

Model organisms and developmental biology

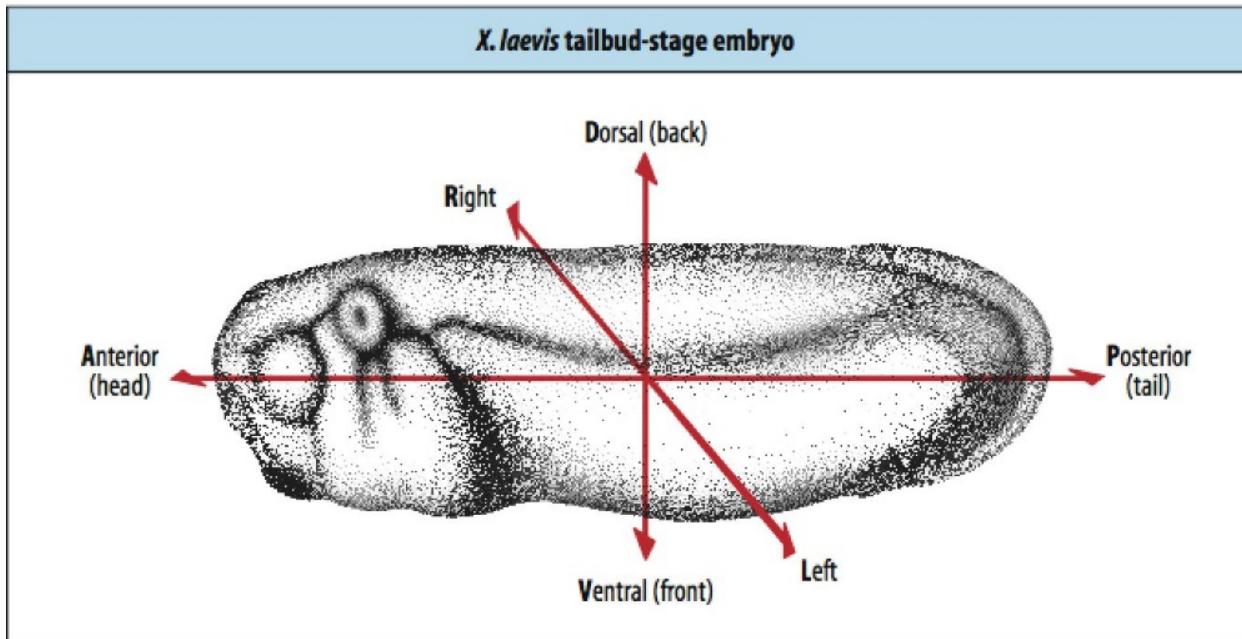
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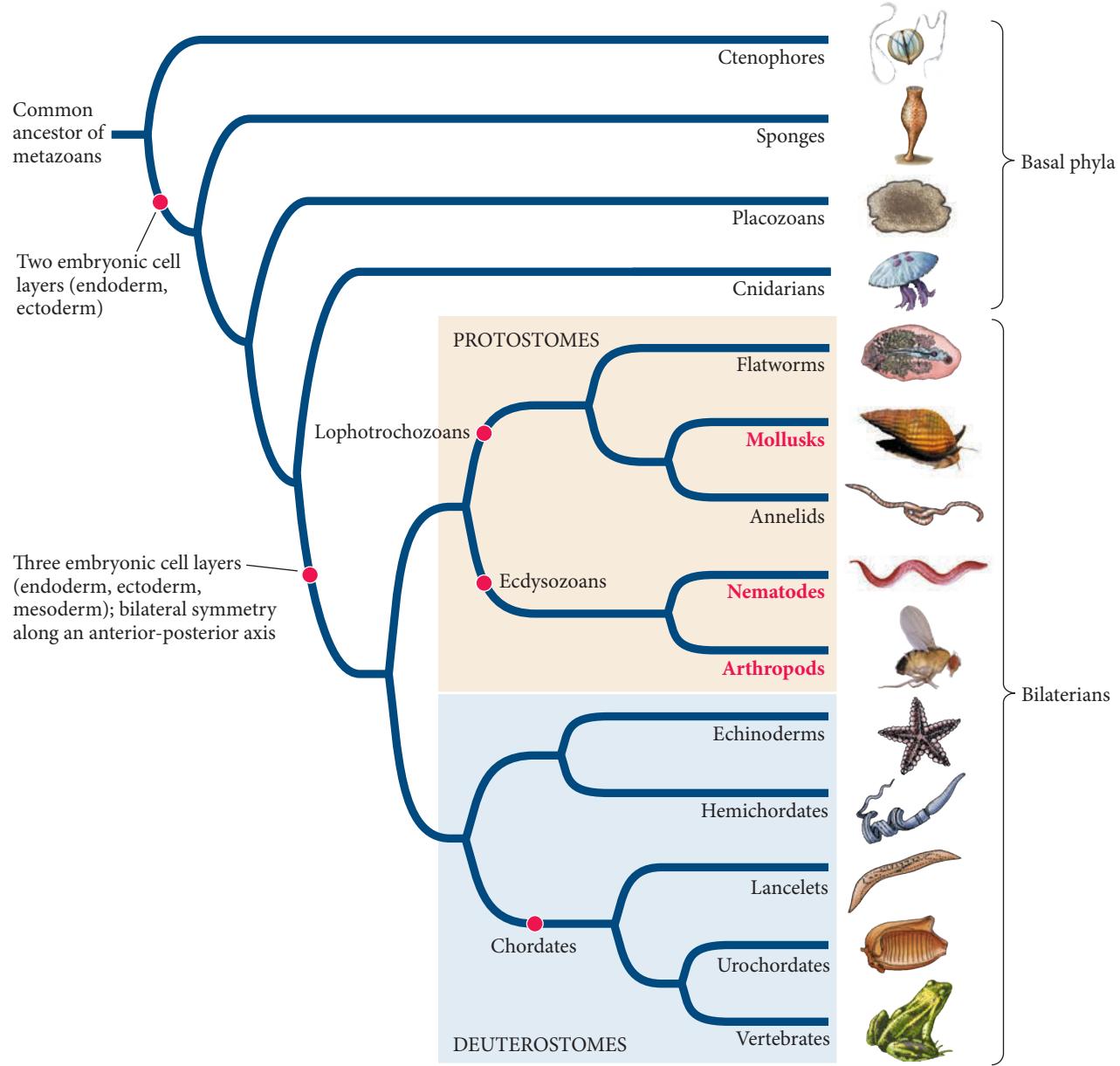
Principles of development

Body plan

- Body plan, establishment of axes (antero-posterior, dorso-ventral, left-right), and germ layers.

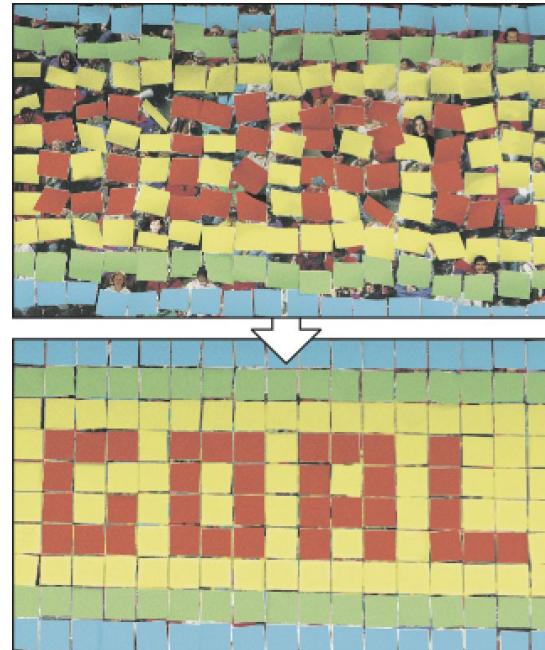
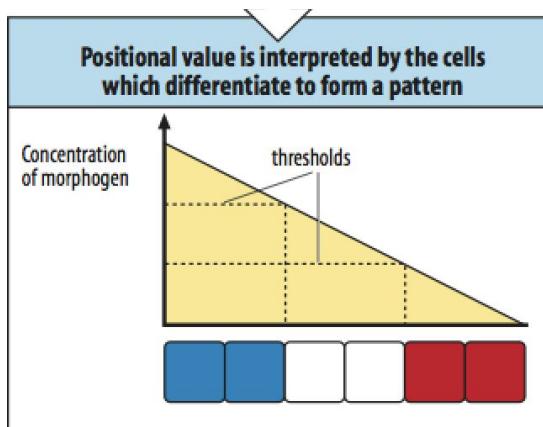


The tree of metazoan (animal) life



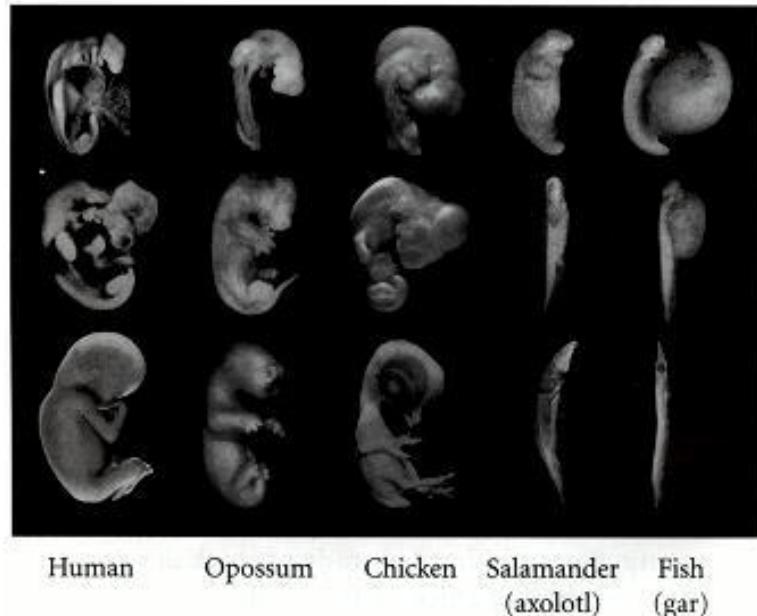
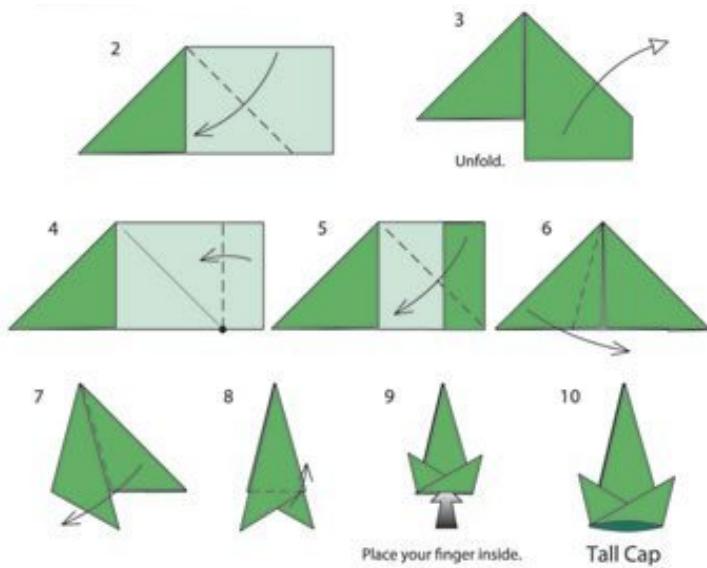
The positional information and its interpretation

- 1. One dimension.
- 2. Positional values has to be related to some boundary or threshold.
- 3. Interpreted by cells.



Generative rather than descriptive

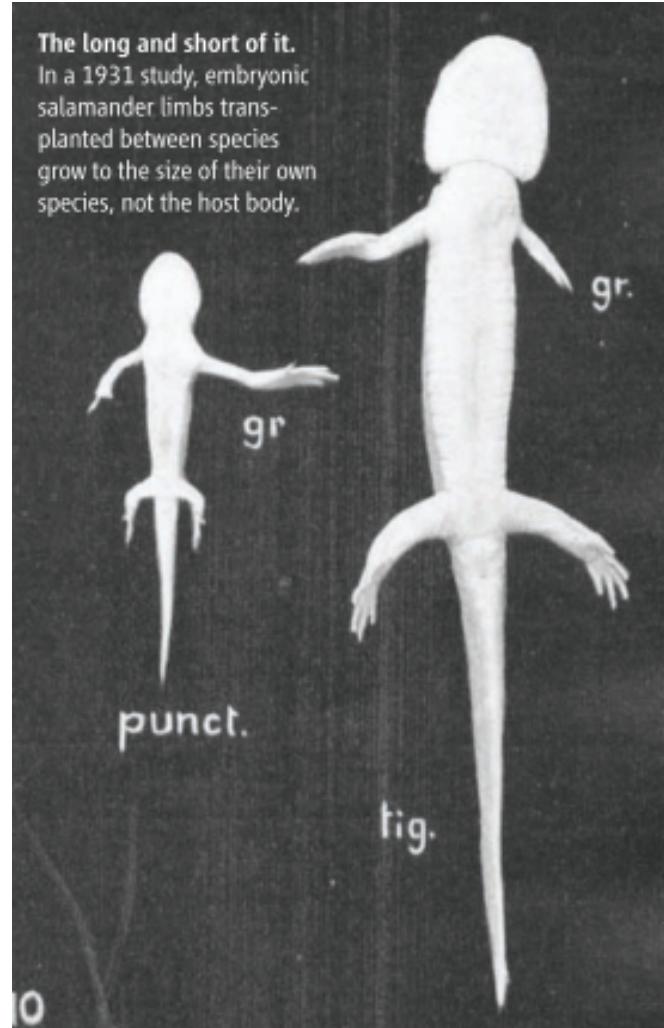
- Generative, instruct how to make an object, like origami.
- Descriptive, describe in detail, eg, size, position, composition, like a blueprint.



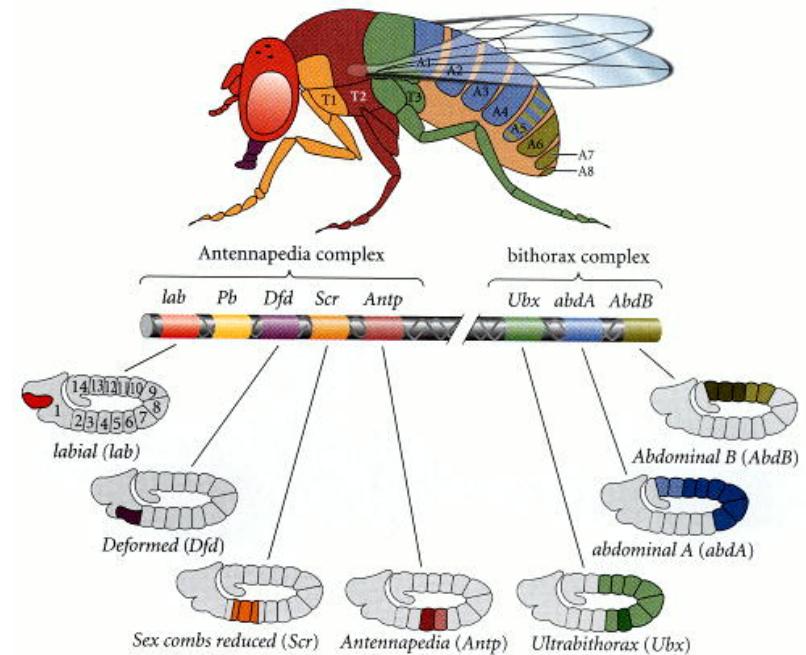
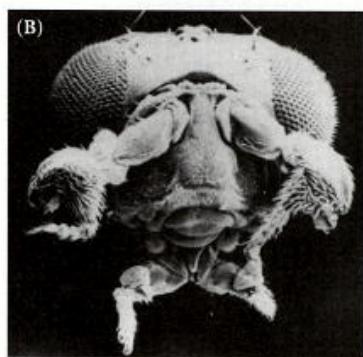
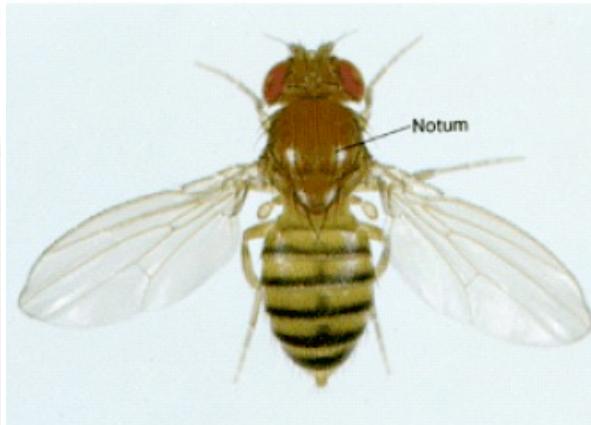
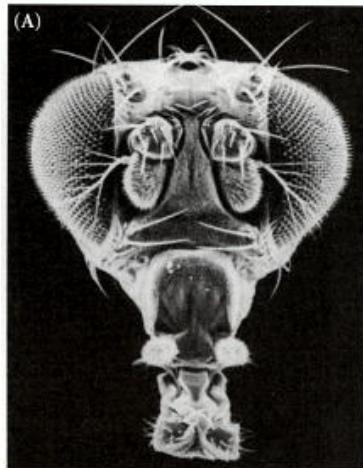
Modularity (模块化)

- Discrete units (modules) , eg. segments and somites.
- Duplication of modules, eg. somites of snake.
- Divergence of modules, eg. wing and holtore, forelimb and hindlimb.
- Both anatomical units and DNA elements are modular.

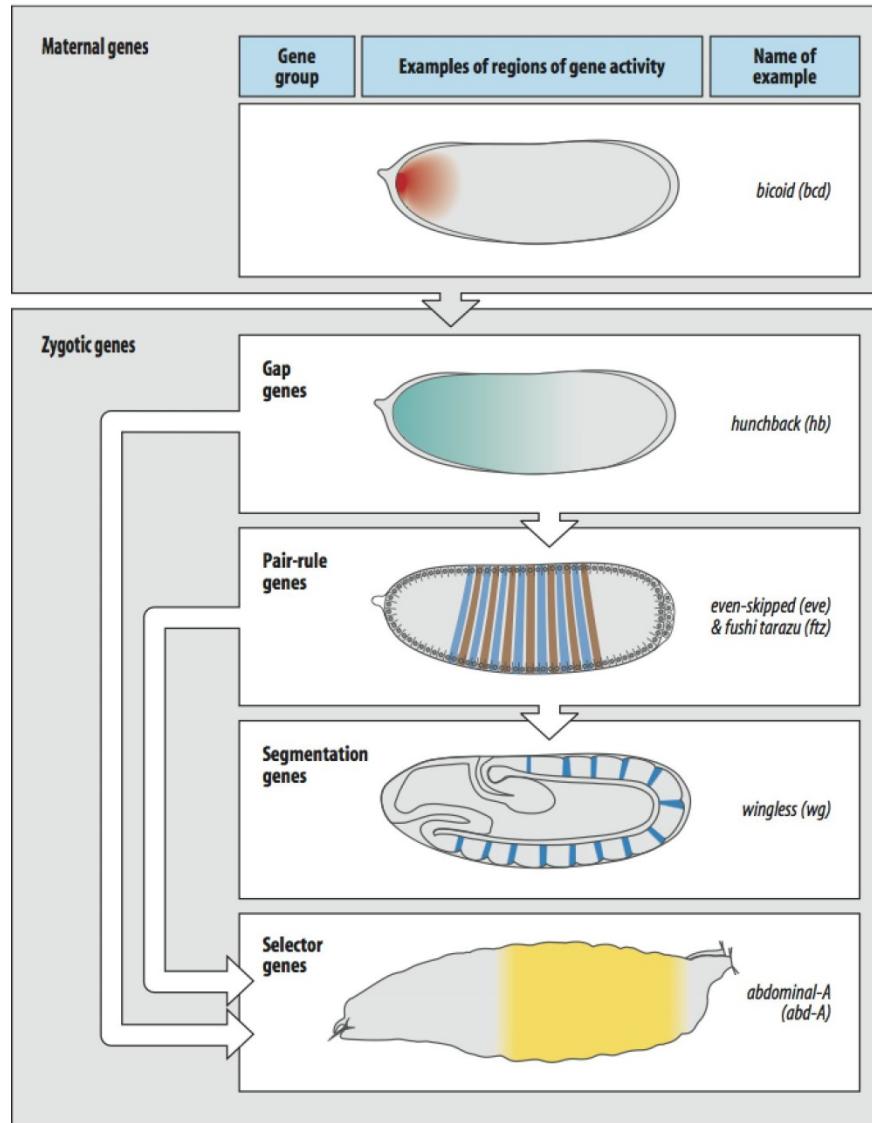
The size of limbs is genetically programmed in salamanders – an illustration of modularity



Homeotic selector genes

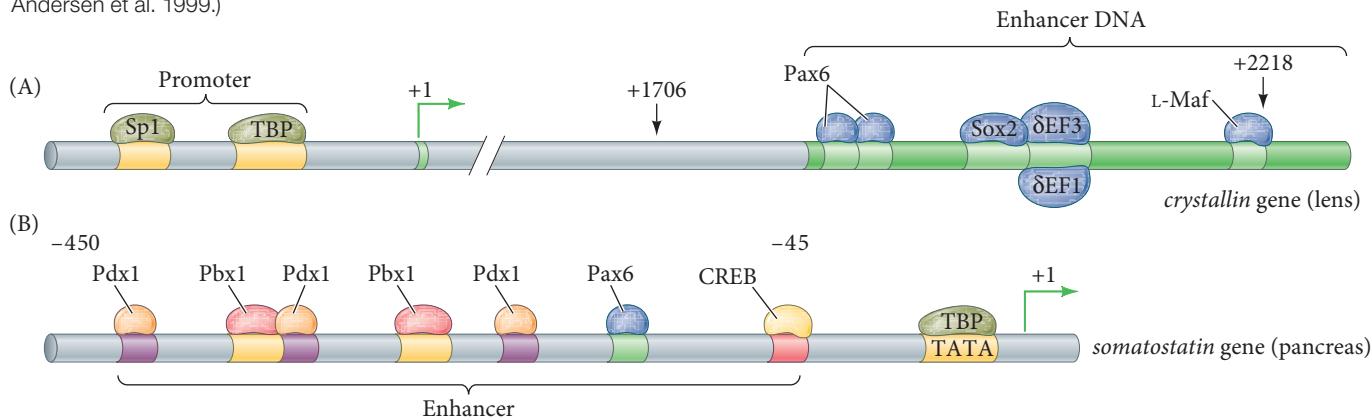


The sequential expression of different sets of genes establishes the body plan



Modular transcriptional regulatory regions using Pax6 as an activator

(Andersen et al. 1999.)



Constrains

约束

- Physical constraints
- Morphogenetic constraints
- Pleiotropic constraints

多效性

Physical constraints

- The laws of diffusion, hydraulics, and physical support are immutable and will permit only certain physical phenotypes to arise.
- Why no vertebrate on wheeled appendages?
- Why no giant insects? For example, 6-foot-tall mosquitoes.

ON GROWTH AND FORM

The Complete Revised Edition



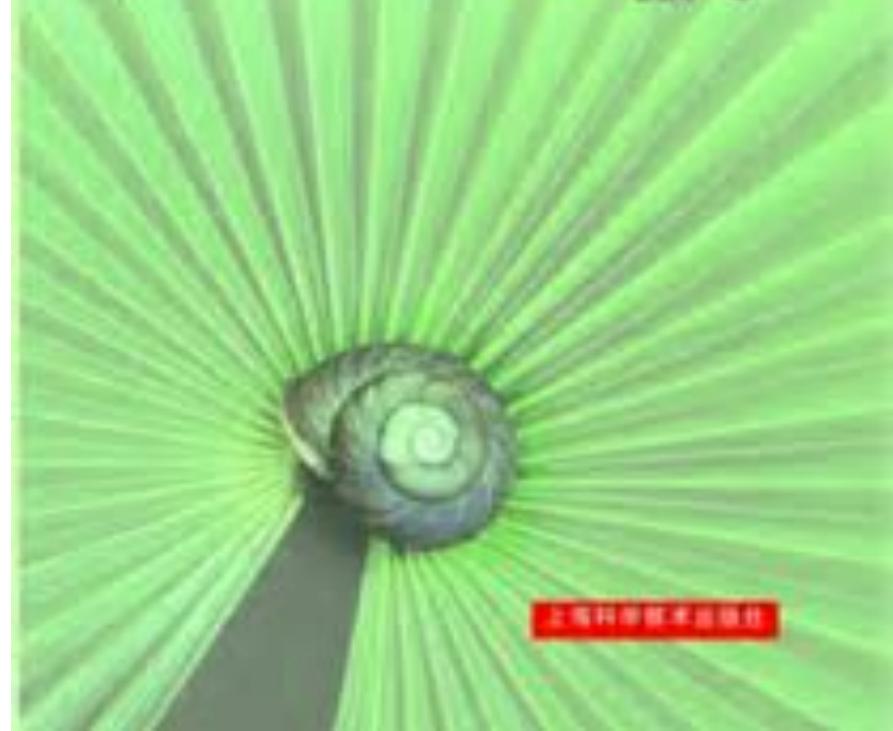
D'Arcy Wentworth Thompson



ON GROWTH
AND
FORM

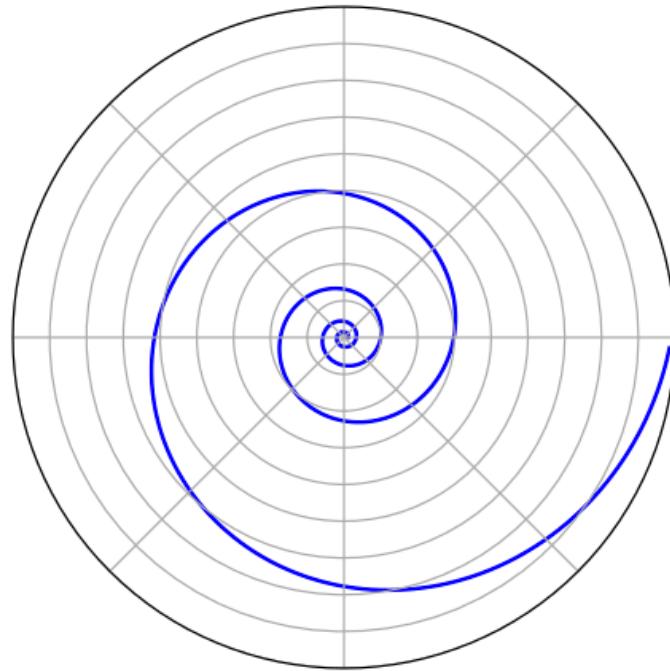
生长和形态

[英] 达西·沃思·汤普森 著
[英] 帕特·阿纳·西斯 绘
王道平 译

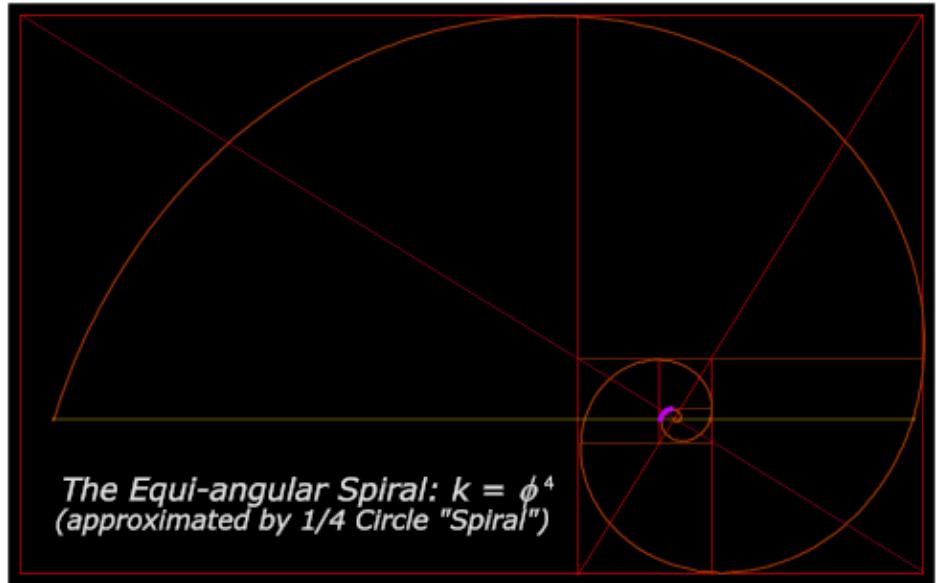
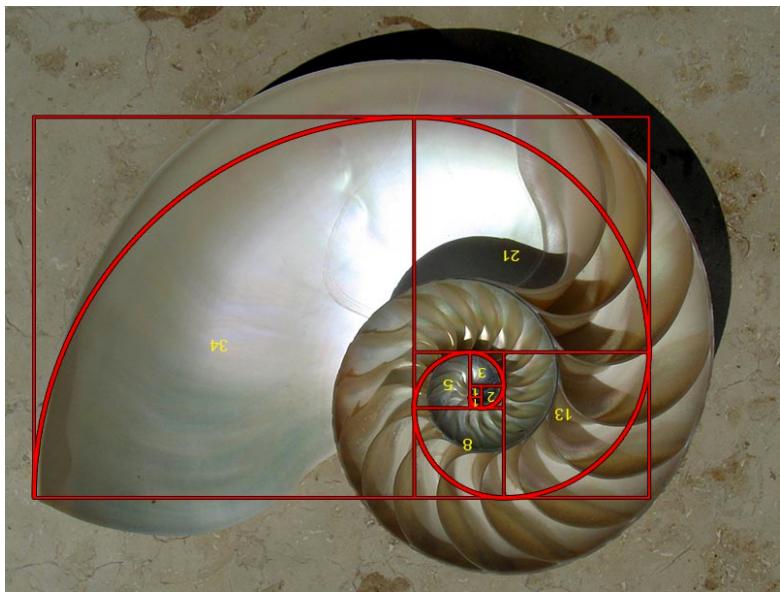


Logarithmic spiral (对数螺线/等角螺线)

$$r = ae^{b\theta}$$

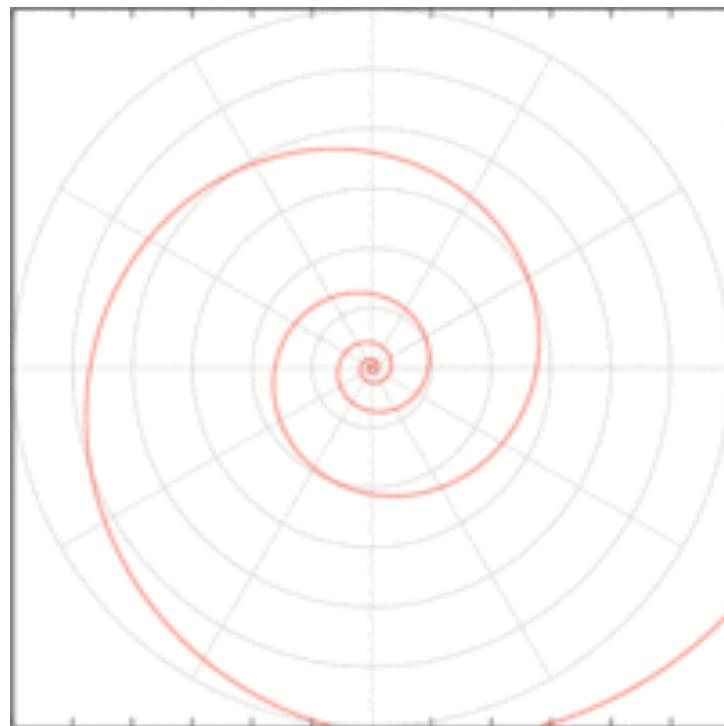


Nautilus and log spiral



在壳的生长中，我们想不出更简单的规律，即它会以同一不变的比例加宽变长；造物主遵循的正是所有规律中最简单的这一条。壳和里面的动物一样，只有大小的生长却无形态的变化；存在这种稳定的生长关系或是形态的恒同性，正是等角螺线的本质所在，也可以作为其中一种定义的根据。

Log spiral is self-similar

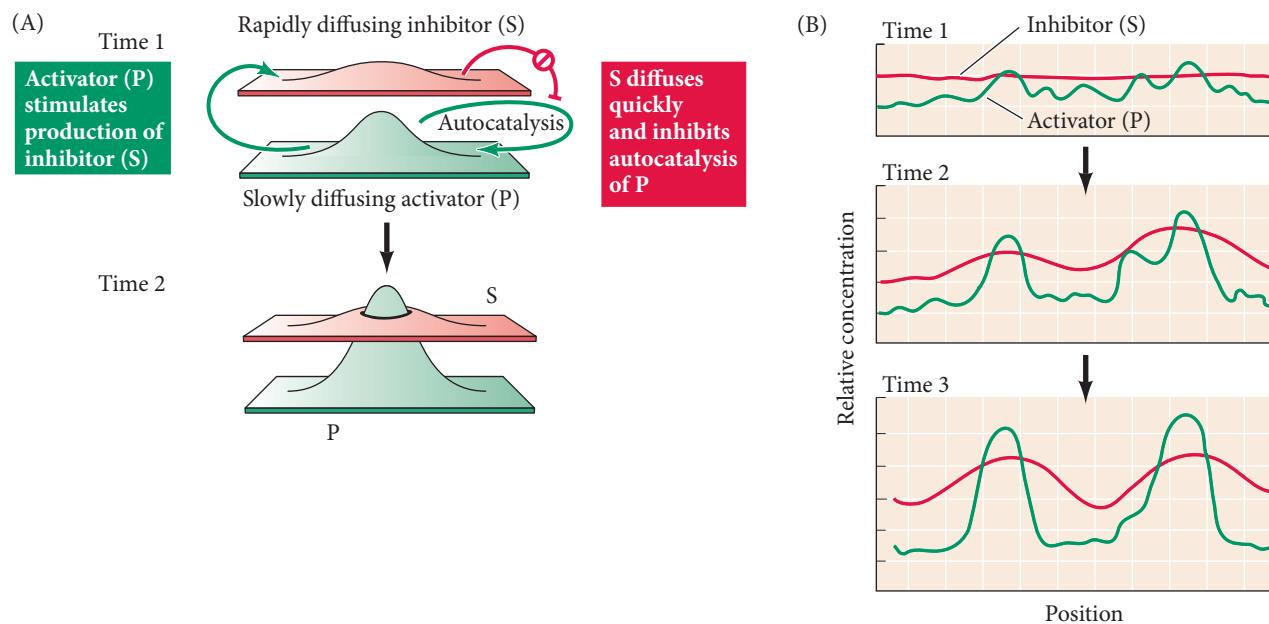


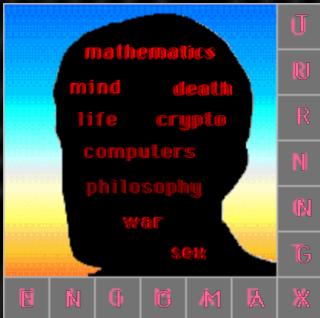
Morphogenetic constraints

- Bateson (1894) and Alberch (1989) noted that when organisms depart from their normal development, they do so in only a limited number of ways.
- For instance, although there have been many modifications of the vertebrate limb over 300 million years, some modifications are never seen.
- Such as a middle digit shorter than its surrounding digits, or an insect with 8 legs.

Reaction-diffusion mechanism, formulated by Alan Turing (1952)

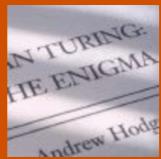
- Reaction-diffusion mechanism is a way of generating complex chemical patterns out of substances that are initially homogeneously distributed. This patterning would not occur in the presence of a single morphogen, but that it could be achieved by two homogeneously distributed substances.





Alan Turing: The Enigma

Website maintained by biographer [Andrew Hodges](#)

This website is an electronic extension of the biography

Alan Turing: The Enigma,

and provides a [Book Update](#) section.

Who was Alan Turing?

Founder of computer science, mathematician, philosopher,
codebreaker, strange visionary and a gay man before his time:

Statement of apology by the Prime Minister, Gordon Brown, 10 September 2009:

... a quite brilliant mathematician... whose unique contribution helped to turn the tide of war... horrifying that he was treated so inhumanely... **in music by the Pet Shop Boys, 23 July 2014.**



THE CHEMICAL BASIS OF MORPHOGENESIS

BY A. M. TURING, F.R.S. *University of Manchester*

(Received 9 November 1951—Revised 15 March 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

Two-component reaction–diffusion equations [\[edit\]](#)

Two-component systems allow for a much larger range of possible phenomena than their one-component counterparts. An important idea that was first proposed by Alan Turing is that a state that is stable in the local system can become unstable in the presence of diffusion.^[9]

A linear stability analysis however shows that when linearizing the general two-component system

$$\begin{pmatrix} \partial_t u \\ \partial_t v \end{pmatrix} = \begin{pmatrix} D_u & 0 \\ 0 & D_v \end{pmatrix} \begin{pmatrix} \partial_{xx} u \\ \partial_{xx} v \end{pmatrix} + \begin{pmatrix} F(u, v) \\ G(u, v) \end{pmatrix}$$

a plane wave perturbation

$$\tilde{\mathbf{q}}_k(\mathbf{x}, t) = \begin{pmatrix} \tilde{u}(t) \\ \tilde{v}(t) \end{pmatrix} e^{i\mathbf{k}\cdot\mathbf{x}}$$

of the stationary homogeneous solution will satisfy

$$\begin{pmatrix} \partial_t \tilde{u}_k(t) \\ \partial_t \tilde{v}_k(t) \end{pmatrix} = -k^2 \begin{pmatrix} D_u \tilde{u}_k(t) \\ D_v \tilde{v}_k(t) \end{pmatrix} + \mathbf{R}' \begin{pmatrix} \tilde{u}_k(t) \\ \tilde{v}_k(t) \end{pmatrix}.$$

Turing's idea can only be realized in four equivalence classes of systems characterized by the signs of the Jacobian \mathbf{R}' of the reaction function. In particular, if a finite wave vector \mathbf{k} is supposed to be the most unstable one, the Jacobian must have the signs

$$\begin{pmatrix} + & - \\ + & - \end{pmatrix}, \quad \begin{pmatrix} + & + \\ - & - \end{pmatrix}, \quad \begin{pmatrix} - & + \\ - & + \end{pmatrix}, \quad \begin{pmatrix} - & - \\ + & + \end{pmatrix}.$$

This class of systems is named *activator-inhibitor system* after its first representative: close to the ground state, one component stimulates the production of both components while the other one inhibits their growth. Its most prominent representative is the FitzHugh–Nagumo equation

$$\begin{aligned} \partial_t u &= d_u^2 \nabla^2 u + f(u) - \sigma v, \\ \tau \partial_t v &= d_v^2 \nabla^2 v + u - v \end{aligned}$$

with $f(u) = \lambda u - u^3 - \kappa$ which describes how an action potential travels through a nerve.^{[10][11]} Here, d_u , d_v , τ , σ and λ are positive constants.

When an activator-inhibitor system undergoes a change of parameters, one may pass from conditions under which a homogeneous ground state is stable to conditions under which it is linearly unstable. The corresponding bifurcation may be either a Hopf bifurcation to a globally oscillating homogeneous state with a dominant wave number $k = 0$ or a Turing bifurcation to a globally patterned state with a dominant finite wave number. The latter in two spatial dimensions typically leads to stripe or hexagonal patterns.

REVIEW

Reaction-Diffusion Model as a Framework for Understanding Biological Pattern Formation

Shigeru Kondo^{1*} and Takashi Miura²

The Turing, or reaction-diffusion (RD), model is one of the best-known theoretical models used to explain self-regulated pattern formation in the developing animal embryo. Although its real-world relevance was long debated, a number of compelling examples have gradually alleviated much of the skepticism surrounding the model. The RD model can generate a wide variety of spatial patterns, and mathematical studies have revealed the kinds of interactions required for each, giving this model the potential for application as an experimental working hypothesis in a wide variety of morphological phenomena. In this review, we describe the essence of this theory for experimental biologists unfamiliar with the model, using examples from experimental studies in which the RD model is effectively incorporated.

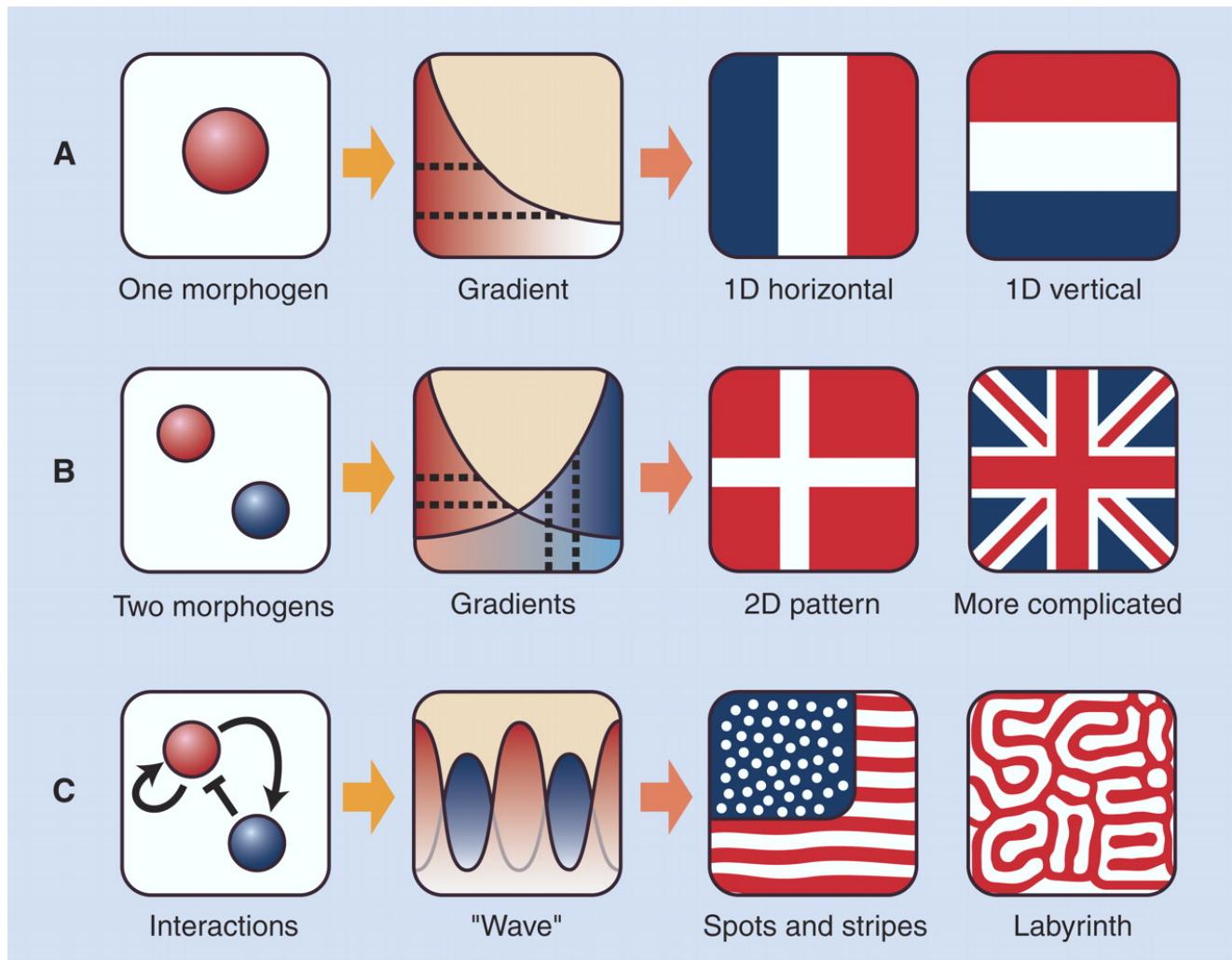
Over the past three decades, studies at the molecular level have revealed that a wide range of physiological phenomena are regulated by complex networks of cellular or molecular interactions (*1*). The complexity of such networks gives rise to new problems, however, as the behavior of such systems often defies immediate or intuitive understanding. Mathematical approaches can help facilitate the understanding

work, local sources of morphogens are needed to form the gradient. In such cases, the positional information made by the system is dependent on the prepattern (Fig. 1, A and B). By introducing the reaction, the system gains the ability to generate various patterns independent of the prepattern (Fig. 1C). Unfortunately, Turing died soon after publishing this seminal paper, but simula-

tion studies of the model have shown that this system can replicate most biological spatial patterns (*4–6*). Later, a number of mathematical models (*4*) were proposed, but most followed Turing's basic idea that "the mutual interaction of elements results in spontaneous pattern formation." The RD model is now recognized as a standard among mathematical theories that deal with biological pattern formation.

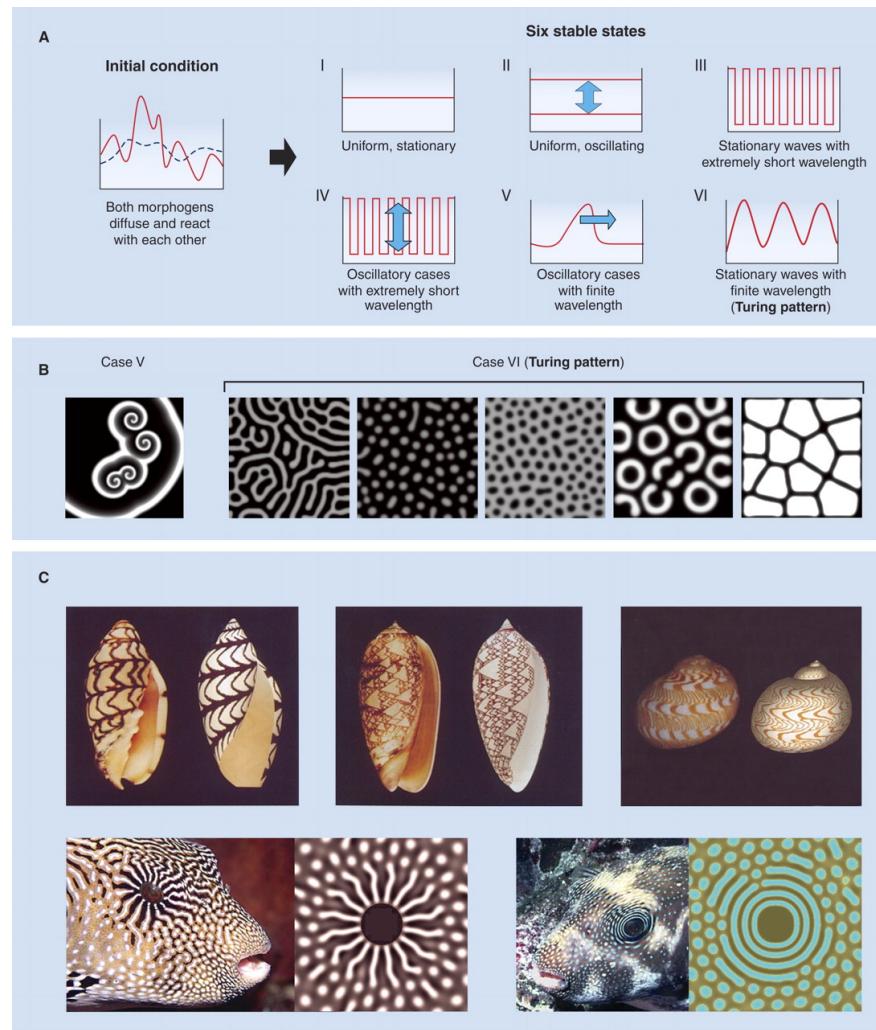
However, this model has yet to gain wide acceptance among experimental biologists. One reason is the gap between the mathematical simplicity of the model and the complexity of the real world. The hypothetical molecules in the original RD model have been so idealized for the purposes of mathematical analysis that it seems nearly impossible to adapt the model directly to the complexity of real biological systems. However, this is a misunderstanding to which experimental researchers tend to succumb. The logic of pattern formation can be understood with simple models, and by adapting this logic to complex biological phenomena, it becomes easier to extract the essence of the underlying mechanisms. Genomic data and new analytic technologies have shifted the target of developmental research from the identification of molecules to understanding the behavior of complex networks, making the RD model even more important as a tool for theoretical analysis.

Fig. 1 Schematic drawing showing the difference between the morphogen gradient model and Turing model.



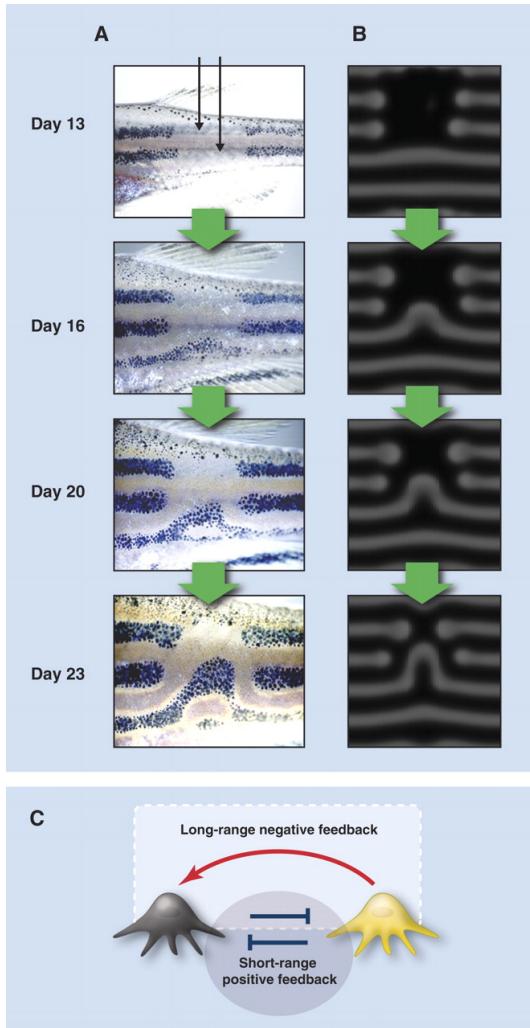
Shigeru Kondo, and Takashi Miura Science 2010;329:1616-1620

Fig. 2 Schematic drawing showing the mathematical analysis of the RD system and the patterns generated by the simulation.



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Fig. 3 Movement of zebrafish stripes and the interaction network among the pigment cells.

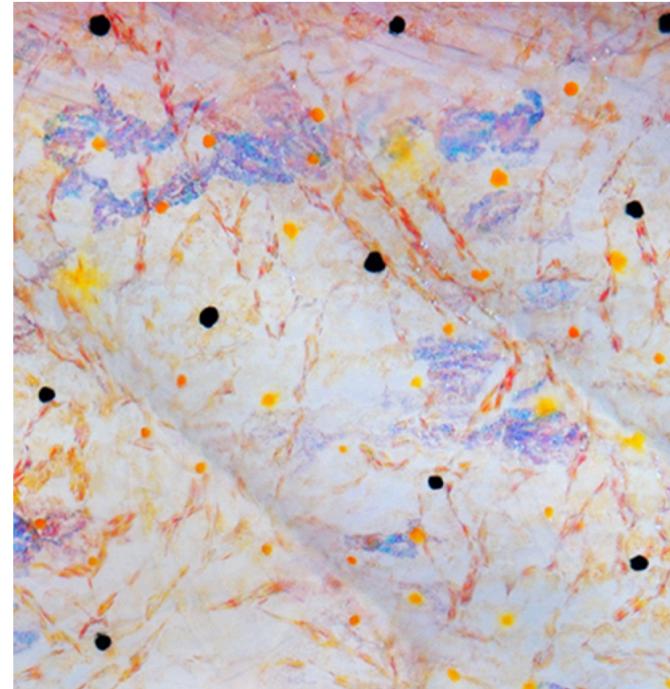


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PIGMENT PATTERN
STEM CELLS
ADULT FORM

genetics
development
evolution

zebrafish



Lab receives 5-year \$2.6 million R35 MIRA grant from NIH

New facilities at University of Virginia

Macrophages relay signals between pigment cells needed for stripe development, in *Science*

Adult pigment cell lineages differentially depend on thyroid hormone, in *Science*

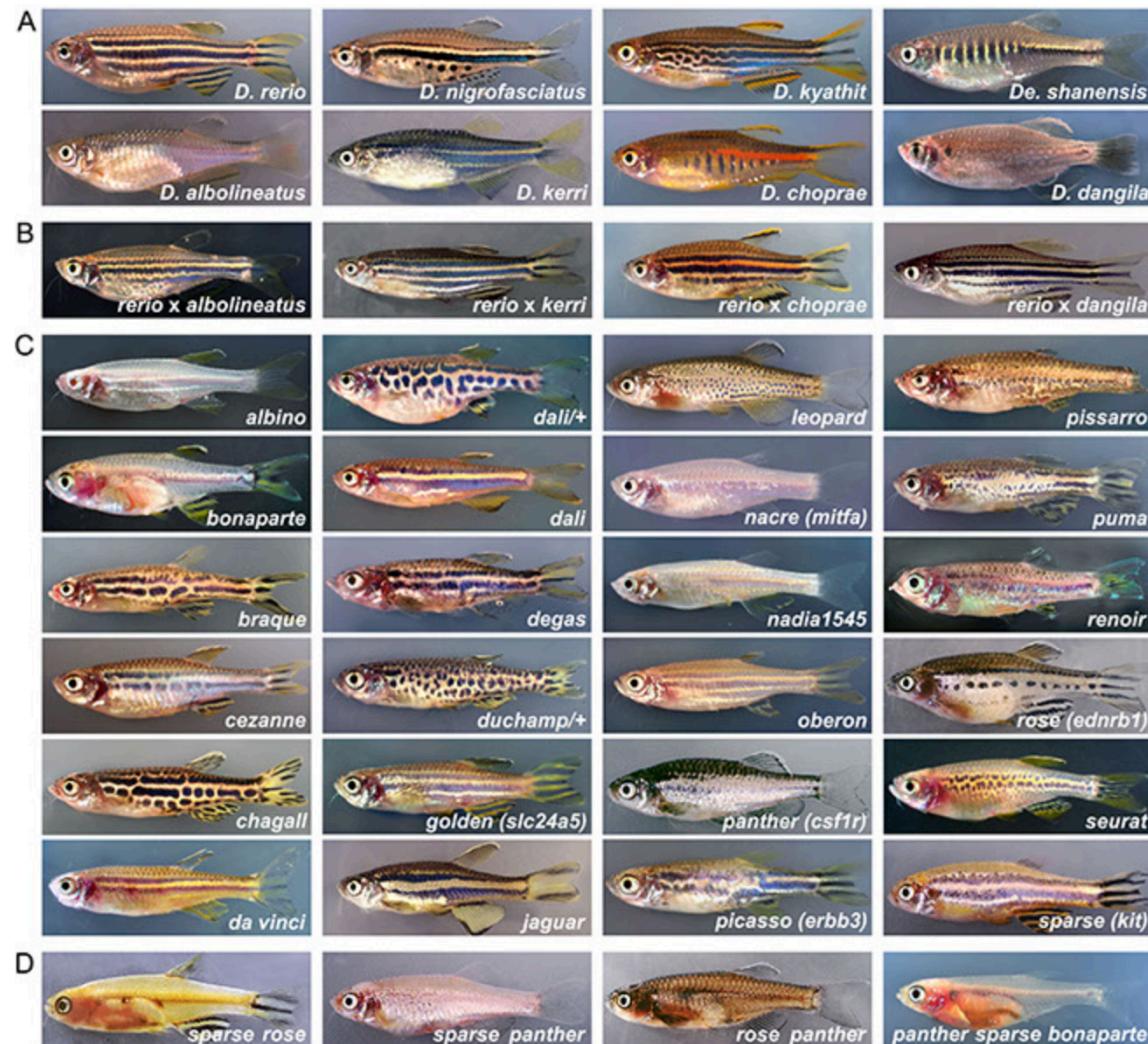
Pigment pattern

Overview

Pigmentation is one of the most striking vertebrate traits and is a classic and enduring system for studying cellular mechanisms of pattern formation, differentiation and morphogenesis. We use the diversity of pigment patterns among zebrafish mutants and closely related species to dissect how these patterns form and how the underlying genes and cell behaviors evolve.

Our studies have identified essential roles for interactions among pigment cell classes and between pigment cells and their environment. Mutational analyses of zebrafish, *Danio rerio*, have allowed us to identify genes required for these interactions, whereas genetic and other approaches have identified pathways that contribute to interspecific pattern differences.

Current efforts aim to identify new genes and cell behaviors responsible for stripe orientation and boundary formation in zebrafish, and to uncover changes in gene regulatory networks between species. Approaches include genomics, genetics and transgenesis, and time-lapse imaging using zebrafish and other danios.

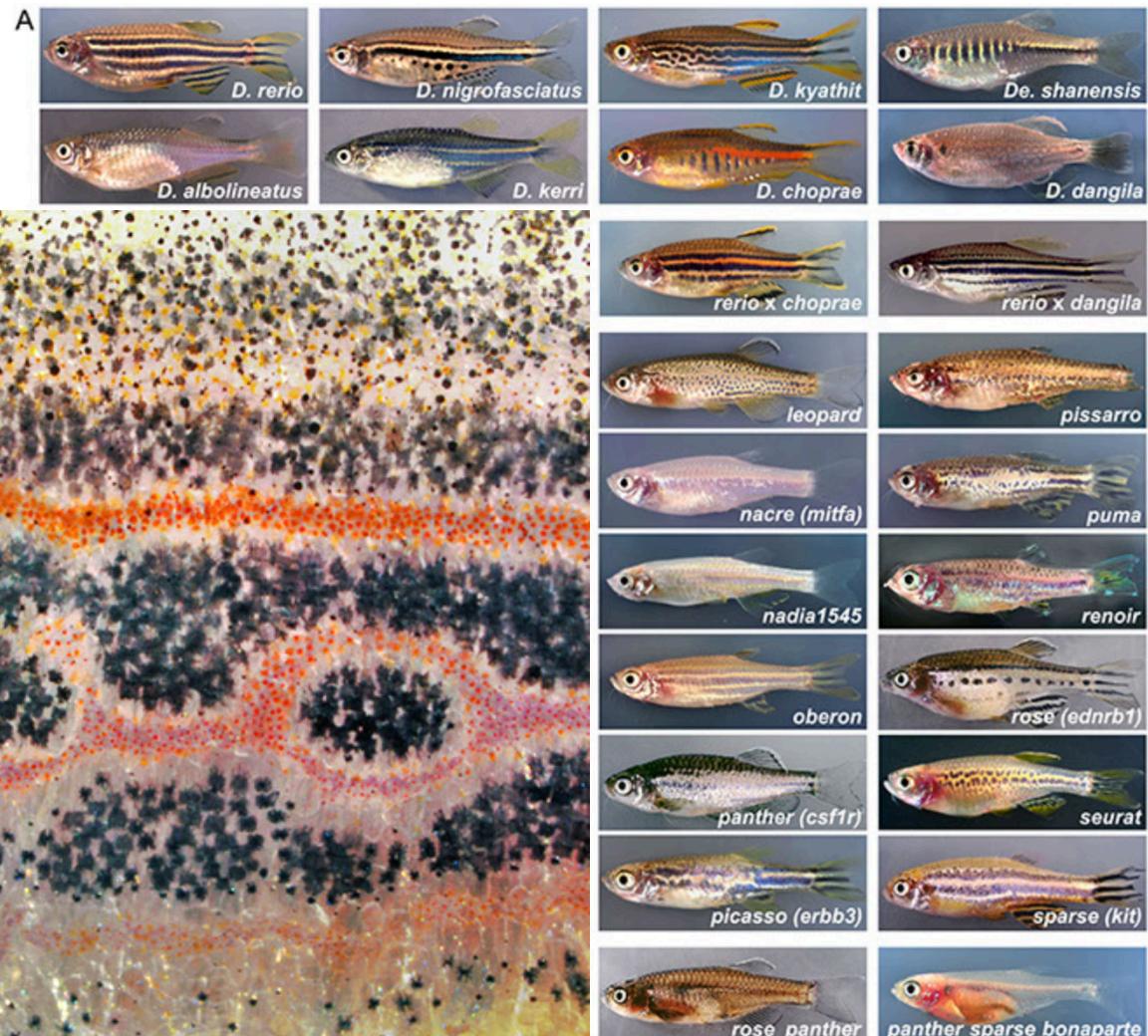
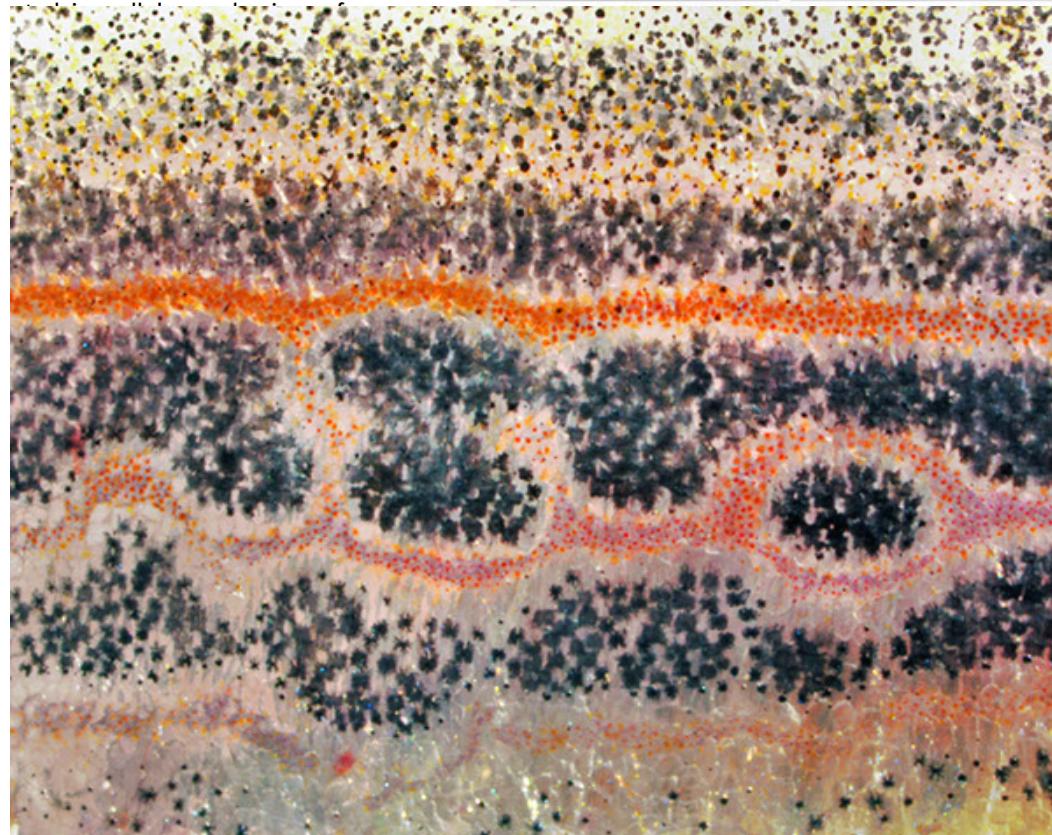


Diverse pattern phenotypes of *Danio* species (A), hybrids (B) and zebrafish mutants (C,D).

Pigment pattern

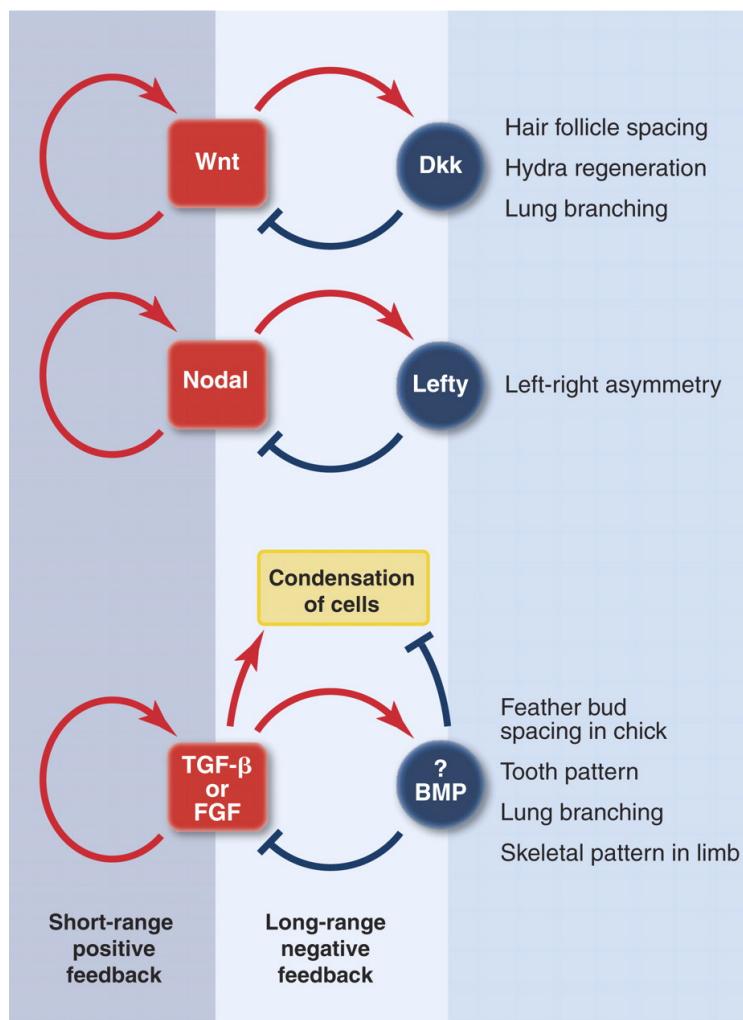
Overview

Pigmentation is one of the most striking vertebrate traits and is a classic and enduring system for



Diverse pattern phenotypes of *Danio* species (A), hybrids (B) and zebrafish mutants (C,D).

Fig. 4 Possible networks of protein ligands may give rise to Turing patterns in the embryo.



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impossible. It is likely that all traits influenced and provided the context for the evolution of others (31).

REFERENCES AND NOTES

- J. Gauthier, L. F. Gall, Eds., *New Perspectives on the Origin and Early Evolution of Birds* (Peabody Museum of Natural History, New Haven, CT, 2001).
- G. Dyke, G. Kaiser, Eds., *Living Dinosaurs: the Evolutionary History of Modern Birds* (Wiley, Chichester, UK, 2011).
- J. Gauthier, *Mém. Calif. Acad. Sci.* **8**, 1–55 (1986).
- P. C. Sereno, *Annu. Rev. Earth Planet. Sci.* **25**, 435–489 (1997).
- K. Padian, A. J. de Ricqlès, J. R. Horner, *Nature* **412**, 405–408 (2001).
- T. A. Dececchi, H. C. E. Larsson, *Evolution* **67**, 2741–2752 (2013).
- F. E. Novas, M. D. Ezcurra, F. L. Agnolín, D. Pol, R. Ortiz, *Rev. Mus. Argentino de Cienc. Nat. n.s.* **14**, 57–81 (2012).
- A. H. Turner, D. Pol, J. A. Clarke, G. M. Erickson, M. A. Norell, *Science* **317**, 1378–1381 (2007).
- M. T. Carrano, in *Amniote Paleobiology*, M. T. Carrano, T. J. Gaudin, R. W. Blob, J. R. Wible, Eds. (Univ. of Chicago Press, Chicago, 2006), chap. 8.
- D. W. E. Hone, T. M. Keesey, D. Pisani, A. Purvis, *J. Evol. Biol.* **18**, 587–595 (2005).
- R. B. Sookias, R. J. Butler, R. B. J. Benson, *Proc. Biol. Sci.* **279**, 2180–2187 (2012).
- B.-A. S. Bhullar *et al.*, *Nature* **487**, 223–226 (2012).
- A. M. Heers, K. P. Dial, *Trends Ecol. Evol.* **27**, 296–305 (2012).
- V. Allen, K. T. Bates, Z. Li, J. R. Hutchinson, *Nature* **497**, 104–107 (2013).
- M. N. Puttick, G. H. Thomas, M. J. Benton, *Evolution* **68**, 1497–1510 (2014).
- R. B. J. Benson *et al.*, *PLOS Biol.* **12**, e1001853 (2014).
- D. K. Zelenitsky *et al.*, *Science* **338**, 510–514 (2012).
- X. Zheng *et al.*, *Science* **339**, 1309–1312 (2013).
- R. B. J. Benson, J. N. Choiniere, *Proc. Biol. Sci.* **280**, 20131780 (2013).
- Materials and methods are available as supplementary materials on *Science* Online. Data files are archived on Dryad Digital Repository (doi:10.5061/dryad.jm6pj).
- P. Godfrat *et al.*, *Nature* **498**, 359–362 (2013).
- X. Xu *et al.*, *Nature* **484**, 92–95 (2012).
- J. N. Choiniere *et al.*, *Science* **327**, 571–574 (2010).
- P. Christiansen, R. A. Farina, *Hist. Biol.* **16**, 85 (2004).
- A. J. Drummond, M. A. Suchard, D. Xie, A. Rambaut, *Mol. Biol. Evol.* **29**, 1969–1973 (2012).
- A. J. Drummond, S. Y. W. Ho, M. J. Phillips, A. Rambaut, *PLOS Biol.* **4**, e88 (2006).
- M. Pagel, A. Meade, *BayesTraits: Software and Documentation* (2013); www.evolution.reading.ac.uk/BayesTraitsV2Beta.html.
- L. E. Zanno, P. J. Makovicky, *Proc. Biol. Sci.* **280**, 20122526 (2013).
- J. Hanken, D. B. Wake, *Annu. Rev. Ecol. Syst.* **24**, 501–519 (1993).
- O. W. M. Rauhut, C. Foth, H. Tischlinger, M. A. Norell, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 11746–11751 (2012).
- T. S. Kemp, *Proc. Biol. Sci.* **274**, 1667–1673 (2007).

MODELING DIGITS

Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients

J. Raspopovic,^{1*} L. Marcon,^{1*} L. Russo,¹ J. Sharpe^{1,2†}

During limb development, digits emerge from the undifferentiated mesenchymal tissue that constitutes the limb bud. It has been proposed that this process is controlled by a self-organizing Turing mechanism, whereby diffusible molecules interact to produce a periodic pattern of digital and interdigital fates. However, the identities of the molecules remain unknown. By combining experiments and modeling, we reveal evidence that a Turing network implemented by Bmp, Sox9, and Wnt drives digit specification. We develop a realistic two-dimensional simulation of digit patterning and show that this network, when modulated by morphogen gradients, recapitulates the expression patterns of Sox9 in the wild type and in perturbation experiments. Our systems biology approach reveals how a combination of growth, morphogen gradients, and a self-organizing Turing network can achieve robust and reproducible pattern formation.

Digits form in a periodic pattern that alternates digital and interdigital fates along the anterior-posterior (AP) axis of the limb bud. Traditionally, this pattern has been explained by a positional information model (1) based on an AP gradient of Sonic hedgehog (Shh) (2, 3). However, embryonic and genetic manipulations (4, 5) have shown that digit patterning is independent of Shh and may be instead controlled by a self-organizing mechanism. Over three decades ago, it was proposed that such a mechanism could be a Turing system (6, 7), in which a diffusible activator and inhibitor (8) interact and self-organize to form the periodic digit pattern. Recent work has strengthened this hypothesis (9); however, two important questions remain to be addressed.

First, although a number of mathematical Turing models have been proposed to explain the periodic digit pattern (10, 11), no computer simulation has been able to correctly reproduce the expression patterns of digit markers over time and space. Second, the diffusible molecules that implement the Turing network have not yet been identified. Transforming growth factor-β (TGF-β) molecules were proposed as activators in a Turing

To identify the molecules that control digit specification, it is crucial to distinguish the genes involved in early digit patterning from downstream differentiation factors. We therefore analyzed the expression of the earliest known skeletal marker *Sox9* (16) and identified embryonic day 11.5 (E11.5) as the earliest stage that shows a periodic digital pattern (Fig. 1A). We also performed micromass cultures with E11.5 Sox9-EGFP (enhanced green fluorescent protein) limb autopods (17) and found that cells create a periodic Sox9 pattern by 15 hours, faster than previously reported (18), with dynamics reminiscent of a two-dimensional (2D) Turing simulation (Fig. 1B and movie S1). We observed that the periodic pattern formed even when the culture was initiated with *Sox9*⁻ or *Sox9*⁺ cells sorted by fluorescence-activated cell sorting (FACS) (Fig. 1, B and C, and movies S2 and S3), confirming that *Sox9* is dynamically regulated by a self-organizing patterning mechanism.

When *Sox9* is knocked out, all the genes that reflect a digital or interdigital pattern (e.g., *Bmp2*, *Chordin*, *Noggin*) lose their normal periodic expression (19), suggesting that *Sox9* itself is part of the Turing network rather than a downstream

impossible. It is likely that all traits influenced and provided the context for the evolution of others (31).

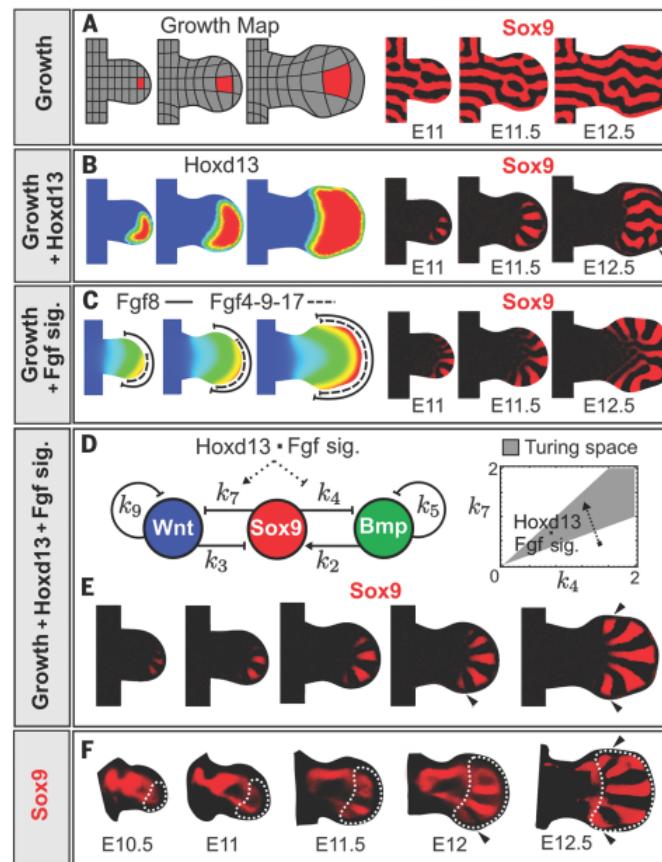
REFERENCES AND NOTES

- J. Gauthier, L. F. Gall, Eds., *New Perspectives on the Origin and Early Evolution of Birds* (Peabody Museum of Natural History, New Haven, CT, 2001).
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- J. Gauthier, *Mém. Calif. Acad. Sci.* **8**, 1–55 (1986).
- P. C. Sereno, *Annu. Rev. Earth Planet. Sci.* **25**, 435–489

MODELING DIGITS

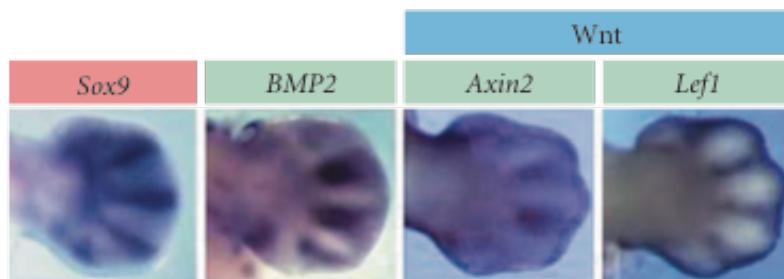
Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients

Fig. 3. Realistic computer simulation of digit patterning. (A) When the BSW model was simulated inside an experimental limb growth map (left), Sox9 (red) formed a pattern with randomly oriented stripes biased along the PD axis (right). (B) Experimental *Hoxd13* expression was mapped into the growing model (left, heat-color map: blue = 0 and red = 1). With the *Hoxd13* modulation, the model creates a digit-like pattern (right), which eventually shows digit bifurcation (arrowhead). (C) *Fgf* expression in the AER was mapped into the model (solid line for *Fgf8*, dashed line for *Fgf4-9-17*) and used to simulate an *Fgf* signaling gradient (left, heat-color map: blue = 0 and red = 1). With the *Fgf* modulation, the model predicted a radially oriented Sox9 pattern with bigger wavelength toward the distal tip (right). (D) When *Fgf* and *Hoxd13* jointly modulate the parameters k_4 and k_7 , the system shifts (dashed arrow) into the Turing space (gray region). (E) The simulated Sox9 pattern recapitulates the main features of (F) the experimental Sox9 expression in the digits, outlined by the white dotted lines. Arrowheads mark the late appearance of digits 5 and 1.



A BMP-Sox9-Wnt Turing- type mechanism governs digit formation

(A) Expression patterns

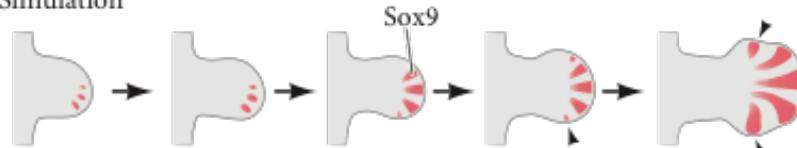


(B) Turing model

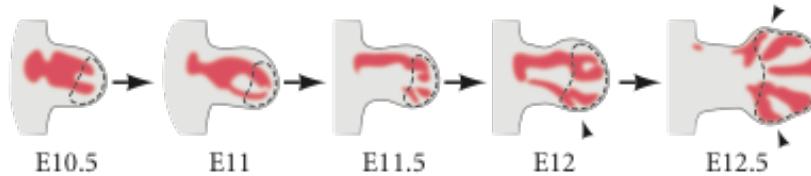


(C)

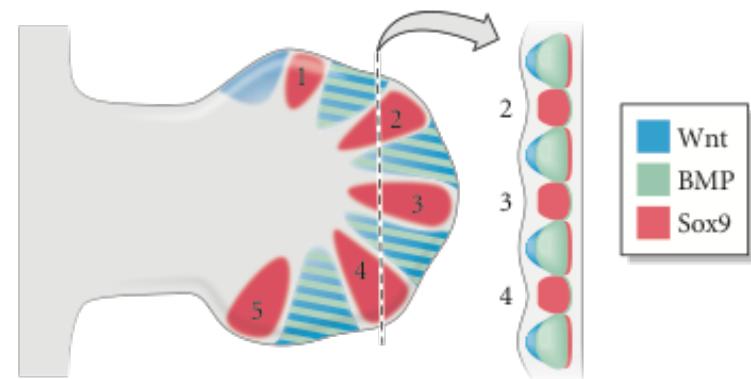
Simulation



Known *Sox9* expression



(D) Late periodic digit pattern



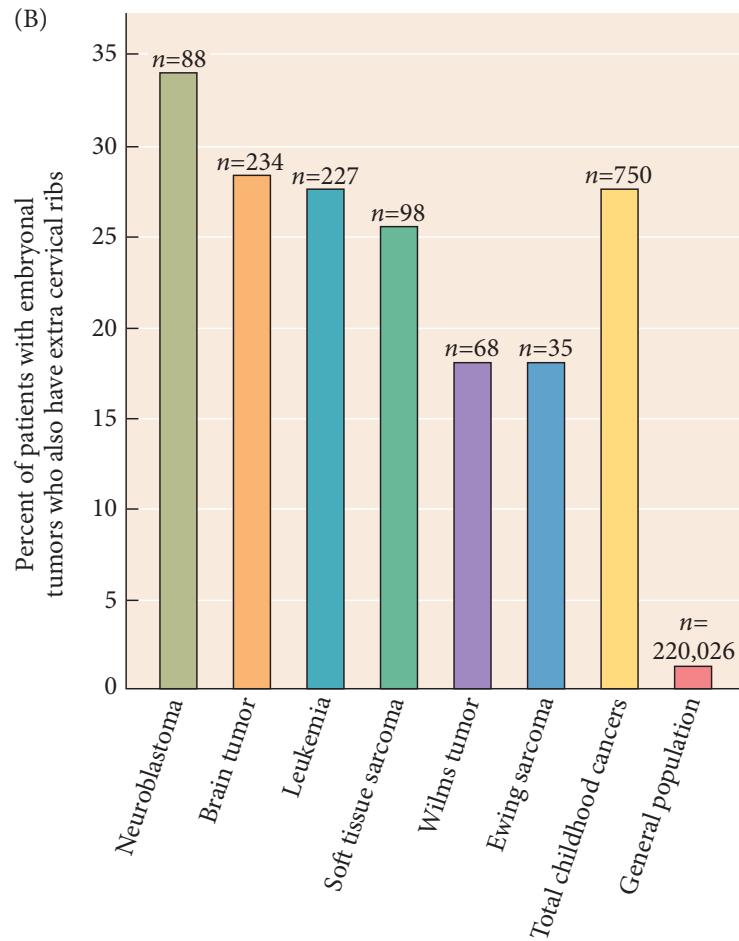
Pleiotropic constraints

- Pleiotropy, the ability of a gene to play different roles in different cells, is the “opposite” of modularity, involving the connections between parts rather than their independence.
- Galis speculates that mammals have only seven cervical vertebrae (whereas birds may have dozens) because the Hox genes that specify these vertebrae have become linked to stem cell proliferation in mammals.
- The intraembryonic selection against having more or fewer than seven cervical ribs appears to be remarkably strong. At least 78% of human embryos with an extra anterior rib (i.e., six cervical vertebrae) die before birth, and 83% die by the end of the first year. These deaths appear to be caused by multiple congenital anomalies or cancers.

Extra cervical ribs are associated with childhood cancers



Extra cervical ribs are associated with childhood cancers. (A) Radiogram showing an extra cervical rib. (B) Patients with extra cervical ribs die before birth. They often develop cancers very early in life. This indicates against changes in the number of mammary glands. (After Galis et al. 2006, courtesy of F. Galis.)



Self-organization

Central dogma of molecular biology

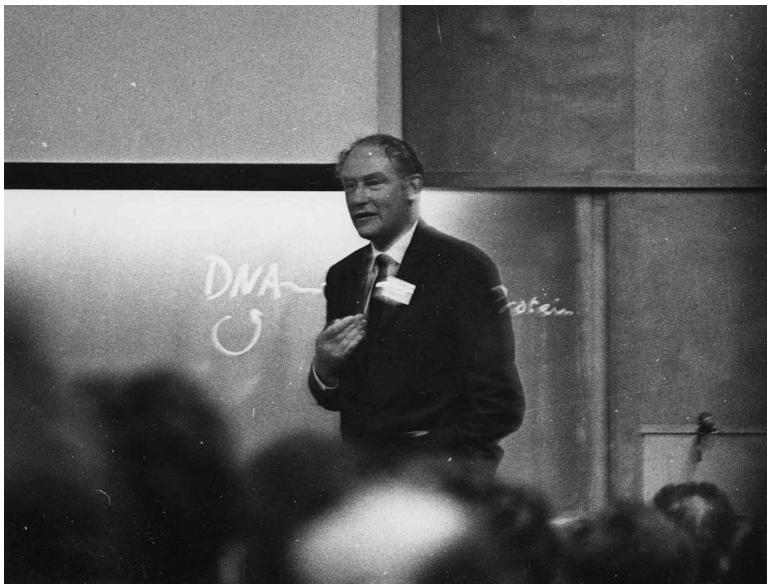


Fig 2. Crick speaking at the 1963 Cold Spring Harbor Symposium. Note the drawing of the central dogma on the blackboard. Credit: Cold Spring Harbor Laboratory.

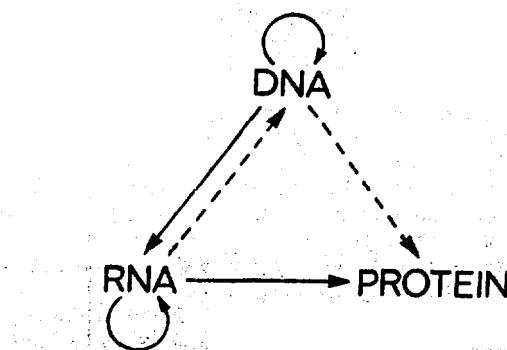
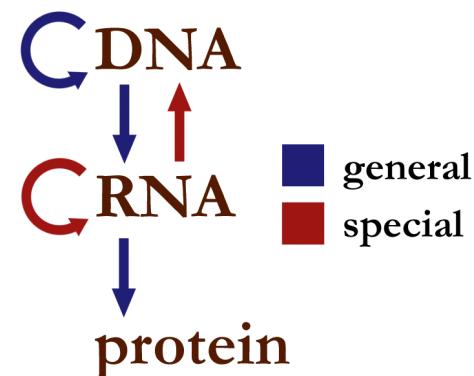


Fig. 2. The arrows show the situation as it seemed in 1958. Solid arrows represent probable transfers, dotted arrows possible transfers. The absent arrows (compare Fig. 1) represent the impossible transfers postulated by the central dogma. They are the three possible arrows starting from protein.



ESSAY

60 years ago, Francis Crick changed the logic of biology

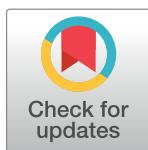
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Abstract

In September 1957, Francis Crick gave a lecture in which he outlined key ideas about gene function, in particular what he called the central dogma. These ideas still frame how we understand life. This essay explores the concepts he developed in this influential lecture, including his prediction that we would study evolution by comparing sequences.



OPEN ACCESS

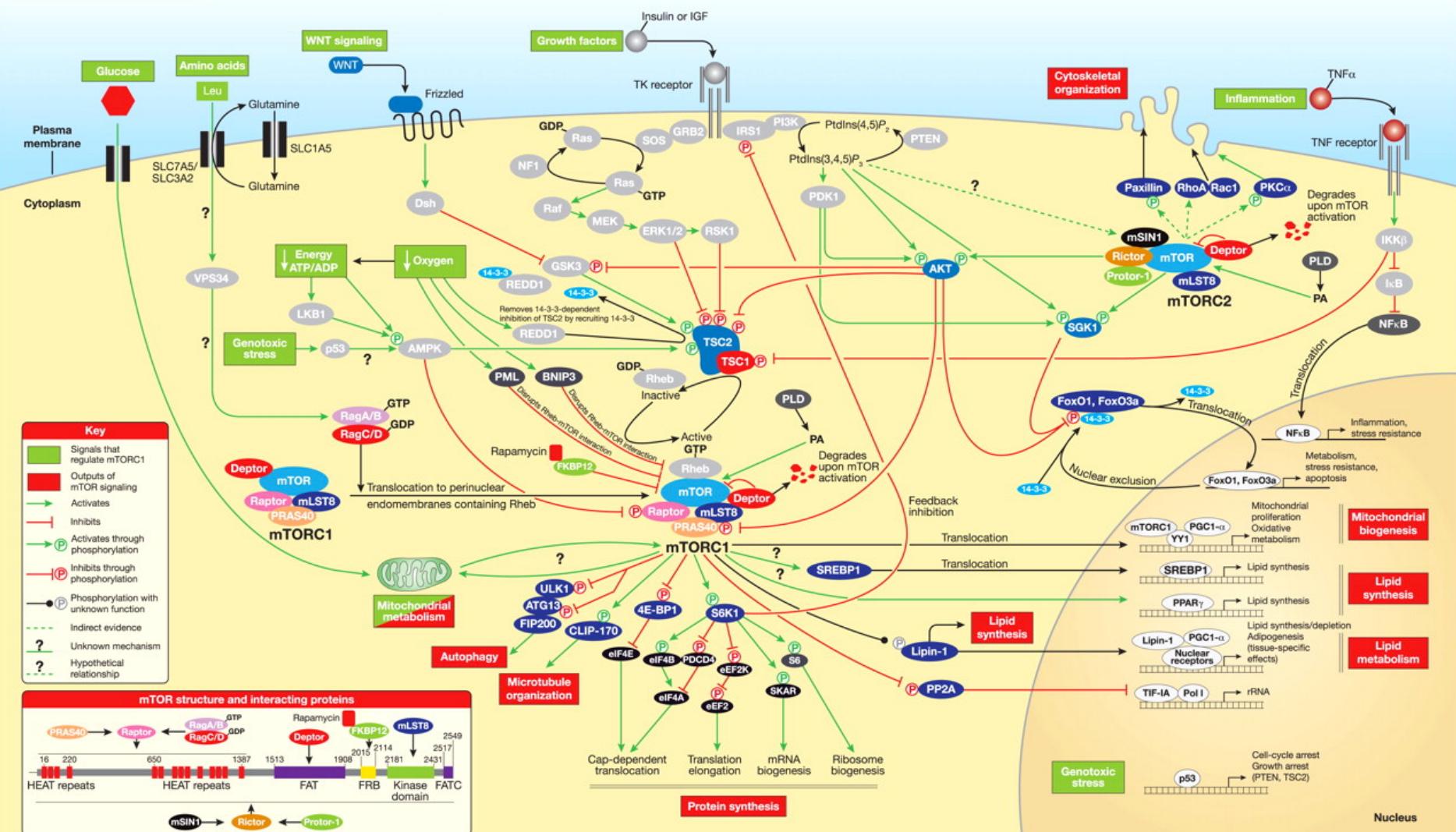
Citation: Cobb M (2017) 60 years ago, Francis Crick changed the logic of biology. PLoS Biol 15(9): e2003243. <https://doi.org/10.1371/journal.pbio.2003243>

Introduction

This month marks the 60th anniversary of one of the most significant lectures in the history of biology. It was given on 19 September 1957 by Francis Crick as part of a Society for Experimental Biology symposium on the Biological Replication of Macromolecules, held at University College London. Originally entitled ‘Protein synthesis,’ the title acquired a magisterial introductory ‘On’ during writing up for publication the following year [1]. The lecture went far further than its title suggested: as Crick pointed out in the opening paragraph, he also addressed ‘the other central problems of molecular biology—those of gene action and nucleic acid synthesis.’

mTOR Signaling at a Glance

Mathieu Laplante and David M. Sabatini



Abbreviations:

- 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ATG13, autophagy-related gene 13; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CLIP170, CAP-GLY domain containing linker protein 1; Deptor, DEP domain-containing mTOR-interacting protein; Dsh, Disheveled; eEF2, eukaryotic translation elongation factor 2; eEF2K, eEF2 kinase; elF, eukaryotic translation initiation factor; ERK1/2, extracellular-signal-regulated kinase 1/2; FAT, FRAP-ATM-TTRAP; FATC, FAT-carboxy-terminal; FIP200, focal adhesion kinase family-interacting protein of 200 kDa; FK506, binding protein of 12 kDa; FoxO1/3a, forkhead box O1/3a; FRB, FKBP12-rapamycin binding domain; GRIP, growth factor receptor-bound protein 2; GSK3, glycogen synthase kinase 3; HEAT, huntingtin-elongation factor 3 regulatory subunit A of p210 α -TOR1; IGF, insulin-like growth factor; TK, tyrosine kinase; IKK β , IKB kinase- β ; IRS1, insulin receptor substrate 1; IKB, inhibitor of NF κ B; LKB1, serine-threonine kinase 11; MEK, mitogen-activated protein kinase kinase; mLST8, mammalian lethal with Sec13 protein 8; mSIN1, mammalian stress-activated protein kinase interacting protein; mTORC, mammalian target of rapamycin complex; NF κ B, nuclear factor- κ B; PA, phosphatidic acid; PDCD4, programmed cell death 4; PDK1, phosphoinositide-dependent kinase 1; PGC1- α , PPAR γ coactivator 1- α ; PI3K, phosphoinositide 3-kinase; PKC α , protein kinase C α ; PLD, phospholipase D; PML, promyelocytic leukemia; Pol I, RNA polymerase I; PP2A, protein phosphatase 2A; PPAR γ , peroxisome proliferator-activated receptor; PRAS40, proline-rich AKT substrate 40 kDa; Protor-1, protein observed with Rictor 1; PtdIns(3,4,5)P₃, phosphatidylinositol (3,4,5)-triphosphate; PtdIns(4,5)P₂, phosphatidylinositol (4,5)-bisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; Ras, Ras-related GTP binding protein; Raptor, regulatory-associated protein of mTOR; REDD1, transcriptional regulation of DNA damage response 1; Rheb, Ras homolog enriched in brains; Rictor, rapamycin-insensitive companion of mTOR; RSK1, ribosomal S6 kinase; S6K1, p70 ribosomal S6 kinase 1; SGK1, serum- and glucocorticoid-induced protein kinase 1; SKAR, S6K1 allyl/REF-like target; SLC, solute carrier; SOS, son of sevenless; SREBP1, sterol regulatory element binding protein 1; TIF-IA, tripartite motif-containing protein 24; TNF α , tumor necrosis factor- α ; TSC, tuberous sclerosis complex; ULK1, unc-51-like kinase 1; VPS34, vacuolar protein-sorting-associated protein 34; YY1, yin-yang 1.

phosphatidic acid; PDCD4, programmed cell death 4; PDK1, phosphoinositide-dependent kinase 1; PGC1- α , PPAR γ coactivator 1- α ; PI3K, phosphoinositide 3-kinase; PKC α , protein kinase C α ; PLD, phospholipase D; PML, promyelocytic leukemia; Pol I, RNA polymerase I; PP2A, protein phosphatase 2A; PPAR γ , peroxisome proliferator-activated receptor; PRAS40, proline-rich AKT substrate 40 kDa; Protor-1, protein observed with Rictor 1; PtdIns(3,4,5)P₃, phosphatidylinositol (3,4,5)-triphosphate; PtdIns(4,5)P₂, phosphatidylinositol (4,5)-bisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; Ras, Ras-related GTP binding protein; Raptor, regulatory-associated protein of mTOR; REDD1, transcriptional regulation of DNA damage response 1; Rheb, Ras homolog enriched in brains; Rictor, rapamycin-insensitive companion of mTOR; RSK1, ribosomal S6 kinase; S6K1, p70 ribosomal S6 kinase 1; SGK1, serum- and glucocorticoid-induced protein kinase 1; SKAR, S6K1 allyl/REF-like target; SLC, solute carrier; SOS, son of sevenless; SREBP1, sterol regulatory element binding protein 1; TIF-IA, tripartite motif-containing protein 24; TNF α , tumor necrosis factor- α ; TSC, tuberous sclerosis complex; ULK1, unc-51-like kinase 1; VPS34, vacuolar protein-sorting-associated protein 34; YY1, yin-yang 1.

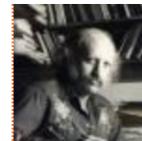
Eric H. Davidson

In Memoriam

Davidson, a developmental biologist, was a pioneer researcher and theorist of the gene regulatory networks that perform complex biological processes, such as the transformation of a single-celled egg into a complex organism. His work helped to reveal how the DNA sequences inherited in the genome are used to initiate and drive forward the sequence of steps that result in development.

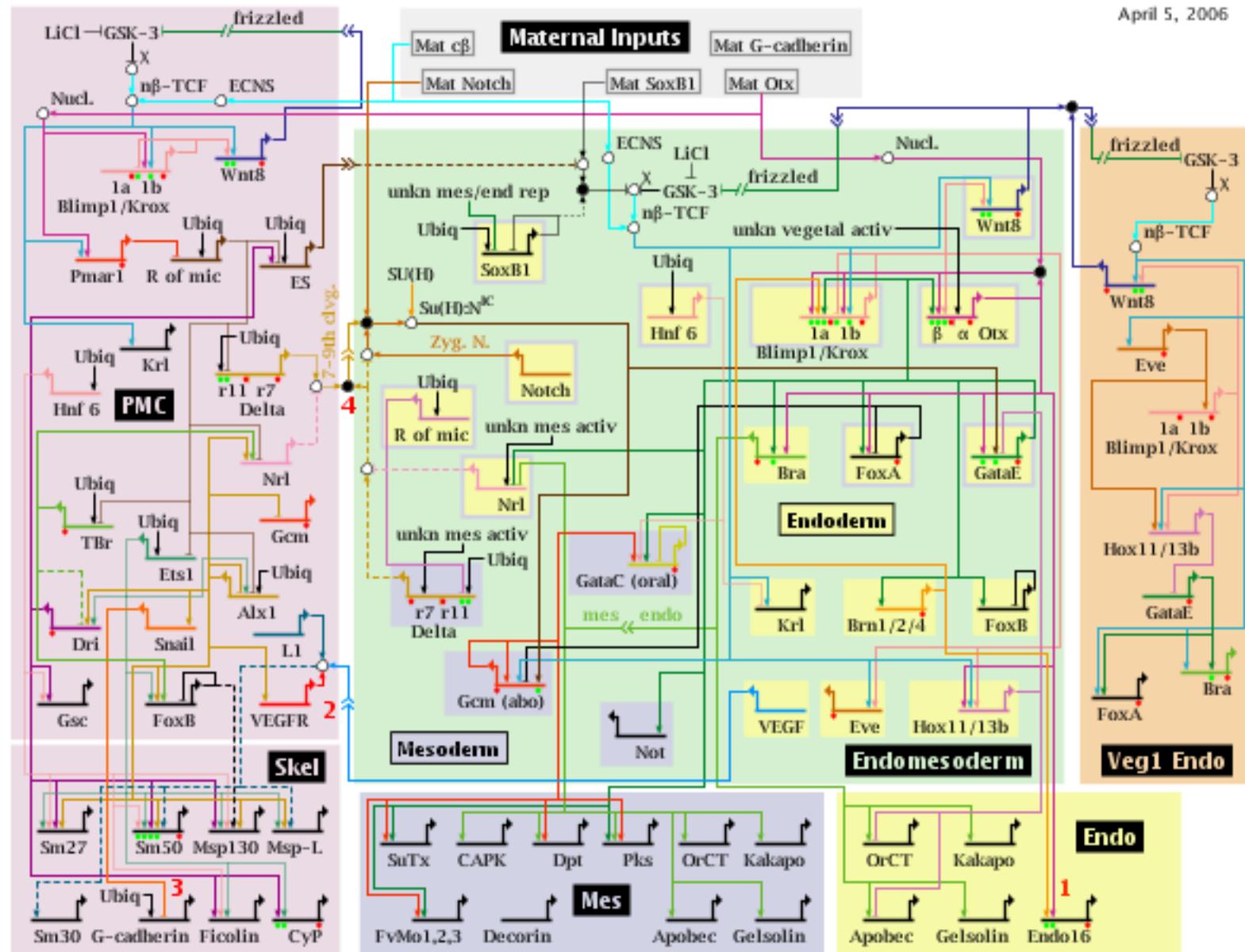
His research emphasized quantitative understanding of biological mechanisms and the logic functions encoded in genetic networks, and focused on the question of how the genomic DNA could encode not only protein sequences but also the complex "software" needed for differentiating cell types in the right places and proportions to make complex animals.

Davidson initially focused on quantitative methods for analyzing



Endomesoderm Specification to 30 Hours

April 5, 2006

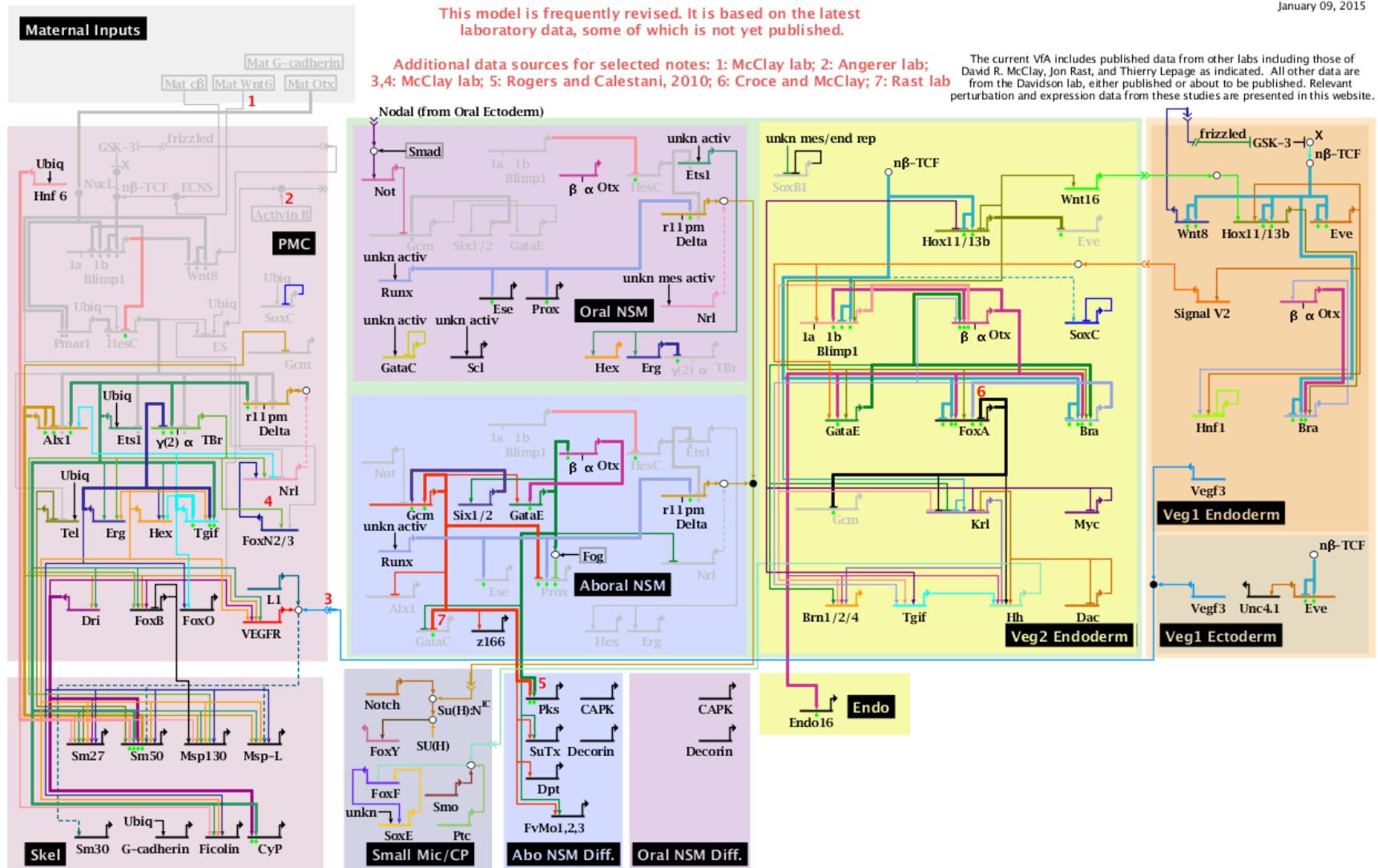


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
unkn = unknown; Nucl. = nuclearization; χ = β -catenin source;
n β -TCF = nuclearized b- β -catenin-Tcf1; ES = early signal;
ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

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Endomesoderm Specification 21 to 30 Hours

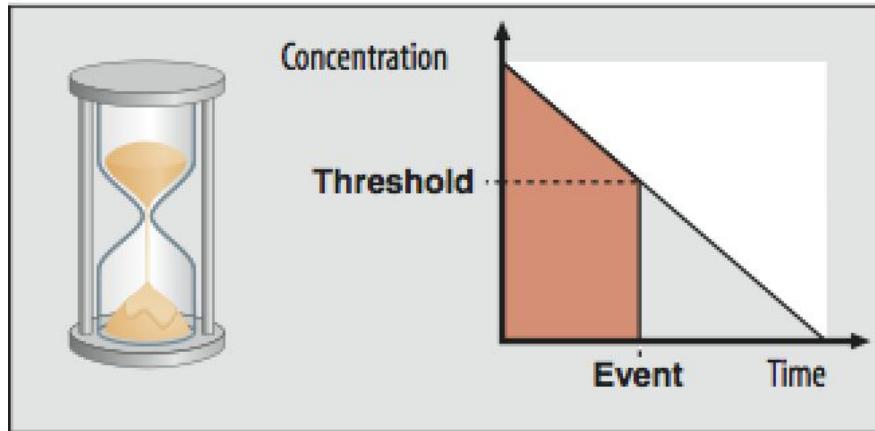
January 09, 2015



Ubiquit = ubiquitous; Mat = maternal; activ = activator; rep = repressor;
unkn = unknown; Nucl. = nuclearization; x = β-catenin source;
nβ-TCF = nuclearized b-β-catenin-Tcf1; ES = early signal;
ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

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A timing mechanism that could operate in MBT(Mid-blastula transition)/development



1. Suppression of cleavage but not DNA synthesis does not alter MBT.
2. Nor are cell-cell interactions. Dissociated blastomeres. Seems to be the ratio of DNA to cytoplasm. Chick and mouse.
3. Increase DNA artificially. More sperm. Inject DNA.
4. Some kind of suppressive factors. Like Morphogen.

Mid-blastula transition or Maternal-to-zygote transition

- The transition from the early rapid biphasic (only M and S phases) mitoses of the embryo (cleavage) to a stage characterized by (1) mitoses that include the “gap” stages (G1 and G2) of the cell cycle, (2) loss of synchronicity of cell division, and (3) transcription of new (zygotic) mRNAs needed for gastrulation and cell specification.
- The embryonic stage when maternally provided mRNAs are degraded and control of development is handed over to the zygote’s own genome; often occurs in the mid-blastula stage. Seen in many different animal groups.

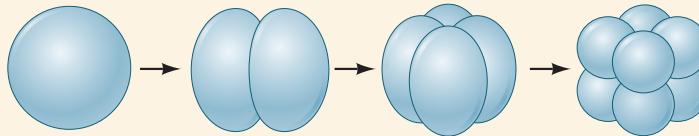
I. HOLOBLASTIC (COMPLETE) CLEAVAGE

A. Isolecithal

(Sparse, evenly distributed yolk)

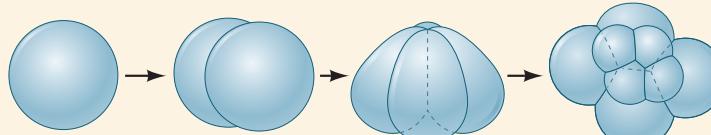
1. Radial cleavage

Echinoderms, amphioxus



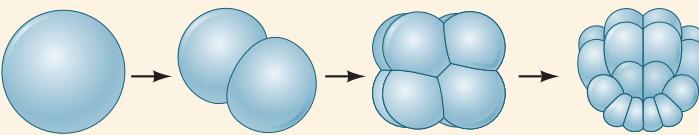
2. Spiral cleavage

Annelids, molluscs, flatworms



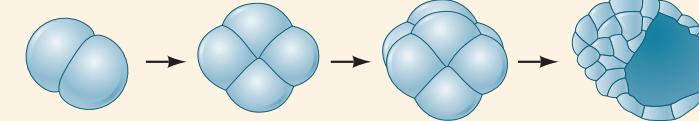
3. Bilateral cleavage

Tunicates



4. Rotational cleavage

Mammals, nematodes

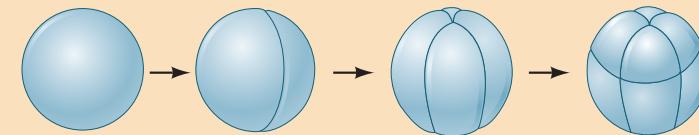


B. Mesolecithal

(Moderate vegetal yolk disposition)

Displaced radial cleavage

Amphibians



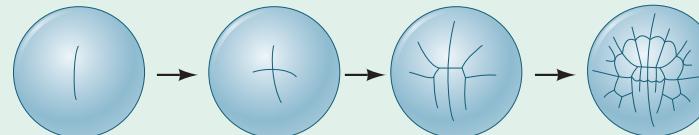
II. MEROBLASTIC (INCOMPLETE) CLEAVAGE

A. Telolecithal

(Dense yolk throughout most of cell)

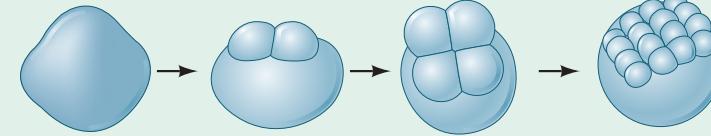
1. Bilateral cleavage

Cephalopod molluscs



2. Discoidal cleavage

Fish, reptiles, birds

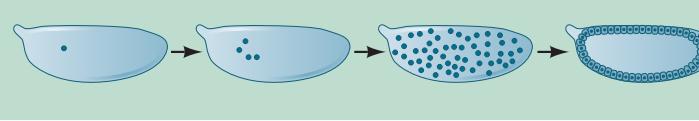


B. Centrolecithal

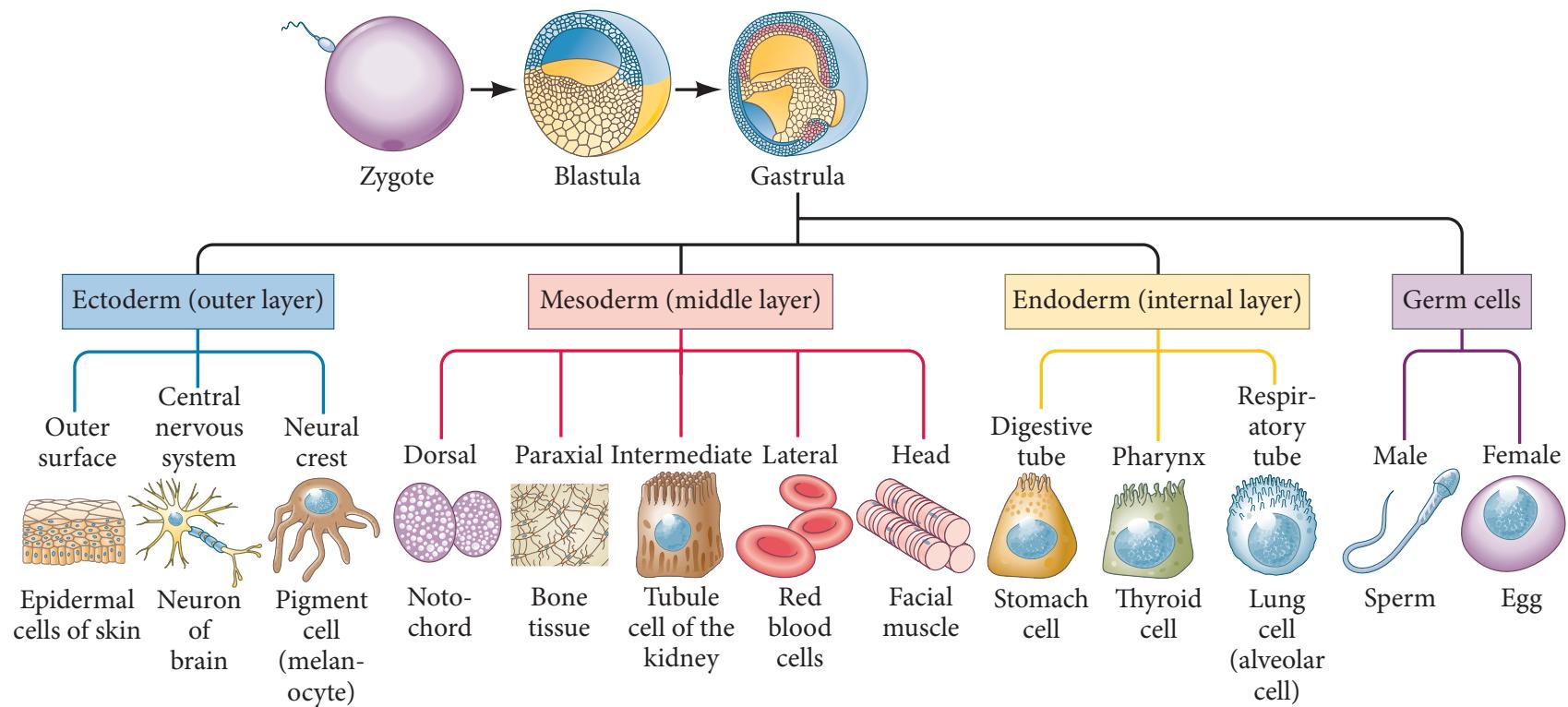
(Yolk in center of egg)

Superficial cleavage

Most insects

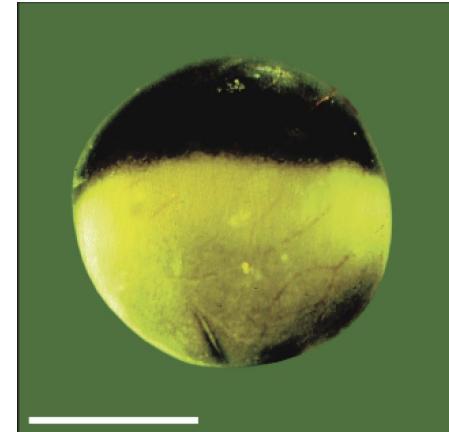


The dividing cells of the fertilized egg form three distinct embryonic germ layers. Each of the germ layers gives rise to myriad differentiated cell types

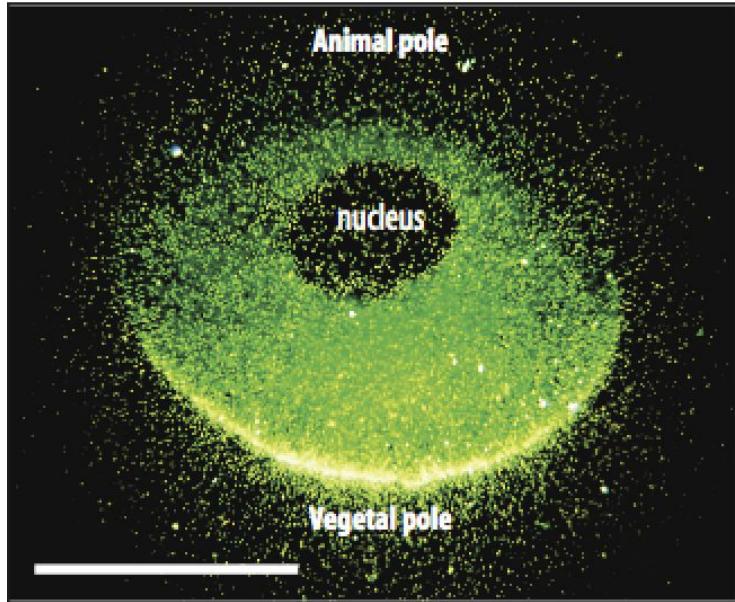


The animal-vegetal axis is maternally determined in *Xenopus* and zebrafish

- 1. The animal pole is uppermost.
- 2. The egg nucleus is located close to animal pole.
- 3. The *Xenopus* egg contains large amounts of maternal mRNAs and proteins. For example, there is sufficient histone protein for the assembly of more than 10,000 nuclei.
- 4. Most of the developmentally important products end up in the vegetal half.

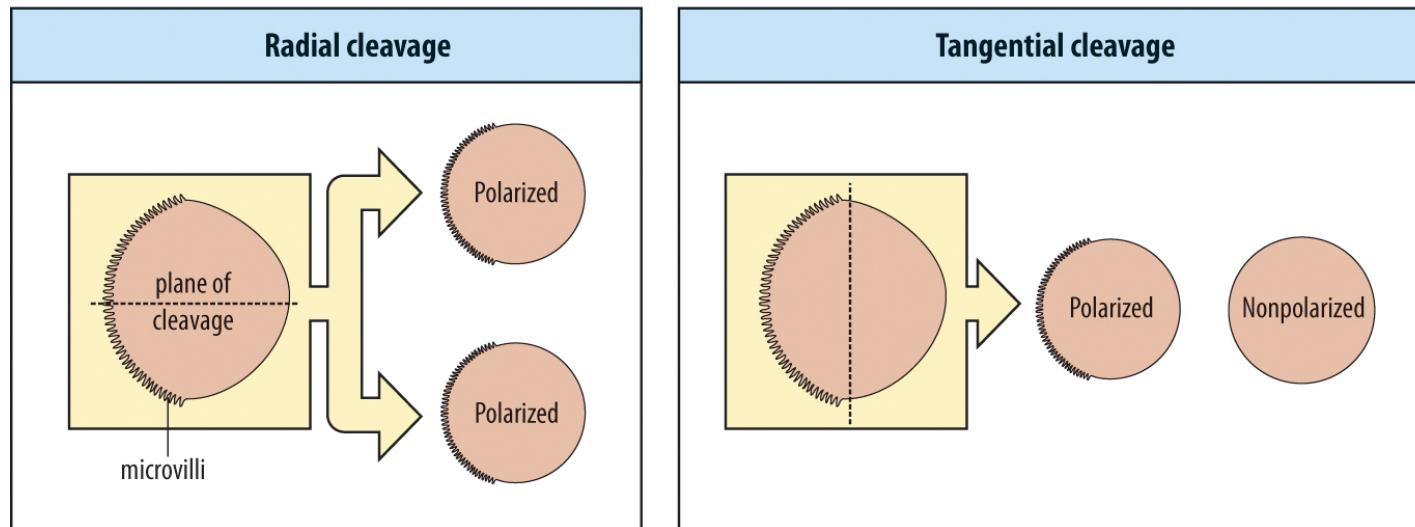
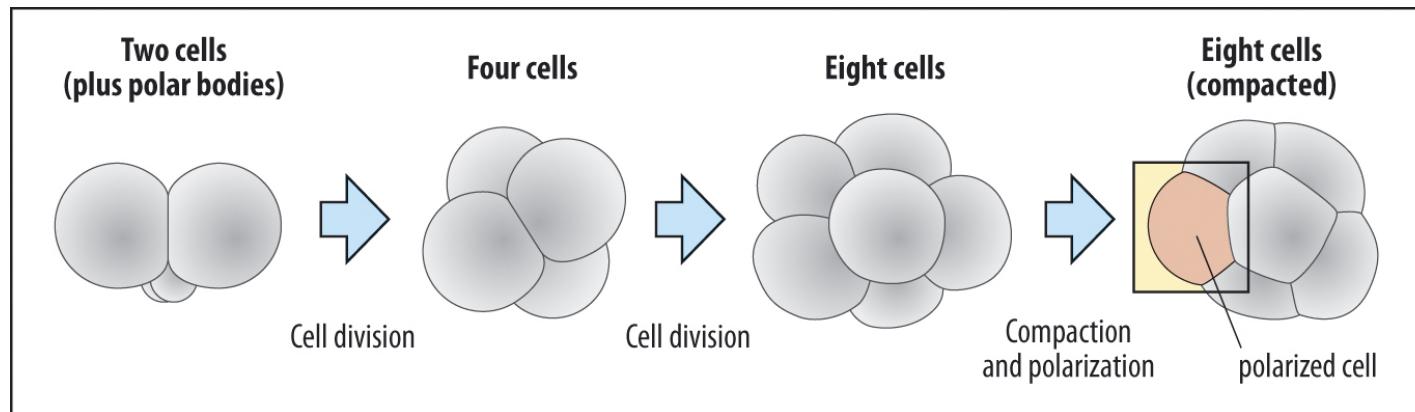


Usually the maternal mRNAs are only translated after fertilization



- *Vg-1* (left panel), mesoderm induction.
- *Xwnt-11*, dorso-ventral axis.
- *VegT*, endoderm and mesoderm specification.

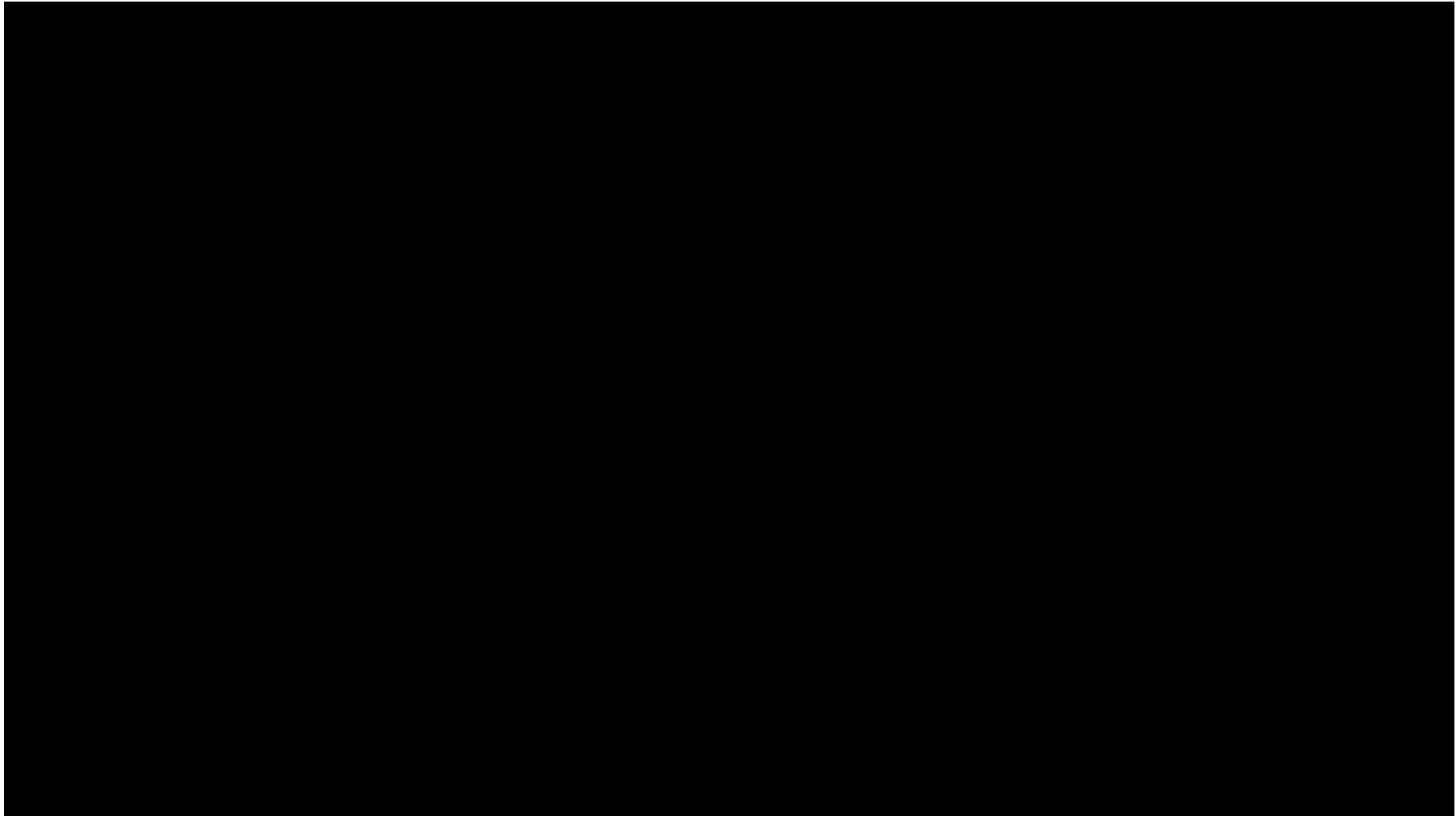
Polarization of cells during cleavage of the mouse embryo



Self-organization

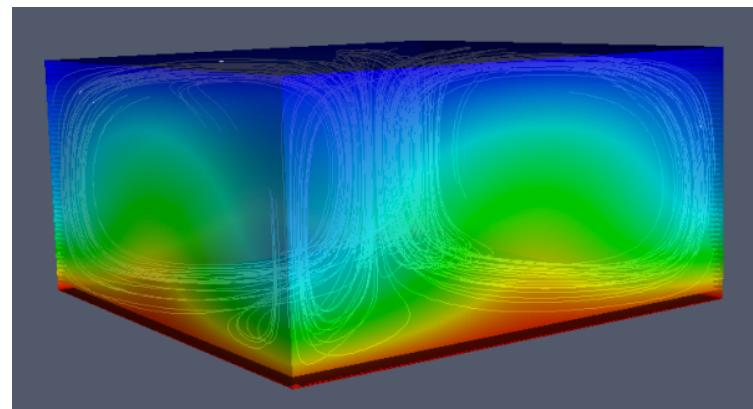
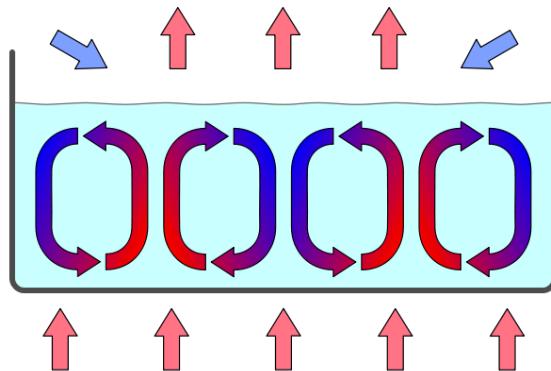
- **Self-organization**, also called spontaneous order (in the social sciences), is a process where some form of overall order arises from local interactions between parts of an initially disordered system. The process is spontaneous, not needing control by any external agent. **It is often triggered by random fluctuations**, amplified by positive feedback. The resulting organization is wholly decentralized, distributed over all the components of the system. As such, the organization is typically robust and able to survive or self-repair substantial perturbation. Chaos theory discusses self-organization in terms of islands of predictability in a sea of chaotic unpredictability.
- Self-organization occurs in many physical, chemical, biological, robotic, and cognitive systems.
- Self-organization in biology can be observed in spontaneous folding of proteins and other biomacromolecules, formation of lipid bilayer membranes, pattern formation and morphogenesis in developmental biology, the coordination of human movement, social behavior in insects (bees, ants, termites), and mammals, flocking behavior in birds and fish.

The Belousov-Zhabotinsky Oscillating Reaction



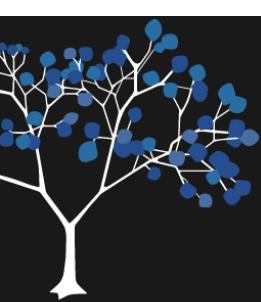
Rayleigh–Bénard convection

- Rayleigh–Bénard convection is a type of natural convection, occurring in a plane horizontal layer of fluid heated from below, in which the fluid develops a regular pattern of convection cells known as Bénard cells. Rayleigh–Bénard convection is one of the most commonly studied convection phenomena because of its analytical and experimental accessibility. The convection patterns are the most carefully examined example of self-organizing nonlinear systems.



Flow visualization of Benard-Marangoni convection





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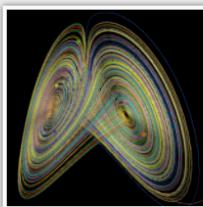
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More Is Different

Broken symmetry and the nature of the hierarchical structure of science.

P. W. Anderson

The reductionist hypothesis may still be a topic for controversy among philosophers, but among the great majority of active scientists I think it is accepted without question. The workings of our minds and bodies, and of all the animate or inanimate matter of which we have any detailed knowledge, are assumed to be controlled by the same set of fundamental laws, which except under certain extreme conditions we feel we know pretty well.

It seems inevitable to go on uncritically to what appears at first sight to be an obvious corollary of reductionism: that if everything obeys the same fundamental laws, then the only scientists who are studying anything really fundamental are those who are working on those laws. In practice, that amounts to some astrophysicists, some elementary particle physicists, some logicians and other mathematicians, and few others. This point of view, which it is the main purpose of this article to oppose, is expressed in a rather well-known passage by Weisskopf (1):

Looking at the development of science in the Twentieth Century one can distinguish two trends, which I will call "intensive" and "extensive" research, lacking a better terminology. In short: intensive research goes for the fundamental laws, extensive research goes for the ex-

The author is a member of the technical staff of the Bell Telephone Laboratories, Murray Hill, New Jersey 07974, and visiting professor of theoretical physics at Cavendish Laboratory, Cambridge, England. This article is an expanded version of a Regents' Lecture given in 1967 at the University of California, La Jolla.

less relevance they seem to have to the very real problems of the rest of science, much less to those of society.

The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear, and the understanding of the new behaviors requires research which I think is as fundamental in its nature as any other. That is, it seems to me that one may array the sciences roughly linearly in a hierarchy, according to the idea: The elementary entities of science X obey the laws of science Y.

X	Y
solid state or	elementary particle
many-body physics	physics
chemistry	many-body physics
molecular biology	chemistry
cell biology	molecular biology
•	•
•	•
psychology	physiology
social sciences	psychology

But this hierarchy does not imply that science X is "just applied Y." At each stage entirely new laws, concepts, and generalizations are necessary, requiring inspiration and creativity to just as great a degree as in the previous one. Psychology is not applied biology, nor is biology applied chemistry.

In my own field of many-body physics, we are, perhaps, closer to our fundamental, intensive underpinnings than in any other science in which non-trivial complexities occur, and as a result we have begun to formulate a general theory of just how this shift from quantitative to qualitative differentiation takes place. This formulation, called the theory of "broken symmetry," may be of help in making more generally clear the breakdown of the constructionist converse of reductionism. I will give an elementary and incomplete explanation of these ideas, and then go on to some more general speculative comments about analogies at

INTRODUCTION AND OPENING ESSAY

What Don't We Know?

D. Kennedy and C. Norman

In Praise of Hard Questions

T. Siegfried

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Anniversary Editorial

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To mark its 125th year of publication, *Science* has been running a series of

THE QUESTIONS

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- > [What is the Biological Basis of Consciousness?](#)
- > [Why Do Humans Have So Few Genes?](#)
- > [To What Extent Are Genetic Variation and Personal Health Linked?](#)
- > [Can the Laws of Physics Be Unified?](#)
- > [How Much Can Human Life Span Be Extended?](#)
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- > [How Does a Single Somatic Cell Become a Whole Plant?](#)
- > [How Does Earth's Interior Work?](#)
- > [Are We Alone in the Universe?](#)
- > [How and Where Did Life on Earth Arise?](#)
- > [What Determines Species Diversity?](#)
- > [What Genetic Changes Made Us Uniquely Human?](#)
- > [How Are Memories Stored and Retrieved?](#)
- > [How Did Cooperative Behavior Evolve?](#)
- > [How Will Big Pictures Emerge from a Sea of Biological Data?](#)

Why Do Humans Have So Few Genes?

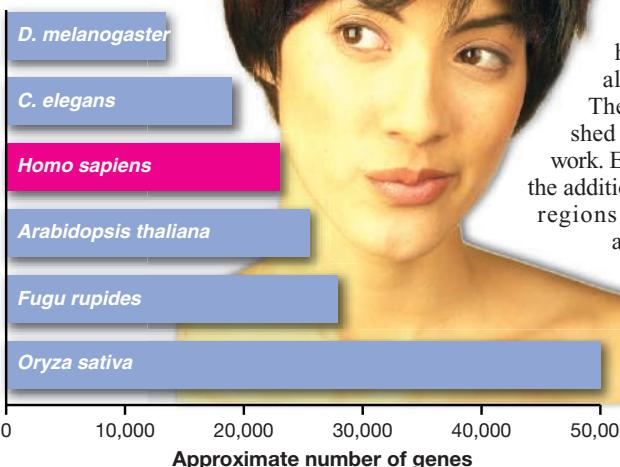
When leading biologists were unraveling the sequence of the human genome in the late 1990s, they ran a pool on the number of genes contained in the 3 billion base pairs that make up our DNA. Few bets came close. The conventional wisdom a decade or so ago was that we need about 100,000 genes to carry out the myriad cellular processes that keep us functioning. But it turns out that we have only about 25,000 genes—about the same number as a tiny flowering plant called *Arabidopsis* and barely more than the worm *Caenorhabditis elegans*.

That big surprise reinforced a growing realization among geneticists: Our genomes and those of other mammals are far more flexible and complicated than they once seemed. The old notion of one gene/one protein has gone by the board: It is now clear that many genes can make more than one protein. Regulatory proteins, RNA, noncoding bits of DNA, even chemical and structural alterations of the genome itself control how, where, and when genes are expressed. Figuring out how all these elements work together to choreograph gene expression is one of the central challenges facing biologists.

In the past few years, it has become clear that a phenomenon called alternative splicing is one reason human genomes can produce such complexity with so few genes. Human genes contain both coding DNA—exons—and noncoding DNA. In some genes, different combinations of exons can become active at different times, and each combination yields a different protein. Alternative splicing was long considered a rare hiccup during transcription, but researchers have concluded that it may occur in half—some say close to all—of our genes. That finding goes a long way toward explaining how so few genes can produce hundreds of thousands of different

proteins. But how the transcription machinery decides which parts of a gene to read at any particular time is still largely a mystery.

The same could be said for the mechanisms that determine which genes or suites of genes are turned on or off at particular times and places. Researchers are discovering that each gene needs a supporting cast of hundreds to get its job done. They include proteins that shut down or activate a gene, for example by adding acetyl or methyl groups to the DNA. Other proteins, called transcription factors, interact with the genes more directly: They bind to landing sites situated near the gene under their control. As with alternative splicing, activation of different combinations of landing sites makes possible exquisite control of gene expression, but researchers have yet to figure out exactly how all these regulatory elements really work or how they fit in with alternative splicing.



In the past decade or so, researchers have also come to appreciate the key roles played by chromatin proteins and RNA in regulating gene expression. Chromatin proteins are essentially the packaging for DNA, holding chromosomes in well-defined spirals. By slightly changing shape, chromatin may expose different genes to the transcription machinery.

Genes also dance to the tune of RNA. Small RNA molecules, many less than 30 bases, now share the limelight with other gene regulators. Many researchers who once focused on messenger RNA and other relatively large RNA molecules have in the past 5 years turned their attention to these smaller cousins, including microRNA and small nuclear RNA. Surprisingly, RNAs in these various guises shut down and otherwise alter gene expression. They also are key to cell differentiation in developing organisms, but the mechanisms are not fully understood.

Researchers have made enormous strides in pinpointing these various mechanisms.

By matching up genomes from organisms on different branches on the evolutionary tree, genomicists are locating regulatory regions and gaining insights into how mechanisms such as alternative splicing evolved.

These studies, in turn, should shed light on how these regions work. Experiments in mice, such as the addition or deletion of regulatory regions and manipulating RNA, and computer models should also help. But the central question is likely to remain unsolved for a long time: How do all these features meld together to make us whole?

—ELIZABETH PENNISI

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CREDIT: JEFFREY MAMES

Loose ends

Francisco Crick in Paradiso Sydney Brenner



Richard Dawkins has written another book on evolution. I haven't read it, but I noticed that one reviewer thought that the force of Dawkins' arguments was becoming diluted by a combination of militant atheism and over-flamboyant

prose. To conservative scientists like me, the idea of selfish genes, while certainly snappy, leads to ignoring the biology surrounding the genes and, in the end, to a distorted view of evolution. I do sympathize with Dawkins, however: he faces a tough problem in trying to convince people that natural selection explains evolution.

The resistance does not come from any profound religious beliefs, but rather from a deep feeling that it can't work. It's very difficult for anybody to believe that making random changes in a television set, or even in the plans for a factory

be absolutely explicit about how things should act in time; causality must be obeyed, and if X causes Y, then X must appear before Y. We also like hierarchical systems to make explicit the flow of control.

I used to think that these principles of modularity, rigorous sequentiality, and hierarchical control might underlie the structure and function of all elaborate systems. They are certainly true for writing a large piece of software or making a watch; in each case, even small departures from the original construction will produce a mess. I now believe that while these principles may be at the heart of artificial engineering, natural engineering is different. Biological systems have processes which are more flexibly organized and capable of displaying more resistance to lethal alterations, and have more versatility in adaptive responses.

Thus the evolution paradox resolves itself as follows. If we persist in thinking that natural systems are like artificial ones, we will need a designer to impose the same constraints on natural systems as we impose on artificial ones. And, just as for artificial systems, somebody would have to 'go back to the drawing board' to get something new. Of course, in nature, there is no going back to the drawing board: if something does not work, it is simply discarded and

landing on a distant planet, scientists discover two organisms; one emits yellow light, the other blue light, and there is evidence that one evolved from the other. If we were to assume that each had emission lamps, with sodium vapour in one and potassium in the other, we would require nuclear transmutation to convert one into the other. On the other hand, if we had a white light source and a prism and a slit, we could easily see how errors in the embryological development of the slit could lead to changes in the emission. In fact, all kinds of light emission become possible.

I shared an office with Francis Crick for twenty years in Cambridge. At one time he was interested in embryology and spent a lot of time thinking about imaginal discs in *Drosophila*. One day, he threw the book he was reading down onto his desk with an exasperated cry. "God knows how these imaginal discs work." In a flash I saw the whole story of Francis arriving in heaven and Peter welcoming him with "Oh Dr Crick, you must be tired after your long journey. Do sit down, have a drink and relax." "No," says Francis, "I must see this fellow, God; I have to ask him a question." After some persuasion, the angel agrees to take Francis to God. They cross the middle part of heaven, and finally right at the back, across the railway tracks, they come to a shed, with a

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This story was a particular favourite of an Italian Minister of Science.

Thanks!

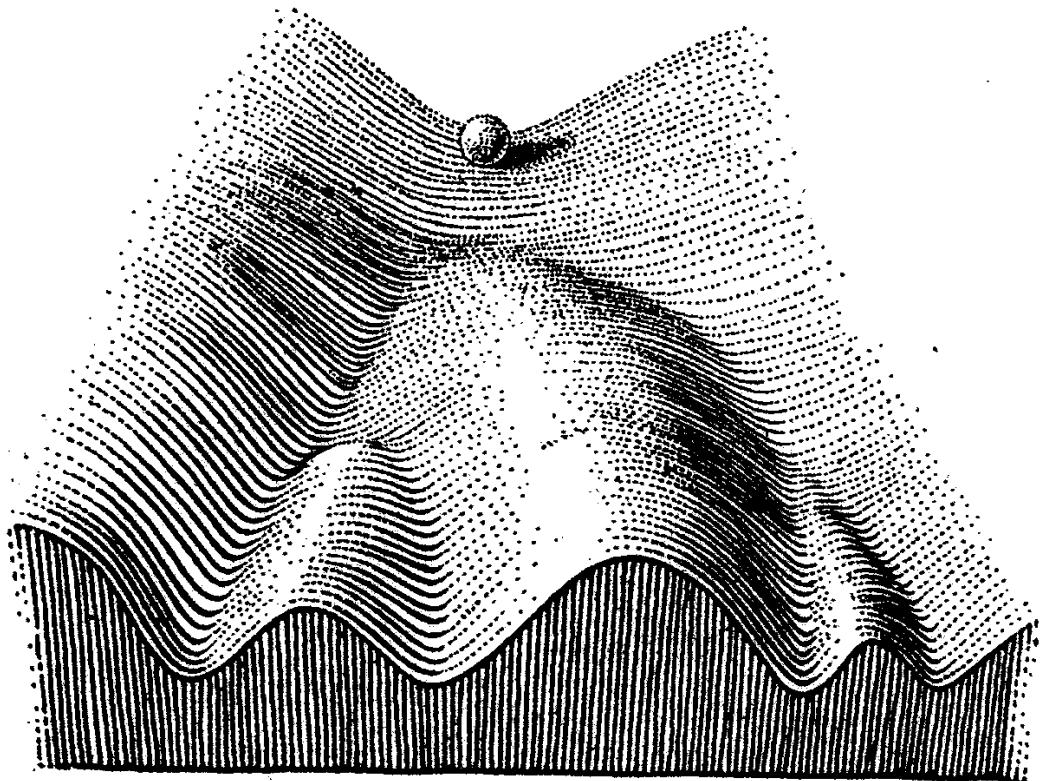


FIGURE 4

Part of an Epigenetic Landscape. The path followed by the ball, as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg. There is first an alternative, towards the right or the left. Along the former path, a second alternative is offered; along the path to the left, the main channel continues leftwards, but there is an alternative path which, however, can only be reached over a threshold.

THE STRATEGY OF THE GENES

A Discussion of Some Aspects of
Theoretical Biology

C. H. Waddington

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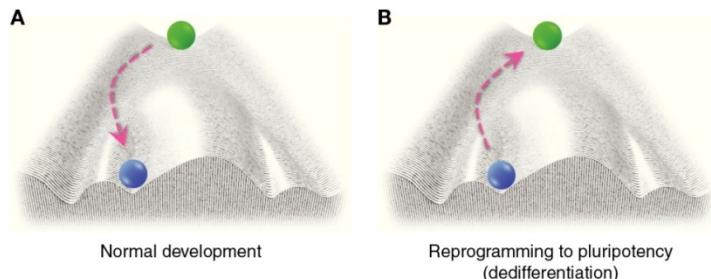


Figure 1. Cellular reprogramming depicted as a trajectory in Waddington's epigenetic landscape. (A) A cell's normal developmental trajectory can be traced starting from a pluripotent cell (green ball) at the top of the hill to its final differentiated state (blue ball), illustrating how epigenetics contributes to cell fate determination during development. (B) A terminally differentiated cell (blue ball) can be reprogrammed back to pluripotency when exposed to a cocktail of transcription factors.

Epigenetics, Second Edition © 2015 Cold Spring Harbor Laboratory Press

- 发育的普适性机制，有没有，是什么，怎么样用。
- 接近相同的DNA怎样解读，产生了接近相同的个体。