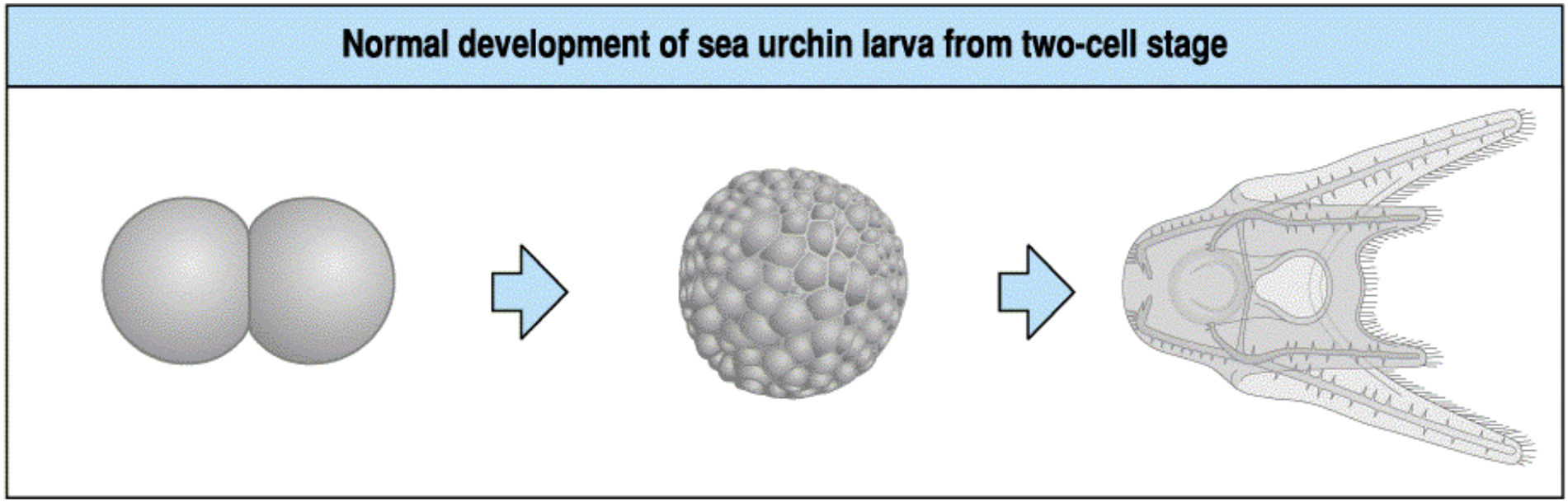
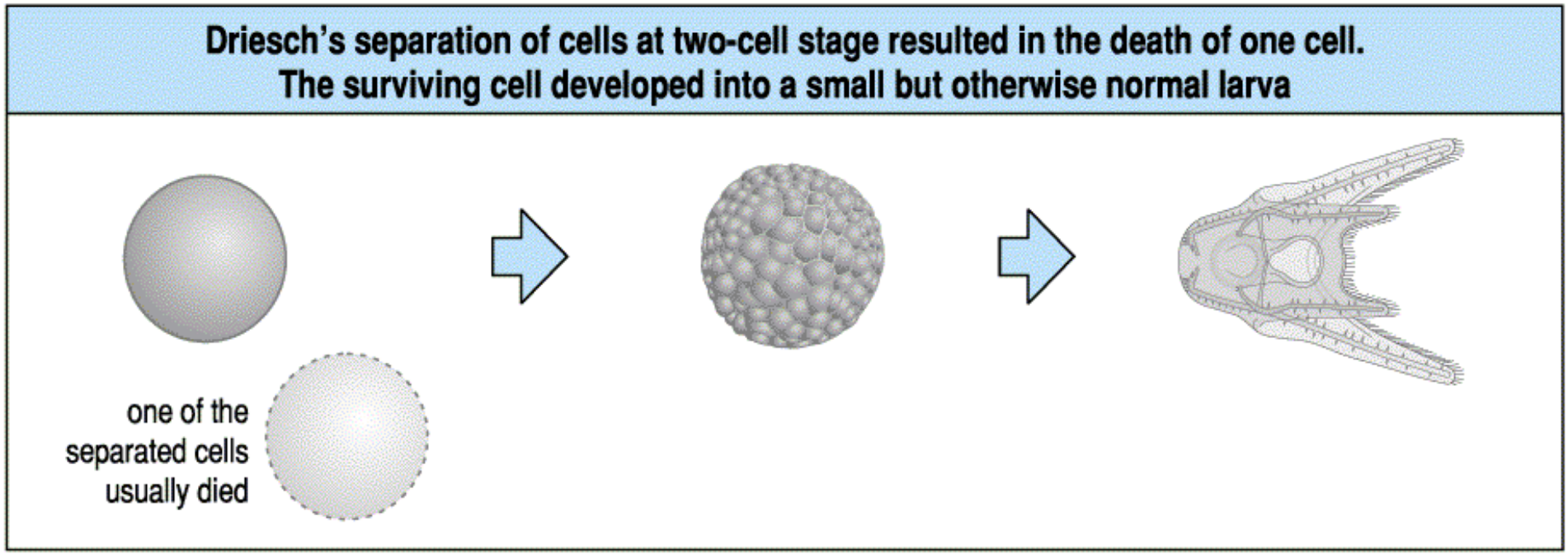
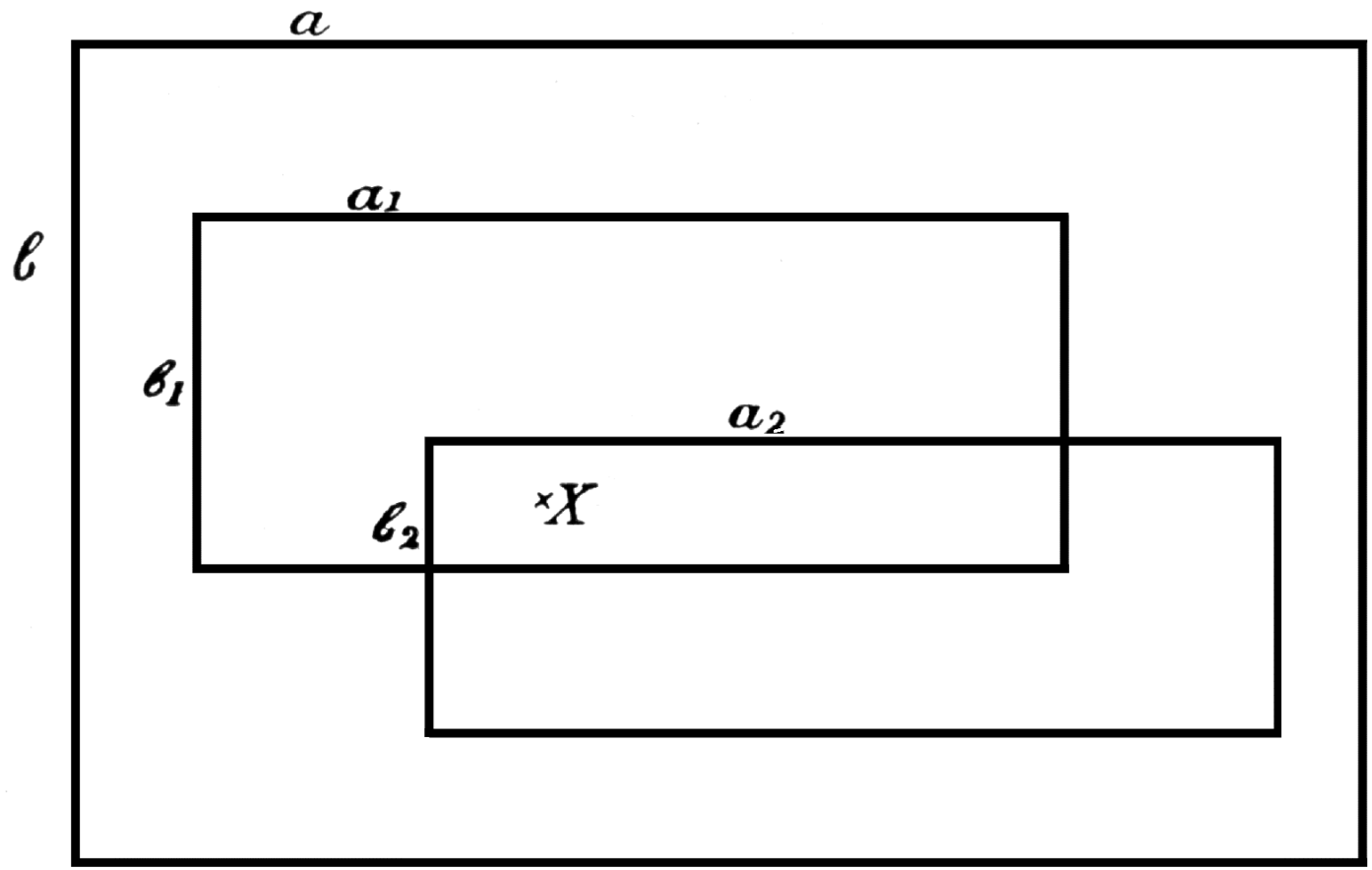
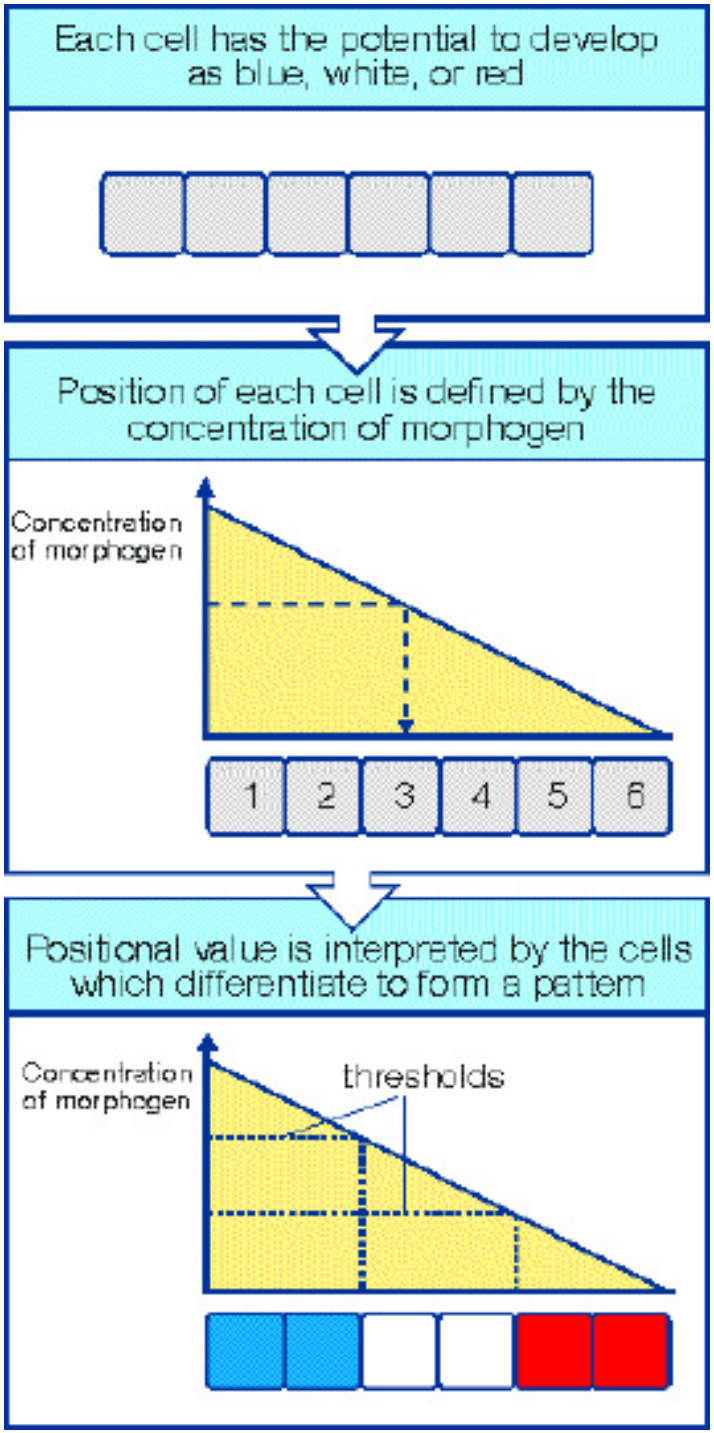
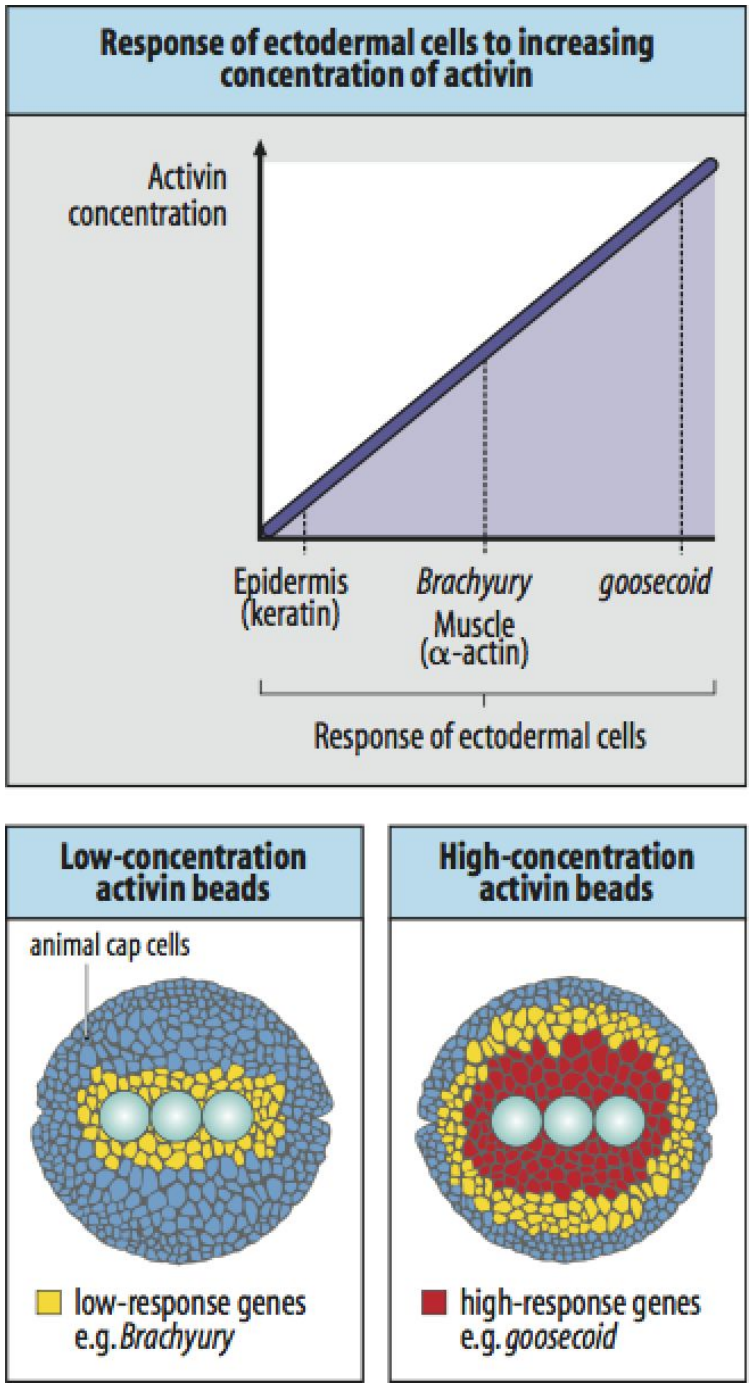

Normal development of sea urchin larva from two-cell stage

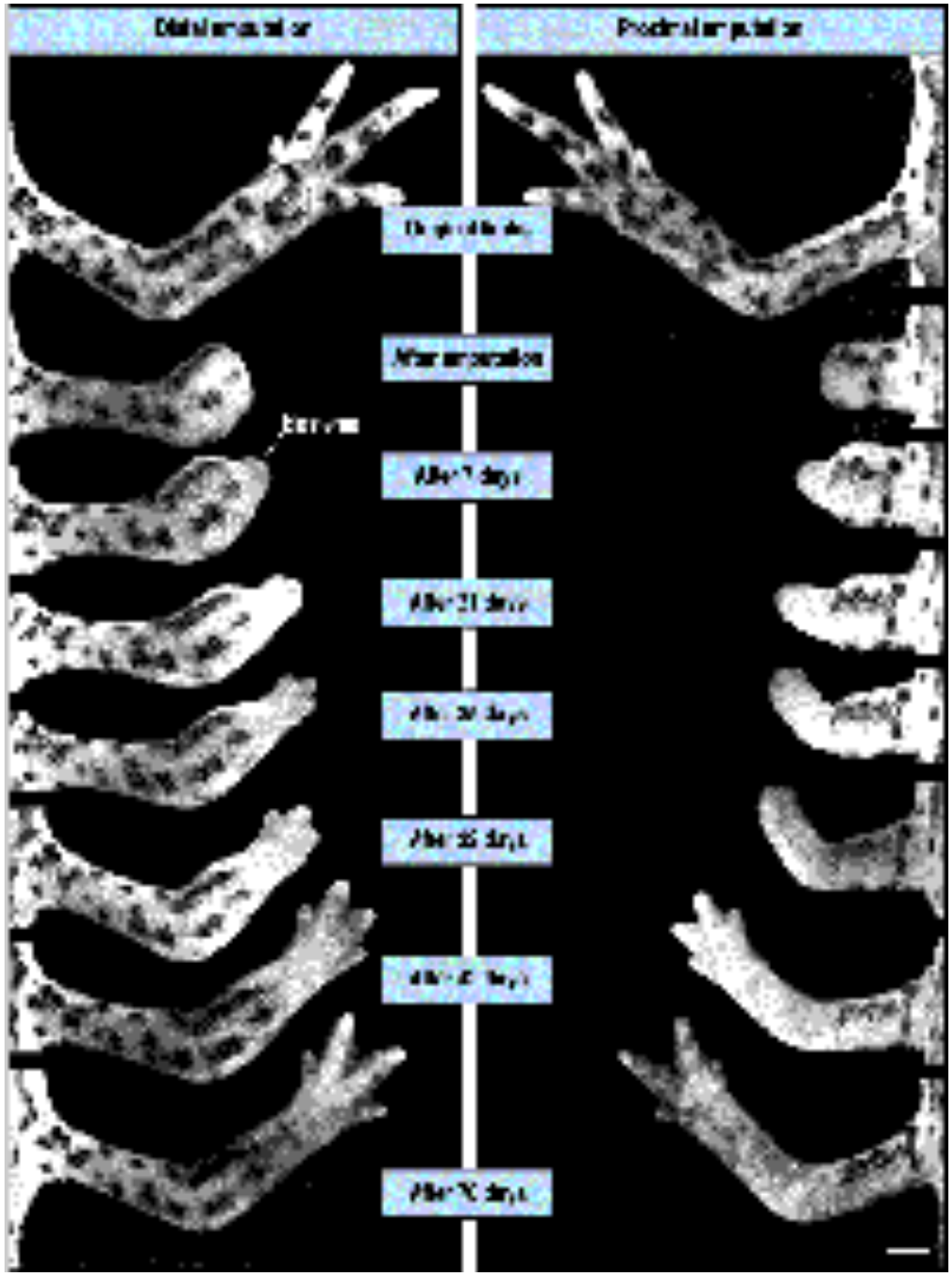

Driesch's separation of cells at two-cell stage resulted in the death of one cell.
The surviving cell developed into a small but otherwise normal larva
one of the separated cells usually died

Driesch's entelechy

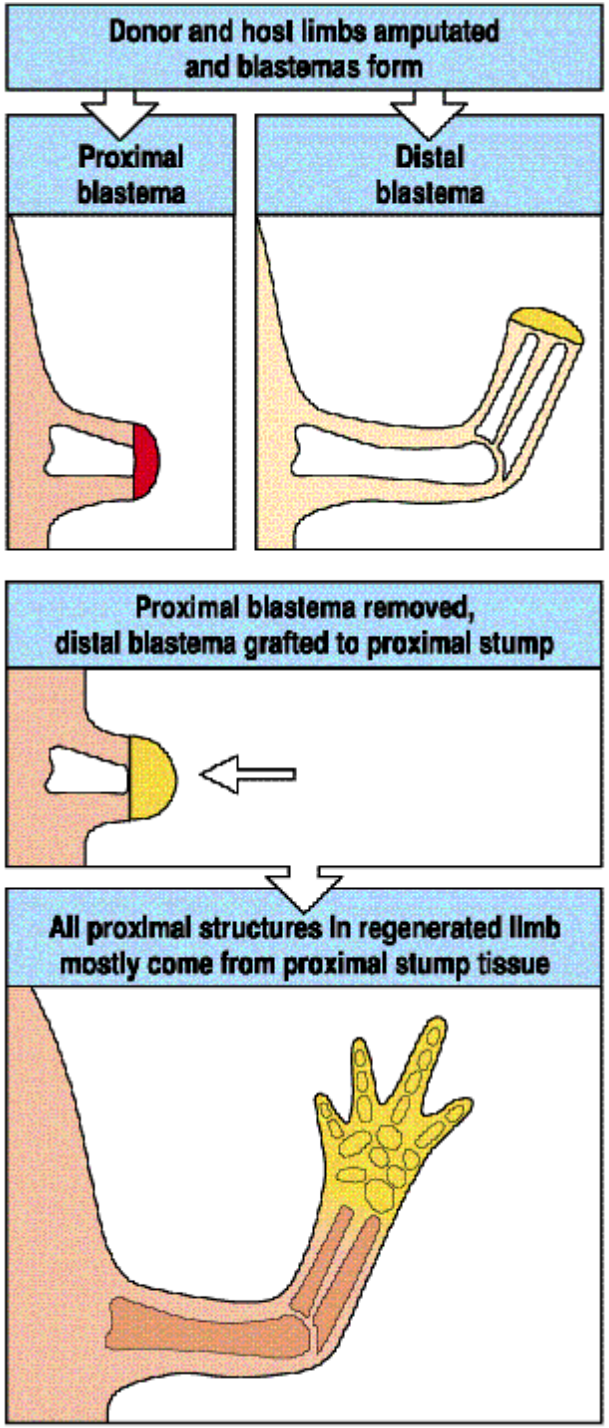



Each cell has the potential to develop as blue, white, or red
Position of each cell is defined by the concentration of morphogen
Concentration of morphogen
1
2
3
4
5
6
Positional value is interpreted by the cells which differentiate to form a pattern
Concentration of morphogen
thresholds

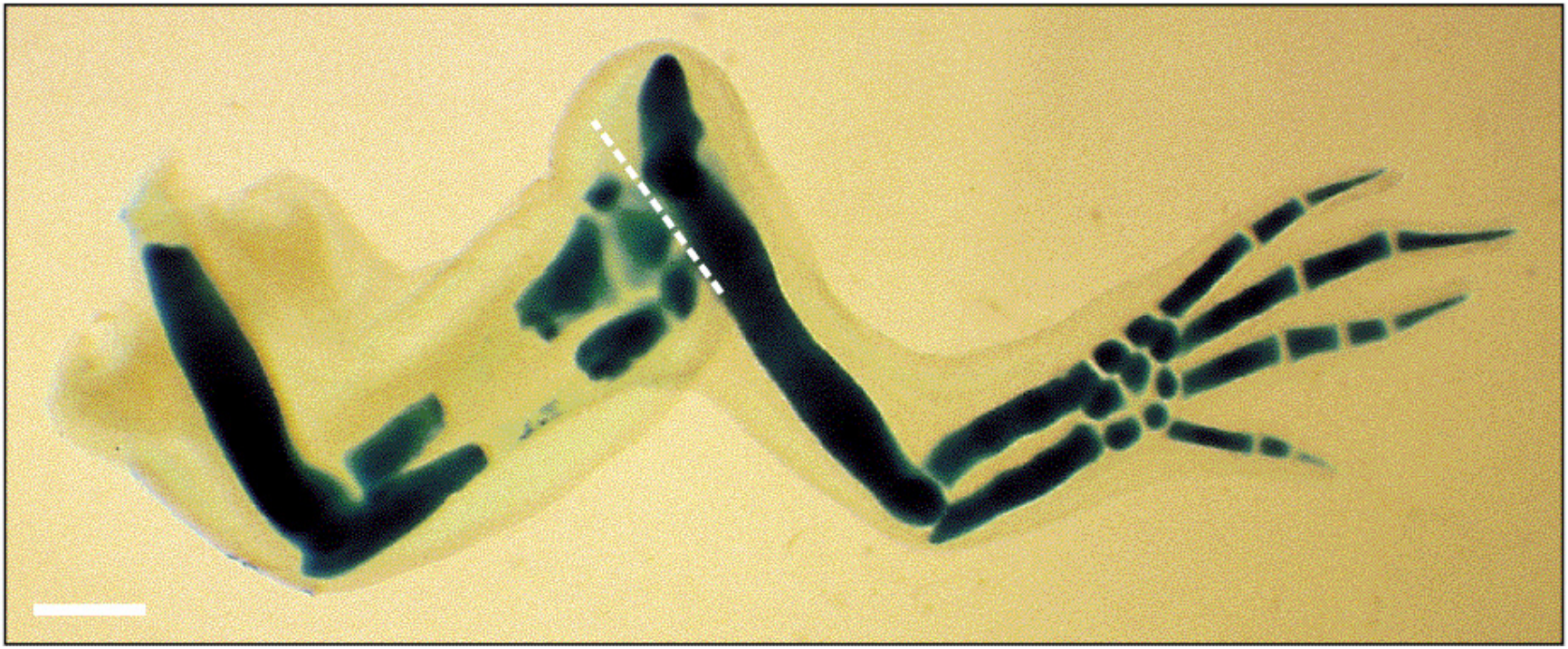

Response of ectodermal cells to increasing concentration of activin
Activin concentration
Epidermis (keratin)
Brachyury
Muscle (α-actin)
goosecoid
Response of ectodermal cells
Low-concentration activin beads
animal cap cells
low-response genes e.g. Brachyury
High-concentration activin beads
high-response genes e.g. goosecoid



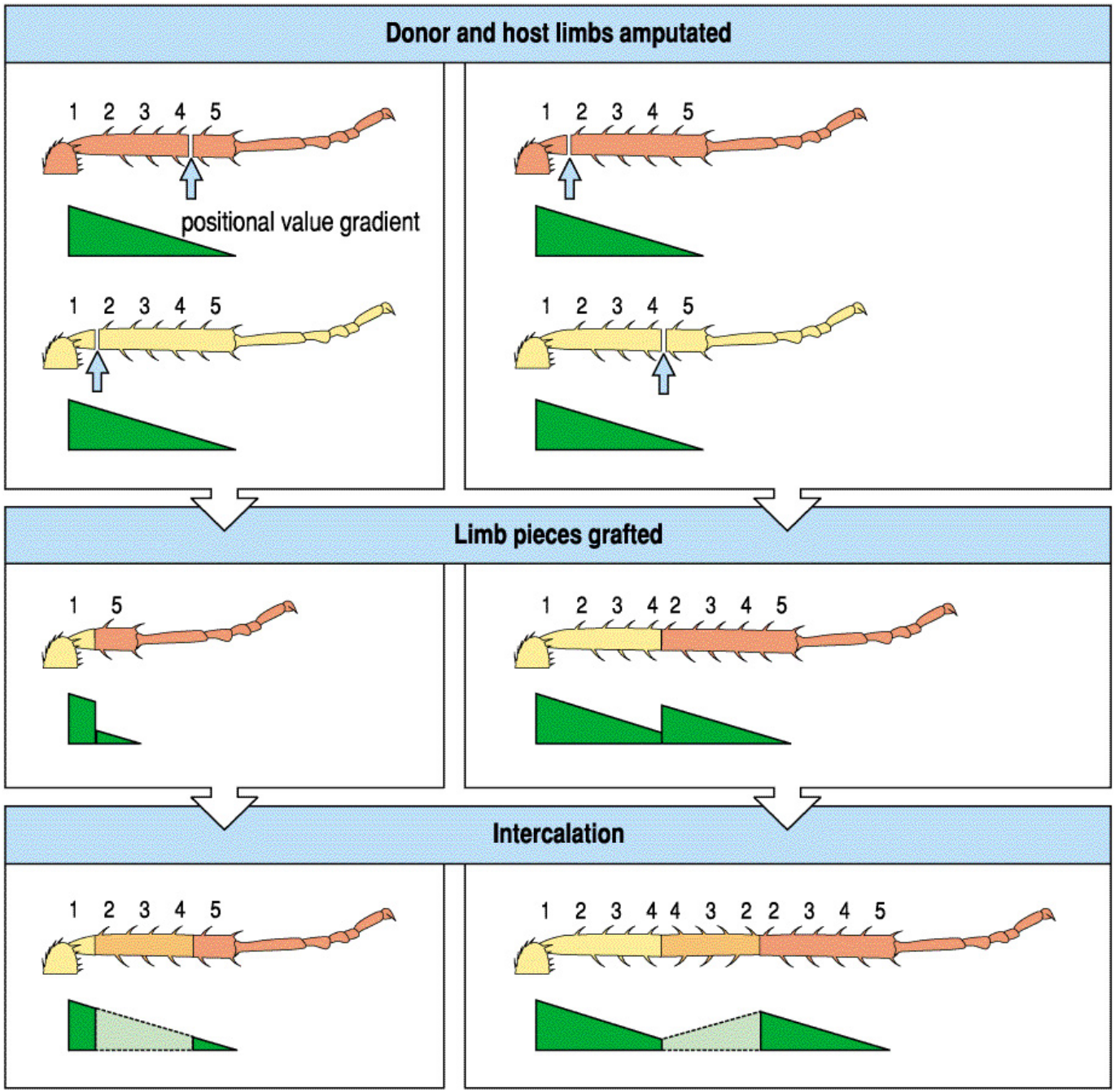
What is the molecular basis of positional values?

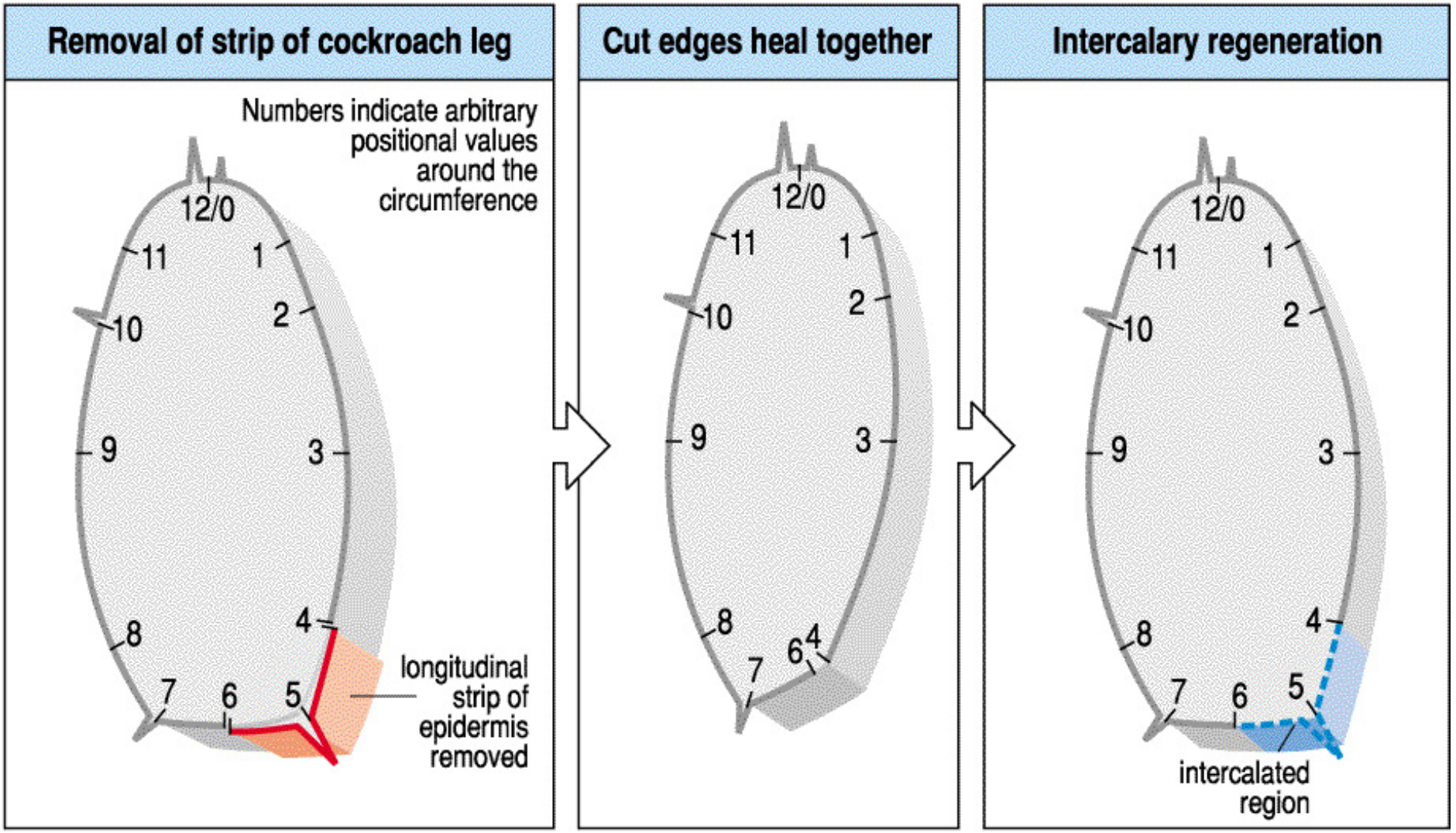


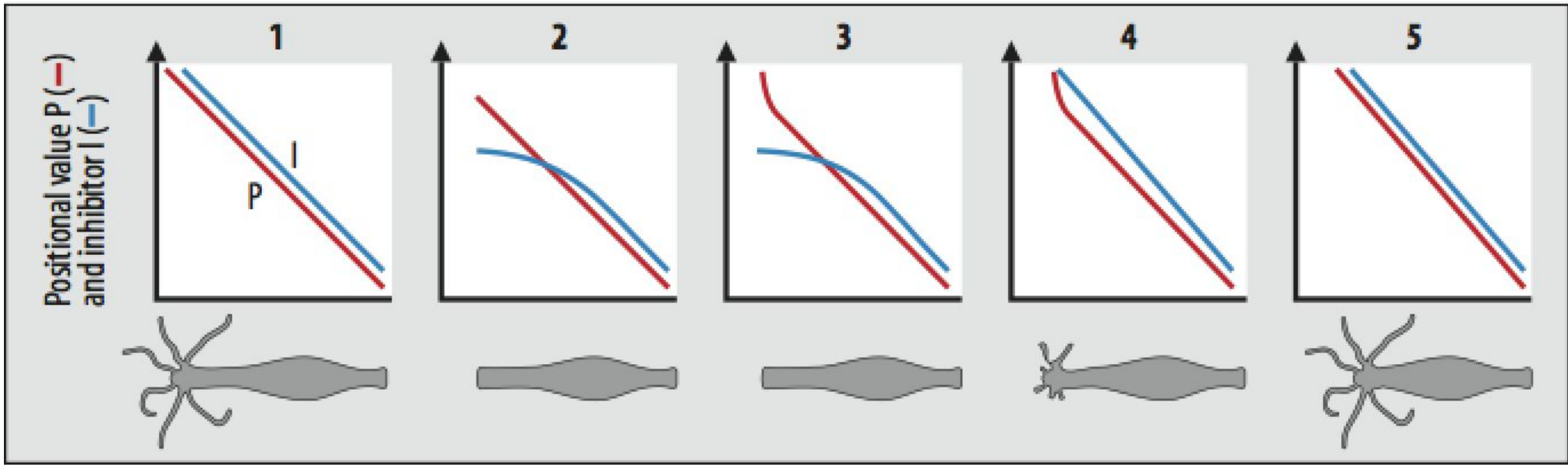
Prod 1 has a 5-fold difference along the Newt limb - this is equivalent to about a 2% difference over each cell

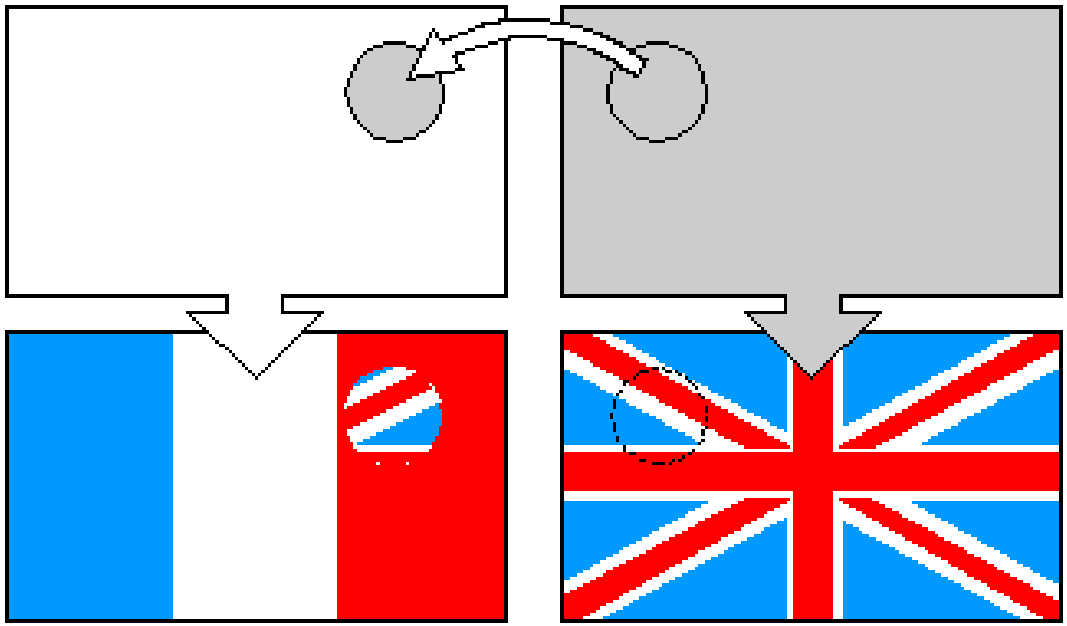


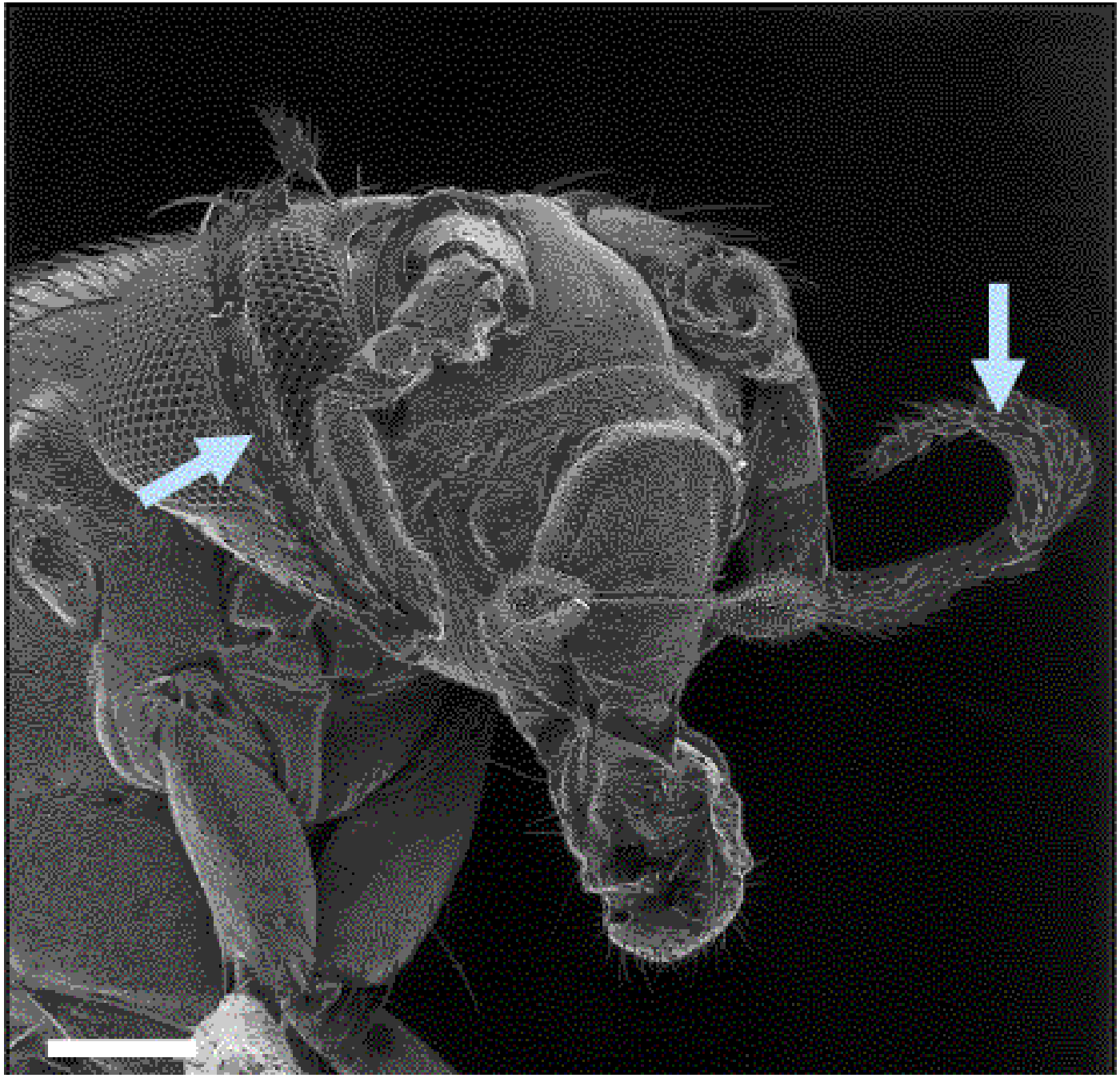
Retinoic acid alters positional values continuously


Donor and host limbs amputated
1 2 3 4 5
positional value gradient
1 2 3 4 5
1 2 3 4 5
1 2 3 4 5
Limb pieces grafted
1 5
1 2 3 4 2 3 4 5
Intercalation
1 2 3 4 5
1 2 3 4 4 3 2 2 3 4 5


Removal of strip of cockroach leg
Numbers indicate arbitrary positional values around the circumference
12/0
1
2
3
4
5
6
7
8
9
10
11
longitudinal strip of epidermis removed
Cut edges heal together
Intercalary regeneration
intercalated region

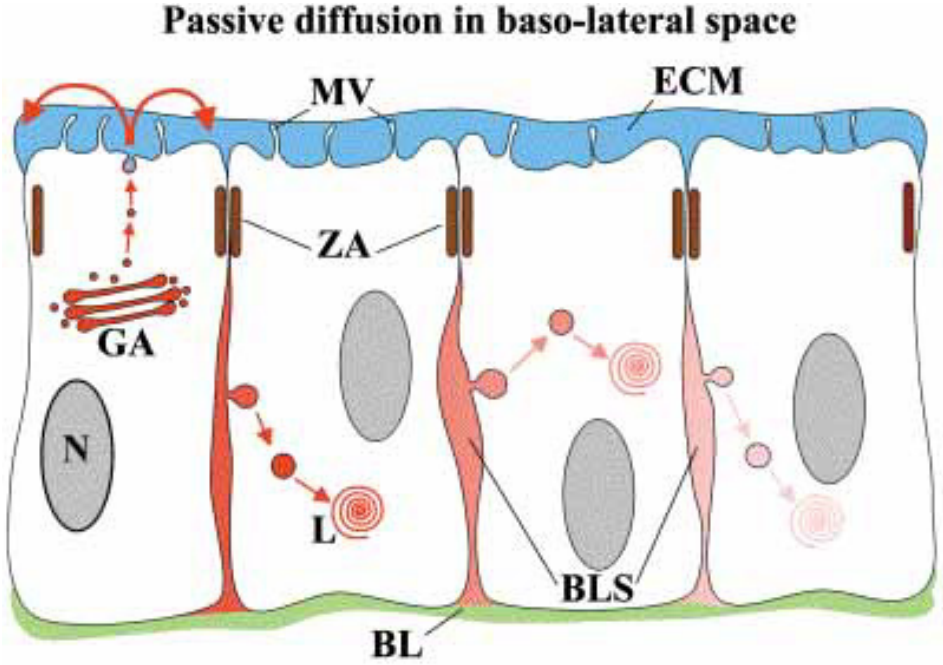

Positional value P (–)
and inhibitor I (–)
1
2
3
4
5
I
P

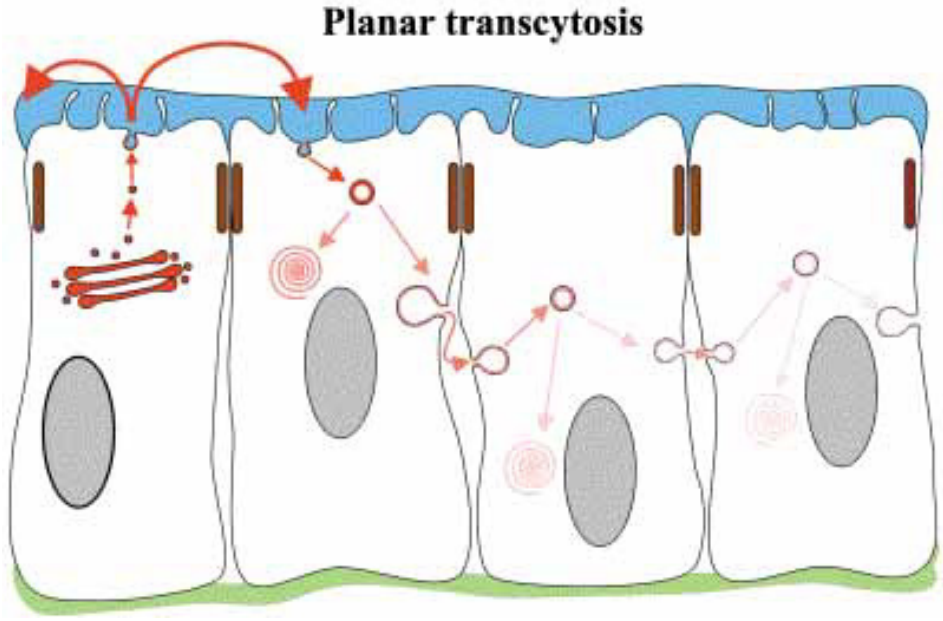


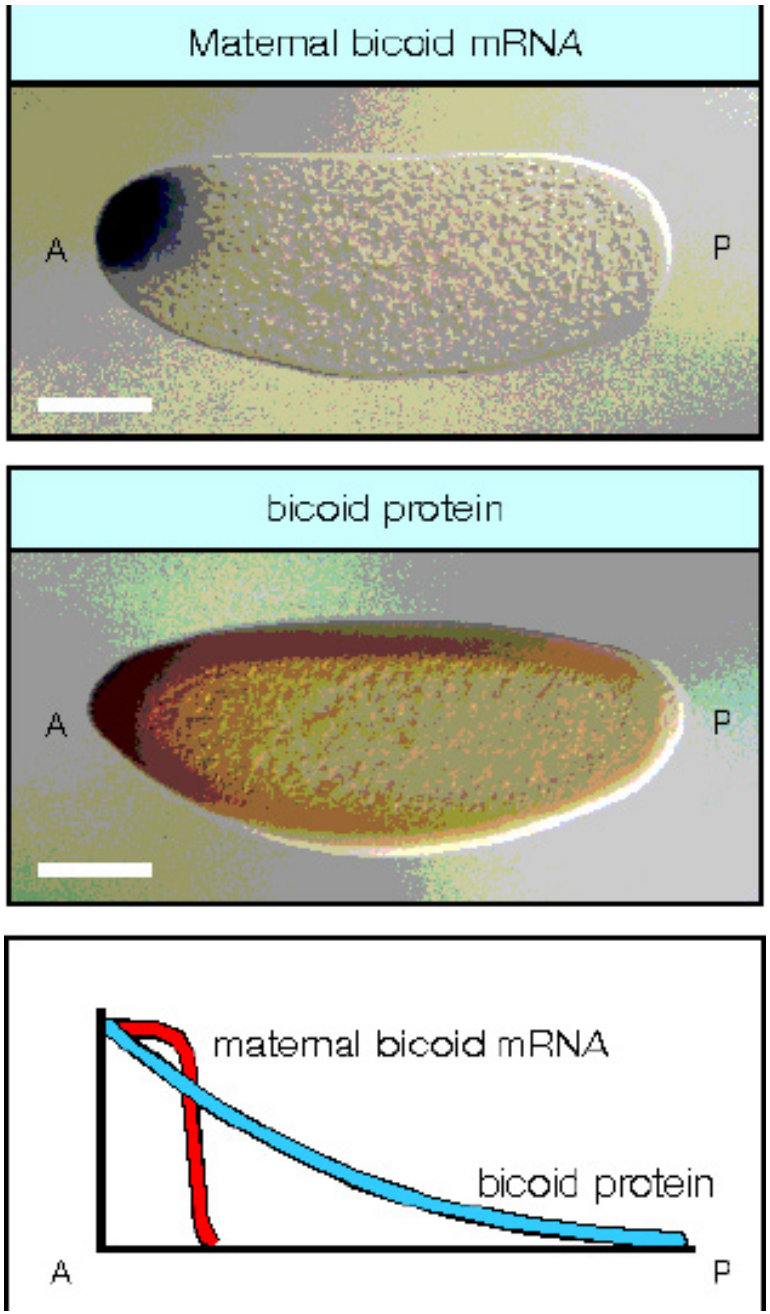


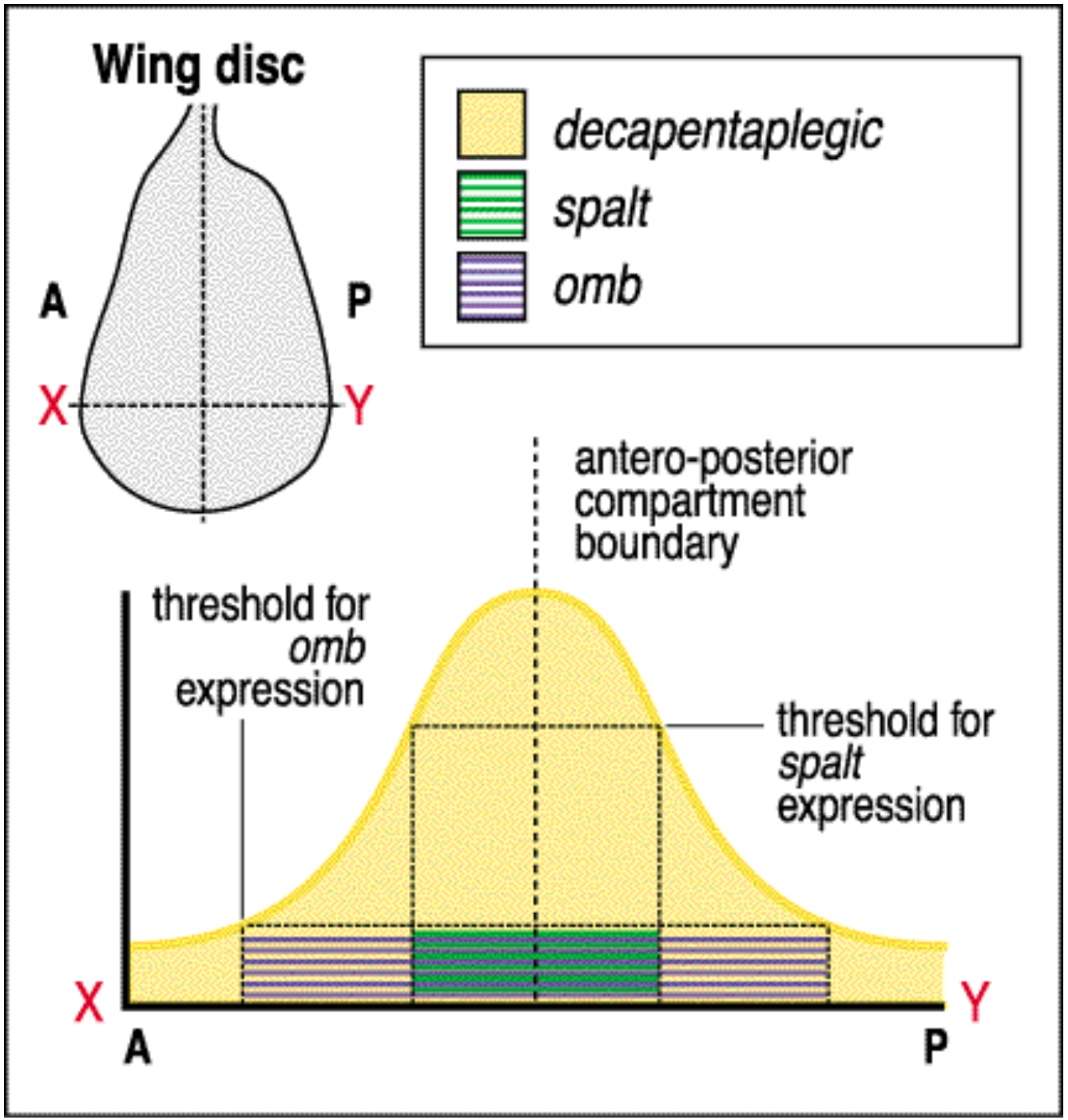
How can positional information be specified? Most models are based on diffusion of a morphogen which seems unreliable. Some models for the fly involve endocytosis and others for the limb, time.

There is no good quantitative evidence for any of the many gradients that have been described.eg.Dpp,Chordin, BMP, Hedgehog


Passive diffusion in baso-lateral space
MV
ECM
ZA
GA
N
L
BLS
BL


Planar transcytosis

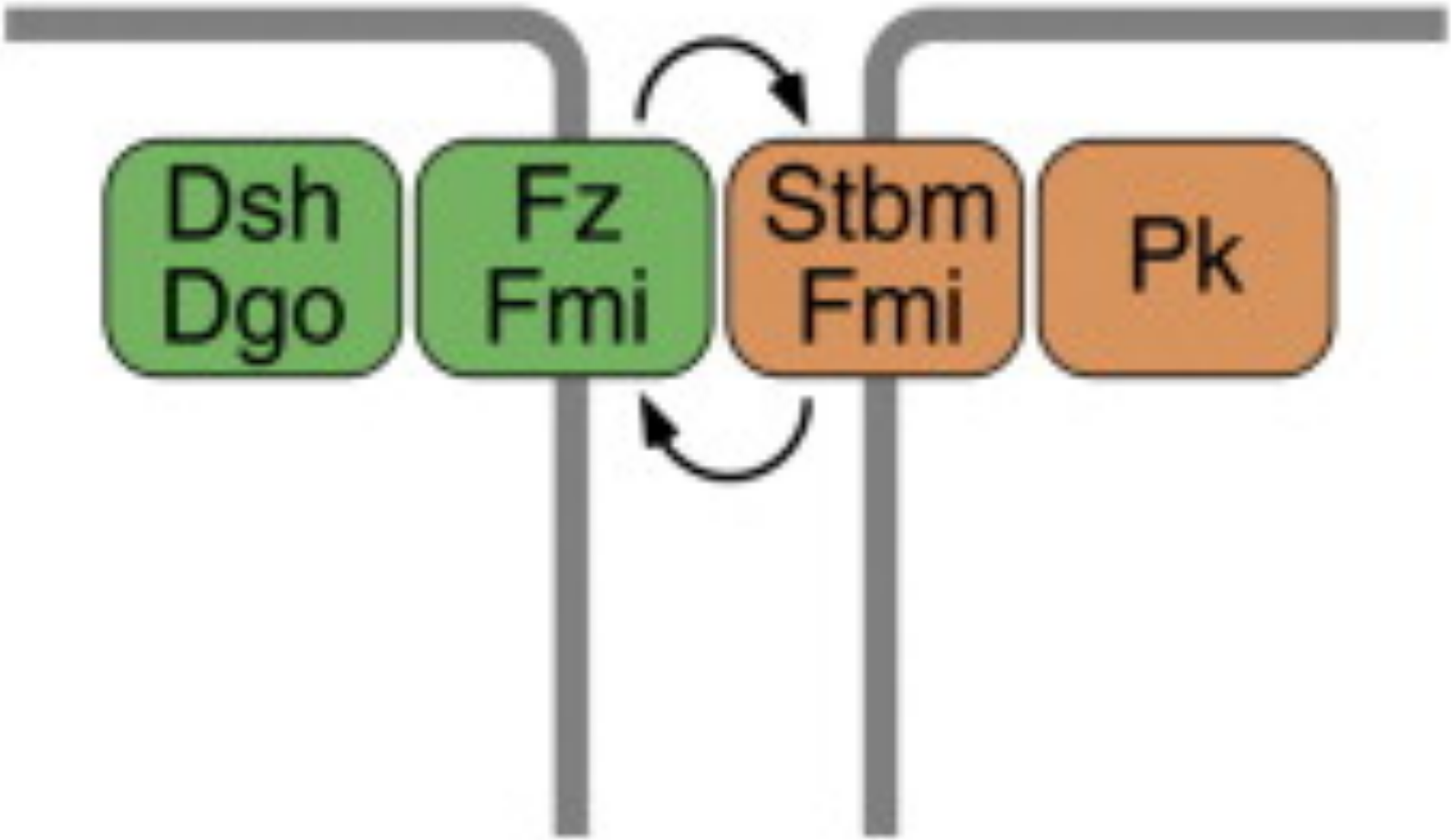

Maternal bicoid mRNA
A
P
bicoid protein
A
P
maternal bicoid mRNA
bicoid protein
A
P


Wing disc
A
P
X
Y
decapentaplegic
spalt
omb
antero-posterior
compartment
boundary
threshold for
omb
expression
threshold for
spalt
expression
X
Y
A
P

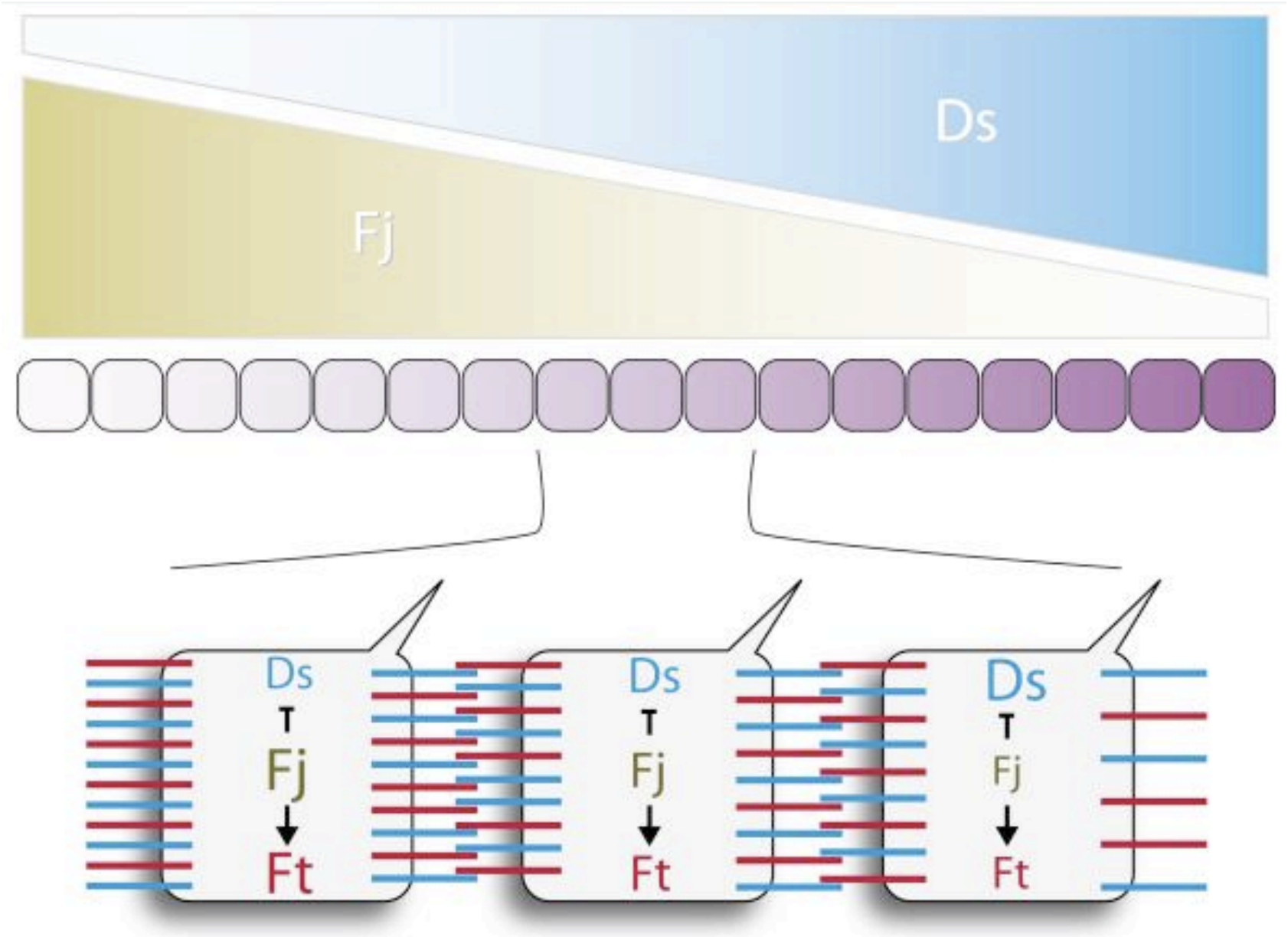
Dynamin-dependent endocytosis was required for spreading of Dpp, but not Wg.

White et.al

RA promotes and Fgf suppresses RA degradation,thereby linking the shapes of RA and Fgf gradients in zebrafish. Computational models suggest that this linkage helps make RA-mediated patterning robust.



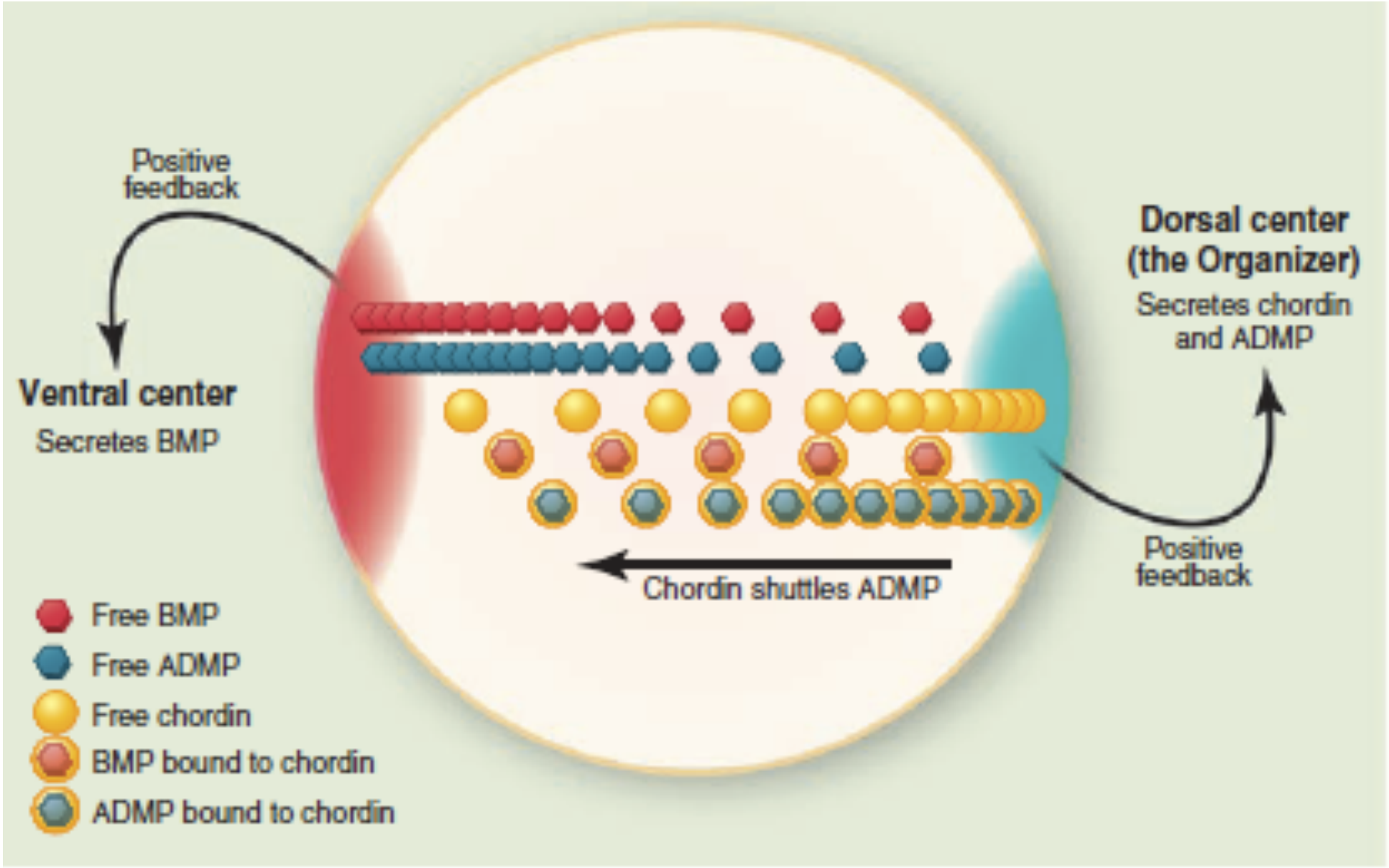
D

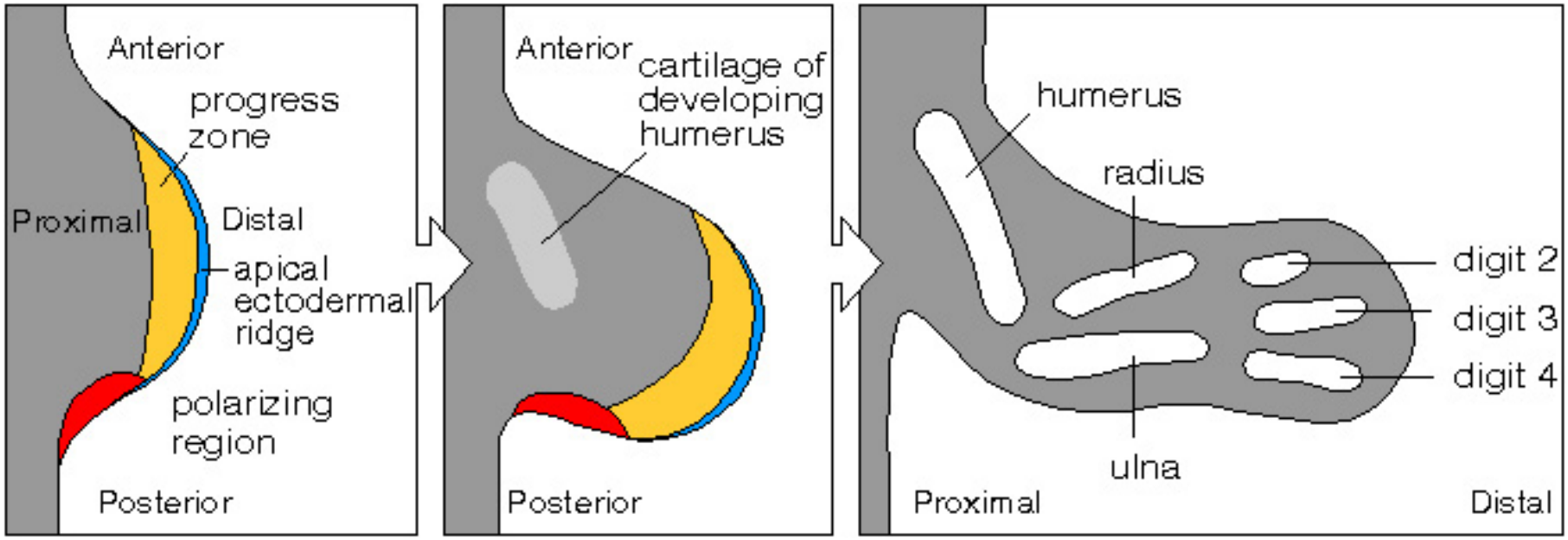

Ds
Fj
Ds
T
Fj
Ft
Ds
T
Fj
Ft
Ds
T
Fj
Ft

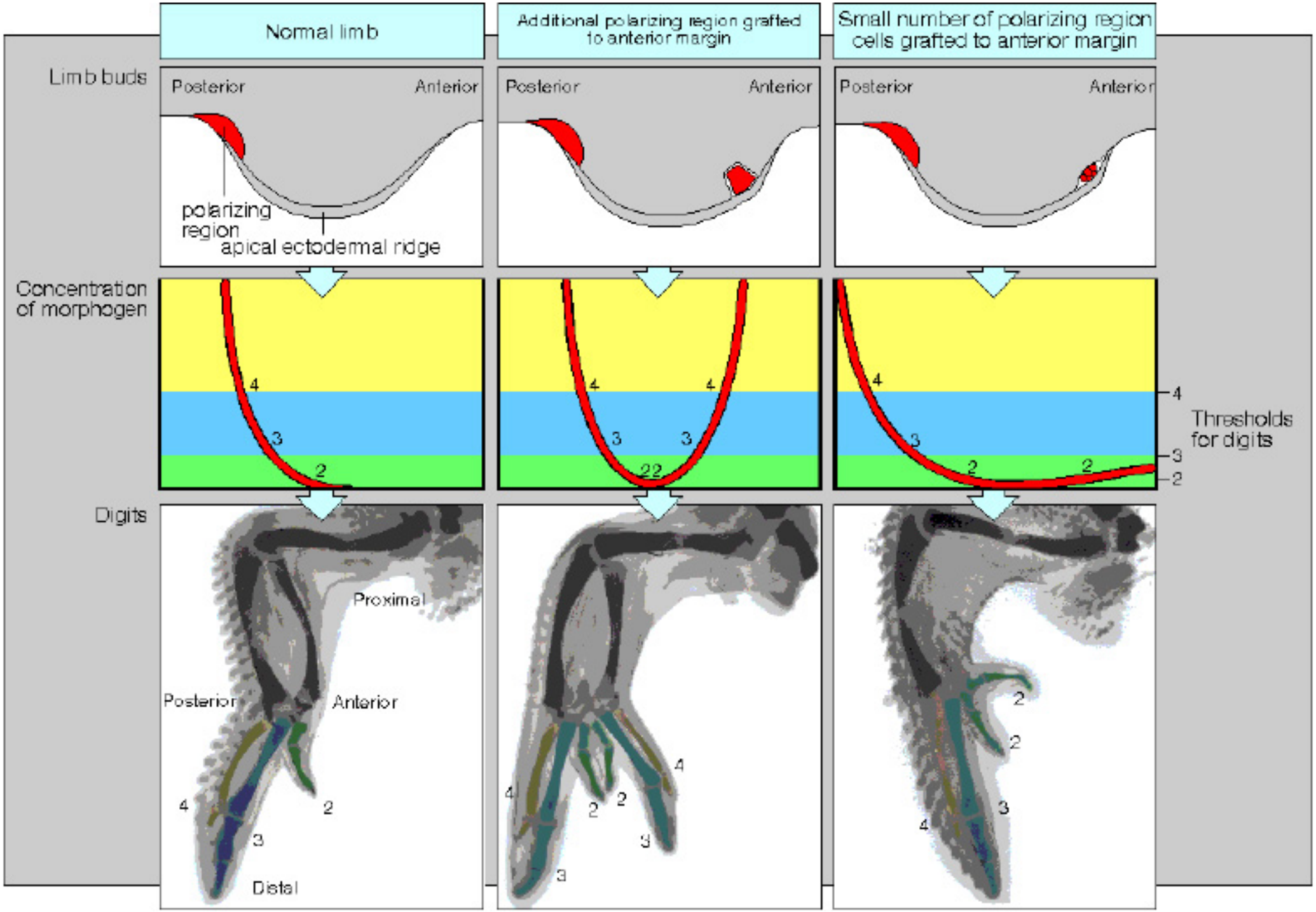
Monk

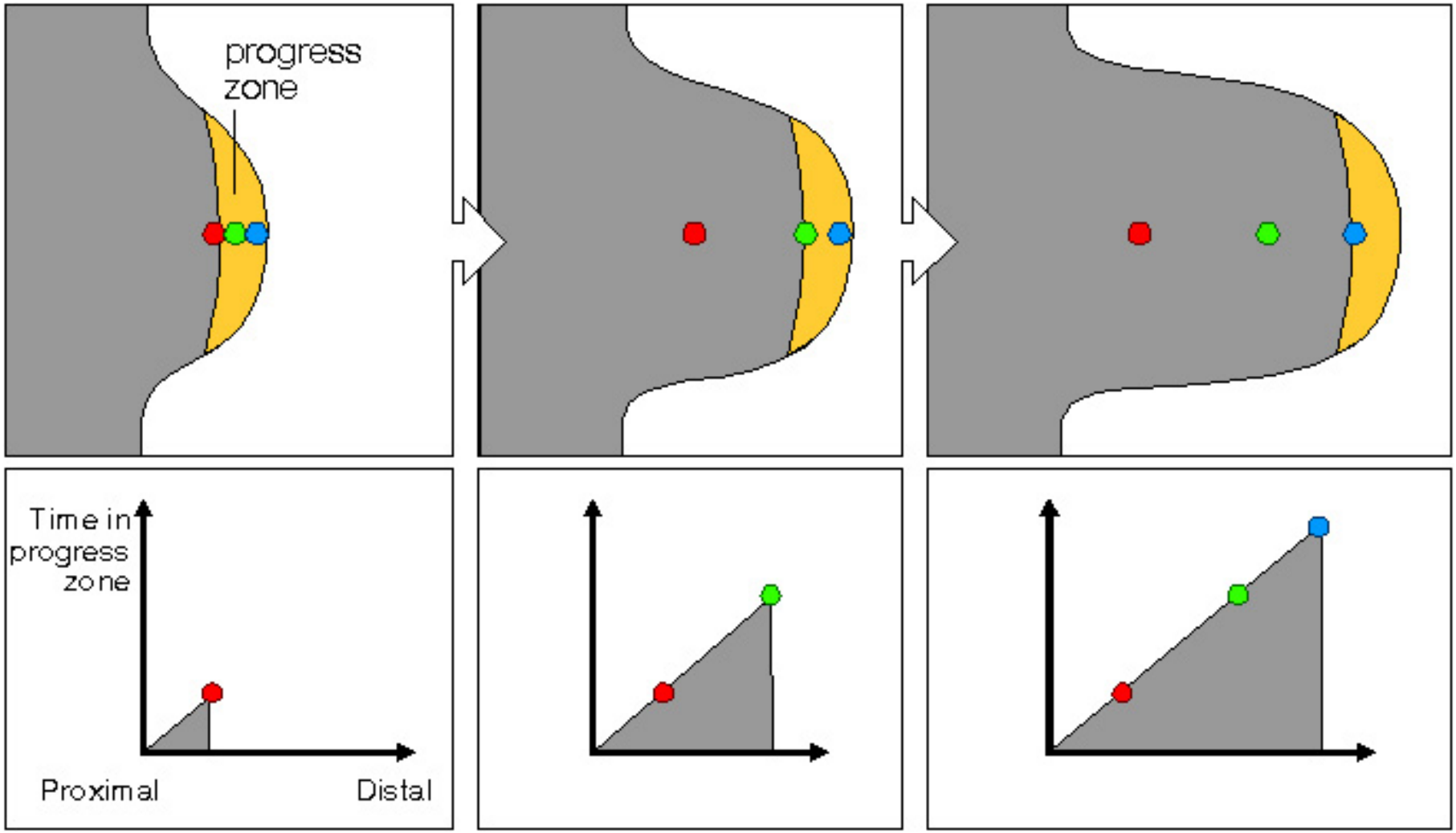
Our results predict that the regulation of Hedgehog transport and stability by glypicans, as well as multiple overlapping feedbacks in the Hedgehog response network, can combine to enhance the robustness of positional specification against variability in Hedgehog levels.

There is a scaling effect which most models of morphogens do not take into account. There are several proposed mechanisms such as two diffusible molecules that emanate from opposing poles and define the activation profile through their ratio. A model based on expansion-repression by Ben-Zvi and Barkai (2010) suggests that scaling emerges as a natural consequence of a feedback topology.

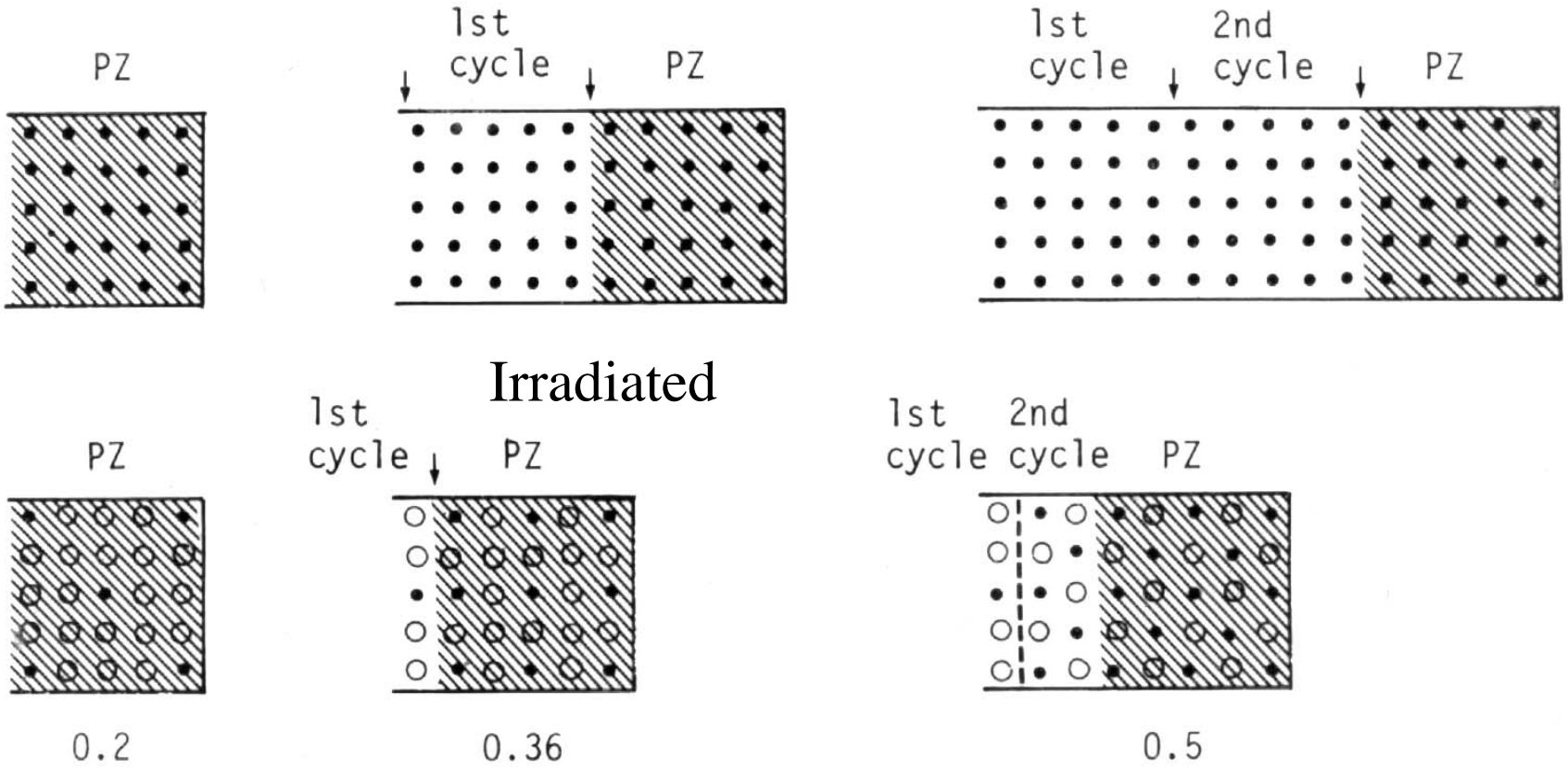

Positive feedback
Ventral center
Secretes BMP
Dorsal center (the Organizer)
Secretes chordin and ADMP
Positive feedback
Chordin shuttles ADMP
Free BMP
Free ADMP
Free chordin
BMP bound to chordin
ADMP bound to chordin


Anterior
progress zone
Proximal
Distal
apical ectodermal ridge
polarizing region
Posterior
Anterior
cartilage of developing humerus
Posterior
humerus
radius
digit 2
digit 3
digit 4
ulna
Proximal
Distal

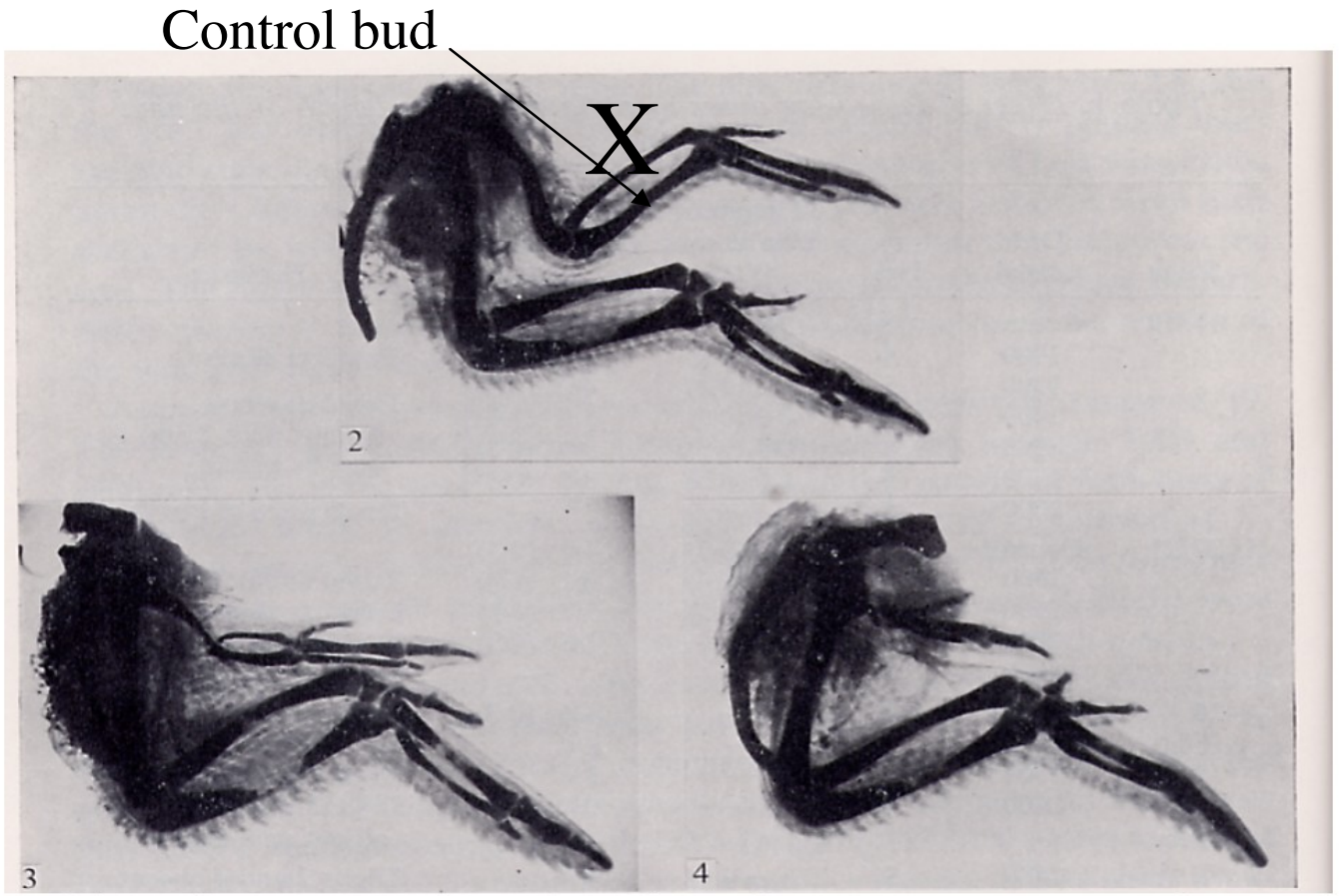

Normal limb
Additional polarizing region grafted to anterior margin
Small number of polarizing region cells grafted to anterior margin
Limb buds
Posterior
Anterior
polarizing region
apical ectodermal ridge
Concentration of morphogen
4
3
2
22
Thresholds for digits
Digits
Proximal
Distal


progress
zone
Time in
progress
zone
Proximal
Distal

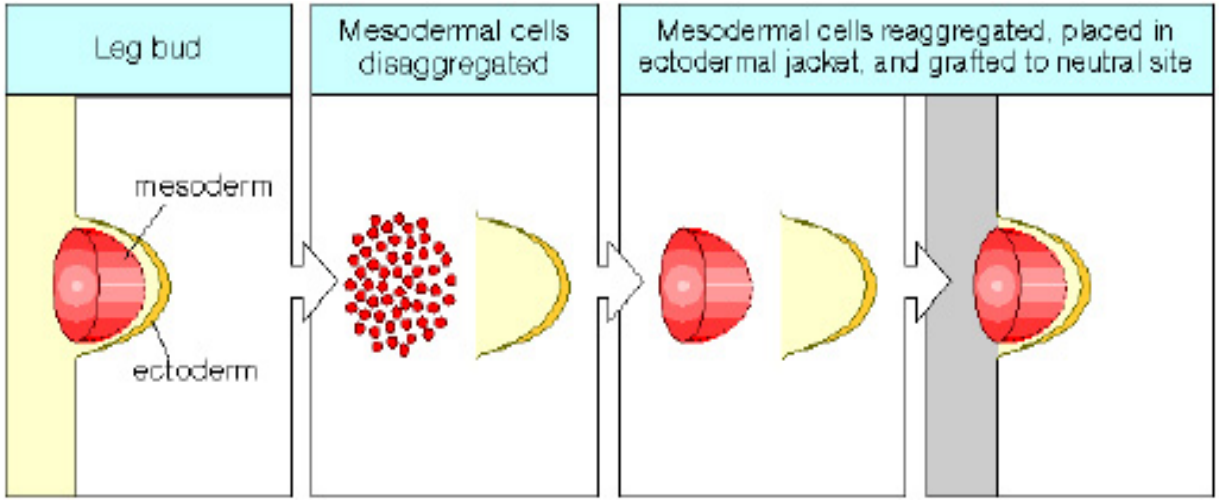
Death in the progress zone leads to loss of proximal elements

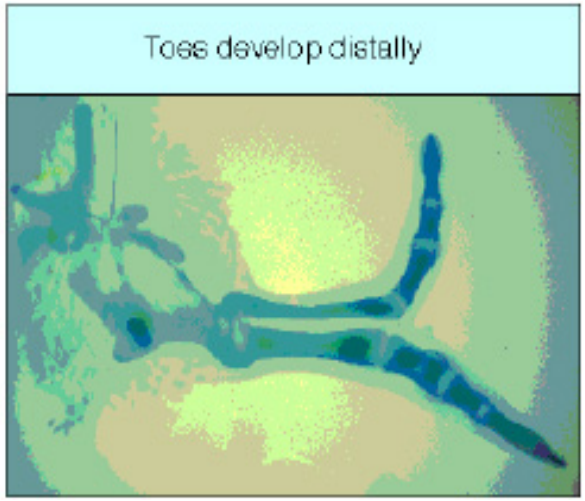


Death in the progress zone - loss proximal elements



Irradiation - proximal elements are lost


Leg bud
Mesodermal cells disaggregated
Mesodermal cells reaggregated, placed in ectodermal jacket, and grafted to neutral site
mesoderm
ectoderm


Toes develop distally


f

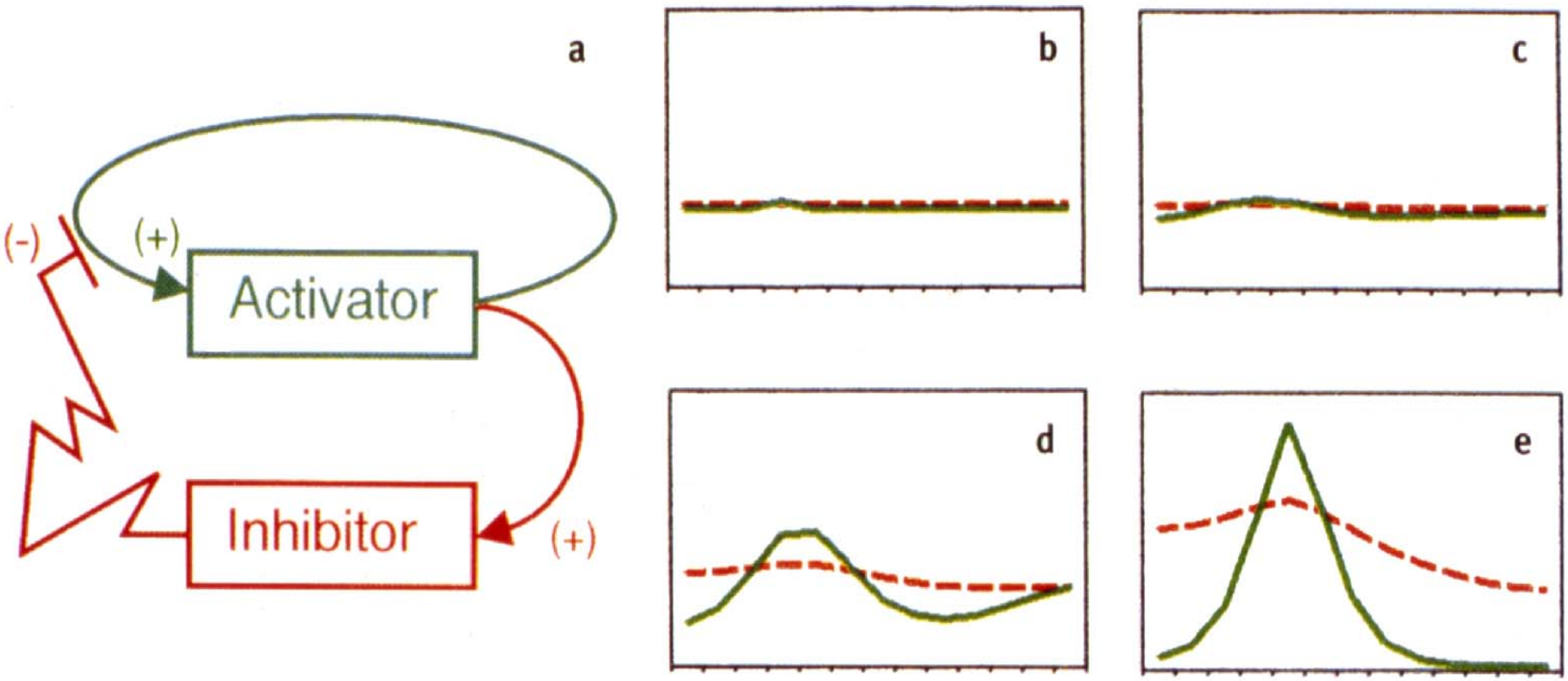
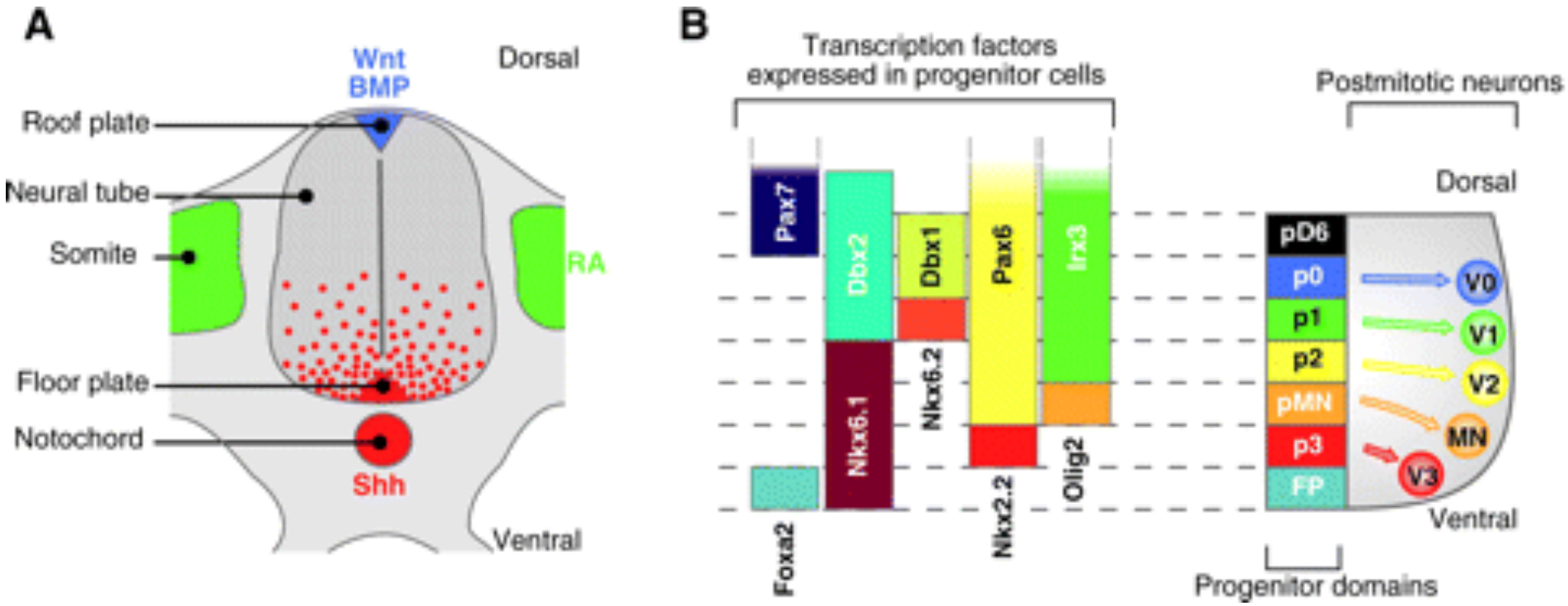


Figure 2.2. Pattern formation by autocatalysis and long-range inhibition. (a) Reaction scheme. An activator catalyses its own production and that of its highly diffusing antagonist, the inhibitor. (b-e) Stages in pattern formation after a local perturbation. Computer simulation in a linear array of cells. A homogeneous distribution of both substances is unstable. A minute local increase of the activator (—) grows further until a steady state is reached in which self-activation and the surrounding cloud of inhibitor (- - - -) are balanced [S22].

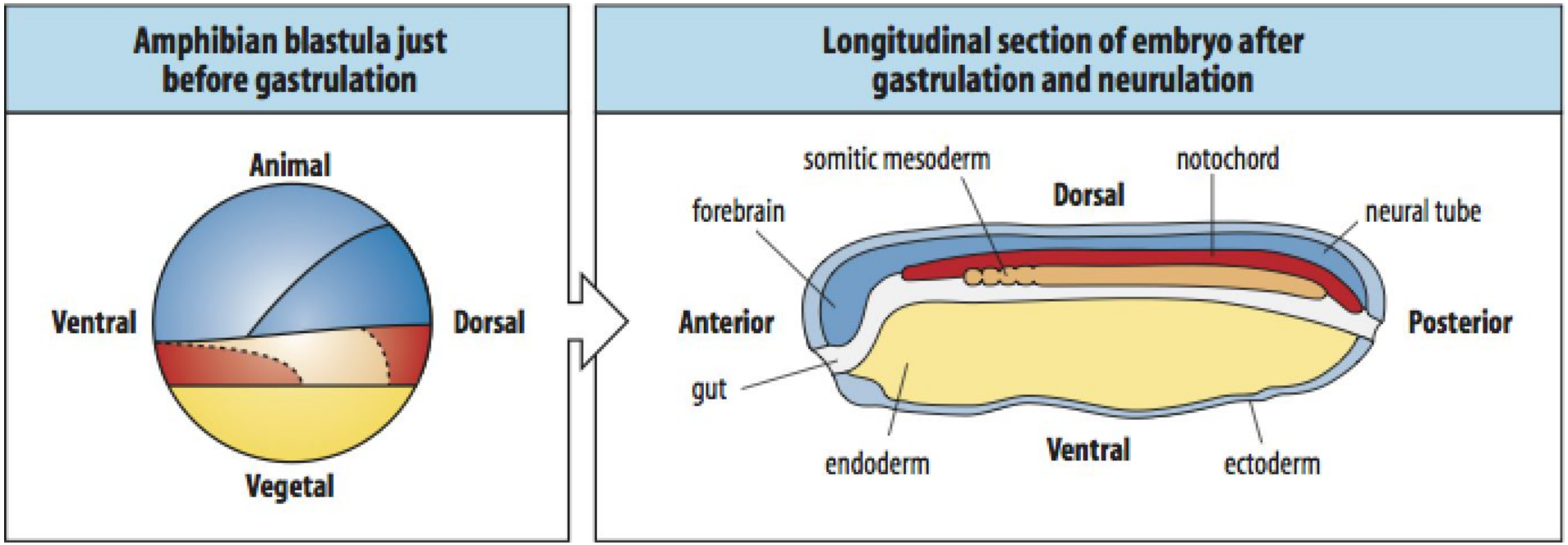
The way in which a signalling gradient regulates differential gene expression in a concentration-dependent manner raises several mechanistic issues.

The most detailed model of how gradients can be interpreted comes from how Shh signalling from the notochord assigns the positional identities of distinct neuronal subtype progenitors throughout the ventral neural tube.

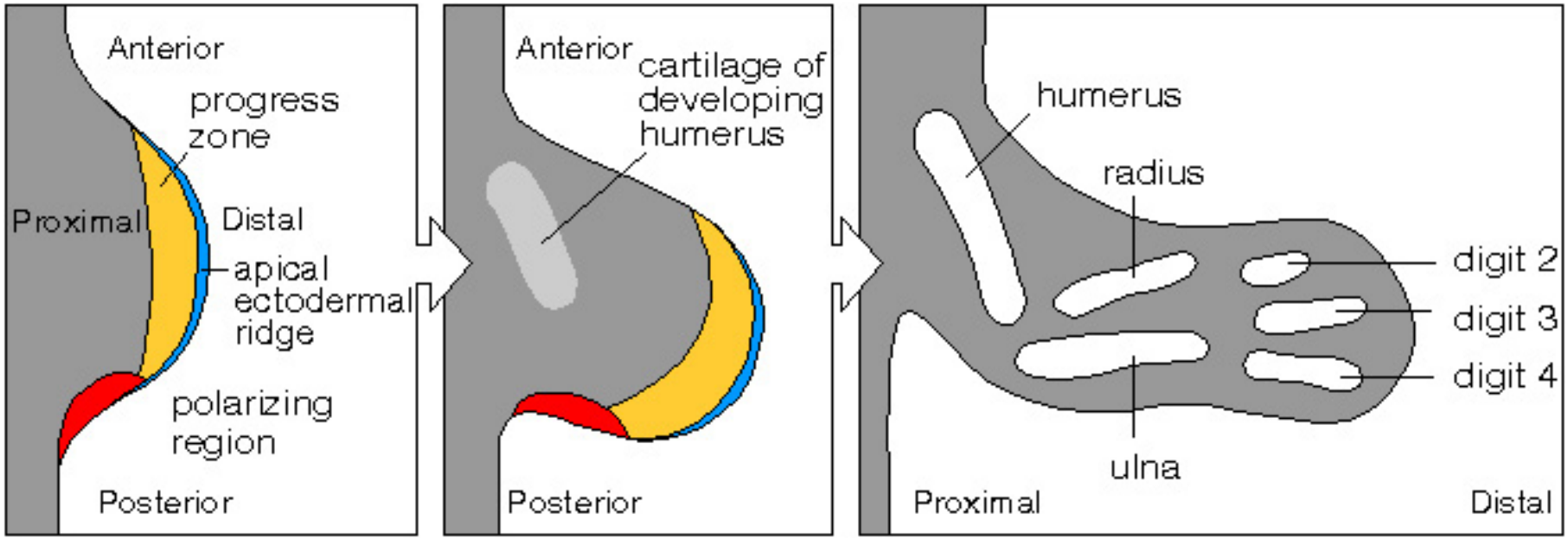
The duration of signalling is important not only for the assignment but also for the refinement and maintenance of positional identity.


A
Wnt
BMP
Dorsal
Roof plate
Neural tube
Somite
RA
Floor plate
Notochord
Shh
Ventral
B
Transcription factors
expressed in progenitor cells
Postmitotic neurons
Pax7
Dbx2
Dbx1
Pax6
Irx3
Nkx6.1
Nkx6.2
Olig2
Foxa2
Nkx2.2
Dorsal
pD6
p0
p1
p2
pMN
p3
FP
V0
V1
V2
MN
V3
Ventral
Progenitor domains
C

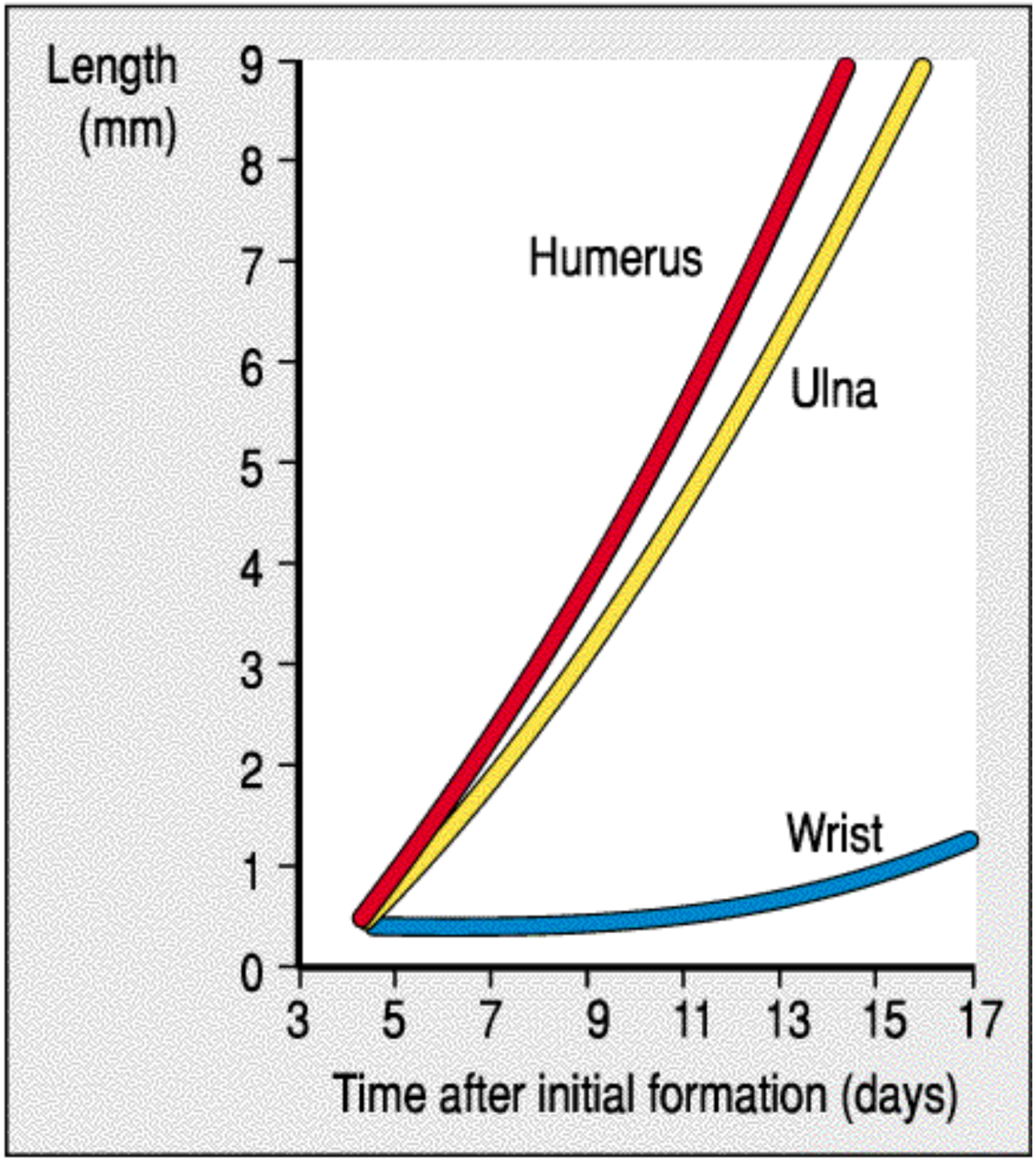
Chordin, a secreted BMP antagonist, is expressed in the dorsal region while on the opposite side BMPs
are expressed at high levels. Wnt signals are strong in the posterior region and weaken anteriorly. Cells at different positions within these two Cartesian axes may read these morphogen gradients.

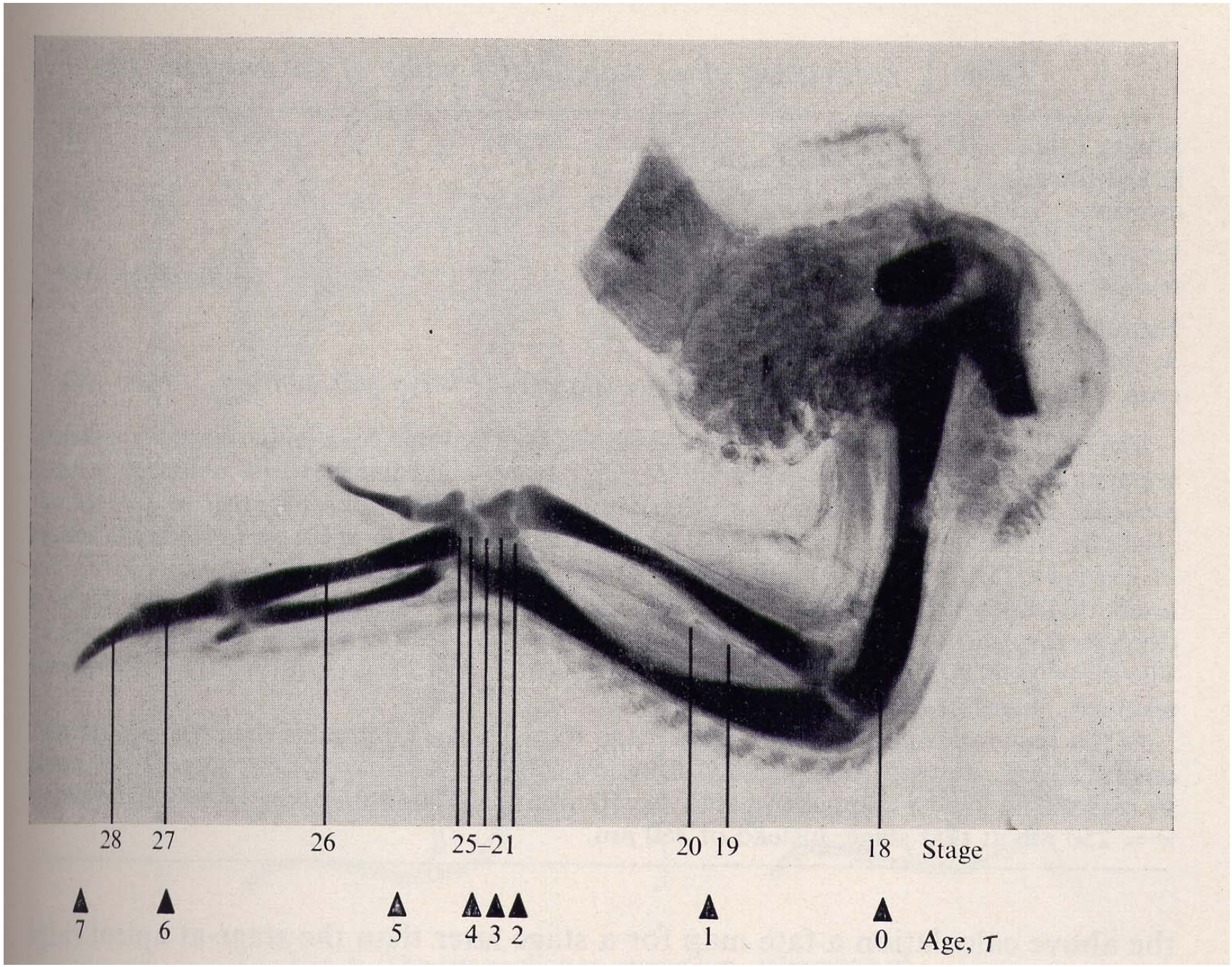

Amphibian blastula just before gastrulation
Animal
Ventral
Dorsal
Vegetal
Longitudinal section of embryo after gastrulation and neurulation
somitic mesoderm
notochord
Dorsal
forebrain
neural tube
Anterior
Posterior
gut
endoderm
Ventral
ectoderm

There is however, no good evidence for the quantitative aspects of any of the gradients just described, or details how they are set up.


Anterior
progress zone
Proximal
Distal
apical ectodermal ridge
polarizing region
Posterior
Anterior
cartilage of developing humerus
Posterior
humerus
radius
digit 2
digit 3
digit 4
ulna
Proximal
Distal

Growth limb elements




28
27
26
25–21
20
19
18
Stage
7
6
5
4
3
2
1
0
Age, τ