Modeling the genotype-phenotype map: from networks to dynamics

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Research Foundation Flanders
Opening new horizons

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Outline

- Genotype-phenotype map: why evo-devo needs a mechanistic view
- GRNs are filling this role
- Limitations of GRN-based explanations
- Going “beyond networks”: dynamic mechanistic explanations that rely on modeling

Genotype-phenotype map

A process in which genes contribute to the formation of complex and differentiated end-states

The synthetic problem and the genotype–phenotype relation in cellular metabolism

J. Burns
University of Edinburgh

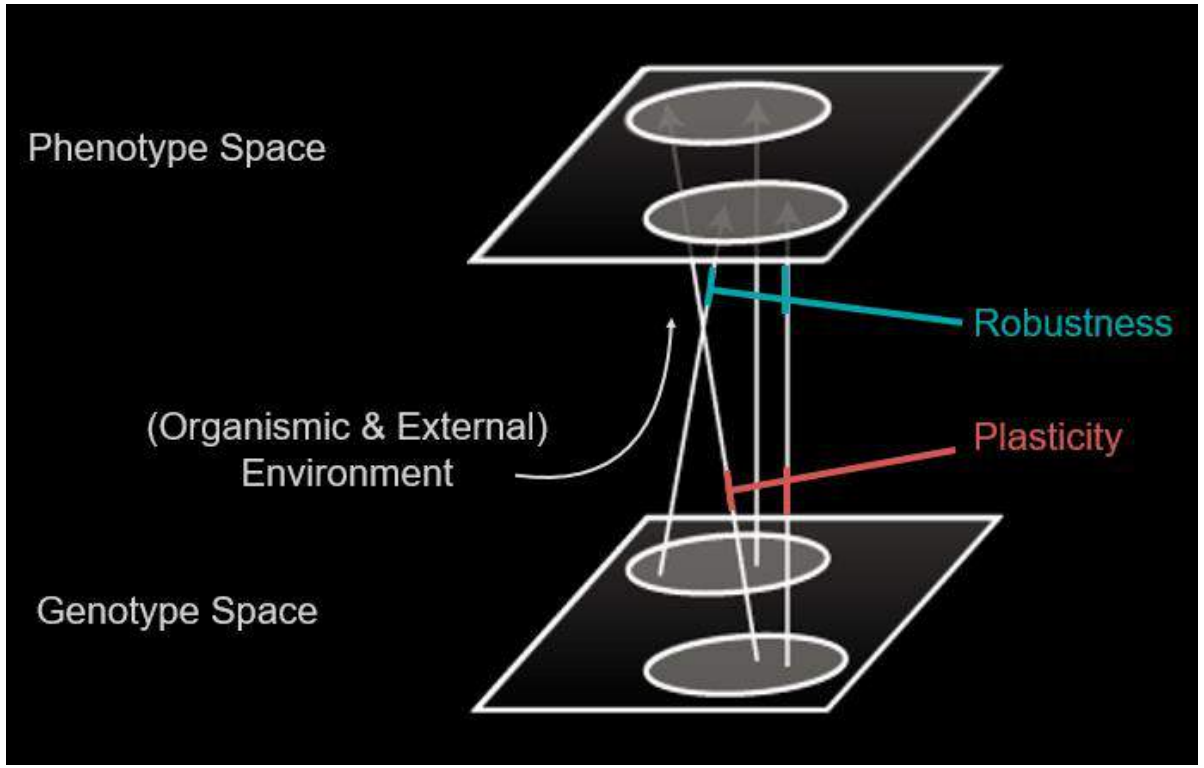
Introduction. The basic problem to be discussed in this paper is how our knowledge of cellular components can be used to gain insight into quantitative aspects of theoretical synthetic systems constructed from them. It is the quantitative phenotype, arising from the genotypic prescription and the environment, which is of critical importance for the cell's survival and which therefore features in population genetic theory. A study of this 'synthetic problem' would thus, by providing genotype–phenotype mappings for simple synthetic systems, help to connect two major areas of biological theory : the biochemical and the population genetic.

Burns J (1970) The synthetic problem and the genotype-phenotype relation in cellular metabolism. In: *Towards a Theoretical Biology, Vol. III*, ed. Waddington CH. Edinburgh, UK: Edinburgh University Press, 47–51.

Mechanistic understanding of GP map

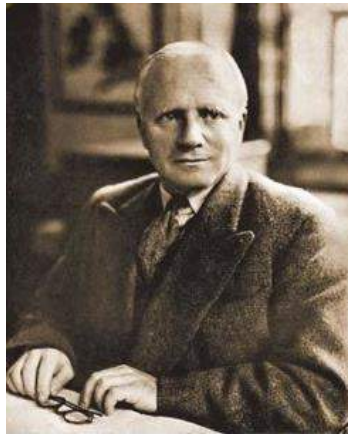
Needed for:

- Understanding how production of variation is related to sorting
- Explaining phenotypic plasticity and robustness
- Understanding variational properties and evolvability



The Causal Completeness Principle

Walter Garstang
(1868–1949)



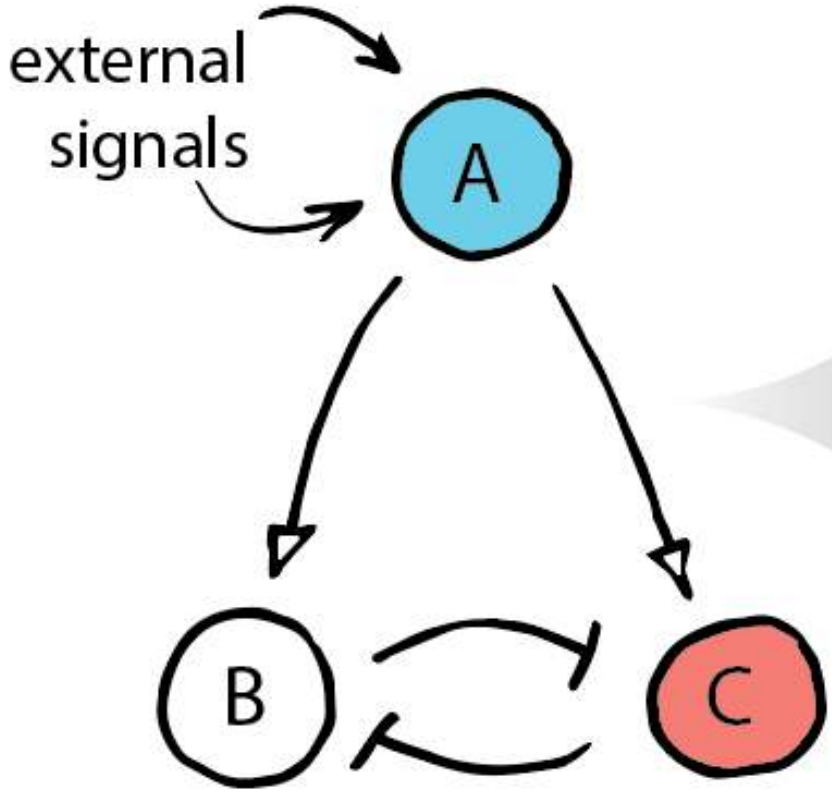
Gavin de Beer
(1899–1972)

Richard Goldschmidt
(1878–1958)

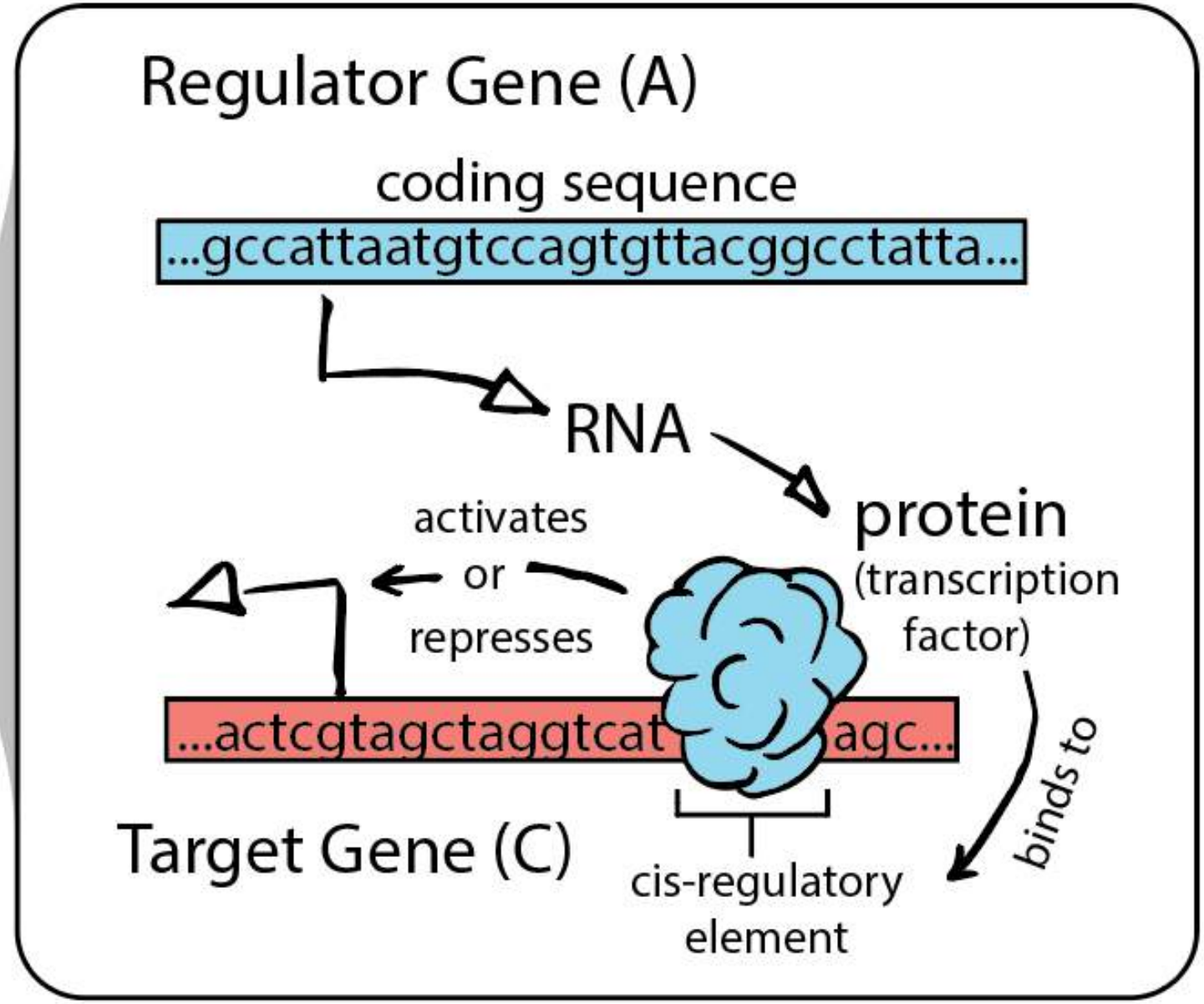
Conrad Hal Waddington
(1905–1975)

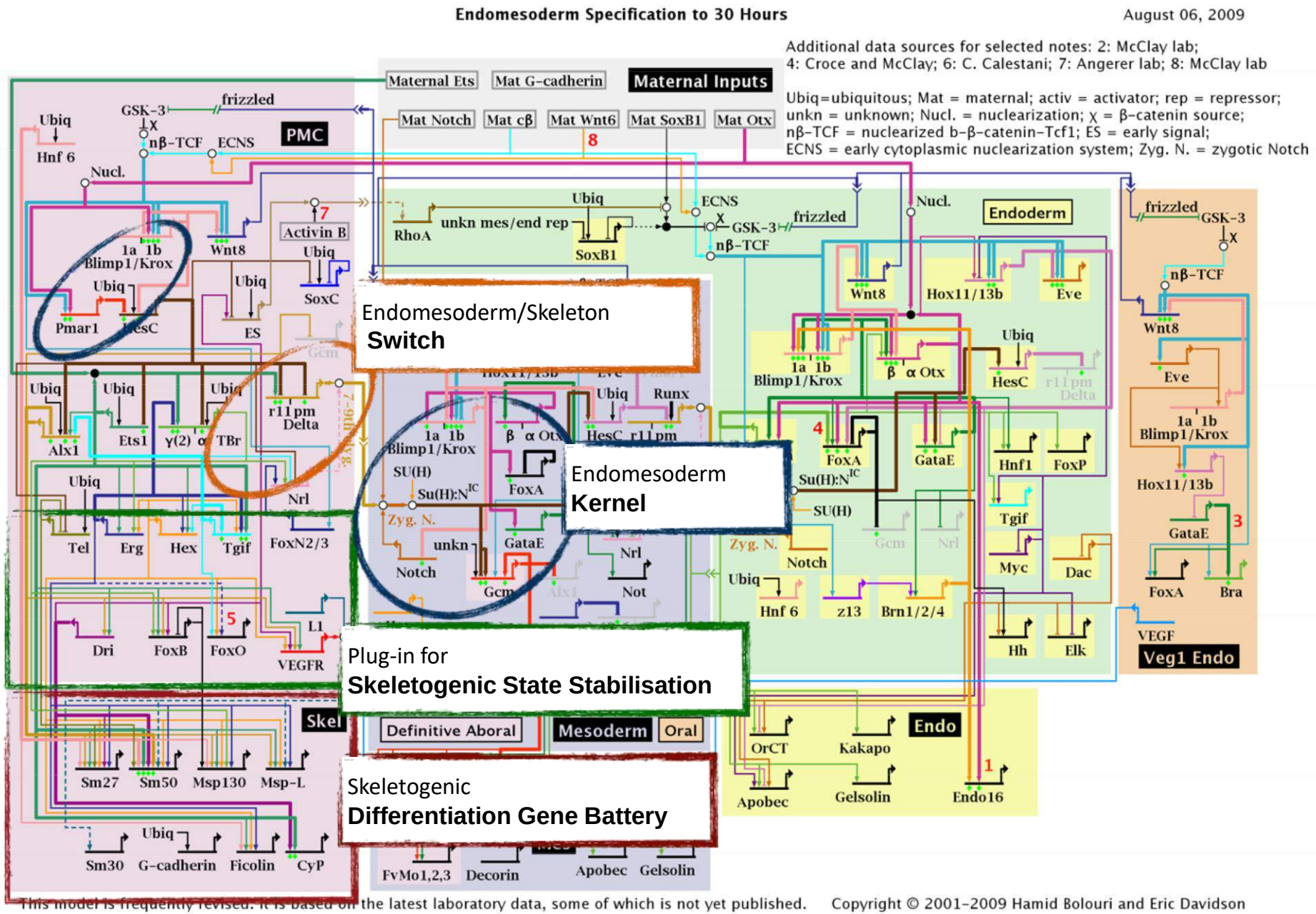
"In order to achieve a modification in adult form, evolution must modify the embryological processes responsible for that form. Therefore, an understanding of evolution requires an understanding of development."

Amundson (2005). *The Changing Role of the Embryo in Evolutionary Thought*. Cambridge University Press.



Gene Regulatory Network (GRN)




Endomesoderm Specification to 30 Hours
August 06, 2009
Additional data sources for selected notes: 2: McClay lab;
4: Croce and McClay; 6: C. Calestani; 7: Angerer lab; 8: McClay lab
Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
unkn = unknown; Nucl. = nucleariization; χ = β-catenin source;
nβ-TCF = nuclearized b-β-catenin-Tcf1; ES = early signal;
ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch
Maternal Ets
Mat G-cadherin
Maternal Inputs
Mat Notch
Mat cβ
Mat Wnt6
Mat SoxB1
Mat Otx
PMC
Endoderm
Endomesoderm/Skeleton
Switch
Endomesoderm
Kernel
Plug-in for
Skeletogenic State Stabilisation
Skeletogenic
Differentiation Gene Battery
Skel
Definitive Aboral
Mesoderm
Oral
Endo
Veg1 Endo
This model is frequently revised. It is based on the latest laboratory data, some of which is not yet published.
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Genetic causation

Early genetics: genes are difference-making causes, not productive causes

Genetic causation

Saying that a Mendelian factor *causes* a character "does not assume that any one factor produces a particular character directly and by itself, but only that a character in one organism may differ from a character in another because the sets of factors in the two organisms have one difference."

Morgan TH et al (1915) *The mechanism of Mendelian heredity*. New York: Henry Holt, p. 212.

Genetic causation

If changing one gene correlates with a change in eye color, then we can justifiably call that gene a cause of eye color, even though "the character is the product of a number of genetic factors and of environmental conditions."

Morgan TH et al (1915) *The mechanism of Mendelian heredity*. New York: Henry Holt, p. 210.

Genetic causation

Early genetics: genes are difference-making causes, not productive causes

Today: GRNs are difference-making causes and productive causes

“Evolution and development emerge as twin outputs of the same mechanistic domain of regulatory system genomics.”

Davidson EH (2010) Emerging properties of animal gene regulatory networks. *Nature* 468: 918.

Genetic Mechanism 2.0
Gene Regulatory Networks

"Once it includes all or almost all specifically expressed regulatory genes,
a GRN constitutes an explanation of why the events of development occur."

Oliveri *et al.* (2008). *Proc Natl Acad Sci U.S.A.* 105, p. 5961.

"The spatial causes of developmental events
after the earliest stages of dependence on egg cytoarchitecture
are essentially all **programmed in the genomic control system**."

Oliveri *et al.* (2008). *Proc Natl Acad Sci U.S.A.* 105, p. 5961.

"Development and evolution of the body plan, and execution of physiological responses,
devolve causally from the regulatory genome."

Davidson (2010). *Nature* 468, p. 918.

"**A given sub-circuit structure implies a given function** […]
what the circuit can do depends directly on its structure."

Davidson (2010). *Nature* 468, p. 911.

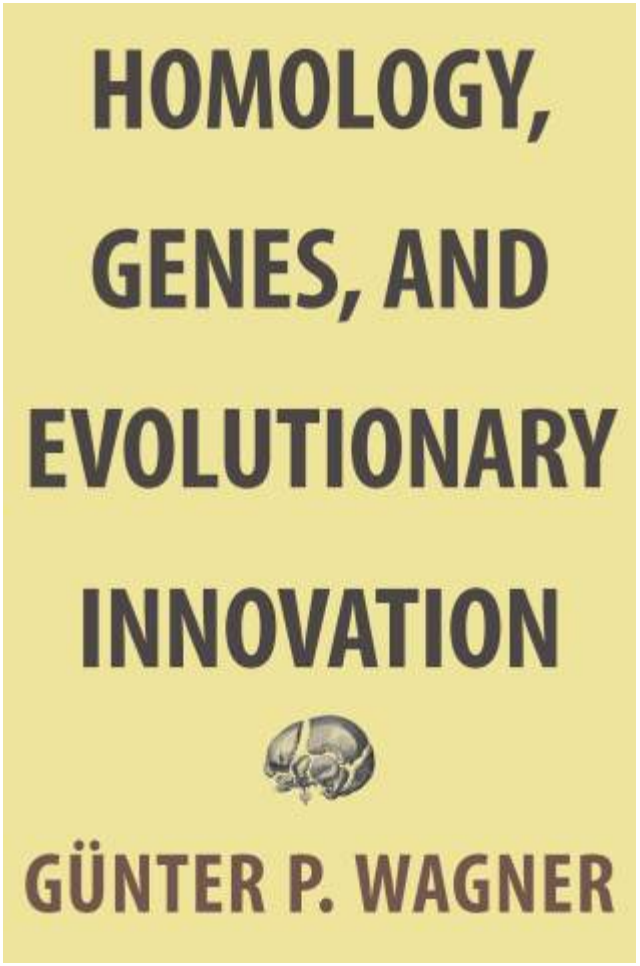
"Several types of network subcircuits have been identified so far,
each associated with specific regulatory functions."

Peter & Davidson (2017). *Proc Natl Acad Sci U.S.A.* 114, p. 5862.

Genetic theory of homology

Central obstacle to genetic theories of homology:

there is abundant variation in the genetic causes of the same characters



Character Identity versus Character State

Lepidoptera

Diptera

Coleoptera

Character Identity
Broad-sense homology based on continuity of lineages.
Here: forewings vs. hindwings.

Character State:
Characters vary in size, shape & colour.
Here: wings, halteres & elytra.

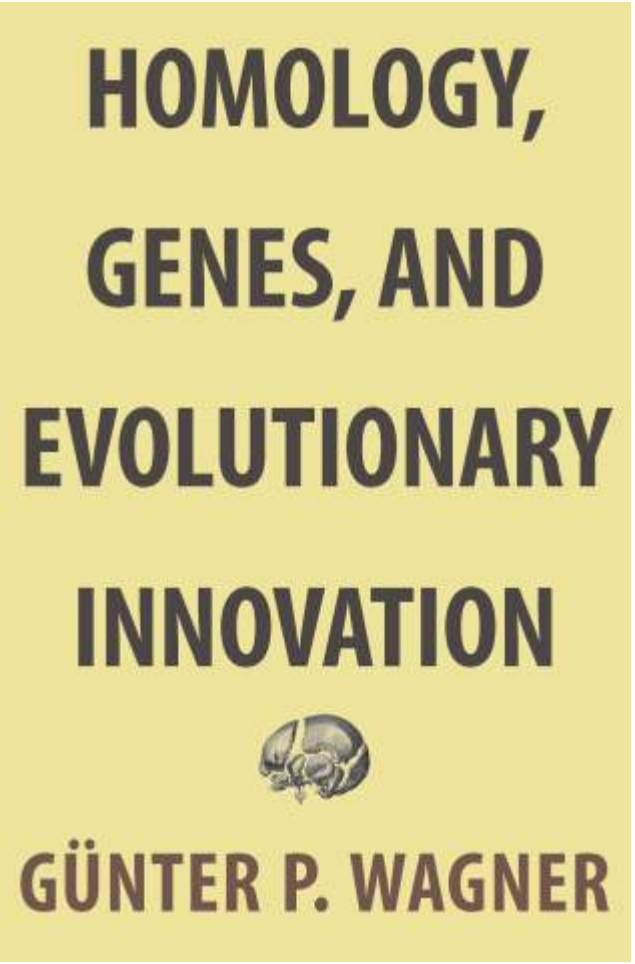
Wagner (2007). *Nat Rev Genet* 8: 473.
Wagner, *Homology, Genes, and Evolutionary Innovation*, Princeton Univ Press, 2014.

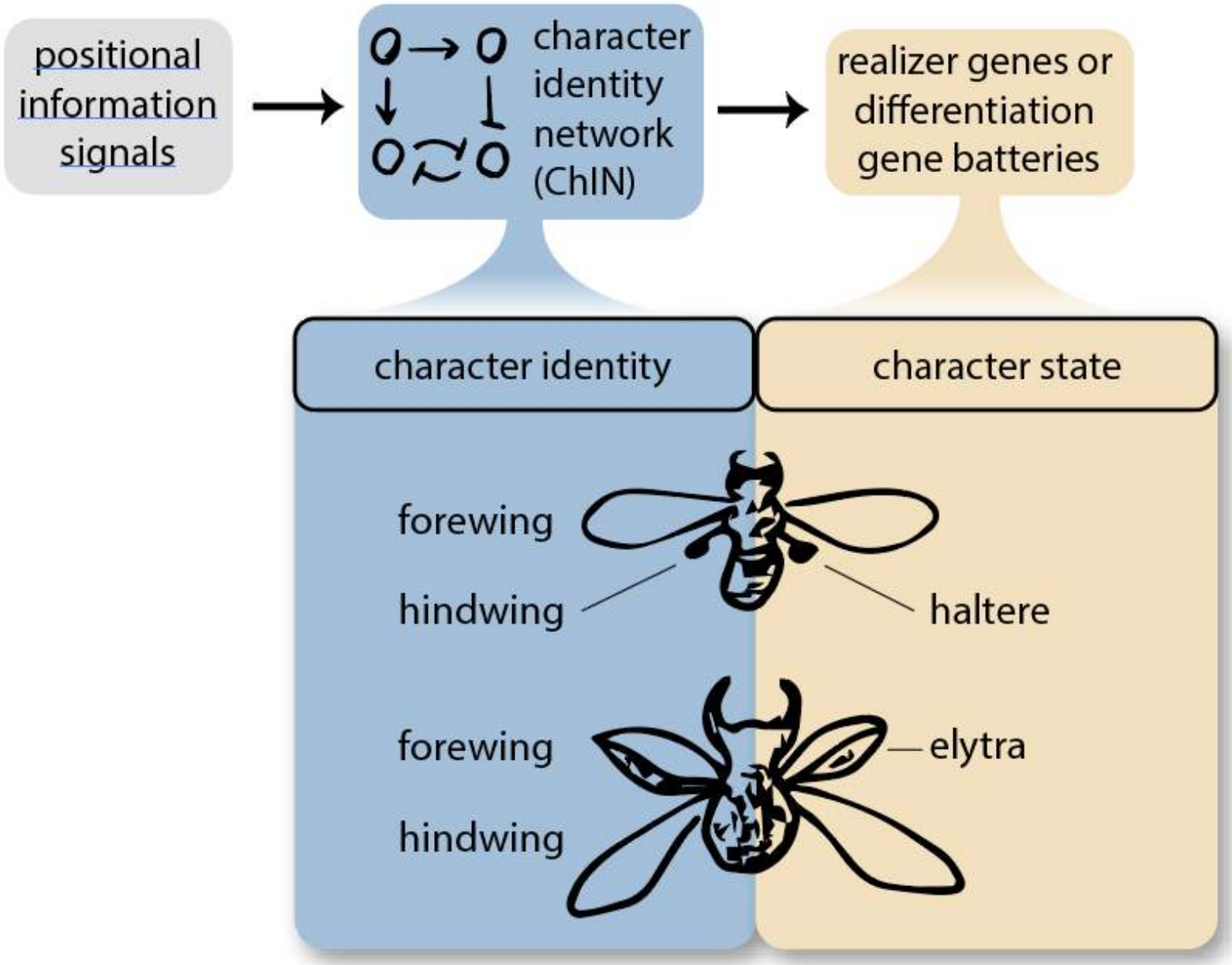
Genetic theory of homology

Central postulate:

“The distinction between character identity and character states […] is reflected in the genetic architecture of development in which character identity has a different genetic substrate than character states” (Wagner 2014, 94).

Character Identity Networks (ChINs)




positional information signals
character identity network (ChIN)
realizer genes or differentiation gene batteries
character identity
character state
forewing
hindwing
haltere
forewing
hindwing
elytra

Three problems

- Determinism
- Correspondence
- Diachronicity

Determinism

Davidson: a genetic program explains the resemblances between parents and offspring

Determinism

Problems:

- Regulatory processes occur at all levels of organization
- Non-genetic inheritance
- Transmission depends on cell state and organismic activity
- “Program” hard to map onto biological reality
  - Instructions and substrate are the same
  - Recursive
- Replicated program is not the only way to reliably reproduce phenotypes

Determinism as abstraction strategy

GRNs include the difference-making causes, so we can abstract from cell state and dynamics

Depends on 1:1 correspondence between network structure, cellular dynamics, and phenotypic outcomes

The problem of correspondence

"There is no a priori reason to believe that the same instantiation of a developmental mechanism underlies a conserved developmental process in even closely related organisms."

Von Dassow & Munro (1999). *J Exp Zool (Mol Dev Evol)* 285: 307

Evolution at GRN and phenotypic level is dissociable

George von Dassow

Ed Munro

The problem of correspondence

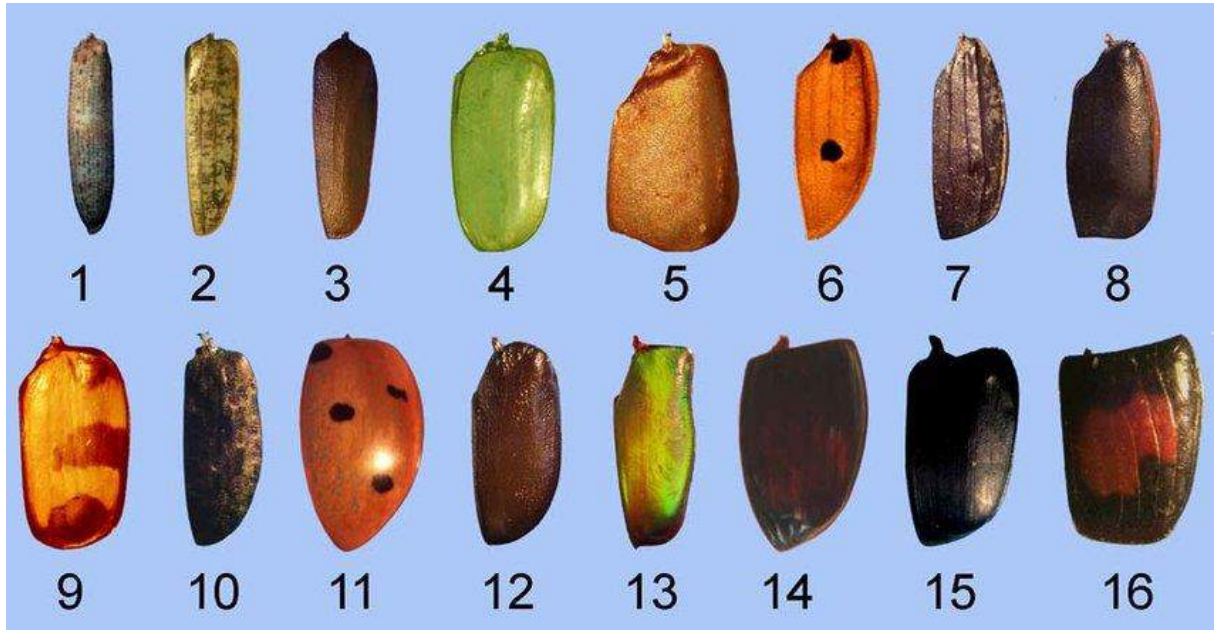
When the same GRNs produce different outcomes, and different GRNs produce the same outcome, GRNs do not include the difference-making causes

George von Dassow

Ed Munro

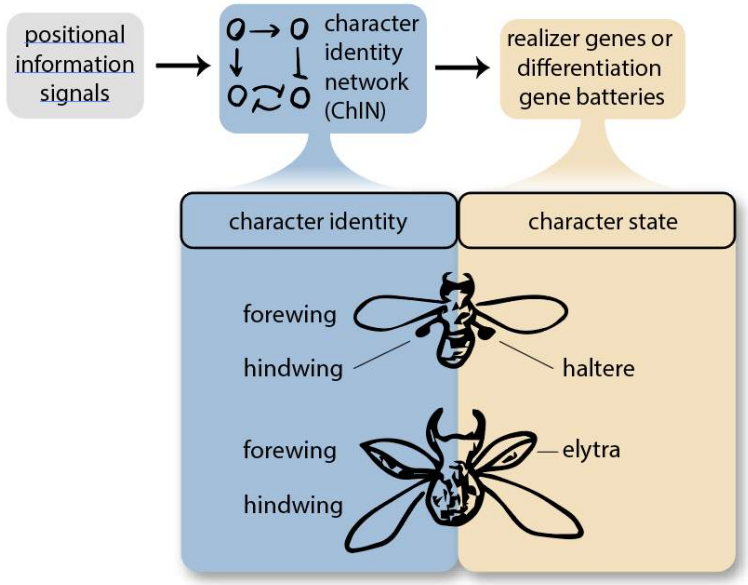
Morphological homology cannot require network homology

The Problem of Correspondence: Character Definition



Frantsevich *et al.* (2014). *Arthropod Struct Dev* 43: 523.

Coleoptera



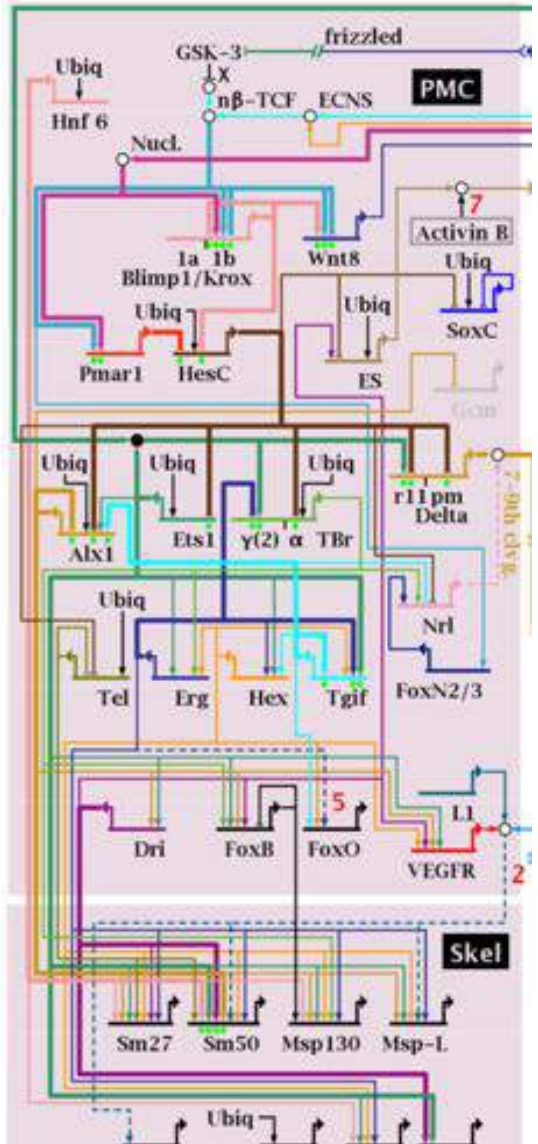
Character Identity
here: elytron

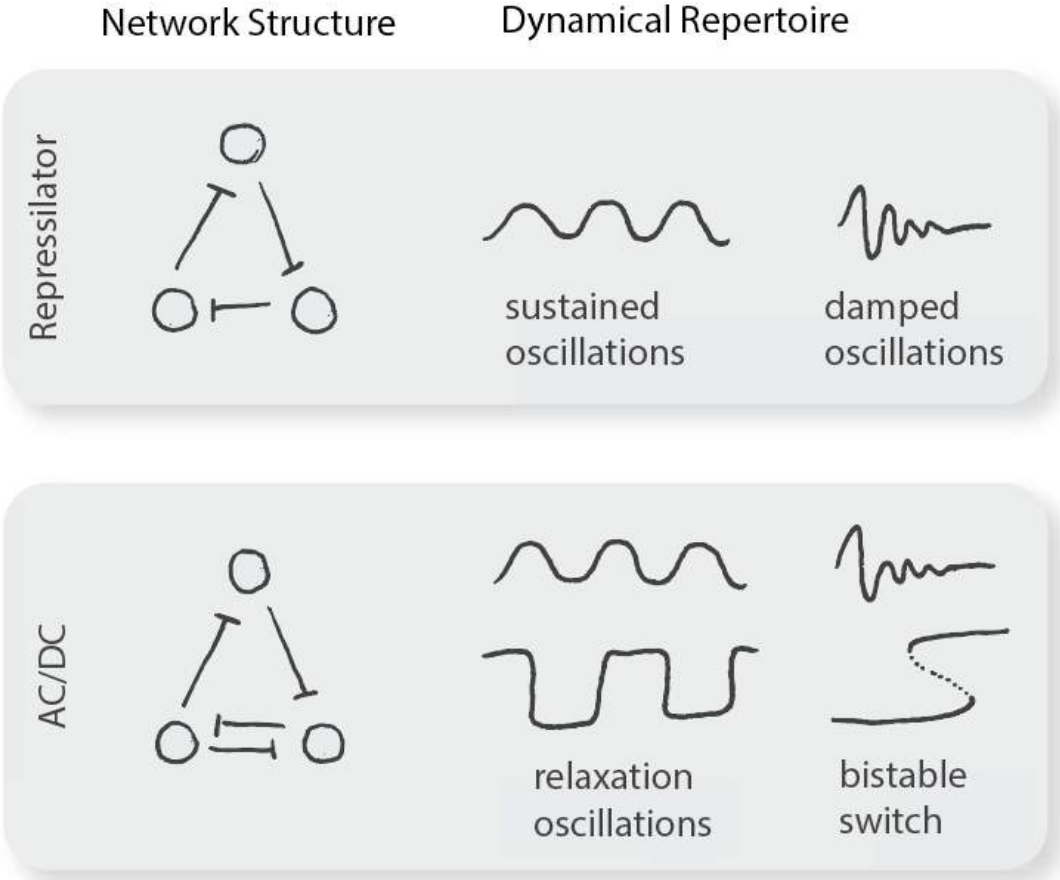
Character State:
here: shape, pattern, root position

Wagner (2007). *Nat Rev Genet* 8: 473.
Wagner, *Homology, Genes, and Evolutionary Innovation*, Princeton Univ Press, 2014.

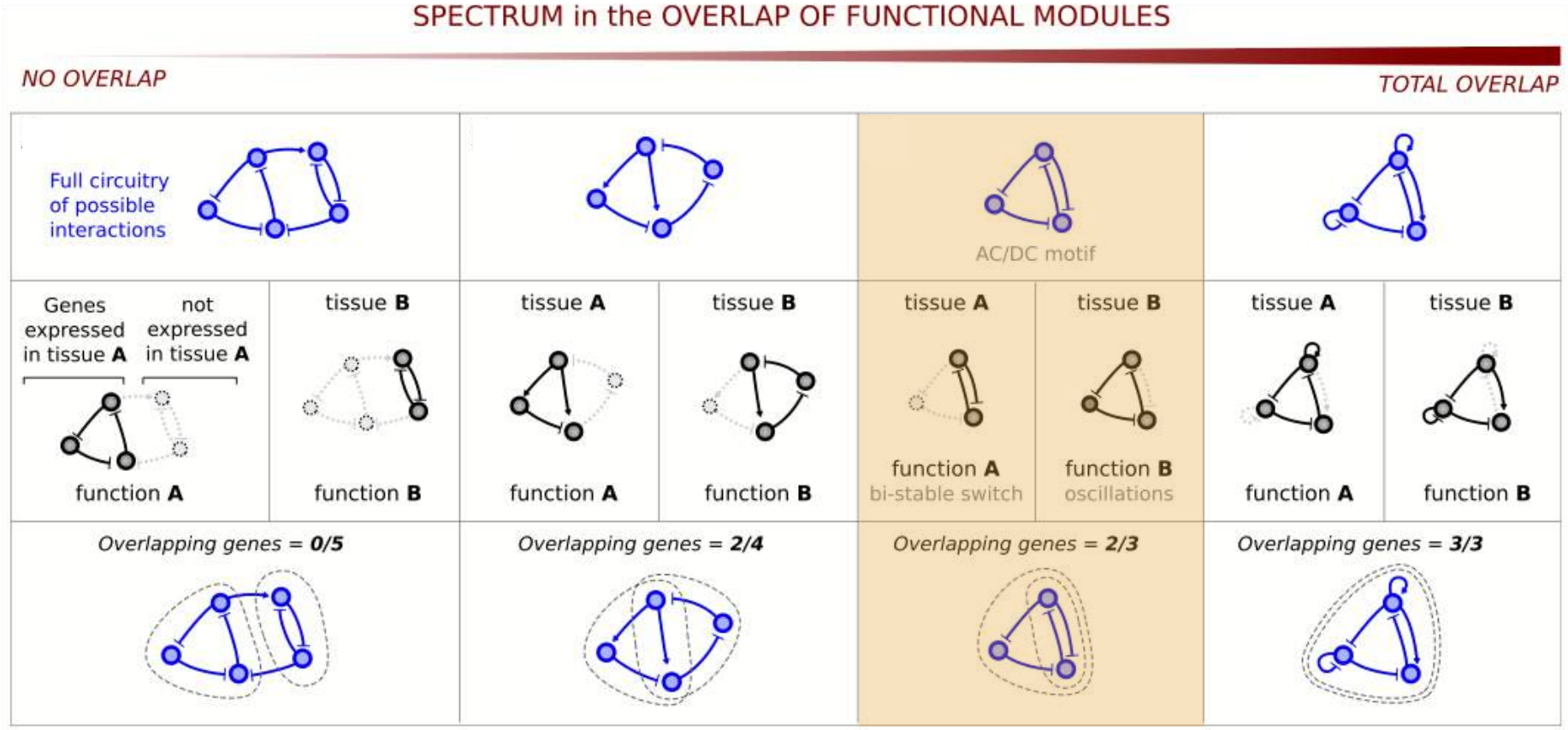
Diachronicity

Do network sub-circuits “imply” specific behaviors?





Most Multi-Functional Circuits are not Modular!

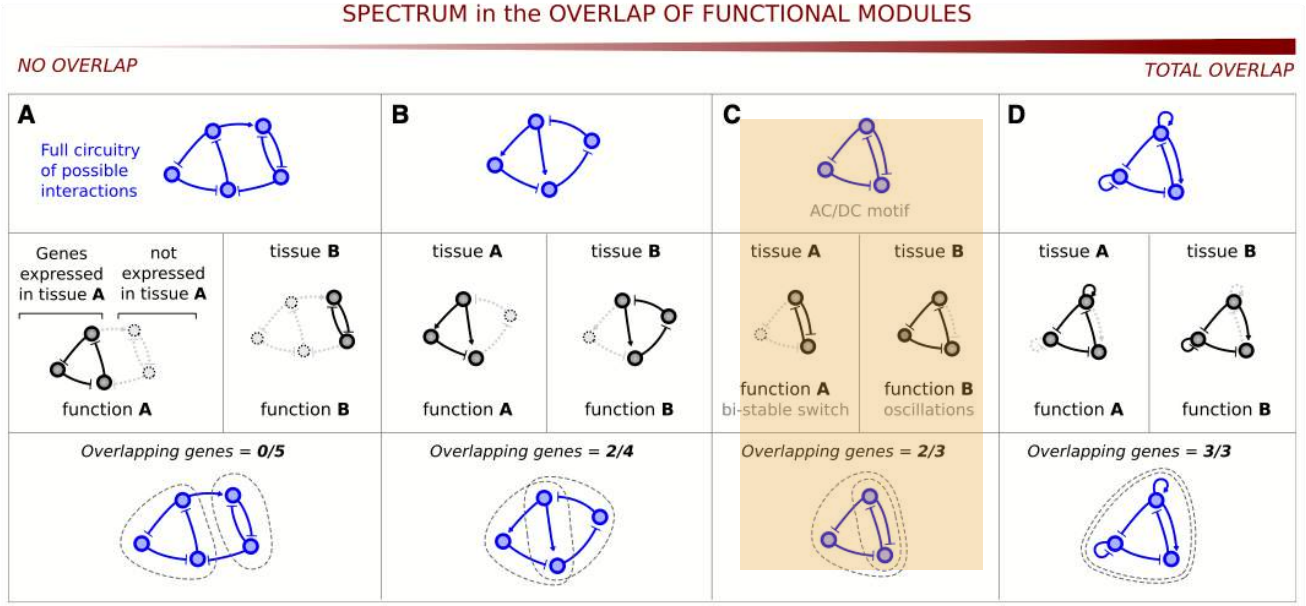


Jiménez *et al.* (2017). *Mol Syst Biol* 13: 925.

Multifunctional circuits

- “G-value paradox”
- Searching for additional sources of complexity in the genome

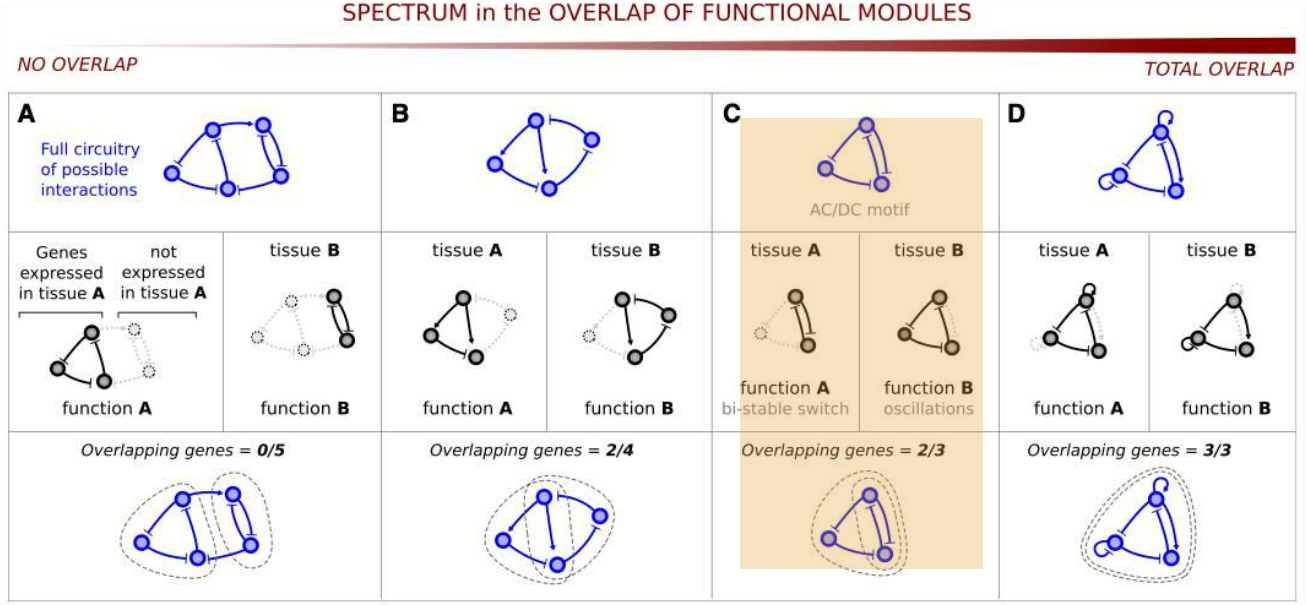
- Additional organismic complexity might not derive from additional molecular components



Jiménez *et al.* (2017). *Mol Syst Biol* 13: 925.

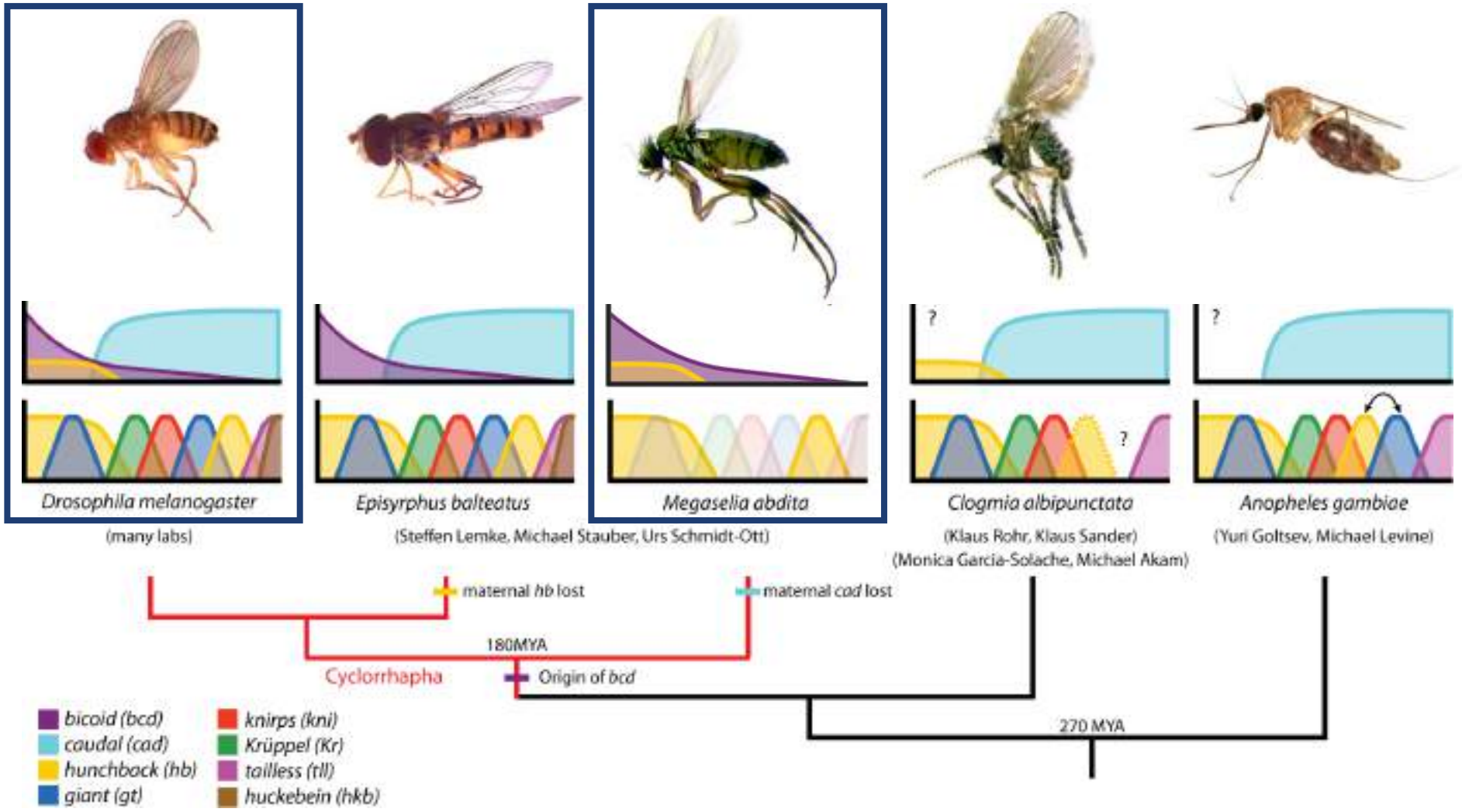
Determinism, correspondence, diachronicity

- Structure alone does not <u>determine</u> process/outcome
- Same networks <u>correspond</u> to different functions
- Mechanistic understanding requires <u>diachronic</u> perspective

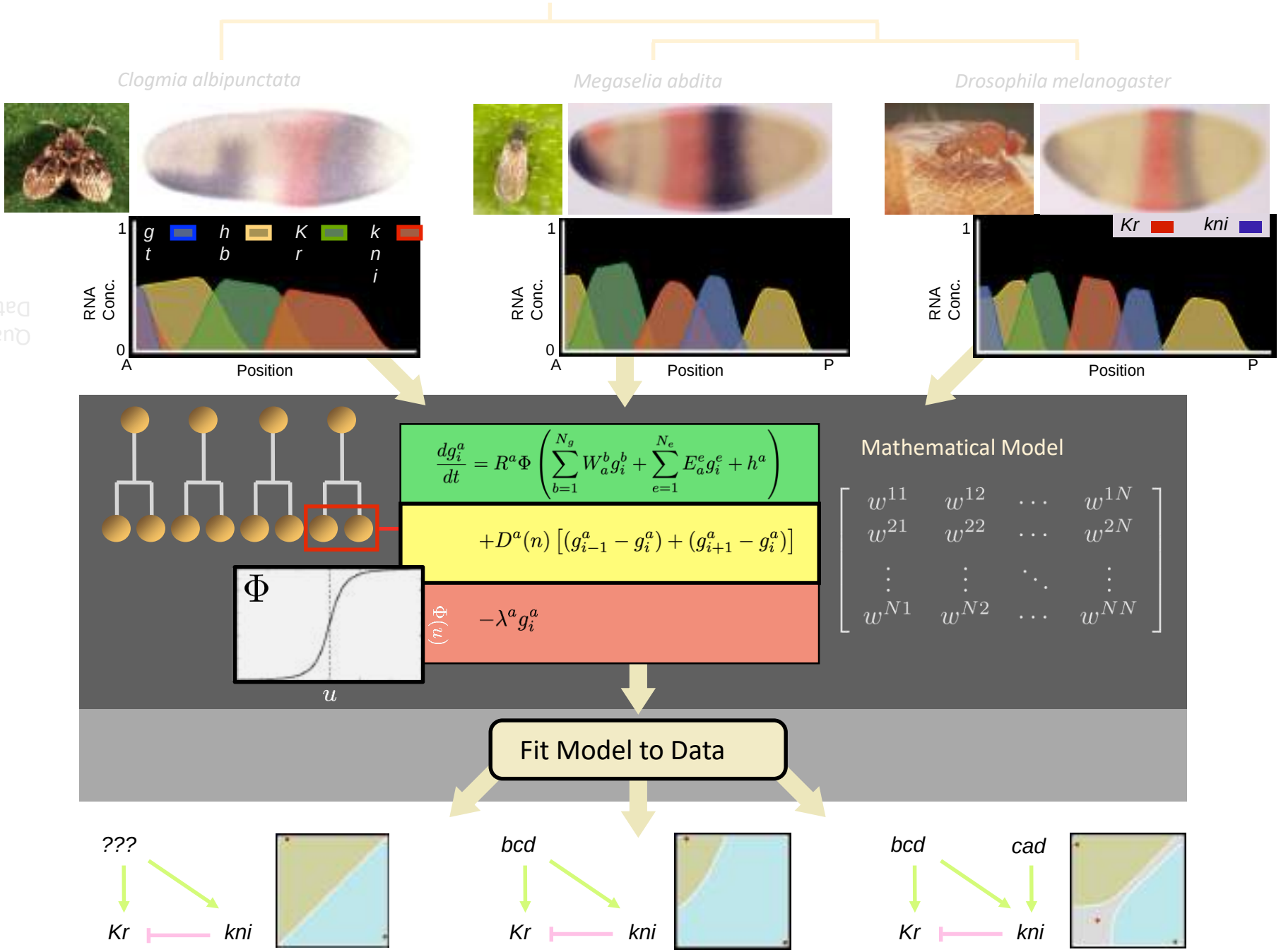


Jiménez *et al.* (2017). *Mol Syst Biol* 13: 925.

Dynamical Modules in Continuous Patterning Systems: Evolution of the Gap Gene System

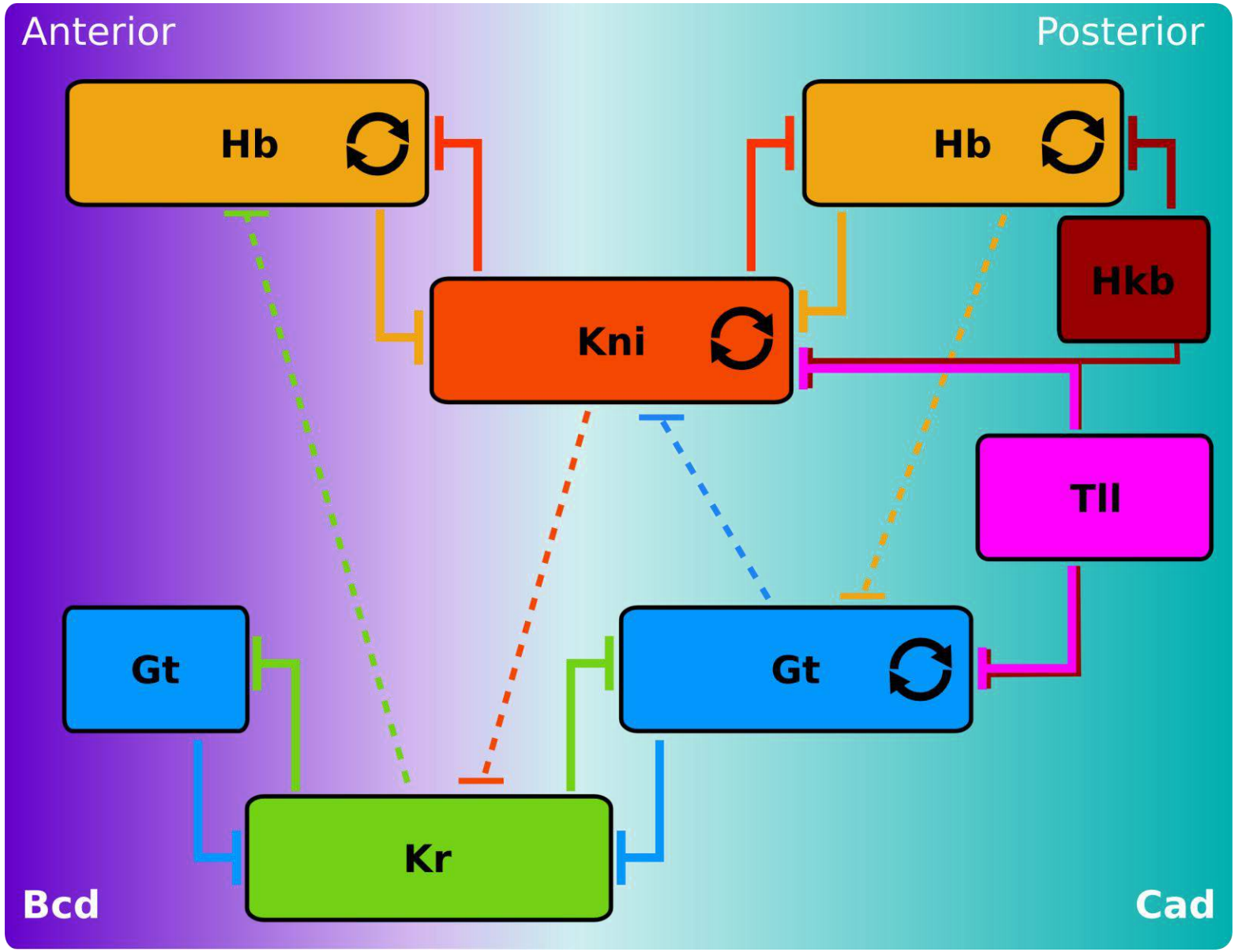


Wotton *et al.* (2015). *eLIFE* 4: e04785.



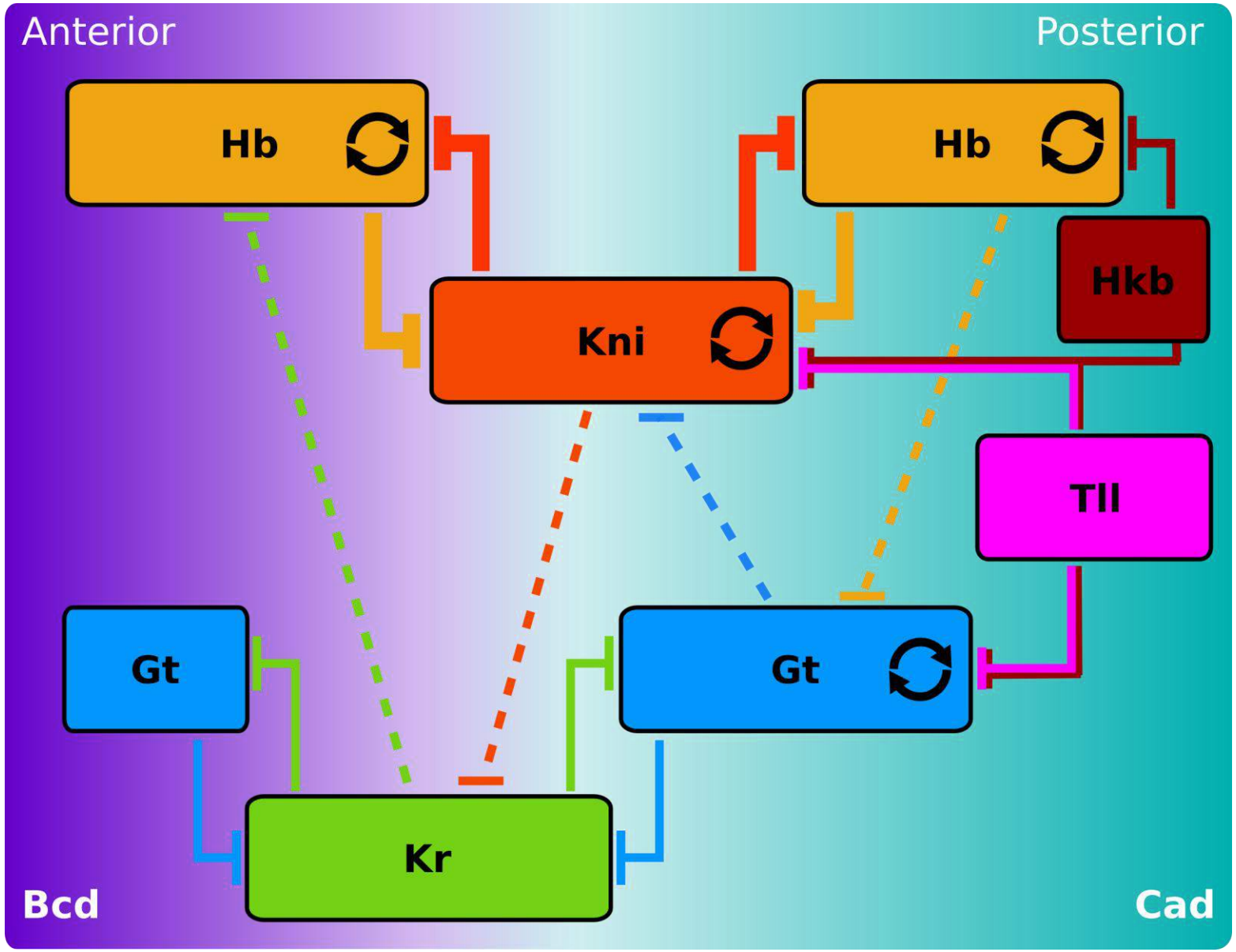
reverse-engineering reviewed in: Jaeger & Crombach (2012). In: *Evolutionary Systems Biology* (Soyer, ed.). Springer.

Reverse-engineering *Drosophila* gap genes



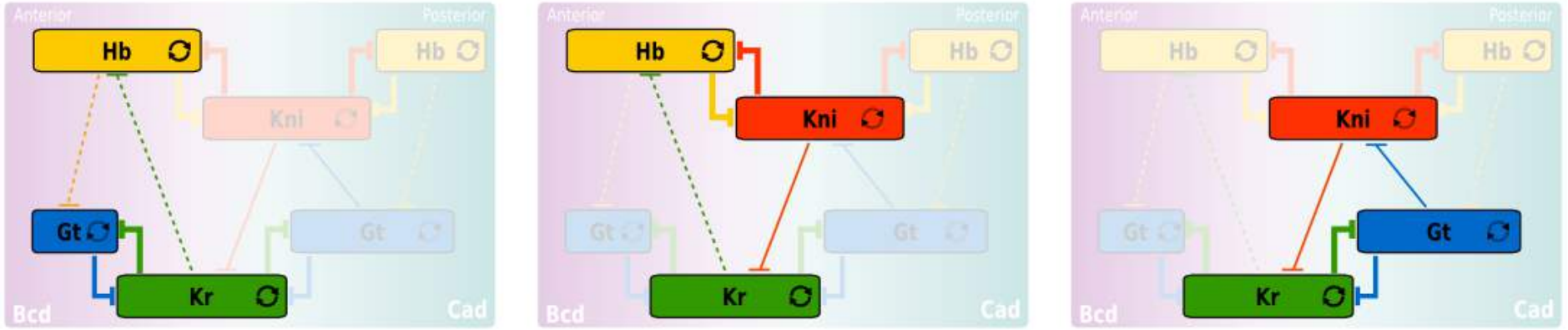
slightly modified from Crombach *et al.* (2012). *PLoS Comp Biol* 8: e1002589.

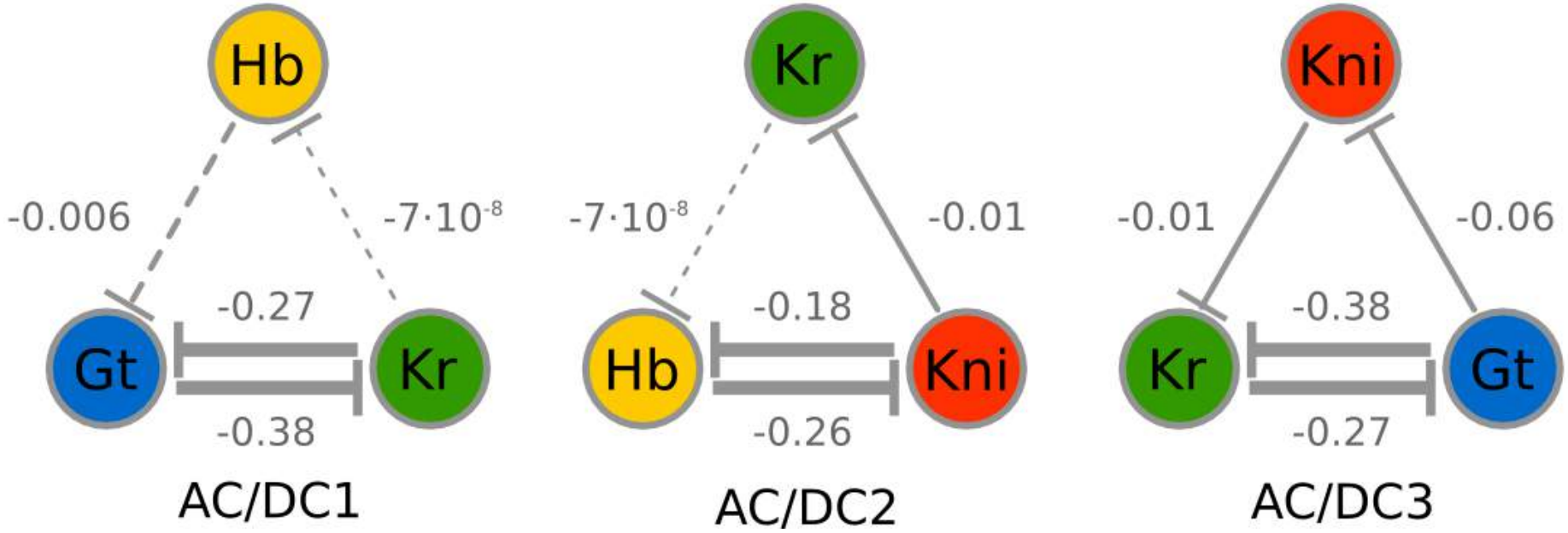
Megaselia: quantitative developmental system drift



Wotton *et al.* (2015). *eLIFE* 4: e04785.

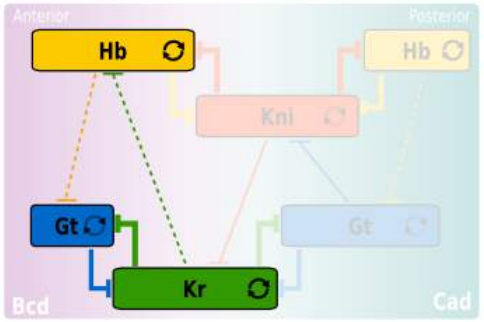
One type of sub-circuit drives both dynamical regimes



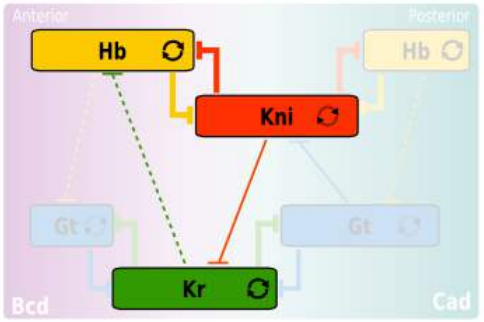


Verd *et al.* (2019) *eLIFE*.

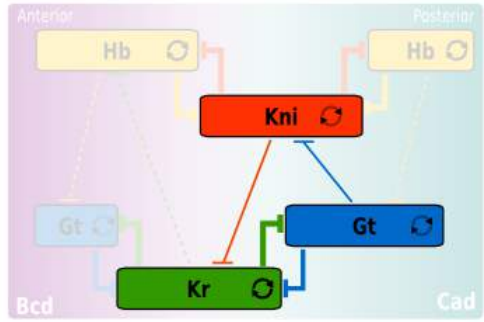
Evolvability through criticality in dynamical modules



AC/DC1



AC/DC2



AC/DC3

Drosophila melanogaster

~180Myrs

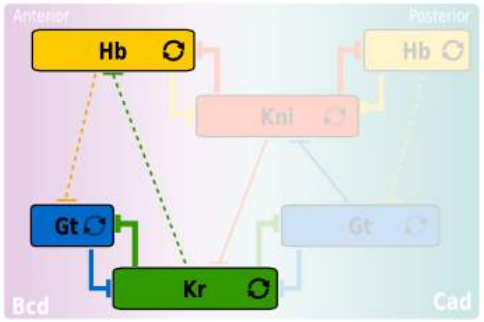
Megaselia Abdita

	AC/DC1	AC/DC2	AC/DC3
Drosophila melanogaster	Multi-stable Switch	Critical	Damped Oscillator
Megaselia Abdita	Critical	Damped Oscillator	Damped Oscillator

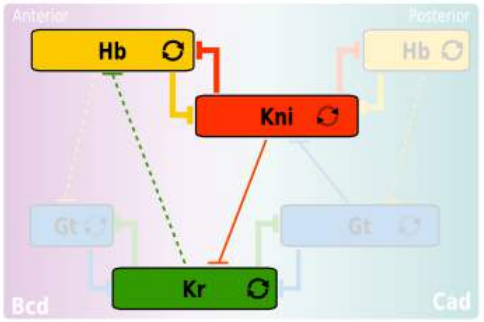
Verd *et al.* (2019) *eLIFE*.

Evolvability through criticality in dynamical modules

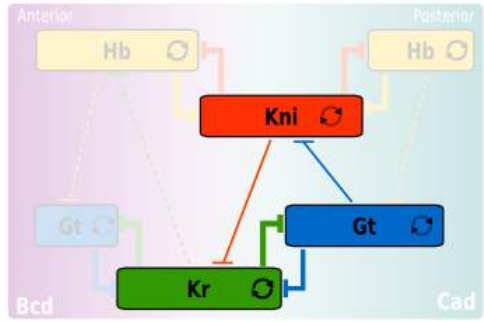
(with a big tip of the hat to Stuart Kauffman and his “Edge of Chaos”)



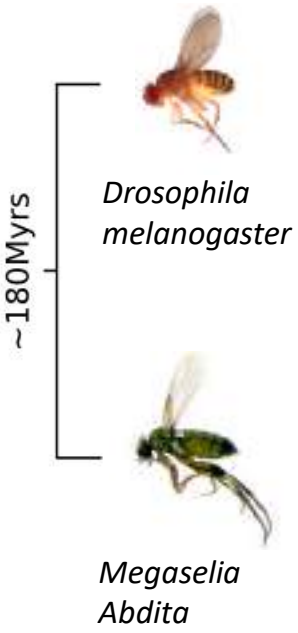
AC/DC1

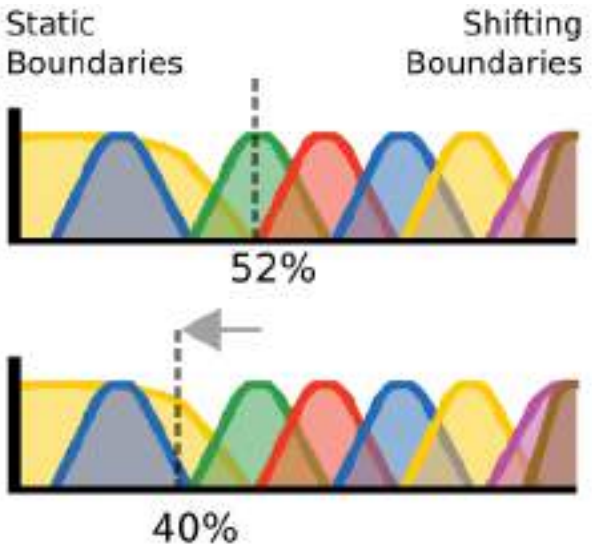


AC/DC2



AC/DC3





Spatio-temporal arrangement of gap domains conserved.

Bifurcation boundary between dynamical regimes evolutionarily labile.

→ differential evolvability of different expression features

Verd *et al.* (2019) *eLIFE*.

Beyond networks?

Modeling

Mechanistic decomposition relies on perturbational methods

These methods only identify components that are necessary for a process, not the mechanism that is sufficient to produce it

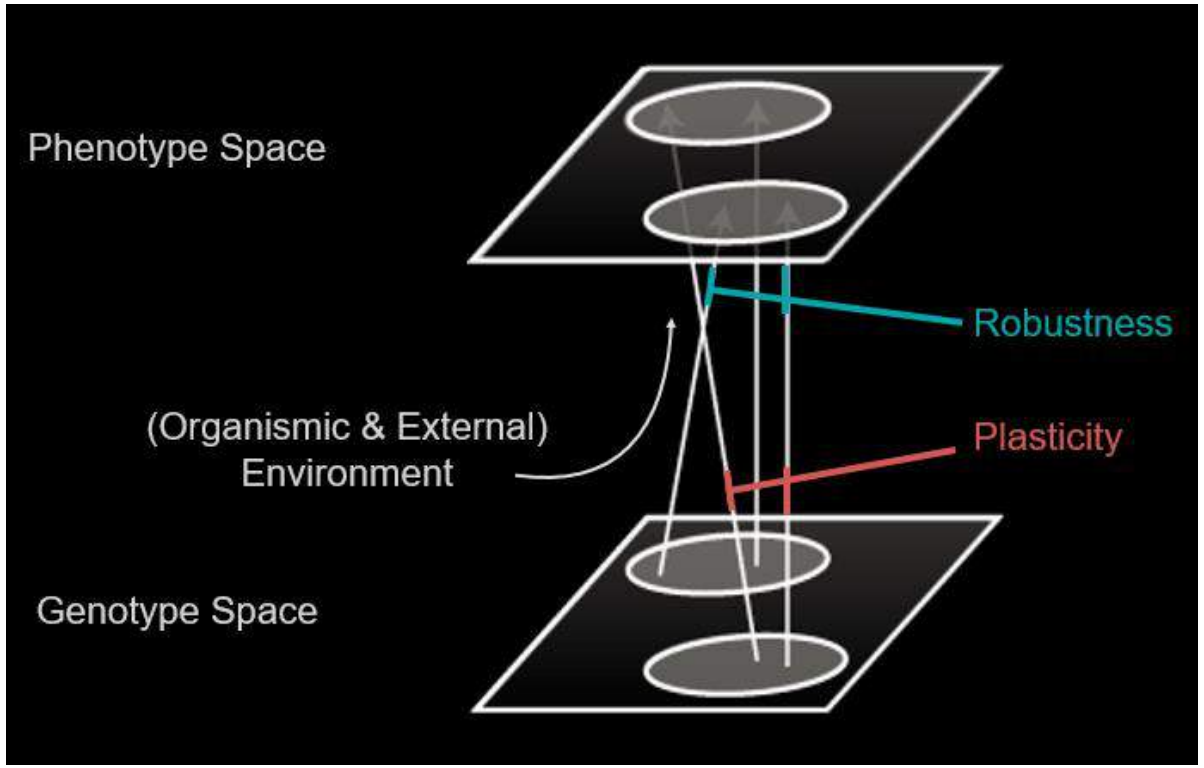
Reason: **complexity** and **nonlinearity**

Mechanistic decomposition into network structures, and recomposition into dynamical processes, are complementary and both necessary

Mechanistic understanding of GP map

Needed for:

- Understanding how production of variation is related to sorting
- Explaining phenotypic plasticity and robustness
- Understanding variational properties and evolvability



Mechanistic understanding of GP map

- GRNs are playing this role
- But network thinking falls short of fulfilling the mechanistic research agenda of evo-devo
- Problems:
  - Determinism
  - Correspondence
  - Diachronicity
- Fundamental problem: GRNs are static, *whereas much of the difference-making action in development lies in complex activities and nonlinear interactions*

Proposed alternative: integrate dynamical modeling

- Resolves diachronicity by introducing dynamics
- Attenuates (but does not eliminate) correspondence by causally connecting networks, behaviors, and phenotypes
- Avoids determinism because it integrates non-genetic factors

- To become “mechanistic,” evo-devo must become “processual”

Thank you!

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