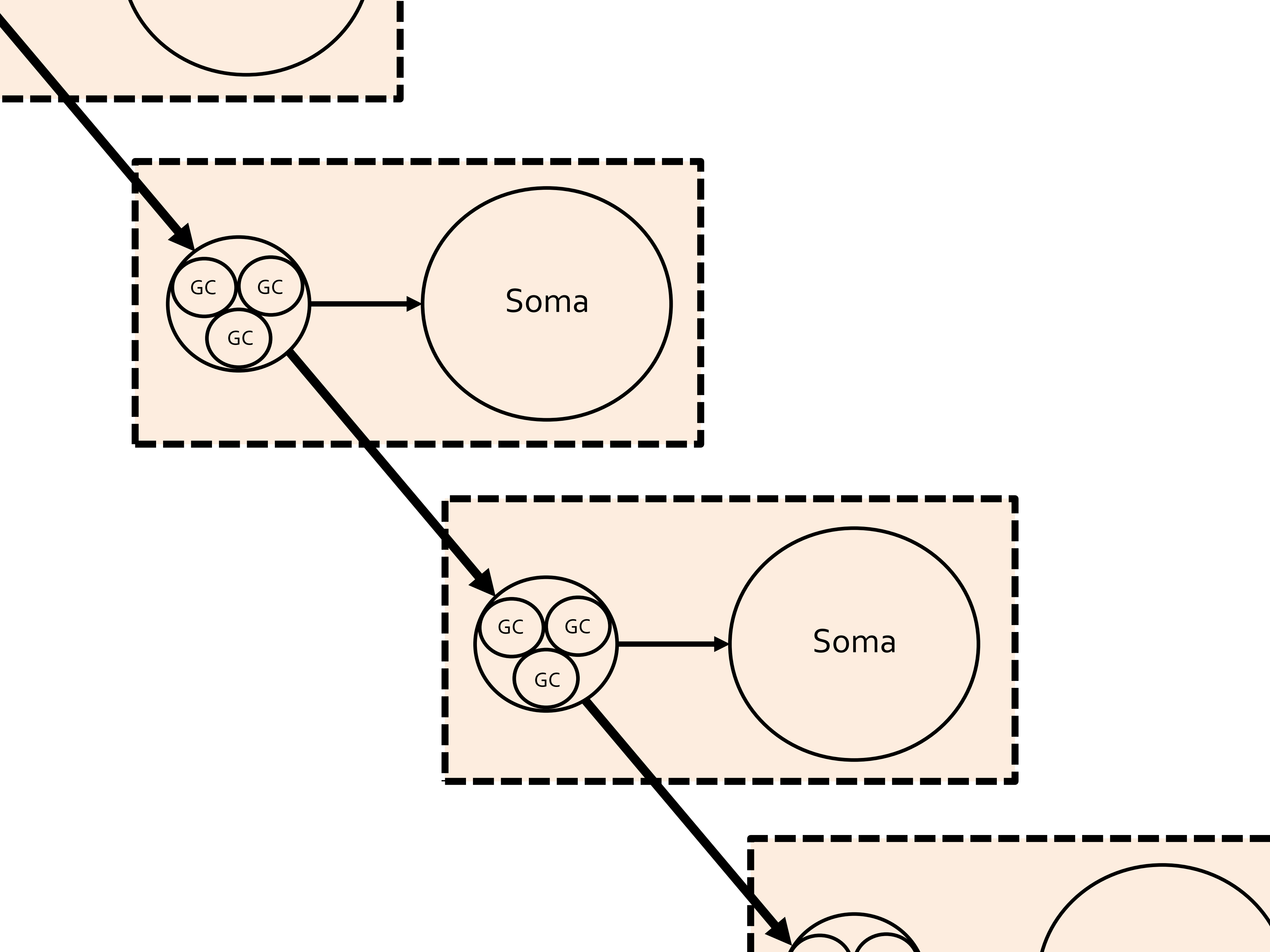
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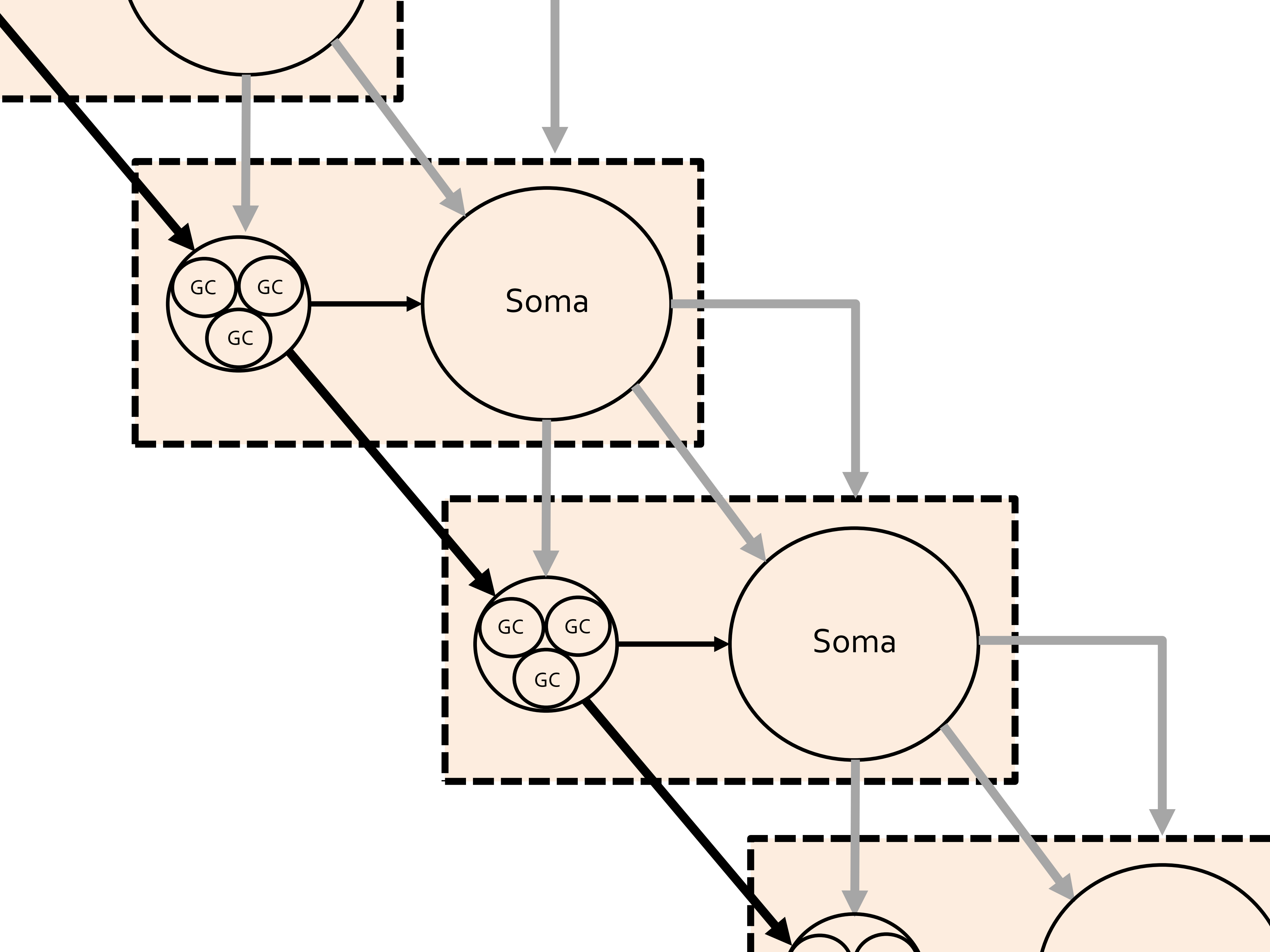

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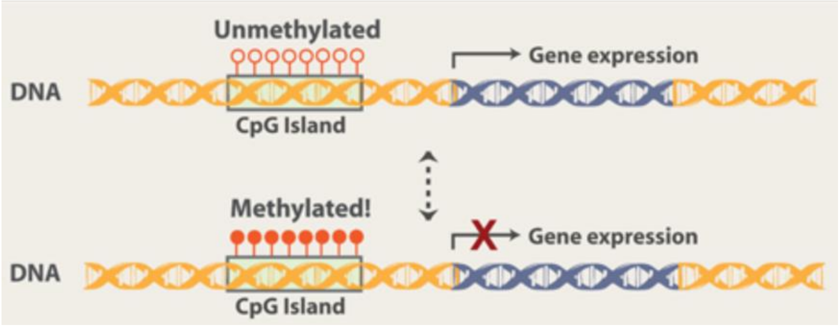
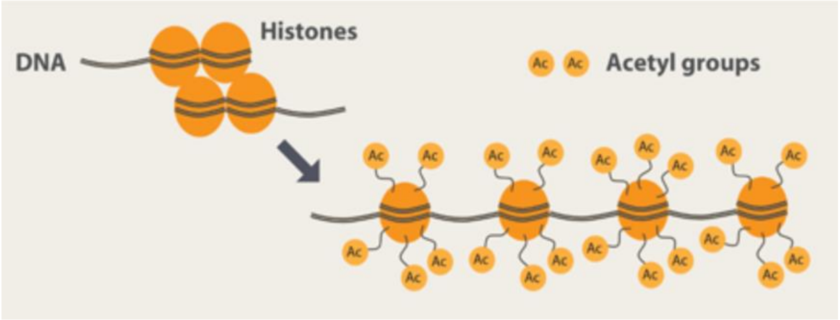
How do epigenetic mechanisms fit?

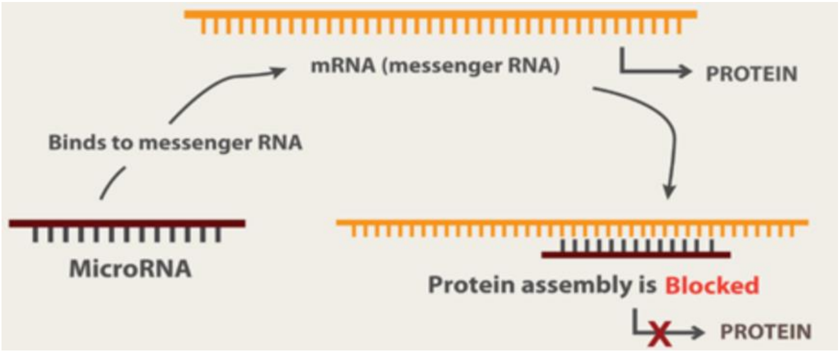
- **DNA methylation**



- **Histone modification**



- **MicroRNA action**

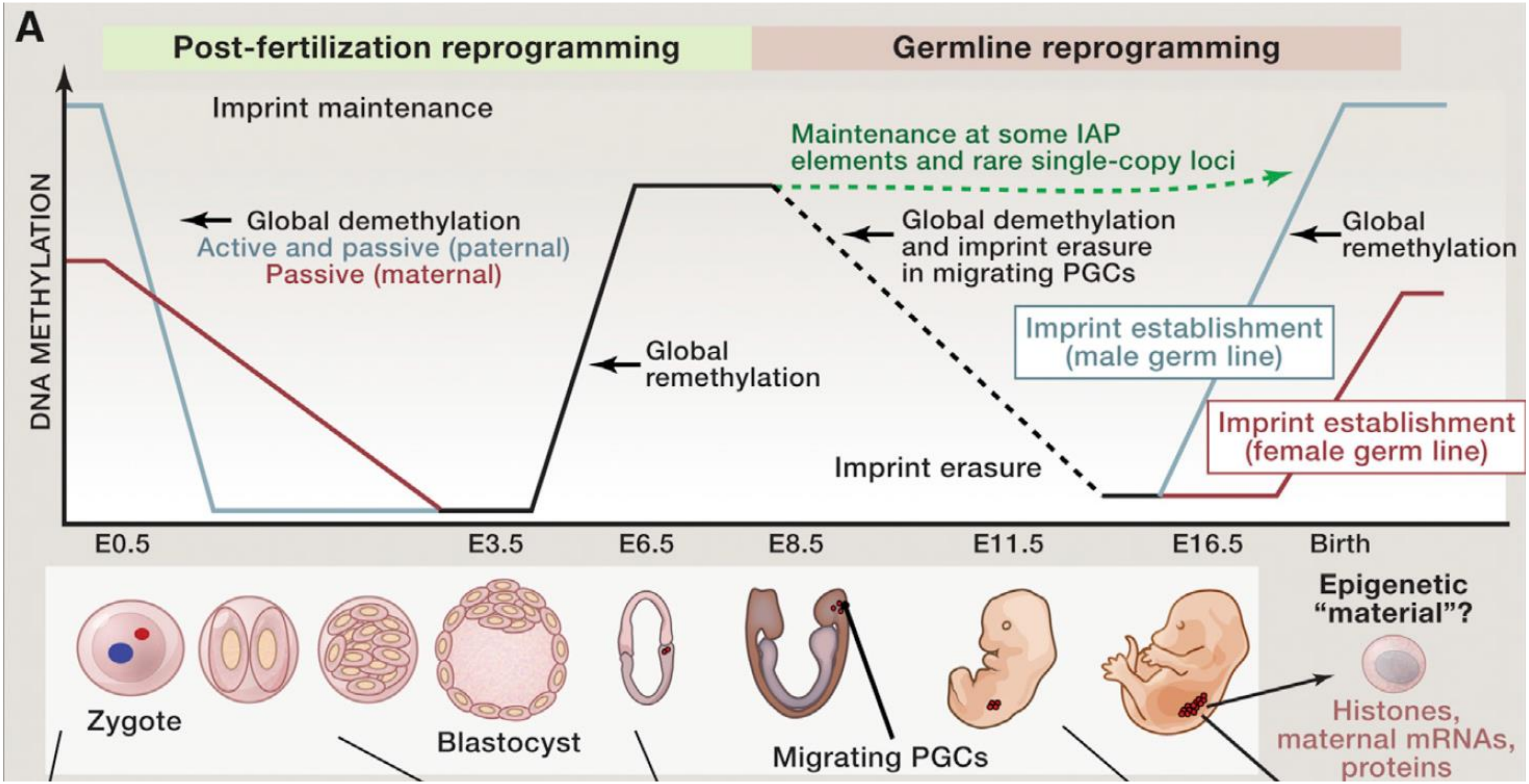


http://knowingneurons.com/2013/06/13/your-brain-on-epigenetics/

- **Epigenetic "marks" usually reset between generations!**

Transgenerational epigenetic inheritance

- **Limited scope in mammals: double resetting**



Heard & Martiensson 2014. Cell

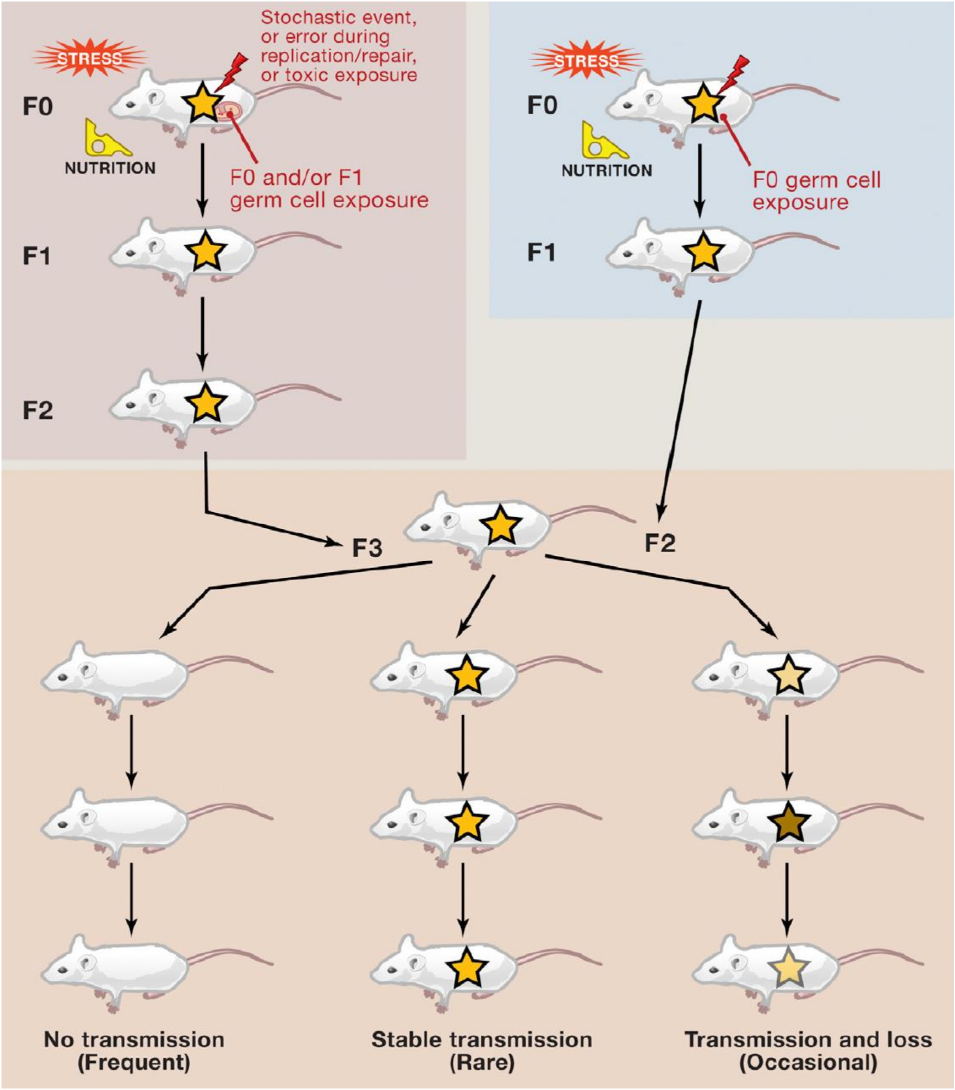
Between-generation epigenetic inheritance

Intergenerational

(e.g. parental effects)

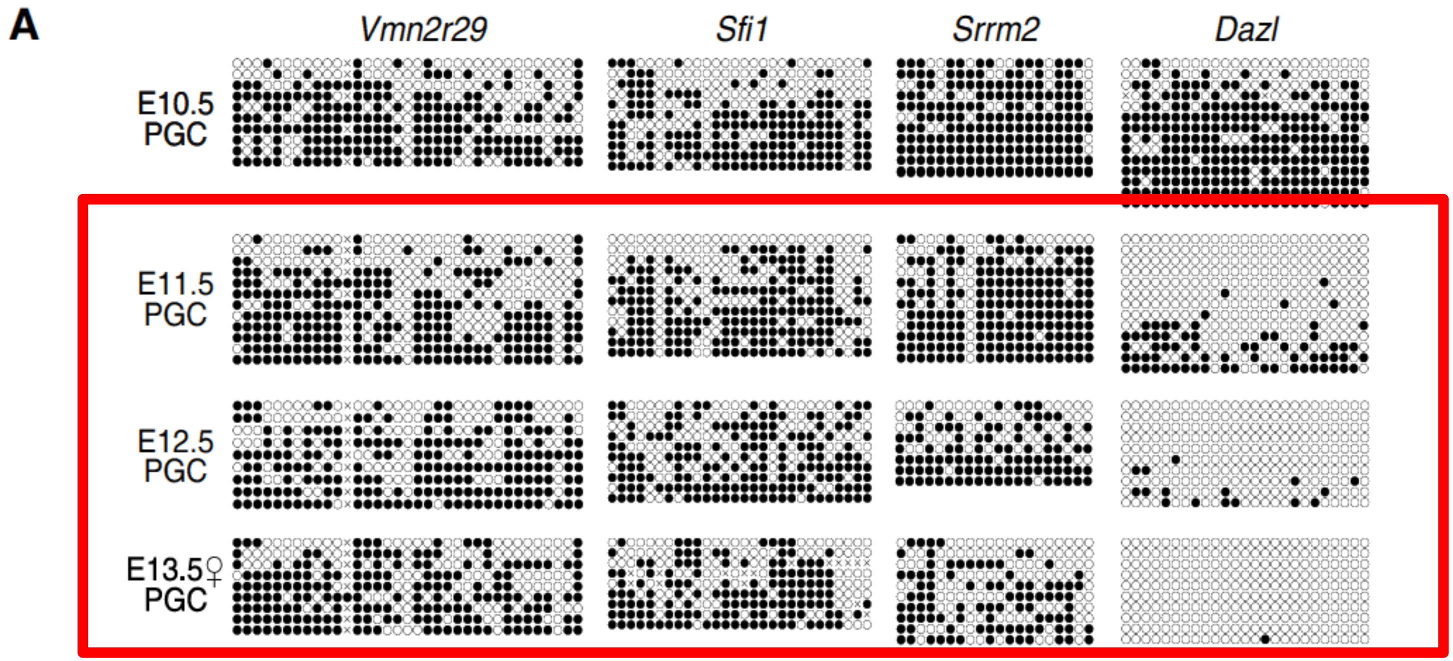
Transgenerational

Resistance against resetting,
partial resetting,
incomplete resetting



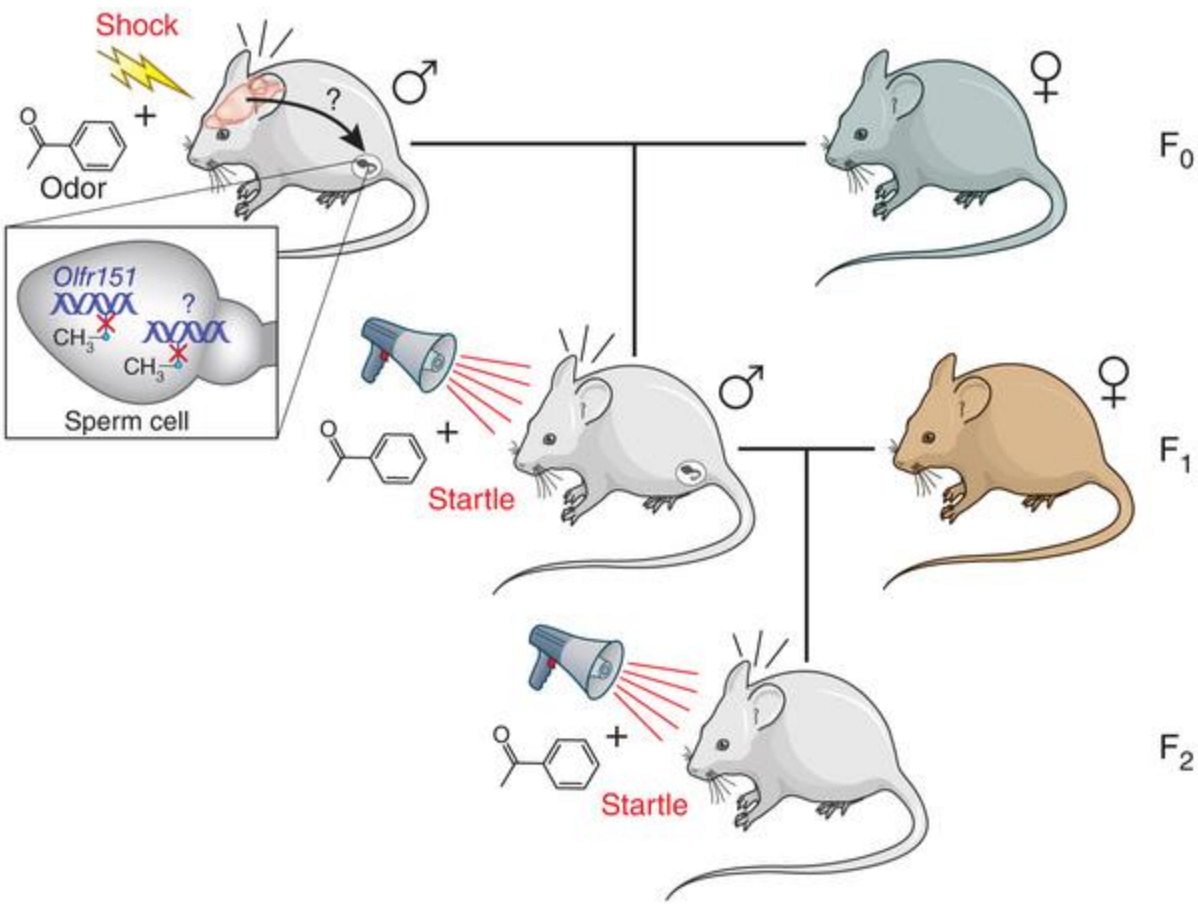
Heard & Martiensson 2014. Cell

Methylation can escape reprogramming in the primordial germ cells



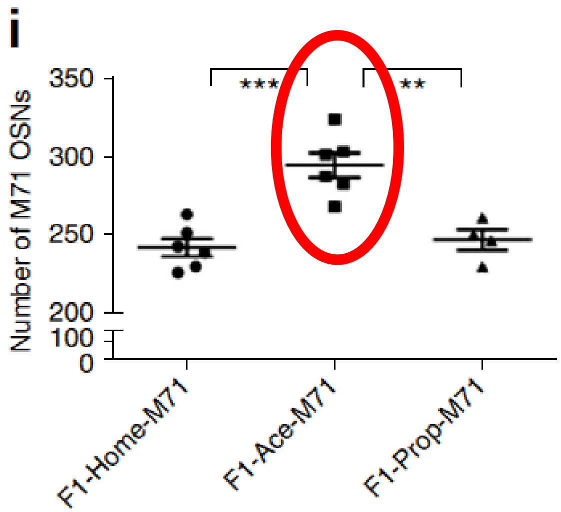
Hackett et al. 2013. Science

Directional trans-generational plasticity in mice

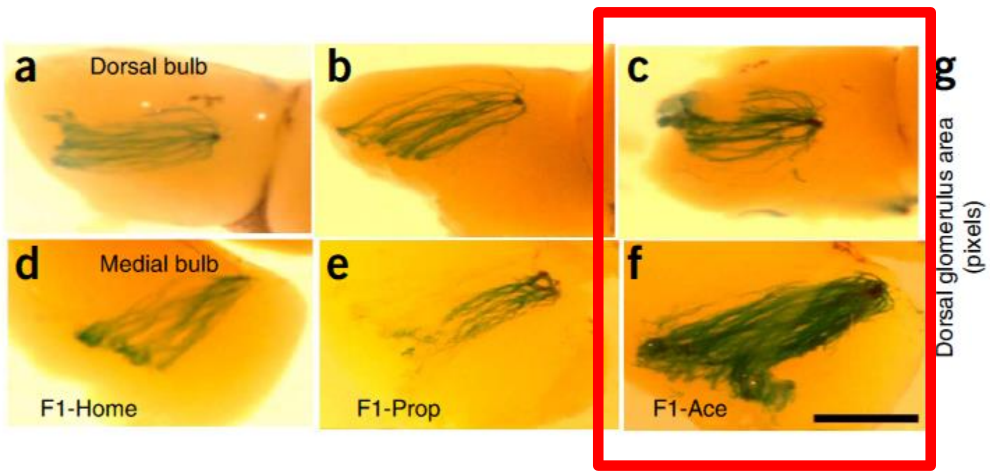


Dias & Ressler 2014. Nat Neurosci

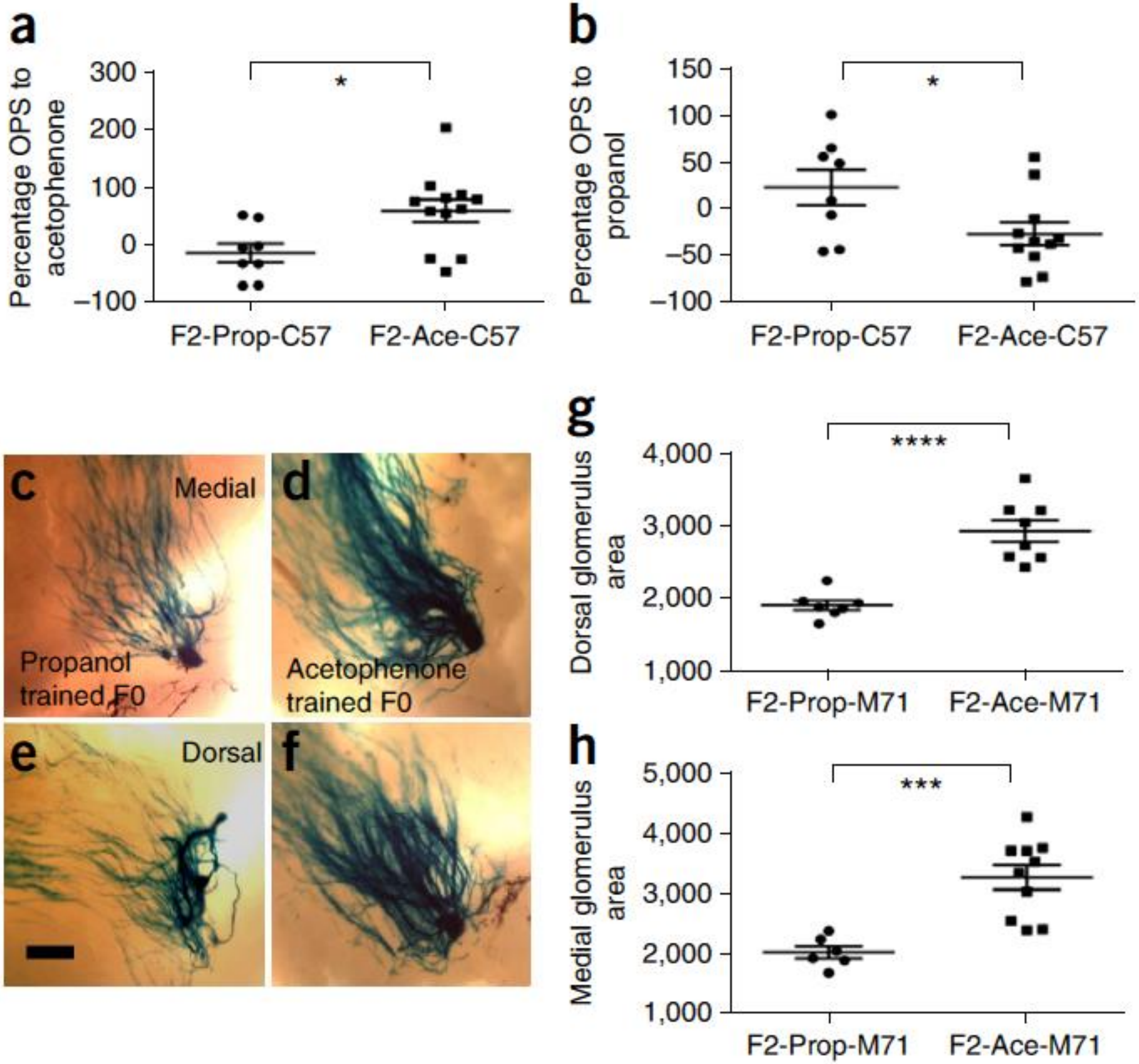
Directional trans-generational plasticity in mice



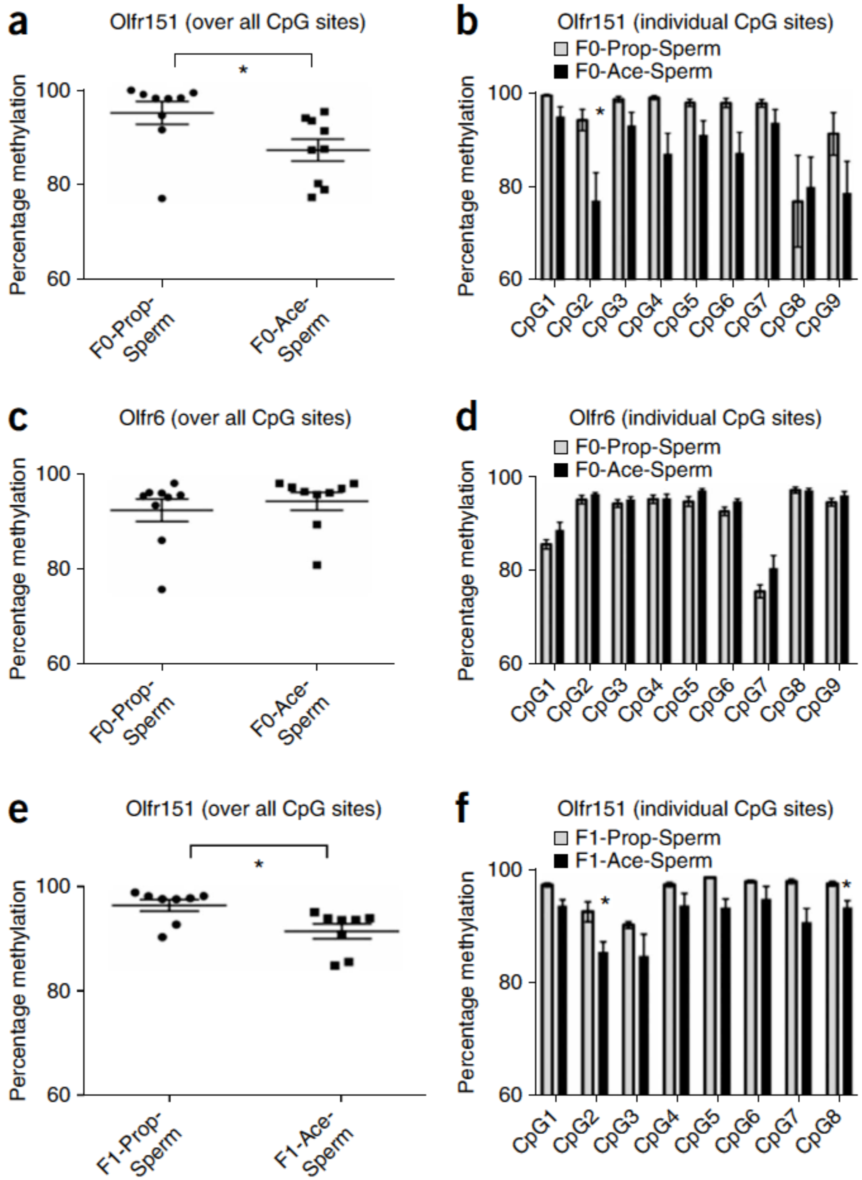
Offspring of male mice exposed to acetophenone have heightened sensitivity and larger glomeruli in the corresponding olfactory bulb



Dias & Ressler 2014. Nat Neurosci



Dias & Ressler 2014. Nat Neurosci



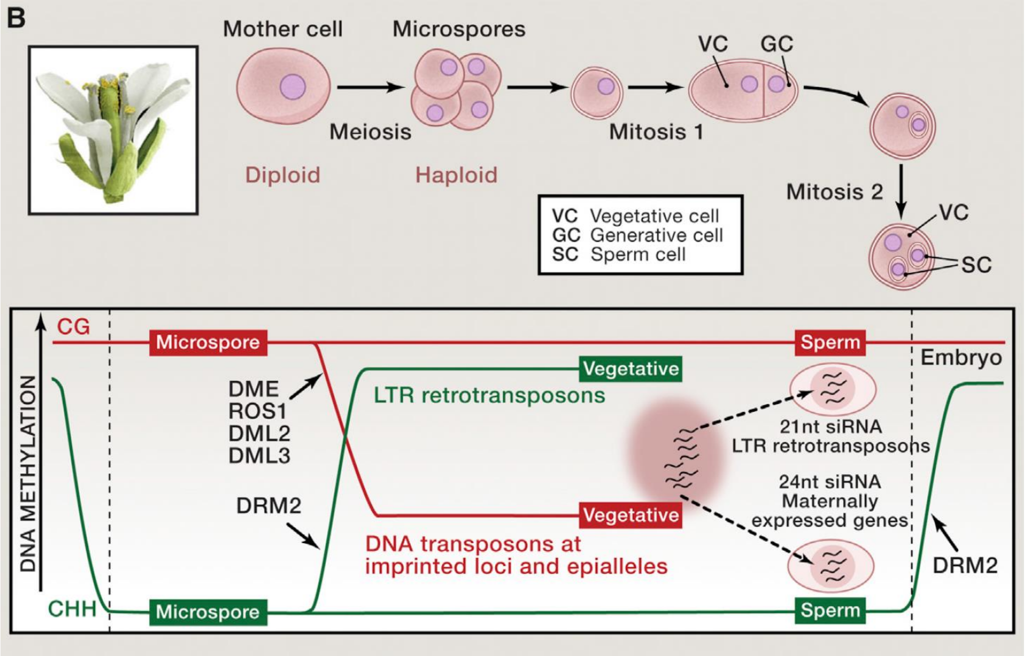
Summary

- 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

Dias & Ressler 2014. Nat Neurosci

Transgenerational epigenetic inheritance

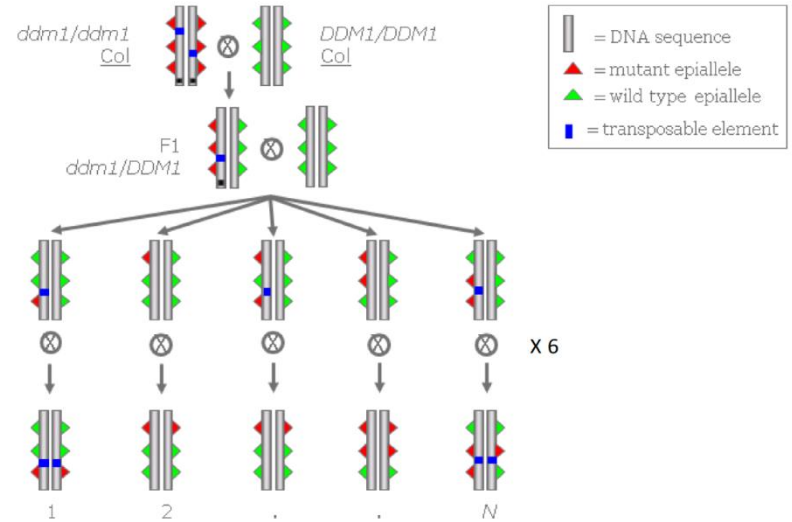
- More likely in plants: less extensive resetting

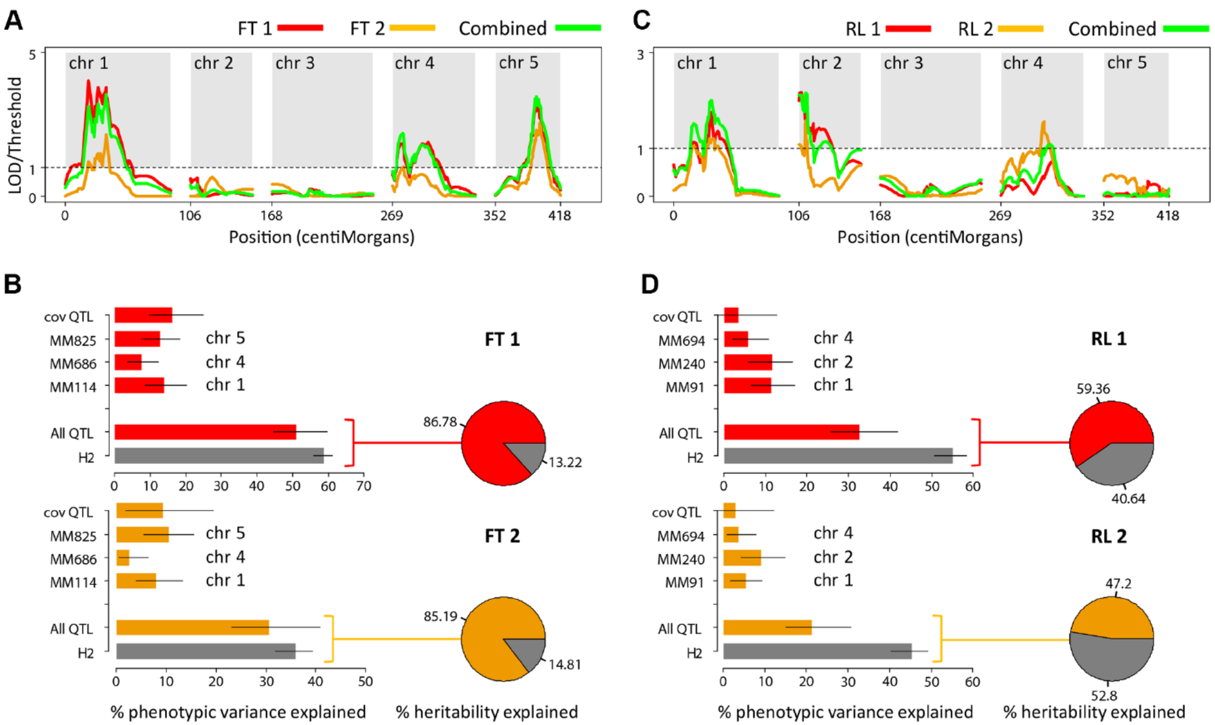


- Epigenetic states inherited 10s of generations

Johannes et al. 2009. PLoS Genet; Cortijo et al. 2014. Science

Stable epigenetic inheritance in Arabidopsis

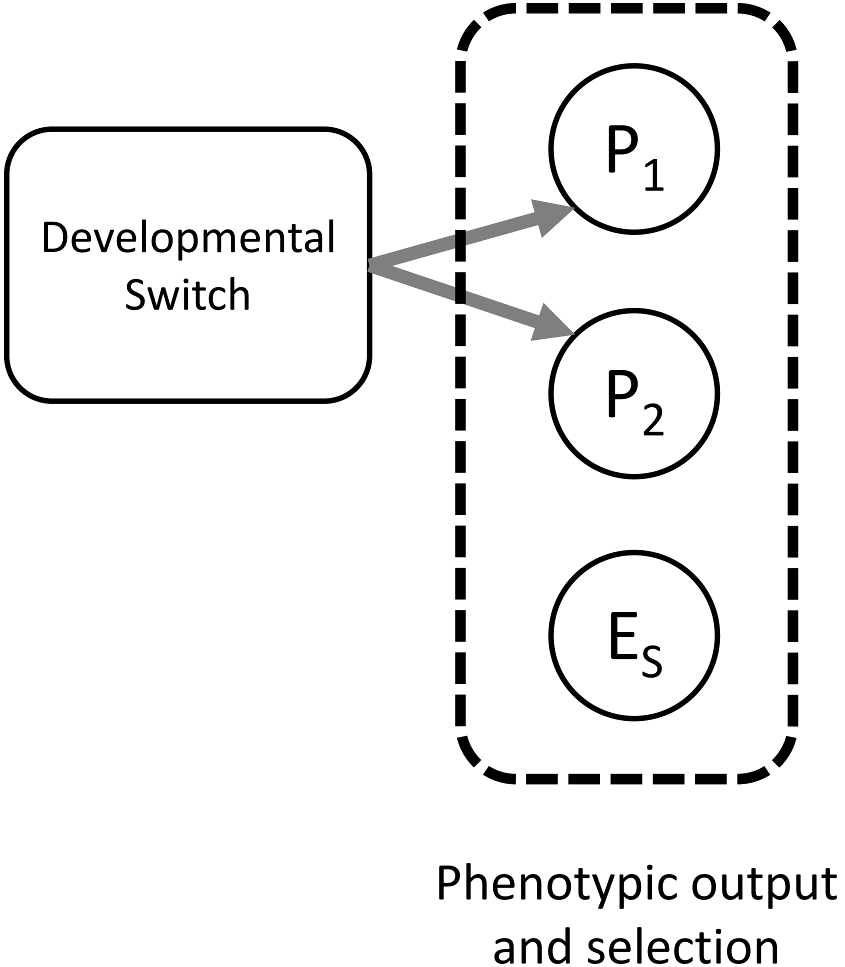




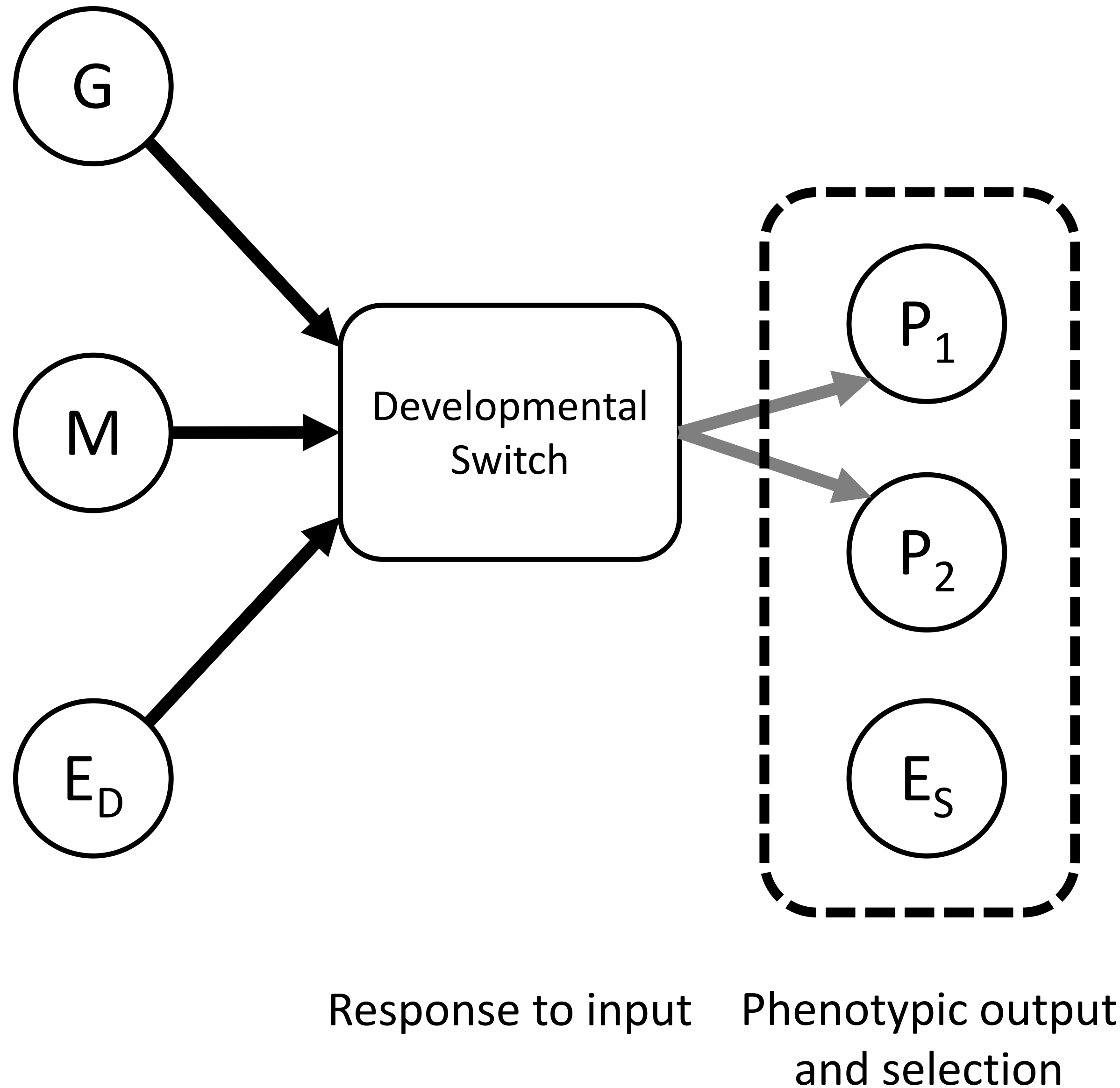
QTL mapping and percent variance explained in flowering time (left) and root length (right)

Cortijo et al. 2014. Science

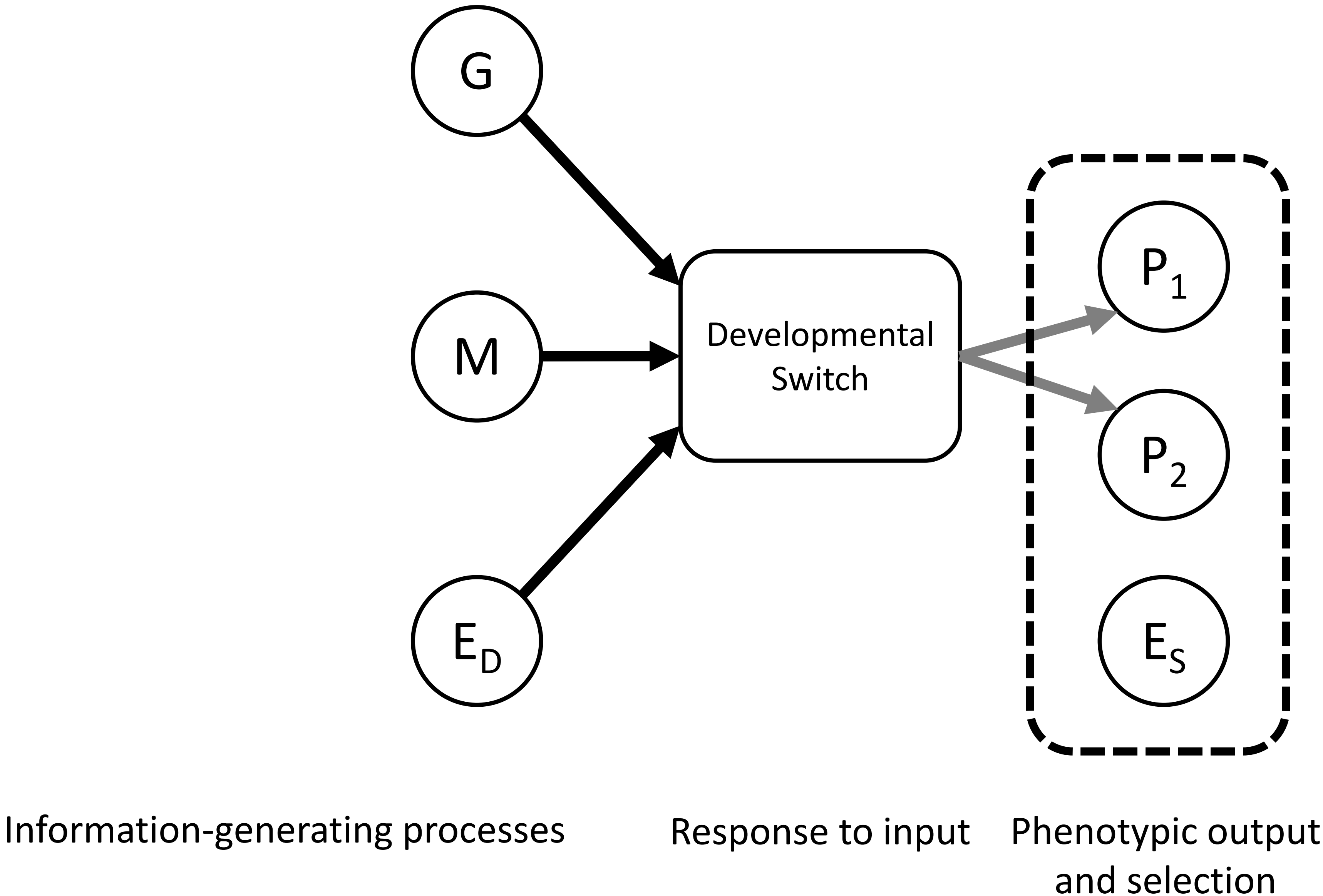
Can incomplete resetting be adaptive?



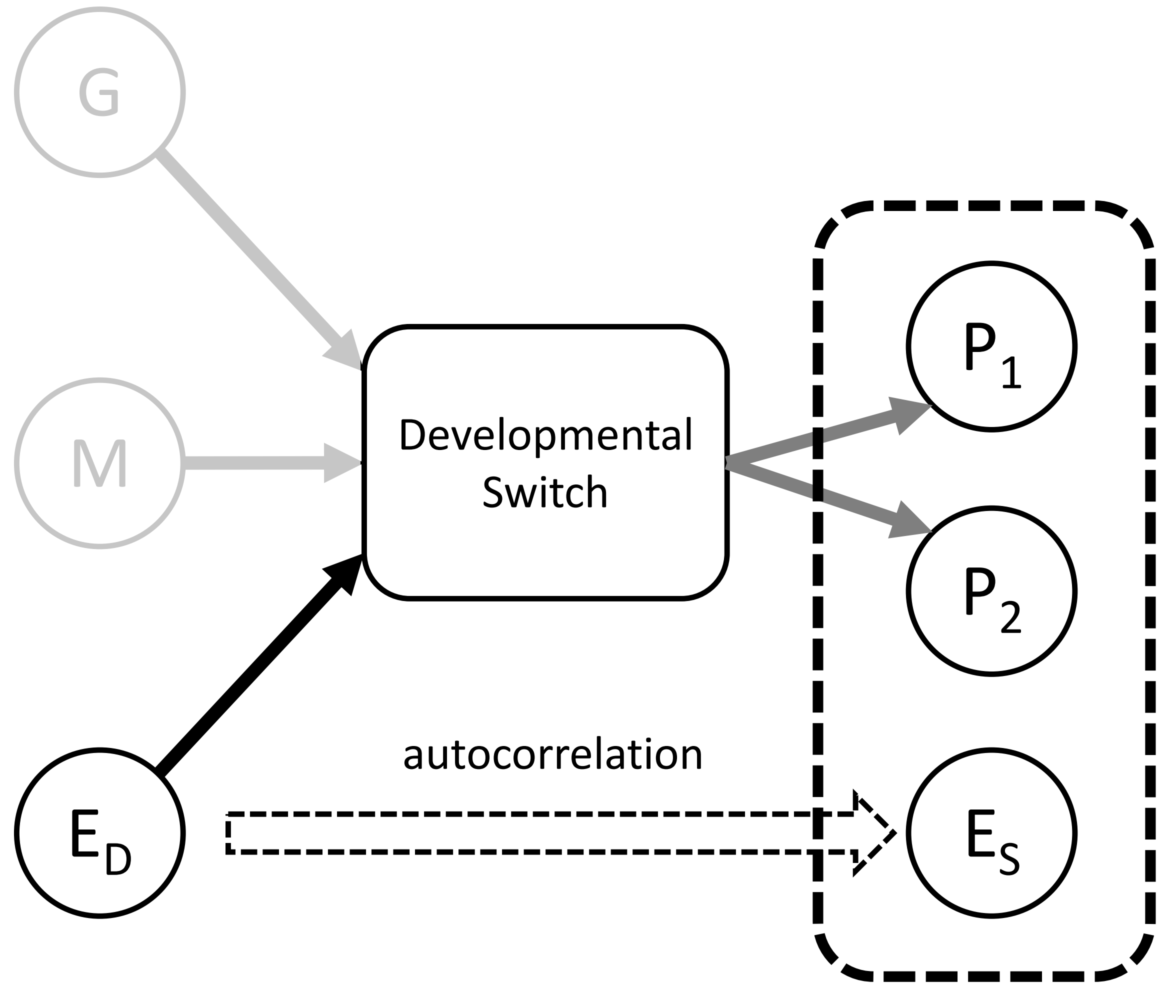
English et al. 2015. PLoS One; see also Shea et al. 2011; McNamara et al. 2016. Ecol Lett



English et al. 2015. PLoS One



English et al. 2015. PLoS One

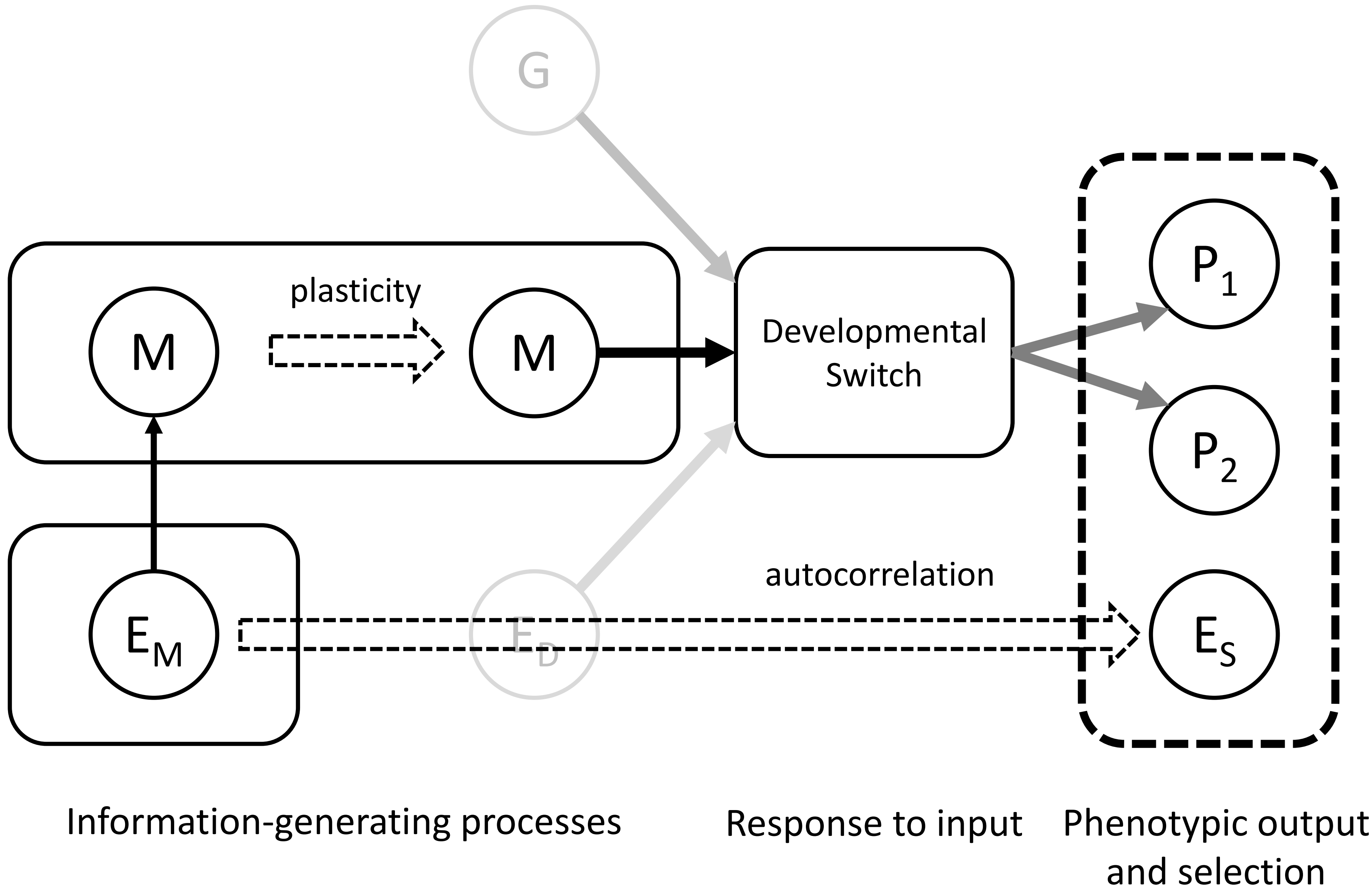


Information-generating processes

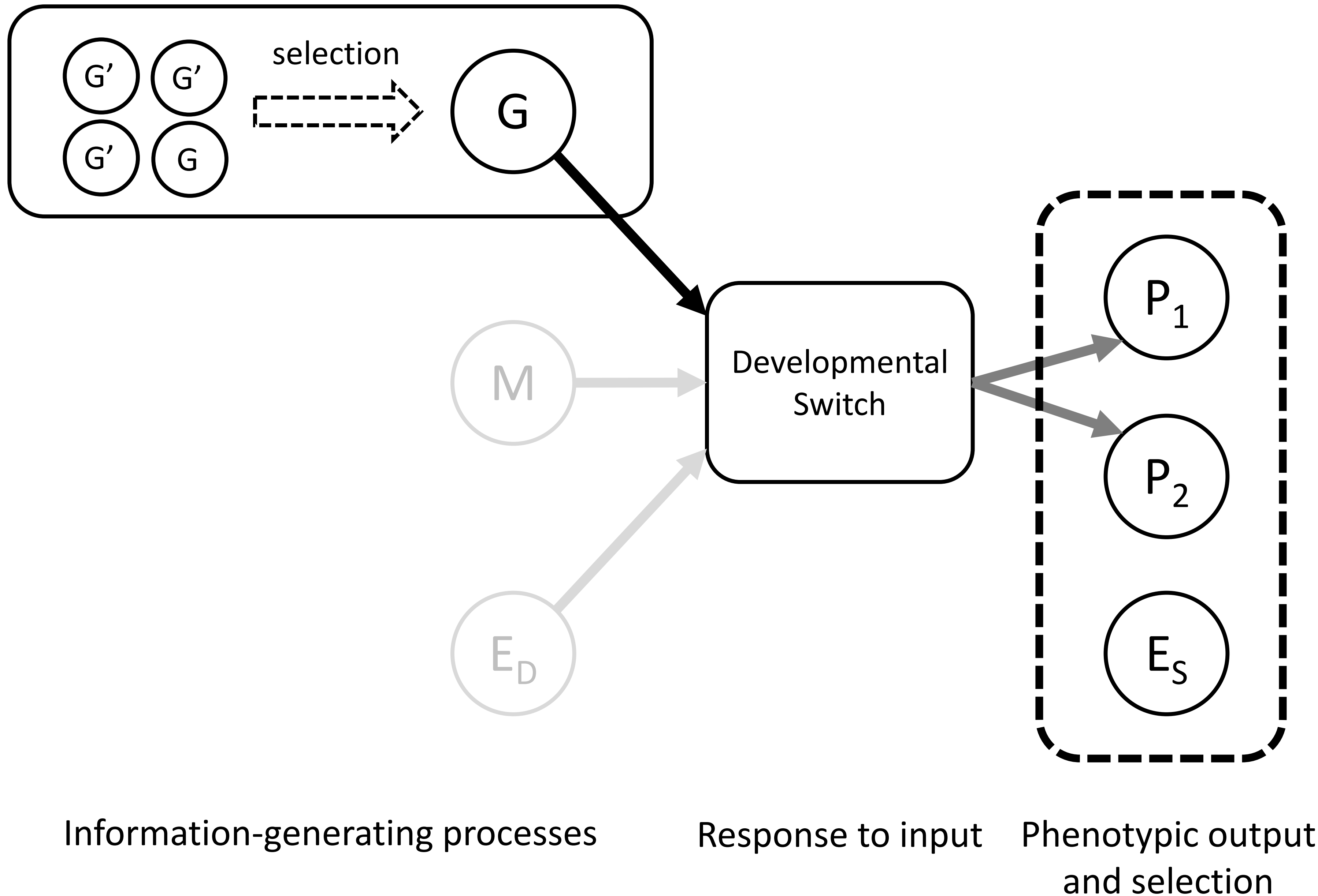
Response to input

Phenotypic output and selection

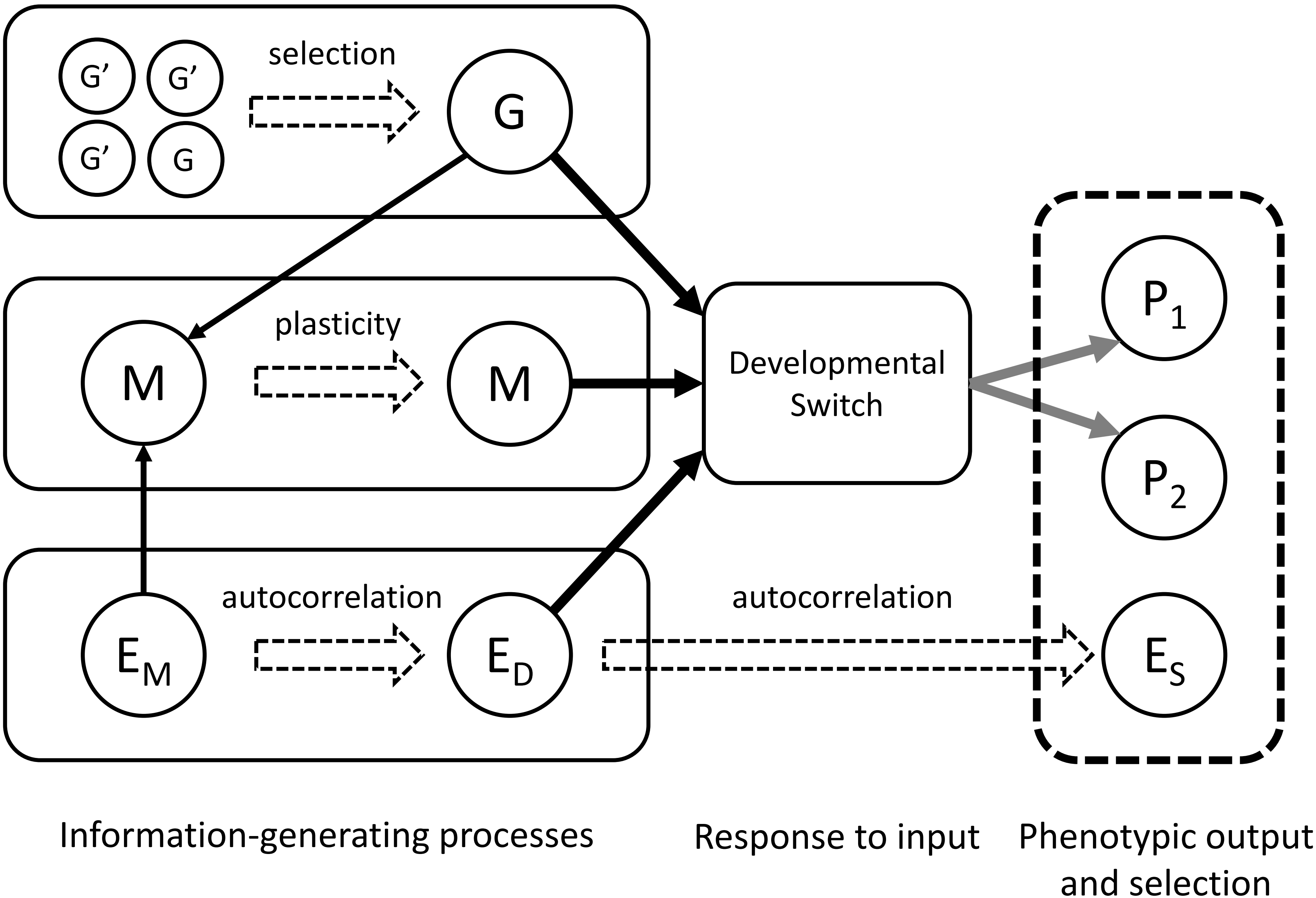
English et al. 2015. PLoS One



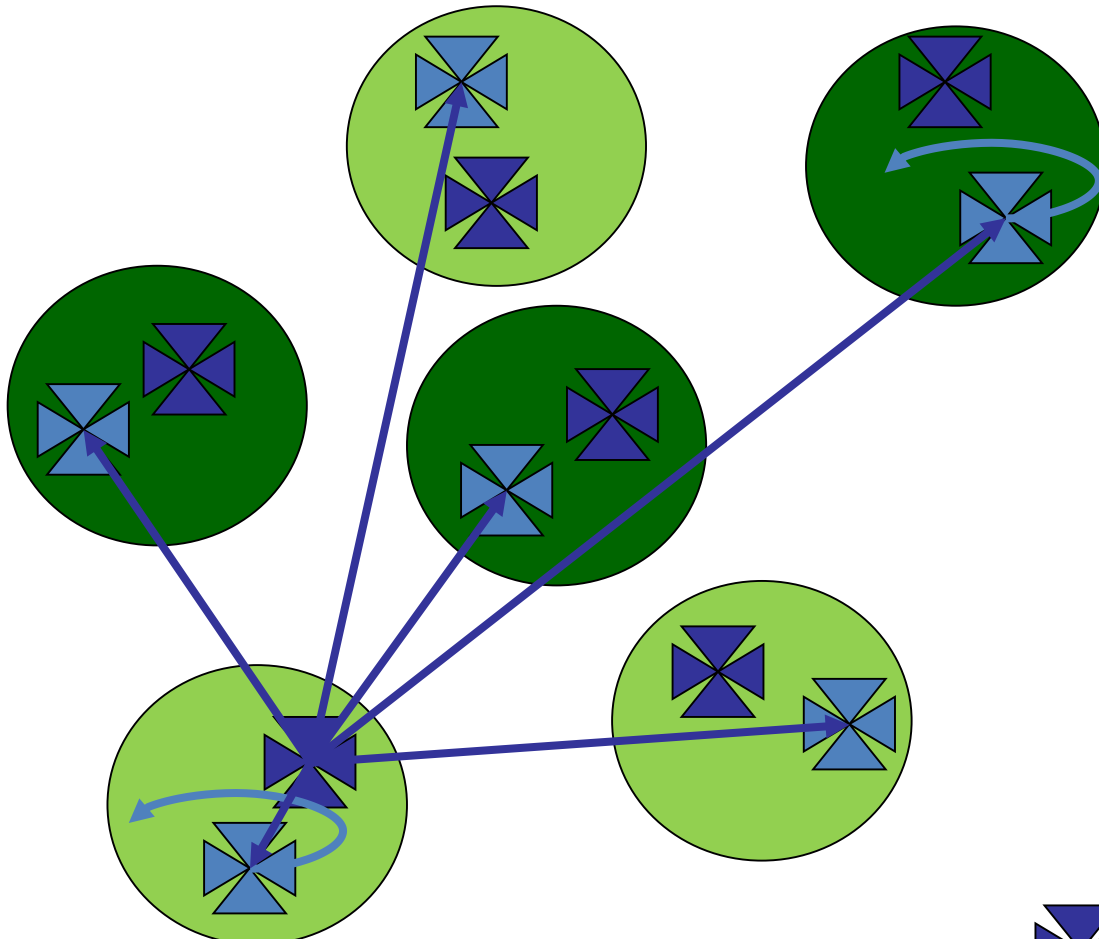
English et al. 2015. PLoS One



English et al. 2015. PLoS One

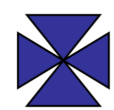


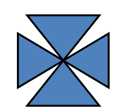
English et al. 2015. PLoS One

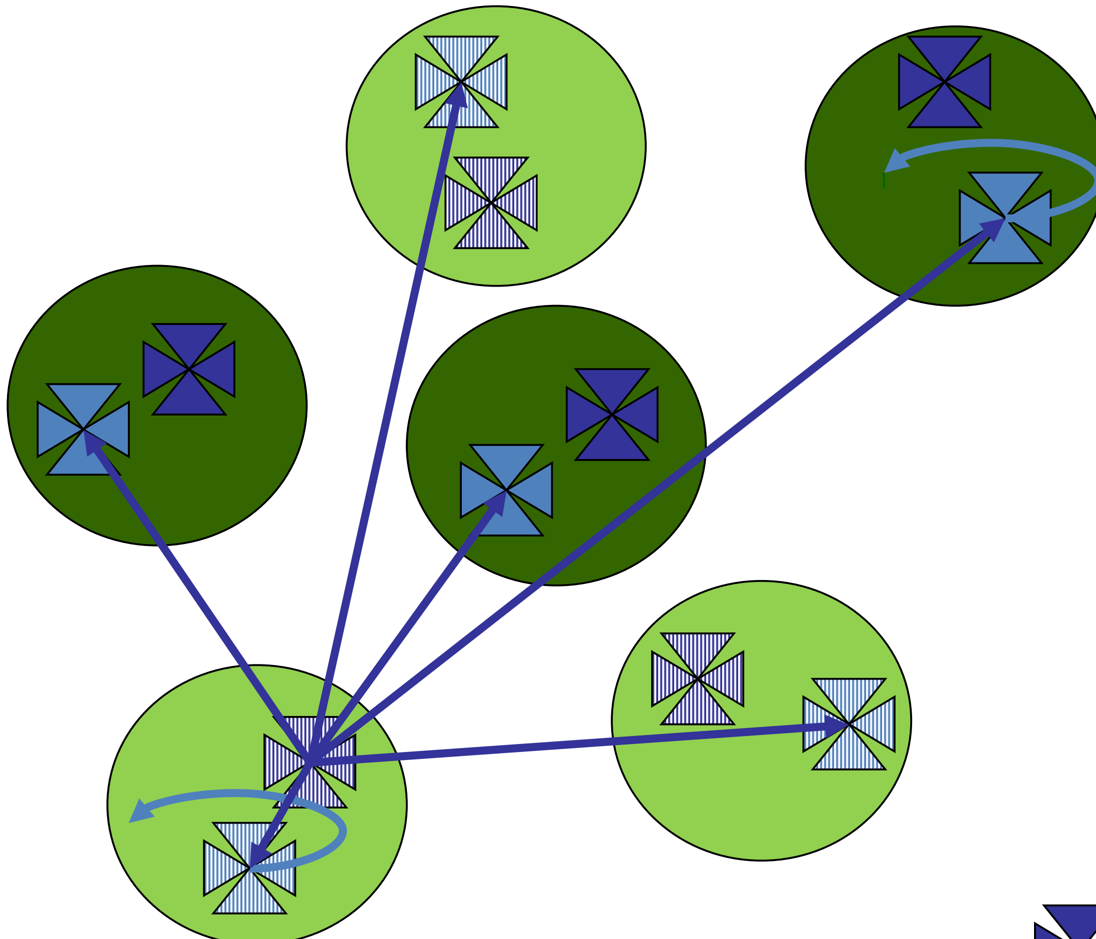


C. americanum

Galloway & Etterson 2007. Science

 MALE FLOWER

 FEMALE FLOWER



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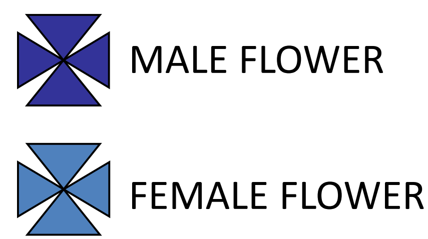
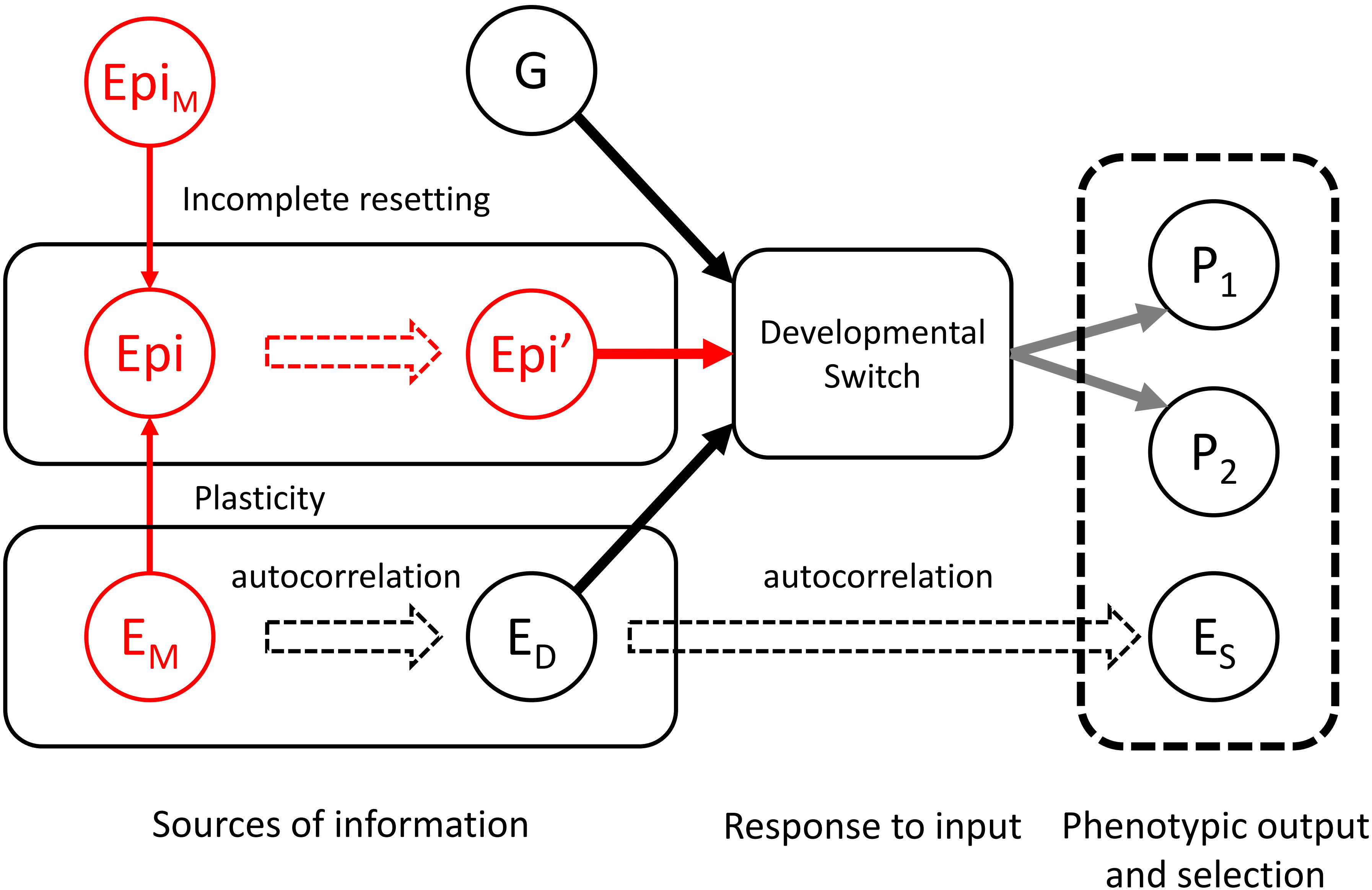
Galloway & Etterson 2007. Science



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

Uller et al. 2015. Proc B; see also Rivoire & Leibler 2014. PNAS

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- **Evolution of 3 parameters**

Uller et al. 2015. Proc B; see also Rivoire & Leibler 2014. PNAS

Fluctuating environment

- First order autoregressive process (AR1)

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

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

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

$r = 0$ no correlation

$r = 1$ perfect correlation

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e_t noise fluctuations □ $\mathrm{normal}(0, \sigma_e^2)$

Dynamics epigenetic marks

- **Changes in individual offspring:**

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

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

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

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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

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

Uller et al. 2015. Proc B

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

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Uller et al. 2015. Proc B

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Uller et al. 2015. Proc B

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Uller et al. 2015. Proc B

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Uller et al. 2015. Proc B

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

Uller et al. 2015. Proc B

Main results

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

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

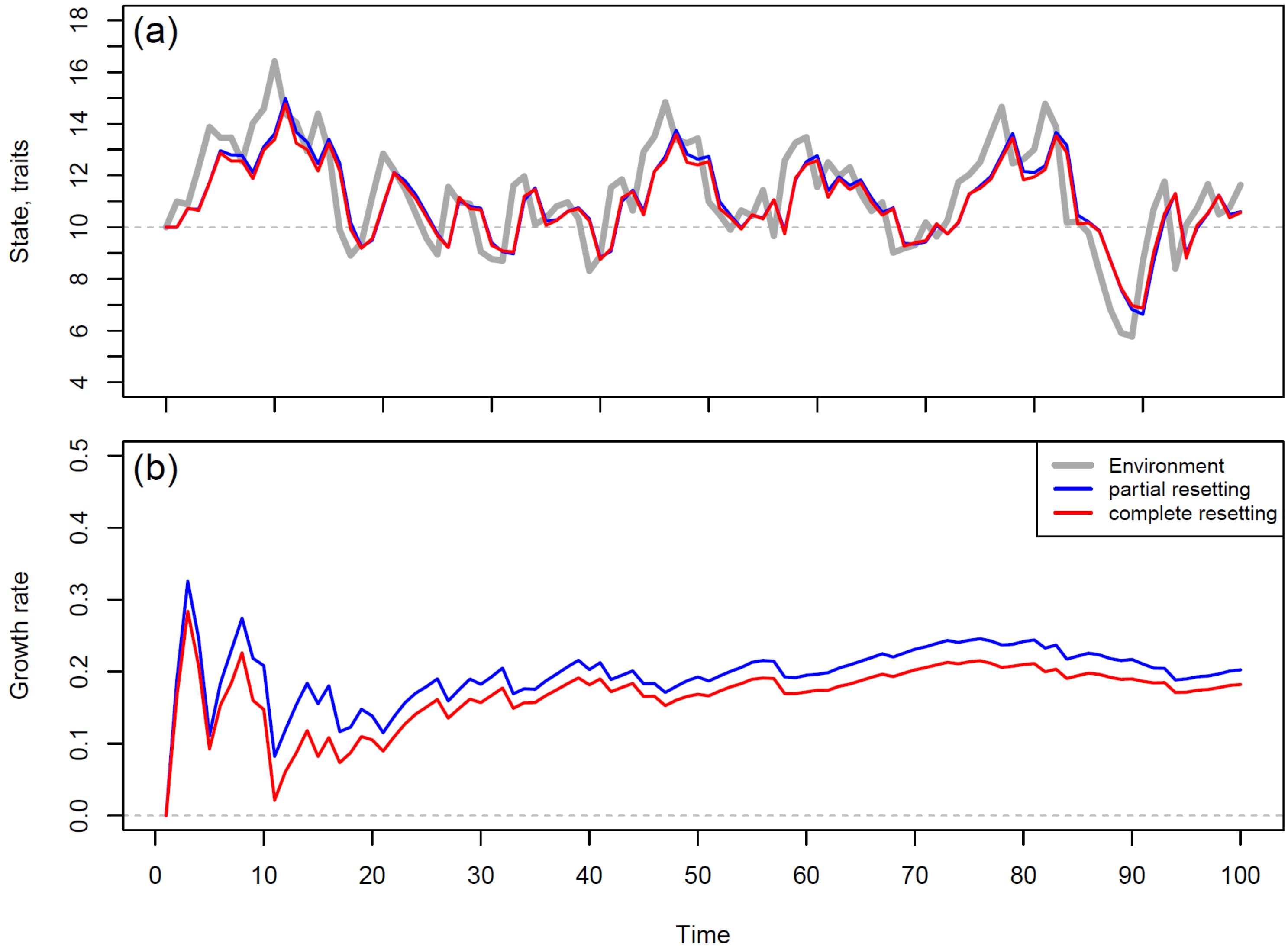
In other words: incomplete resetting

+ Protects against maternal & developmental "errors" in stable environment

– Slows down adaptation to changing environment

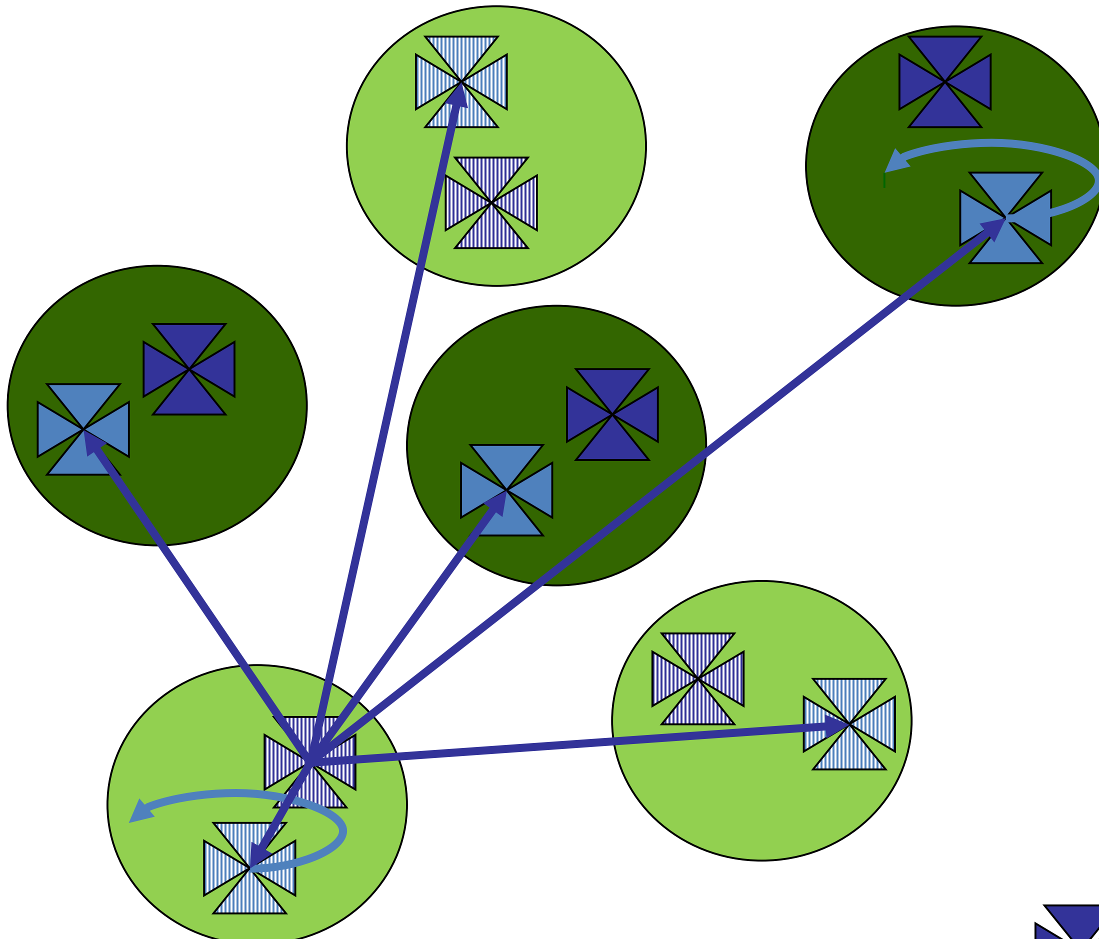
Uller et al. 2015. Proc B

Numerical example



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

Uller et al. 2015. Proc B



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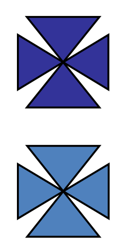
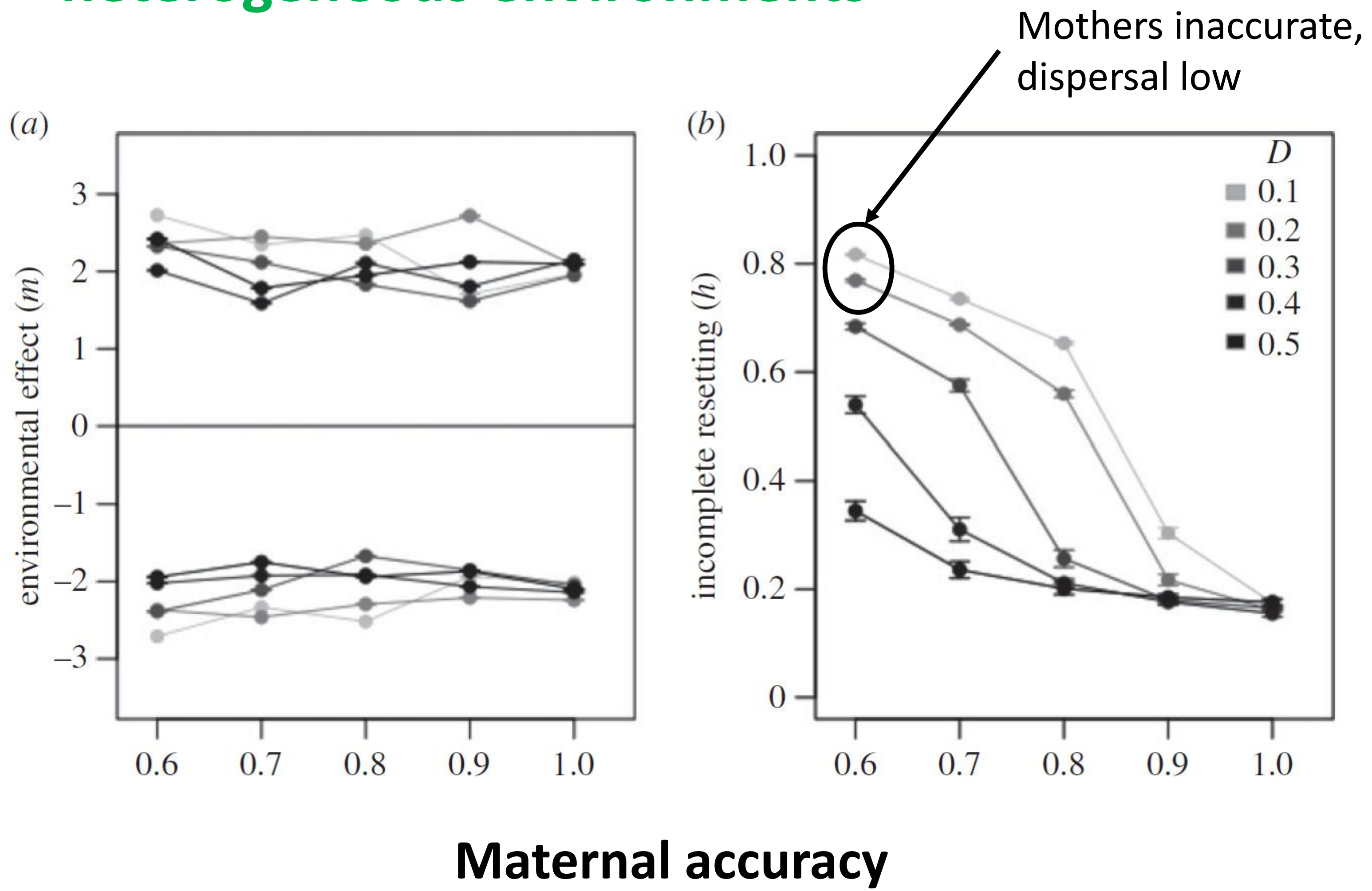


MALE FLOWER

FEMALE FLOWER

Individual-based simulations

- Qualitative results carry over to spatially heterogeneous environments



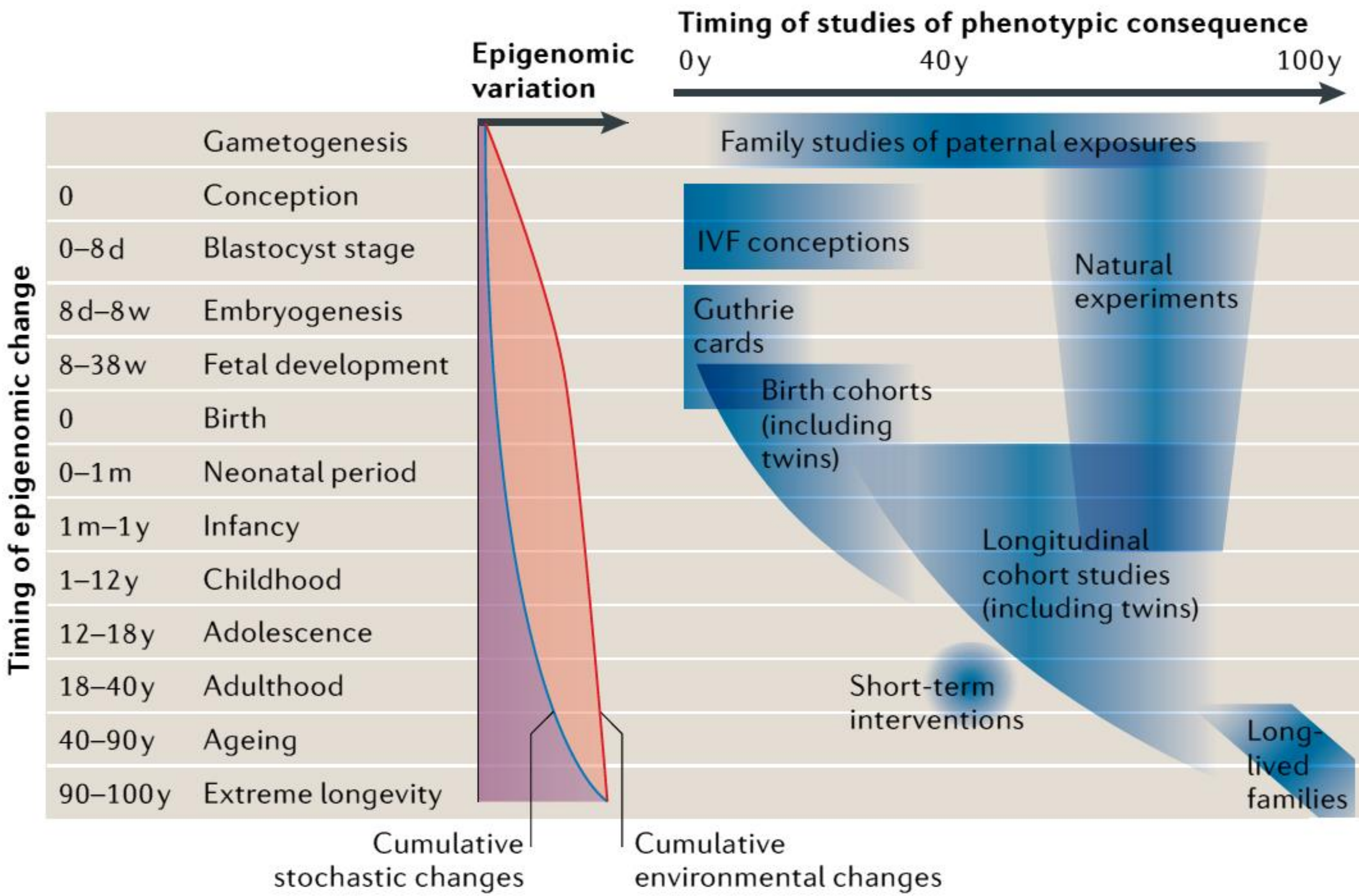
Uller et al. 2015. Proc B

Population epigenetics

Why population epigenetics?

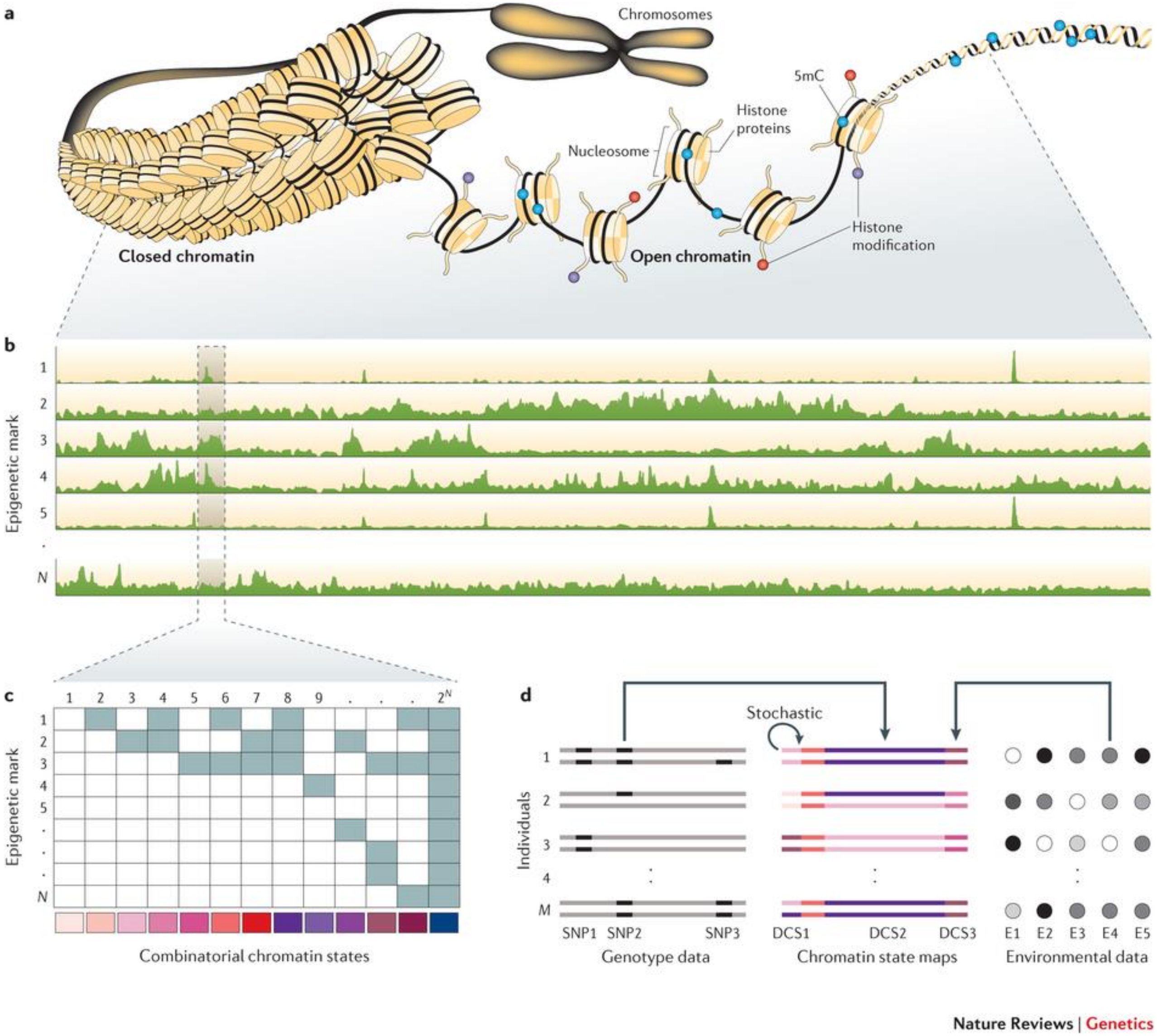
- Identify associations with phenotypic, environmental and genetic factors
- Test for transgenerational inheritance
- Role of epigenetic variation (inherited or not) in adaptive evolution

Study designs for studying epigenetic variation in human populations



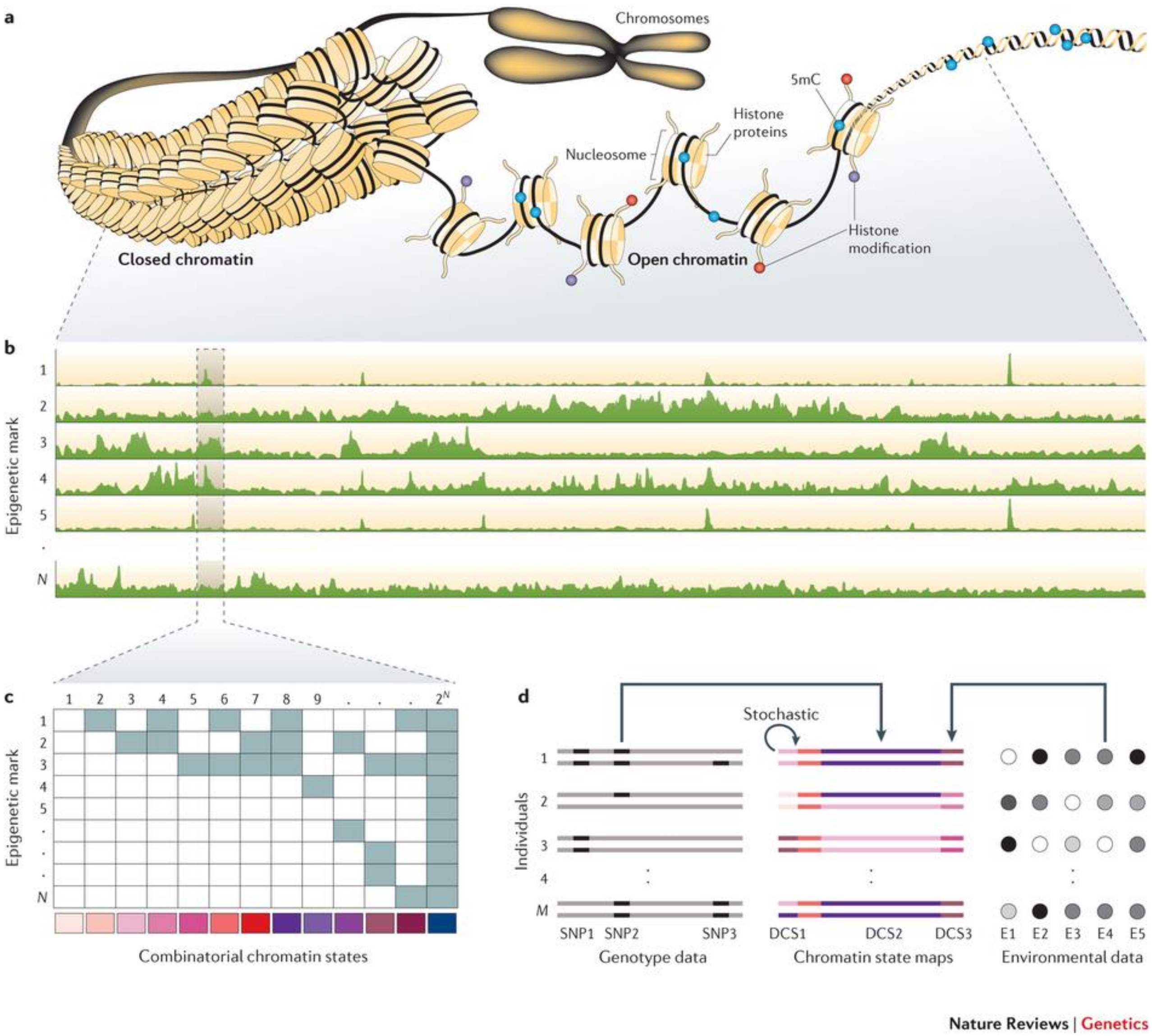
Mills & Heijmans 2012. Nat Rev Genet

Population epigenetic data - workflow



Taudt et al. 2016 Nat Rev Genet

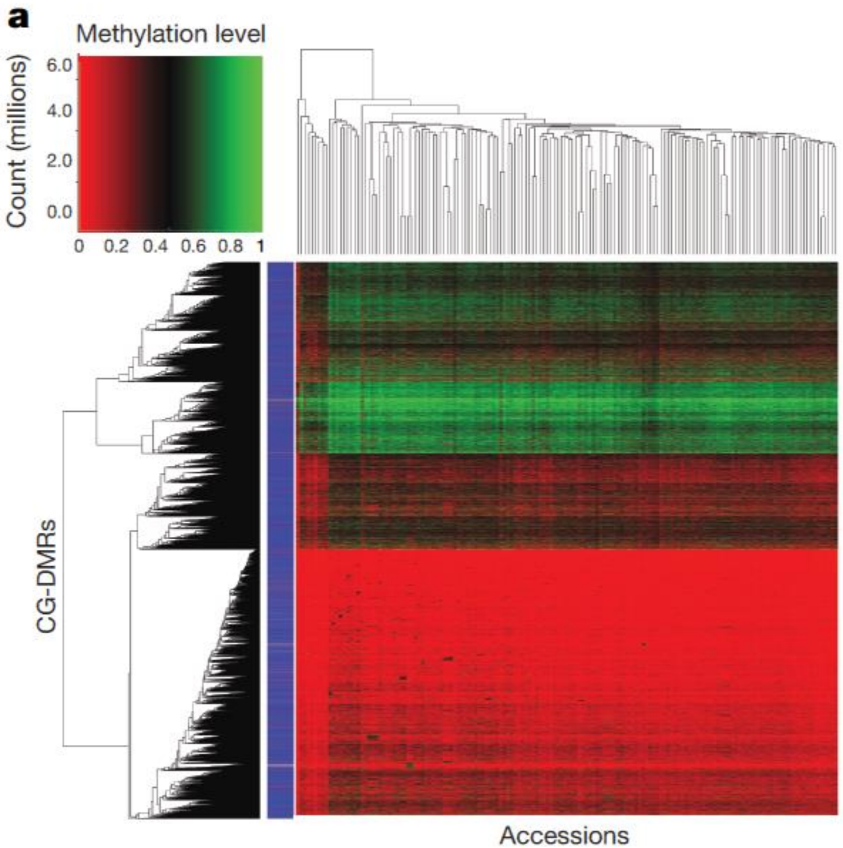
"The statistical challenge is to try to identify these causal factors from millions of measured SNPs and a large number of environmental factors"



Taudt et al. 2016 Nat Rev Genet

Population epigenetics I. Genomic patterns

Columns are genotypes



Rows are differentially methylated regions (DMRs)

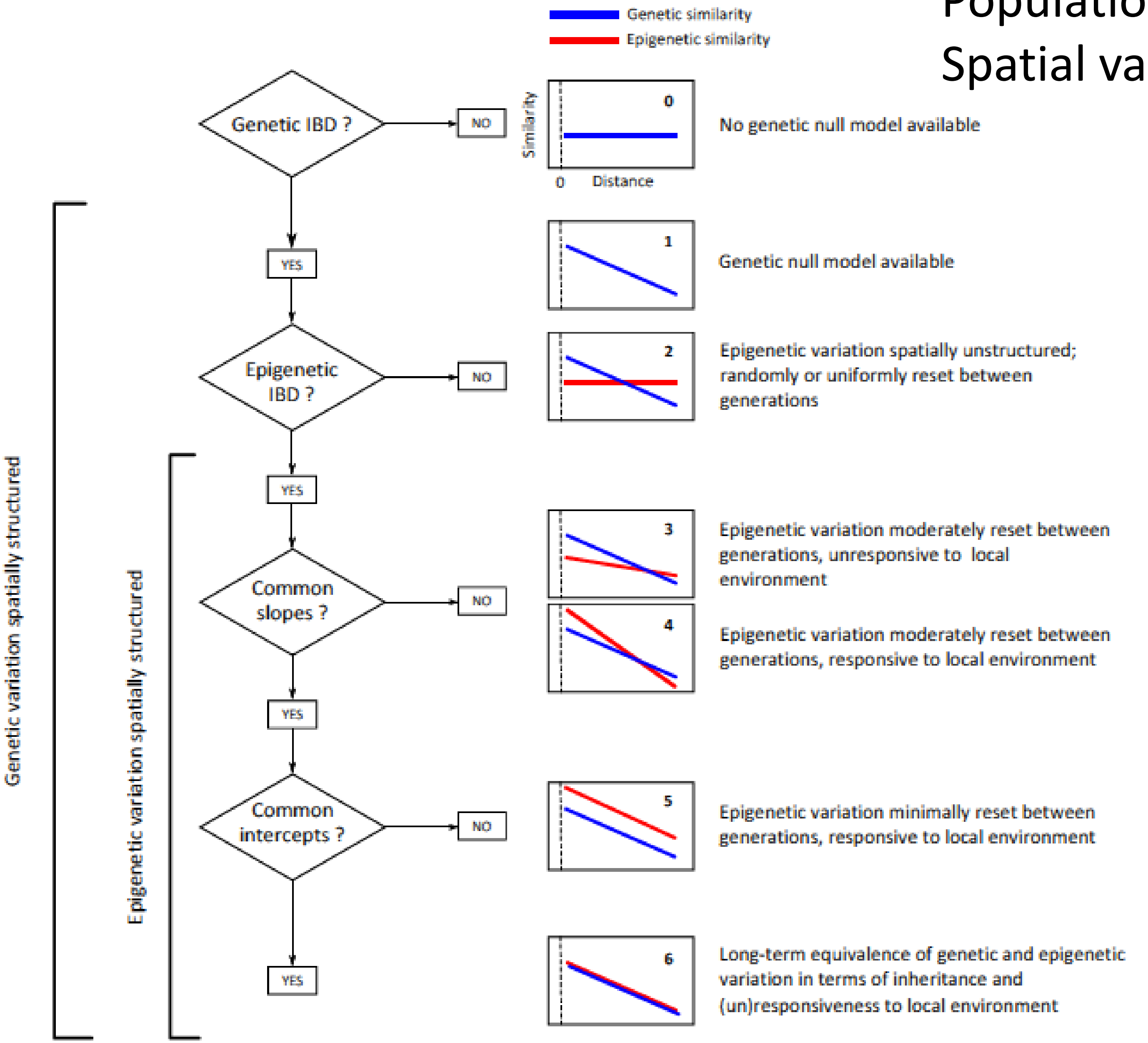
Transposons

Genes

Average methylation

Schmitz et al. 2013 Nature

Population epigenetics II. Spatial variation



Herrera 2016. Mol Ecol

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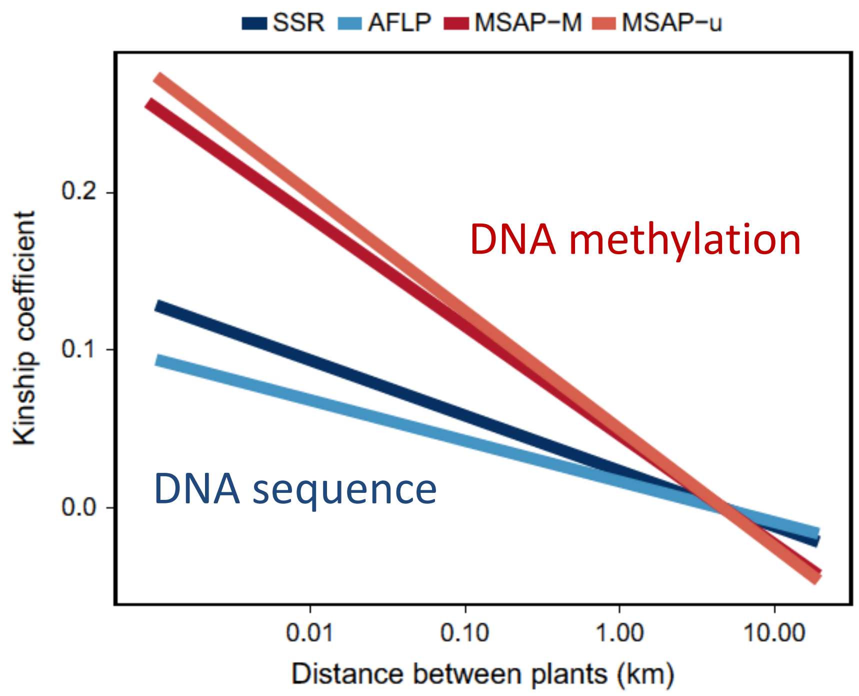
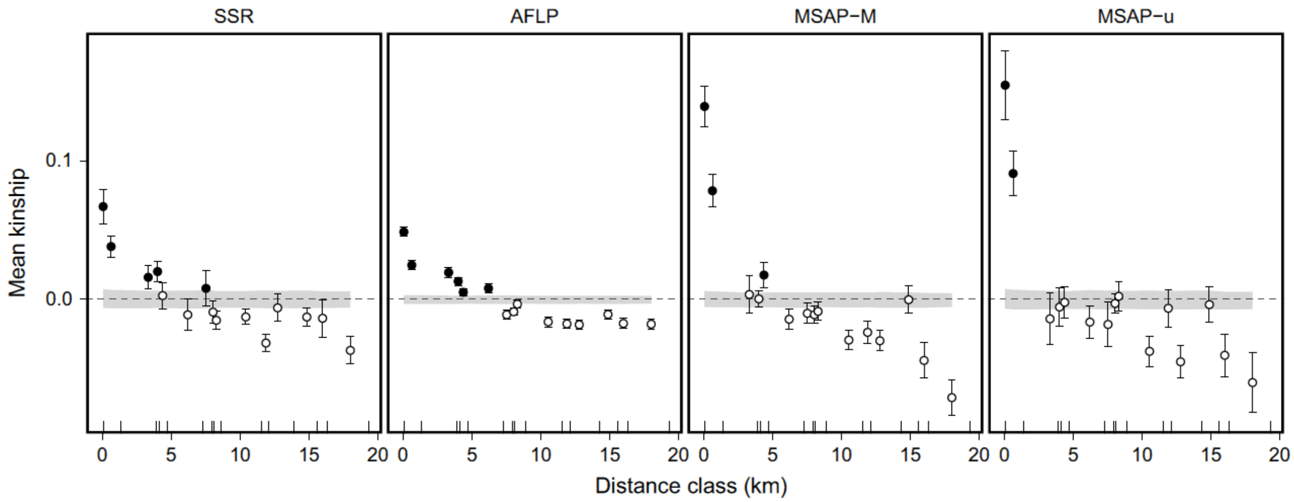
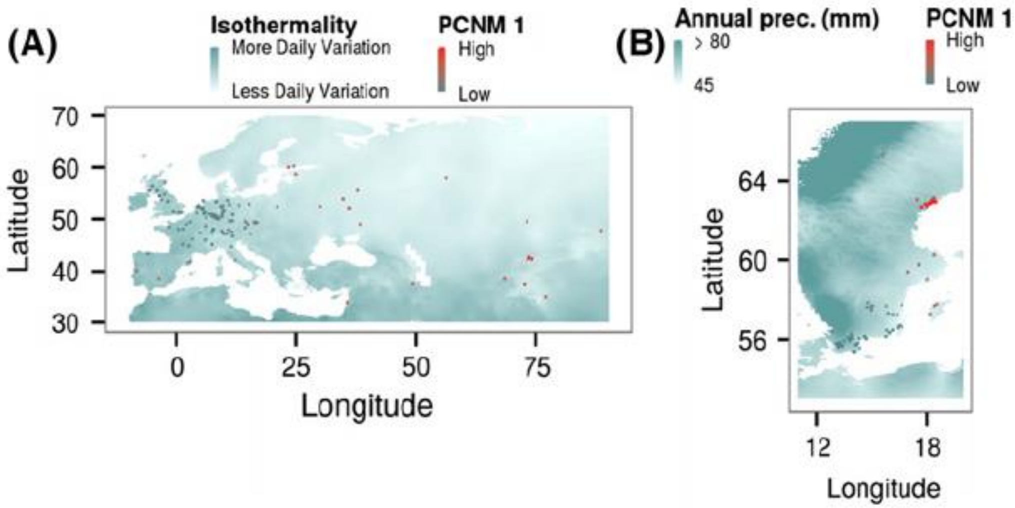




Herrera 2016. Mol Ecol

Population epigenetics III. Association with climate



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

Keller et al. 2016. Mol Ecol

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

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Joost van den Heuvel
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www.ullergroup.se

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