L1.1: Cells By the Numbers

Prof. Rickus
In this video …

• Why ground our selves in the numbers?
• Size & Volume of Single Cells
• Mass, Composition
• Meaning of Concentration in a Cell
• Time Scales of Cells
• Raw Materials & Energy Costs to make 1 Cell
• Pressure & Force
Why Start with the Numbers?

- Build **intuition** of the micro/nano/cellular world
- Erase **misconceptions**
  - Propagate and influence our thinking
- Sometimes the **only way**
  - Even simple **nonlinear** systems can be difficult to predict or understand without a mathematical model
- **Design** is inherently quantitative
- Determine **physical limitations** of design
Why Start with the Numbers?

• Engineers wouldn’t design a manufacturing process without calculating the raw material and energy costs.

• Engineers wouldn’t design a pumping system without calculating the pressure head and flowrate.

• So why would you engineer a cell without running the numbers?
## Size & Volume

### E. coli

- **Phys. Biology of the Cell**

### S. cerevisiae

- **Mariska Lilly et al. FEMS Yeast Res 2009;9:1236-1249**

### Human Fibroblast

- **Phys. Biology of the Cell**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. Coli</em> (culture)</td>
<td>~1 μm³</td>
</tr>
<tr>
<td></td>
<td>~1 fL</td>
</tr>
<tr>
<td><em>S. Cerevisiae</em></td>
<td>~1000 μm³</td>
</tr>
<tr>
<td></td>
<td>~1 pL</td>
</tr>
<tr>
<td>Human Fibroblast</td>
<td>~10000 μm³</td>
</tr>
<tr>
<td></td>
<td>~10 pL</td>
</tr>
</tbody>
</table>
**E. coli:**

a frame of reference

- Most studied, quantified and engineered cell
- About 1 – 2 microns
- Much smaller than a typical human cell

Figure 2.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Mass

Dry Mass of 1 *E. coli* ~ 0.5 pg

~50% of cell dry mass is protein

Molecular Factories.

What is the minimum # of cells you would need to produce X g of protein in Y amount of time?

How many glucose molecules would a cell need to make 100 more cells?

Ref. Nature Education Scitable
Table 2.1: Observed macromolecular census of an *E. coli* cell. (Data from F. C. Neidhardt et al., *Physiology of the Bacterial Cell*, Sinauer Associates, 1990 and M. Schaechter et al., *Microbe*, ASM Press, 2006.)

<table>
<thead>
<tr>
<th>Substance</th>
<th>% of total dry weight</th>
<th>Number of molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macromolecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>55.0</td>
<td>$2.4 \times 10^6$</td>
</tr>
<tr>
<td>RNA</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>23S RNA</td>
<td>10.6</td>
<td>19,000</td>
</tr>
<tr>
<td>16S RNA</td>
<td>5.5</td>
<td>19,000</td>
</tr>
<tr>
<td>5S RNA</td>
<td>0.4</td>
<td>19,000</td>
</tr>
<tr>
<td>Transfer RNA (4S)</td>
<td>2.9</td>
<td>200,000</td>
</tr>
<tr>
<td>Messenger RNA</td>
<td>0.8</td>
<td>1,400</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>9.1</td>
<td>$22 \times 10^6$</td>
</tr>
<tr>
<td>Lipopolysaccharide (outer membrane)</td>
<td>3.4</td>
<td>$1.2 \times 10^6$</td>
</tr>
<tr>
<td>DNA</td>
<td>3.1</td>
<td>2</td>
</tr>
<tr>
<td>Murein (cell wall)</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Glycogen (sugar storage)</td>
<td>2.5</td>
<td>4,360</td>
</tr>
<tr>
<td><strong>Total macromolecules</strong></td>
<td></td>
<td><strong>96.1</strong></td>
</tr>
<tr>
<td><strong>Small molecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolites, building blocks, etc.</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Inorganic ions</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total small molecules</strong></td>
<td></td>
<td><strong>3.9</strong></td>
</tr>
</tbody>
</table>

Table 2.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Mass of 1 Cell Changes with Time

![Graph showing cell mass and DNA per nucleus over time, with cell division points.](source)

Figure 3.21b Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Cellular Interior is a Crowded Space

Very different than the dilute aqueous solutions of traditional study

How do we think about concentration?

\[ V_{E.~Coli} \approx 1 \text{ fL} \]
Concentration

Rule of Thumb:
2 nM is about 1 molecule in 1 cell of *E. coli*

\[ V_{E.coli} \cong 1 \text{ fL} \]

\[
\frac{1 \text{ molecule}}{\text{cell}} \times \frac{\text{cell}}{10^{-15} L} \times \frac{\text{mol}}{6.02 \times 10^{23}}
\]

\[ = 1.7 \times 10^{-9} M \]

Working range of most biochemistry is in nM – μM

Figure 2.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
## Time

Biology covers >23 orders of magnitude of time

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
<th>Units seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme to convert 1 molecule</td>
<td>1 s – 1μs</td>
<td>10^{-6} s</td>
</tr>
<tr>
<td>Neuronal action potential</td>
<td>ms</td>
<td>10^{-3} s</td>
</tr>
<tr>
<td>Transcribe a gene in E. coli</td>
<td>~ 1 min</td>
<td>60 s</td>
</tr>
<tr>
<td>Transcribe a gene in human cells</td>
<td>~30 minutes</td>
<td>1.8\times10^3 s</td>
</tr>
<tr>
<td>Typical protein half-life in a cell</td>
<td>min – hrs</td>
<td>10^2 – 10^6 s</td>
</tr>
<tr>
<td>E. coli doubling time</td>
<td>20 min</td>
<td>1.2 \times 10^3 s</td>
</tr>
<tr>
<td>Max. Human lifespan</td>
<td>~ 100 years</td>
<td>~1\times10^9 s</td>
</tr>
<tr>
<td>Lifespan sequoia tree</td>
<td>3000 years</td>
<td>2 \times10^{14} s</td>
</tr>
<tr>
<td>Max. evolutionary timescale</td>
<td>4 billion years</td>
<td>10^{17} s</td>
</tr>
</tbody>
</table>
How long does it take to make a cell?

<table>
<thead>
<tr>
<th>Cell</th>
<th>Doubling Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. Coli</strong> (culture)</td>
<td>20 min</td>
</tr>
<tr>
<td>Budding <strong>S. Cerevisiae</strong></td>
<td>100 min</td>
</tr>
<tr>
<td>Mammalian Cells (culture)</td>
<td>24 – 36 hrs</td>
</tr>
<tr>
<td><strong>E. Coli</strong> (human GI)</td>
<td>40 hrs</td>
</tr>
<tr>
<td><strong>Bacillus subtillis</strong></td>
<td>120 hrs</td>
</tr>
<tr>
<td>Mammalian (in vivo)</td>
<td>hrs – days - death</td>
</tr>
<tr>
<td>Neurons</td>
<td>Non-dividing</td>
</tr>
</tbody>
</table>

- Context Dependent
- Implications for Gene Expression
  - Overall Proteome
  - Dynamics

Manufacturing – Raw Materials & Costs

heterotrophy
organic nutrient

PO$_4^{3-}$

fueling

SO$_4^{2-}$

NH$_4^+$

fueling products

biosynthesis

building blocks

polymerization

macromolecules

assembly

structures

autotrophy
CO$_2$ + inorganic energy source

phototrophy
CO$_2$ + light

**energy**

ATP, ion gradient

**precursor metabolites**

- glucose 6-phosphate
- fructose 6-phosphate
- pentose 5-phosphate
- sedoheptulose
- 7-phosphate
- erythrose 4-phosphate
- triose phosphate
- 3-phosphoglycerate
- phosphoenolpyruvate
- acetyl coenzyme A
- 2-oxoglutarate
- succinyl coenzyme A
- oxaloacetate
- pyruvate

**reducing power**

NAD(P)H

**fatty acids (≈8)**

- lipid
- lipopoly-saccharide
- envelope
- flagella
- pili

**sugars (≈25)**

- glycogen
- murein
- pili

**amino acids (≈21)**

- protein
- cytosol
- ribosomes
- nucleoids

**nucleotides (≈8)**

- RNA
- DNA

Figure 5.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
**Energy Costs**

How much energy to make a cell?

ATP is a primary currency

http://www.nature.com/scitable/topicpage/cell-energy-and-cell-functions-14024533

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**Table 5.2:** Biosynthetic cost in ATP equivalents to synthesize the macromolecules of a single *E. coli* cell.

<table>
<thead>
<tr>
<th>Class</th>
<th>Biosynthetic cost (aerobic) – ATP equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>$4.5 \times 10^9$</td>
</tr>
<tr>
<td>DNA</td>
<td>$3.5 \times 10^8$</td>
</tr>
<tr>
<td>RNA</td>
<td>$1.6 \times 10^9$</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>$3.2 \times 10^9$</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>$3.8 \times 10^8$</td>
</tr>
<tr>
<td>Peptidoglycan</td>
<td>$1.7 \times 10^8$</td>
</tr>
<tr>
<td>Glycogen</td>
<td>$3.1 \times 10^7$</td>
</tr>
</tbody>
</table>

Table 5.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
Pressure & Forces

- Phage are viruses that infect bacteria
- Must pack DNA into the formed capsid using a motor protein
- Pressure can be used to eject DNA into a cell

- $F \sim 10$’s of pN
- $P_{\text{capsid}} \sim 1-6\text{MPa}$
- Velocity $\sim 5 – 150 \text{ bp/s}$

http://phagesdb.org/phages/RageTheFage/

Smith et al Nature 413, 748-752 (2001)
Resources ...

- Physical Biology of the Cell

More resources...

- BioNumbers

http://microsite.garlandscience.com/pboc2/  
http://bionumbers.hms.harvard.edu
Coming up...

• Cells as Machines
  – Engineering functions:
  – sensors, oscillators, pumps, reactors

• Bio-inspiration for Engineering Design
  – Case study of Photoreceptor as a Cellular Device: photon detector