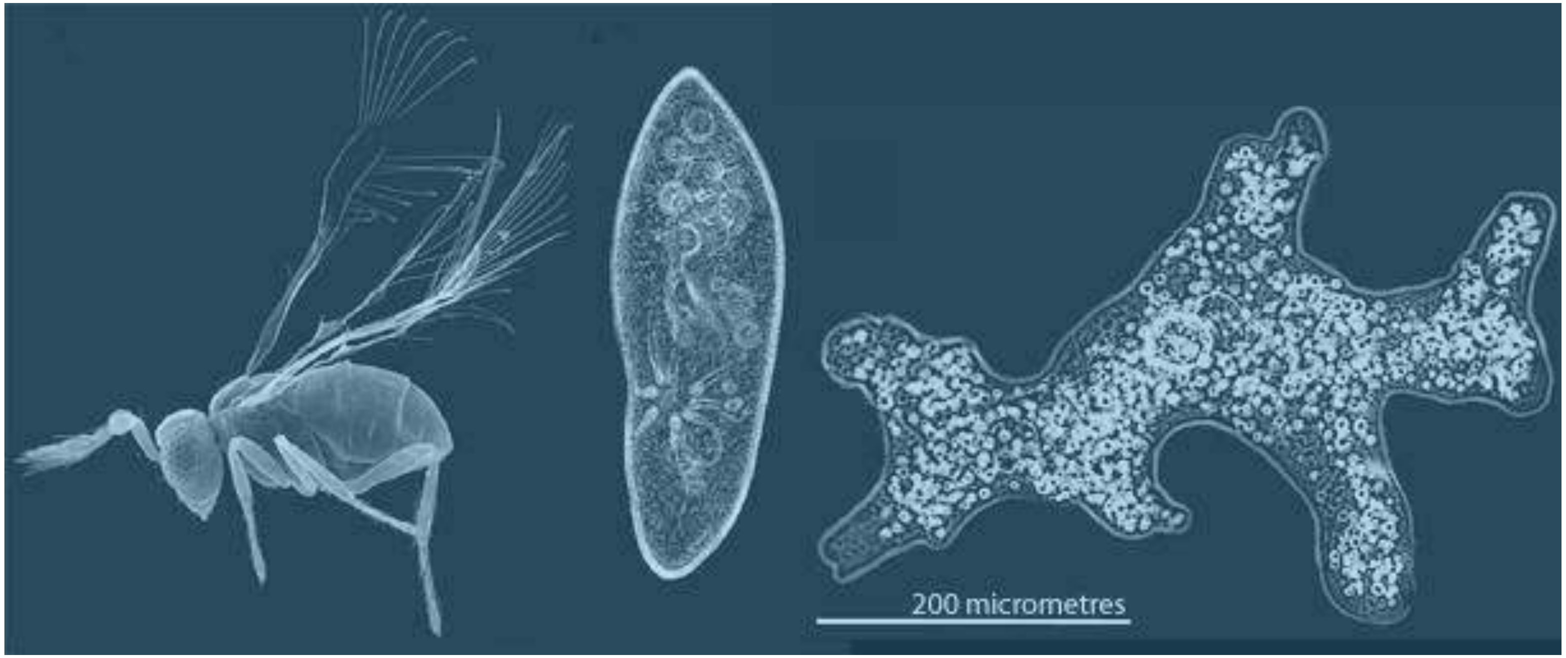
How are growth and biological size encoded?



Course 1: Introduction

Thomas Lecuit
chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

Development as an Unfolding and Growth process

- Preformationism:

Development is an unfolding (entwicklung, déploiement) process, associated with growth.

The unfolding and growth is explained mechanically

Forms are not mechanically explained (creationism)

230 ESSAY DE DIOPTRIQUE.

que la tête feroit peut-être plus grande à proportion du reſte du corps, qu'on ne l'a deſſinée icy.

ART. XC.

Au reſte, l'œuf n'eſt à proprement parler que ce qu'on appelle *placenta*, dont l'enfant, aprés y avoir demeuré un certain temps tout courbé & comme en peloton, briſe en s'étendant & en s'allongeant le plus qu'il peut, les membranes qui le couvroient, & poſant ſes pieds contre le *placenta*, qui reſte attaché au fond de la matrice, ſe pouſſe ainſi avec la tête hors de ſa priſon ; en quoi il eſt aidé par la mere, qui agitée par la douleur qu'elle en ſent, pouſſe le fond de la matrice en bas, & donne par conſequent d'autant plus d'occaſion à cet enfant de ſe pouſſer dehors & de venir ainſi au monde.

L'experience nous apprend que beaucoup d'animaux ſortent à peu prés de cette maniere des œufs qui les renferment.

ART. XCI.

L'on peut pouſſer bien plus loin cette nouvelle penſée de la generation, & dire que chacun de ces animaux mâles, renferme lui-même une infinité d'autres

Nicolaas Hartsoeker (1656-1725)

Development as a gradual Elaboration of Form

- Epigenesis:

William Harvey (1578-1657).
Gradual elaboration of biological forms.
Follows a finalist, vitalist philosophy (inspired form Aristotelian entelechy)

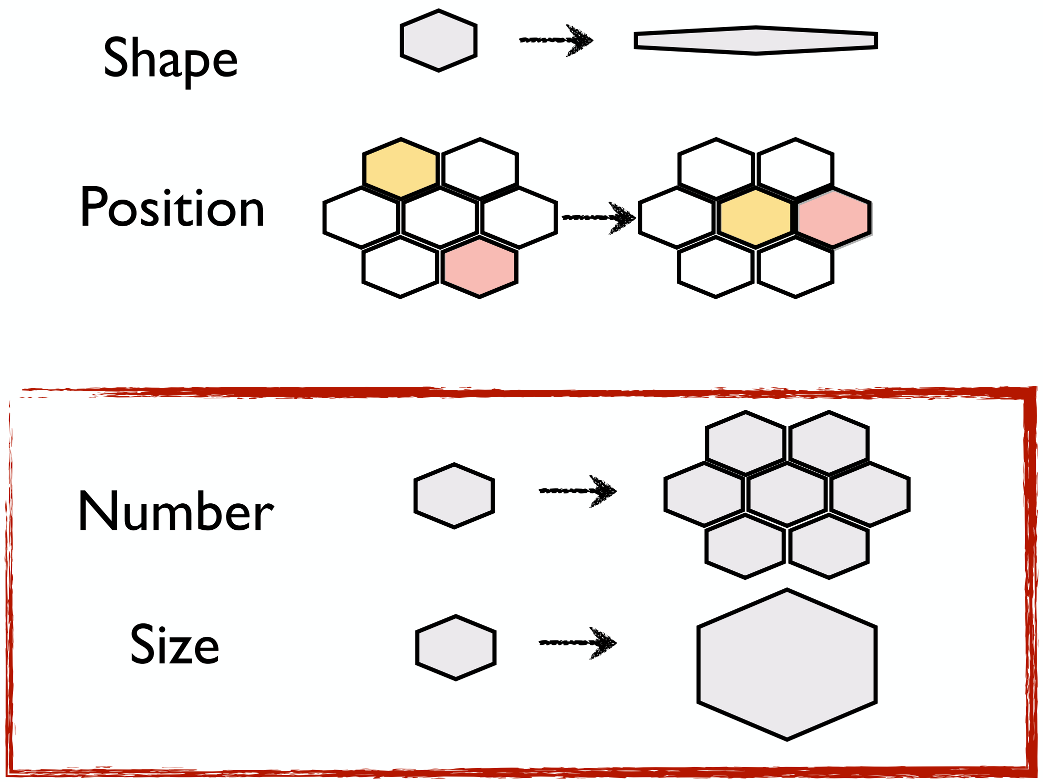
In generatione per *metamorphosin*, quasi sigillo impresso, vel pro-
plasmate concinnata finguntur; materia scilicet tota transformata.
Animal autem, quod per *epigenesin* procreatur, materiam simul attra-
hit, parat, concoquit, & eadem utitur: formatur simul, & augetur.

« un animal qui est créé par *épigénèse*, attire, prépare, élabore et utilise le matériau tout à la fois ; **les processus de formation et de croissance se produisent en même temps**. »

Exercitationes de Generatione Animalium
Exercitatio 44. Londres 1651
William Harvey

• Development: Encoding Shape and Size

- 2017-2018: How shape is encoded by Genes, Mechanics and Geometry
- 2018-2019: How size is encoded by Genes, Energy, Mechanics and Geometry



→ Deformation

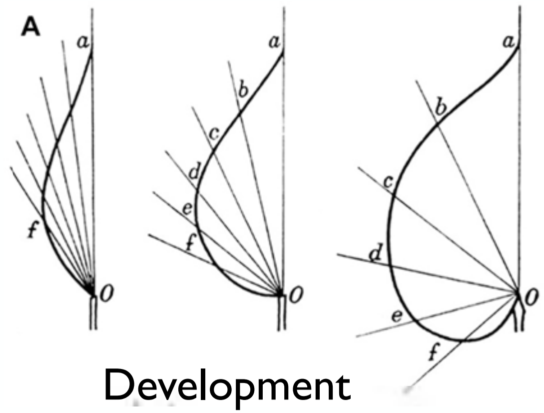
Proliferation & Growth
viewed as scalar or, better, as tensor
(a component of strain tensor)
see Course 18 Dec 2018,
Tissue Elongation

Guirao et al. K. Sugimura, F. Graner and Y. Bellaïche. *eLife* 4:e08519 (2015)

R. Etournay et al. F. Jülicher and S. Eaton. *eLife* 4:e07090. (2015)

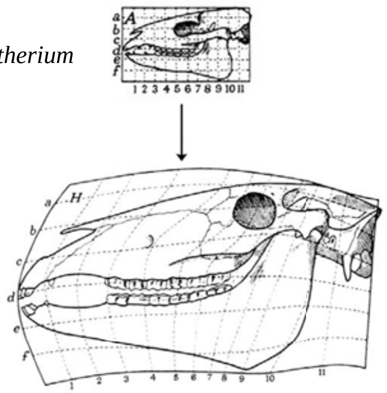
• d'Arcy Thompson: Laws of Growth

- Theory of transformations
- Laws of Growth relate animal forms in development and evolution



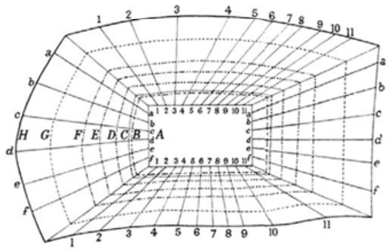
Development

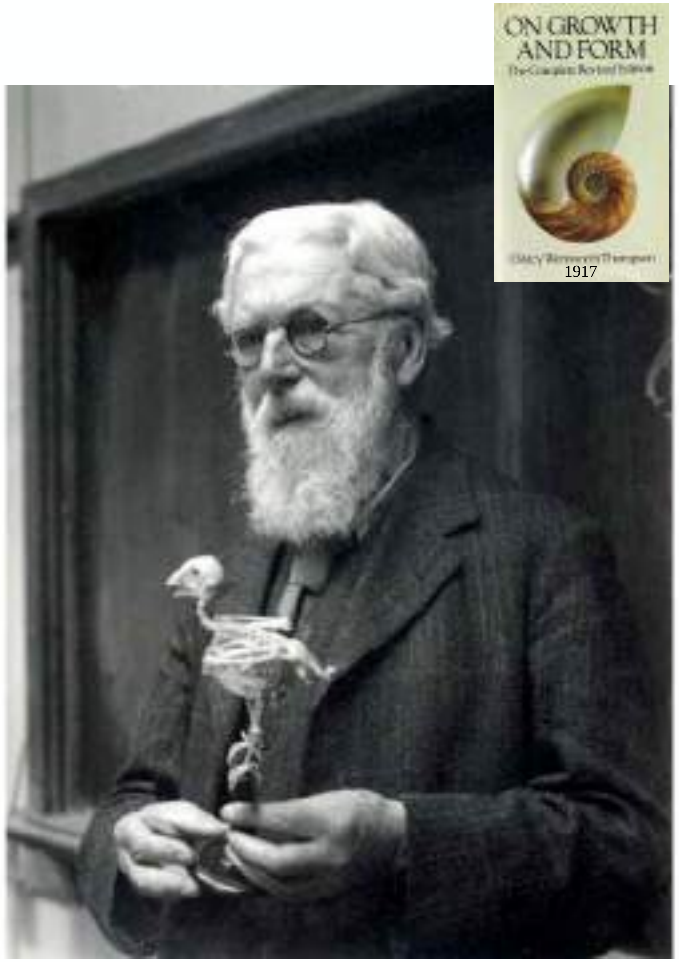
Hyracotherium



Equus

Evolution

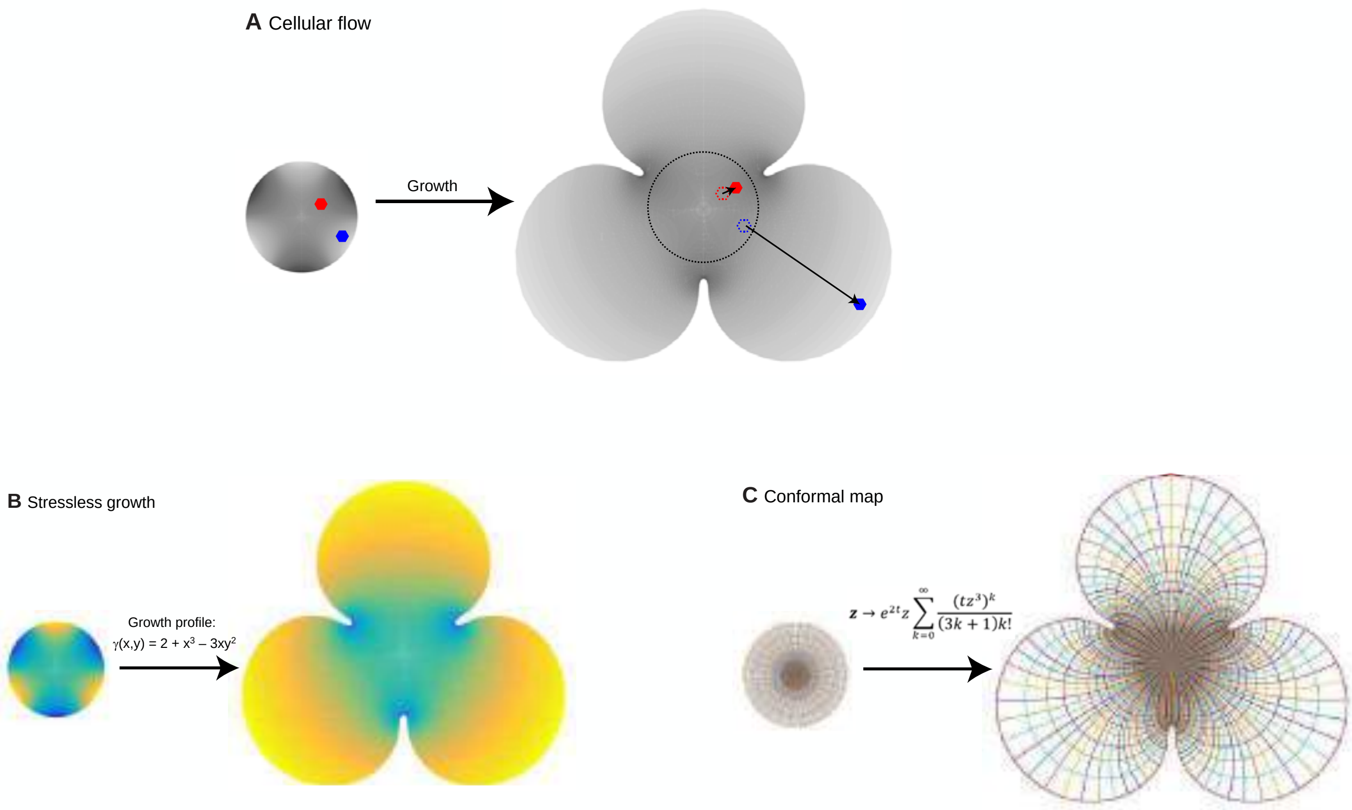




d'Arcy Wentworth Thompson (1860-1948)

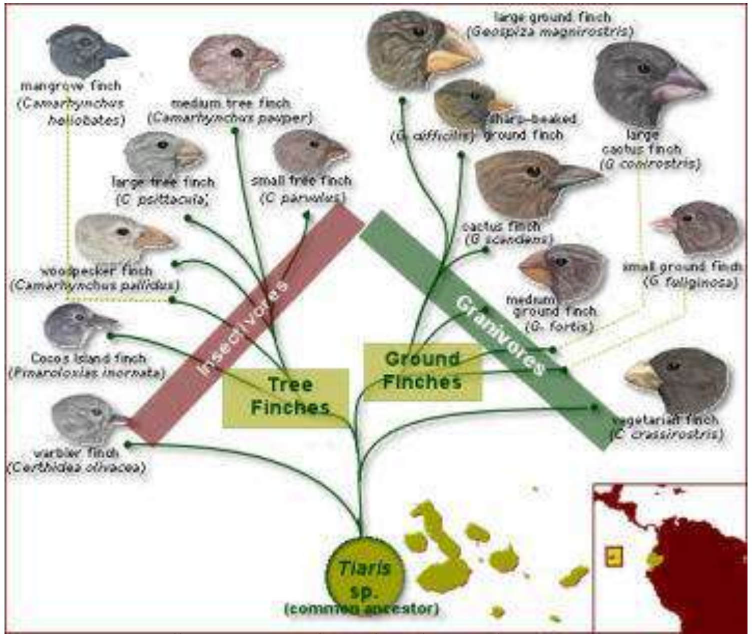
• Growth induced deformations affect Shape

Time	Space	Tissue Processes
Rates	Strain tensor	Shape remodelling Growth



K. Irvine and B. Shraiman. *Development* (2017) 144, 4238-4248 doi:10.1242/dev.151902

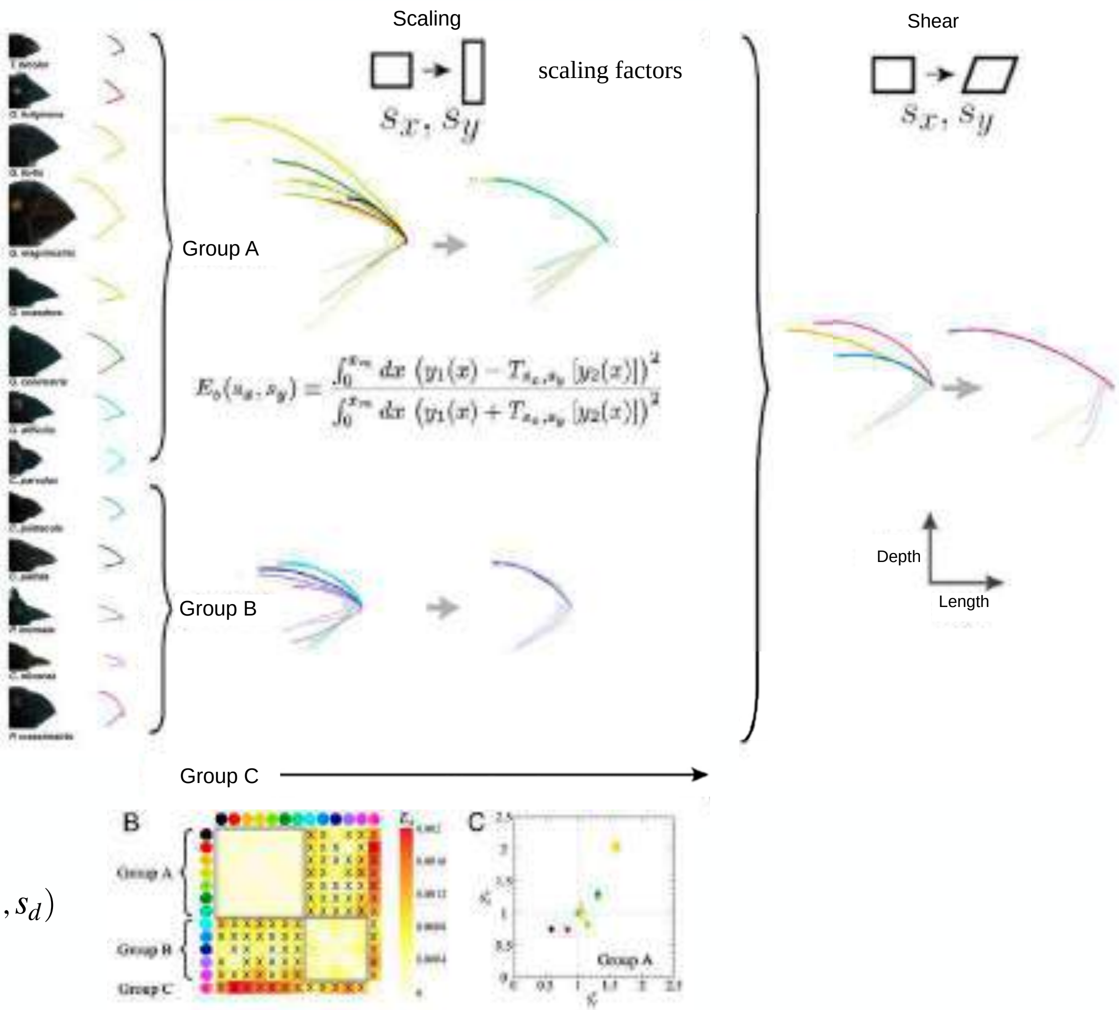
• Theory of transformation: beak growth and shape



http://bioweb.uwlax.edu/bio203/f2012/volk_sara/finch%20tree.jpg

Search scaling factors that minimise $E_s(s_\ell, s_d)$

• Affine transformations relate the shape of the beaks of all Darwin's finches

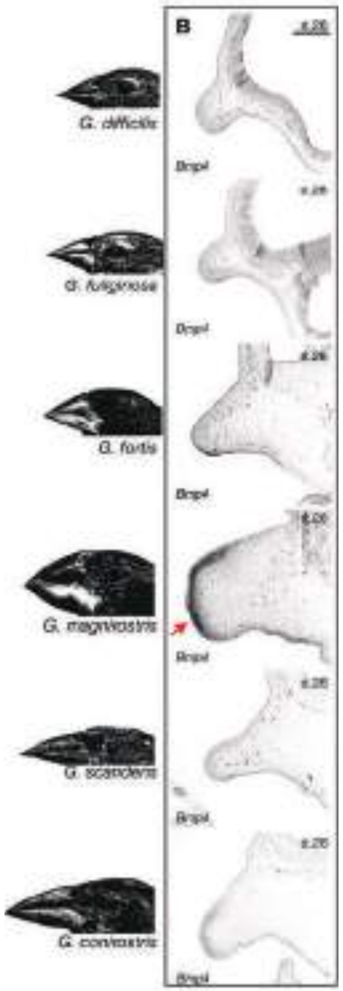


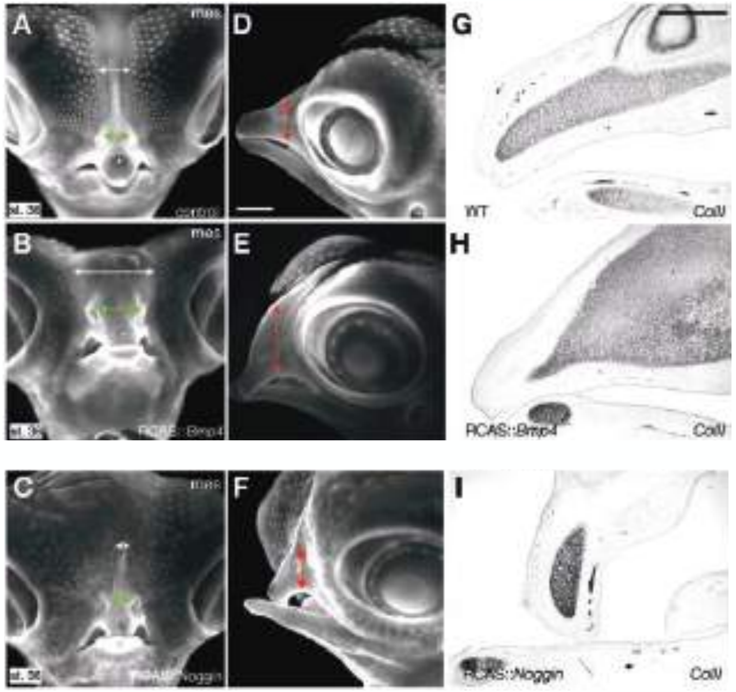
O. Campas et al. and A. Abzhanov, M. Brenner. PNAS (2010) 107:3356–3360

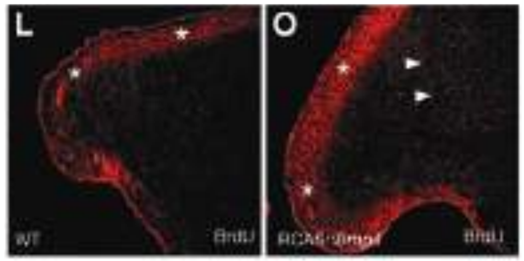
A. Abzhanov Development (2017) 144, 4284-4297 doi:10.1242/dev.137505

• Theory of transformation: beak growth and shape

- Correlation between beak size/shape and BMP4 expression across species
- BMP4 expression in the mesenchyme induces its growth (depth)
- CaM controls beak length



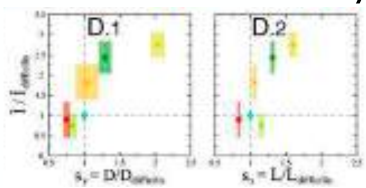


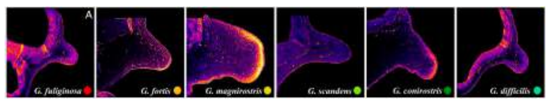


A. Abzhanov et al, C. Tabin. *Science.* (2004). 305:1462-1465

A. Abzhanov et al, C. Tabin, *Nature*. (2006)

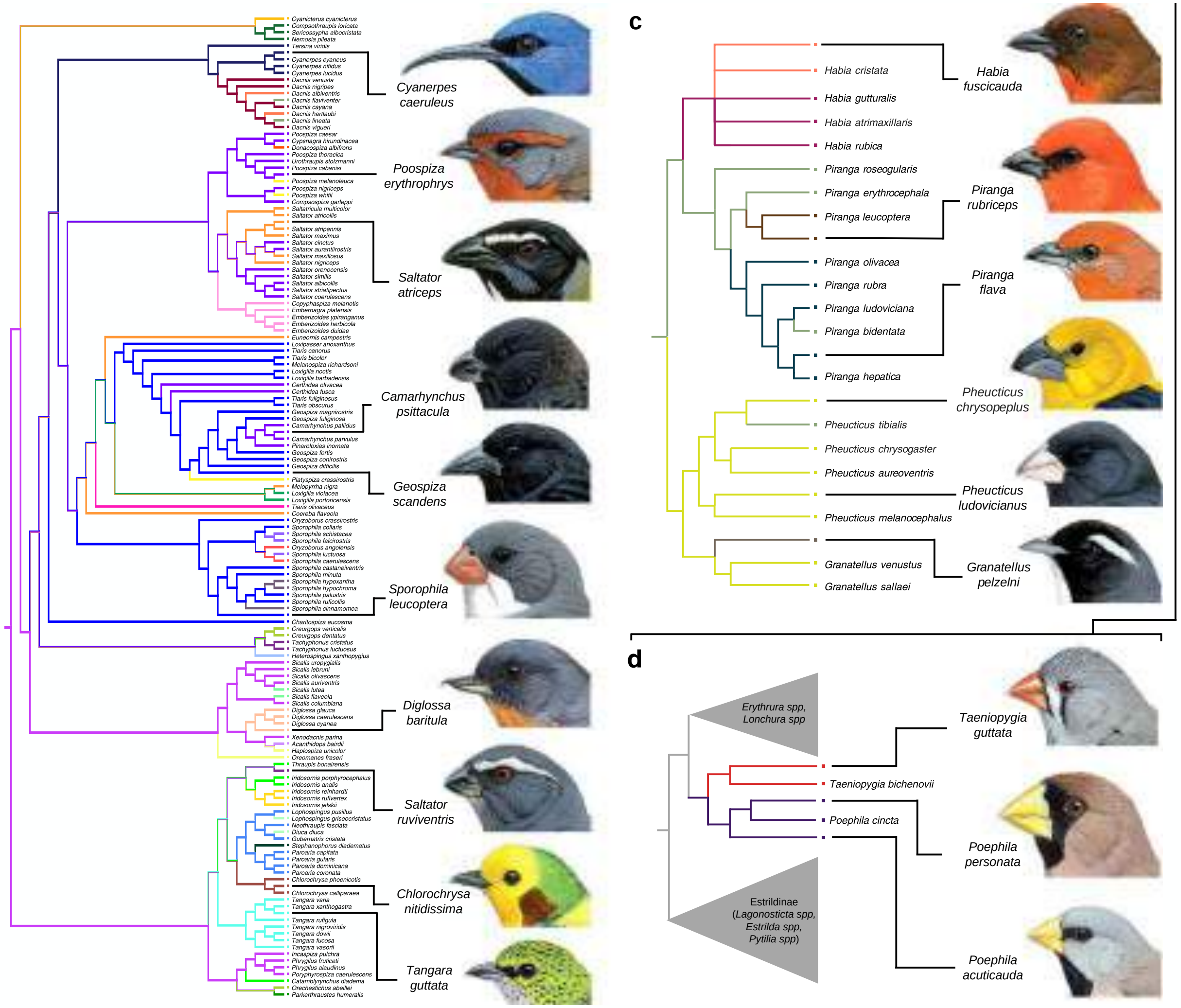
Correlation between BMP4 mesenchymal expression and scaling factors





O. Campas et al. and A. Abzhanov, M. Brenner. PNAS (2010) 107:3356–3360

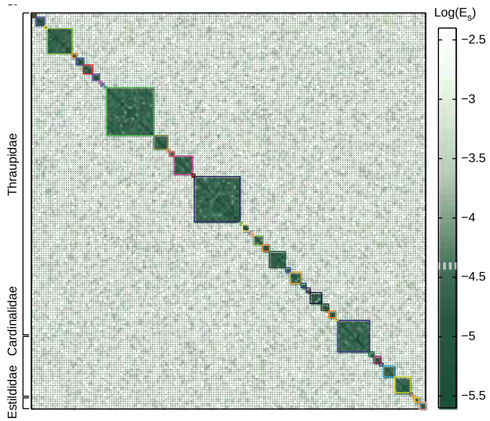
- Theory of transformation: beak growth and shape



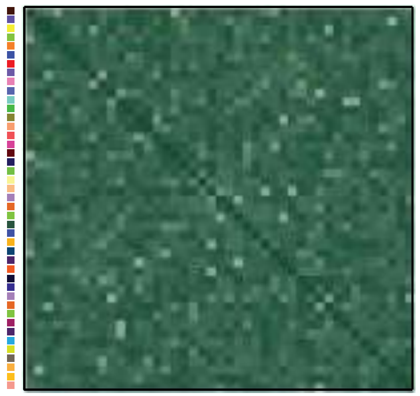
J. Fritz et al, A. Abzhanov & M. Brenner. Nature Communications | 5:3700 | DOI: 10.1038/ncomms4700

• Theory of transformation: beak growth and shape

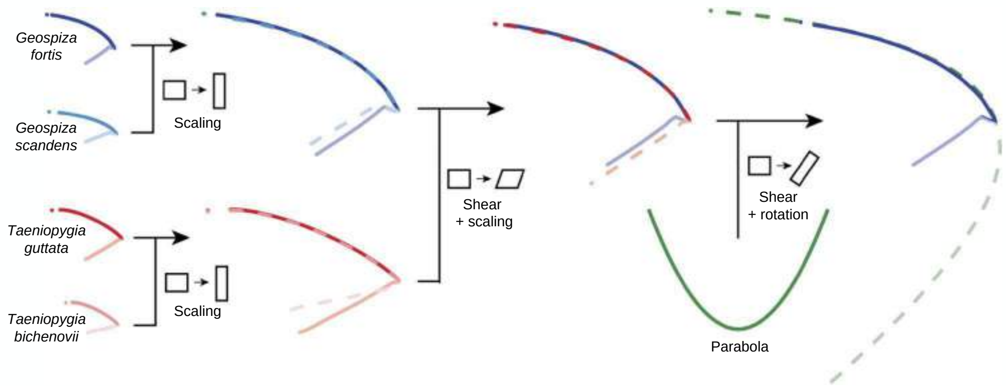
Scaling transformation



Shear



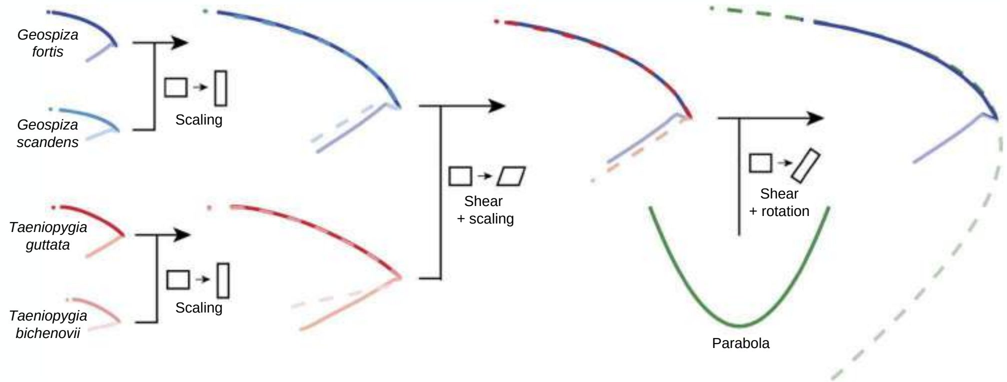
Hierarchical collapse of all beak shapes into a parabolic curve $0 = Ax^2 + Bxy + cy^2 + Dx + Ey.$



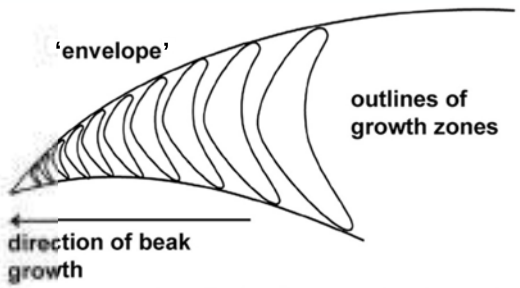
J. Fritz et al, A. Abzhanov & M. Brenner. Nature Communications | 5:3700 | DOI: 10.1038/ncomms4700

• Theory of transformation: beak growth and shape

All beak shapes hierarchically collapse into a parabolic curve $0 = Ax^2 + Bxy + cy^2 + Dx + Ey.$



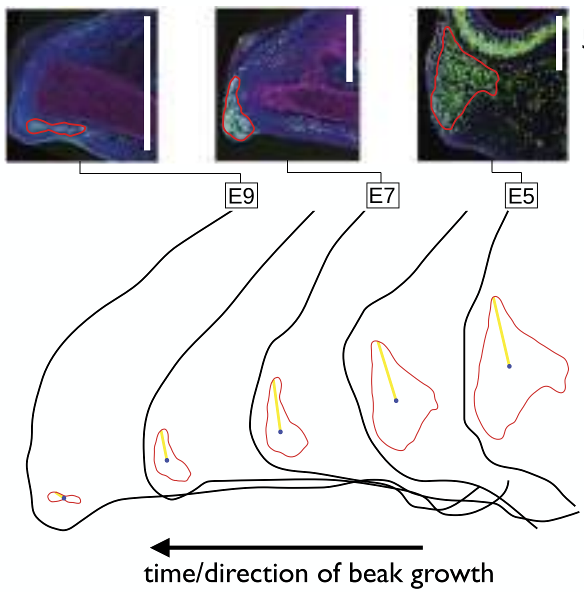
The shape is determined by the envelope of the growth zone as it decays at the tip of the developing beak



$$0 = Ax^2 + Bxy + cy^2 + Dx + Ey$$

$$E(\varphi)= \int |y_u(x)-p_u(x,\varphi)|dx+ \int |y_l(x)-p_l(x,\varphi)|dx$$

The growth zone shrinks at a constant rate over time until it disappears



J. Fritz et al, A. Abzhanov & M. Brenner. Nature Communications | 5:3700 | DOI: 10.1038/ncomms4700

• Development: Encoding Shape and Size

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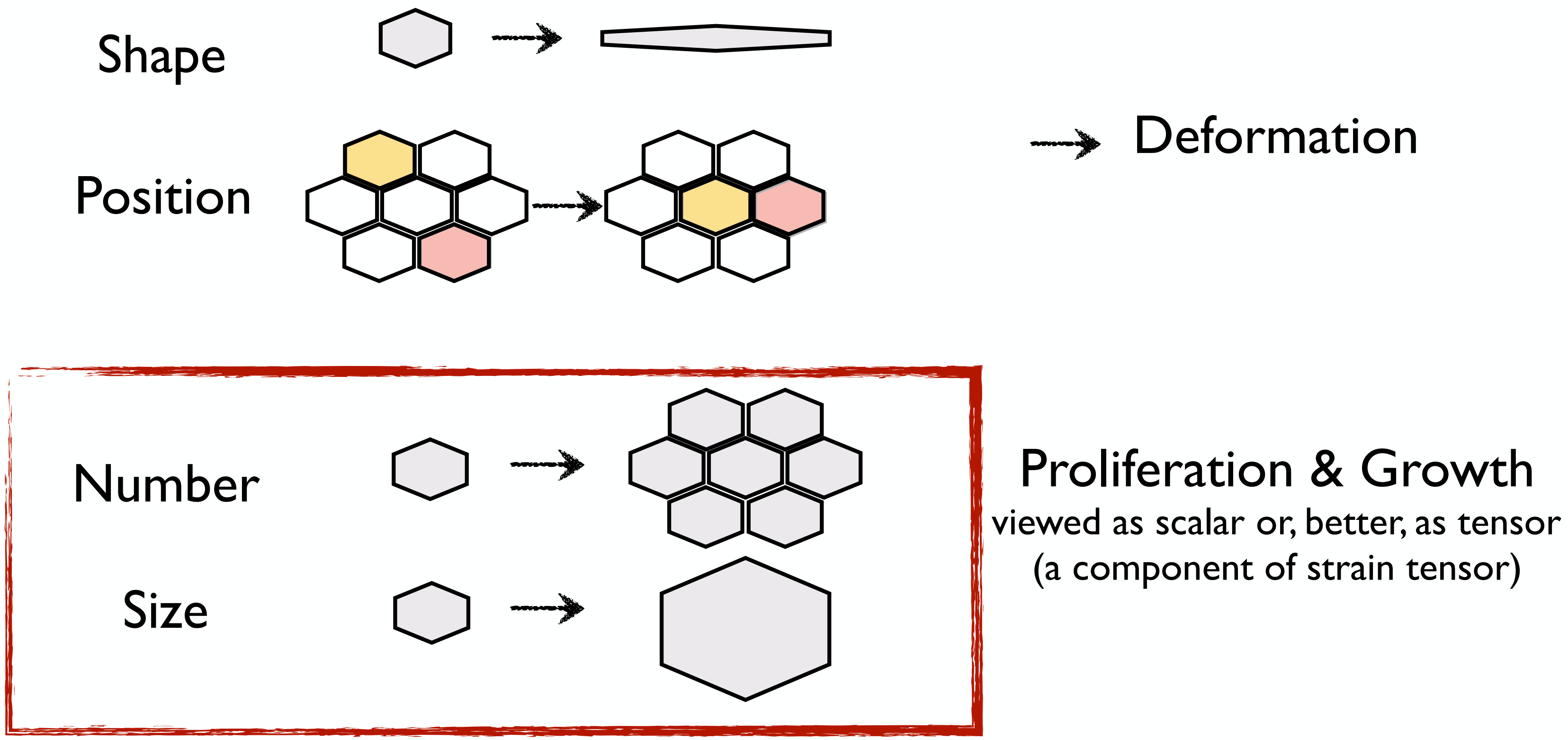
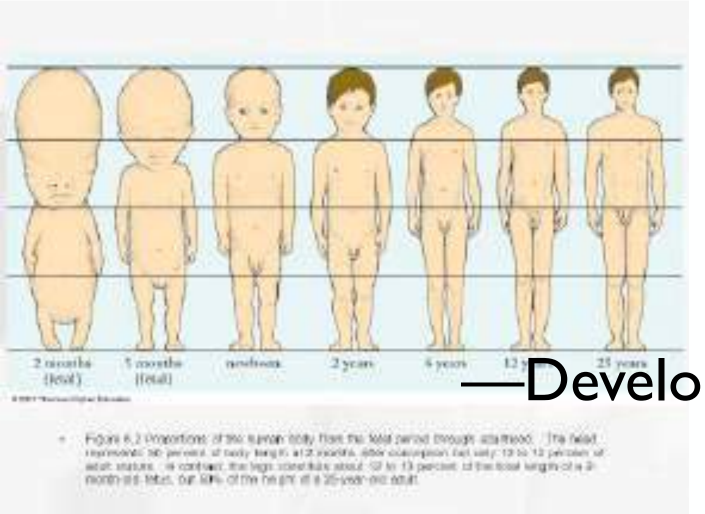


- The **Big questions**

- What *drives* growth?
  — Cellular, tissue, organ and organism scales
  — Energy source, transformation and delivery?
  — What sets the rate of growth?

- What *stops* growth? (ie. what is the size-meter)?
  — Cells, organs and organisms stop growing.
  — What sets proportions within and across scales?
  — Is size determined by rate or duration of growth?
  — What is measured? size, time, concentration, mechanics?

• Growth control



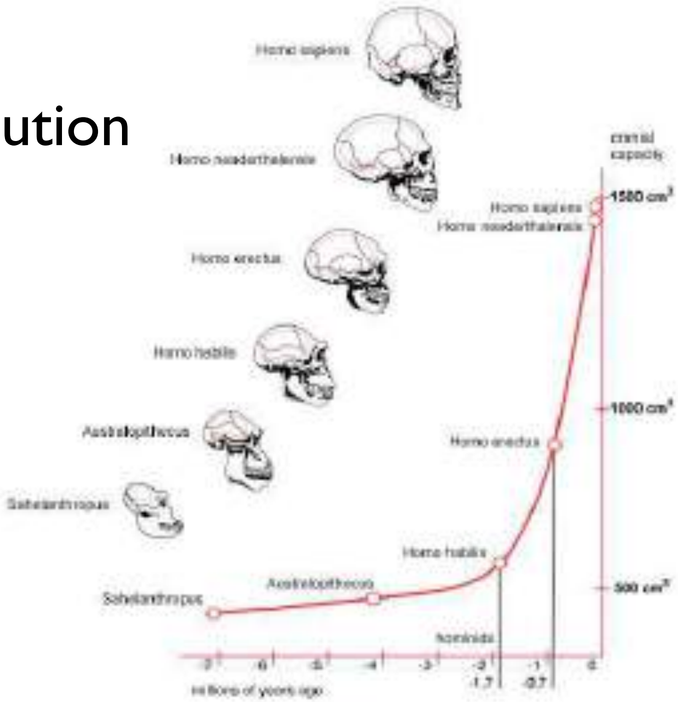
https://www.filthymonkeymen.com/2016/04/14/human-body-evolved-by-accident/hominid_brain_cavity_size/

—Development

—Evolution

Control
&
Constraints

—Disease: tumour



• Growth control

Control & Constraints

—Genetics/Signalling

eg. IGF1, IGFR genes in dogs

N. Sutter et al. *Science*. (2007) 316:114.
M. Rimbaud et al. *Genome Res.* (2013) 23:1985

—Mechanics

eg. thigmomorphogenesis (touch)

Arabidopsis thaliana Dereth Phillips, Rice University

https://fr.wikipedia.org/wiki/Thigmomorphogen%C3%A8se

—Hormones/epigenetics

eg. Sexual dimorphism

image copyright Chris Grossman

♂ 2.4m/300kg
♀ 1.8m/100kg

—Diet

http://www.myrmecos.net/2009/01/19/a-textbook-image-ant-castes/

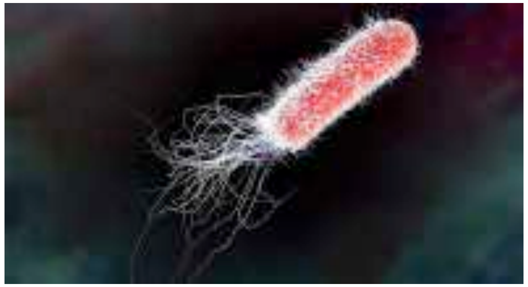
Camponotus discolor male, queen, and worker

Royalactin: bees

UAS-RoI *ppl>RoI*

M. Kamakura *Nature* (2011) 473:478
doi:10.1038/nature10093

- Life covers an (extremely) cast range of scales



length 10^{-6} m
volume 1 fl (10^{-15} l)
mass 10^{-12} g

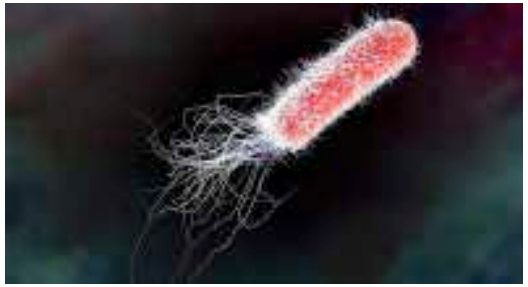
mass $x10^{20}$

length 30 m
volume
mass $1.5\ 10^{8}$ g

mass $x10^{21}$

$1.5\ 10^{9}$ g

- Life covers an (extremely) large range of scales



length 10^{-6} m
volume 1 fl (10^{-15} l)
mass 10^{-12} g

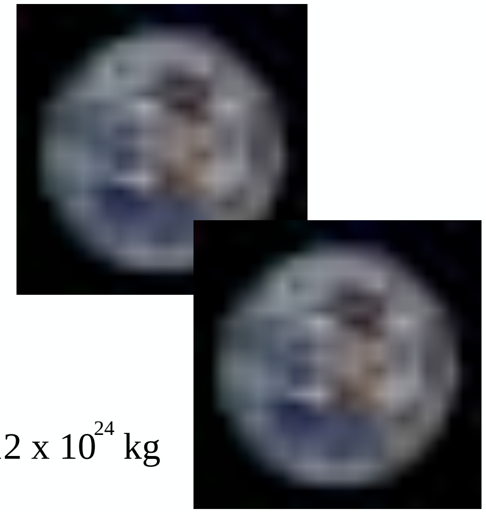
mass x10^{20} →

length 30 m
volume
mass 1.2 10^{8} g

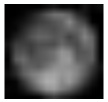
Blue whale

12 x 10^{4}kg

x10^{20} →

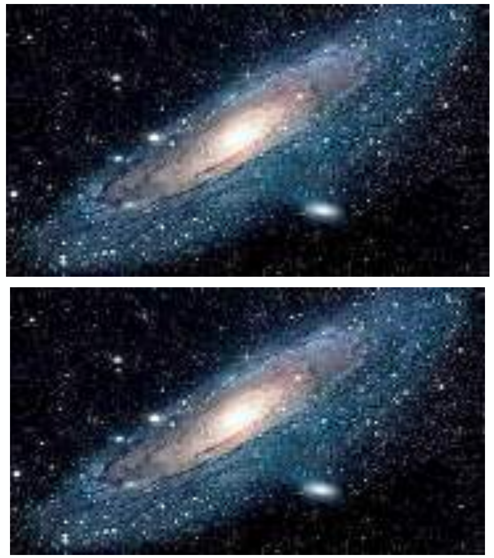


12 x 10^{24} kg



7.3 ×10^{22} kg

x10^{20} →



• Life covers an (extremely) large range of scales —Implications for growth control

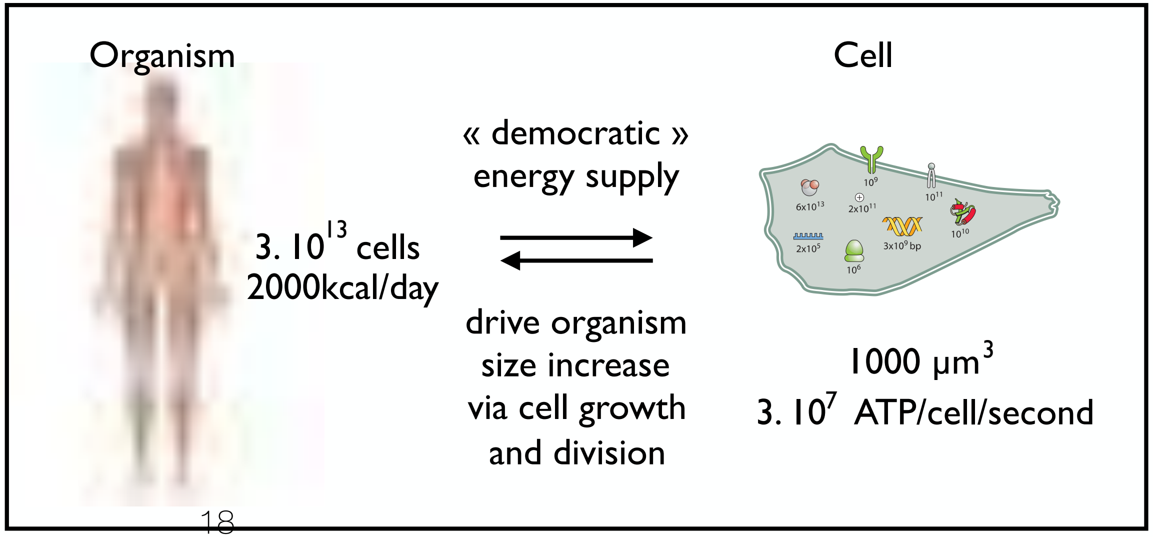
— There are many orders of magnitude difference between size of unit of growth (cell) and the size of multicellular organisms

For instance few 10.000 billion cells in human
and even more in larger mammals (10^{17} in blue whales).
Eukaryotic cell size is rather universal centred around a few 1000 µm^3

— Delivery of energy to every single cell in an organism is a huge challenge
— Control over energy supply and energy conversion at local, universal cellular scale
— Such a control is essential: absence of energy supply causes cell death within few min

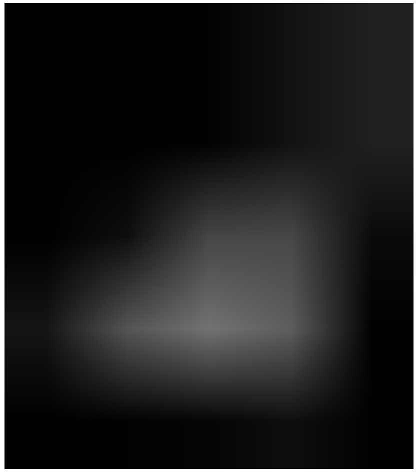
[humans turnover half their body weight (80 moles) in ATP per day to sustain the active, living state of all cells (3. 10^13): this is about 3. 10^7 ATP/cell/second].

— What underlies the efficacy and democratic nature of resource management and growth control in an organism?



• Scaling biological forms: Growth and Pattern

— How can similar design scale up and down?
— What are the links between growth and pattern formation to ensure such scaling properties?



Megaphragma mymaripenne

Vespa crabro

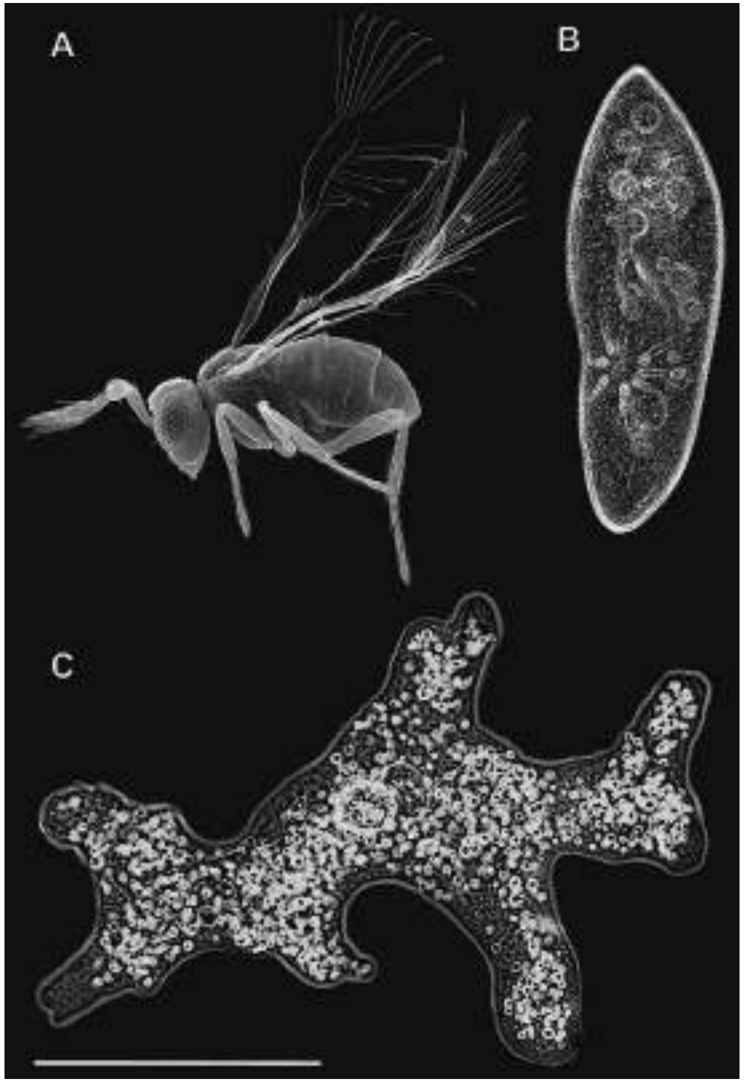
Alexey Polilov. *Arthropod Structure & Development* 41 (2012) 29e34

• Scaling biological forms

— How can similar design scale up and down?
— What are the links between growth and pattern formation to ensure such scaling properties?

	Length	
Megaphragma mymaripenne	55 mm	X 300
Vespa crabro	0.17 mm	

• Scaling biological forms



Megaphragma mymaripenne

Paramecium caudatum

Amoeba proteus

Scale bar for A-C is 200 µm.

Alexey Polilov. *Arthropod Structure & Development* 41 (2012) 29e34

• Scaling biological forms

— How can similar design scale up and down?

— What are the links between growth and pattern formation to ensure such scaling properties?

https://www.aquariumgallery.com.au/products/clown-fish-aquacultured

	Length			
Megaphragma mymaripenne	55 mm	X 300	clown fish	7.7 cm
Vespa crabro	0.17 mm		blue whale	25 m

• Scaling biological forms

— How can similar design scale up and down?
— What are the links between growth and pattern formation to ensure such scaling properties?

Paedophryne amauensis

Rittmeyer et al. *PlosOne* **7** (1): e29797— https://doi.org/10.1371/journal.pone.0029797

https://www.alamy.com/stock-photo-american-bullfrog-rana-catesbeiana-underside-of-female-19382034.html

• Growth before birth and growth after birth

— Embryonic growth is in proportion much larger than growth after birth

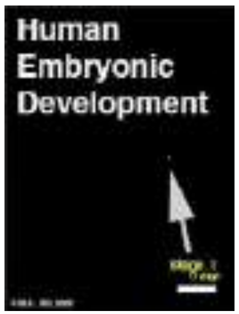
$\times 10^{10}$

L=100µm

L=5cm

L=50cm

	embryo
mouse	10^{6}
human	10^{10}
whale	10^{13}



https://embryology.med.unsw.edu.au/embryology/images/3/34/Embryo_stages_002.mp4

x20

L=175cm

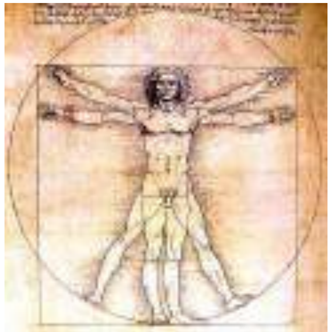
- Growth before birth and growth after birth in mammals

— Growth after birth can be within similar range in vastly differently sized mammals
— Embryonic growth can mark size differences between different species

M=3.5kg

x20 →

M=70kg

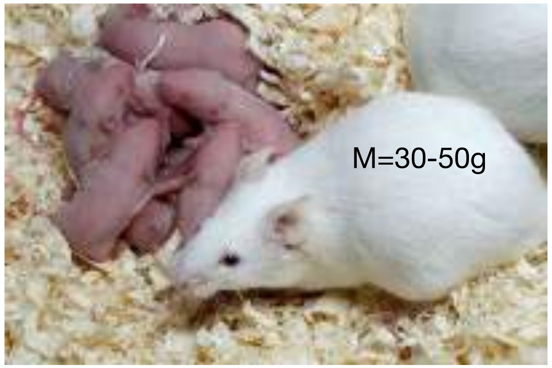


Fold size increase

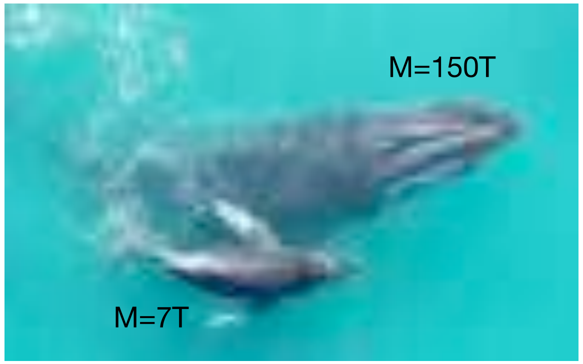
	embryo	adulte
mouse	10^{6}	20
human	10^{10}	20
whale	10^{13}	20

M=1.5-2.0g

x20



x20



• Growth before birth and growth after birth

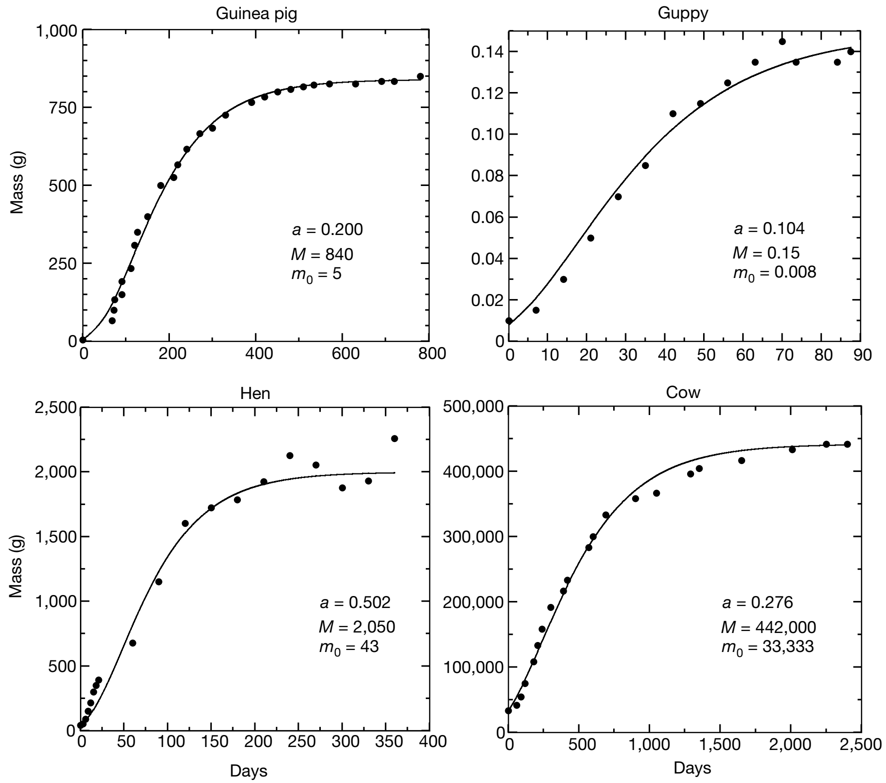
Geoffrey West

—Relative mass increase after birth can also vary and account for size difference in adult animals, especially across phyla (teleosts, avians, mammals)

Table 1 Values of several parameters for various organisms

Organism	a	m_0	M	M/m_0
Cow	0.28	33.3 kg	442 kg	13
Pig	0.31	0.90 kg	320 kg	320
Rabbit	0.36	0.12 kg	1.35 kg	11
Guinea pig	0.21	5 g	840 g	168
Rat	0.23	8 g	280 g	35
Shrew	0.83	0.3 g	4.2 g	14
Heron	1.56	3 g	2.7 kg	900
Hen	0.47	43 g	2.1 kg	48
Robin	1.9	1 g	22 g	22
Cod	0.017	0.1 g	25 kg	$2.5\ 10^5$
Salmon	0.026	0.01 g	2.4 kg	$2.4\ 10^5$
Guppy	0.10	0.008 g	0.15 g	19
Shrimp	0.027	0.0008 g	0.075 g	93

a, see equation (3); m_0, birth mass; M, asymptotic mass. Also shown are the negative mean values of the slopes of plots of $\ln[R(t)/R(0)]$ versus $at/4M^{1/4}$ which is predicted to have a universal value of 1; $R \equiv [1-(m/M)^{1/4}]$ is the proportion of metabolic power devoted to growth.



m: mass at time t
m_0: mass at birth
M: mass at death

G. West, J. Brown and B. Endquist. NATURE | VOL 413 | 11 OCTOBER 2001

• YET: « Universality » of ontogenic growth (ie. after birth)?

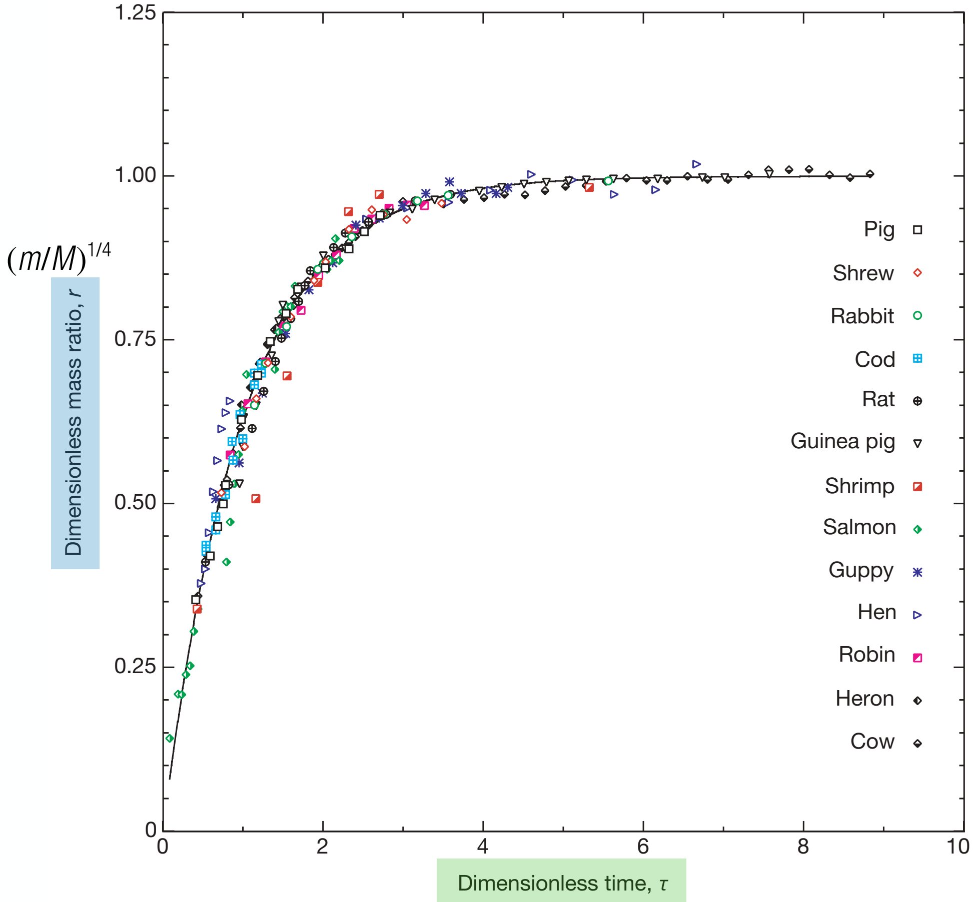
Geoffrey West

—Points to universal features, ie. constraints for growth of animals after birth.

$$r = 1 - e^{-\tau}$$

See: Cours 2: 19 Nov 2019

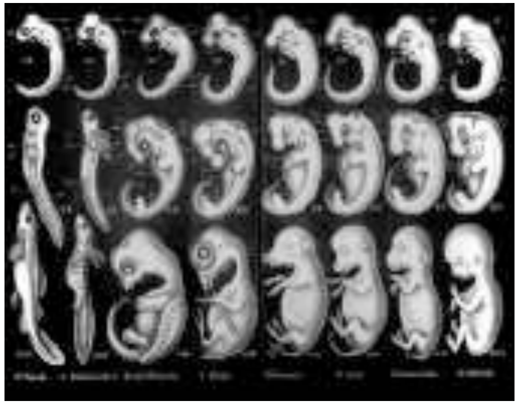
m: mass at time t
m_0: mass at birth
M: mass at death



$$\tau \equiv at/4M^{1/4} - \ln[1 - (m_0/M)^{1/4}].$$

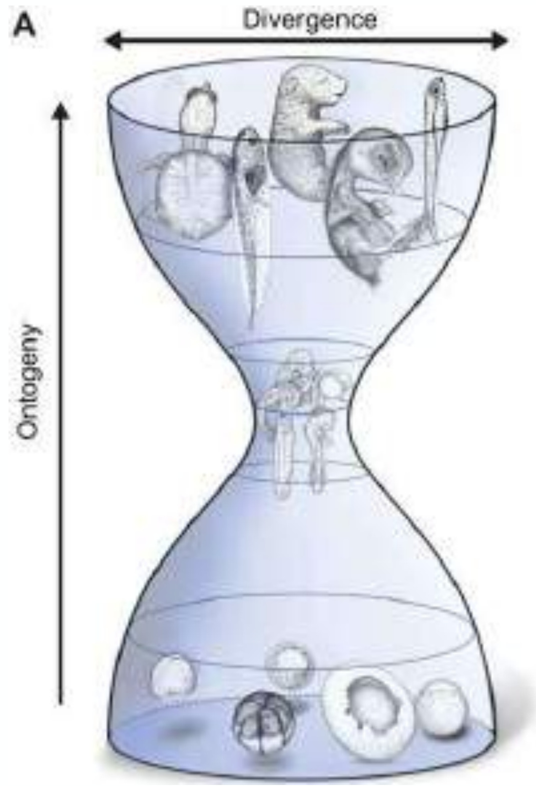
G. West, J. Brown and B. Endquist. NATURE | VOL 413 | 11 OCTOBER 2001

• Embryo size is (apparently) constrained at the phylotypic stage



Haeckel 's phylotypic stage

Vertebrate



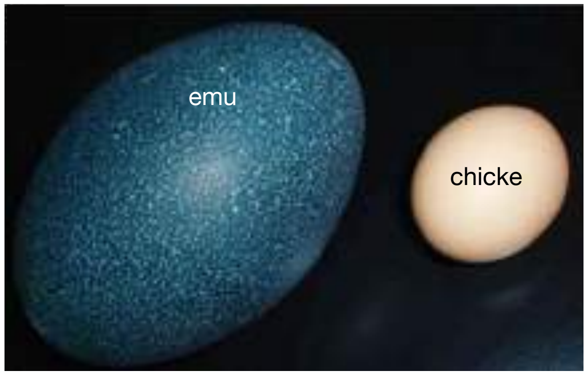
The Hourglass model:

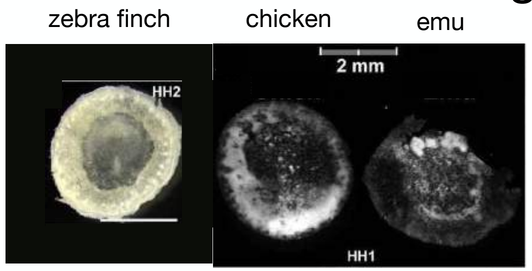
mid-embryonic organogenesis (phylotypic period) represents the stage of highest morphological conservation

N. Irie and S. Kuratani.
Development (2014) 141, 4649-4655
doi:10.1242/dev.107318

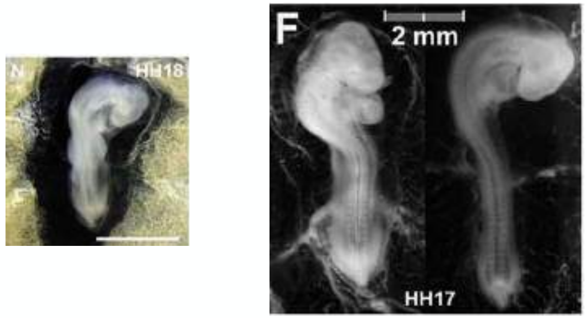
• Embryo size is (apparently) constrained at the phylotypic stage

—Birds of vastly different adult size show modest differences during embryogenesis





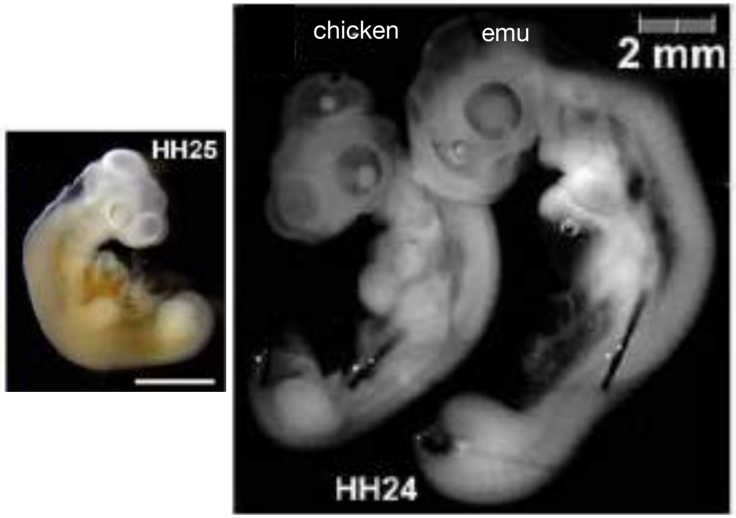
Blastula stage: Same size



End of gastrulation and neural tube closure

Similar size

(order of magnitude)

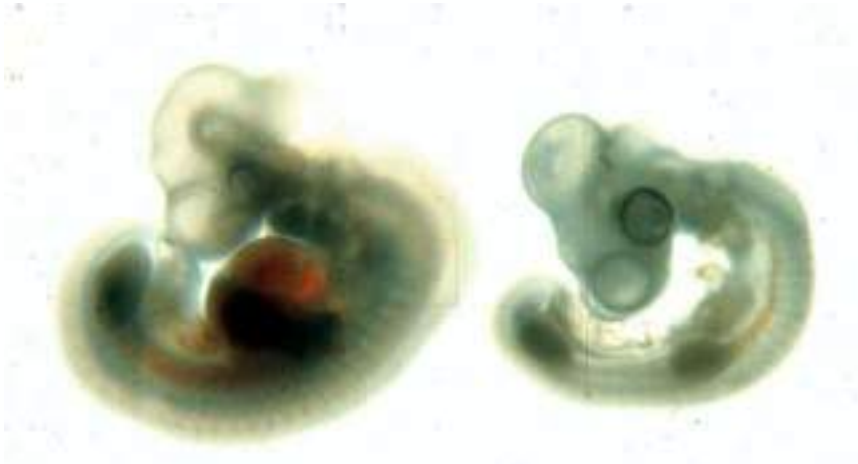


S-S. Mak et al, R. Ladher & G. Sheng. *Genesis* (2015) 53:669–677

H. Nagai et al, R. Ladher & G. Sheng. Dev. Dynamics. (2011) 240:162–175

- Embryo size is (apparently) constrained at the phylotypic stage

—Human and bird embryos have similar size at the phylotypic stage despite very different growth rates



human embryo
(6 weeks)

chick embryo
(4 days)

(courtesy of O. Pourquié (Harvard University)

Embryonic growth rate is 10 fold slower in human compared to chick yet their size at the phylotypic stage is similar

- **Growth** and **Form**: what are the links between size control and pattern formation?

• Origins of constraints on embryo size: Patterning

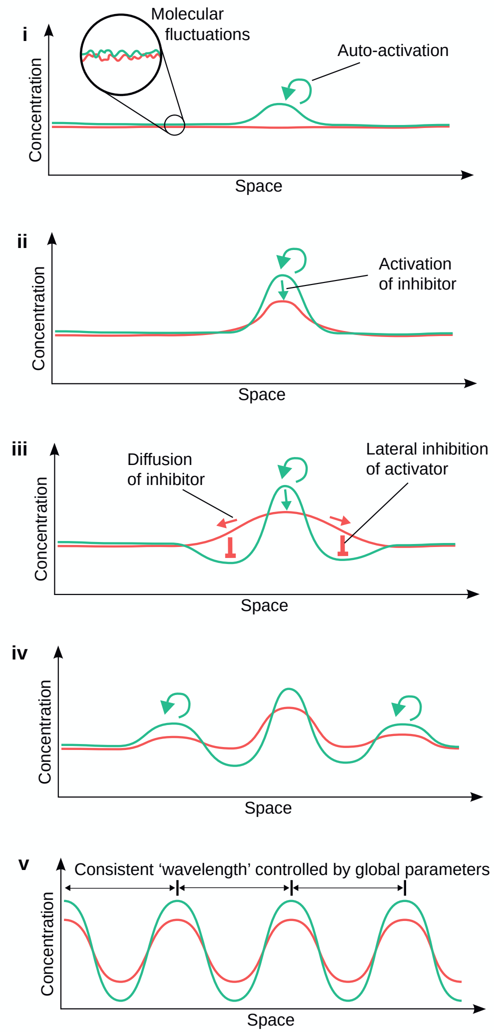
Alan Turing
(1912-1954)

Turing Instabilities:

- Length scales emerge from reaction/ diffusion scheme
- No proper scaling with size of field

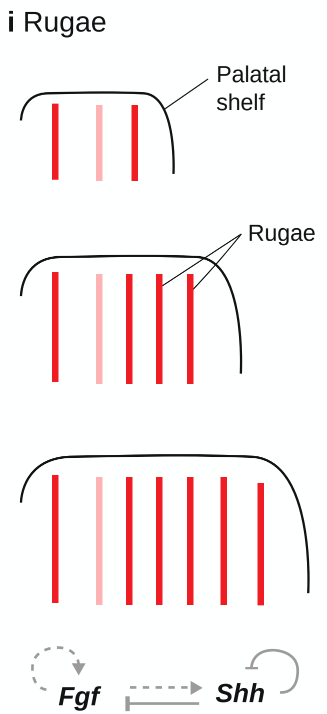
Local Excitation - Global Inhibition model
(activator-inhbitor scheme)

(*i.e.* local instability and global stabilisation)

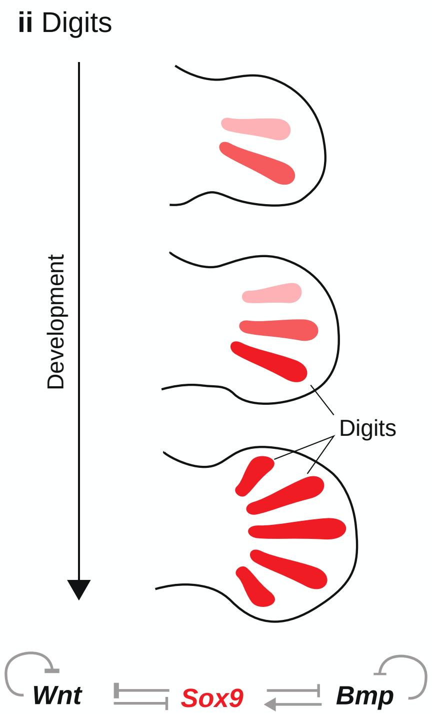


J. Green and J. Sharpe. *Development* (2015) 142, 1203-1211 doi:10.1242/dev.114991

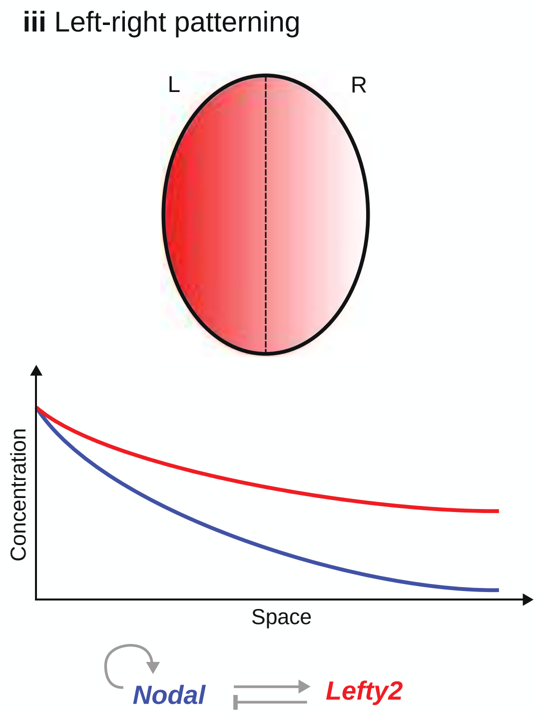
• Origins of constraints on embryo size: Patterning



Economou, A. D., et al. and Green, JBA. (2012). *Nat. Genet*. 44, 348-351.



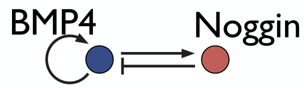
Raspopovic, J.,et al. and Sharpe, J. (2014). *Science* 345, 566-570.

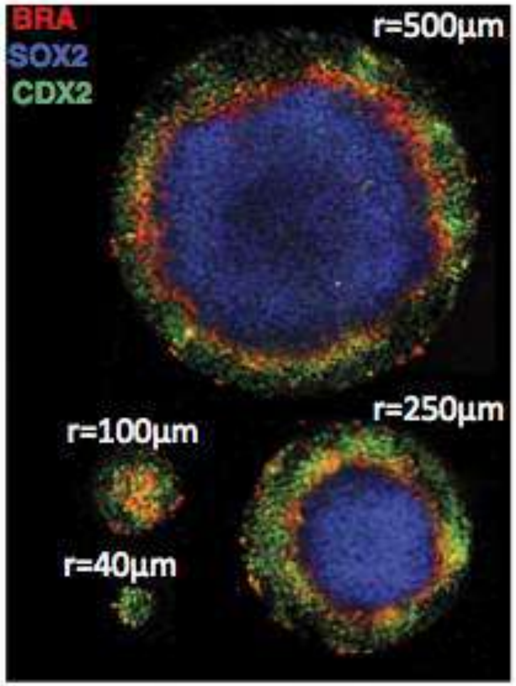


Müller, P., et al. and Schier, A. F. (2012). *Science* 336, 721-724.

J. Green and J. Sharpe. *Development* (2015) 142, 1203-1211 doi:10.1242/dev.114991

• Origins of constraints on embryo size: Patterning



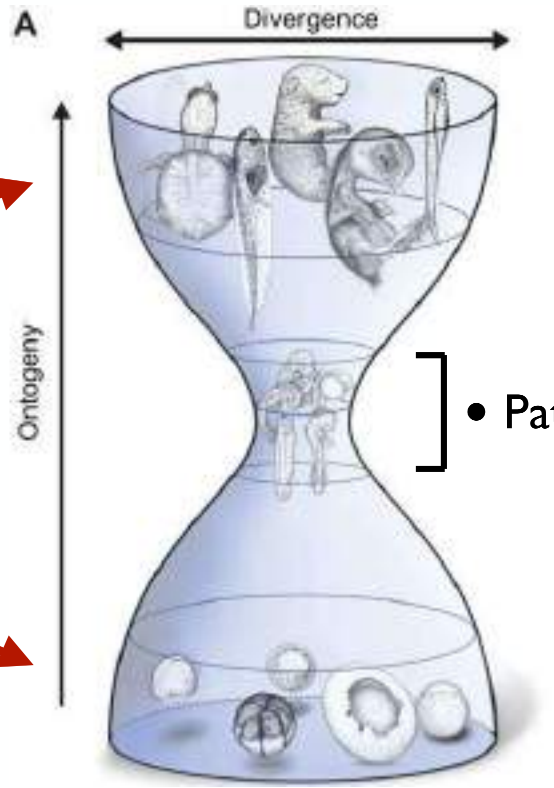


Etoc et al., A. Brivanlou, E. Siggia. 2016, Developmental Cell 39, 302–315 http://dx.doi.org/10.1016/j.devcel.2016.09.016

• Constraints on growth fashioned developmental strategies

Constraint #1: Growth phases occur prior to and after developmental patterning occurs

- Postembryonic Growth
- Growth before development: Oogenesis



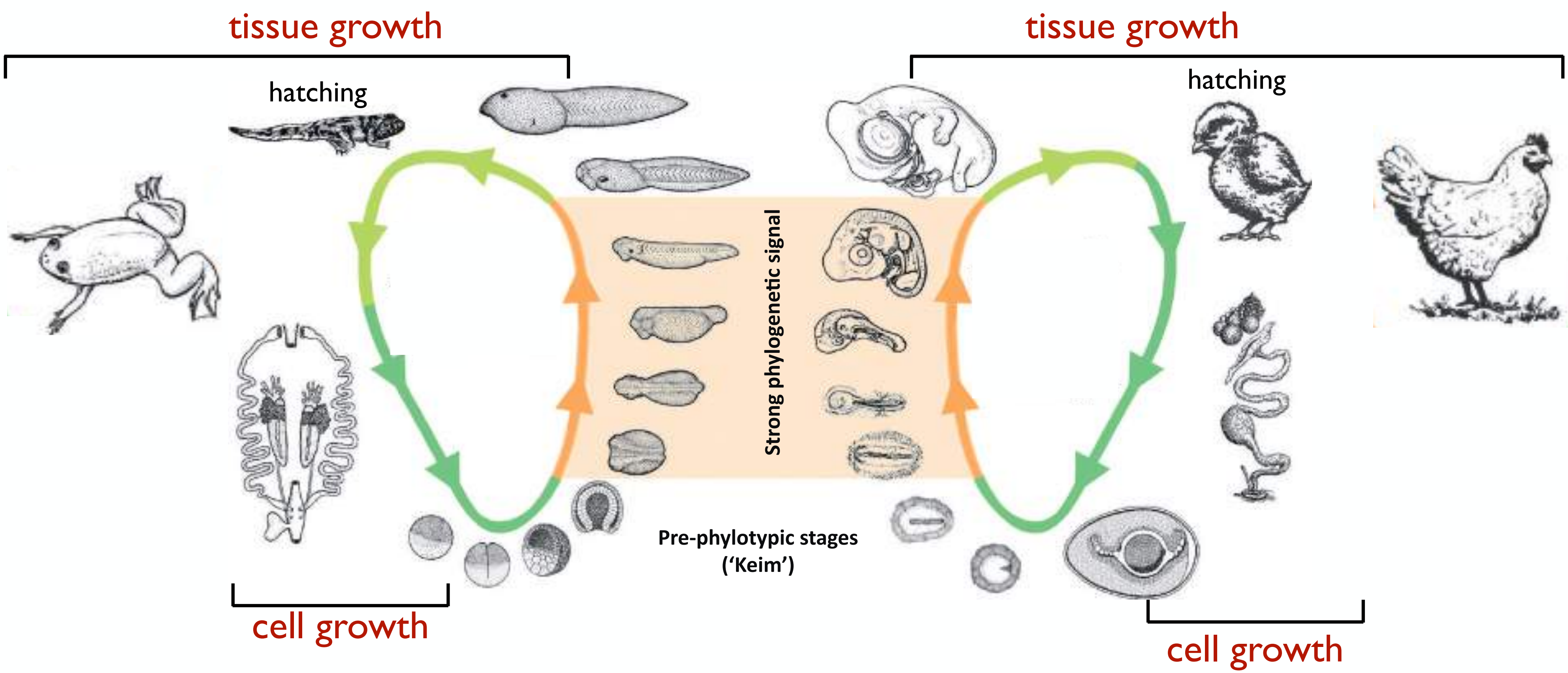
• Patterning

A. Abzhanov *Trends in Genetics* (2013), Vol. 29, No. 12

• Constraints on growth fashioned developmental strategies

— External development: big egg, and growth post hatching

The hatching animal needs to be large enough to feed



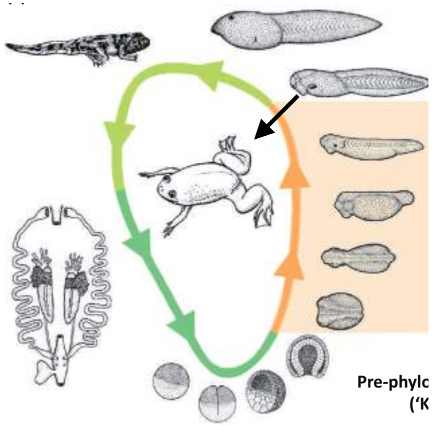
A. Abzhanov *Trends in Genetics* (2013), Vol. 29, No. 12

• Constraints on growth fashioned developmental strategies

— Progenesis: accelerated development reduces the size in amphibians

direct development (without larval stage)

Paedophryne amauensis 8mm



Rittmeyer et al. *PlosOne* **7** (1): e29797— https://doi.org/10.1371/journal.pone.0029797

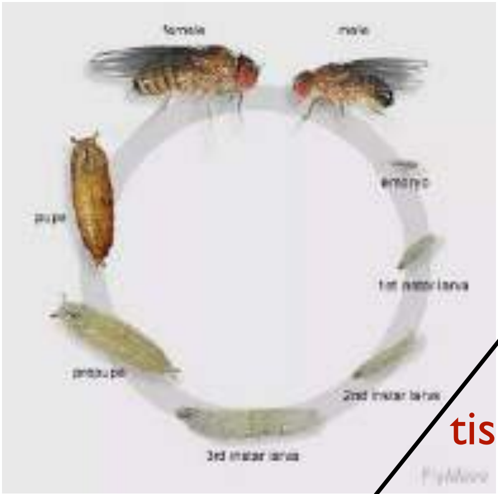
• Constraints on growth fashioned developmental strategies

— External development: big egg, and growth post hatching

The hatching animal needs to be large enough to feed

Insects

Drosophila melanogaster



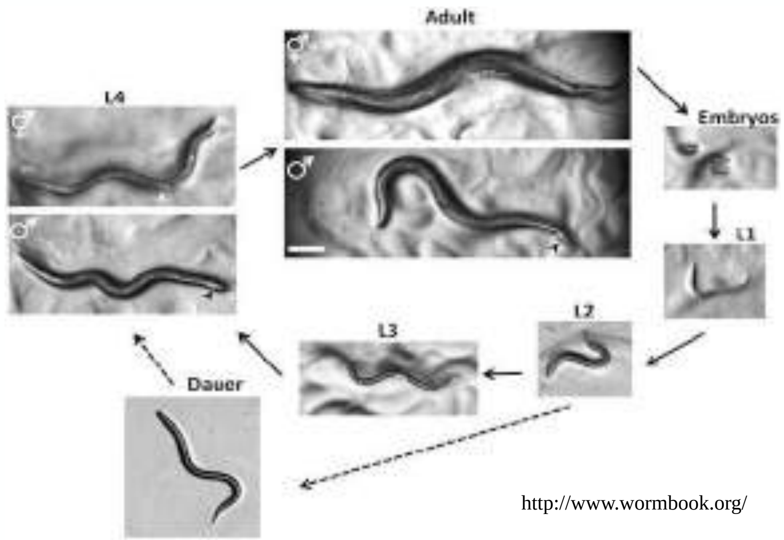
tissue growth

s://www.pinterest.es/pin/534803142973194887/?autologin=true

https://www.reddit.com/r/pics/comments/1mmuir/the_goliath_beetle/

Goliathus cacicus

Nematodes

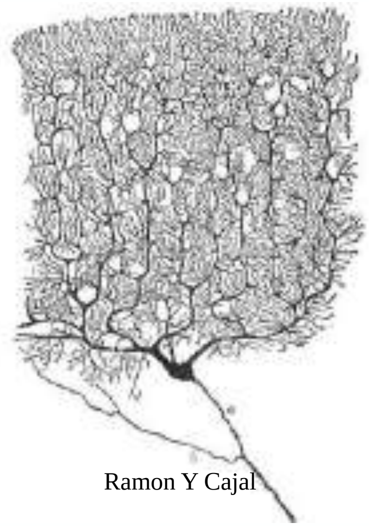


http://www.wormbook.org/

tissue growth

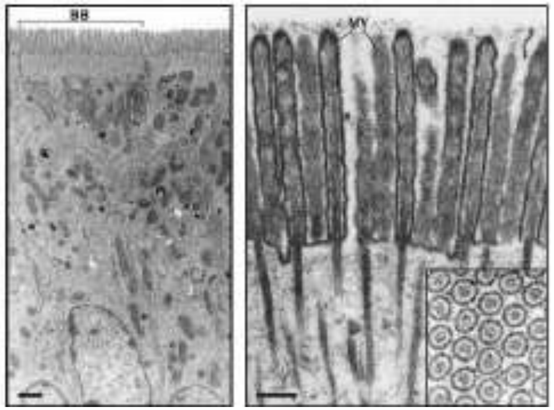
• Other major constraint:
—Conflict between cell division and differentiation

- Cell growth and division often coincide, producing cells of stable volume
- But Growth and Division are also often uncoupled
- Constraint #2 : Differentiated cells cannot divide.



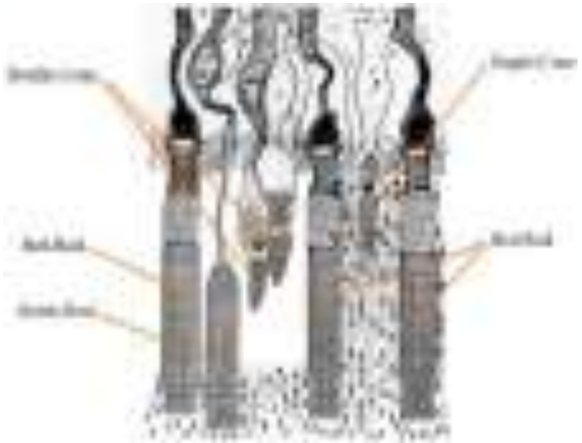
Ramon Y Cajal

neuron



Crawley SW et al 2014 DOI: 10.1083/jcb.201407015

brush border epithelial cell



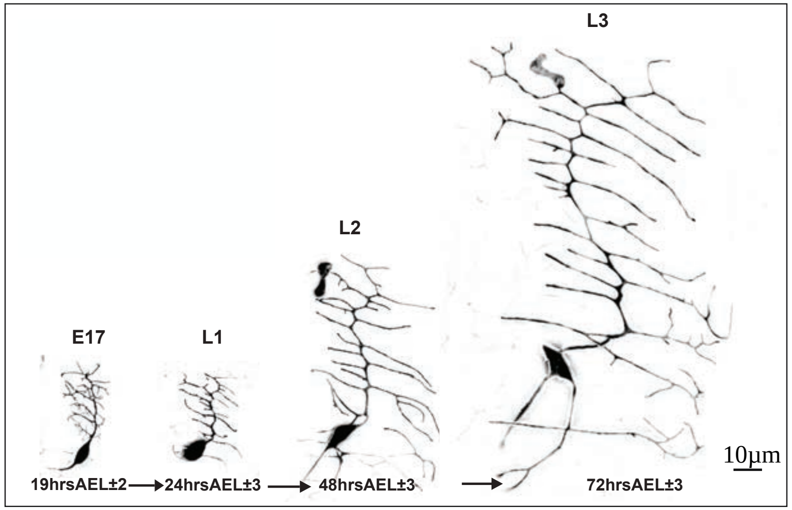
Zhang Q et al 2015. DOI: 10.1038/srep09595

photoreceptors

• Other major constraint:
—Conflict between cell division and differentiation

- Differentiated cells cannot divide
- SOLUTIONS:

1. Growth of a differentiated cell

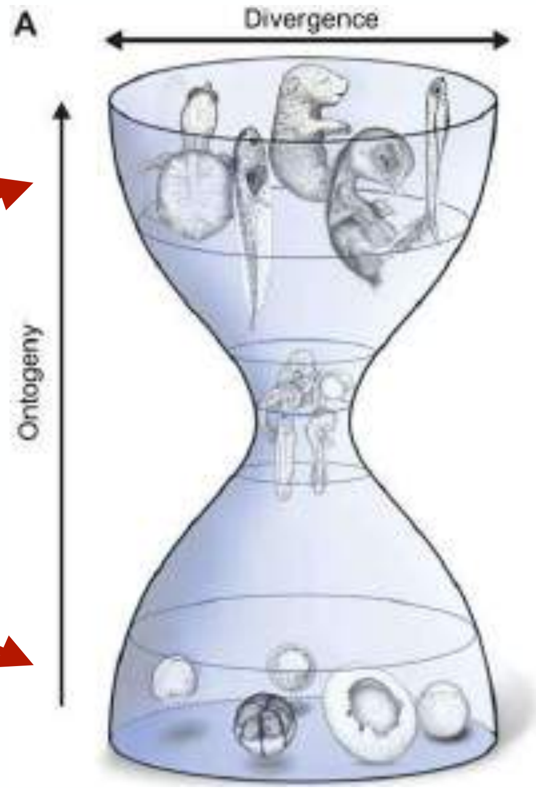


Amrutha Palavalli, IBDM, Marseille

2. Delay of differentiation: cell proliferation, use of a stem cell based lineage. Indirect development in insects, placental development etc.

• Constraints on growth fashioned developmental strategies

Constraint #1: Growth phases occur prior to and after developmental patterning occurs
Constraint #2 : Differentiated cells cannot divide.



- Postembryonic Growth
(cell growth or proliferation and delayed differentiation)

- Growth before development: Oogenesis
(cell growth)

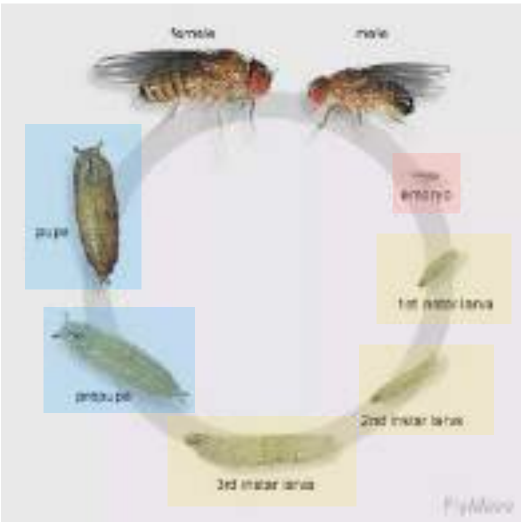
A. Abzhanov *Trends in Genetics* (2013), Vol. 29, No. 12

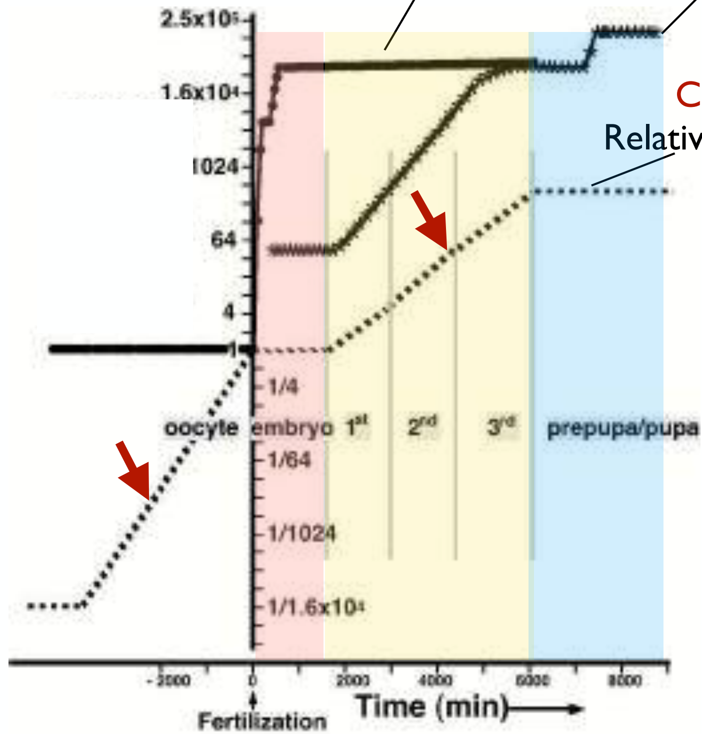
Cell growth and cell proliferation in Insects

Insect indirect development:

— Cell growth occurs in the main phases of developmental growth

— Delayed differentiation of adult tissues (imaginal discs and histoblasts)



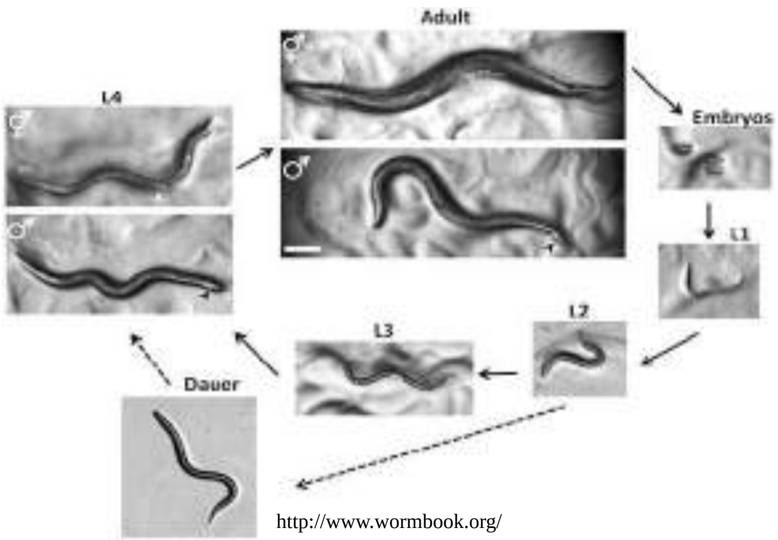


In "Cell Growth" Ed. Michael Hall, Martin Raff & George Thomas, Cold Spring Harbor Press, CSH NY 2004

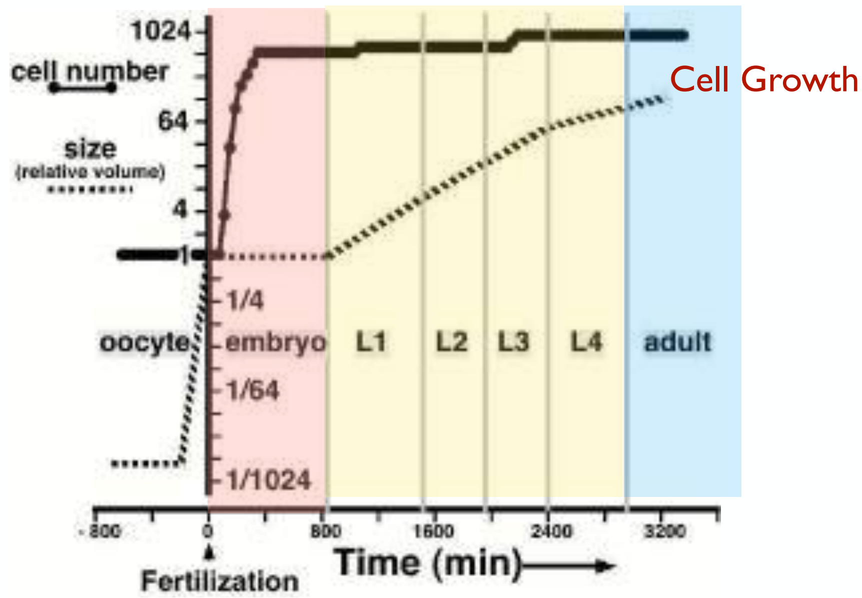
Growth and cell proliferation in Nematodes

Nematodes: e.g. *C. elegans* and *Ascaris lumbricoides*

— Cell growth occurs in the main phases of developmental growth



http://www.wormbook.org/



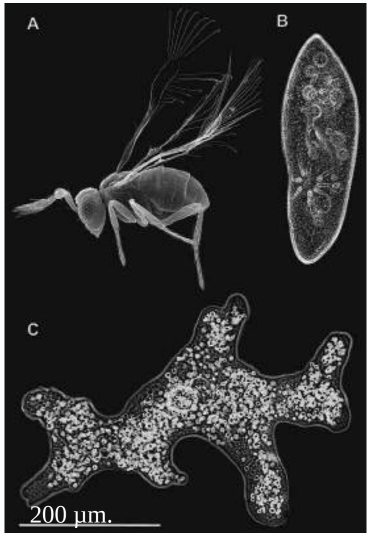
In “Cell Growth” Ed. Michael Hall, Martin Raff & George Thomas, Cold Spring Harbor Press, CSH NY 2004

Cell volume variation

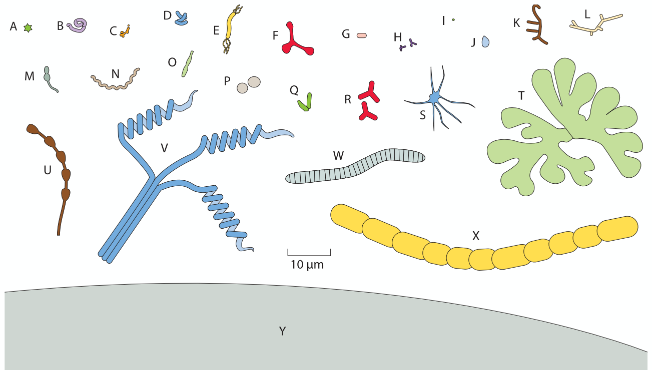
Prokaryotic and Eukaryotic cells explore a wide range of volumes

cell type	average volume (µm^3)	BNID
sperm cell	30	109891, 109892
red blood cell	100	107600
lymphocyte	130	111439
neutrophil	300	108241
beta cell	1,000	109227
enterocyte	1,400	111216
fibroblast	2,000	108244
HeLa, cervix	3,000	103725, 105879
hair cell (ear)	4,000	108242
osteoblast	4,000	108088
alveolar macrophage	5,000	103566
cardiomyocyte	15,000	108243
megakaryocyte	30,000	110129
fat cell	600,000	107668
oocyte	4,000,000	101664

Mammalian cells



Alexey Polilov. *Arthropod Structure & Development* 41 (2012) 29e34



Microbial cells

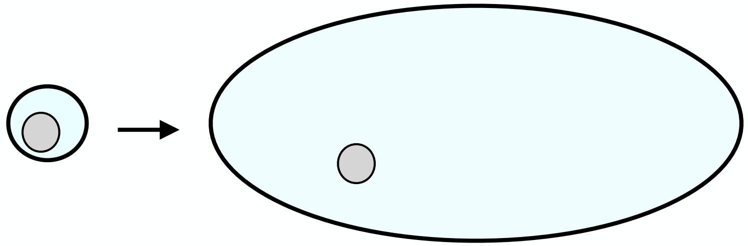
Protists

Cell Biology by the numbers. Ron Milo, Rob Phillips, *illustrated* by Nigel Orme. *Garland Science* 2012

• A major constraint on cell growth:
— Constraint #3: transcription and ribosome assembly

- As a cell grows, the nucleus becomes very small with respect to cell volume:
  — transcriptional capacity becomes limited

- However the translational capacity scales with cell cytoplasmic volume:
  — ribosomal density remains constant
  — the rate of ribosomal assembly is critical: rRNA transcription
  — mRNA transcription is also critical



- <u>Time scale to double transcripts in a cell:</u>

— at maximum polymerase loading a gene produces new transcript every 2 s (1 polymerase every 60 nucleotides, rate of elongation of, on average 30nt/s)

—100.000 to 1000.000 mRNAs.
Some transcripts are present in a few thousand copies

—Doubling the amount of these transcripts can take several hours for a haploid genome

Table 1. Transcription rate measured across organisms and conditions. All values measured at 37°C except *D. melanogaster* measured at 22°C.

organism	rate (nt/s)	BNID
E. coli	10-100	104900, 104902, 101904, 108488, 108490, 108487, 100060
Monkey cell line	100	105113
H. sapiens	6-70	105566 , 100661, 100662
D. melanogaster	25	111484

property	*E. coli*	budding yeast	mammalian (HeLa line)
cell volume	0.3–3 μm^3	30–100 μm^3	1,000–10,000 μm^3
proteins per μm^3 cell volume		$2–4\times10^6$	
mRNA per cell	10^3-10^4	10^4–10^5	10^5–10^6
proteins per cell	~10^6	~10^8	~10^{10}

Cell Biology by the numbers. Ron Milo, Rob Phillips, *illustrated* by Nigel Orme. *Garland Science* 2012

- <u>Nurturing massive cell growth:</u>

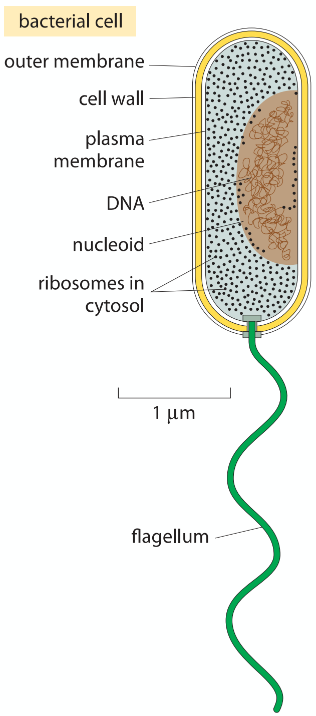
—some cells (oocyte) grow about 100.000 times in volume
—this would take >2000 days for haploid genome

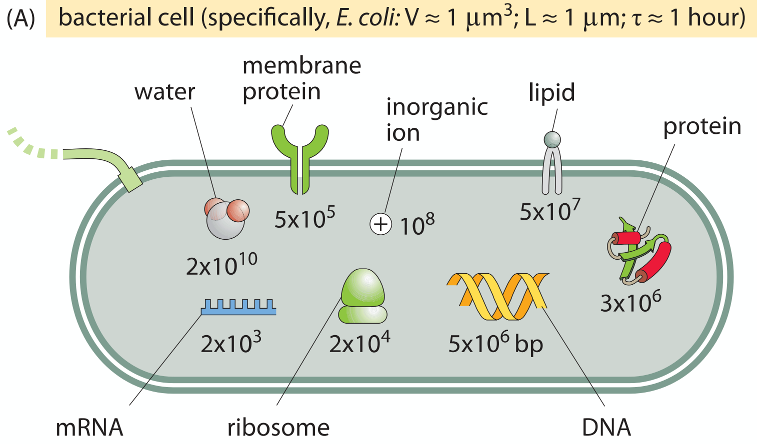
✔ Polyploidy can boost very significantly transcriptional capacity and, thereby, cell growth

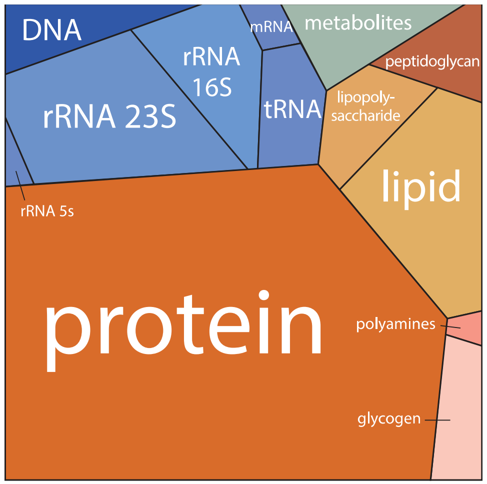
• A major constraint on cell growth:

— Constraint #3: transcription and ribosome assembly

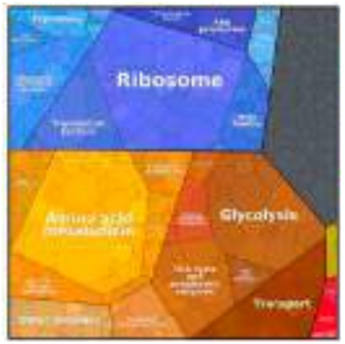
- Ribosomes comprise a significant fraction of a cell dry mass: 10-15% of proteome, 15-25% of dry cell mass
- 20.000 ribosomes in *E. coli*







Proteome of *E. coli*



Liebmeister et al, R. Milo. PNAS (2013)
www.pnas.org/cgi/doi/10.1073/pnas.1314810111

• A major constraint on cell growth:
— Constraint #3: transcription and ribosome assembly

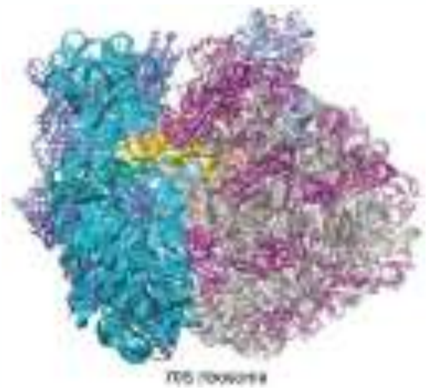
- Ribosomes comprise a significant fraction of cells dry mass (about 10%)
- Millions of ribosomes in eukaryotic cells

- Unlike ribosomal proteins which can be amplified from a pool of mRNAs, rRNAs are structural components of ribosomes (60%) that are produced in large quantities (80% of total RNAs in a cell)
- This requires a large transcriptional capacity of rRNAs
- rRNA amplification enables faster, large scale assembly of ribosomes.

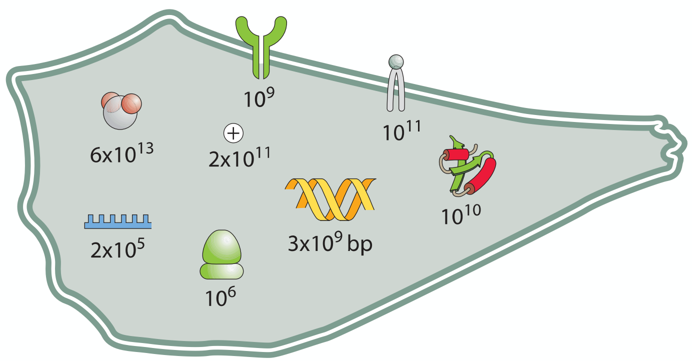
In eukaryotes, ribosomes contain 79–80 proteins and 4 cytopl. rRNAs (28S, 5.8S, 5S, and 18S subunits), and 2 mitoch. rRNAs.

In humans: 3 cytoplasmic RNAs are encoded by a single transcription unit (45S)

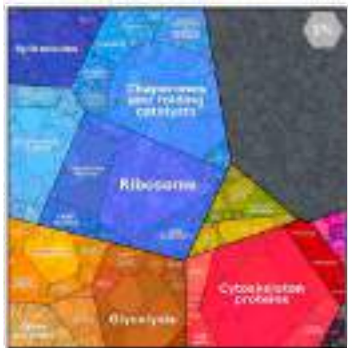
The 45S rDNA is organised into 5 clusters on 5 chromosomes
Many copies of the rRNA genes organised in tandem arrays: 200-300 for 5S, 100-200 for 45S.



(C) mammalian cell (specifically, HeLa: $V \approx 3000\ \mu m^3$; $L \approx 20\ \mu m$; $\tau \approx 1$ day)



H. sapiens (HeLa cell line)



proteome

Liebmeister et al, R. Milo. PNAS (2013)
www.pnas.org/cgi/doi/10.1073/pnas.1314810111

Science 02 Sep 2005:
Vol. 309, Issue 5740, pp. 1508-1514
DOI: 10.1126/science.1111771

- In *Xenopus* oocytes, an additional amplification step of rDNA occurs (replication) to nurture massive cell growth

Brown DD, Dawid IB. 1968. Science 160: 272– 280.
Gall JG. 1968. Proc Natl Acad Sci 60: 553–560.
Oocyte nuclei contain extrachromosomal replicas of the genes for ribosomal RNA.

• Growth of differentiated cell: polyploidy

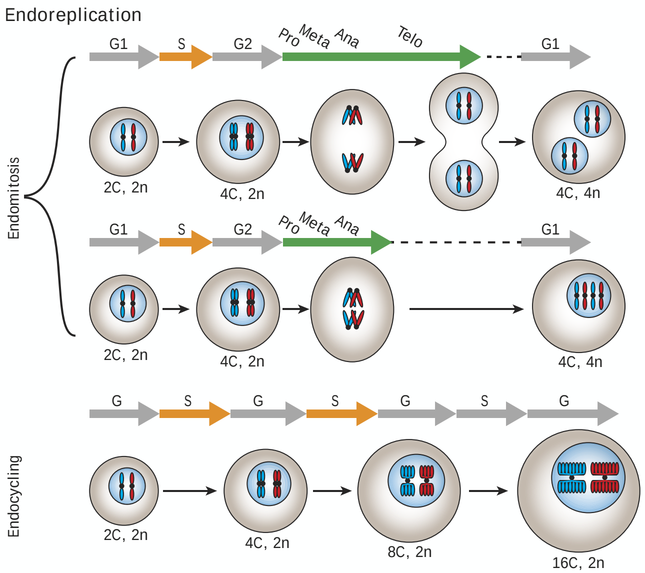
- There is a widespread occurence of polyploidy (vertebrates, invertebrates plants, protists, etc)
- Polyploidy almost always coincides with cell size increase

Cell Type	Organ	Organism	Maximum Ploidy	Cell Cycle	Function of Increased Ploidy
Fol, Eisen Cells	Epithelium	O. dioica	1300C	Endocycle	Control body size and nutritive input?
Subperineurial Glia (SPG)	Nervous System	Drosophila	32C	Endocycle and Endomitosis	Increased cell size to maintain blood-brain barrier
Trophoblast Giant Cell (TGC)	Placenta	Rodents	512C	Endocycle	Increased cell size for placental barrier?
Kerantinocytes	Skin	Mouse Human	12C	Endocycle and Endomitosis	Increased cell size for protective function of skin?
Giant Cells	Leaf and Sepal	Arabidopsis	16C	Endocycle	Controls curvature of leaves and sepals
Scale-building cells	Wing	Manduca	16C-64C	Endocycle	Determines cell size and thus pigmented regions
Rectal Papillae	Intestine	Drosophila	8C	Endocycle	Endocycle followed by mitotic divisions necessary for papillae formation and control of salt and water absorption
Syncytial Yolk Nuclei	Embryo	Zebrafish	8C-40C	? Endocycle	? Function
Giant Neuron	Nervous System	Aplysia	200,000C	? Endocycle	Sufficient neuronal size to innervate large area
Giant Neuron	Nervous System	Limax Slug	10,000C	? Endocycle	Sufficient neuronal size to innervate large area
Cardiomyocytes	Heart	Mouse	4C-8C	Endomitosis Endocycle	Mechanism for cell growth postnatally and in response to cardiac damage
Megakaryocyte	Blood	Mammals	128C	Endomitosis	Large cell size required for sufficient platelet production
Trichomes	Leaf	Arabidopsis	32C	Endocycle	Controls formation and branching in trichomes
Nurse cells	Ovary	Drosophila	512C	Endocycle	Synthesis and transport maternal stockpiles to oocyte
Follicle cells	Ovary	Drosophila	16C	Endocycle	Synthesis of eggshell
Hypodermal cell (Hyp7)	Hypodermis	*C. elegans* nematodes	12C	Endocycle	Endocycling to increase ploidy following cell fusion. Ploidy levels control body size
Hepatocytes	Liver	Mammals	16C	Endomitosis Endocycle	First observed step in regeneration

T. Orr-Weaver *Trends Genet*. (2015) ; 31(6): 307–315

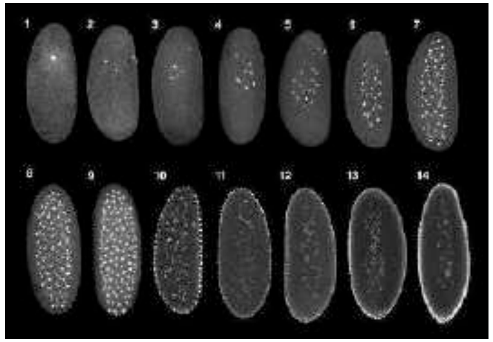
• Growth of differentiated cell: polyploidy

- Polyploidy results from endoreplication by endomitosis or endocycling

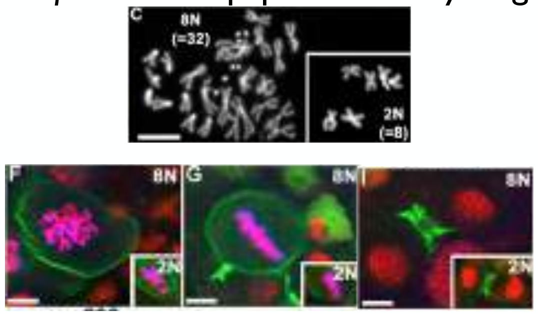


Øvrebø JI. & Edgar B. Development (2018) 145, dev156034. doi:10.1242/dev.156034

Drosophila embryo syncitium: endomitosis

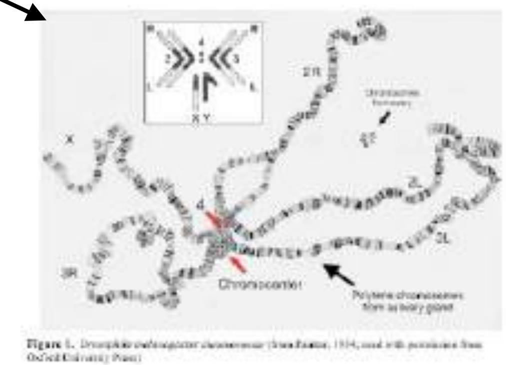


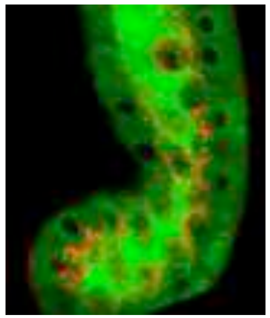
Drosophila rectal papillae: endocycling



DT. Fox, J Gall and A. Spradling GENES & DEVELOPMENT 24:2294–2302 (2010)

Drosophila salivary gland: endocycling

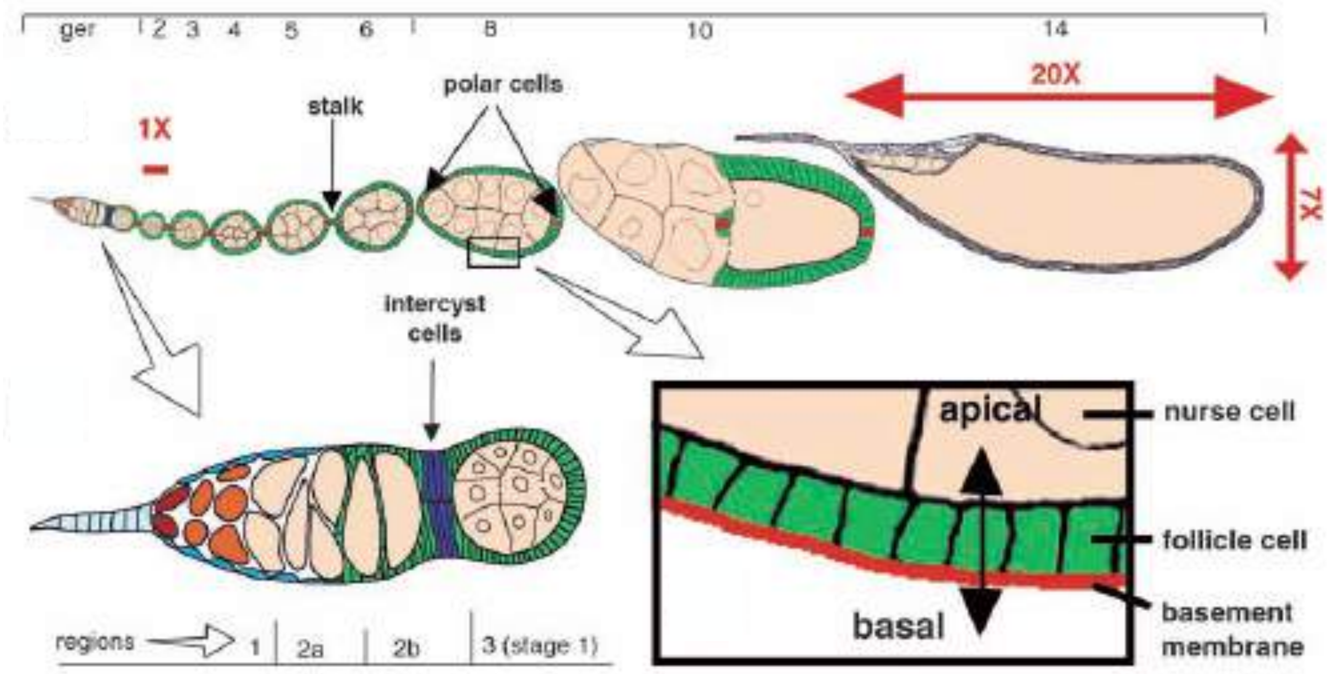




http://shilolabweb.weizmann.ac.il/

• Growth of differentiated cell: polyploidy

Examples: *Drosophila* oocyte: both endomitosis (16 nurse cells are connected due to incomplete cytokinesis) and encoreplication (512C)

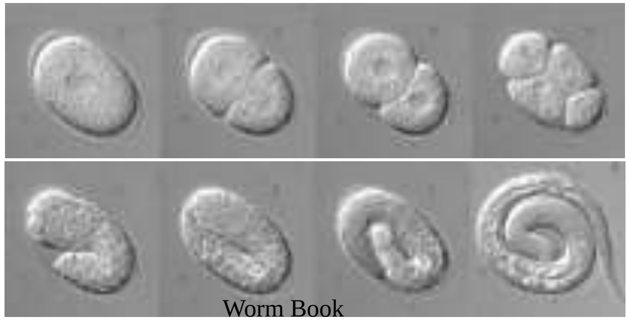


H. Frydman and A. Spradling. *Development* 128, 3209-3220 (2001)

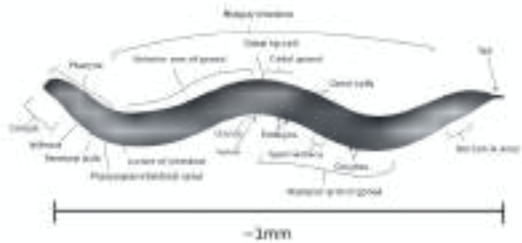
• Growth of differentiated cell: polyploidy

- Small (C. elegans) and Large (Ascaris sp) worms have same embryo size (50µm)
- Larval growth determines final size.
- In large worms the cell number and 3D organisation is the same as in small worms, but cell size is massively different (4mm for intestinal in *Strongylus equus* intestine cell).

C. elegans

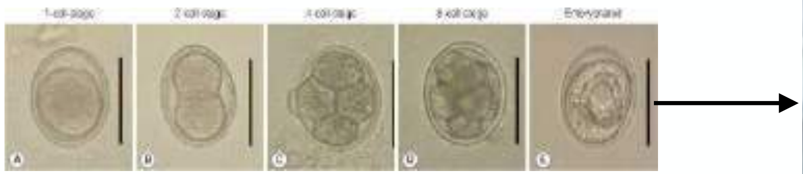


Worm Book



https://en.wikipedia.org/wiki/Caenorhabditis_elegans

Ascaris suum/lumbricoides



M-K Kim et al. *The Korean Journal of Parasitology* 2012; 50(3): 239-242.

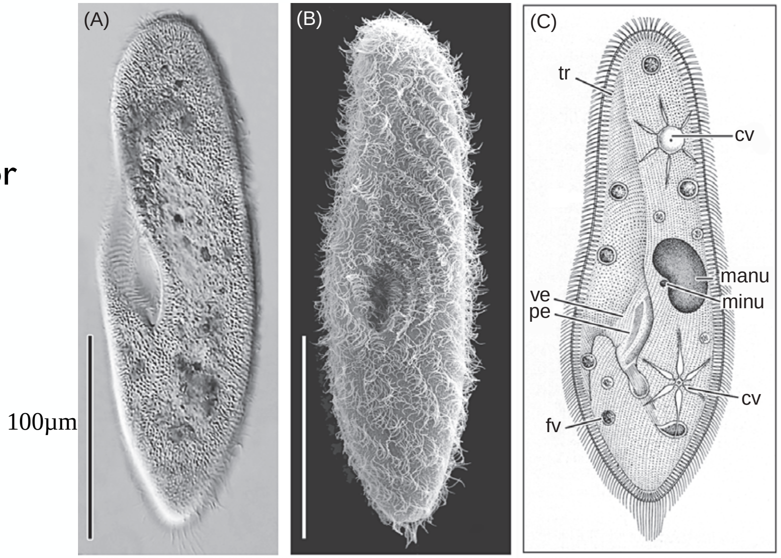
https://en.wikipedia.org/wiki/Ascaris_suum

« Comparisons of neuronal morphologies in the retrovesicular ganglia of *Ascaris* and C. *elegans* suggest that each neuron in *Ascaris* can be assigned a corresponding homolog in **C.***elegans.* These data provide further evidence for a remarkable conservation of neuronal morphology in nematodes despite large differences in size and habitat. »

Journal of Comparative Neurology 284374-388 (1989)

• Growth of differentiated cell: polyploidy in Ciliates

- Ciliates form an extremely vast phylum that separated from ancestors of plants and animals 1 billion years ago
- All ciliates have micronuclei (« germline ») and macronuclei (for vegetative growth).
- macronuclei range from 4C to 800C.



Paramecium caudate

K. Hausmann and R. Allen. METHODS IN CELL BIOLOGY, VOL. 96
DOI: 10.1016/S0091-679X(10)96007-X

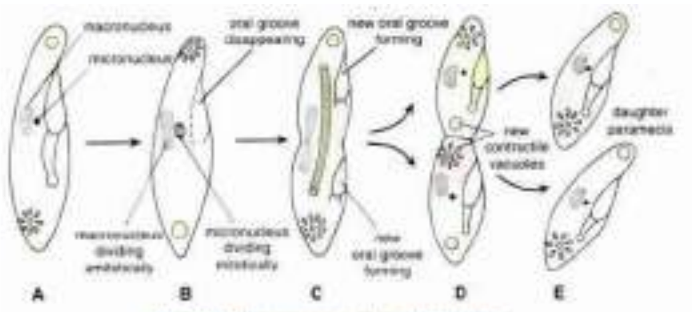
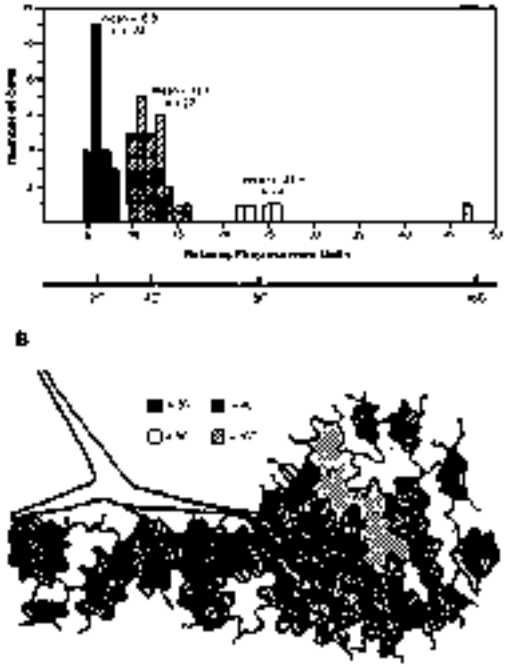


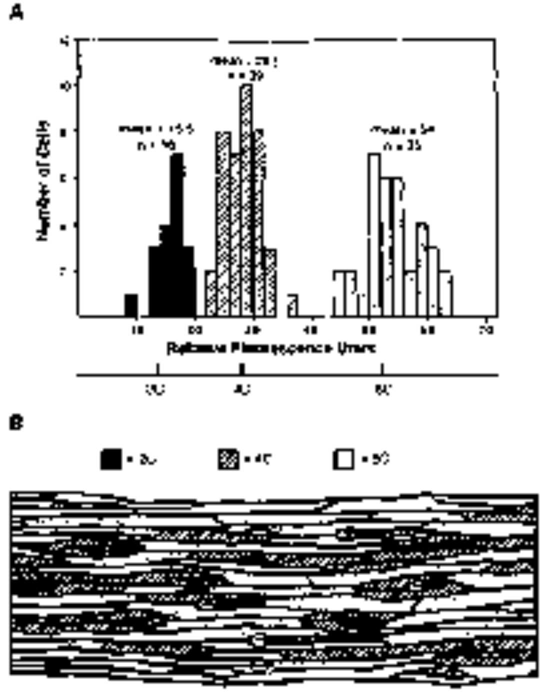
Fig. 28.20. *Paramecium caudatum*. Binary fission.

Stentor roeseli

• Growth of differentiated cell: endocycles in Plants

- Endocycles in plant cells both in leaves and stems
- Cell ploidy varies from 2C -16C
- Ploidy correlates with cell size





Ploidy — Surface — Volume

Table 1. A Summary of the Relationship between Nuclear DNA Quantity and Cell Size for Epidermal Pavement Cells in Arabidopsis

Cells	Nuclear Genome Size	No. of Cells (% of Total)	Avg. Cell Perimeter in µm (Range)	Avg. Cell Area in µm² (Range)	Avg. Surface Area/Cell in µm² (Range)[a]	Avg. Cell Volume in µm³ (Range)[b]
Stem cells (n = 92)	2C	18 (20%)	138 (79–193)	814 (244–1070)	2867 (1446–4346)	7368 (2928–12840)
	4C	39 (42%)	382 (137–612)	2471 (575–4056)	9650 (2794–15144)	29852 (6900–48672)
	8C	35 (38%)	667 (379–1299)	5254 (2822–9513)	18751 (11418–34614)	63048 (33864–114156)
Leaf cells (n = 110)	2C	40 (36%)	96 (38–200)	480 (154–1331)	1818 (888–4662)	4800 (1540–13310)
	4C	53 (48%)	199 (101–350)	1495 (584–3053)	4949 (2178–9260)	14950 (5840–30530)
	8C	16 (15%)	372 (251–461)	3794 (2116–4845)	11306 (8742–13474)	37940 (21160–48450)
	16C	1 (1%)	642	8153	22726	81530

[a] Total cell surface area was calculated for each cell as the sum of two times the measured cell area plus the perimeter times the cell depth (determined from microscopic observation).
[b] Cell volume was calculated for each cell as the cell area times the cell depth.

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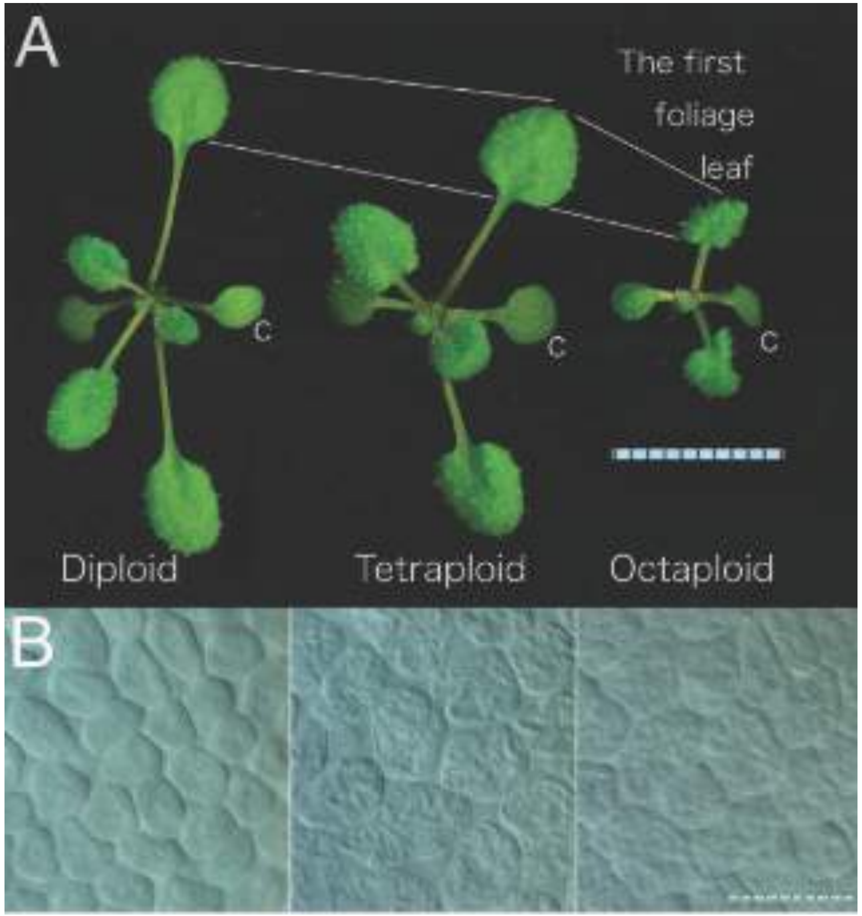
J.E. Melaragno et al . *The Plant Cell* (1993); 5: 1661-1668

• Growth of differentiated cell: endocycles in Plants

- Polyploidy induces cell growth in *Arabidopsis*



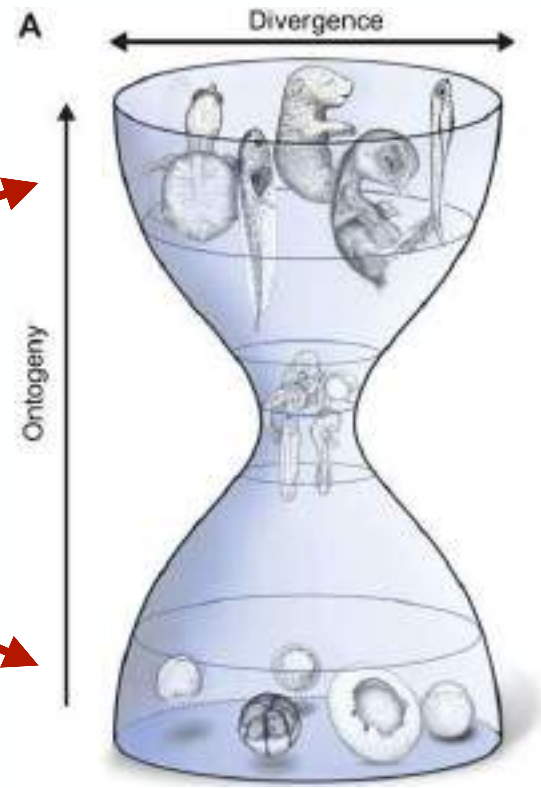
doi:10.1371/journal.pbio.0060174.g002

• Constraints on growth fashioned developmental strategies

Constraint #1: Growth phases occur prior to and after developmental patterning occurs
Constraint #2 : Cell scale: Differentiated cells cannot divide.
Constraint #3 : Cell scale: Transcription and ribosome assembly

- Postembryonic Growth
(polyploidy or delayed differentiation)

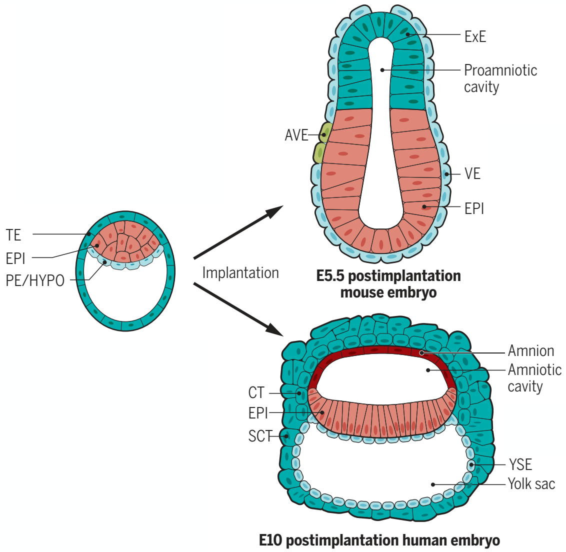
- Growth before development: Oogenesis
(polyploidy)



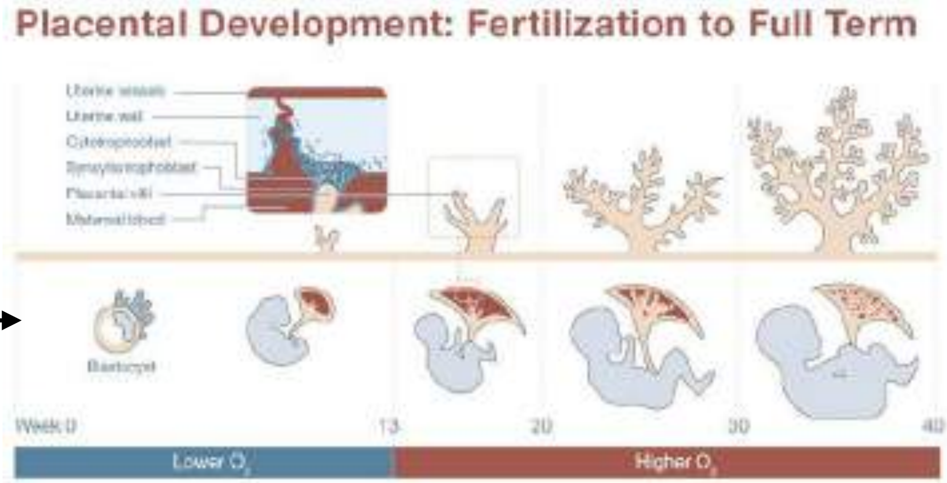
A. Abzhanov *Trends in Genetics* (2013), Vol. 29, No. 12

• Relaxation of growth constraints in Mammals

—Viviparous development: slow growth by proliferation in a protected environment (enables growth of enormous animals at birth)



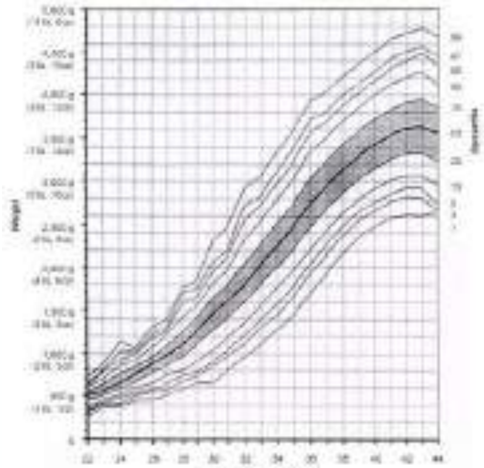
M. Shahbazi , E. Siggia and M. Zernicka-Goetz *Science* 364, 948–951 (2019)



https://www.nichd.nih.gov/research/supported/HPP/form

- Small egg at fertilisation
- Long proliferation phase associated with gradual growth
- Substantial growth in utero post development: long process

mouse: 0.05g to 1.5g — 21 days
human: 0.05g to 3.5 kg — 270 days
whale: 0.05g to 7T — 480-590 days



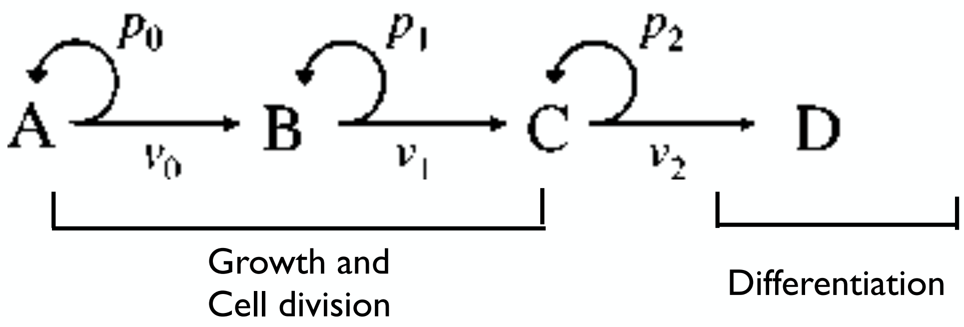
https://www.aafp.org/afp/1998/0801/p453.html

• Relaxation of growth constraints in Mammals

—Viviparous development: slow growth by proliferation in a protected environment

—Proliferation and delayed differentiation in a stem cell based lineage

—Cell lineages balance growth (of stem cell pool and intermediates, called transit amplifying cells) and terminal differentiation.

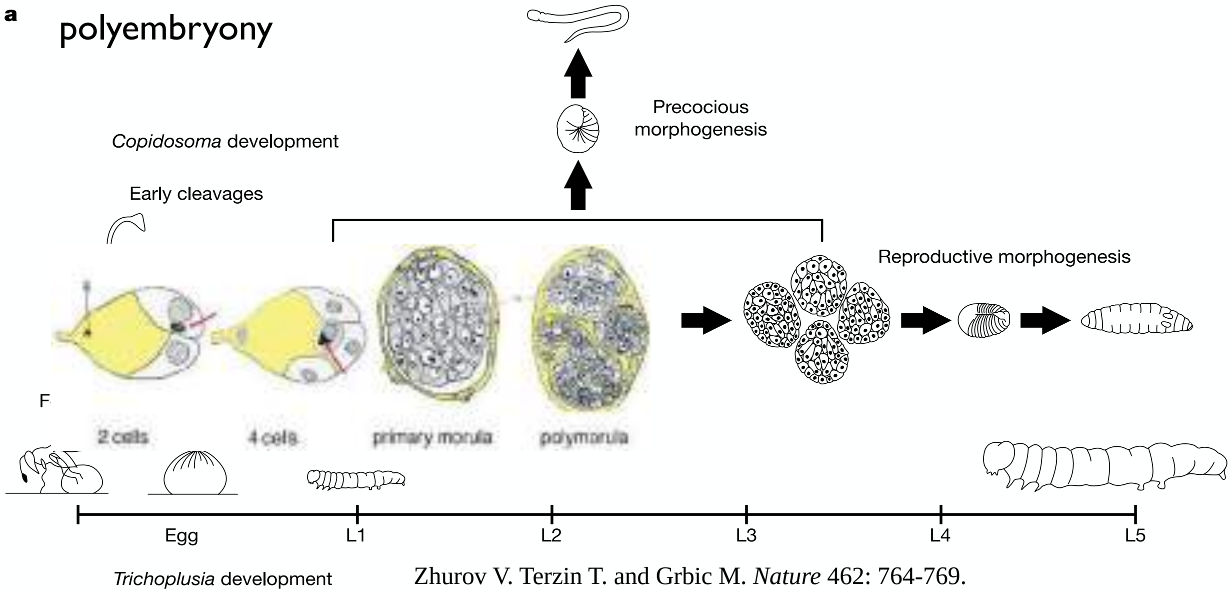


• Relaxation of growth constraints in endoparasites

— endo-parasitic development: using a host larva or egg as a uterus

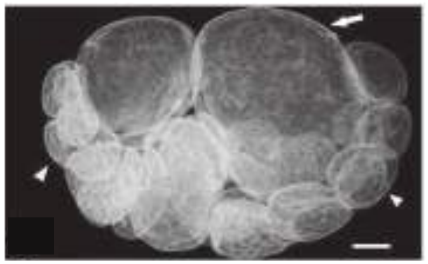
Trichoplusia

A large caterpillar is akin to a uterus

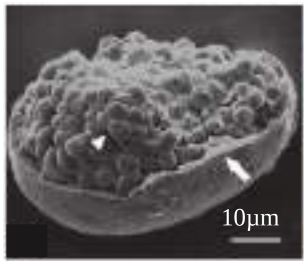


Zhurov V. Terzin T. and Grbic M. *Nature* 462: 764-769.
C. Extavour. *BioEssays* 26:1263–1267, ß 2004

polymorula



morula



Grbic M. et al. Strand M. *Development* 122:795-804 (1996)

• Relaxation of growth constraints in endoparasites

— Miniaturization in endoparasitic wasps

Vesparum de Xenos

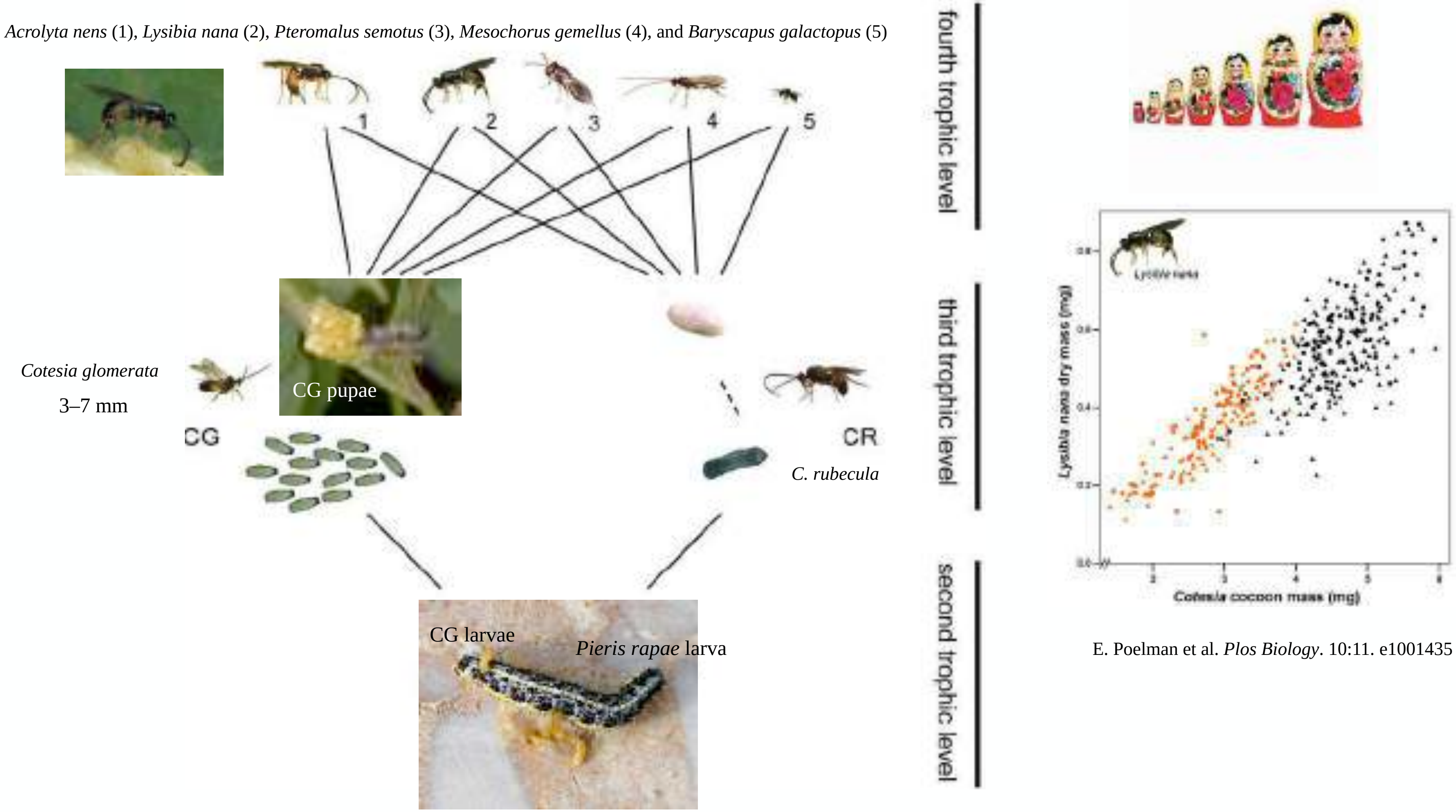
Trissolcus japonicus

A samurai wasp (*Trissolcus japonicus*) lays an egg inside a brown marmorated stink bug (*Halyomorpha halys*)

• Relaxation of growth constraints in endoparasites

— Hyperparasitisms: « russian dolls » and miniaturisation

Acrolyta nens (1), *Lysibia nana* (2), *Pteromalus semotus* (3), *Mesochorus gemellus* (4), and *Baryscapus galactopus* (5)



E. Poelman et al. *Plos Biology*. 10:11. e1001435

https://en.wikipedia.org/wiki/Cotesia_glomerata

http://erikpoelman.com/site/hyperparasitoids/

• Summary

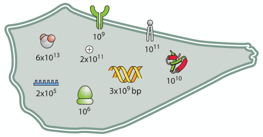
1. Cells and organisms explore sizes over many orders of magnitude:
   — suggests high plasticity
2. Embryonic and post-embryonic growth both contribute to animal size
3. Yet, organism size is extremely constrained
4. Constraint #1: embryo size is constrained when body pattern is established:
   —Most growth occurs prior to or after this stage.
5. Constraint #2: differentiated cells cannot divide which implies:
   —Growth of differentiated cells or delayed differentiation
6. Constraint #3: cell growth is limited by transcription and ribosome assembly rates:
   —Cell polyploidy is a universal solution
7. Relaxation of constraints in placental and endo-parasitic development
   —Slow development is permitted in the protected environment of mother/host.
   —Stem cell based development and growth of lineage.

- Motor, Constraints and Regulation of Growth

Energy supply

carbohydrates
amino-acids
ions etc

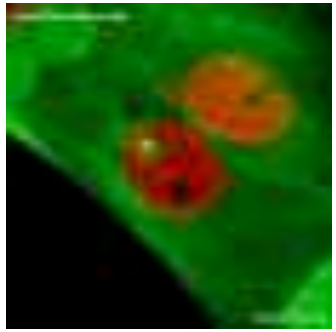
Metabolism



Synthesis:
ATP, amino-acids, proteins, lipids, carbohydrates, etc

H_2O flux

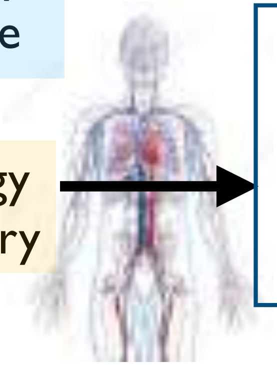
Cell growth, division



kidney cell

Energy uptake

Energy delivery



Energy → Metabolism → Cell growth division

Kidney, liver

Feedback #3 coordination

Organ growth

Size-meter

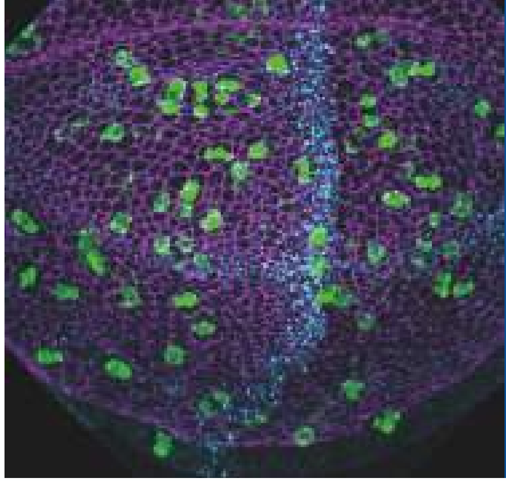
Gut, muscle, bones, …

Feedbacks: #1 Patterning, #2 Mechanics

Programmed vs Self-organised regulation of Growth

- hierarchical
- modular
- deterministic rules (ie. genetically encoded)

- no hierarchy
- **feedbacks**
- statistical rules



COLLÈGE DE FRANCE 1530

CHAIRE DYNAMIQUES DU VIVANT
Année académique 2019-2020

Thomas LECUIT

Moteurs, contraintes et régulations de la croissance

Cours les mardis de 10h à 11h30
Amphithéâtre Guillaume Budé

Cours :

12 novembre 2019	Introduction : comment la taille biologique est-elle codée ?
19 novembre 2019	Lois d'échelle, allométrie et croissance des organismes
26 novembre 2019	Croissance des organes et contrôle interne
03 décembre 2019	Contrôle interne et patterning
10 décembre 2019	Contrôle interne et mécanique
17 décembre 2019	Coordination et symétrie - Conclusion

Colloque :

Contraintes et plasticité au cours du développement et de l'évolution
(avec Denis Duboule, chaire Évolution des génomes et développement)

Le mardi 30 juin et le mercredi 1er juillet, de 9h à 18h
Amphithéâtre Maurice Halbwachs