L2.1: Cellular Architecture:
Design Principles of Organelle Size

What principles and design parameters determine the size of cellular organelles?

AGRICULTURAL & BIOLOGICAL ENGINEERING
PURDUE UNIVERSITY PHYSIOLOGICAL SENSING FACILITY
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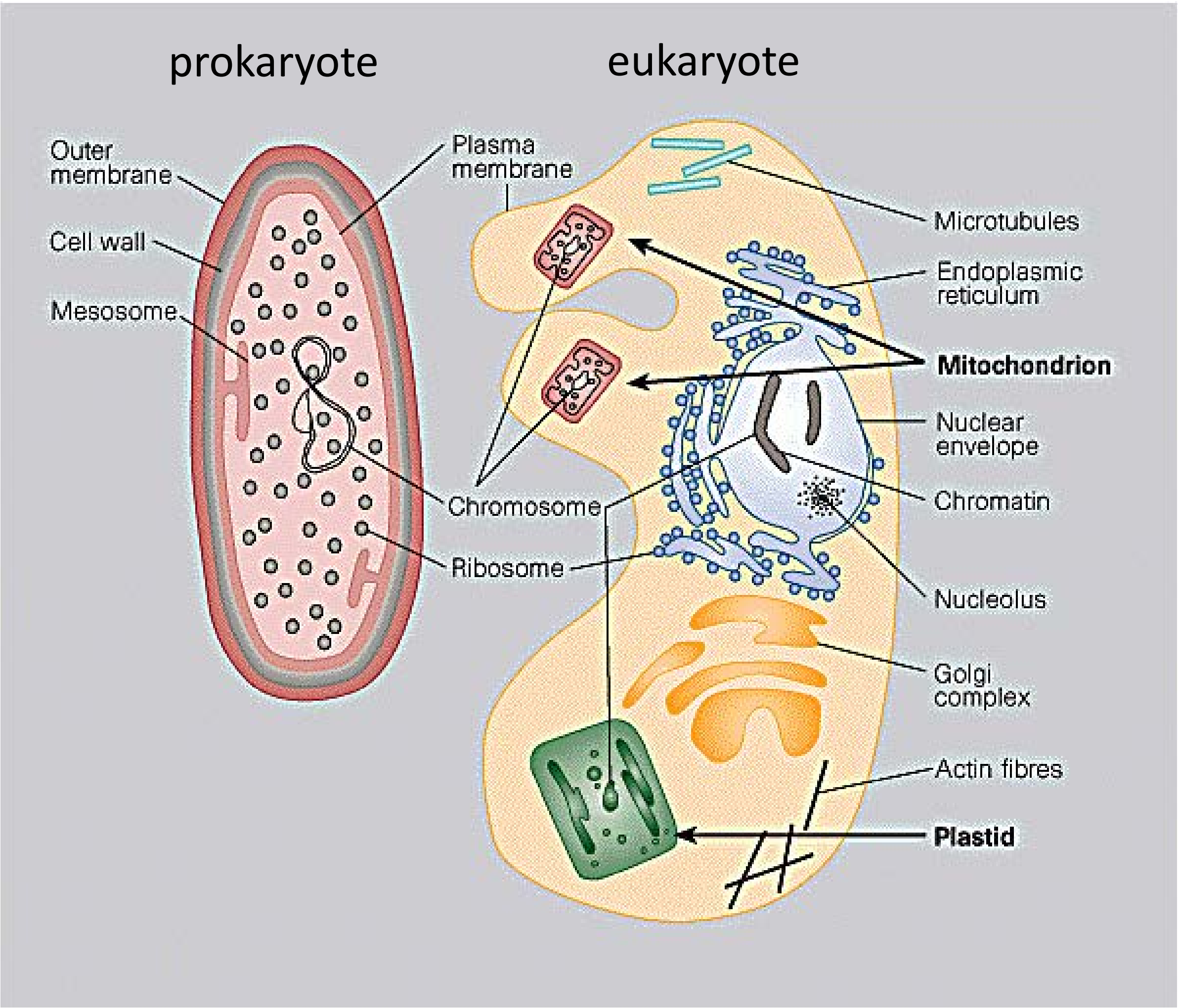
This Lecture …

- Ponder questions of organelle size and scaling
    - Example: $V_{nucleus} : V_{cell}$

- Three design principles of organelle size control
    1. Molecular ruler
        - e.g. bacteriophage tail
    2. Quantal Synthesis
    3. Dynamic Assembly
        - e.g. algae flagella



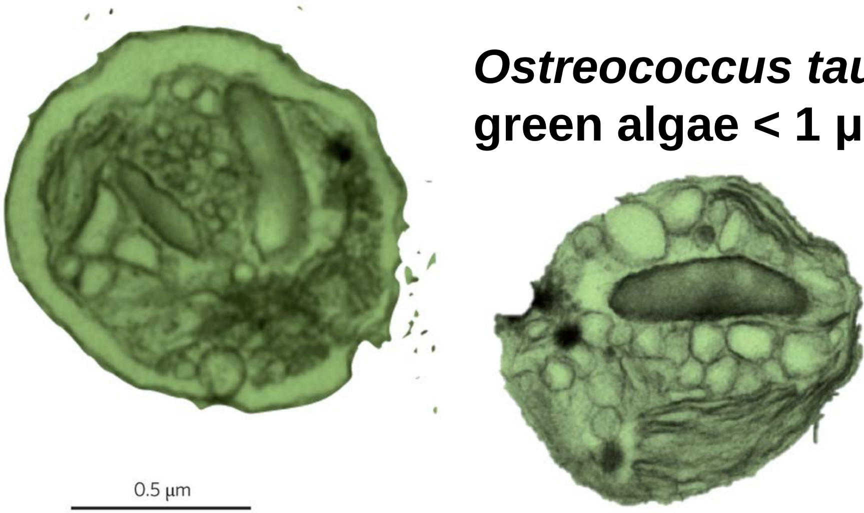
Typical Prokaryotic Cell

- Outer membrane
- Cell wall
- No membrane bound nucleus
- Lacks other major organelles
- DNA in chromosome
- DNA in plasmids

Typical Eurkaryotic Cell

- 1 nucleus
- 2 centrioles
- 1 endoplasmic reticulum
- Multiple mitochondria
- Many ribosomes
- *plants/algae multiple many plastids (e.g. chloroplasts)

eukaryotic cells come in many different shapes and sizes



Ostreococcus tauri
green algae < 1 µm

Hutchins. Nature Climate Change 3, 183–184 (2013)
Image by Elisa Schaum, Univ. of Edinburgh.

Xenopus Frog Egg >1 mm

Feric & Brangwynne Nature Cell Biology 15, 1253–1259 (2013)

Do bigger cells make more or bigger organelles?

Do bigger cells have bigger nuclei?

How do cells sense and control organelle size and number?

What is the impact?

Fundamental Question of Scaling in Cells

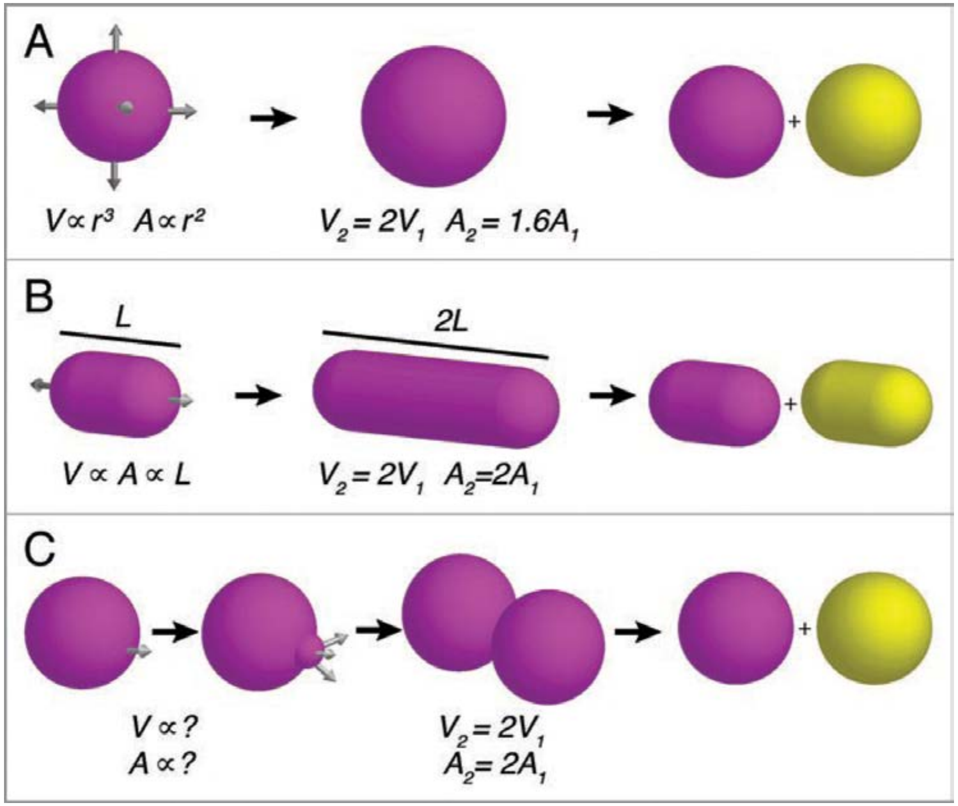
“ ’*Everywhere Nature works true to scale, and everything has its proper size accordingly*.’ With these words,[1] D’Arcy Wentworth Thompson elegantly identifies what remains as one of the great mysteries in science: **the regulation of the sizes of biological organisms and their substructures**.”

References.

1. ***Thompson*** *DW. On Growth and Form. Dover 1992 edition. Cambridge, England: Cambridge University Press 1942; 24.*
2. *Yee-Hung M.* ***Chan*** *, Wallace F. Marshall “Scaling properties of cell and organelle size.” Organogenesis Vol. 6, Iss. 2, 2010*

When cells divide, they first double their volume.

area scaling & therefore surface to volume ratio depends on how cells divide



Isotropic Growth
e.g. approximated in mammalian cells

Long Axis Grown
e.g. fission yeast

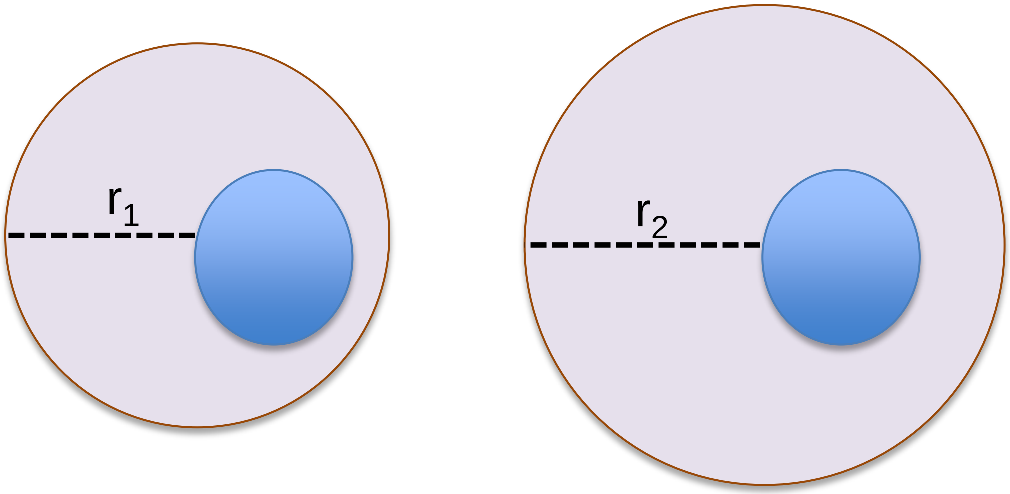
Polarized Growth
e.g. budding yeast

- Surface contains receptors that are is the primary interface with the extracellular environment.
- Changes in $A_{surface}$ alter receptor density unless compensated
- $A_{surface}$ / V ratio may alter intracellular signaling response to environment

Published in: Yee-Hung M. Chan; Wallace F. Marshall; *Organogenesis* **2010,** 6, 88-96.
DOI: 10.4161/org.6.2.11464

Consider transport between surface and nucleus

Consider hypothetical case if cell 2 is twice as big as cell 1 but has same size nucleus



Cell 1: V_1
r_1
t_1

Cell 2: $V_2 = 2V_1$
$r_2 = 2^{1/3} r_1 = 1.26\ r_1$
$t_2 = 1.26^2 = 1.6\ t_1$

Volume scales with r^3

Average transport distance between nucleus and cell surface increases

Diffusion times, t, scale with square of distance, x^2

If distance is longer, passive diffusion times & therefore signaling times may increase*

Cell surface to nucleus is a major "highway" for cell signaling
Relay external information to influence gene expression response.

Where t = time for a molecule to traverse the radius of the cells*

** not accounting for any active transport mechanism*

Transport is critical to function of intracellular organelles. Geometry & scaling will alter transport behavior

Table 1. Summary of characteristics and functions of various organelles related to size scaling

	Shape	Number	Functions	Transport	Capacity
Nucleus	Single compartment, central	One	Storage of genetic information (only one/two copies normally), transcription	Nuclear pores mediate transport of mRNA, ribosomes, etc.	DNA storage and transcription in lumen, transport through membrane
ER	Many: distributed tubular network, large sheets, nuclear envelope	One network	Protein/membrane synthesis, translocation, trafficking	Deliver proteins/lipids via budding vesicles into the secretory pathway or via diffusion	Ca^{2+} storage in lumen, protein translation and lipid synthesis in membrane
Golgi	Multiple disc-like cisternae, sometimes arranged in a stack	One to multiple	Trafficking/sorting of proteins, posttranslational modification, lipid synthesis	Proteins enter and exit by secretory vesicle delivery and budding	Modification of proteins in lumen and membrane, vesicle fusion/budding at membrane
Vacuole/ Lysosome	Clustered or distributed spherical compartment(s)	One to multiple individuals	Waste degradation, storage and recycling, stress response, autophagy	Membrane channels and vesicle fusion deliver membrane, cytoplasm, proteins, etc.	Lumen is where much of processing, storage and buffering occurs
Mitochondria	Varies: distributed linear network common, sometimes clumped	One network containing many individuals	Respiration, lipid synthesis	Metabolites and products of respiration transferred across membrane	Length and amount are related to respiratory capacity
Peroxisome	Individual small spherical structures	Multiple individuals	Waste processing	Individual organelles are carried along cytoskeleton	Increases with number and individual size
Flagella/ Cilia	Elongated and tubular	One or multiple individuals	Movement, chemical sensing	Cell-cilium transport occurs through a membrane pore, intraciliary transport along central microtubules	Length affects stroke/ beating pattern, cell motility

Transport summarizes factors relevant to transport across the organelle membrane or between the organelle and other parts of the cell. Capacity refers to what morphology parameters are likely to affect which organelle functions. Entries are meant as general descriptions and there are many exceptions.

Published in: Yee-Hung M. Chan; Wallace F. Marshall; *Organogenesis* **2010,** 6, 88-96.
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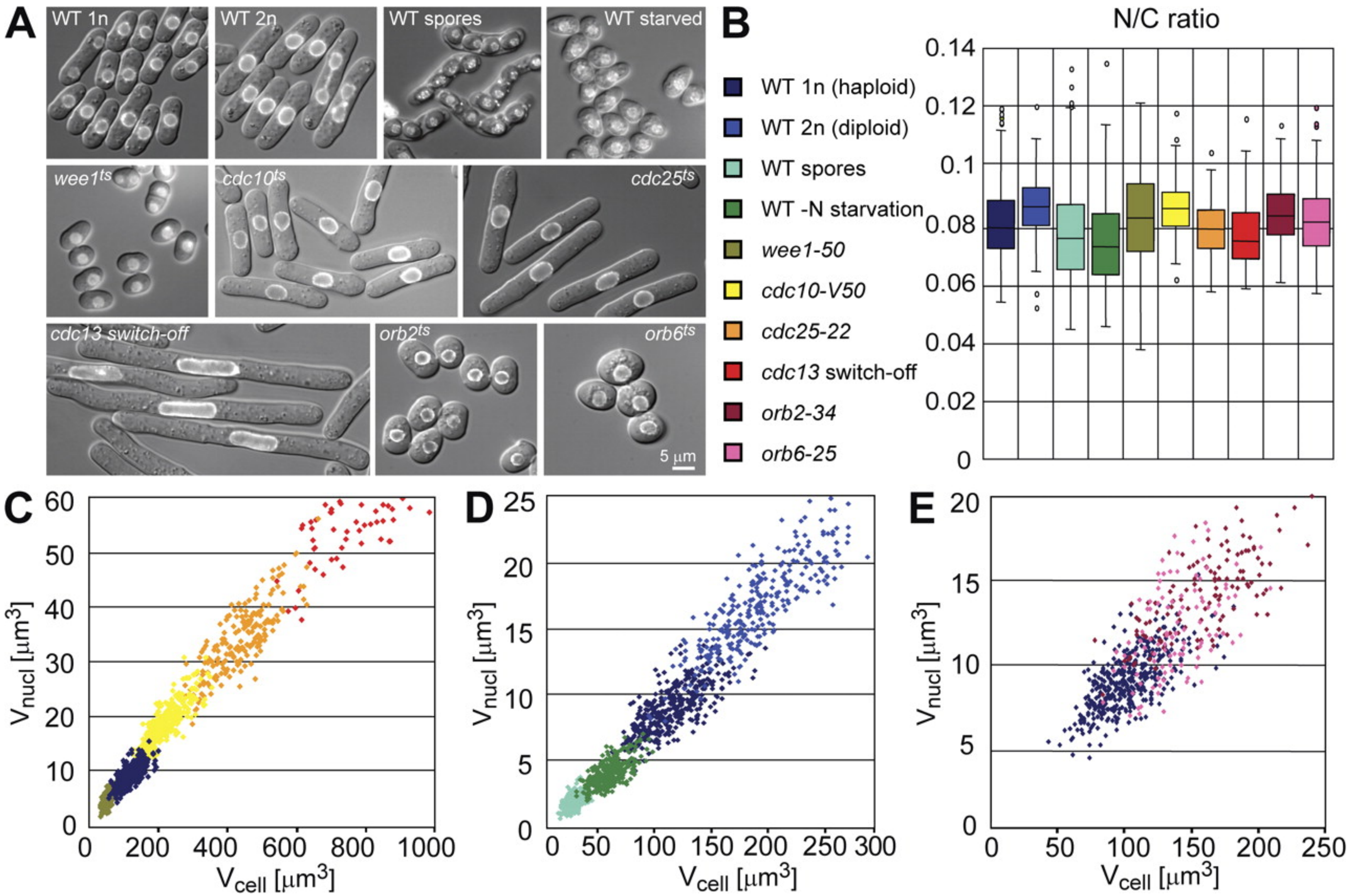
What happens in real cells?

Does the cell scale the nucleus size with the cell volume?

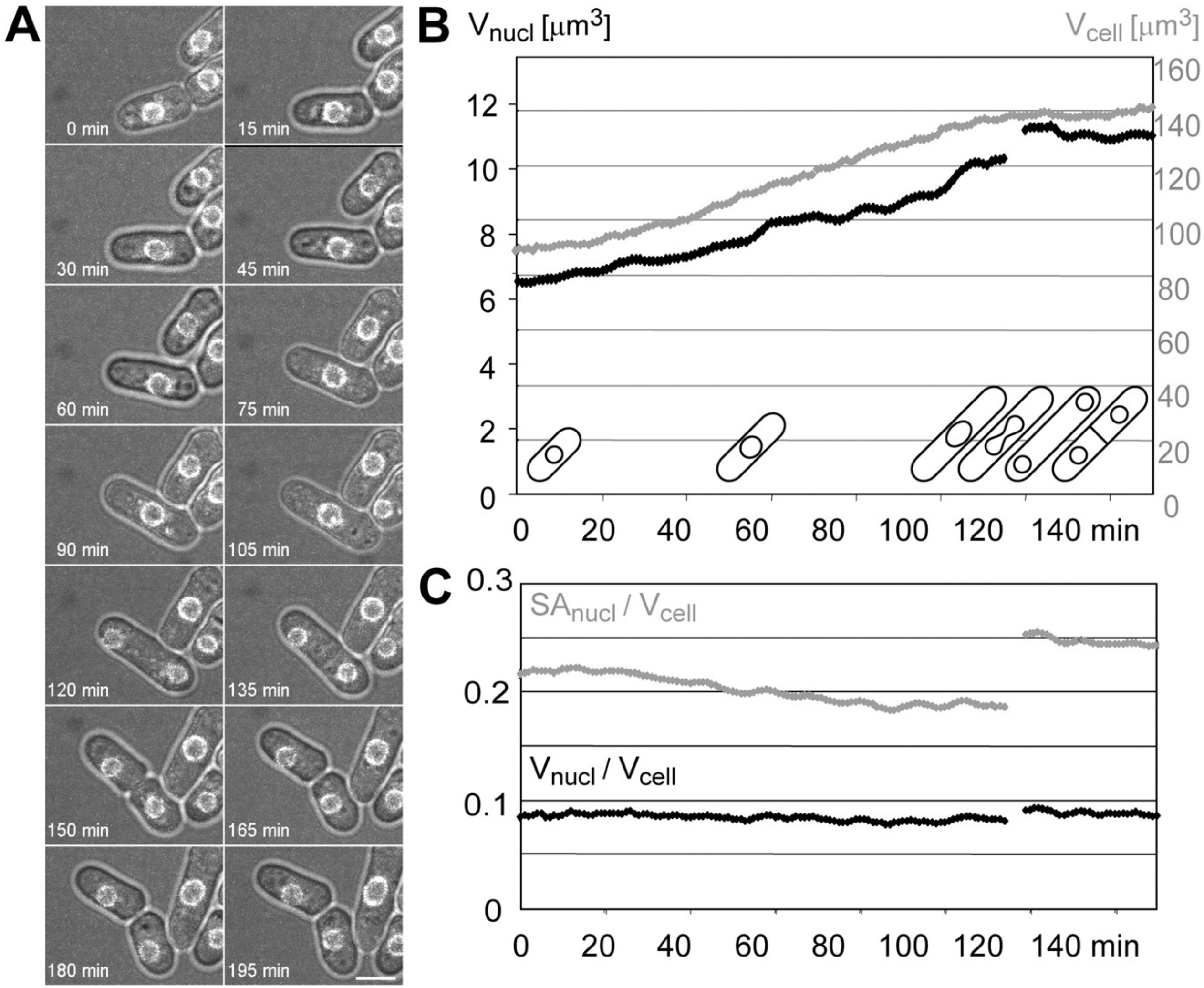
Nuclear and cell size correlate over a large range in cell size and shape.



Frank R. Neumann, and Paul Nurse J Cell Biol 2007;179:593-600

Fission Yeast

$V_{nucleus}$ / V_{cell} ratio is constant throughout cell cycle.



Volume of the nucleus

Frank R. Neumann, and Paul Nurse J Cell Biol 2007;179:593-600

Where else might this be biologically relevant?

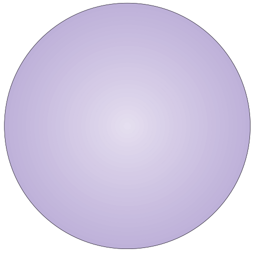
- **Cancer?**
  - cell nucleus is often enlarged and abnormal in cancer cells ….

- What is **biophysical consequence** on transport/signaling of an abnormally large nucleus?

What are the **design principles** that drive and control organelle size and shape?

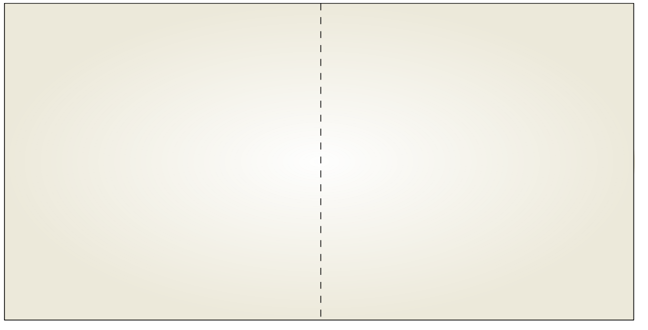
Design principles used determine organelle size in cells

Principle 1
Molecular Ruler
(structurally controlled)



Principle 2
Quantal Synthesis
(stoichiometry controlled)

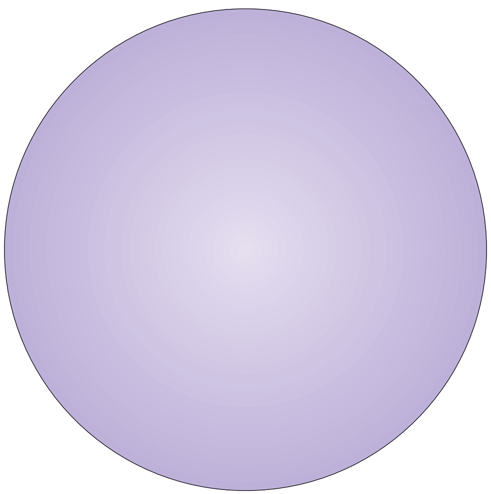
Principle 3
Dynamic Assembly
(kinetically controlled)



Rafelski & Marshall. Nature Reviews Molecular Cell Biology 9, 593-602 (August 2008)

Principle 1. Molecular Ruler

- Length of a particular molecule (usually a protein) determines the length of a larger structure
- Often driven by self-assembly
  - E.g. ruler molecule controls when self-assembly terminates



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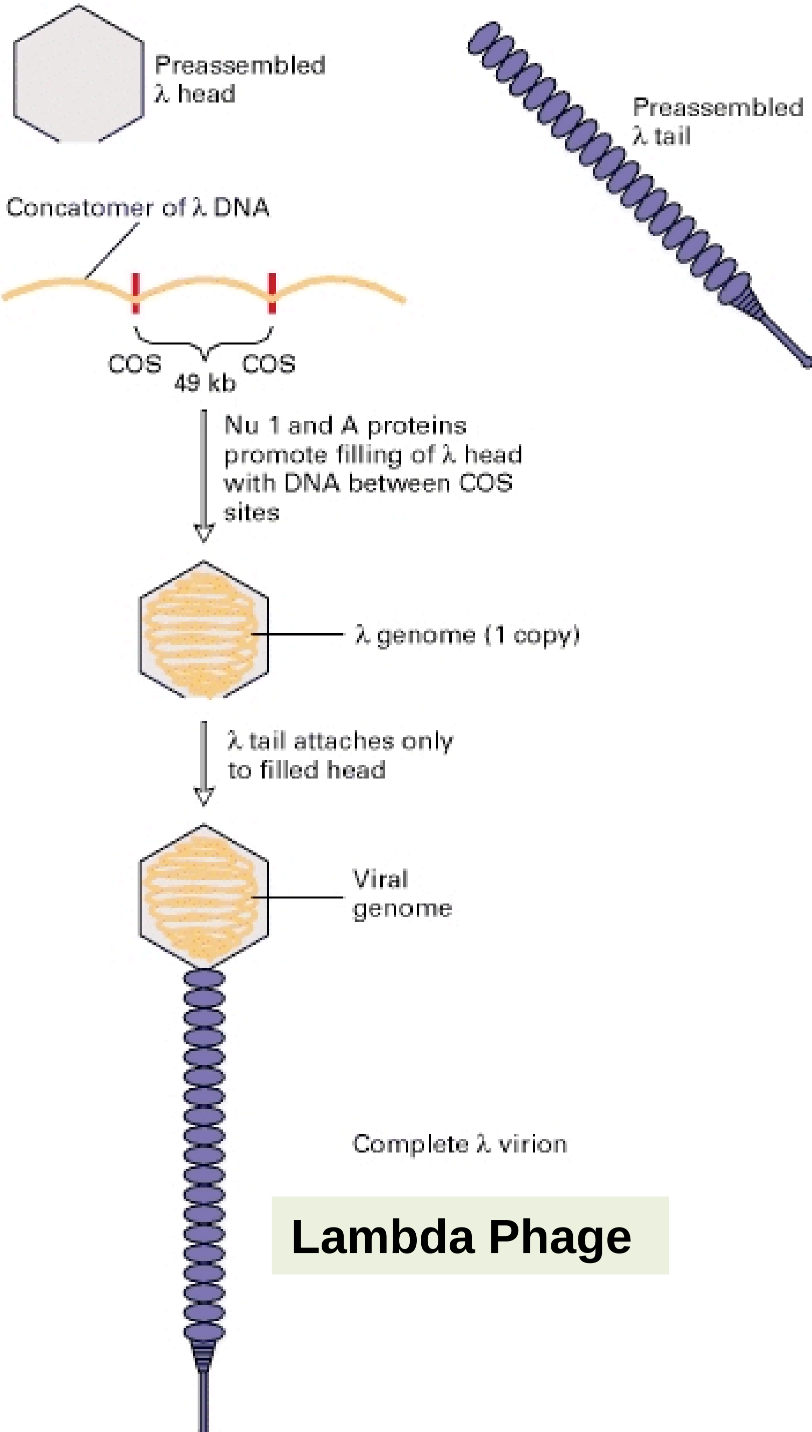


Lambda Phage

Tail length of Bacteriophage

Tail is made of self assembled proteins.

Organized in a disk structure

Lambda phage has a characteristic tail length

The # of disks determines the tail length

How does the system know when to stop adding disks to achieve the characteristic tail?

Molecular Cell Biology. 4th edition.
Lodish H, Berk A, Zipursky SL, et al.
New York: W. H. Freeman; 2000.
http://www.ncbi.nlm.nih.gov/books/NBK21696/figure/A1614

First clues were from mutants

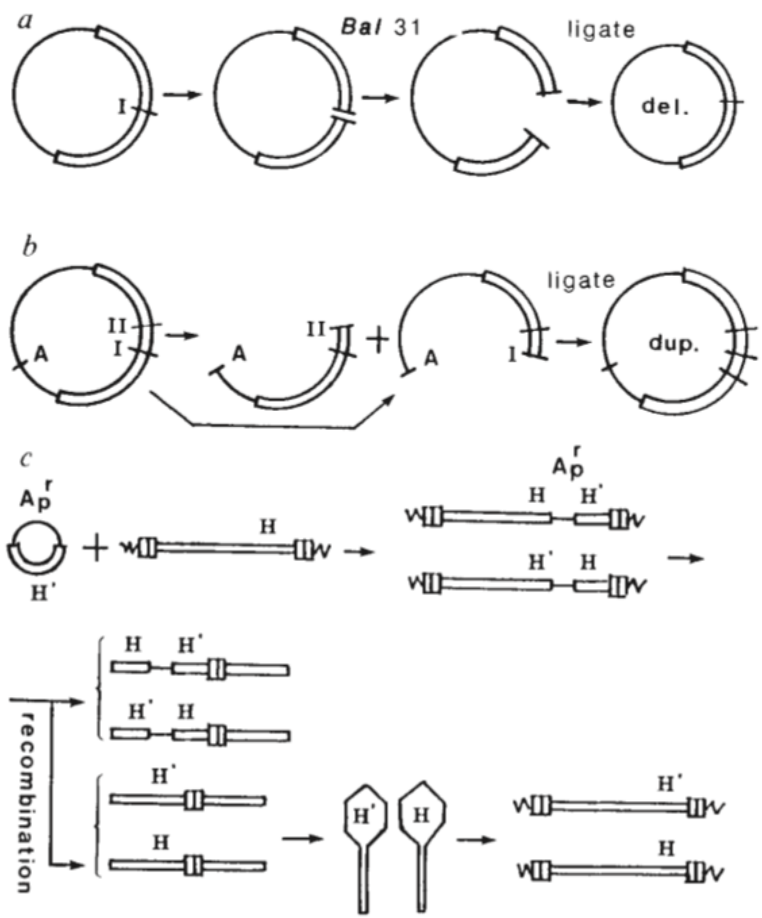
Roger Hendrix
Ph.D. with James Watson at Harvard
http://www.biology.pitt.edu/person/roger-hendrix

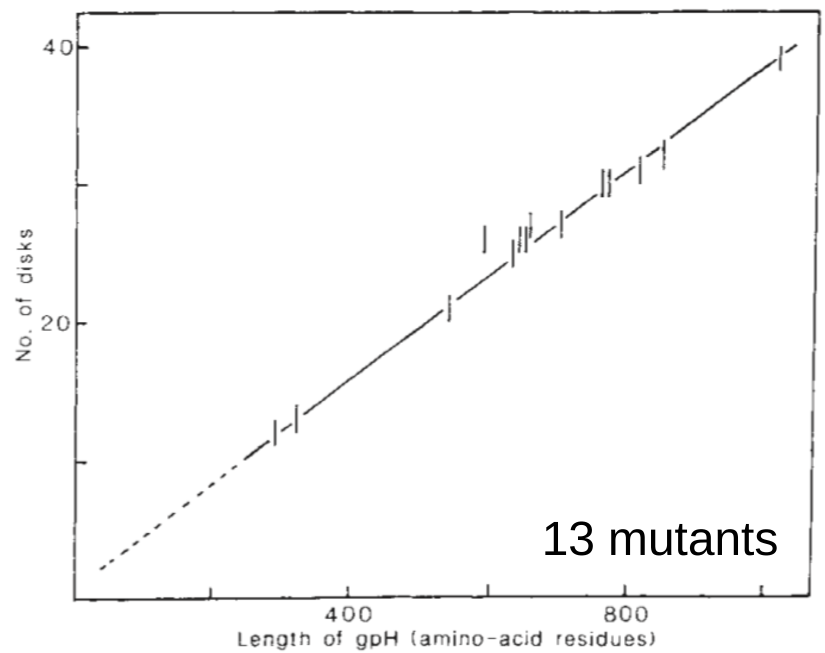
Observed that lambda phage with mutations (deletions) in gene H had shorter tails.

Katsura & Hendrix. Cell (1984)

Made systematic deletions and duplication of sequence of gene H to make it longer or shorter

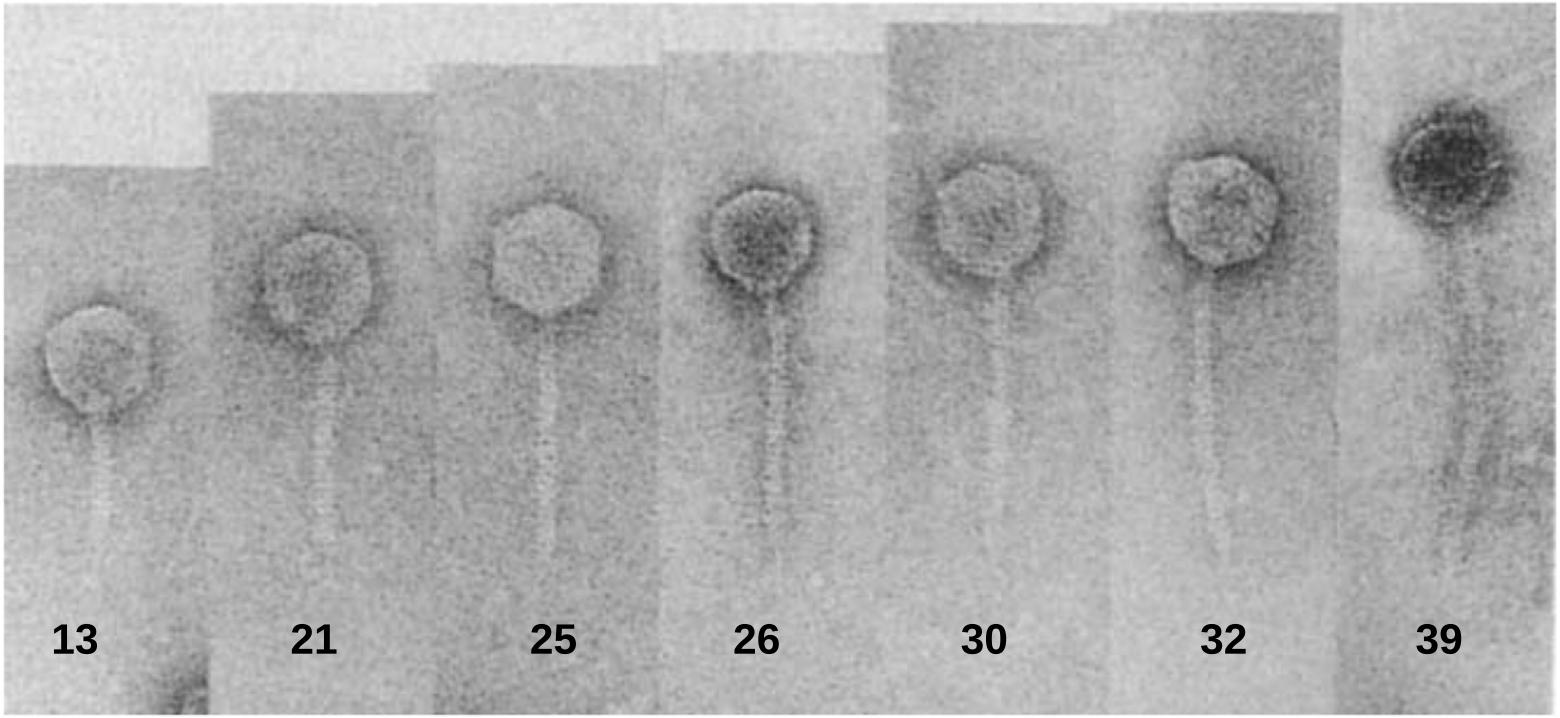
Number of disks in the tail correlates linearly with length of Gene H product (protein)





Katsura. "Determination of bacteriophage λ tail length by a protein ruler". Nature 327 (1987)

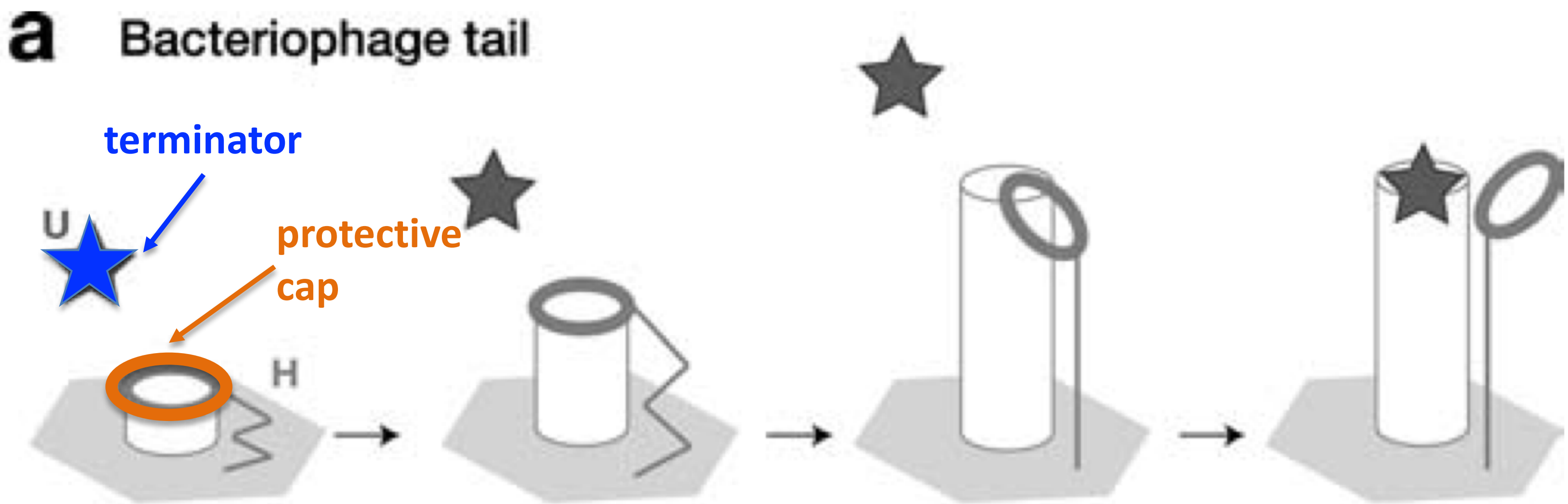
-----------------------deletions ------------------------------- wt insertion



#Tail Disks

Katsura. Nature 327 (1987)

Mechanism of gene product H acts as a molecular ruler



1. Tail assembles on initiator at capsid
2. **gpH** caps the growing end of the tail. Protects from the terminator gene product U (**gpU**).
3. **gpH** is also attached at capsid
4. Tail grows. **gpH** becomes stretched.
5. When **gpH** is fully extended, cap pops off and end no longer protected
6. Growth terminator **gpU** binds. Blocks elongation
7. Tail is fixed at set length determined by length of **gpH**

Wallace F. Marshall
Annu. Rev. Cell Dev. Biol. 2004. 20:677–93

Coming up …

Continue Control of Organelle Size

- Principle 2: Quantal Synthesis
- Principle 3: Dynamic Assembly
  - Flagella Growth Model