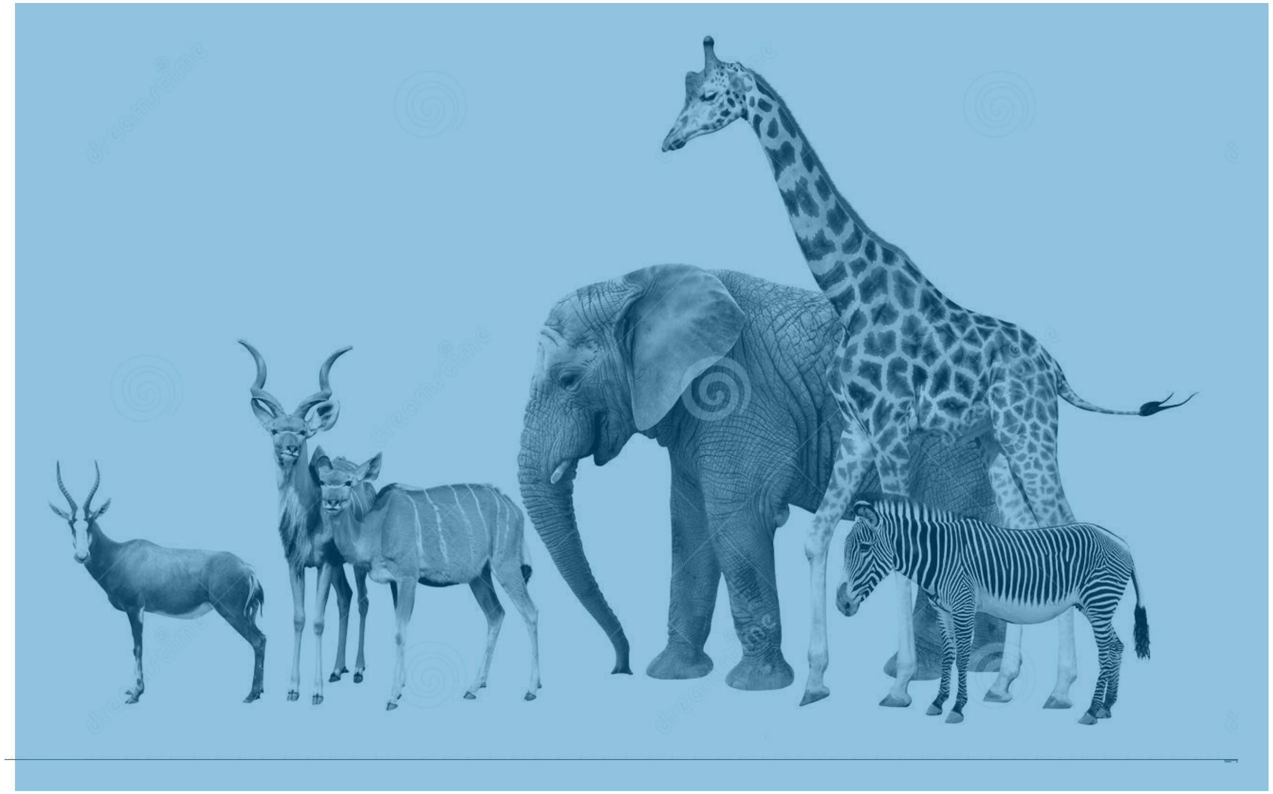
Organism and Tissue Growth



Course 2: Scaling laws

Thomas Lecuit

chaire: Dynamiques du vivant

COLLÈGE
DE FRANCE
1530

• 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
5. Constraint #2: differentiated cells cannot divide which implies:
   —Cell growth or delayed differentiation
6. Constraint #3: cell growth is limited by transcription and ribosome assembly . 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.

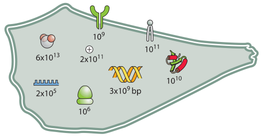
- Motor, Constraints and Regulation of Growth

Energy supply

carbohydrates
amino-acids
ions etc

→

Metabolism

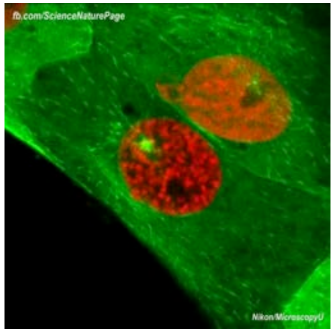


Synthesis:
ATP, amino-acids, proteins,
lipids, carbohydrates, etc

H_2O flux

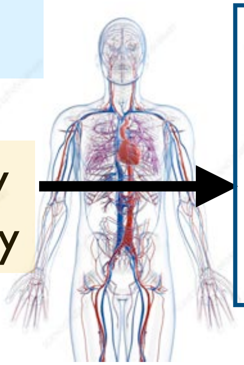
→

Cell growth,
division



kidney cell

Energy uptake
↓
Energy delivery



Energy → Metabolism → Cell growth division

→ Kidney, liver
→ Organ growth
→ Gut, muscle, bones, …

Feedback #3 coordination

Size-meter

Feedbacks: #1 Patterning, #2 Mechanics

• Isometry: growth that keeps proportions

— Isometry: geometric similarity

In the absence of gravity, geometric similarity is expected

Volume V or Mass $W \propto L^3$

$$L \propto W^{1/3}$$

https://www.thoughtco.com/l

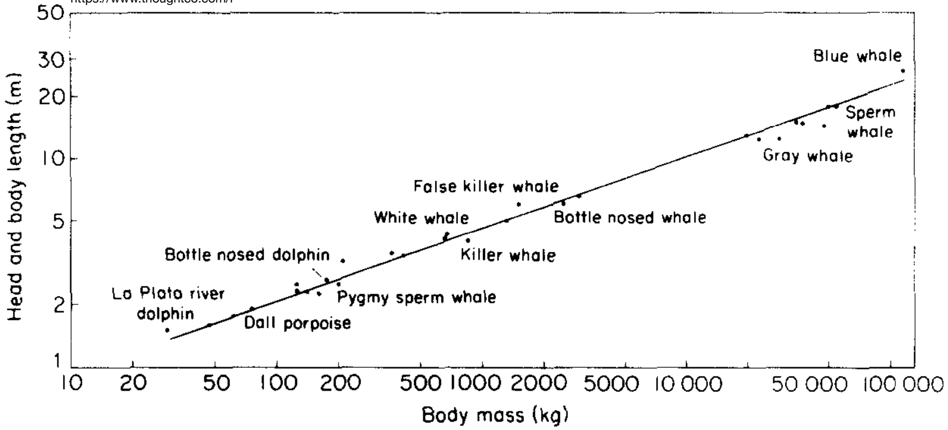


FIG. 1 Correlation of head-and-body-length, L, with body mass, M, in 24 sea mammals (29 values). The equation of the regression line is $L = 0{\cdot}44\, M^{0{\cdot}339}$ (correlation coefficient $r = 0{\cdot}997$, 95% confidence limits for the exponent: 0·330–0·348.) (Data from Walker, 1975.)

A. Economos *The Journal of Theoretical Biology* 103:167-172 (1983)

• Isometry: growth that keeps proportions

— Isometry: geometric similarity

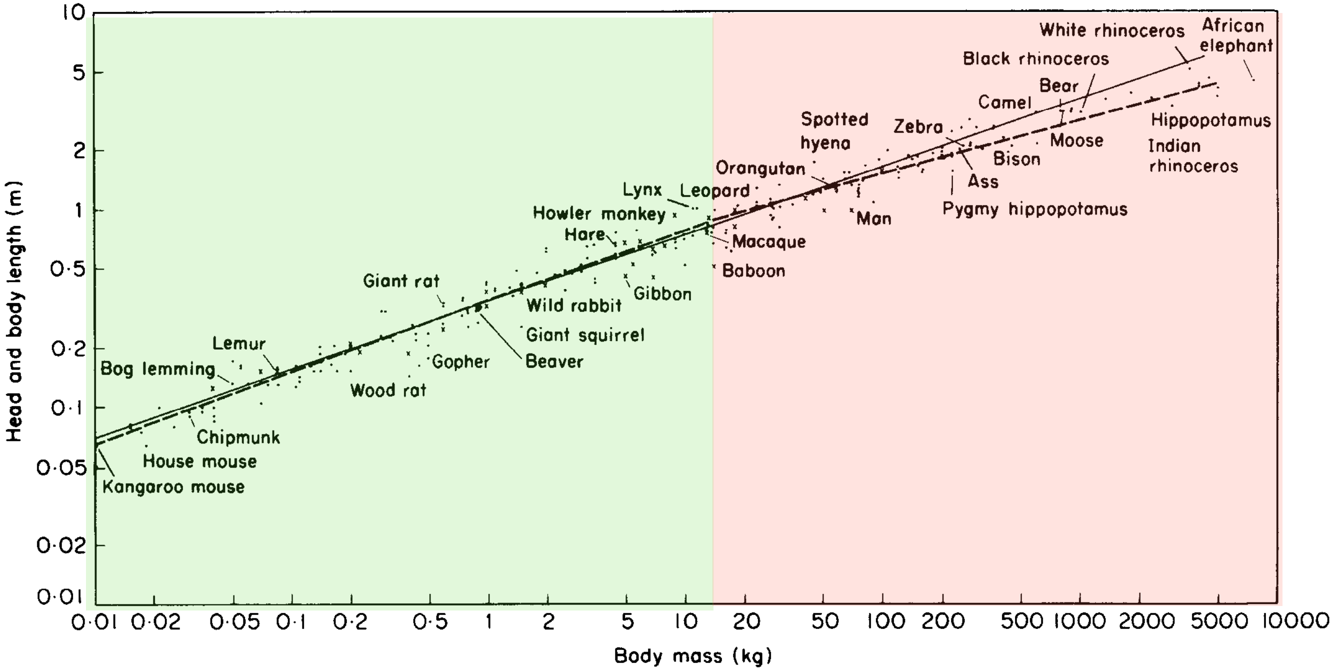
Geometric similarity for small terrestrial mammals

$\mathrm{L} \sim \mathrm{d}$ and $\mathrm{L} \propto \mathrm{W}^{1/3}$

—Allometry:
deviation from geometric similarity

$(M \leq 20\ \mathrm{kg})$: $L = 0{\cdot}329 M^{0{\cdot}336}$

$(M > 20\ \mathrm{kg})$: $L = 0{\cdot}441\, M^{0{\cdot}266}$



A. Economos *The Journal of Theoretical Biology* 103:167-172 (1983)

• Allometry: the law of relative growth

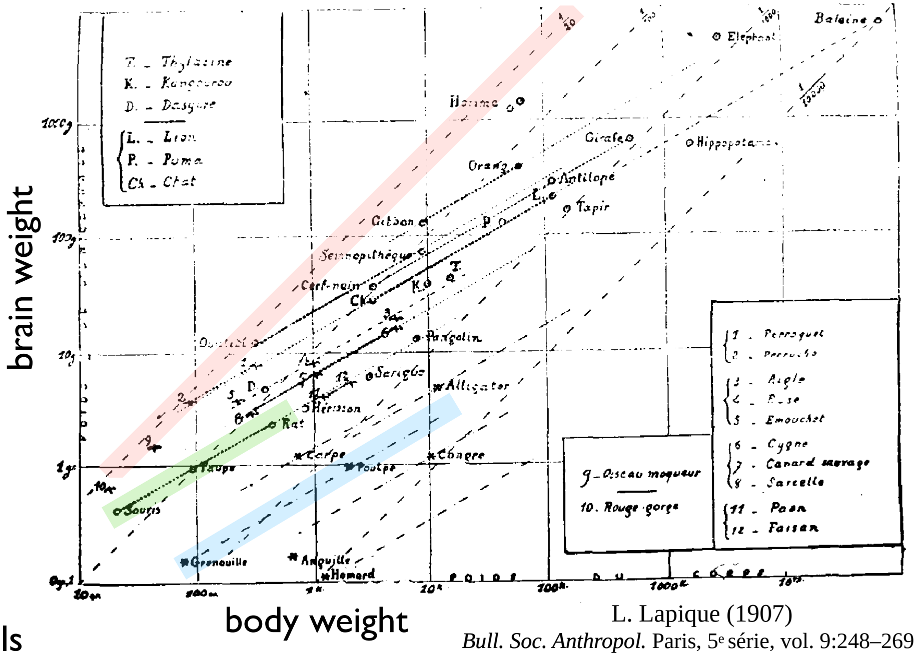
- Eugène Dubois (1897): dutch naturalist, studies the relation between the weights of the brain and body.
  Distinction between size and cephalisation

  — Power law: $e = c.\, s^{r}$

  encephalon | soma

- Louis Lapique (1907): french physiologist used Dubois's formula (isoneural lines)

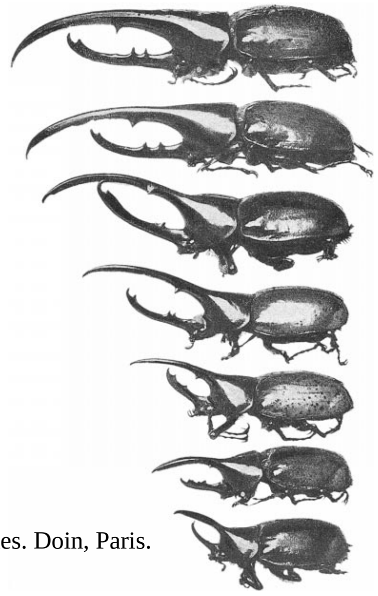
🟥 Hypothetical isometry: coefficient 1
🟩 Dubois' calculation for mammals: coefficient 0.56
🟦 Hypothesis for birds, frogs and other non-mammals



L. Lapique (1907)
Bull. Soc. Anthropol. Paris, 5^{e} série, vol. 9:248–269

- Albert Pézard and Christian Champy : relative growth studies.

  — isogonic and heterogonic growth (Pézard)
  — harmonic and dysharmonic growth (Champy)



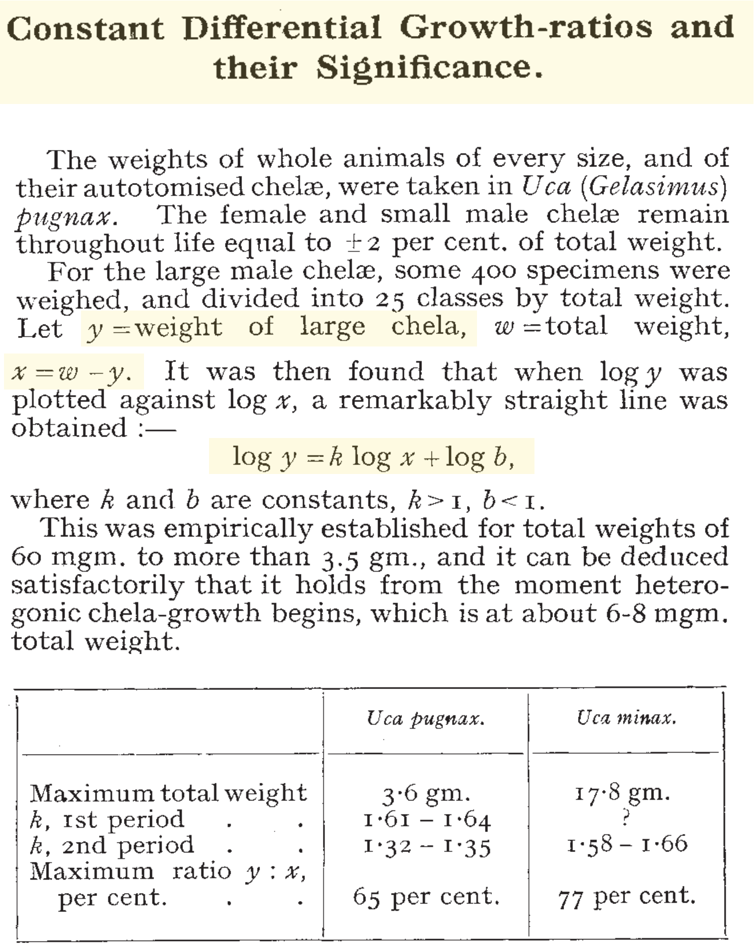
C. Champy (1924) Sexualité et hormones. Doin, Paris.

Thomas LECUIT 2019-2020

Jean Gayon. *American Zoologist*, (2000) 40(5):748-758

• Allometry: the law of relative growth

- Julian Huxley: study of fiddler crabs in MBL, Woods Hole



Constant Differential Growth-ratios and their Significance.

The weights of whole animals of every size, and of their autotomised chelæ, were taken in *Uca* (*Gelasimus*) *pugnax*. The female and small male chelæ remain throughout life equal to ± 2 per cent. of total weight.

For the large male chelæ, some 400 specimens were weighed, and divided into 25 classes by total weight. Let y = weight of large chela, w = total weight, $x = w - y$. It was then found that when $\log y$ was plotted against $\log x$, a remarkably straight line was obtained :—

$$\log y = k \log x + \log b,$$

where k and b are constants, $k > 1$, $b < 1$.

This was empirically established for total weights of 60 mgm. to more than 3.5 gm., and it can be deduced satisfactorily that it holds from the moment heterogonic chela-growth begins, which is at about 6-8 mgm. total weight.

	Uca pugnax.	*Uca minax.*
Maximum total weight	3·6 gm.	17·8 gm.
k, 1st period . .	1·61 – 1·64	?
k, 2nd period . .	1·32 – 1·35	1·58 – 1·66
Maximum ratio $y : x$, per cent. . .	65 per cent.	77 per cent.

Julian S. Huxley 1887-1975

Fiddler crabs

https://www.earth.com/news/fiddler-crabs-separate-light/

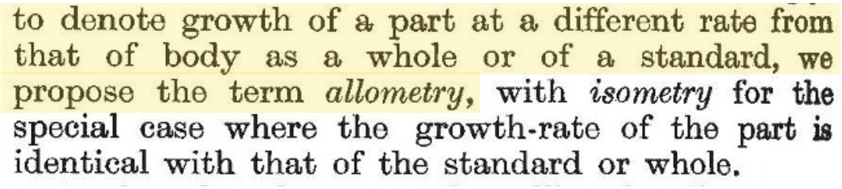
https://petponder.com/fiddler-crab-care

Huxley, J. S. 1924. *Nature* 114:895–896.

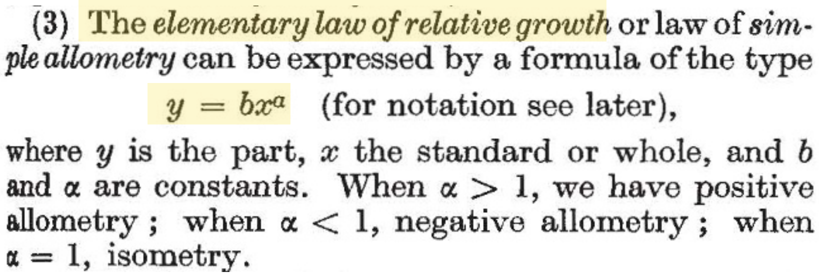
Allometry: law of relative growth

- Julian Huxley and Georges Teissier: Coin « isometry » and « allometry » in 1936 together with power law description of relative growth
- Power law description reflects self-similarity or scale invariance: $f(x) = b.\,x^a$ so $f(cx) = c^a.\,b.x^a \propto f(x)$

Huxley, J. S. and G. Teissier. 1936*a*. Terminology of relative growth. *Nature* 137:780–781.
Huxley, J. S. and G. Teissier. 1936*b*. Terminologie et notation dans la description de la croissance relative. C*omptes rendus séances soc. biol. fil.* 121: 934 –937.



to denote growth of a part at a different rate from that of body as a whole or of a standard, we propose the term *allometry*, with *isometry* for the special case where the growth-rate of the part is identical with that of the standard or whole.



(3) The *elementary law of relative growth* or law of *simple allometry* can be expressed by a formula of the type

$$y = bx^a \quad \text{(for notation see later),}$$

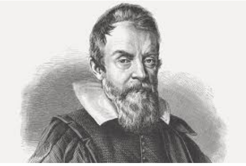
where y is the part, x the standard or whole, and b and α are constants. When $\alpha > 1$, we have positive allometry; when $\alpha < 1$, negative allometry; when $\alpha = 1$, isometry.

Julian S. Huxley 1887-1975

Georges Teissier 1900-1972

• Allometry: deviation from geometric similarity

— Mechanical considerations:

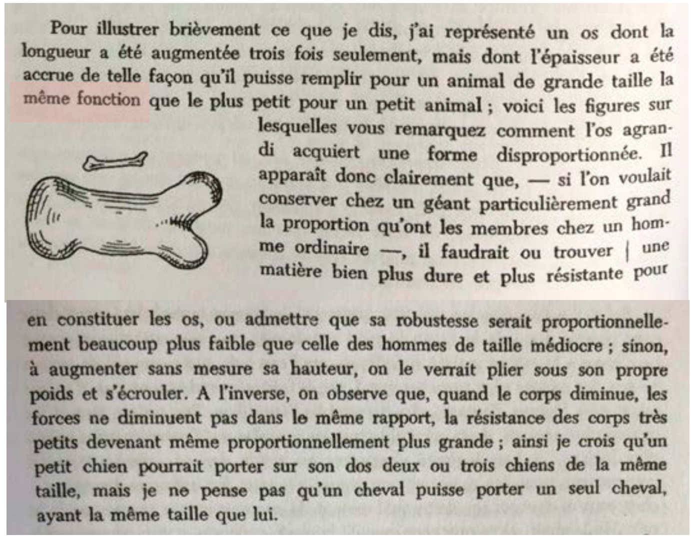


Galileo

DISCORSI
E
DIMOSTRAZIONI
MATEMATICHE,
intorno à due nuoue ſcienze
Attenenti alla
MECANICA & i MOVIMENTI LOCALI;
del Signor
GALILEO GALILEI LINCEO,
Filoſofo e Matematico primario del Sereniſſimo
Grand Duca di Toſcana.
Con vna Appendice del centro di grauità d'alcuni Solidi,

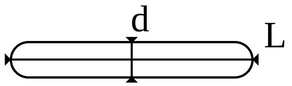
IN LEIDA.
Appreſſo gli Elſevirii. M. D. C. XXXVIII.

Discours et démonstrations mathématiques concernant deux sciences nouvelles sur la mécanique et le mouvement, 1638
Puf, Epiméthée (ed. 1995)



Pour illustrer brièvement ce que je dis, j'ai représenté un os dont la longueur a été augmentée trois fois seulement, mais dont l'épaisseur a été accrue de telle façon qu'il puisse remplir pour un animal de grande taille la même fonction que le plus petit pour un petit animal ; voici les figures sur lesquelles vous remarquez comment l'os agrandi acquiert une forme disproportionnée. Il apparaît donc clairement que, — si l'on voulait conserver chez un géant particulièrement grand la proportion qu'ont les membres chez un homme ordinaire —, il faudrait ou trouver | une matière bien plus dure et plus résistante pour en constituer les os, ou admettre que sa robustesse serait proportionnellement beaucoup plus faible que celle des hommes de taille médiocre ; sinon, à augmenter sans mesure sa hauteur, on le verrait plier sous son propre poids et s'écrouler. A l'inverse, on observe que, quand le corps diminue, les forces ne diminuent pas dans le même rapport, la résistance des corps très petits devenant même proportionnellement plus grande ; ainsi je crois qu'un petit chien pourrait porter sur son dos deux ou trois chiens de la même taille, mais je ne pense pas qu'un cheval puisse porter un seul cheval, ayant la même taille que lui.

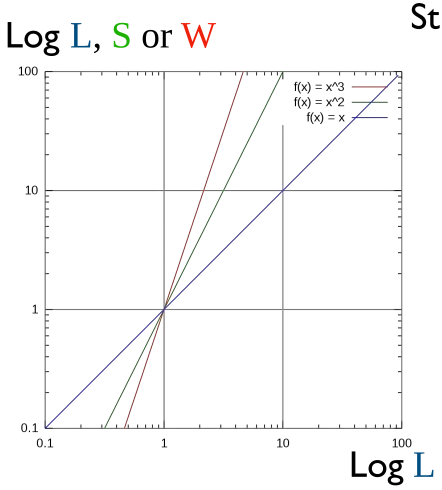
As an animal gets larger, its mechanical strength (eg. Bone sectional area) grows slower than mass and body weight.
So there is a maximal limit to animal size or new morphology is required (eg. larger legs).
— Predicts allometric scaling



(L ~ d)

Section ~ L^2
Volume V ~ L^3
so Mass $W \propto L^3$
Section $S \propto W^{2/3}$

Strength ~ Cross sectional area ~ $L^2 \propto W^{2/3}$



Stress $\sigma = F/S \propto W / W^{2/3} = W^{1/3}$

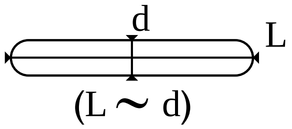
elephant

dog

• Allometry: mechanical considerations

—Elastic similarity: size reflects constraints imposed by elasticity

— maintains similar elastic deformations under equivalent loading conditions



Mass w proportional to body mass W

Size and Shape in Biology

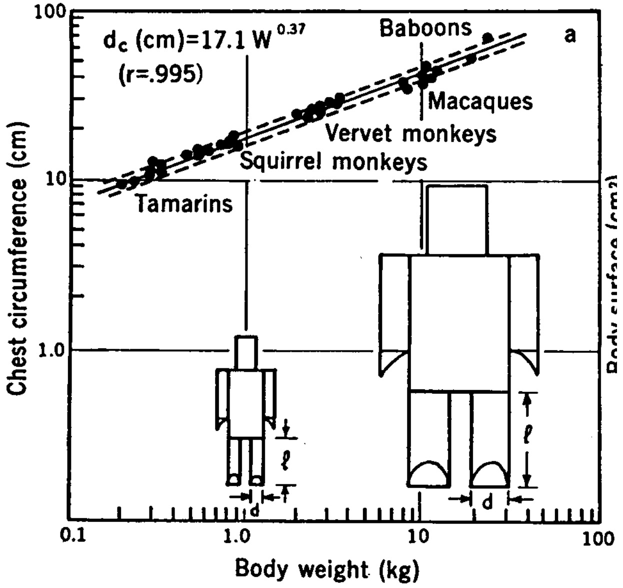
Elastic criteria impose limits on biological proportions, and consequently on metabolic rates.

Thomas McMahon

- Geometric similarity $L \sim d$
- Elastic similarity $L \sim d^{2/3}$

  and $W \propto L.d^2$

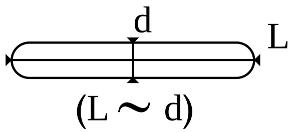
so we have
$$\left| \begin{array}{l} L \propto W^{1/4} \\ d \propto W^{3/8} \end{array} \right. \quad (3/8 = 0.375)$$



McMahon, T. A. (1973). Size and shape in biology. *Science* 179, 1201-1204.

• Allometry: mechanical considerations

—Elastic similarity: size reflects constraints imposed by elasticity



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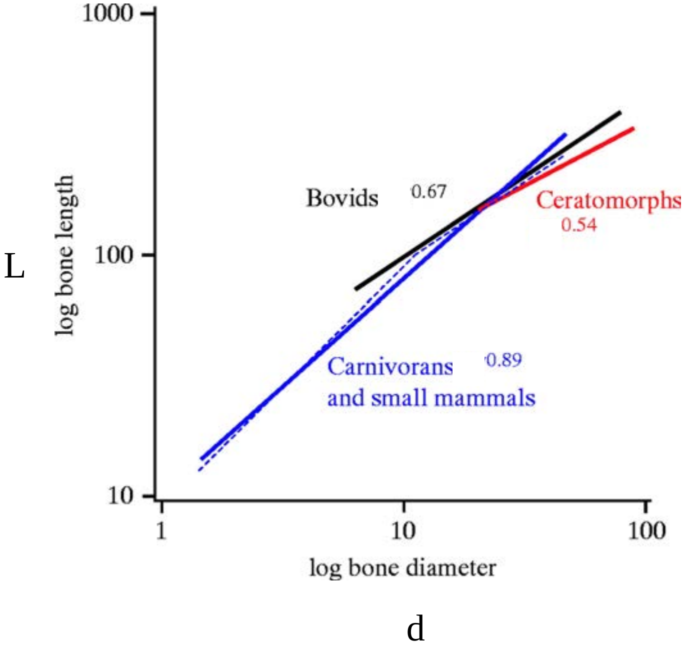
McMahon, T. A. (1973). Size and shape in biology. *Science* 179, 1201-1204.



A. Biewener *The Journal of Experimental Biology* 208, 1665-1676 (2005)

• Allometry: mechanical considerations

—Elastic similarity: size reflects constraints imposed by elasticity

- Geometric similarity $L \sim d$
- Elastic similarity $L \sim d^{2/3} \sim W^{1/4}$

  — maintains similar elastic deformations under equivalent loading conditions

  — ensures elastic stability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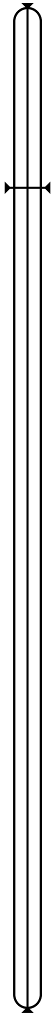
www.regardsurlemonde.fr



L: Tree height

d: diameter

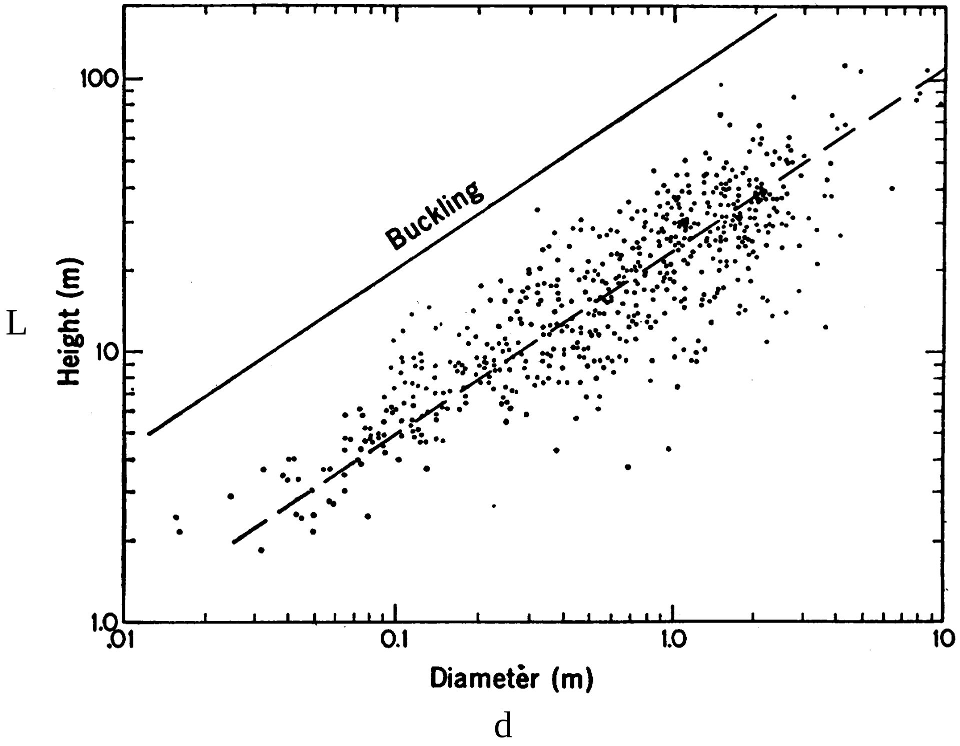
Buckling length

bulk Young modulus

density

$$l_{cr} = 0.851 \left|\frac{E}{\rho}\right|^{1/3} d^{2/3}$$

The size of trees in America is limited by elastic buckling



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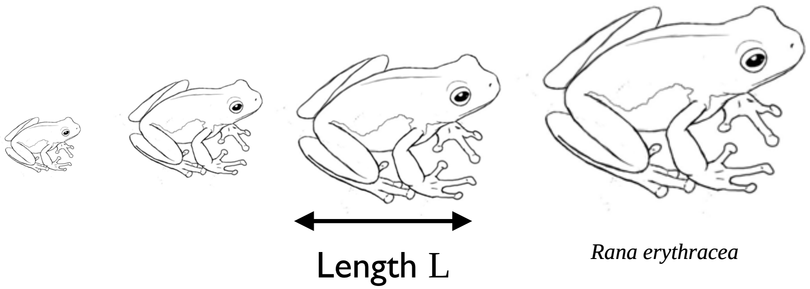
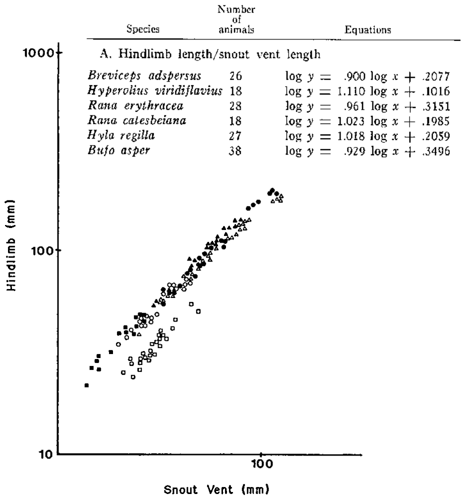
Allometry: mechanical considerations



Rana erythracea

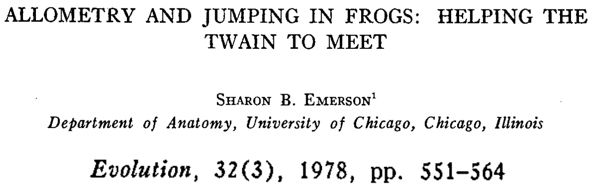
- The length of hindlimb and body scale geometrically



Species	Number of animals	Equations
A. Hindlimb length/snout vent length		
Breviceps adspersus	26	$\log y = .900 \log x + .2077$
Hyperolius viridiflavius	18	$\log y = 1.110 \log x + .1016$
Rana erythracea	28	$\log y = .961 \log x + .3151$
Rana catesbeiana	18	$\log y = 1.023 \log x + .1985$
Hyla regilla	27	$\log y = 1.018 \log x + .2059$
Bufo asper	38	$\log y = .929 \log x + .3496$

Fig. 3. Log-log plot of hindlimb length vs. snout-vent length in six species of frogs. White squares, ***Breviceps adspersus***; black squares, ***Hyperolius viridiflavius***; black triangles, ***Rana erythracea***; black circles, ***Rana catesbeiana***; white circles, ***Hyla regilla***; white triangles, ***Bufo asper***.

Rana erythracea



ALLOMETRY AND JUMPING IN FROGS: HELPING THE TWAIN TO MEET

Sharon B. Emerson[1]
Department of Anatomy, University of Chicago, Chicago, Illinois

***Evolution*, 32(3), 1978, pp. 551–564**

- Isometry: greater acceleration over shorter times in smaller animals should yield constant absolute jump length across sizes (same max distance than larger animal with lower acceleration over longer time)

isometry

allometry

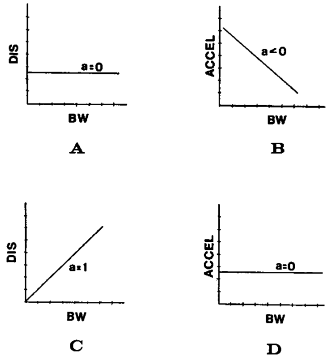
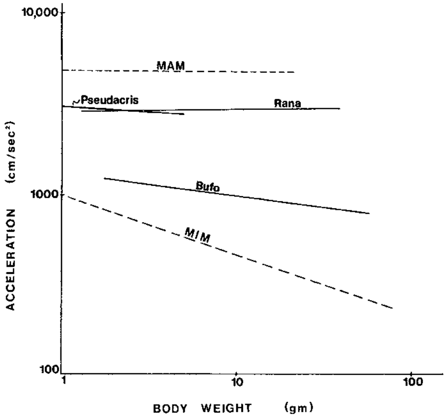
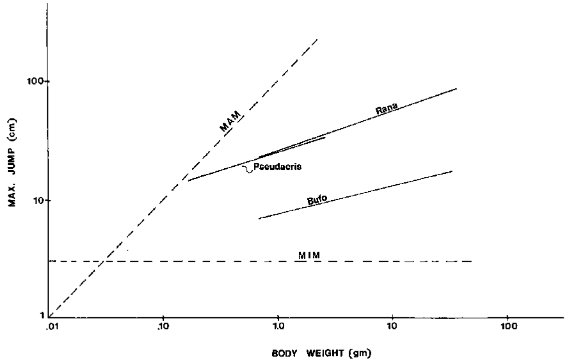


Fig. 1. Predictions of the morphological isometry model ($1A + 1B$). Predictions of the morphological allometry model ($1C + 1D$). a = slope, BW = body weight, dis = max. jump, accel. = acceleration.

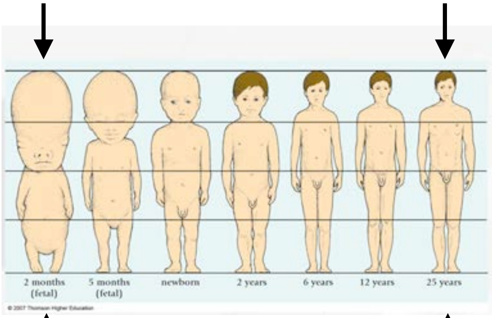




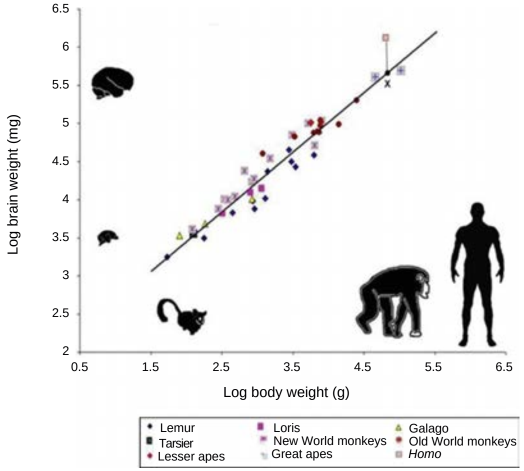
• Allometries

—Dynamic allometry: ontogenic and evolutionary

Head: 50% body length 12.5%

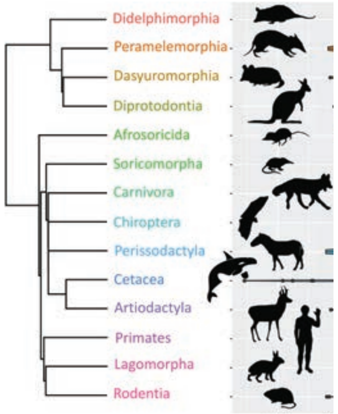


Legs: 12.5% body length 50%

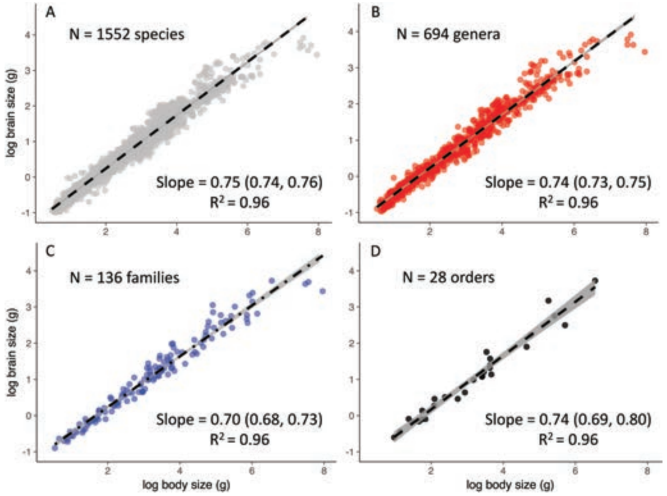


M.A. Rosales-Reynoso et al. *Neurología*. 2018;**33(4)**:254—265

—Static allometry: intra and interspecific



mammals



Burger et al. *Journal of Mammalogy*, 100(2):276–283, 2019

• Scaling Energy and Mass

—Life is a self-sustaining (heritable) organisation of matter brought out of equilibrium locally and persistently

—The organisation, growth, and maintenance at all levels of organisation, molecules, organelles, cells, organs and whole organisms requires constant energy conversion flux

—Evolution is constrained by energy demands, delivery and conversion across scales

⇨ Metabolic rates (Power)

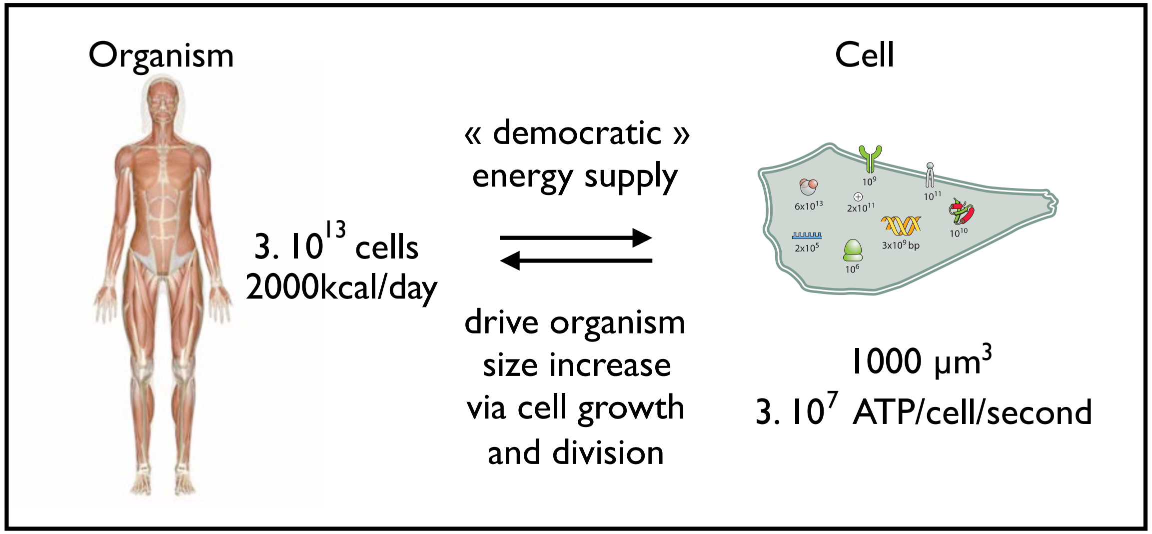
In human: ~100W

How to manage the rate of energy demand for all cells in an organism?

— 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?



Organism

3. 10^{13} cells
2000kcal/day

« democratic » energy supply

drive organism size increase via cell growth and division

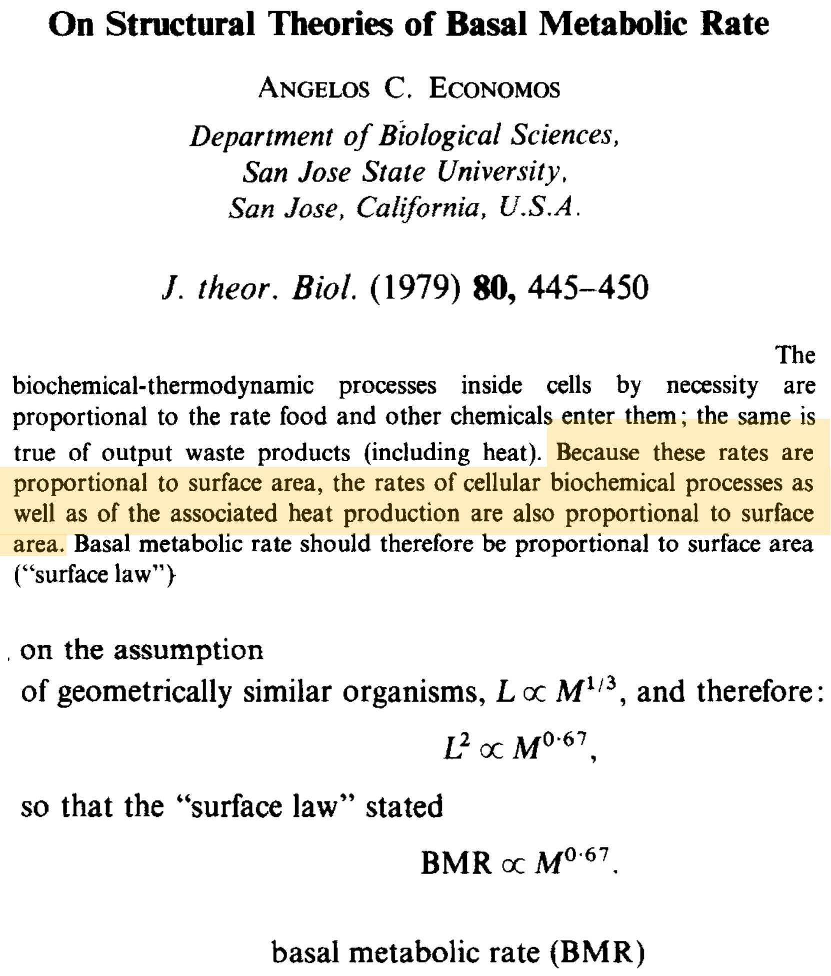
Cell

1000 µm^3
3. 10^7 ATP/cell/second

• Allometry: relation between size and metabolic rate

— size and metabolic power : the « surface law »

If isometry: $B \propto M \propto L^3$, so $B \propto B_0 . M$
yet, …



On Structural Theories of Basal Metabolic Rate

ANGELOS C. ECONOMOS

Department of Biological Sciences,
San Jose State University,
San Jose, California, U.S.A.

J. theor. Biol. (1979) **80,** 445–450

The biochemical-thermodynamic processes inside cells by necessity are proportional to the rate food and other chemicals enter them; the same is true of output waste products (including heat). Because these rates are proportional to surface area, the rates of cellular biochemical processes as well as of the associated heat production are also proportional to surface area. Basal metabolic rate should therefore be proportional to surface area ("surface law")

, on the assumption of geometrically similar organisms, $L \propto M^{1/3}$, and therefore:

$$L^2 \propto M^{0 \cdot 67},$$

so that the "surface law" stated

$$\text{BMR} \propto M^{0 \cdot 67}.$$

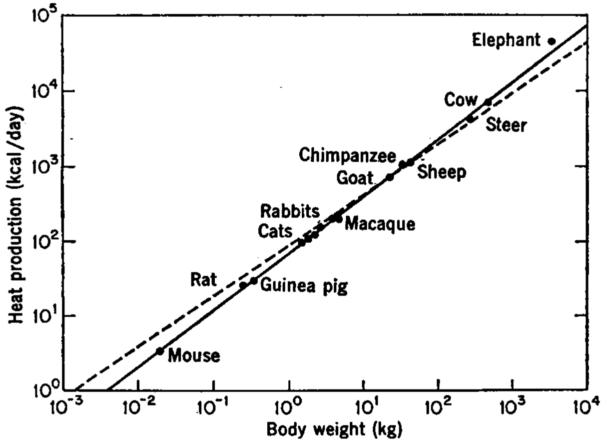
basal metabolic rate (BMR)

however:

Georges TEISSIER,(1927). *Ann. Physiol. Physicochim.* Biol. 4, 1

« Théorie de la similitude biologique »

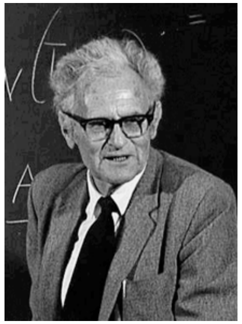
Georges Teissier 1900-1972



• Allometry: relation between size and metabolic rate

$$\boxed{B \propto B_0 M^{3/4}}$$

- power law structure reflects self-similarity or scale invariance



Max Kleiber, 1932

PHYSIOLOGICAL REVIEWS

Vol. 27 OCTOBER, 1947 No. 4

BODY SIZE AND METABOLIC RATE

MAX KLEIBER

Division of Animal Husbandry, College of Agriculture, University of California, Davis

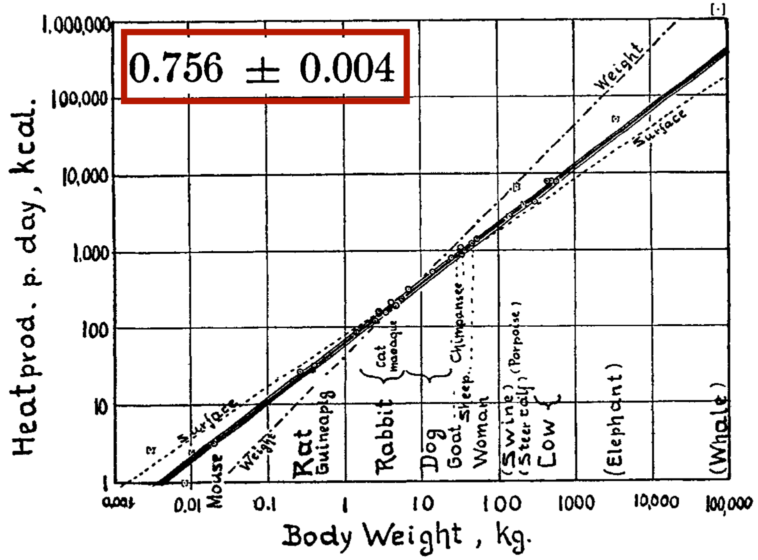


Fig. 1. Log. metabol. rate/log body weight

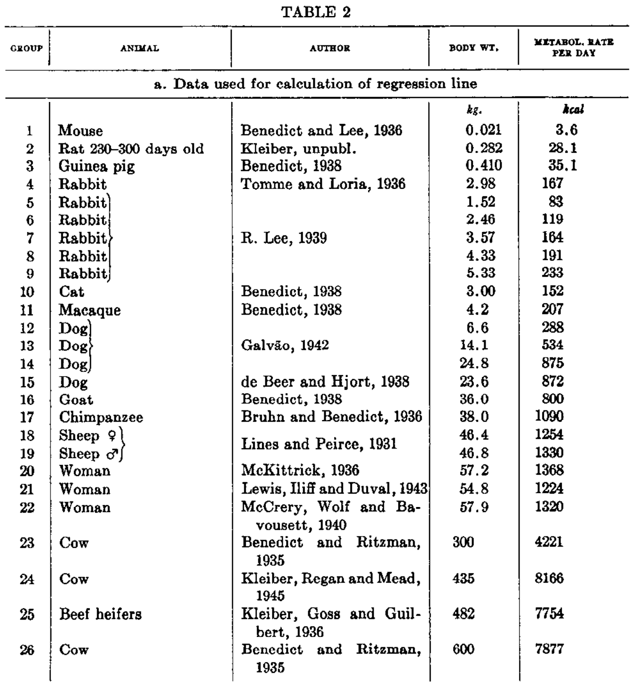


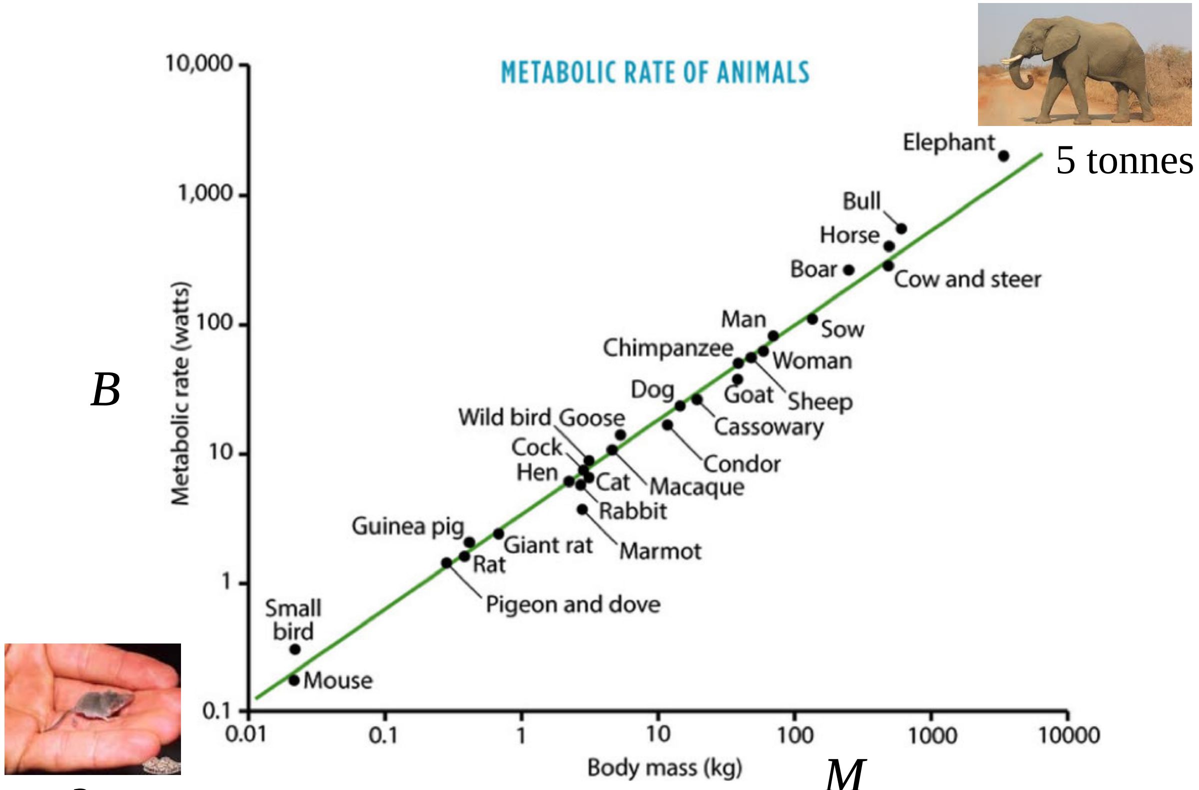
TABLE 2

GROUP	ANIMAL	AUTHOR	BODY WT.	METABOL. RATE PER DAY
a. Data used for calculation of regression line				
			kg.	kcal
1	Mouse	Benedict and Lee, 1936	0.021	3.6
2	Rat 230–300 days old	Kleiber, unpubl.	0.282	28.1
3	Guinea pig	Benedict, 1938	0.410	35.1
4	Rabbit	Tomme and Loria, 1936	2.98	167
5	Rabbit	R. Lee, 1939	1.52	83
6	Rabbit		2.46	119
7	Rabbit		3.57	164
8	Rabbit		4.33	191
9	Rabbit		5.33	233
10	Cat	Benedict, 1938	3.00	152
11	Macaque	Benedict, 1938	4.2	207
12	Dog	Galvão, 1942	6.6	288
13	Dog		14.1	534
14	Dog		24.8	875
15	Dog	de Beer and Hjort, 1938	23.6	872
16	Goat	Benedict, 1938	36.0	800
17	Chimpanzee	Bruhn and Benedict, 1936	38.0	1090
18	Sheep ♀	Lines and Peirce, 1931	46.4	1254
19	Sheep ♂		46.8	1330
20	Woman	McKittrick, 1936	57.2	1368
21	Woman	Lewis, Iliff and Duval, 1943	54.8	1224
22	Woman	McCrery, Wolf and Bavousett, 1940	57.9	1320
23	Cow	Benedict and Ritzman, 1935	300	4221
24	Cow	Kleiber, Regan and Mead, 1945	435	8166
25	Beef heifers	Kleiber, Goss and Guilbert, 1936	482	7754
26	Cow	Benedict and Ritzman, 1935	600	7877

• Allometry: relation between size and metabolic rate

$$B \propto B_0 M^{3/4}$$

—Data from mammals



http://www.physicstoday.org . 2004 American Institute of Physics, S-0031-9228-0409-010-6

—Data from Insects

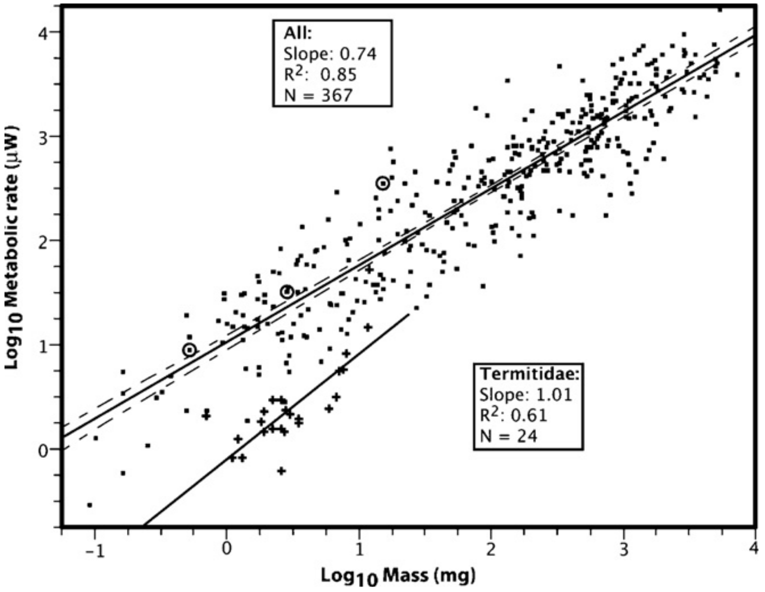


Fig. 1. Correlation of body mass and metabolic rate in insects based on an OLS regression. The dashed line represents a 95% CI for the correlation. A separate correlation is presented for the family Termitidae (crosses; order: Isoptera). Data points circled are the corrected values of metabolic rate for three species of Coleoptera that were incorrectly reported in Chown et al., 2007 (see text).

A.J. Riveros, B.J. Enquist / *Journal of Insect Physiology* 57 (2011) 688–693

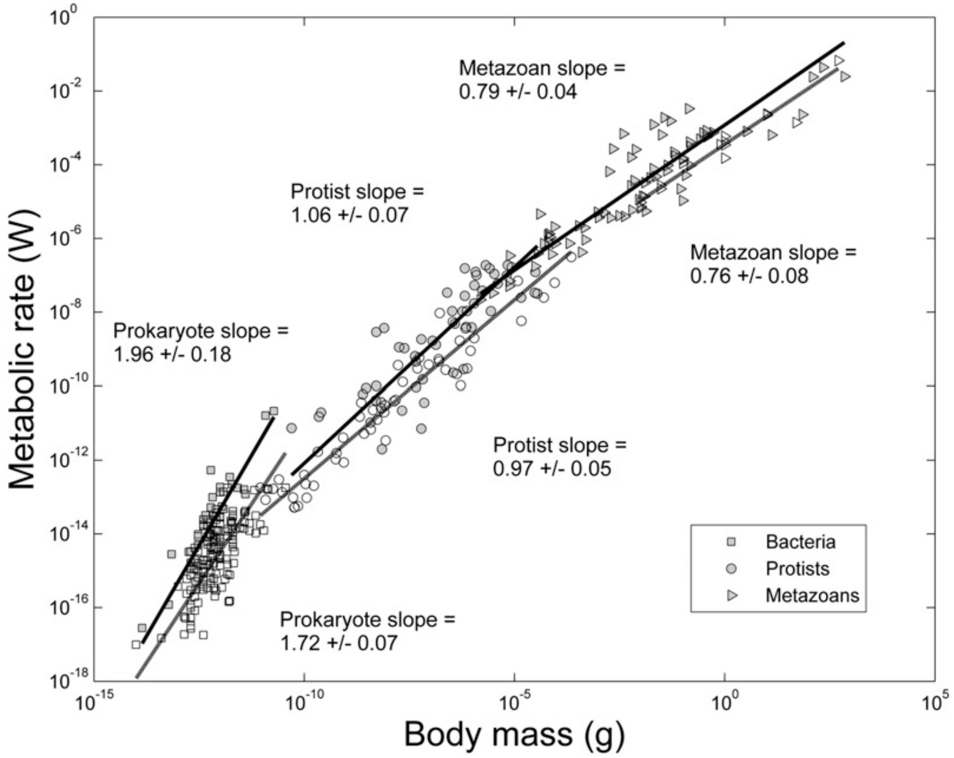
• Allometry: relation between size and metabolic rate

—Data from all metazoans $B \propto B_0 M^{3/4}$

1. Metabolic rate increases sublinearly as size increases
2. Economy of scale: 25% economy as size doubles
3. This means that 1 g of living material consumes less energy per unit of time in large animals than in smaller ones.

• Allometry: relation between size and metabolic rate

—Data from Prokaryotes to Metazoans $B \propto B_0 M^{3/4}$



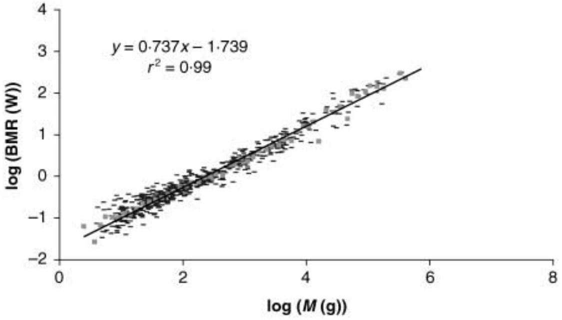
Different scaling patterns across life forms

1. Superlinear scaling for prokaryotes
2. Linear scaling for protists
3. Sublinear scaling for metazoans

John P. DeLonget al. and James H. Brown PNAS (2010) 107:12941-12945
www.pnas.org/cgi/doi/10.1073/pnas.1007783107

• Predominance of quarter power scaling in biology?

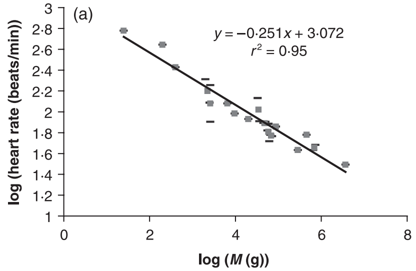
—Many power law exponents in allometric relationships are multiples of ¼
—power law structure reflects self-similarity
—It cannot be a coincidence and suggests the existence of underlying constraints
Individual organisms reveal variations on idealised norm



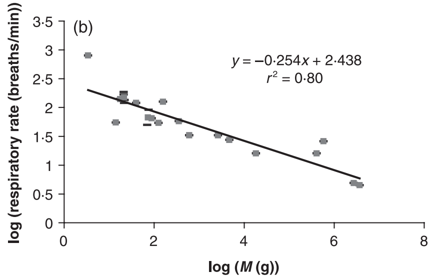
Basal metabolic rate

West, GB and Brown J. (2005) *The Journal of Experimental Biology* 208, 1575-1592

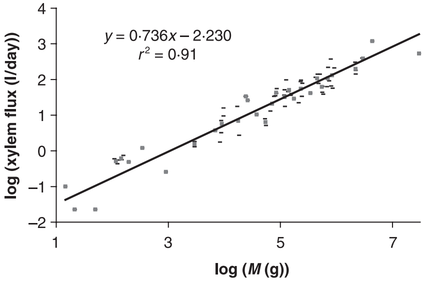
Blood flux



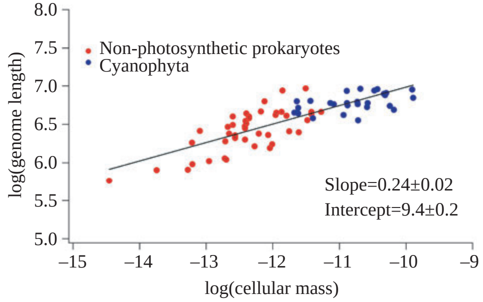
Air flux

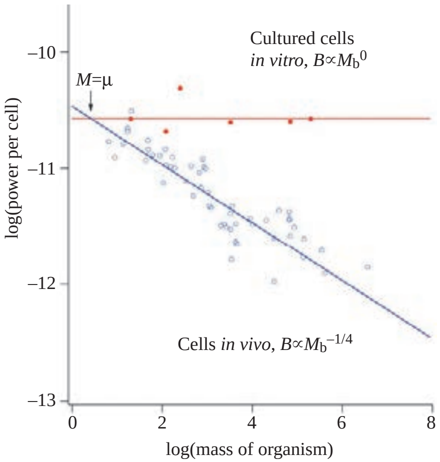


Sap flux



Savage, V. M., Gillooly, J. F., Woodruff, W. H., West, G. B., Allen, A. P., Enquist, B. J. and Brown, J. H. (2004). *Funct. Ecol.* 18, 257-282.



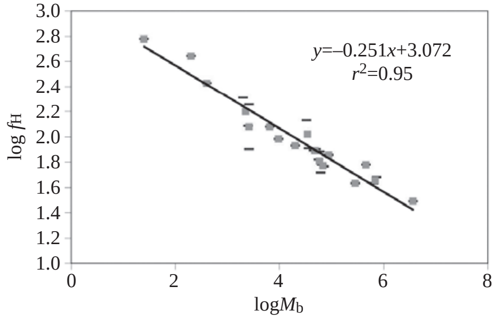


West, G. B., et al. (2002). PNAS 99, 2473-2478.

• Emergence of invariant quantities

—There is a nearly constant heart beat number per lifespan across 6 orders of magnitude differences in animal size: 1.5 billions

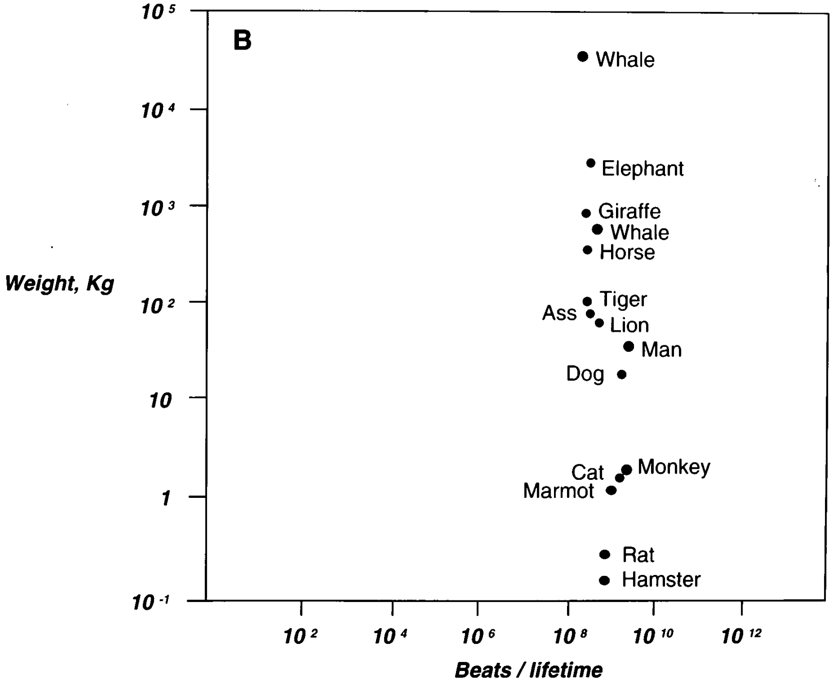
Is this a coincidence or is there a deep underlying reason?



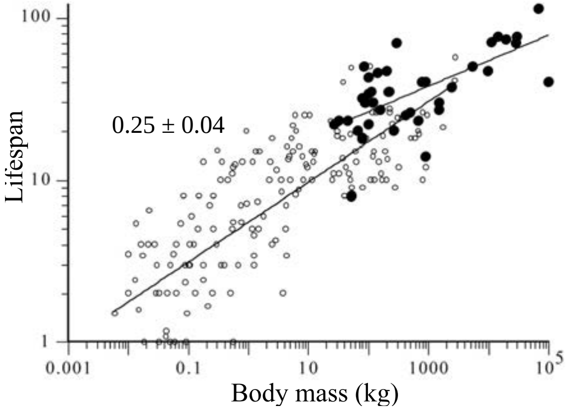
West, GB and Brown J. (2005) *The Journal of Experimental Biology* 208, 1575-1592

$H \propto M^{-1/4}$

$H \,.\, LS \approx \text{constant } k$



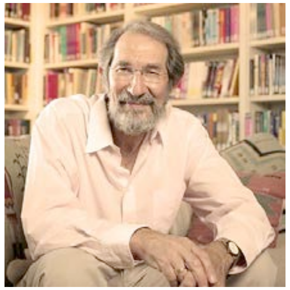
H. Levine. JACC (1997) Vol. 30, No. 4:1104–6



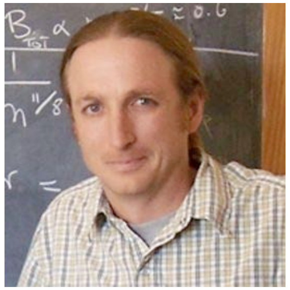
L Wittig. *Biological Reviews* 83 (2008) 259–294

$LS \propto M^{1/4}$

• A theory of allometric scaling: the WBE framework (model)


Geoffrey West

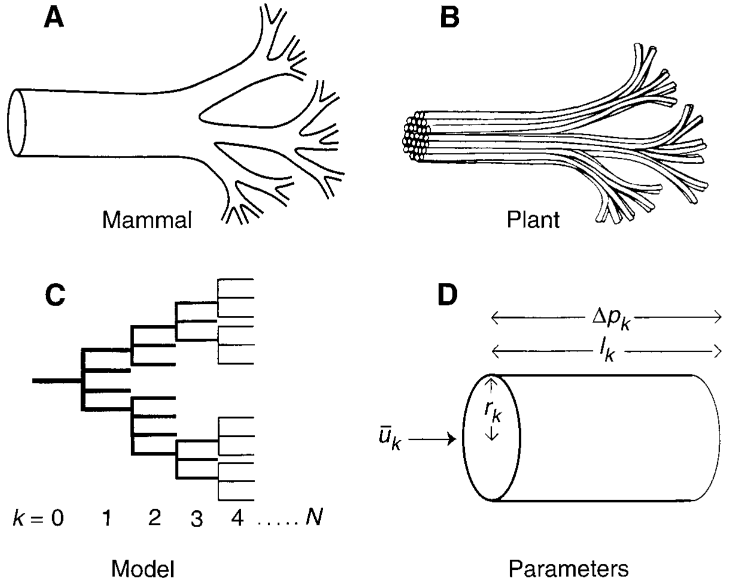

James H Brown


Brian Enquist

A General Model for the Origin of Allometric Scaling Laws in Biology

Geoffrey B. West, James H. Brown,* Brian J. Enquist

- All organisms require efficient energy import and delivery to all cells to ensure energy conversion at the molecular scale within cells
- The model proposes that natural selection solved this problem through the evolution of hierarchical fractal-like branching networks



GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

A theory of allometric scaling: the WBE framework (model)

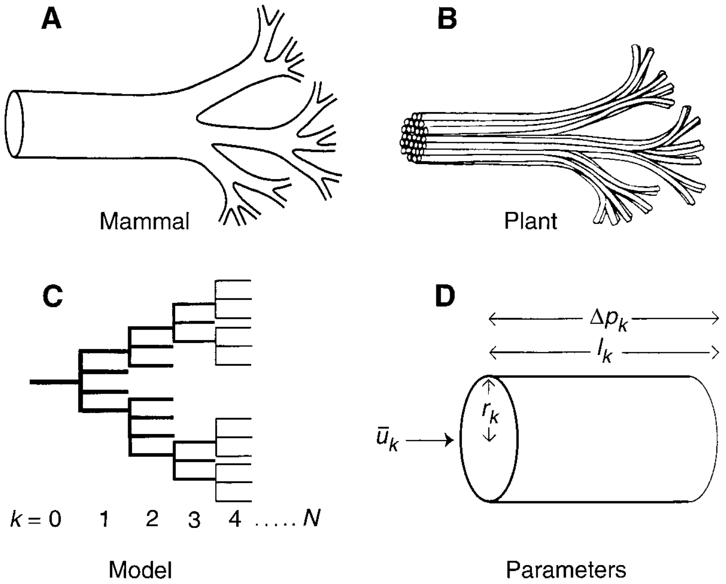
Metabolic power $B \propto M^{a}$

- Three key principles:

1. Networks are space-filling to ensure service to all biologically active entities (eg. cells)

2. The terminal units of the network are invariant
   The terminal units are the sites of energy exchanges. They are not rescaled as the organism grows or as species evolve.

3. The performance of the network is optimised by minimising the energy and parameters required for resource delivery (eg. minimisation of cardiac output in vertebrates)



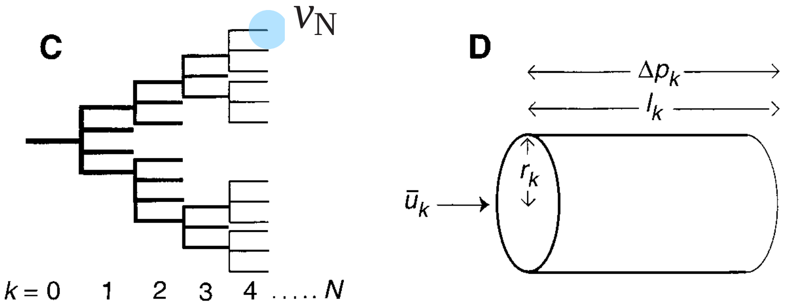
GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A theory of allometric scaling: the WBE framework (model)

1. Networks are space-filling to ensure service to all biologically active entities (eg. cells)

$$\gamma_k \equiv l_{k+1}/l_k$$

$$\gamma_k \approx \underset{\Big|\,\text{branching ratio}}{n^{-1/3}} \approx \gamma$$



Model

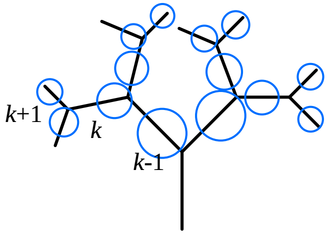
Parameters

- The « service volume » is the volume of cells delivered by each capillary v_N

The total volume supplied is: $V_S = N_N v_N$ where N_N is the number of capillaries

- space-filling at all scales *k* requires that V_S be serviced by the ensemble of volumes v_k

(« democratic » network:
all cells are served)



thus: $V_S \approx N_k v_k$ especially as k=N is large,

since $r_k \ll l_k$, $v_k \approx 4/3\pi(l_k/2)^3$ (geometric approximation)

and fractal, volume-preserving network yields: $4/3\pi(l_k/2)^3 N_k \approx 4/3\pi(l_{k+1}/2)^3 N_{k+1}$

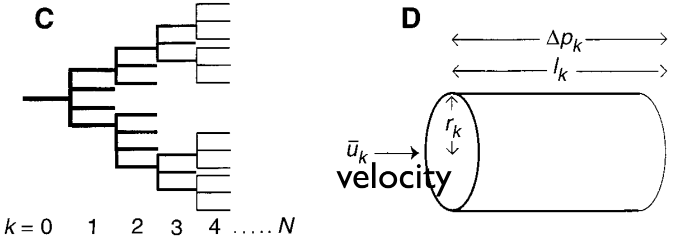
$$\gamma^3_k \equiv (l_{k+1}/l_k)^3 \approx N_k/N_{k+1} = 1/n$$

Therefore: $$\boxed{\gamma_k \approx n^{-1/3} \approx \gamma}$$

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A theory of allometric scaling: the WBE framework (model)

2. The terminal units of the network are invariant
3. Minimization of energy output in the system



Model

Parameters

$\dot{Q}_k$ volume rate of flow

- Blood volume is conserved as it flows through the network:

$$\dot{Q}_0 = N_k \dot{Q}_k = N_k \pi r_k^2 \bar{u}_k = N_c \pi r_c^2 \bar{u}_c$$

This is invariant of body size

- Blood flow rate is proportional to oxygen supply rate and to body metabolism: $\dot{Q}_0 \propto B$

since $B \propto M^a$ then $\dot{Q}_0 \propto M^a$

- Therefore, invariance of capillaries gives an allometric scaling of the number of capillaries to body size.

$$N_c \propto M^a$$

since $N_c = n^N$ then $N = \dfrac{a \ln(M/M_o)}{\ln n}$

which relates scaling of vessel dimensions to body mass: the number of generations scales logarithmically with body size.

- Self-similar fractal network: $\beta_k \equiv r_{k+1}/r_k = \beta$ and energy minimisation $V_b \propto M$ (see later)

$$\gamma_k \equiv l_{k+1}/l_k = \gamma$$

- This yields $\boxed{a = -\dfrac{\ln n}{\ln(\gamma\beta^2)}}$

COLLÈGE DE FRANCE
1530

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A theory of allometric scaling: the WBE framework (model)

3. Minimization of energy output in the system:

In pulsatile network (aorta and arterial system), the minimisation of energy dissipation (principally by minimising reflection at branch points because viscous dissipation is negligible) gives rise to area-preserving branching

$$\pi r_k^2 = n\pi r_{k+1}^2$$

Therefore: $$\boxed{\beta_k \equiv r_{k+1}/r_k = n^{-1/2} = \beta}$$

Summary:

Optimisation: $\beta = n^{-1/2}$

Space-filling: $\gamma = n^{-1/3}$

Invariant termini $a = -\dfrac{\ln n}{\ln(\gamma\beta^2)}$

$$a = 3/4$$

$$\boxed{B \propto M^{3/4}}$$

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A theory of allometric scaling: the WBE framework (model)

- <u>How does energy minimisation gives rise to area-preserving branching?</u>

—Pulsatile network: # hydrodynamic (Navier Stokes) equations
\# wave propagation through an elastic network
\# incompressible blood

Vessel impedance $Z \sim \underbrace{\rho}_{\text{blood density}} \underbrace{c_0}_{\text{velocity}} / \pi \underbrace{r^2}_{\text{vessel radius}}$ $\qquad c_0 \equiv (\underbrace{E}_{\text{vessel wall stiffness}} \underbrace{h}_{\text{wall thickness}} / 2\rho r)^{1/2}$

—Minimisation of energy dissipation in large vessels requires impedance matching at network branching point (avoid wave reflection)

impedance matching leads to area preserving $\pi r_k^2 = \underbrace{n}_{\text{branching ratio}} \pi r_{k+1}^2$ and $r_{k+1}/r_k = n^{-1/2}$

$$\boxed{\beta_k \equiv r_{k+1}/r_k = n^{-1/2} = \beta}$$

impedance matching nearly eliminates dissipation in large vessels subject to pulsatile flow

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

A theory of allometric scaling: the WBE framework (model)

- Minimisation of energy dissipation in non pulsative networks (plants, insects and capillary vessels)

—Consider laminar flow of viscous fluid: Viscous resistance is given by the Poiseuille formula:

$$Z_k = 8\mu l_k / \pi r_k^4$$

blood viscosity

in capillaries where viscosity dominates, energy dissipation cannot be eliminated but only minimised.
This requires area-increasing branching to reduce flow velocity and oxygen diffusion so the network is not strictly self-similar.

$$Z = \sum_{k=0}^{N} \frac{Z_k}{N_k} = \sum_{k=0}^{N} \frac{8\mu l_k}{\pi r_k^4 n^k} \approx Z_c/(1 - n\beta^4/\gamma)N_c$$

invariant, thus $Z \propto N_c^{-1} \propto M^{-a}$
capillary invariance

—Energy minimisation (cardiac output) $W = \dot{Q}_0 \Delta p$ and $\Delta p = \dot{Q}_0 Z$ (‘Ohm’s law’) so $W = \dot{Q}_0^2 Z$

so this requires minimisation of impedance and leads to $\boxed{V_b \propto M}$

and $\beta_k = n^{-1/3}$

Therefore the exponent is strictly ¾ only if network is purely pulsatile

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A theory of allometric scaling: the WBE framework (model)

$$B \propto M^{3/4}$$

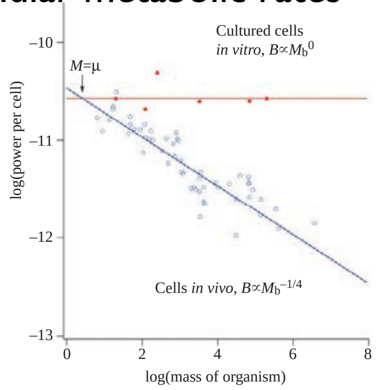
—Direct implications of the theory:

- A unit mass of animals consumes less energy per unit of time in larger animals (economy of scale) B/M_b scales as $M_b^{-1/4}$

If the number of cells N_{cell} scales linearly with body mass, cellular metabolic rates

$B_{cell} = (B/N_{cell})$ scales as $M_b^{-1/4}$

West, G. B., Woodruff, W. H. and Brown, J. H. (2002). PNAS 99, 2473-2478.



- Large animals are more efficient because they need less power to support cells in the body

Reason: The viscous resistance of the vessel network scales as $Z \propto N_c^{-1} \propto M_b^{-3/4}$ so the weight of the pulsatile network dominates the whole network except in small animals

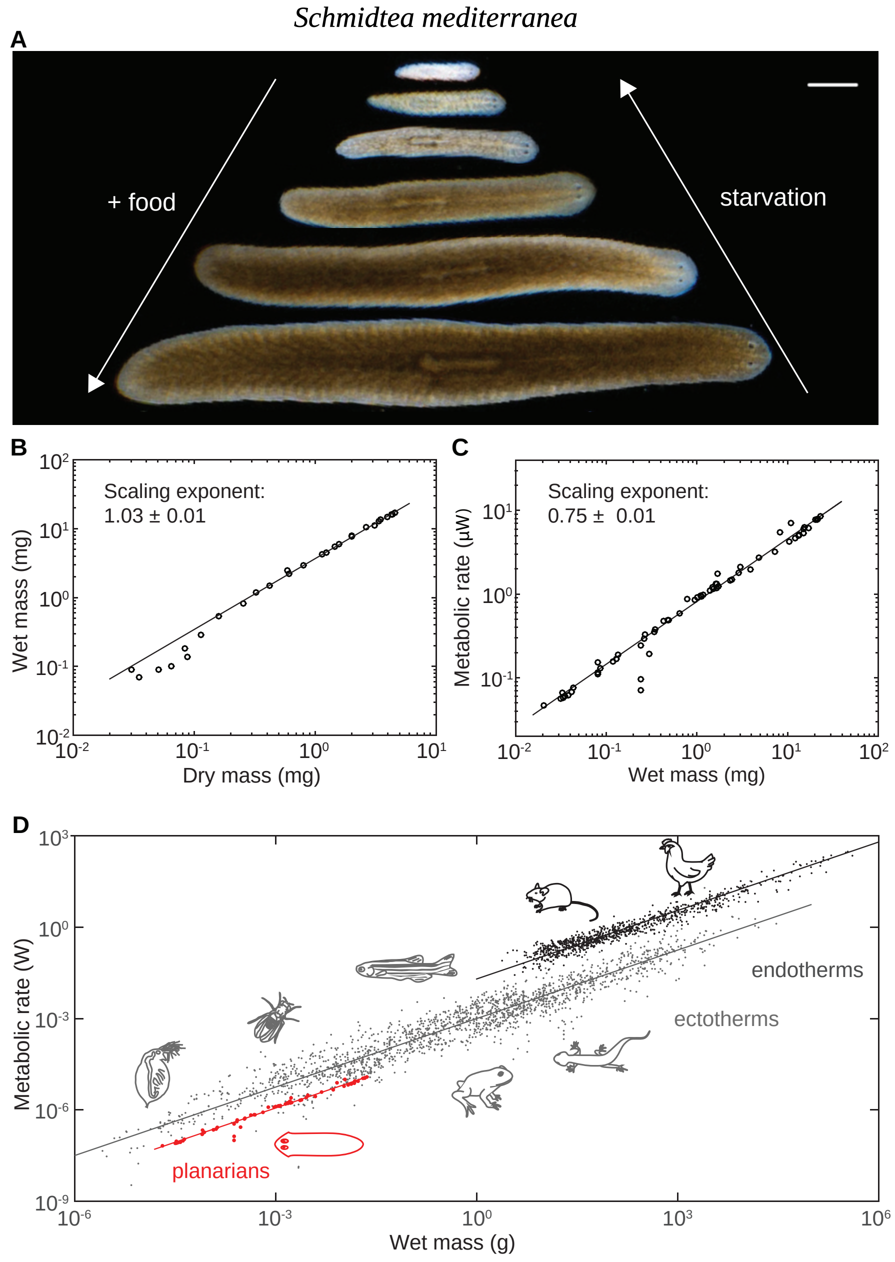
Makes the prediction of what should be the smallest animal where heart beats without pulses due to viscous damping (hydrodynamic resistance is in all branches is maximal) : 1g

- Since blood flow rate scales as $B \propto M^{3/4}$, blood pressure $\Delta p = \dot{Q}_0 Z$ is predicted to be size invariant (same in whale and mouse!)

GB. West, JH. Brown and BJ Enquist *Science*, (1997) 276:122-126
DOI: 10.1126/science.276.5309.122

• A (modified) theory of allometric scaling: planarians

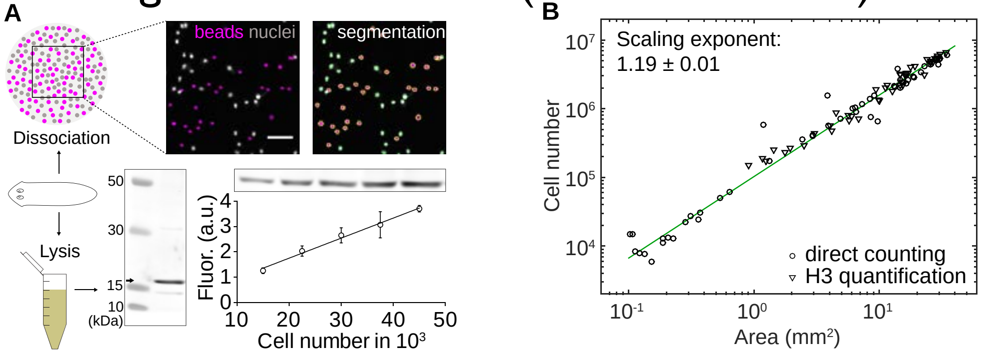
- planarians reversibly grow and de-grow
- planarians follow Kleiber's law



Thommen et al. J. Rink. *eLife* (2019); 8:e38187. DOI: https://doi.org/10.7554/eLife.38187

• A (modified) theory of allometric scaling: planarians

- Changes in animal size (area) reflects changes in cell number (and not cell size)

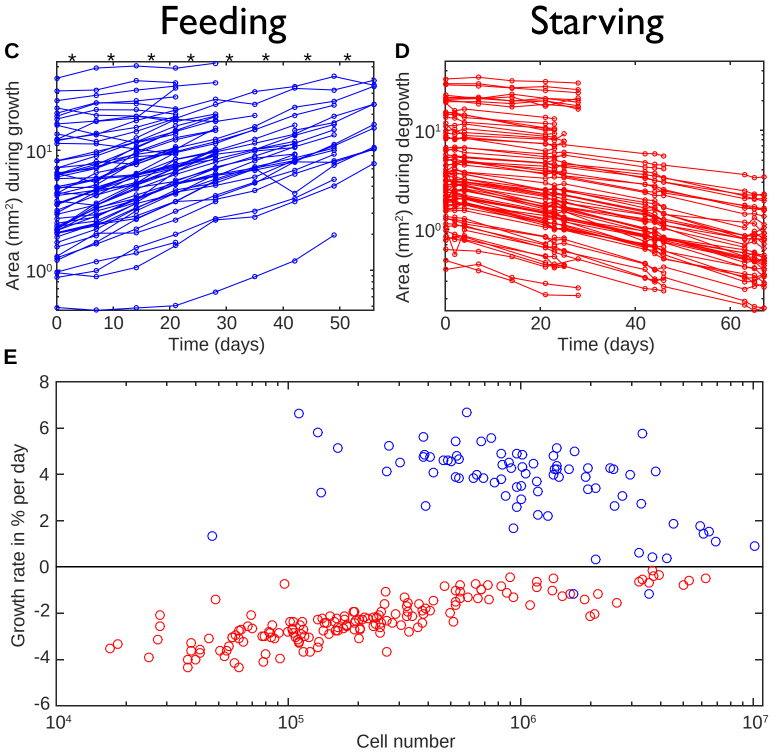


quantitative western blotting of histone H3

- Size-dependence of planarian growth/de-growth dynamics

  — growth rate decreases with size

  — de-growth rate decreases with size



Thommen et al. J. Rink. *eLife* (2019); 8:e38187. DOI: https://doi.org/10.7554/eLife.38187

• A (modified) theory of allometric scaling: planarians

N : cell number

E: animal energy content
e: cell energy content

J: animal energy influx (feeding)
j: cell energy influx

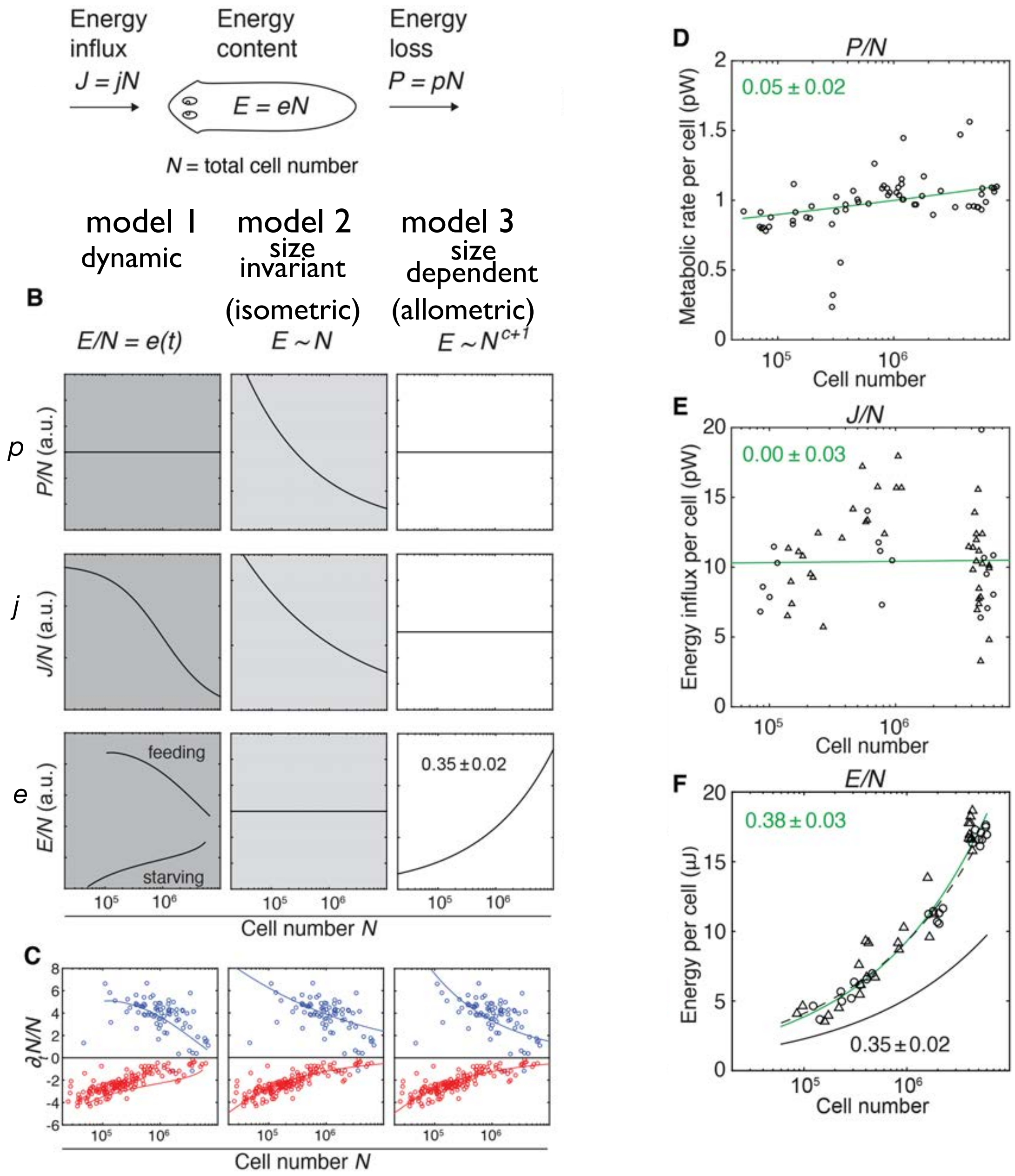
P: animal energy loss (metabolism)
p: cell energy loss

$$dE/dt = d(eN)/dt = J - P$$

$$de/dt = j - p - dN/dt.e$$

- Size independence of cell metabolic rate (P/N)
- Therefore, the size dependence of P/M (which scales as $M^{-1/4}$ based on Kleiber's law) most likely reflects dependence of cell mass M/N on body mass

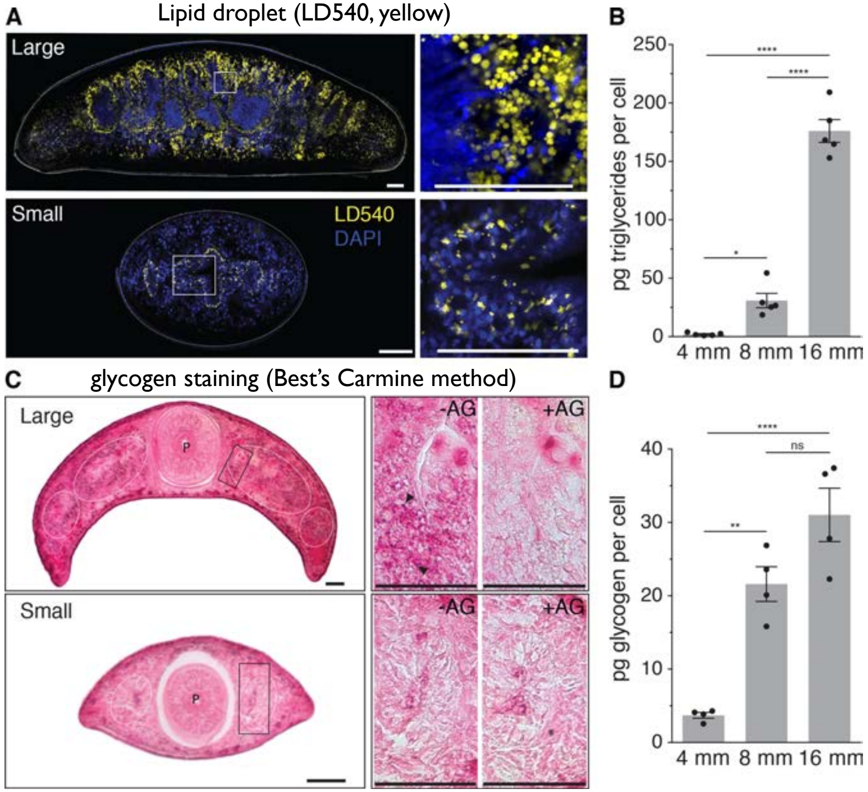
- In the WBE model, the size dependence of P/M reflects size dependence of P/N (which scales as $M^{-1/4}$).



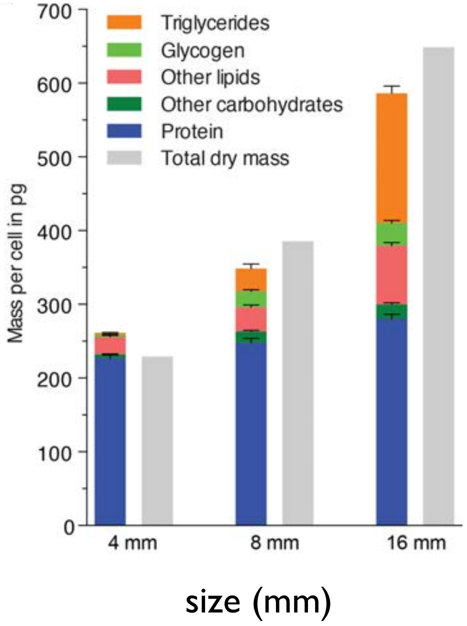
Thommen et al. F. Jülicher and J. Rink. *eLife* (2019); 8:e38187. DOI: https://doi.org/10.7554/eLife.38187

A (modified) theory of allometric scaling: planarians

- Size-dependence of lipid and glycogen storage (suggesting size dependence of mass per cell)



+ AG: pretreatment with amyloglucosidase



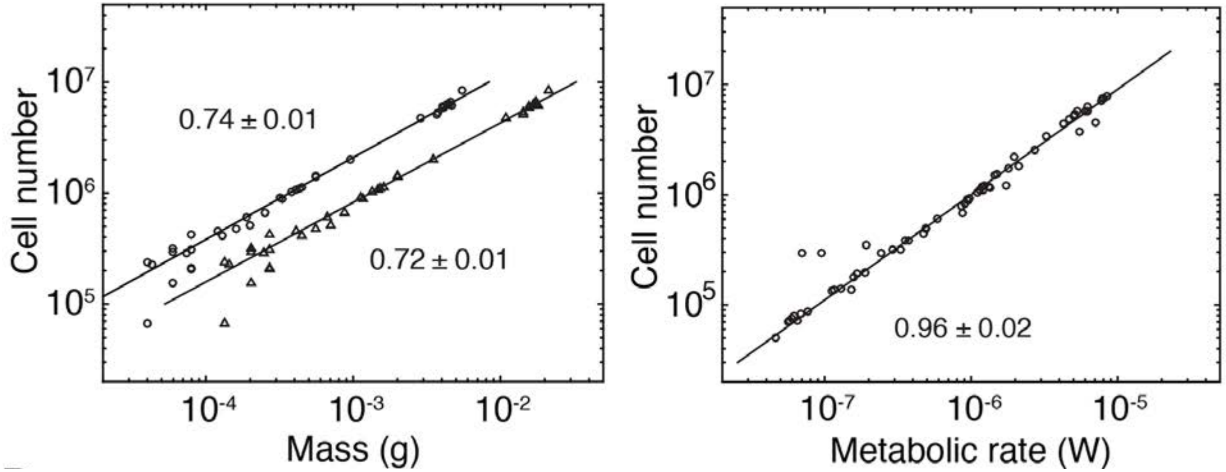
Thommen et al. J. Rink. *eLife* (2019); 8:e38187. DOI: https://doi.org/10.7554/eLife.38187

• A (modified) theory of allometric scaling: planarians

- Allometric scaling of cell number to animal size: $N \propto M^{3/4}$

(ie. size-dependence of mass per cell: $M/N \propto M^{1/4}$)
which reflects size-dependent energy storage

- Isometric scaling of cell number to animal metabolic rate (inferred from Kleiber's law)



- Validity for other organisms? In principle no as it contradicts a feature of the WBE model

In the WBE model, the size dependence of
P/M reflects size dependence of P/N
(which scales as $M^{-1/4}$), which is size independent in planaria

- Humans: prediction of cell number based on metabolic power per cell:

constant and size-independent metabolic rate per cell, $p=P/N$ (1pW), and Kleiber's law $P \propto M^{3/4}$
For 70 kg: 60-200W, hence 6-20 10^{13} cells.

data: 3.8 10^{13} cells. Sender, Fuchs & Milo. PLOS Biology | DOI:10.1371/journal.pbio.1002533

Thommen et al. J. Rink. *eLife* (2019); 8:e38187. DOI: https://doi.org/10.7554/eLife.38187

• Universality of ontogenic growth — WBE framework

- Incoming energy is distributed through a hierarchical branching network to all cells

- Metabolic energy is allocated to :
  —life-sustaining activities (maintenance of cell and tissue organisation, homeostasis)
  —growth (formation of new cells)

Total metabolic rate $$B = \sum_c \Big[\underbrace{N_c B_c}_{\text{power allocated to sustain organism}} + \underbrace{E_c \frac{\mathrm{d}N_c}{\mathrm{d}t}}_{\text{power allocated to growth}}\Big]$$

cell number

cell metabolic rate

energy required to produce a new cell

N_c, E_c and m_c are constant and independent of m

$$\underset{\text{total mass}}{m} = \underset{\text{cell mass}}{m_c} . N_c$$

- Growth equation $$\frac{\mathrm{d}m}{\mathrm{d}t} = \left(\frac{m_c}{E_c}\right)B - \left(\frac{B_c}{E_c}\right)m$$ give $$\boxed{\frac{\mathrm{d}m}{\mathrm{d}t} = am^{3/4} - bm}$$ with $a \equiv B_0 m_c / E_c$, $b \equiv B_c / E_c$.

  and Kleiber's law $$B = B_0 m^{3/4}$$

B_0 constant within taxon (fish, bird, mammal etc)

- This imposes a natural limit to growth due to the imbalance between:
  — energy supply, constrained by invariance of capillary termini, with scales as: $B \propto N_t \propto m^{3/4}$ (see earlier)
  — energy demand, which scales as $N_c \propto m$

  Otherwise (same exponent) growth would not stop: $\mathrm{d}m/\mathrm{d}t \neq 0$

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

Universality of ontogenic growth — WBE framework

- Predicts an asymptotic limit to mass/size $$\frac{\mathrm{d}m}{\mathrm{d}t} = am^{3/4} - bm$$ with $$\left| \begin{array}{l} a \equiv B_0 m_c / E_c \\ b \equiv B_c / E_c . \end{array} \right.$$

asymptotic mass M for $\mathrm{d}m/\mathrm{d}t = 0$

$$\boxed{M = (a/b)^4 = (B_0 m_c / B_c)^4}$$

—<u>within a taxon</u>, a is approximately constant and variation in final mass between species depends on variation in cellular metabolic rate B_c , therefore $b = a/M^{1/4}$

—<u>between taxa</u>, a varies as B_0

Organism	a	m_0	M
Cow	0.28	33.3 kg	442 kg
Pig	0.31	0.90 kg	320 kg
Rabbit	0.36	0.12 kg	1.35 kg
Guinea pig	0.21	5 g	840 g
Rat	0.23	8 g	280 g
Shrew	0.83	0.3 g	4.2 g
Heron	1.56	3 g	2.7 kg
Hen	0.47	43 g	2.1 kg
Robin	1.9	1 g	22 g
Cod	0.017	0.1 g	25 kg
Salmon	0.026	0.01 g	2.4 kg
Guppy	0.10	0.008 g	0.15 g
Shrimp	0.027	0.0008 g	0.075 g

- Law of growth: $$\frac{\mathrm{d}m}{\mathrm{d}t} = am^{3/4}\left[1 - \left(\frac{m}{M}\right)^{1/4}\right]$$ has the following sigmoid solution:

$$\left(\frac{m}{M}\right)^{1/4} = 1 - \left[1 - \left(\frac{m_0}{M}\right)^{1/4}\right] e^{-at/4M^{1/4}}$$

m: mass at time t

m_0: mass at birth

M: final mass

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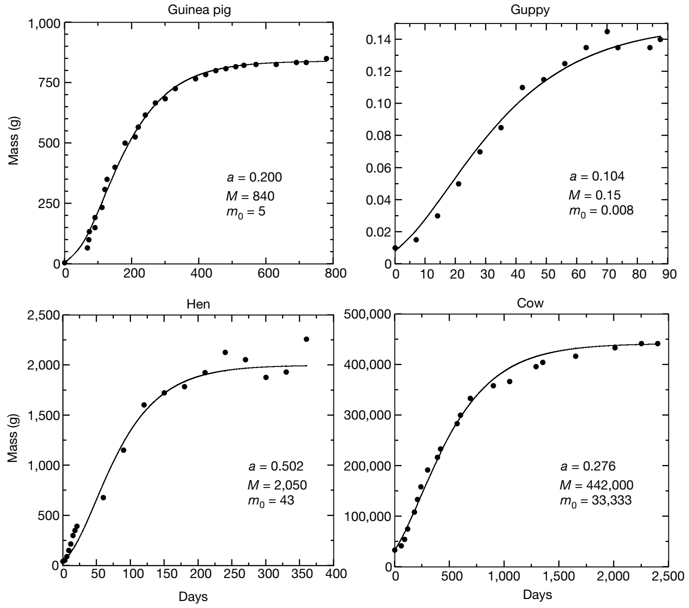
• Universality of ontogenic growth — WBE framework

- **Law of growth**: $$\left(\frac{m}{M}\right)^{1/4} = 1 - \left[1 - \left(\frac{m_0}{M}\right)^{1/4}\right] e^{-at/4M^{1/4}}$$

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

$$a \equiv B_0 m_c / E_c$$
$$b \equiv B_c / E_c.$$



- « Universal » growth

Dimensionless mass $r \equiv (m/M)^{1/4}$

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

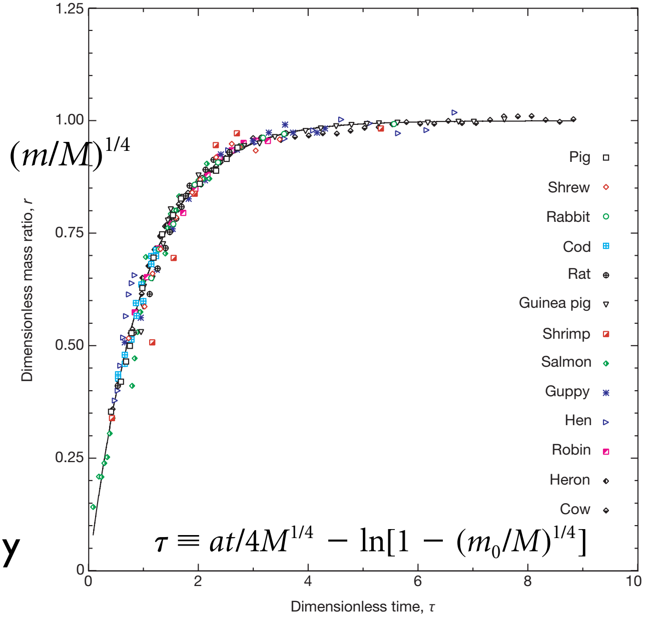
$$\boxed{r = 1 - e^{-\tau}}$$

or $R \equiv 1 - r$ $$R(t) = R(0)e^{-at/4M^{1/4}}$$

$\ln[R(t)/R(0)]$ versus $at/4M^{1/4}$

Organism	Slope
Cow	1.08
Pig	1.08
Rabbit	1.34
Guinea pig	0.91
Rat	1.07
Shrew	0.98
Heron	1.04
Hen	0.72
Robin	1.03
Cod	1.01
Salmon	1.01
Guppy	1.04
Shrimp	0.82

$r \equiv (m/M)^{1/4}$



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

- Interpretation:

r fraction of metabolic power allotted to maintenance

$$N_c B_c / B = (B_c / B_0 m_c) m^{1/4} = (b/a) m^{1/4} = (m/M)^{1/4} = r$$

R fraction allotted to growth has a universal exponentially decreasing behaviour as a function of $at/4M^{1/4}$

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

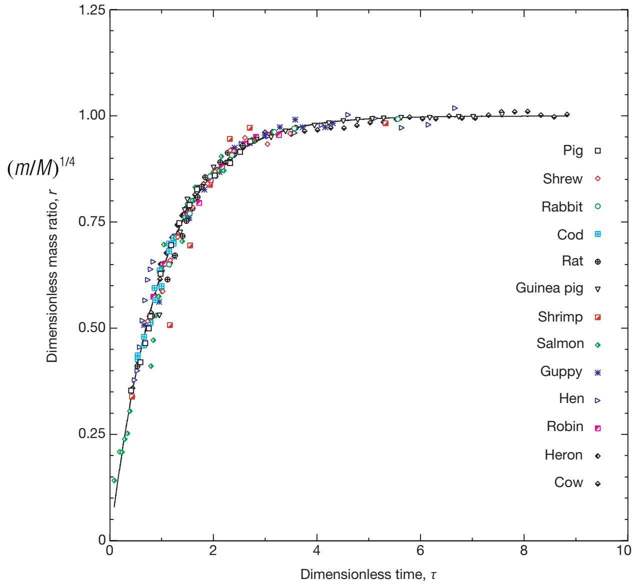
• Universality of ontogenic growth — WBE framework

- Interpretation:

r fraction of metabolic power allotted to maintenance

R fraction allotted to growth $R = 1 - r = 1 - (m/M)^{1/4}$

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



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

For all organisms: when $m/M = 1/15$, $R \approx 50\%$

$m/M = 1/2$, $R \approx 16\%$

The time at which this happens is different for different animals

For cows $m/M = 1/15$ happens at birth (40/600kg)
1 year later $m/M = ½$

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

• Universality of Biological clock —WBE framework

- The Kleiber law relates organism metabolic rate to mass and the WBE model explains the ¾ exponent in terms of constraints from hierarchical branching network

- Question: How to relate whole organism metabolic rate to biochemical reaction within cells?

organism metabolic rate $B = \sum_i R_i$, where R_i is the rate of energy production per chemical reaction i associated with metabolism

$$R_i \propto \underbrace{[\text{reactants}]\text{x}(\text{flux of reactants})}_{\text{allometric constraint}} \text{ x } \underbrace{(\text{kinetic energy of system})}_{\text{Boltzmann factor (temperature dependence)}}$$

allometric constraint

$$\propto M^{3/4}$$

Boltzmann factor (temperature dependence)

$$e^{-E_i/kT}$$

activation energy

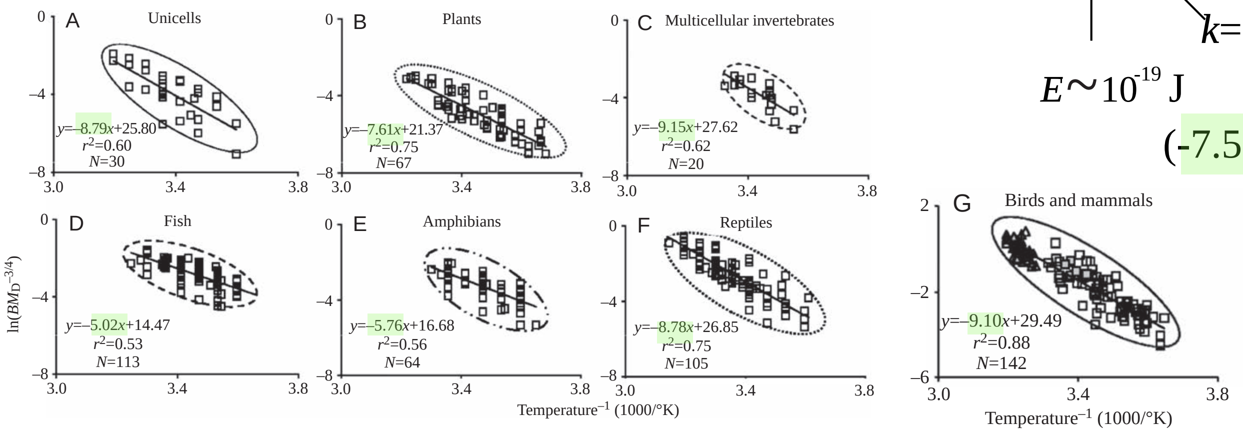
$$\boxed{B \sim M^{3/4} e^{-E_i/kT}}$$

prediction: $\ln(B.M^{-3/4})$ should be linearly related to $1/T$ with slope $a = -E_i/k \sim -7500$ K

$E \sim 10^{-19}$ J

$k = 1.38\ 10^{-23}$ J.K^{-1}

(-7.5K with 1000/K)



Gillooly, J. F., Brown, J. H., West, G. B., Savage, V. M. and Charnov, E. L. (2001). *Science* 293, 2248-2251.

Universality of Biological clock —WBE framework

- A new definition of biological rates and times.

average activation energy for rate limiting chemical reactions: $E \sim 10^{-19}\,\mathrm{J}$

biological rates $R \propto M_b^{-1/4} e^{-E/kT}$

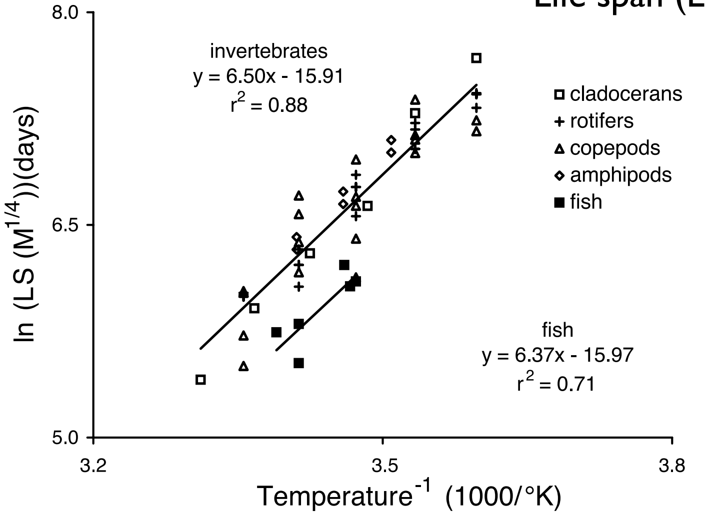
biological times $t \propto M_b^{1/4} e^{E/kT}$

- <u>All animals run the same « clock »</u> adjusted for mass (internal constraint on energy delivery) and temperature (external constraint)

Check effect on DNA mutation rate and evolution in:

Gillooly, J. F., Allen, A. P., West, G. B. and Brown, J. H. (2005). The rate of DNA evolution: Effects of body size and temperature on the molecular clock. PNAS 102, 140-145.

Life span (LS)



Gillooly, J. F., Brown, J. H., West, G. B., Savage, V. M. and Charnov, E. L. (2001). *Science* 293, 2248-2251.

• Universality of Biological clock —WBE framework

—Effects of size and temperature on developmental time.

- Law of growth: $\frac{dm}{dt} = am^{3/4}\left[1 - \left(\frac{m}{M}\right)^{1/4}\right]$ where $a = B_0 m_c / E_c$ is not a constant
- We just saw that $B.M^{-3/4} = B_0 \sim e^{-E_i/kT}$, so $a(T) \propto e^{-E_i/kT}$

therefore $a(T)/a(T_0) = [\exp(-\bar{E}/kT)]/[\exp(-\bar{E}/kT_0)]$.

$(T_c = T - 273)$ temperature in Celcius

$$a(T_c) = a(T_0)e^{(\bar{E}/kT_0^2)(T_c/(1+T_c/T_0))}$$

- During development: $m \ll M$ $dm/dt = am^{3/4}$ so $m = \left(\frac{a(T)t}{4}\right)^4$ or $\frac{t}{m^{1/4}} = \frac{4}{[a(T_0)e^{(\bar{E}/kT_0^2)(T_c/(1+T_c/T_0))}]}$

Logarithm of $\frac{t}{m^{1/4}}$ proportional to $T_c/(1 + (T_c/273))$ with slope $\alpha = -\bar{E}/kT_0^2$

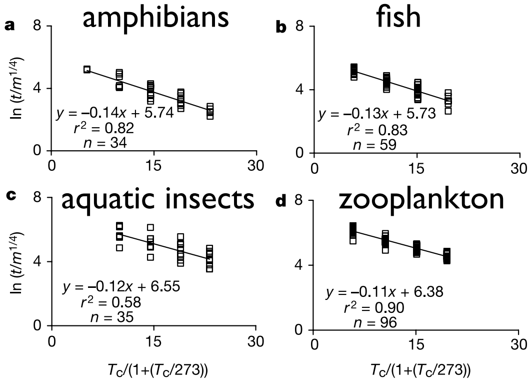
Gillooly, J. F., Charnov, E. L., West, G. B., Savage, V. M. and Brown, J. H. (2002). *Nature* 417, 70-73.

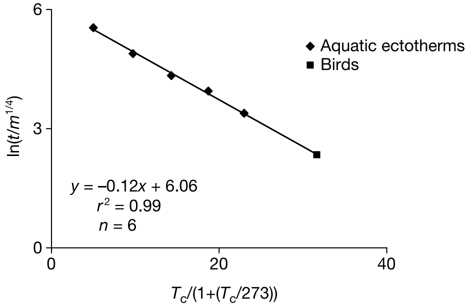
Universality of Biological clock —WBE framework

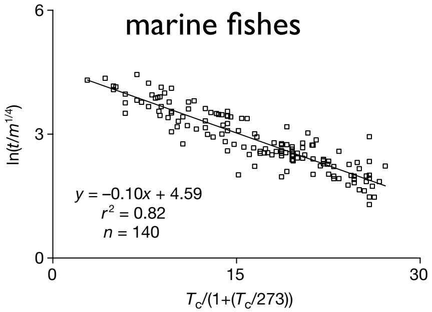
—Effects of size and temperature on developmental time.

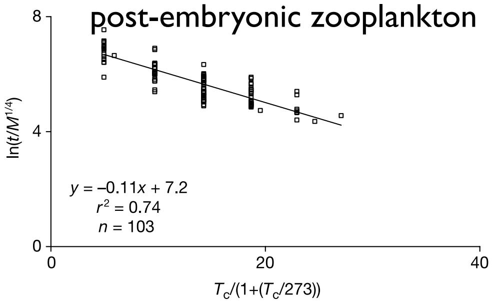
Logarithm of $\frac{t}{m^{1/4}}$ proportional to $T_c/(1+(T_c/273))$ with slope $\alpha = -\bar{E}/kT_0^2$;

intercept $y_{\mathrm{int}} = \ln[4/a(T_0)]$









estimates of a from intercept
close to estimates from growth curves

calculation of $\alpha = -\bar{E}/kT_0^2$; (-0.09 per°C)
close to measurements (-0.12 per°C)

- Temperature and Mass determine much of developmental time
- The new biological clock

$$\boxed{t_B = t(m/m_0)^{-1/4} e^{-\alpha T_c/(1+T_c/T_0)}}$$

where m_0 and T_0 are normalised values (eg. 1 g at 20°C)

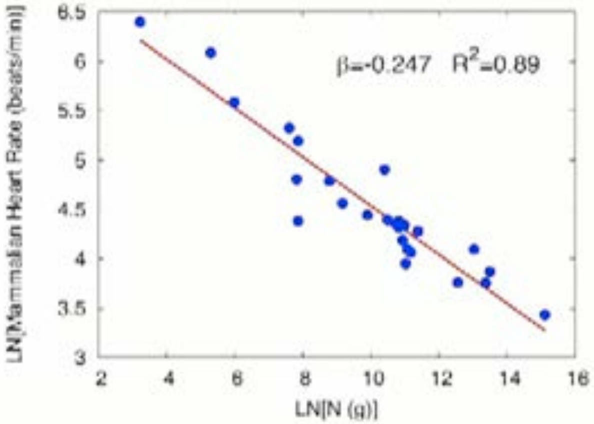
Gillooly, J. F., Charnov, E. L., West, G. B., Savage, V. M. and Brown, J. H. (2002). *Nature* 417, 70-73.

• Universality of Biological clock —WBE framework

$$B = B_0 M_b^{3/4} \qquad t \propto M_b^{1/4} e^{E/kT}$$

2g

5 tonnes



Heart Rate vs. Body Size

A small organism:

1. lives « faster » (clock ticks faster)
2. has higher heart rate
3. Ages faster (free radical production rate is increased)
4. The number of heart beat per lifespan is nearly invariant (∼1.5 billions)

• Conclusions — Scaling Laws

1. Size of animals and plants varies over many orders of magnitude including within a given taxon or families (eg. wasps)
2. Animals and plants show characteristic allometric relationships: relative growth and self-similarity
3. Allometry reflects internal and external constraints in organisation, namely:

   — Mechanical constraints (elastic similarity)
   — Energy delivery

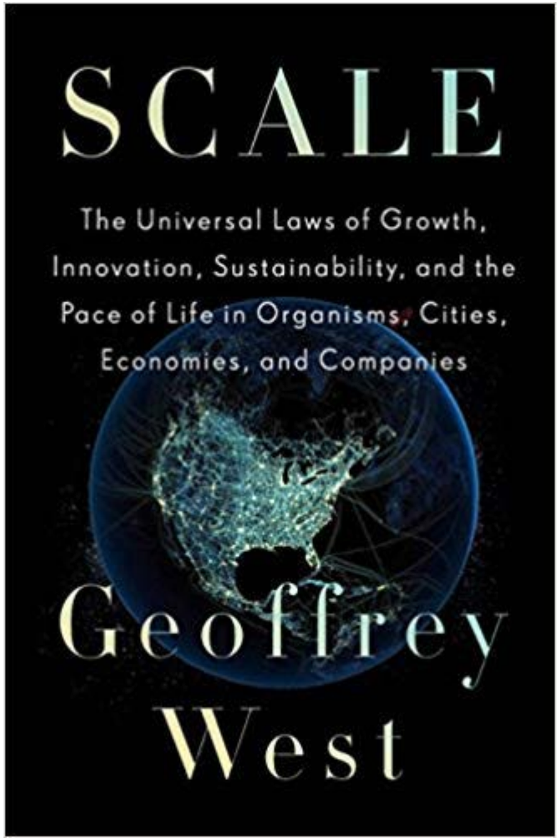
4. The West-Brown-Enquist model provides a quantitative framework that explains the ubiquity of ¼ exponents in allometry, in particular Kleiber's law

   —Key feature: Hierarchical self-similar, space-filling branching network with invariant terminal units and minimisation of energy dissipation

5. The WBE model yields a universal ontogenetic bounded growth curve
6. The WBE model redefines a universal biological clock adjusted for mass and temperature, where the clock ticks slower as size increases.

7. There are obvious limits to this model and some features are incorrect (eg. planarian) but it provides a compelling 0*th* order model to explain organismal growth and size.

• lectures



SCALE

The Universal Laws of Growth, Innovation, Sustainability, and the Pace of Life in Organisms, Cities, Economies, and Companies

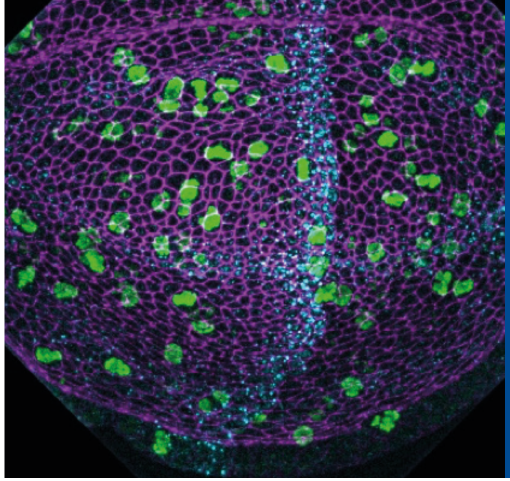
Geoffrey West

Thomas Séon

Les Lois d'échelle

La physique du petit et du grand

Odile Jacob sciences



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