L2.3: Cellular Architecture
Design Principles of Organelle Number

What principles and design parameters determine the number of cellular organelles?
In this Lecture…

- Dynamic Control of Organelle Number
- Cell mechanisms of organelle production / reduction
- Mitochondria
- Chloroplasts
- Plasmid Replication & Model
<table>
<thead>
<tr>
<th>Organellar Networks</th>
<th>Membrane Traffic and Signaling</th>
<th>Protein Delivery and Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elongated and tubular ihrer</td>
<td>One or multiple individuals</td>
<td>One network containing many individuals</td>
</tr>
<tr>
<td>Individual small spherical structures</td>
<td>Multiple individuals</td>
<td>One to multiple individuals</td>
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<tr>
<td>Varies: distributed linear, network common, sometimes clumped spherical compartments</td>
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<td>Movements: chemical sensing, ciliary membrane transport along central microtubules</td>
<td>Waste processing, respiration, lipid synthesis, metabolism and products related to energy transfer</td>
<td>Waste degradation, storage and recycling, endosomal vesicle delivery, membrane channel and membrane fusion, protein synthesis, proteolytic digestion, autophagy, stress response, membrane trafficking and budding</td>
</tr>
<tr>
<td>Cell-cilia transport, cilia beating</td>
<td>Metabolites and products of replication are transferred across membrane</td>
<td>Membrane channels and vesicle fusion deliver proteins to vesicles and budding</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>Individual organelles increase in size</td>
<td>Lumen is vesicle delivery site, vesicle fusion and budding</td>
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</table>

Protein membrane budding vesicles into the lumen is vesicle delivery site, vesicle fusion and budding.
Design Principle: Dynamic Balance

- Similar concept as dynamic assembly for organelle size
- Dynamic balance between production and loss controls number

\[ \frac{dN}{dt} = r_{production} - r_{reduction} \]

- Feedback \rightarrow Rate = f(N)

\[ \frac{dN}{dt} = r_p(N) - r_r(N) \]

Mechanisms of organelle production & reduction

• Increase in number (production):
  – De novo synthesis
  – Division / Fission (e.g. mitochondria)

• Decrease in number (reduction):
  – Fusion of organelles into fewer numbers
  – Degradation
  – Partitioning into daughter cells during cell division

Mitochondria. Example of fission / fusion.

- Do not arise from de novo synthesis
- Production by fission
- Reduction by fusion

Richard J. Youle, and Alexander M. van der Bliek
Science 2012;337:1062-1065
Mitochondrial Fusion and Fission Through the Cell Cycle.

1. Fusion in prep for high energy demand
2. Fission in prep for division
3. Segregation into daughter cells

Leads to question... Are organelles randomly or precisely distributed during division?

When a cell divides, how do the organelle numbers get distributed?

1. Could be random events
   Outcome:
   • 2 daughter cells receive organelle number based on a binomial distribution
   • Like flipping a coin
   • Each chloroplast has a probability of 0.5 of entering 1 of the daughter cells

2. Could be precisely controlled
   Outcome:
   • 2 daughter cells receive more or less equal numbers of organelles.

Ref. Hennis & Birky 1984
When Hennis and Birky looked.

They counted chloroplasts in mother and daughter cells as they were dividing.

They found the data supports something in between.

Data support a stochastic event with tendency toward equal distribution.

The stochastic feature introduces variance that accumulates with cell division numbers, but don’t see evidence of accumulating achloroplast cells.

Ref. Hennis & Birky 1984

Suggests that cells can count their organelles.
Daughter gets Too few → make more?
Daughter gets Too many → make fewer in next round of division?
The question is

• How do cells count their organelles?
• What is the mechanism of feedback to increase or decrease number?
• Feedback control system?
  – Described mathematically
  – Study like any engineered control system
Possible Mechanism for Neg. Feedback

- Organelles produce diffusible signal, $S$
  - $S$ produced at a rate dependent on organelle #
  - Signal has some half life, $k_{1/2}$
  - $S_\infty$ is proportional to organelle number

- Must also consider cell volume, which will concentrate or dilute the signal molecules
Classic Example. Plasmid Replication

- **Diffusible Signal Negative Feedback**
  - control of plasmid replication in bacteria
  - Gene for “S” signal is encoded in the plasmid itself
  - Signal is an inhibitor of plasmid replication
  - Researchers have been working on mathematical models of plasmid copy number regulation for several decades
Plasmids

- “circular”, double-stranded DNA (dsDNA)
- Usually in a supercoiled structure
- separate from a cell’s chromosomal DNA
- occur naturally in bacteria, yeast, and some higher eukaryotic cells
- symbiotic relationship with their host cell
  - e.g. antibiotic resistance genes

http://www.ncbi.nlm.nih.gov/books/NBK21498/#A1586

The Biology of Plasmids. 1996 Summers
Plasmid Replication

- 1 – 100 kb in size
- Replicate independent of host DNA
- Plasmids are segregated to daughter cells during cell division

Model System for Plasmid Regulation by Negative Feedback: ColE1 type plasmids in *E.coli*

\[ S = \text{(RNA I binding)} \]

- RNA II transcription
- (replication primer)
- (origin of replication)

\[ \text{ori} \]

\[ \rightarrow \]

no primer maturation
no DNA replication

\[ \rightarrow \]

primer maturation
DNA replication


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0020403
Common Mathematical Model of Plasmid Replication Control

**Plasmid Rate Equation**
\[
\frac{dp}{dt} = \beta p f(s) - \alpha p
\]

**Soluble Signal Rate Equation**
\[
\frac{ds}{dt} = \beta_2 p - \alpha_2 s
\]

- \( p \) = plasmid conc.
- \( \beta \) = max rate of plasmid replication
- \( f(s) \) = probability of replication
- \( \alpha \) = plasmid dilution rate
- \( \alpha = \ln 2 \div t_d \)
- \( t_d \) = doubling time of cell

- \( s \) = soluble signal (RNA I) conc.
- \( \beta_2 \) = max rate of signal production
- \( \alpha_2 \) = signal degradation rate

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**Hyperbolic Regulation Model**
\[ f(s) = \frac{1}{1 + \frac{s}{s_0}} \]

**Exponential Regulation Model**
\[ f(s) = e^{\frac{-s}{s_0}} \]
Coming up …

- Biological Networks
- Gene Circuits
- Cell dynamics