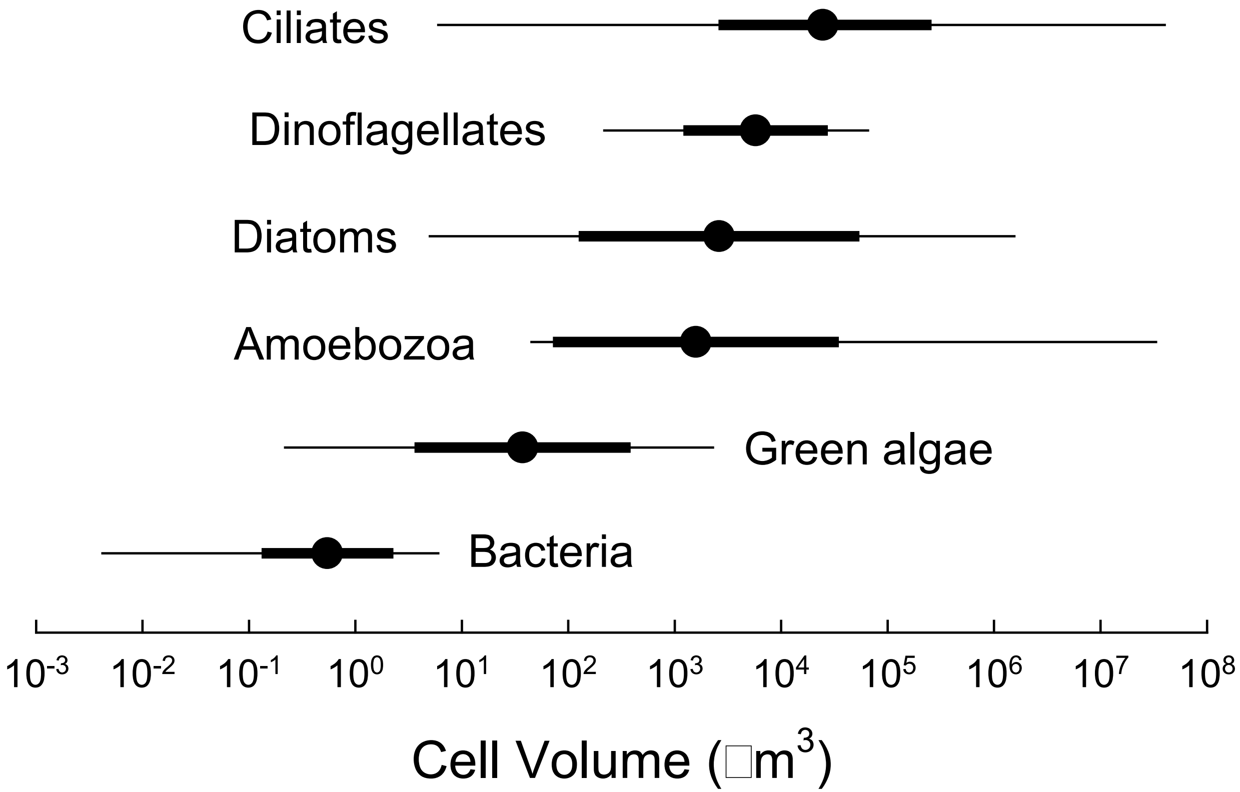
Scaling Laws in Evolutionary Cell Biology: Rules of Life

- Are there biological features that scale with cell size independent of phylogenetic affinity?

- Where this occurs, what determines the quantitative features of scaling, and what constrains evolutionary diversification?
  - Biophysical constraints?
  - Selective disadvantages of discordant combinations?
  - Outcomes of a reduction in the efficiency of selection that increases with cell size?

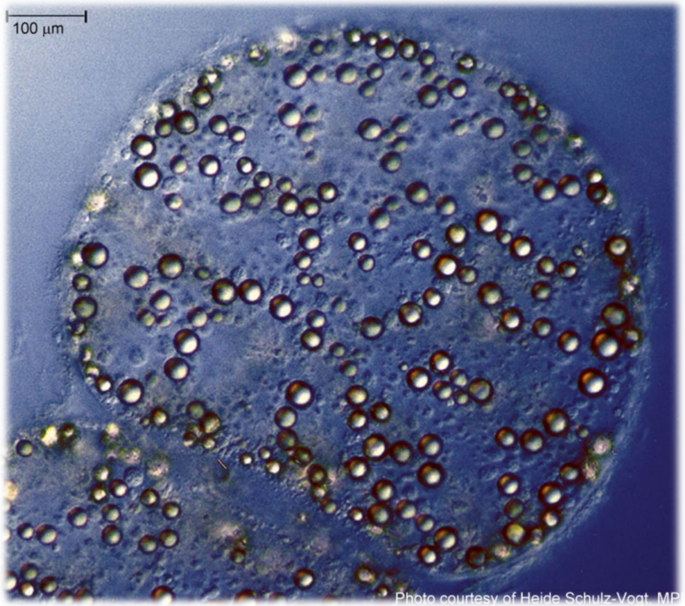
- Do scaling laws at the phylogenetic level reflect those at the within-species / developmental levels?

Cell Volumes Vary by Nearly 11 Orders of Magnitude Among Unicellular Species Across the Tree of Life



Multicellularity adds another
9 orders of magnitude

No fundamental upper limit on cell size for either prokaryotes or eukaryotes, even in terms of complex development?

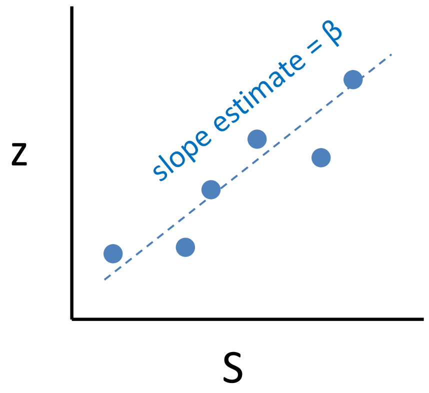


Thiomargarita, a marine-sediment bacterium, up to 0.5 mm in diameter

Caulerpa, a marine green alga, up to meters in length

Do cellular features scale with cell size in predictable ways that transcend species boundaries?

Allometric (power-function) scaling "laws": $z = \alpha S^{\beta}$



z is the measured phenotype of interest

S is a measure of organism size (usually length, mass, or volume)

α is a normalization constant (giving the value of z when $S = 1$)

β is the scaling coefficient

- Log transformation linearizes the function, and allows estimation of the parameters with least-squares linear regression:

$$\log(z) = \log(\alpha) + \beta \log(S)$$

- Fits with β = 1/3, 2/3, or 3/3 are often taken to imply associations with linear, surface, or volumetric measure of the cell.

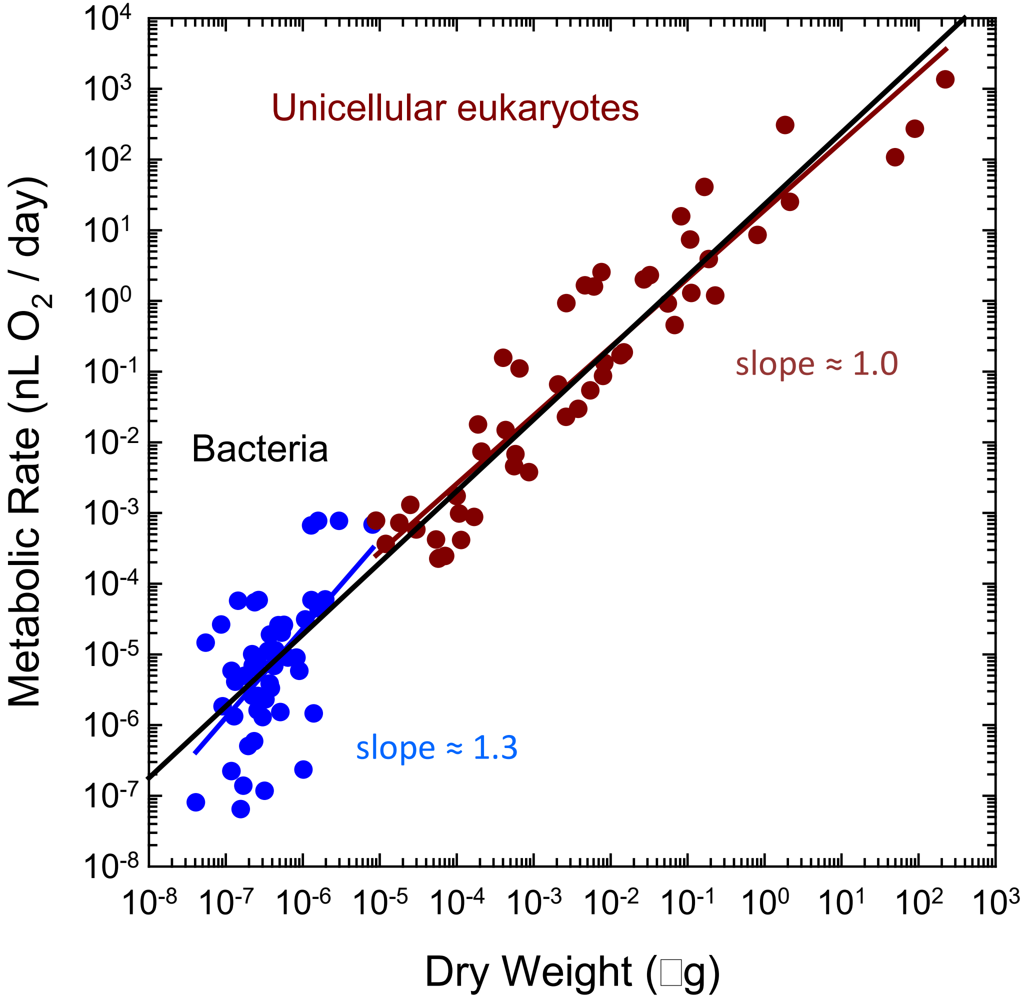
Three Types of Allometry

- Developmental or ontogenetic allometry – trajectories within individuals.

- Intraspecific allometry – among individuals within a species at comparable developmental stages.

- Phylogenetic or evolutionary allometry – among species.

Scaling of Total Metabolic Rate / Cell with Cell Volume



- Possible explanations for “scaling laws”:

  1) inevitable outcomes of biophysical / biochemical limitations?

  2) secondary consequences of evolutionary channeling towards combinations of trait values that maximize fitness?

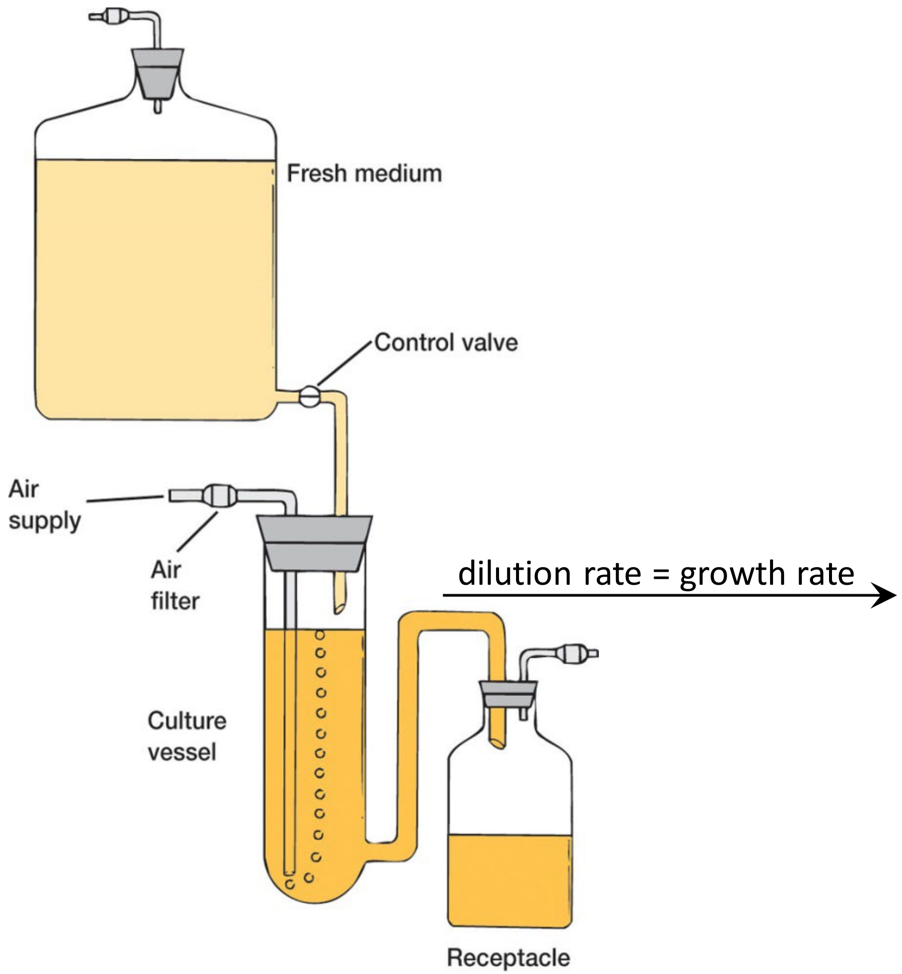
  3) reflections of drift barriers beyond which the efficiency of selection is compromised?

- The behavior here is inconsistent with the 2/3 or 3/4 power-law scaling often invoked in the literature.

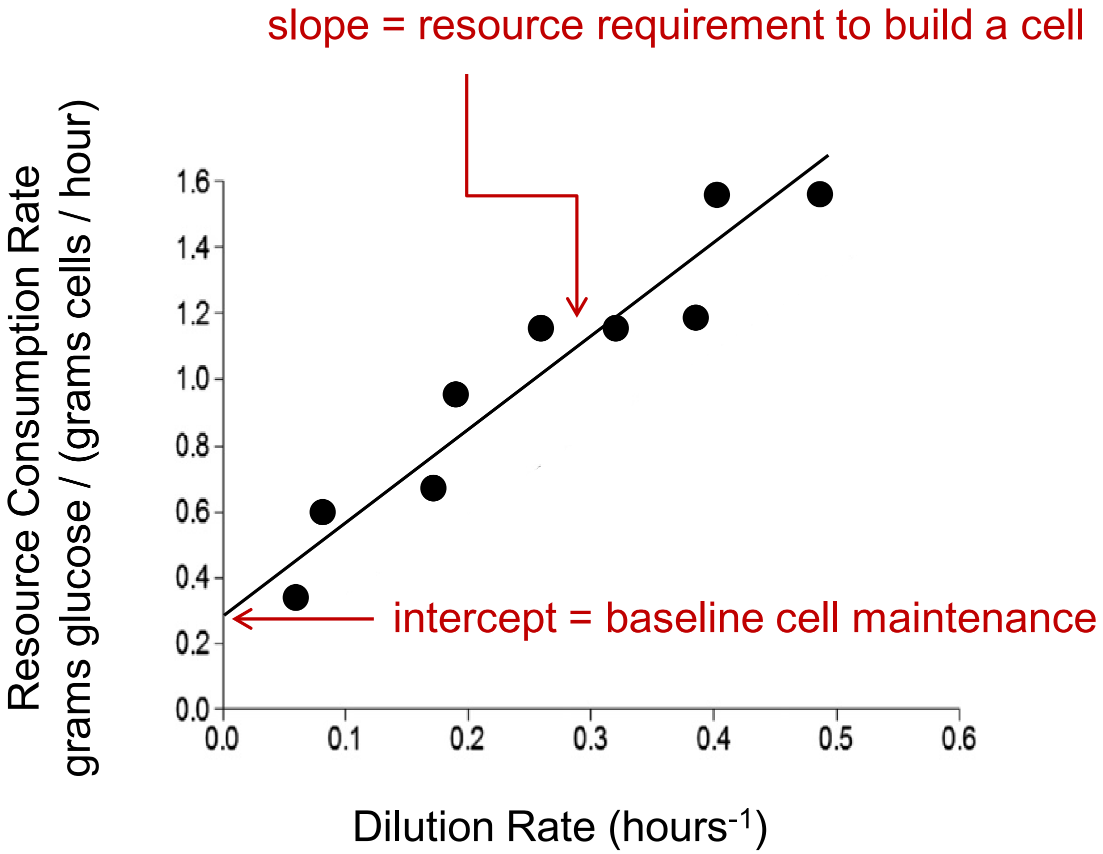
- Why does this scaling differ between bacteria and eukaryotes?

- Despite ease of acquisition, metabolic-rate measures provide little insight into the basic currency of natural selection.

What is the Bioenergetic Cost of Building a Cell?

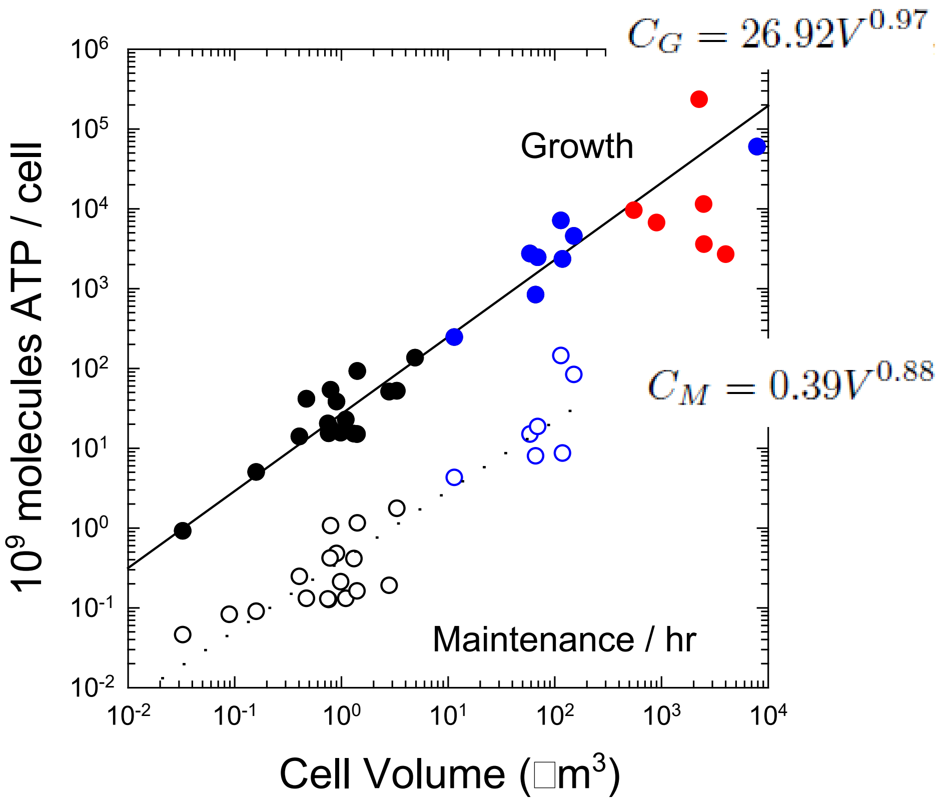


Measuring Cell Maintenance and Growth Requirements With a Chemostat



Pirt plot: from known metabolic pathways, converts resource consumption into ATP equivalents.

Lifetime Energy Requirements of Cells



Bacteria
Unicellular eukaryotes
Multicellular eukaryotes

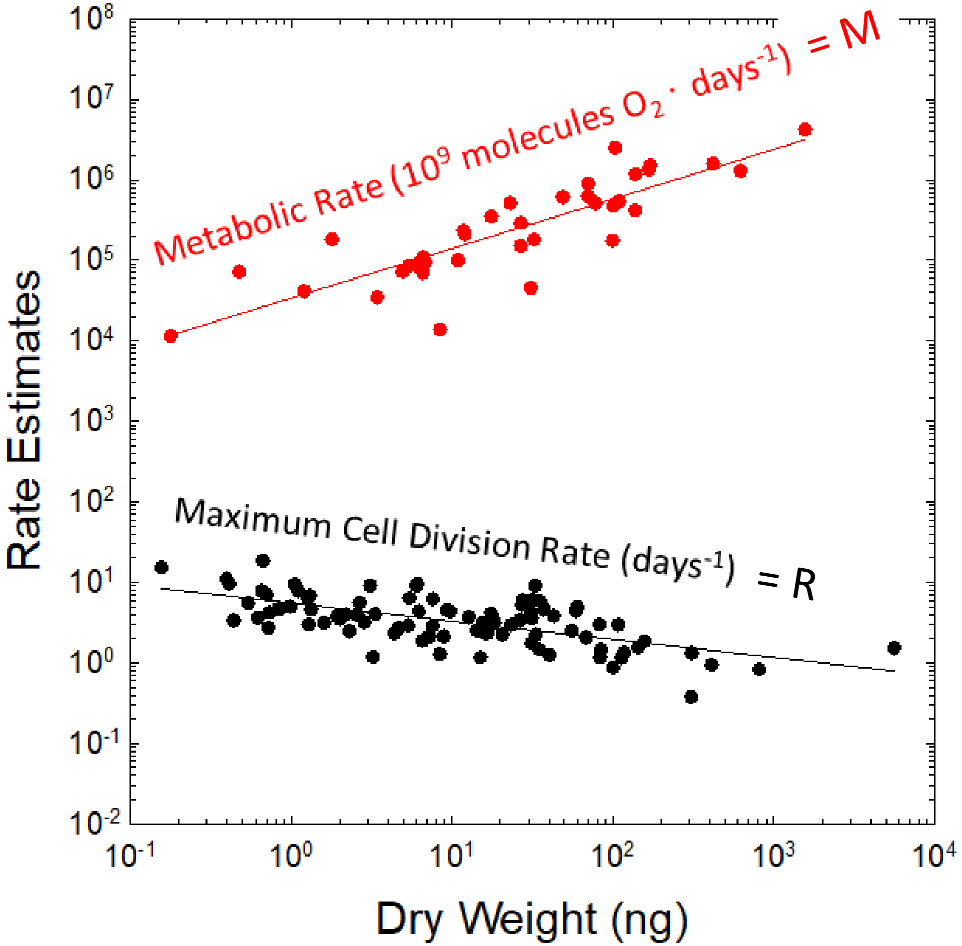
- Scaling is nearly isometric with cell volume.
- Continuous scaling across the prokaryote-eukaryote divide.
- It takes ~27 x 10^9 ATP hydrolyses to build 1 µm^3 of cell volume (an *E. coli* cell).
- What dictates the slopes and intercepts of these functions?

- Total ATP consumption / cell division: $C_T = C_G + tC_M$, where t = cell division time (hours).

Lynch and Marinov (2015)

An Alternative Approach for Cells with Complex Diets

Comparative Data for Ciliated Protozoans



- M/R is the number of O_2 molecules consumed per cell division.
- Observations from biochemistry indicate that the number of ATPs produced per oxygen atom consumed (the so-called P:O ratio) $\approx$ 2.5, so $5M/R$ estimates the number of ATP hydrolyses per cell division used in ATP production.
- Assuming half of energy consumed goes to carbon skeletons, $10M/R$ estimates the total number of ATP equivalents required per cell division,

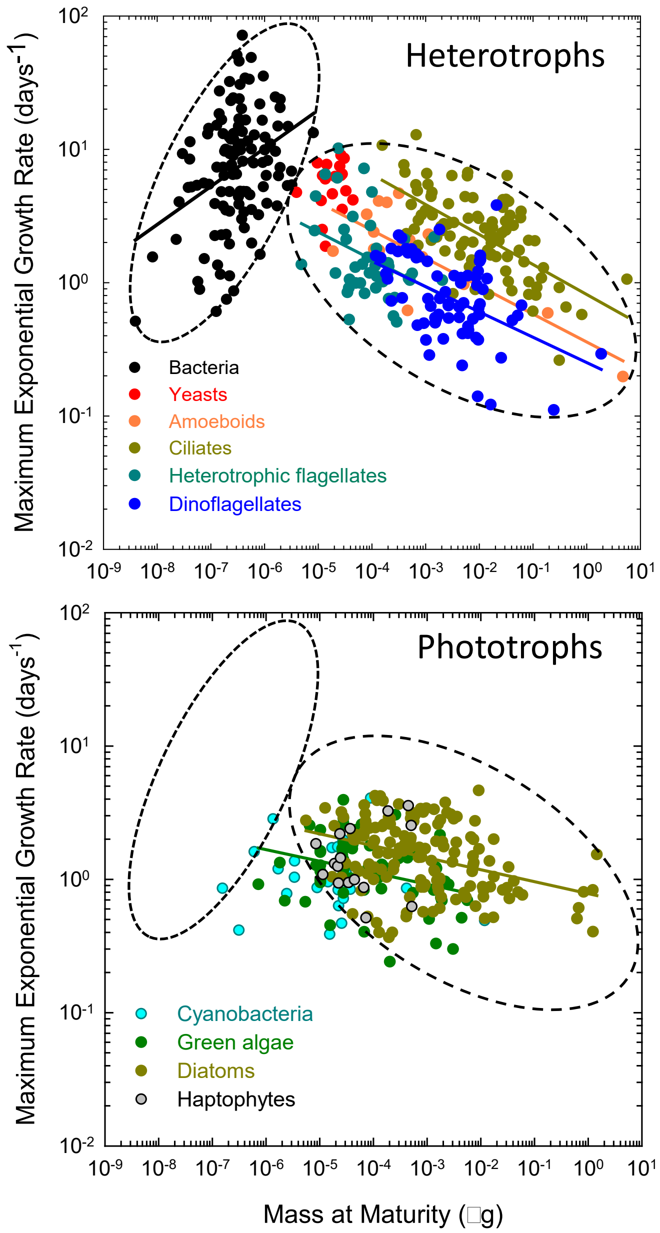
$\approx 115V^{0.77}$ (x 10^9 ATPs), as compared to $27V^{0.88}$ from Pirt approach.

Maximum Growth-Rate Scaling with Size in Unicellular Species Across the Tree of Life

- Bacteria and unicellular eukaryotes scale in opposite directions.

- Eukaryotic data incompatible with other geometric-constraint models:
  - slopes are close to -1/5 for heterotrophic eukaryotes, and -1/10 for phototrophs.
  - inconsistent with both -1/3 and -1/4 scaling predicted by biophysical-constraint models.

- Incompatible with the idea that the origin of mitochondria induced a bioenergetics revolution by freeing large cells from surface-area limitation.



Unsolved Problems

- Why do the energetic requirements for growth / maintenance scale nearly linearly with cell volume across the Tree of Life?
  - Despite the substantial differences among the cytoplasmic constituents of bacteria and eukaryotes, the summed assembly costs of cellular parts (per unit volume) remains roughly the same.

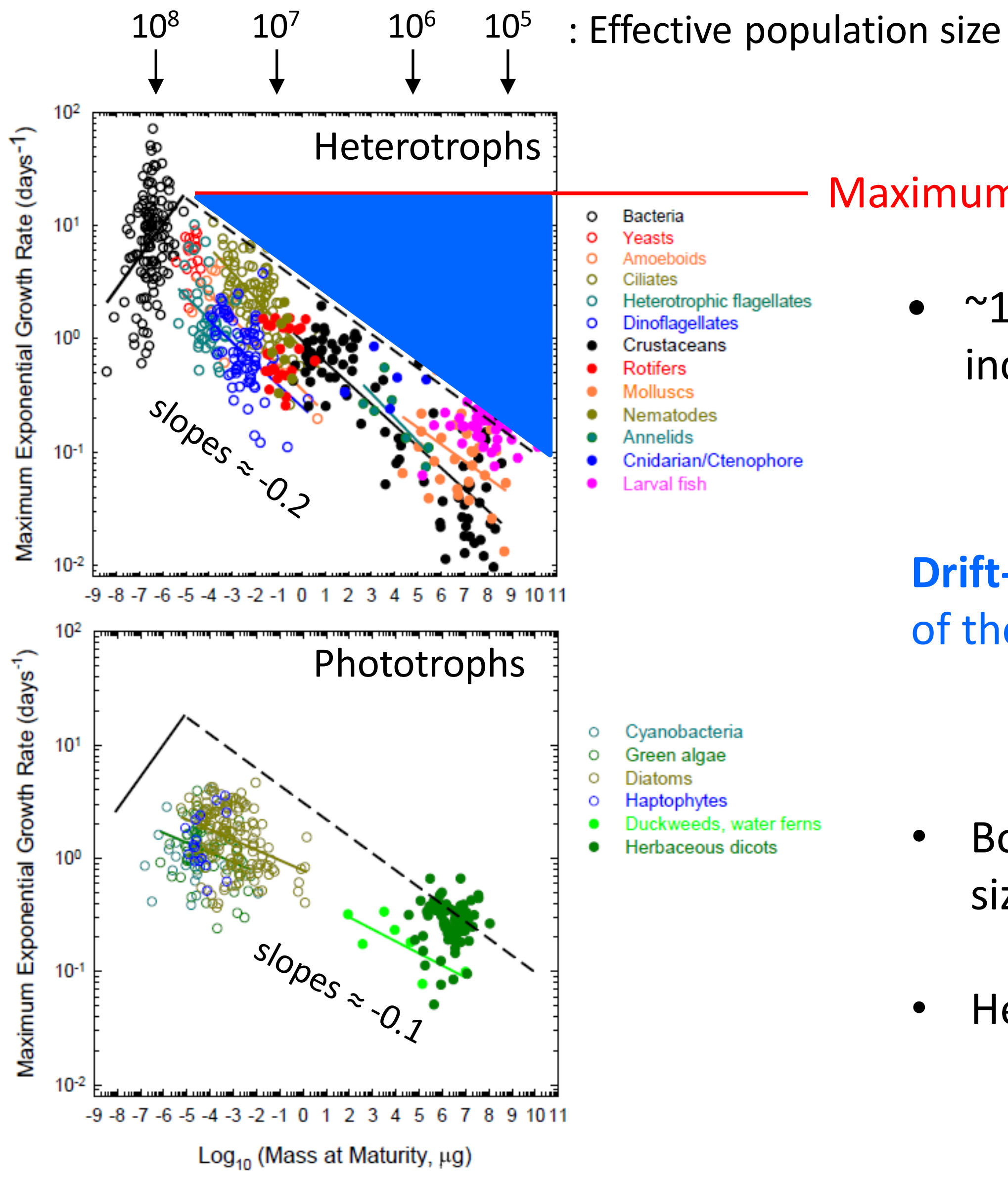
- Why do cells of larger eukaryotes become less efficient (rate of growth per biomass) at transforming energy into growth?

- What dictates the cell-division speed limit?
  - Minimum cell-division times achievable by natural selection (20^o C): $V = 1\ \mu m^3 \rightarrow$ 0.5 hours
    $V = 10^3\ \mu m^3 \rightarrow$ 2 hours
    $V = 10^6\ \mu m^3 \rightarrow$ 8 hours

- Bacteria: a physical (surface area : volume) constraint?

- Eukaryotes: a population-genetic (drift barrier) constraint?

Extension to Multicellular Species: the speed limit to growth is inversely proportional to N_e



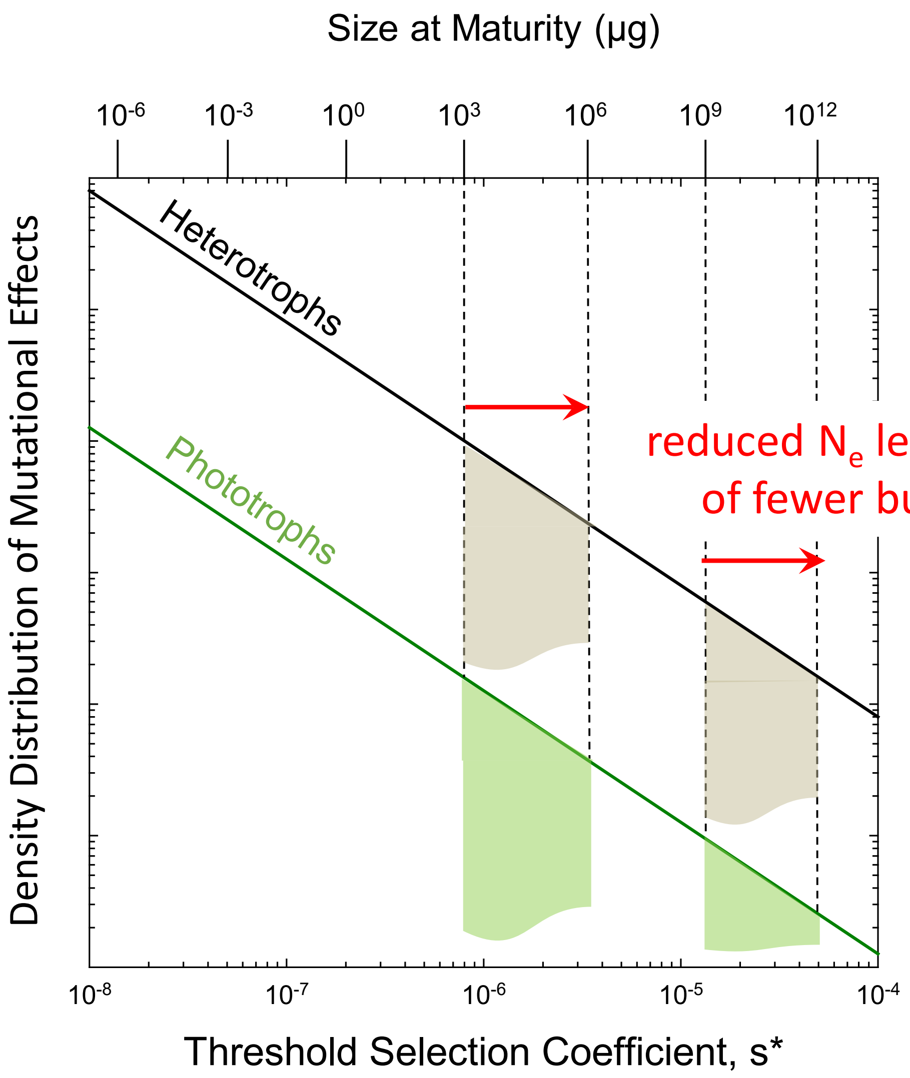
- ~1000x decline in growth potential over 15 order-of-magnitude size increase in eukaryotes.

Drift-Barrier Hypothesis: Missing growth-rate potential is a consequence of the accumulation of mild growth-reducing mutations by random drift.

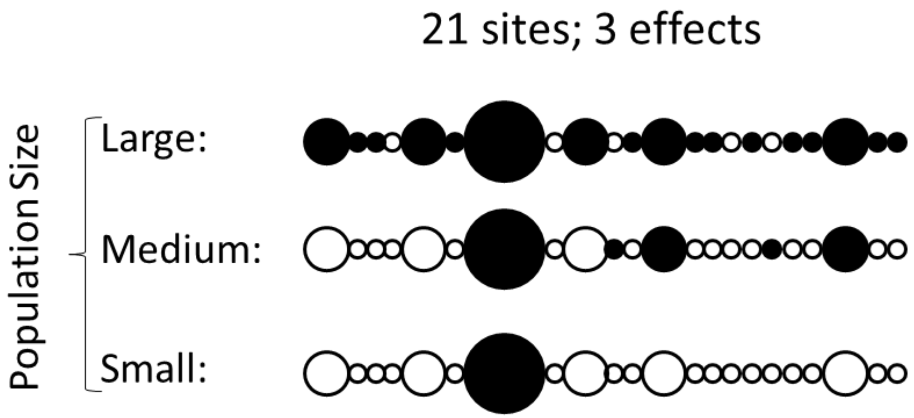
- Both N_e and maximum growth rates scale with the -0.20 power of size at maturity.

- Hence, maximum growth rates scale isometrically with N_e.

Expected Distribution of Mutational Effects to Account for Power-Law Behavior: manifestation of effective neutrality?



reduced N_e leads to progressive fixation of fewer but more deleterious mutations



- **Exponential Distribution**: the number of sites with effect s is proportional to 1/s, which keeps the total load (number × effect) of each fitness class constant.

- This shape is roughly consistent with empirical studies of the distribution of mutational effects in multiple organisms.

The energetics of genome complexity

Nick Lane[1] & William Martin[2]

"….. permitting a remarkable 200,000-fold expansion in the number of genes expressed. This vast leap in genomic capacity was strictly dependent on mitochondrial power, and prerequisite to eukaryote complexity: the key innovation enroute to multicellular life."

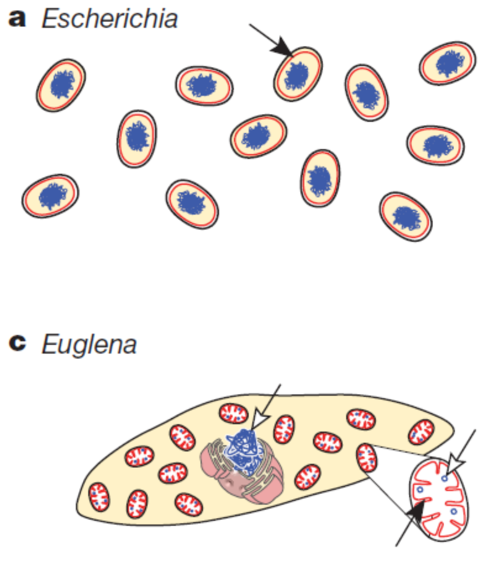
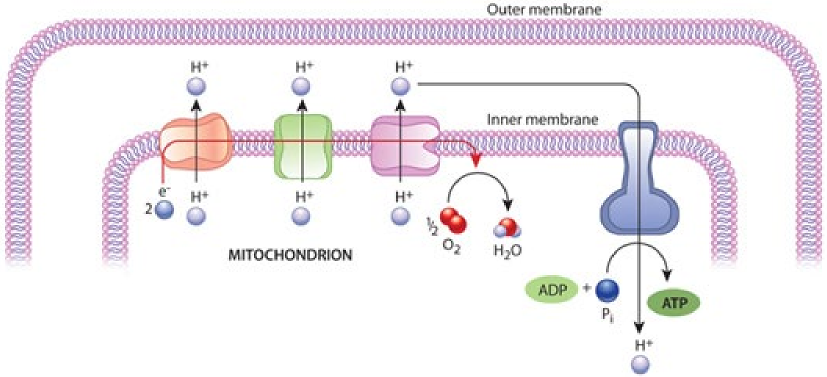


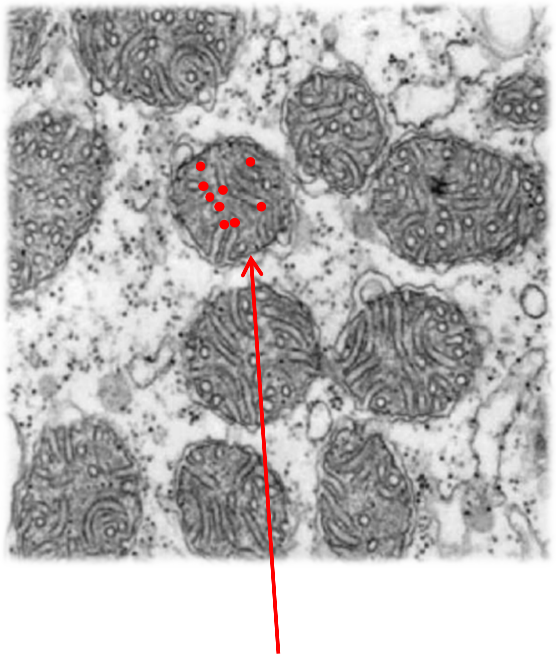
Figure 2 | The cellular power struggle.

- Growth-rate data are inconsistent with the idea that the establishment of the mitochondrion precipitated a bioenergetics revolution essential to eukaryotic diversification.

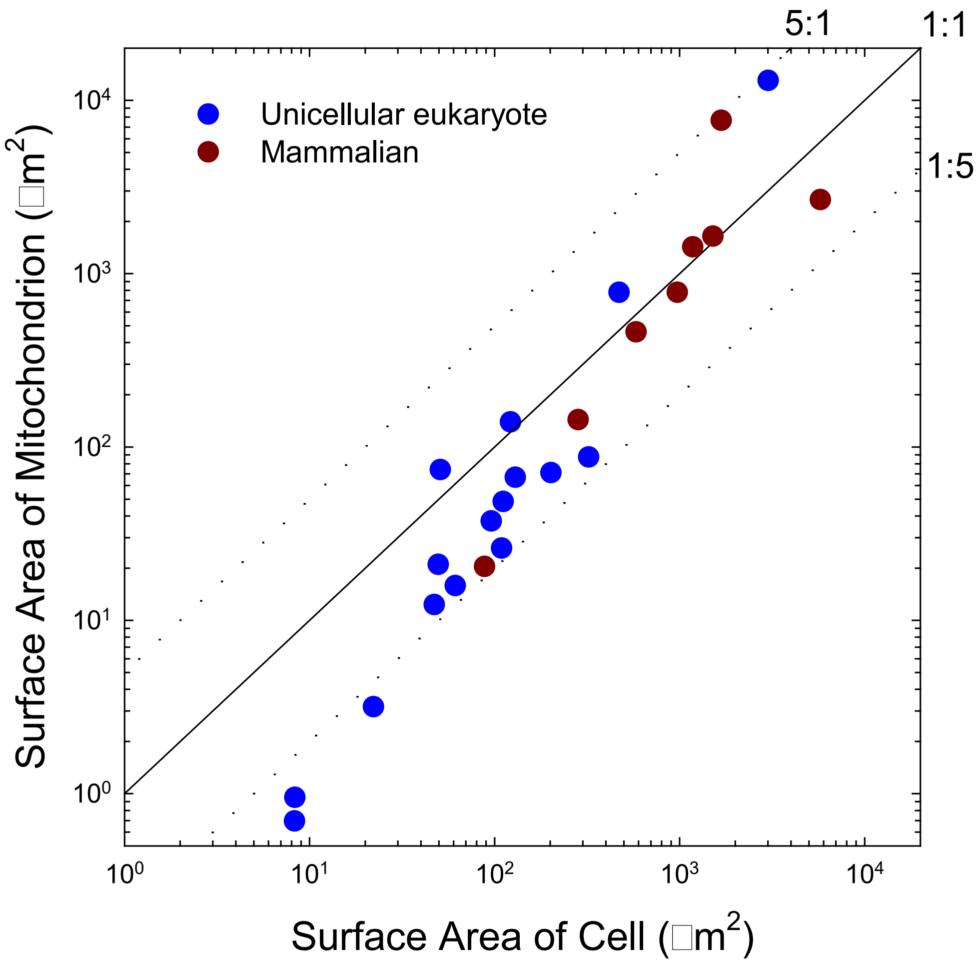
- A diversity of additional observations, including the anatomy and cellular content of mitochondria, ATP synthase, and ribosomes, are also inconsistent with this hypothesis.



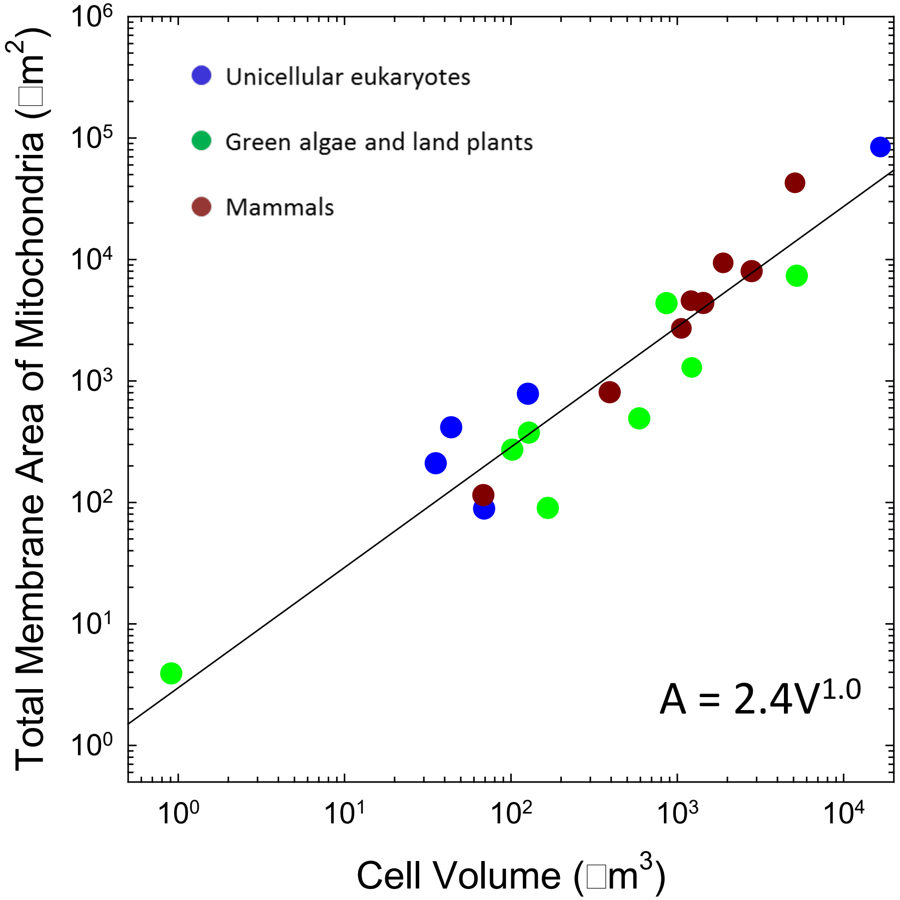
Surface Area of Mitochondria vs. Plasma Membrane



ATP synthase is often restricted to the tips of cristae



Scaling of the Investment in Mitochondrial Membranes



- Total mitochondrial membrane area (inner + outer) scales linearly with cell volume across the Tree of Eukaryotes.

- Total cost of membranes =

  (no. of lipid molecules / surface area)
  x (cost / lipid molecule)
  x surface area

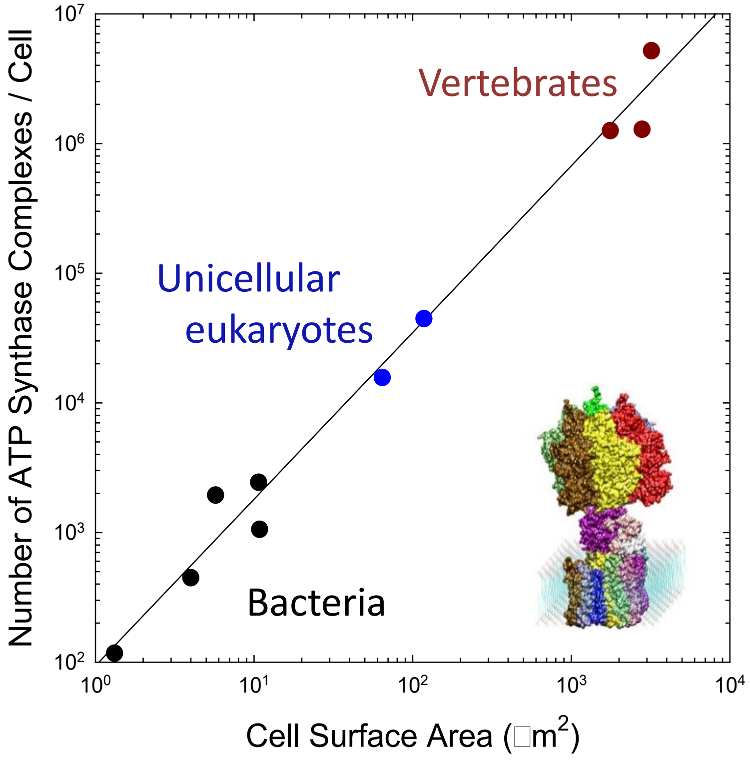
- Relative to total cellular ATP requirements, the cost of mitochondrial membranes

  = $0.05\ V^{0.04} \approx$ 5% of cell's energy budget

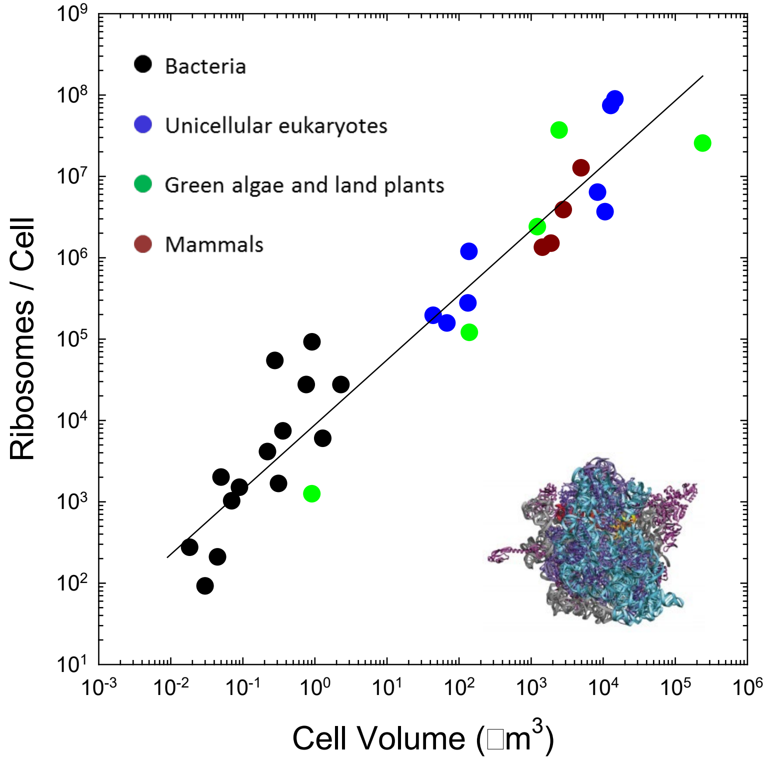
Size-dependent Scaling: Numbers of ATP Synthase Complexes and Ribosomes / Cell

- Continuity of scaling across bacteria and eukaryotes.

$N_{ATP\ synthase} = 94S^{1.3}$



$N_{ribosomes} = 8800V^{0.8}$



Unresolved Issues on the Origin of the Mitochondrion

- Rather than launching an energetic revolution, the mitochondrial-host cell consortium may have been a zero-sum game.

- Why do some bioenergetic scaling laws transcend the prokaryote/eukaryote divide, despite the origin of the mitochondrion?

- What is the requirement for an evolutionary stable mutualism, when it is in the best interests of *both* participants to extract as much out of the interaction as possible?

  - Are mutualisms more than the sum of their parts?

- Is the evolution of the mitochondrion a grand example of the preservation of two ancestral components by complementary degenerative mutations – subfunctionalization?

- Did the mitochondrion pre- or post-date the origin of eukaryotic cellular complexity?

  - How would phagocytosis operate when ATP synthase sat in the cell membrane?

Cavalier-Smith's (1977) Nucleoskeletal Hypothesis

- Selection favors an optimal cell size, dictated by environmental conditions.

- This induces selection for an optimal nuclear volume essential for an appropriate rate of export of mRNAs and ribosomes through nuclear pores.

- Nuclear volume is directly influenced by genome size, and hence selection favors an optimal genome size as a nucleating scaffold (independent of its gene content).

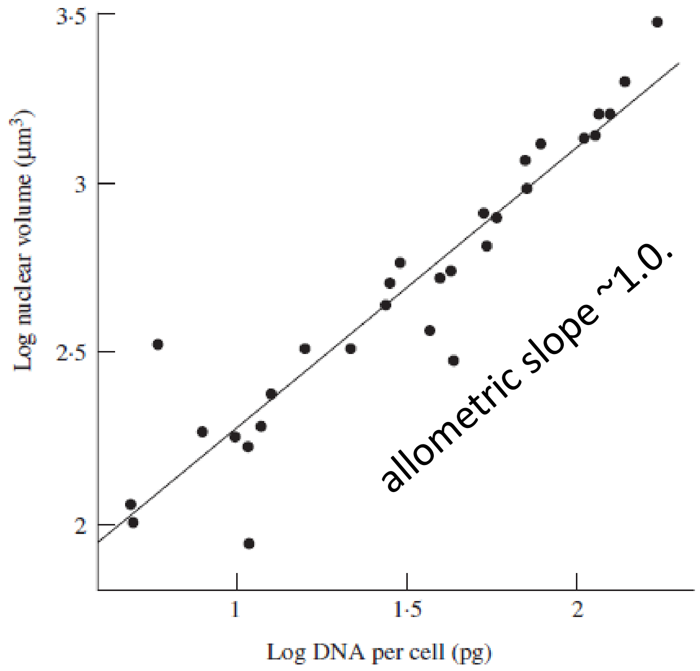
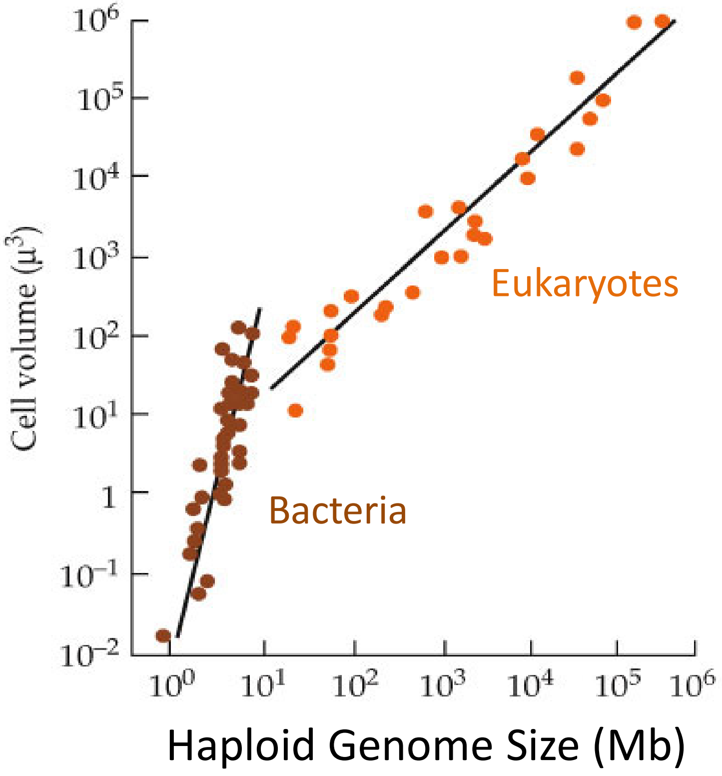


FIG. 3. Scaling of nuclear volume (means of root and shoot meristem cells) with DNA content in 30 species of herbaceous angiosperms. Data from Baetke *et al.* (1967). Slope 0·826. From Cavalier-Smith (1985*a*).

Implications, if correct:

- The huge phylogenetic range of nuclear genome sizes is a consequence of:
  - the indirect effects of selection for alternative cell sizes in different lineages;
  - constraints imposed by the nuclear envelope;
  - the nucleation of its assembly by DNA.



- Genome-size variation does not reflect population-genetic processes such as insertion bias and random genetic drift:
  - the concept of “junk DNA” is overstated;
  - the energetic and mutational costs of excess are irrelevant.

From Shuter et al. (1983)