A systems approach to biology

SB200

Lecture 7
7 October 2008

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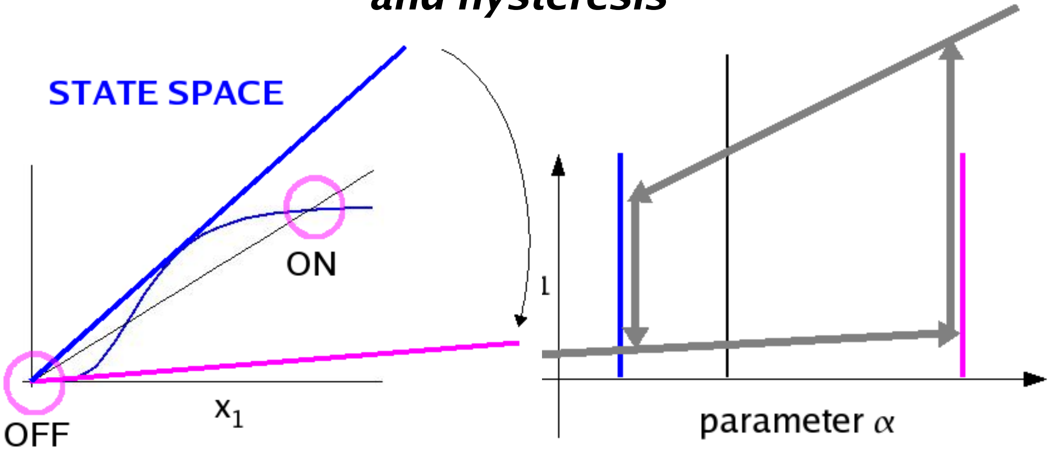
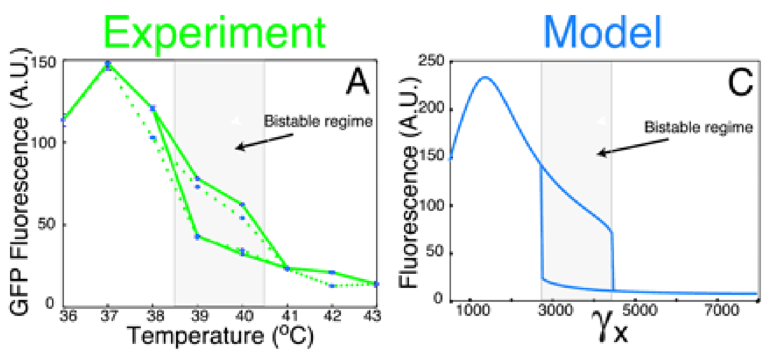
jeremy@hms.harvard.edu

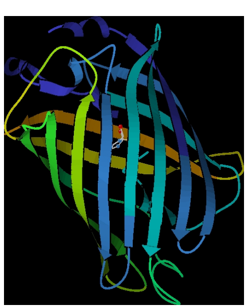
Recap of Lecture 6

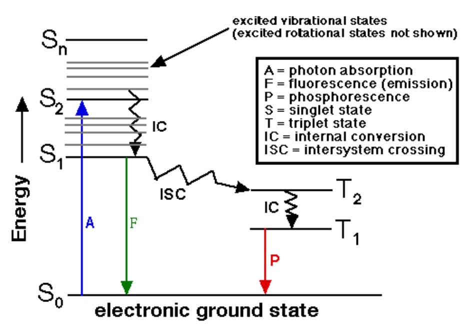
In phage lambda, cooperativity leads to bistability and hysteresis



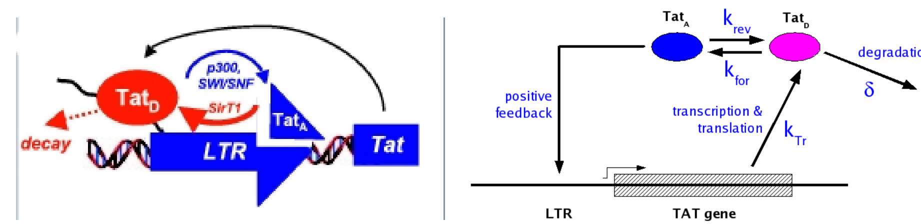


Fluorescence



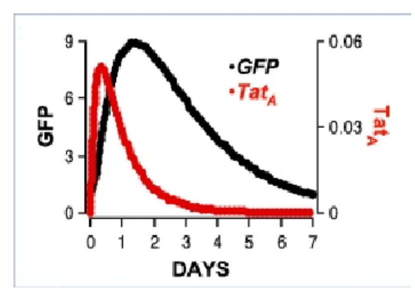


In HIV-1, sequestration provides an alternative way to stabilise the off-state

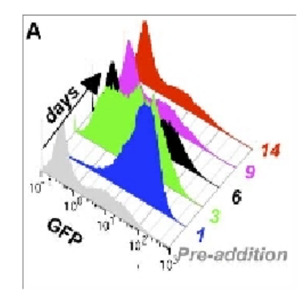


$$\frac{d}{dt}\begin{pmatrix} \text{Tat}_D \\ \text{Tat}_A \end{pmatrix} = \begin{pmatrix} -k_{for} - \delta & k_{rev} + k_{Tr} \\ k_{for} & -k_{rev} \end{pmatrix}\begin{pmatrix} \text{Tat}_D \\ \text{Tat}_A \end{pmatrix}$$

$$\boxed{\delta k_{rev} > k_{for} k_{Tr}}$$



simulation



data

more that one way to skin a cat !!

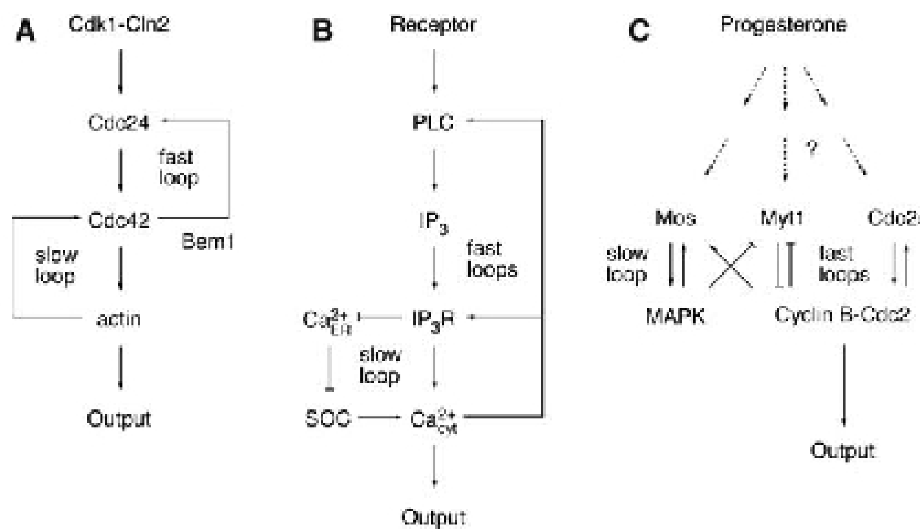
further reading ...

Interlinked Fast and Slow Positive Feedback Loops Drive Reliable Cell Decisions

Onn Brandman,[1,2*] James E. Ferrell Jr.,[1] Rong Li,[2,3,4] Tobias Meyer[1,2]

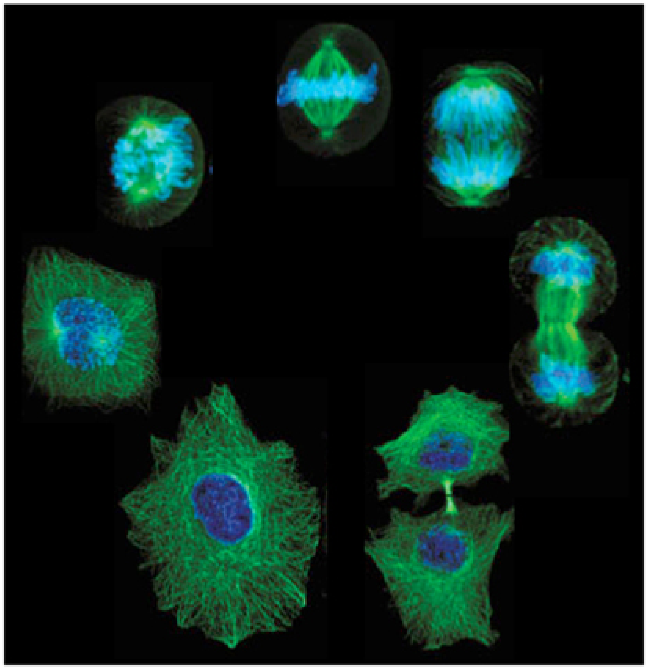
Positive feedback is a ubiquitous signal transduction motif that allows systems to convert graded inputs into decisive, all-or-none outputs. Here we investigate why the positive feedback switches that regulate polarization of budding yeast, calcium signaling, *Xenopus* oocyte maturation, and various other processes use multiple interlinked loops rather than single positive feedback loops. Mathematical simulations revealed that linking fast and slow positive feedback loops creates a "dual-time" switch that is both rapidly inducible and resistant to noise in the upstream signaling system.

21 OCTOBER 2005 VOL 310 SCIENCE www.sciencemag.org



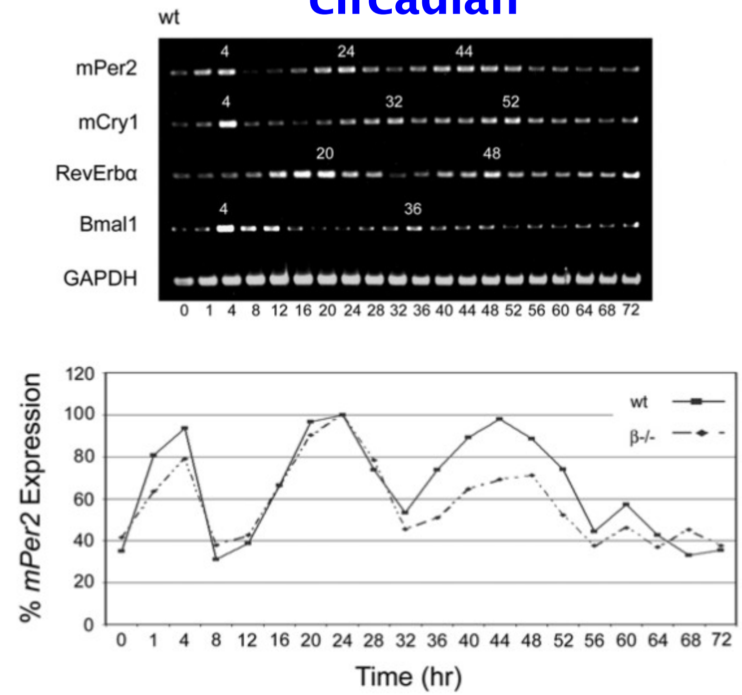
cellular rhythms

cell cycle



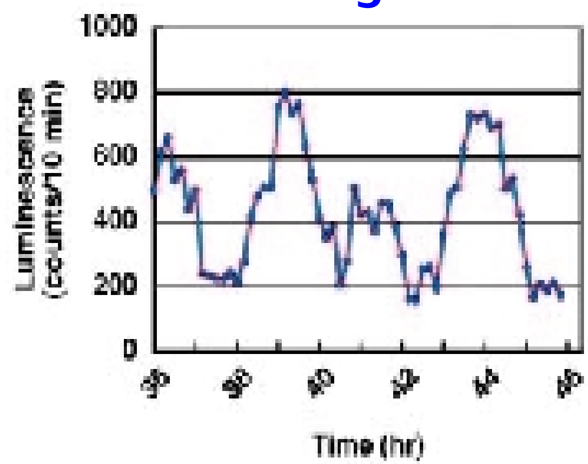
Yong Wan lab, University of Pittsburgh
http://www.cbp.pitt.edu/faculty/yong_wan/index.html

circadian



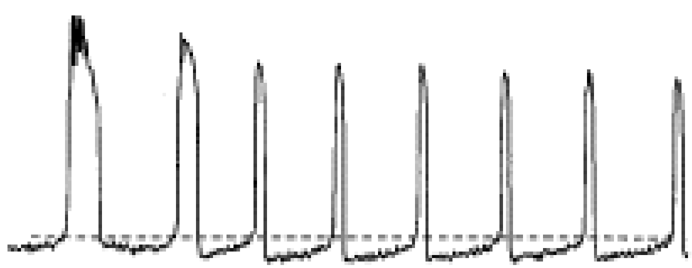
Kaladchibachi et al. Journal of Circadian Rhythms **5**:3 2007

somitogenesis



Masamizu *et al*
"Real-time imaging of the somite segmentation clock",
PNAS **103**:1213-8 2006

calcium

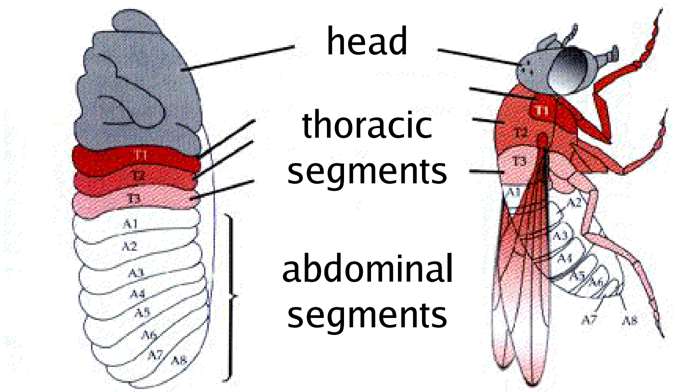


fertilisation induced Ca2+ oscillations recorded in a mouse egg using Fura Red
Halet et al, Biochem Soc Trans **31**:907-11 2003

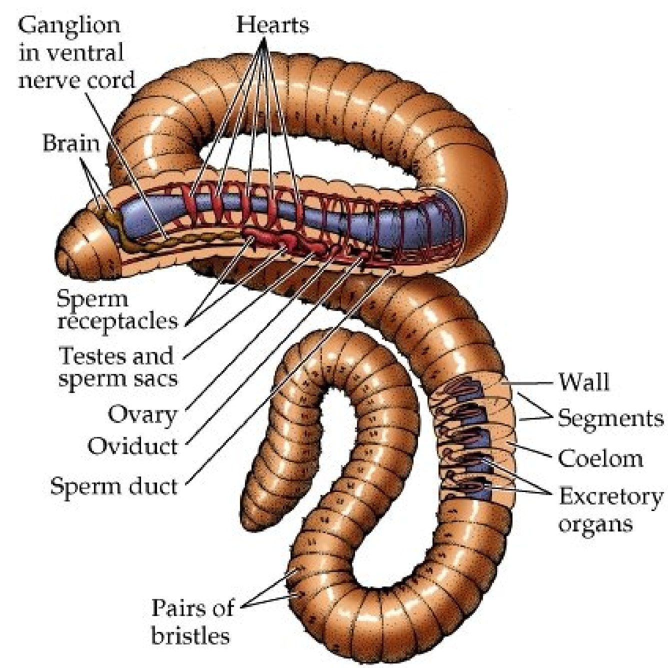
somitogenesis oscillator

spatial patterning from temporal oscillation

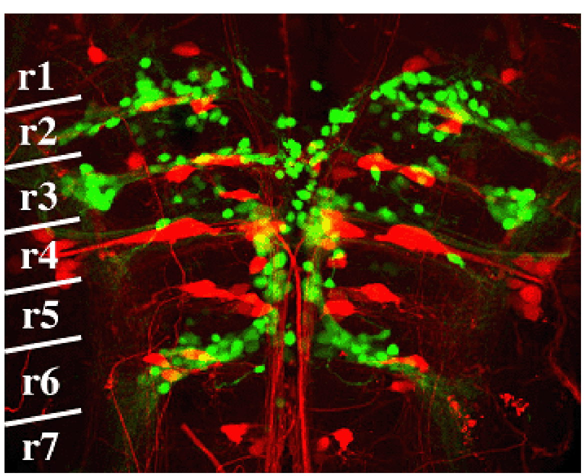
segmentation is a common strategy in metazoan development



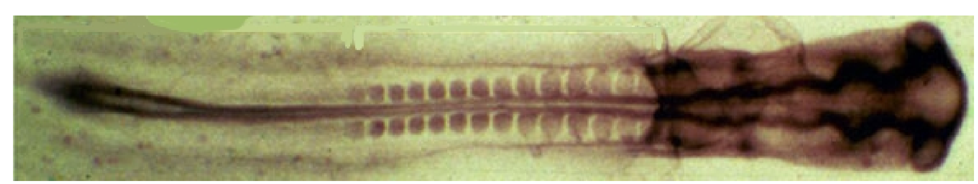
Drosophila



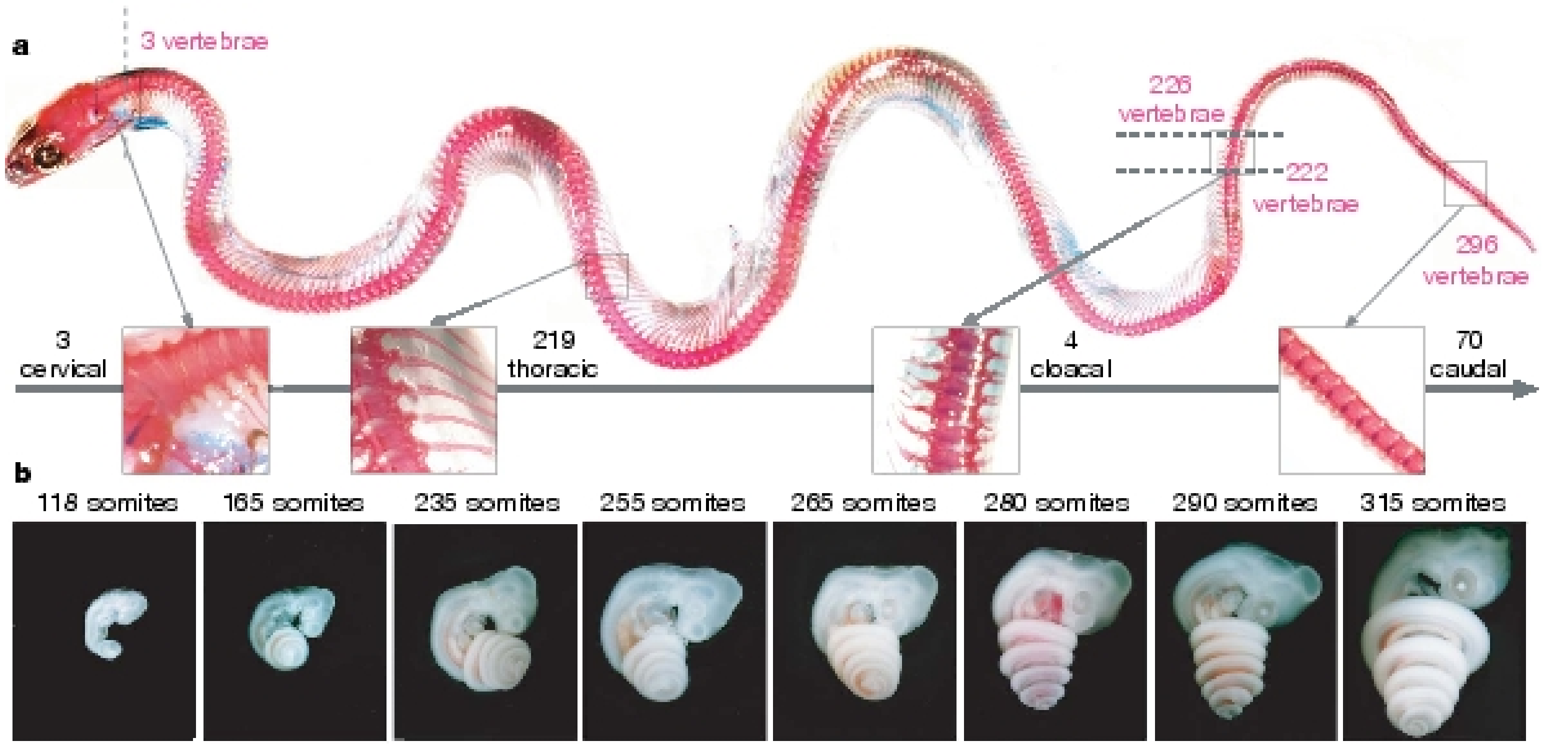
annelid worm



zebrafish



chick



snake

Gomez et al. Nature, **454**:335-9 2008

Drosophila uses a spatial patterning mechanism

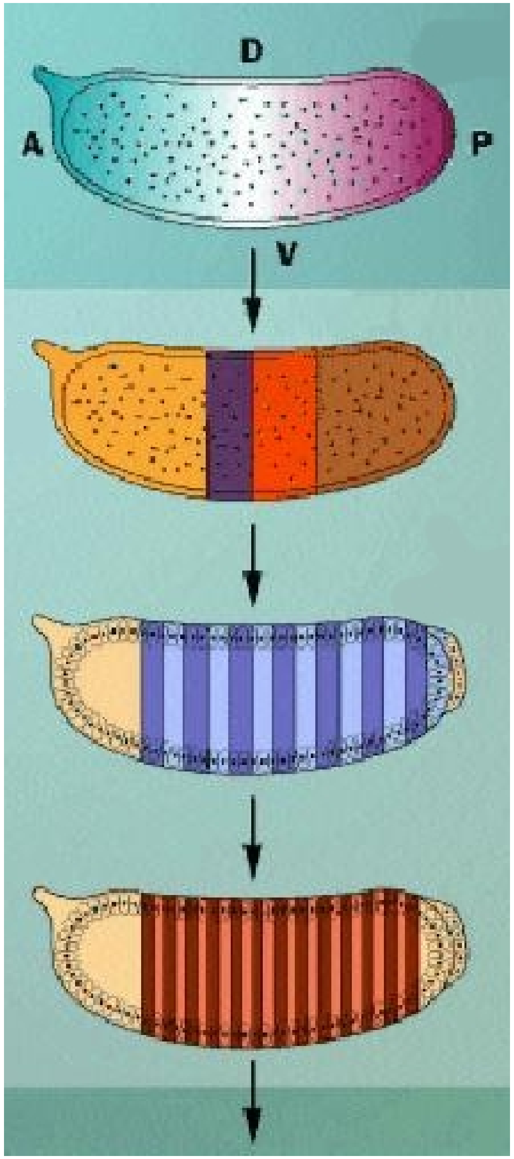
maternal genes lay down positional morphogen gradients

gap genes

pair-rule genes

segment polarity genes

Hox genes



bicoid, nanos

synctial blastoderm stage

hunchback

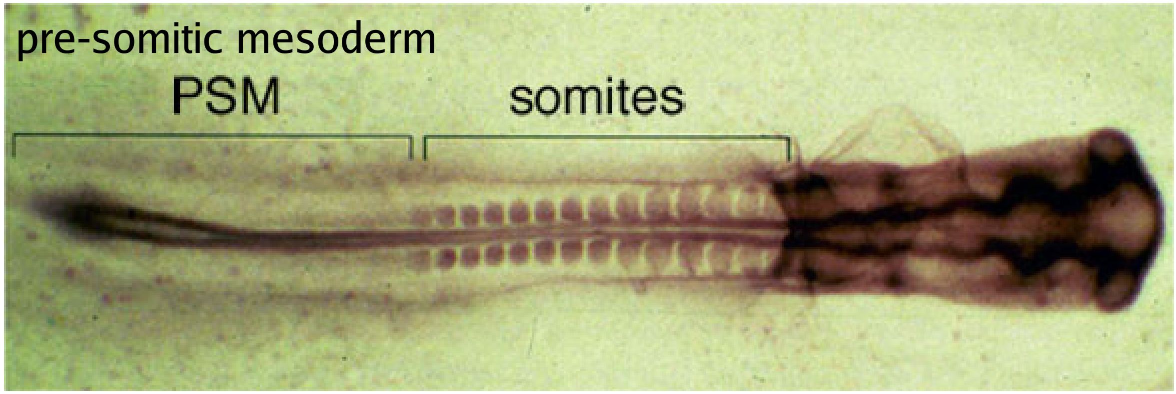
even skipped, hairy

cellularisation

wingless, engrailed

vertebrates use a different mechanism of somitogenesis

Caudal (tail)

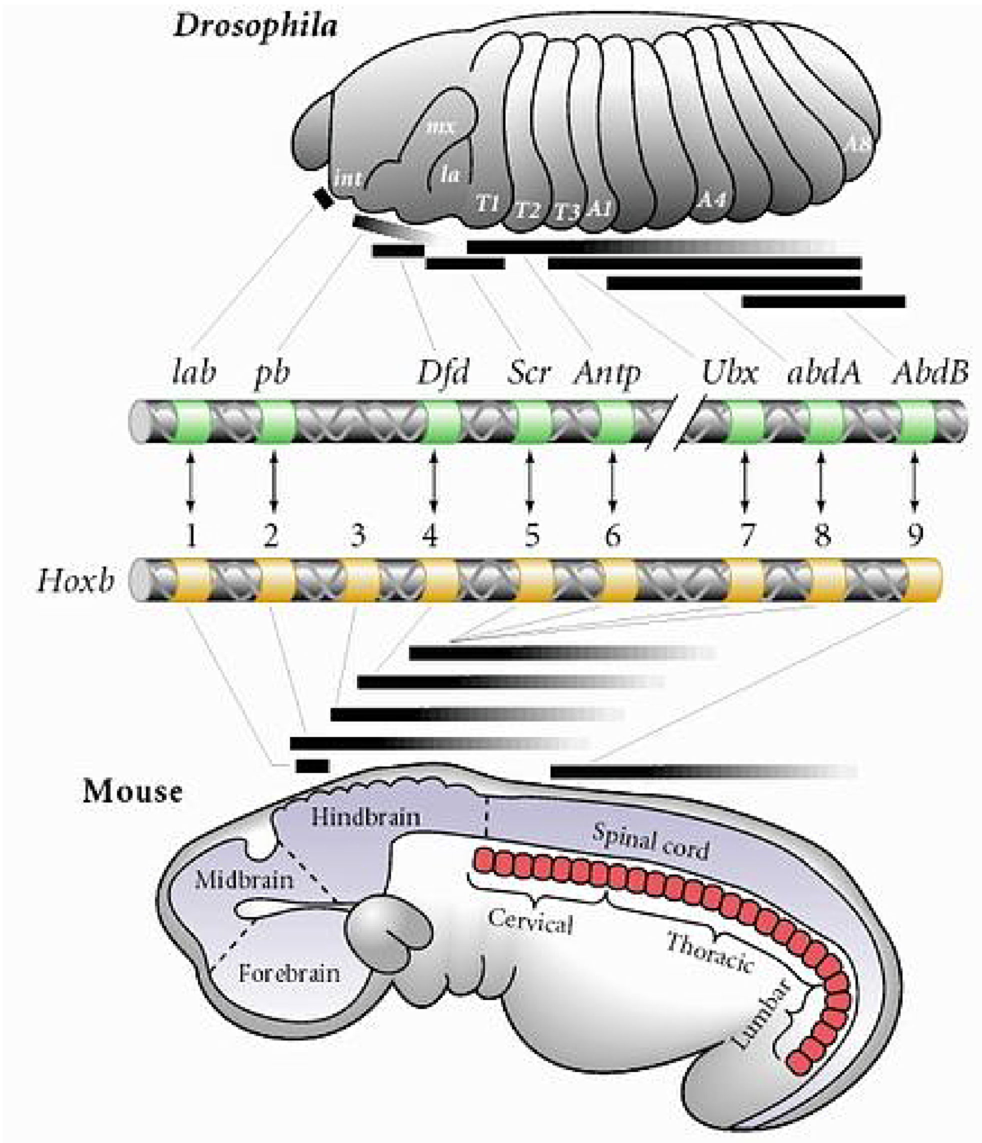


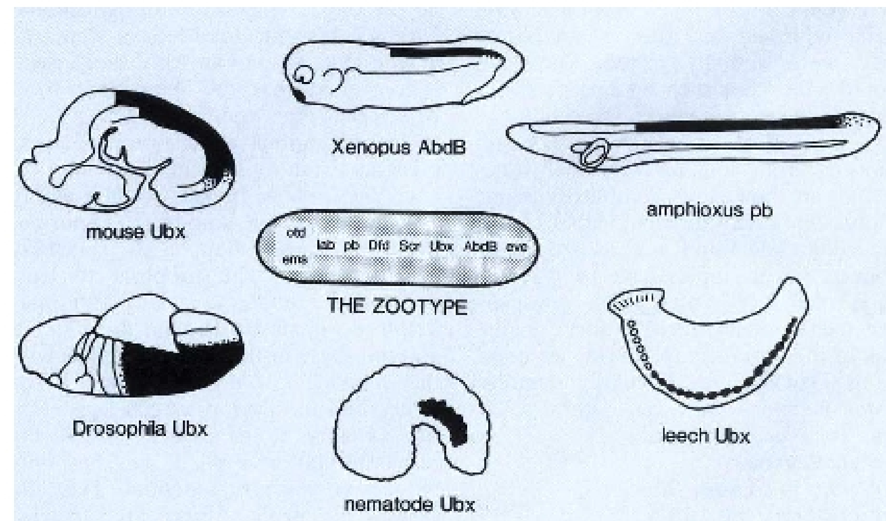
Rostral (head)

chick

somites form sequentially in an anterior to posterior order

but all animals share deeper conservation of Hox genes





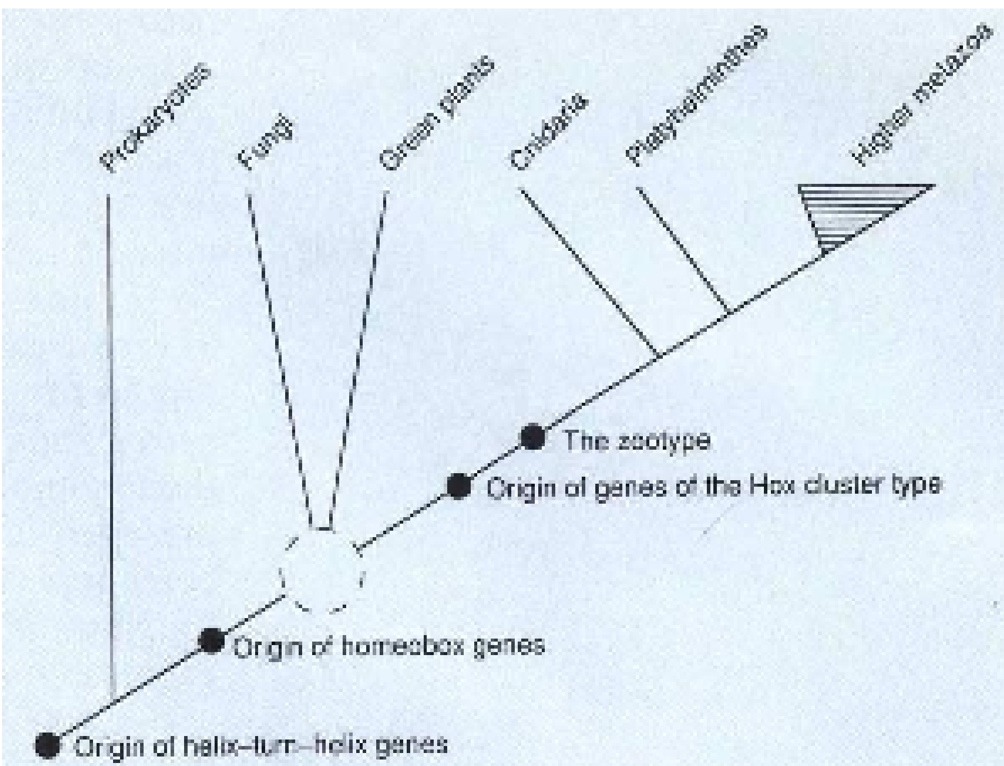
COMMENTARY

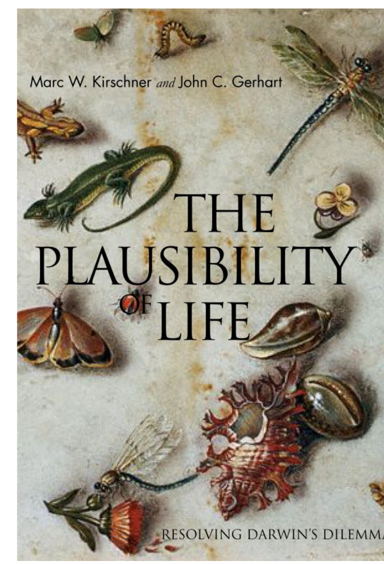
The zootype and the phylotypic stage

J. M. W. Slack, P. W. H. Holland and C. F. Graham

What is it that defines an animal? The definition provided here, made on the basis of developmental biology, suggests methods for resolving phylogenetic problems.

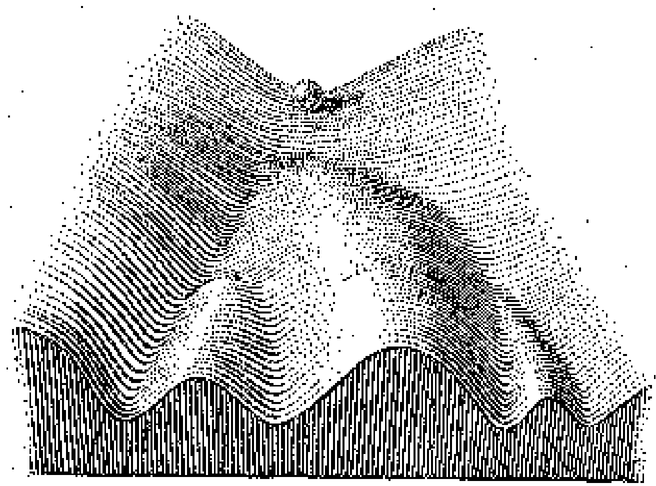
Slack, Holland, Graham. Nature, **361**:490-2 1993



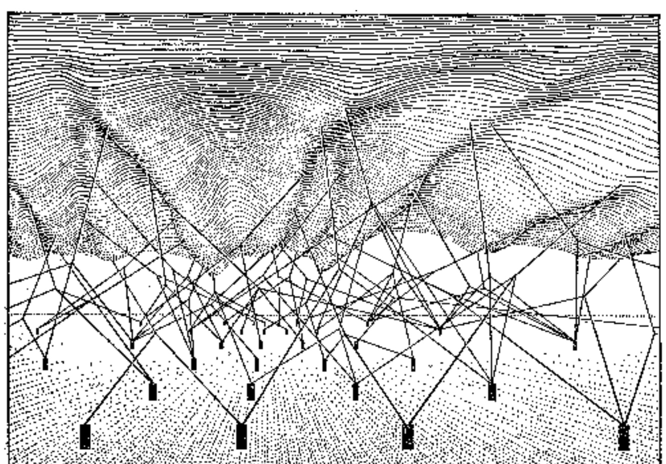


Marc Kirschner and John Gerhart
The Plausibility of Life: Resolving Darwin's Dilemma
Yale University Press, 2005

the interplay between genetic regulatory networks and evolution (EVO/DEVO) had been anticipated



the epigenetic landscape



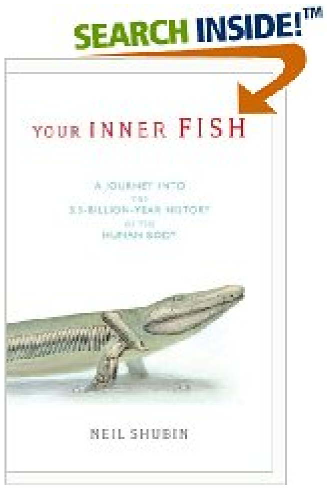
TIMELINE

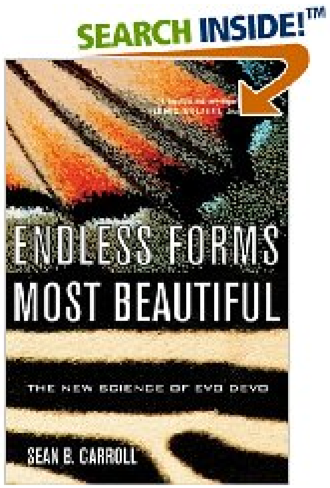
Conrad Hal Waddington: the last Renaissance biologist?

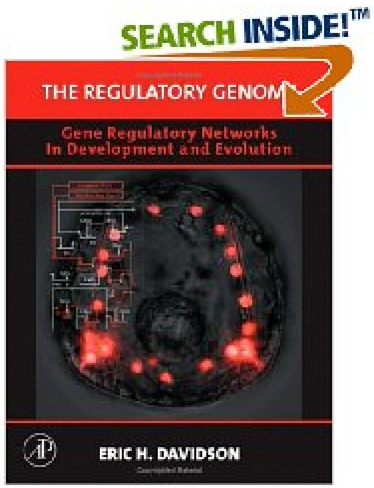
Jonathan M. W. Slack

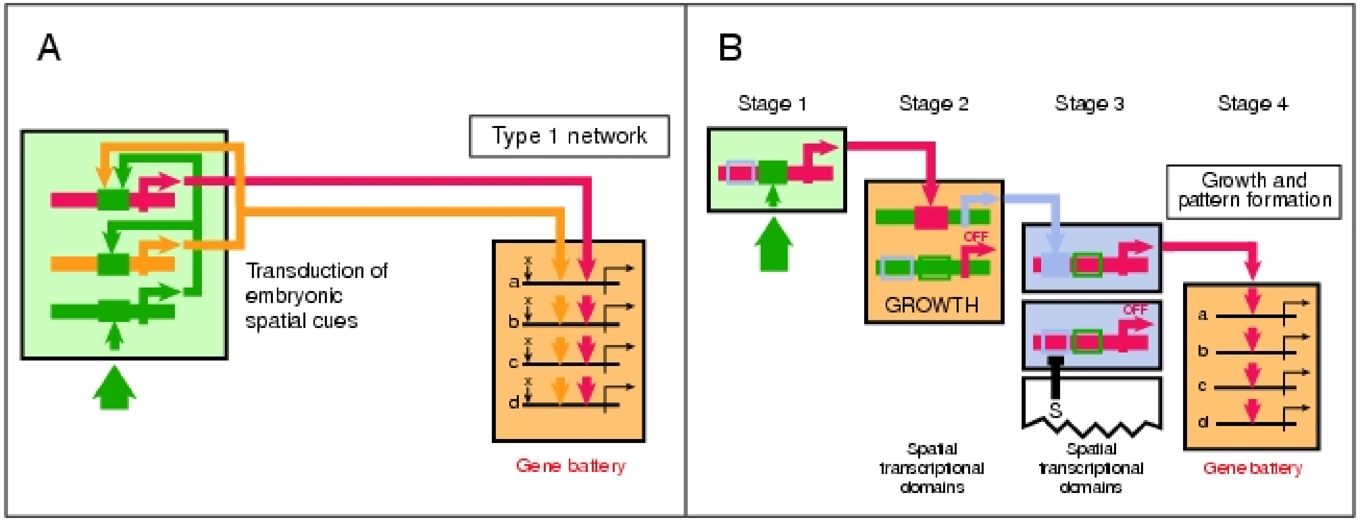
Slack, Nature Reviews Genetics, **3**:889-95 2002

Waddington, **The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology,** George Allen & Unwin 1957







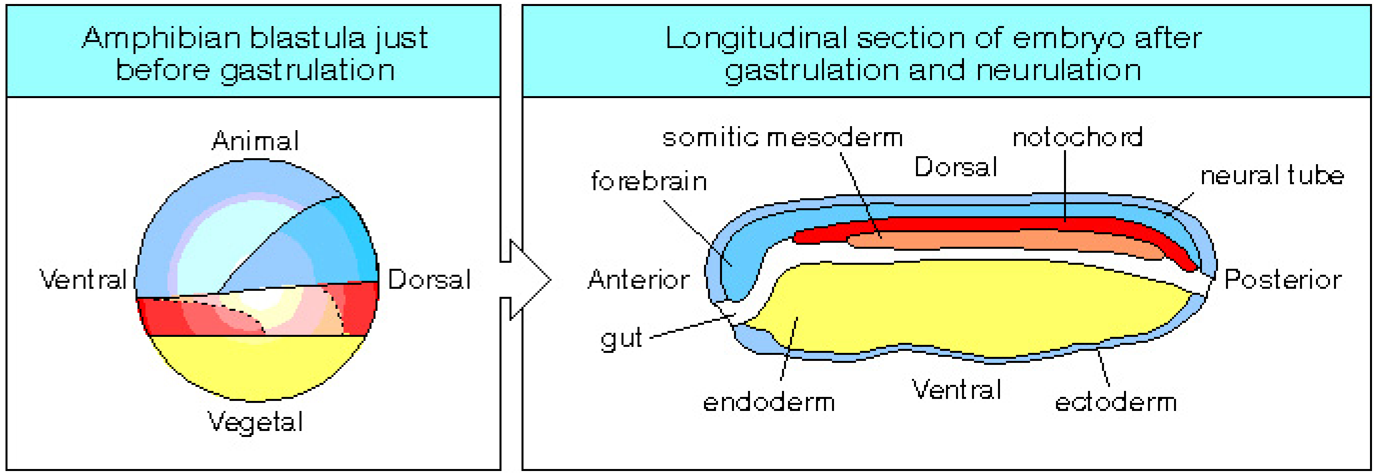


Neil Shubin, **Your Inner Fish**, Pantheon, 2008
Sean Carroll, **Endless Forms Most Beautiful**, W W Norton, 2006
Eric Davidson, **The Regulatory Genome**, Academic Press, 2006
Don Erwin, Eric Davidson, "*The last common bilaterian ancestor*", Development **129**:3021-32 2002

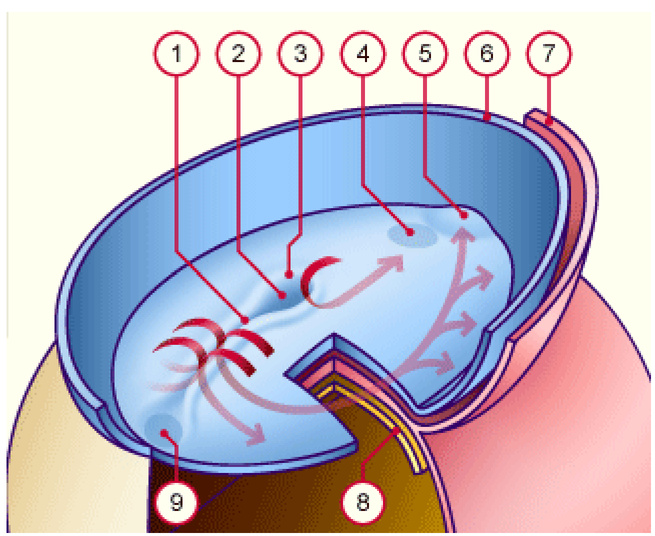
vertebrate gastrulation and neurulation

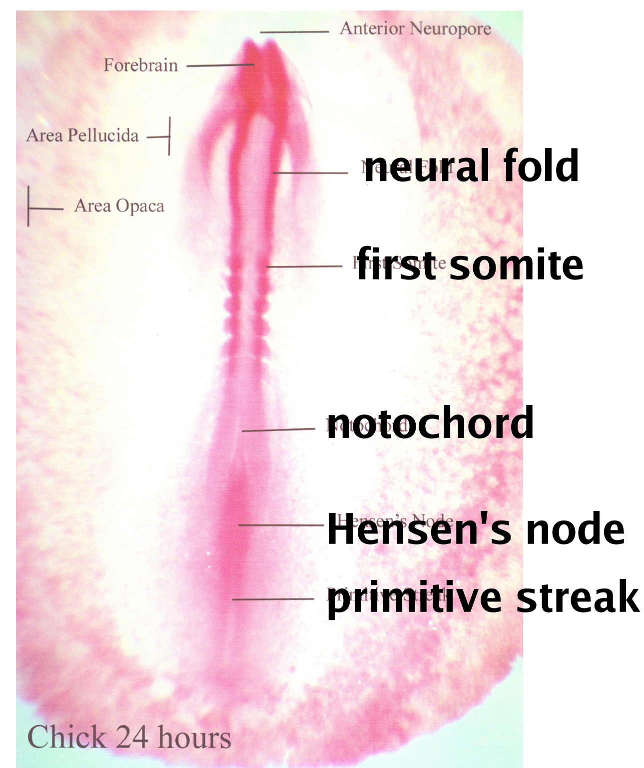
FROG

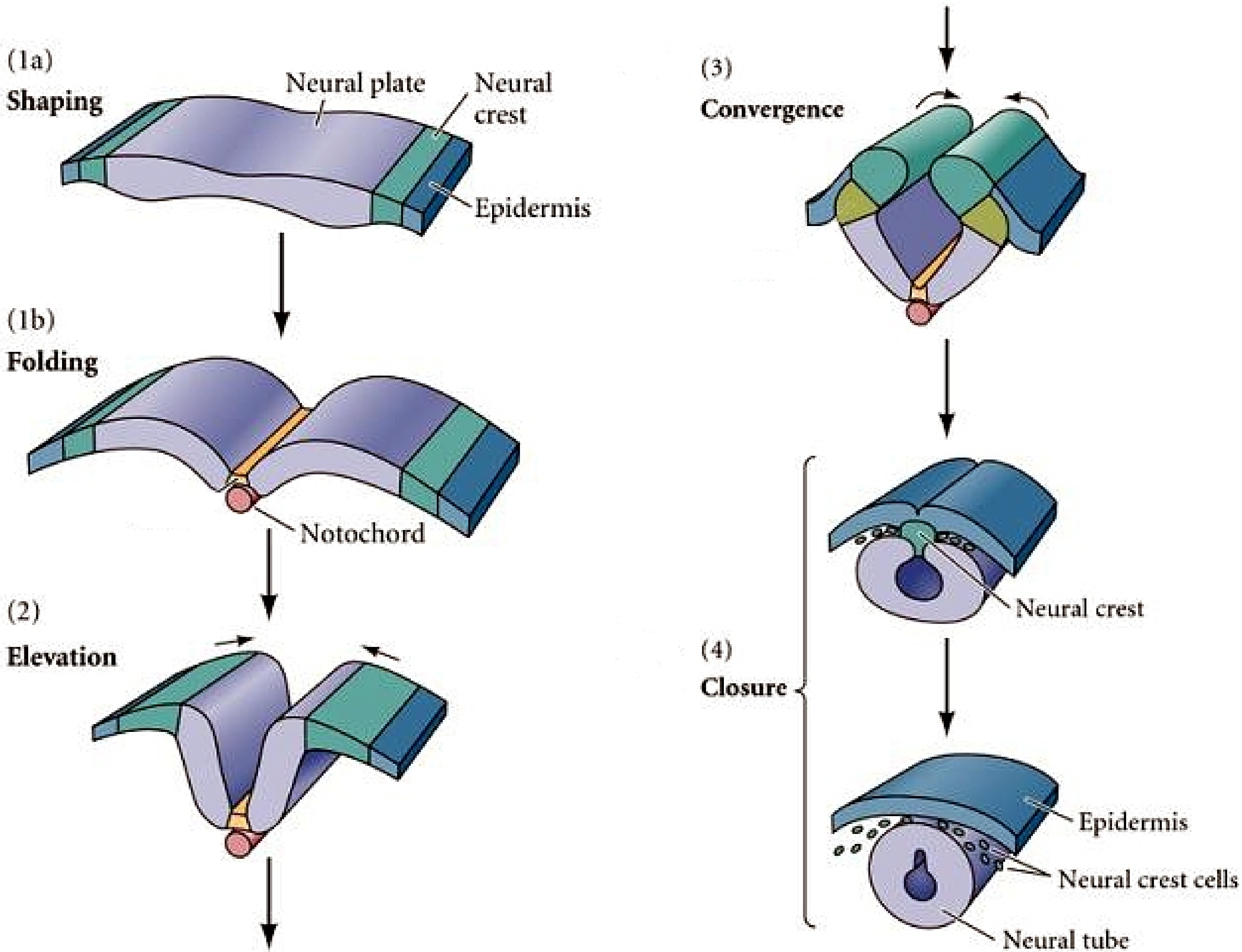
ectoderm
mesoderm
endoderm



CHICK

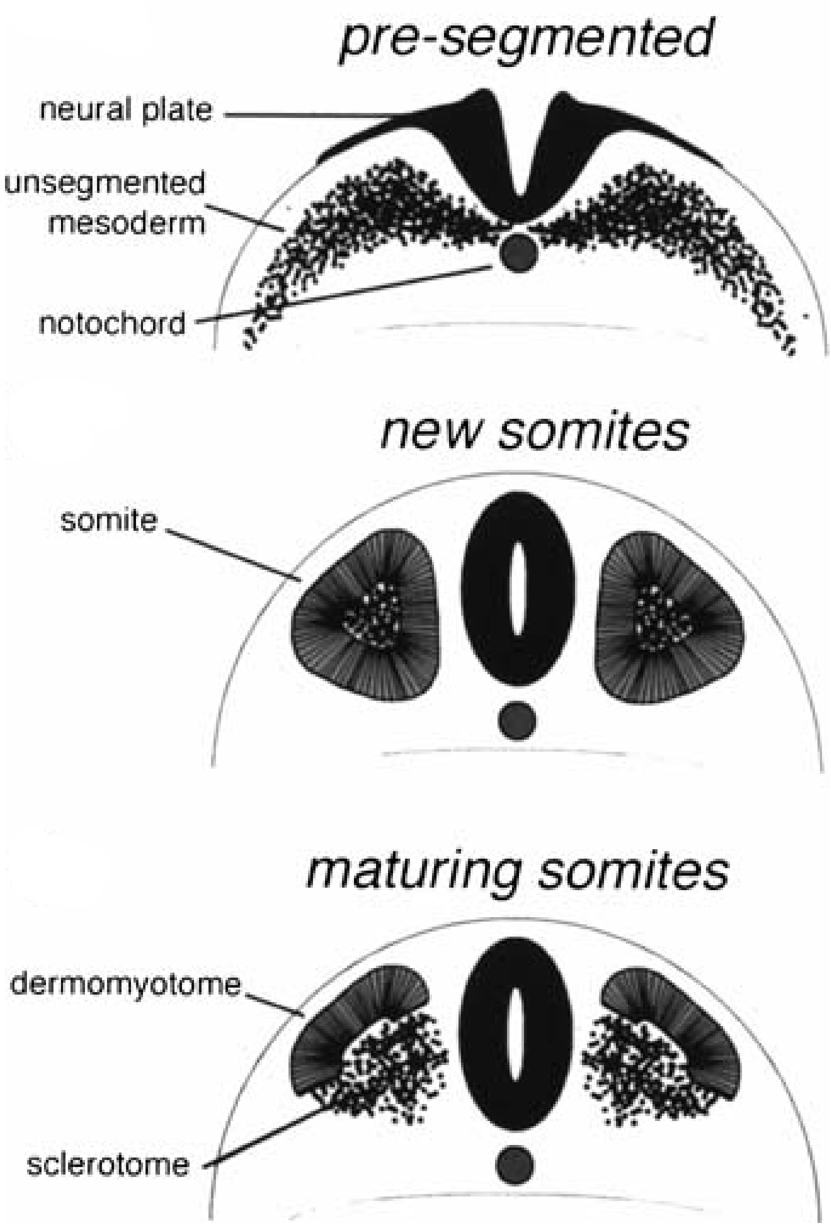


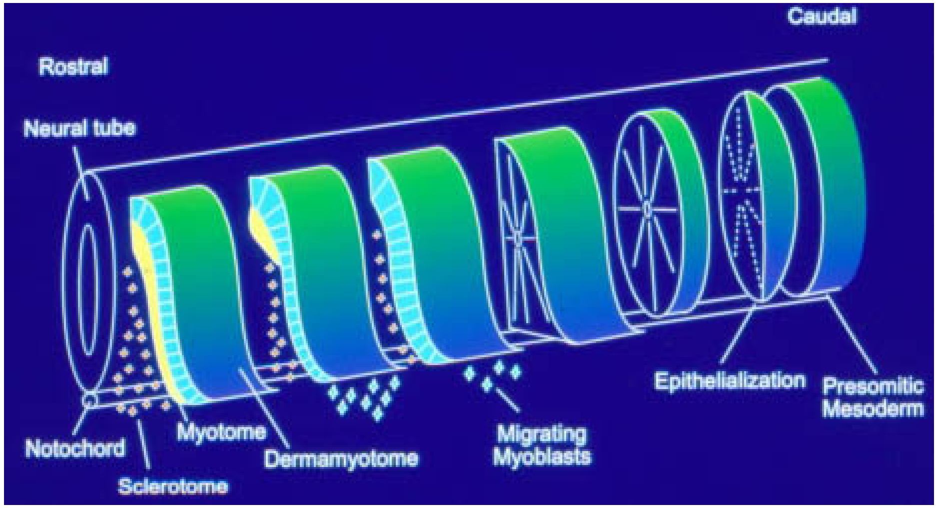


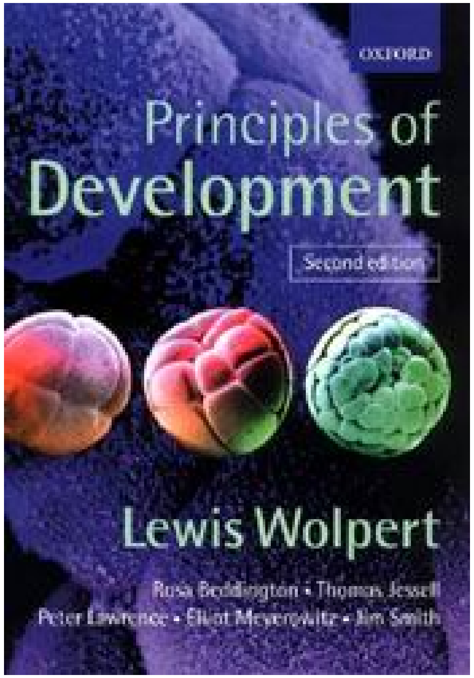

(1a)
Shaping
Neural plate
Neural crest
Epidermis
(1b)
Folding
Notochord
(2)
Elevation
(3)
Convergence
(4)
Closure
Neural crest
Epidermis
Neural crest cells
Neural tube

somitogenesis and differentiation

-

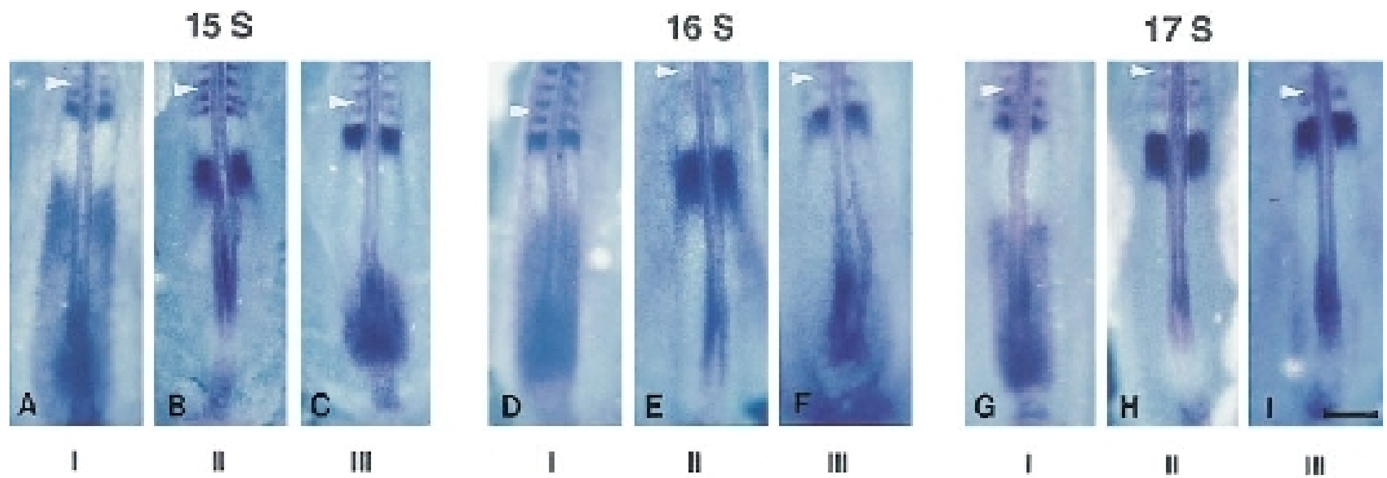




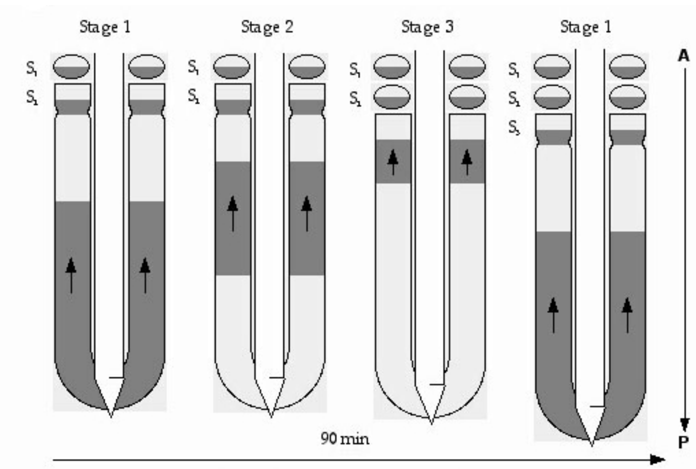


Lewis Wolpert, **Principles of Development**
Oxford University Press, 2002

in-situ hybridisation against c-hairy1 mRNA



c-hairy is the homologue of the Drosophila pair-rule gene and lies downstream of Notch



5-10µM CHX caused 71-84% block of protein synthesis but does not affect the oscillation

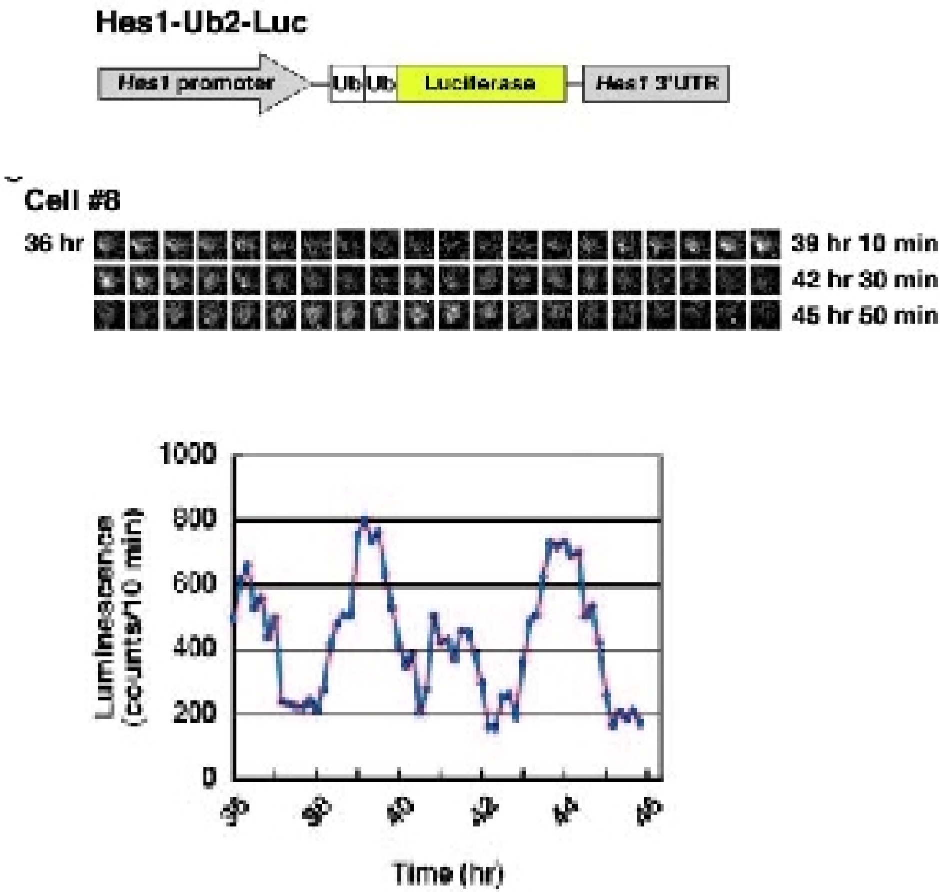
Palmeirim, Henrique, Ish-Horowicz, Pourqui
"Avian hairy gene expression identifies a molecular clock linked to vertebrate segmentation and somitogenesis"
Cell **91**:639-48 1997

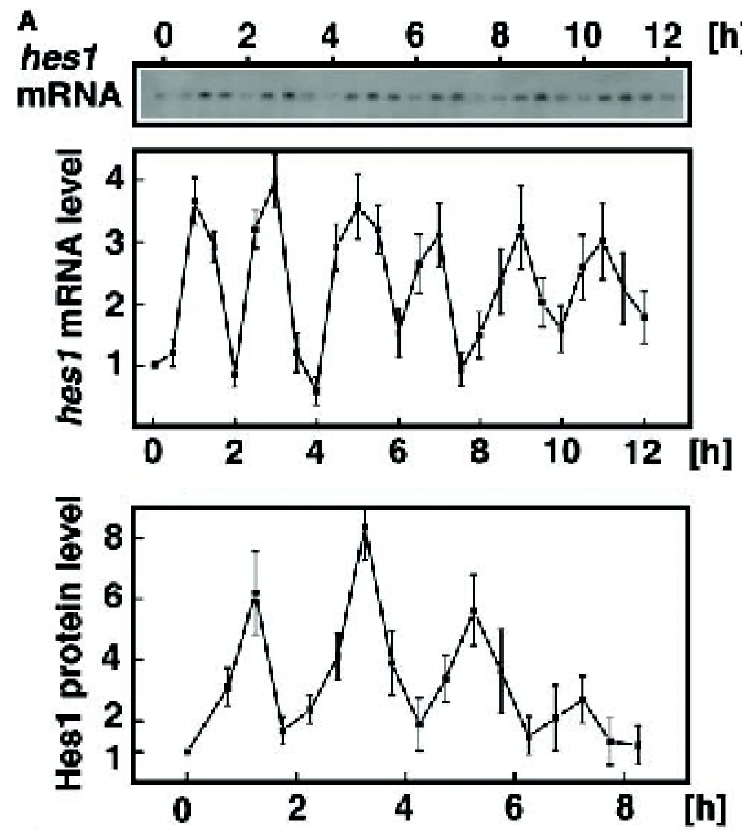
computational reconstruction of somitogenesis clock by Julian Lewis
Appendix to Palmeirim et al paper in Cell **91** 1997

Hes1 oscillation in cultured mouse fibroblasts

single cell

population average





Masamizu *et al*
"Real-time imaging of the somite segmentation clock,"
PNAS **103**:1213-8 2006

Hirata et al
"Oscillatory expression of the bHLH factor Hes1 regulated by negative feedback loop"
Science **298**:840-3 2002

cells in the PSM have an **intrinsic oscillator** with a period of

30 minutes in zebrafish

90 minutes in the chick

120 minutes in mouse

that produces sustained oscillations of cyclic genes

somitogenesis also requires

cell-cell communication (Notch-Delta)

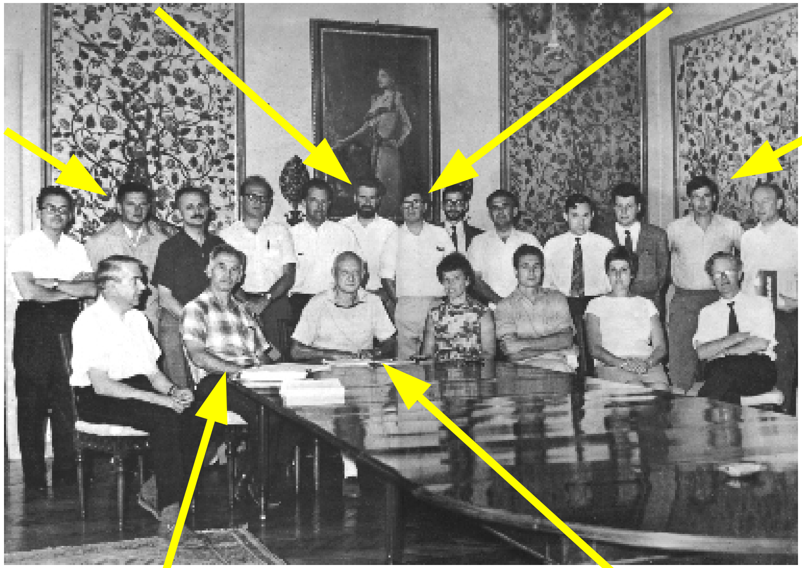
global coordination (Wnt, FGF8, retinoic acid)

Aulehla & Herrmann
"Segmentation in vertebrates: clock and gradient finally joined"
Genes & Development 1**8**:2060-7 2004

intrinsic oscillators in the PSM had been predicted 20 years before

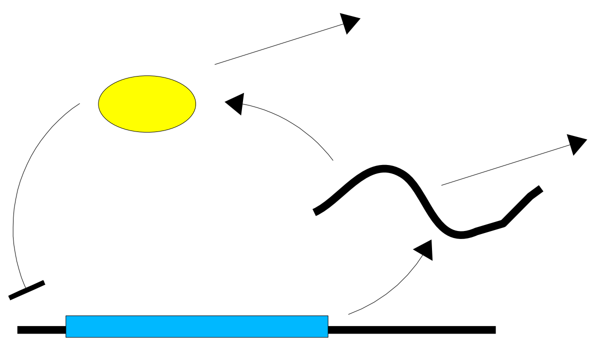
Jonathan Cooke & Chris Zeeman
"A clock and wavefront model for control of the number of repeated structures during animal morphogenesis"
J Theor Biol **58**:455-76 1976

1st *"Towards a Theoretical Biology"* Conference
Villa Serbelloni, Italy, 1966



Graeme Mitchison
"Theory in biology: happy days are here again?" Current Biol **14**:R97-8 2005

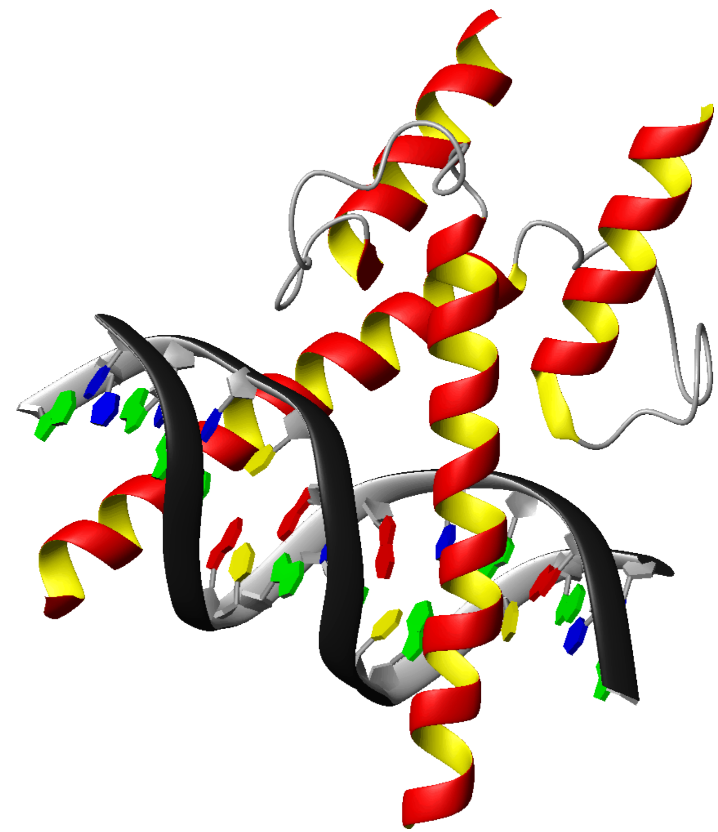
current story – oscillation is driven by a negative feedback loop



bHLH
transcription factors

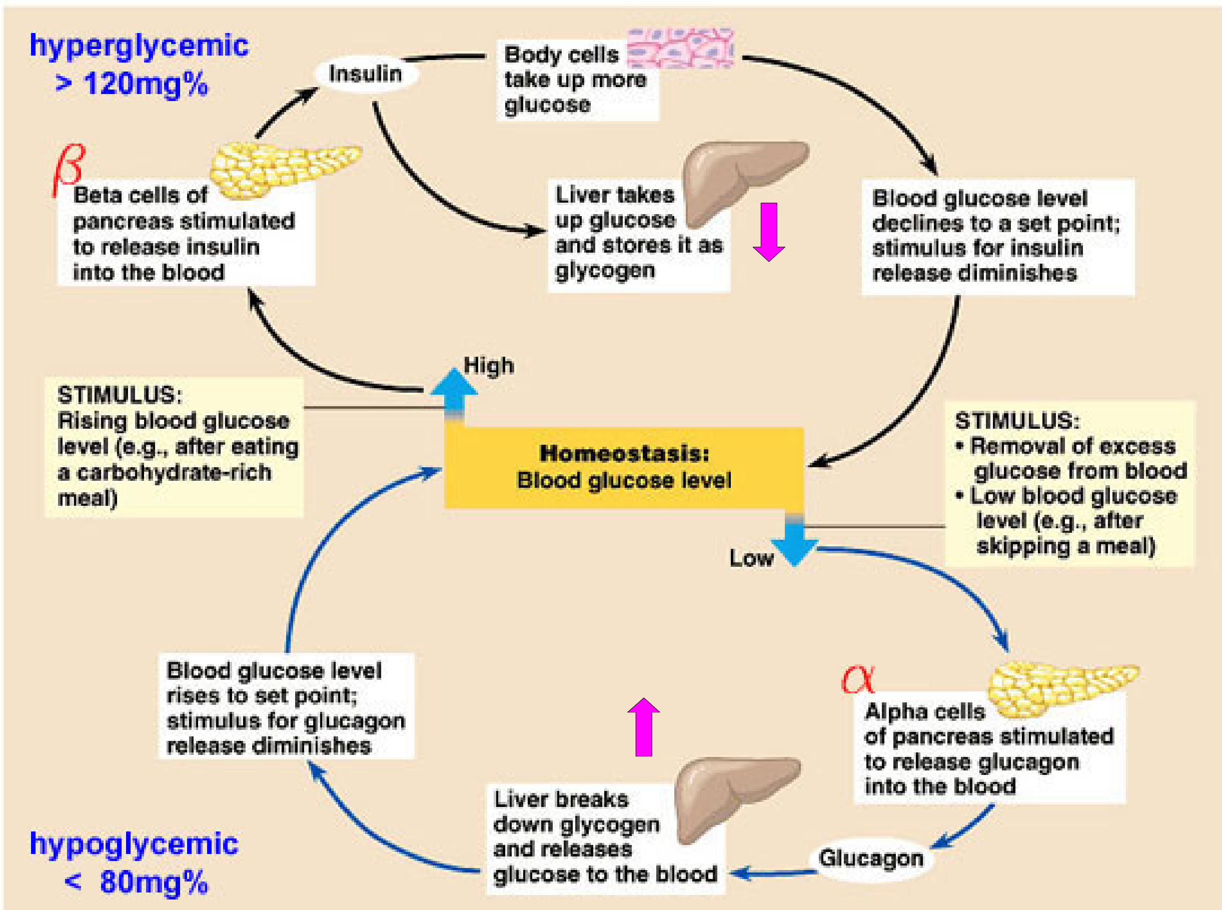
zebrafish
Her1/Her7

mouse
Hes1/Hes7



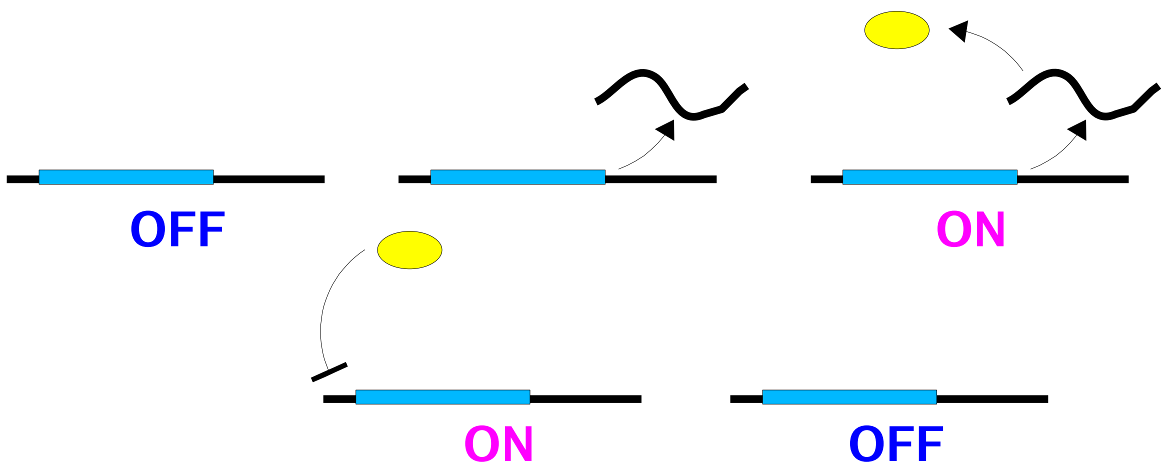
basic Helix-Loop-Helix
transcription factor
(Hypoxia Inducing Factor)

negative feedback loops are widely used to maintain the constancy of the body's internal environment – ħ omeostasis”



Walter Cannon
The Wisdom of the Body, Kegan Paul, 1947

but negative feedback loops can also induce oscillations

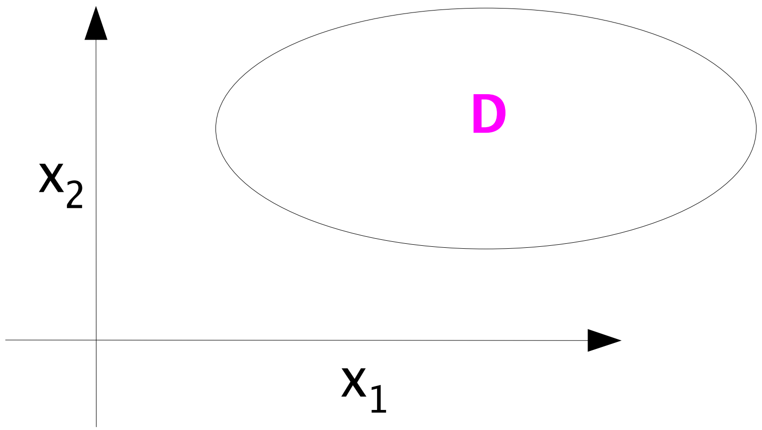


Bendixson's Negative Criterion

strictly 2 dimensional !!!

$$\frac{dx_1}{dt} = f_1(x_1, x_2)$$

$$\frac{dx_2}{dt} = f_2(x_1, x_2)$$



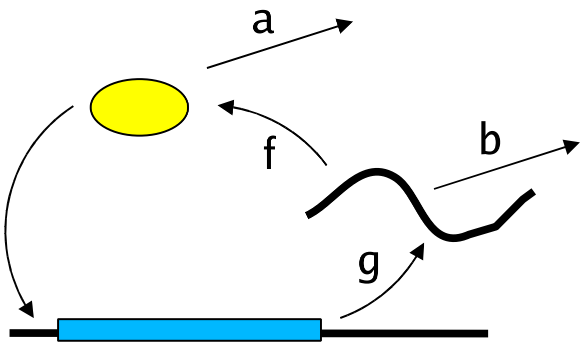
if D is a connected, bounded region **with no holes** and the trace of the Jacobian

$$\mathrm{Tr}(Df) = \frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$$

is never 0 and has the same sign throughout the region

then there are no periodic orbits in D

Proof: follows from Green's theorem $\oint_{\partial D} F.ds = \int_D (\nabla \times F) dA$



$$\frac{dx_1}{dt} = f(x_2) - ax_1$$

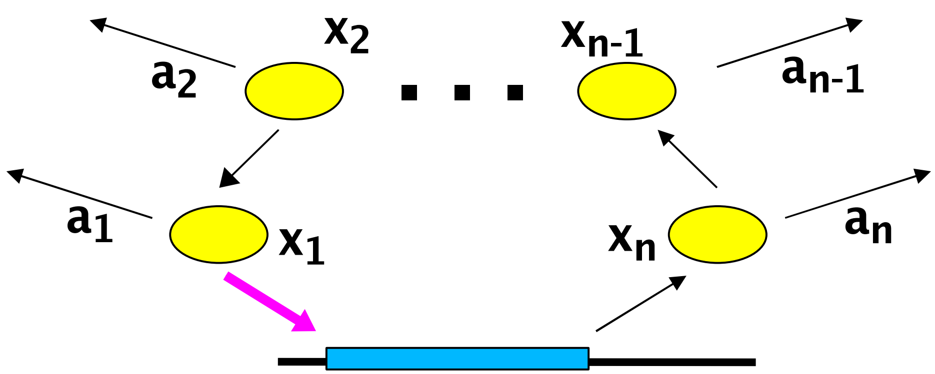
$$\frac{dx_2}{dt} = g(x_1) - bx_2$$

Tr Jacobian = − (a + b) < 0

direct negative feedback does not support sustained oscillations

potential alternatives

- indirect negative feedback (ie: more components)
- explicit accounting for time delays



$$\frac{dx_1}{dt} = x_2 - a_1 x_1$$

$$\frac{dx_2}{dt} = x_3 - a_2 x_2$$

$$\vdots \quad \vdots \quad \vdots$$

$$\frac{dx_{n-1}}{dt} = x_n - a_{n-1} x_{n-1}$$

$$\frac{dx_n}{dt} = \frac{1}{1 + x_1^p} - a_n x_n$$

there are no sustained oscillations if

$$p < \sec^n(\pi/n)$$

John Tyson, Hans Othmer
"The dynamics of feedback control circuits in biochemical pathways"
Progress in Theoretical Biology **5**:1-62 1978

potential alternatives

- indirect negative feedback (ie: more components)
- explicit accounting for time delays

Julian Lewis
"Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator"
Current Biology **13**:1398-408 2003

Nick Monk
"Oscillatory expression of Hes1, p53 and NF-kappaB driven by transcriptional time delays"
Current Biology **13**:1409-13 2003