Life of a bacterium:

- molar composition: $\text{CH}_{1.5}\text{O}_{0.35}\text{N}_{0.24} (+\text{S, P, Mg, Fe, ...})$
- algae (photosynthesis):
  $\text{CO}_2 + \text{H}_2\text{O} + \text{N}_2 + \text{photons} \rightarrow \text{biomass} + \text{O}_2$
- *E. coli* (minimal medium):
  $\text{glucose} + \text{NH}_3 \rightarrow \text{biomass} + \text{CO}_2$

---

**TABLE 1. Typical elemental composition of biological specimen**

<table>
<thead>
<tr>
<th>Element</th>
<th>Tissue$^a$</th>
<th>Bacteria$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>N</td>
<td>0.16</td>
<td>0.14</td>
</tr>
<tr>
<td>H</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>O</td>
<td>0.25</td>
<td>0.23</td>
</tr>
<tr>
<td>P + S + others</td>
<td>0.02</td>
<td>0.10$^c$</td>
</tr>
</tbody>
</table>

[Heldal et al, 1985]
growth of E. coli 

Can we predict GR & yield?

environmental factors: 
nutrient types & conc 
temperature, pH, 
osmolarity, drugs, …

genetic factors: 
enzymes & regulation

Learning from the growth curve

[Monod, Ann Rev Microb. 1949]

- \( \text{OD}_{600} \) = biomass content
  
  \[ 1 \text{ OD} \cdot \text{ml} \approx 0.5 \text{mg CDW} \]

- saturation OD \( \rightarrow \) yield

- (lag: transition from pre-shift phase)

Can we predict GR & yield?

What does it take to replicate a cell?

condition-dependent

biomass

water

protein

RNA

DNA

other
What does it take to replicate a cell?

proteins = defined sequence of 20 amino acids

protein synthesis: ribosomes

>85% of all RNA
up to 1/3 of all proteins

condition-dependent
protein = defined sequence of 20 amino acids

protein synthesis: ribosomes

>85% of all RNA up to 1/3 of all proteins

protein = defined sequence of 20 amino acids

protein synthesis: ribosomes

amino acid & ATP from metabolic reactions

free AA & uncharged tRNAs
metabolism
• sequester & breakdown nutrients
  – derive energy
  – generate carbon precursors
  – sequester N, S, P, metals
• biosynthesis
  (“precursors” to “building blocks”)
  – amino acid
  – nucleic acid
  – lipids
  – co-enzyme (or ‘co-factor’)
• degradation/recycling (e.g., mRNA)

• typical biochemical reaction:
  \[ S + C\cdot b \rightleftharpoons S\cdot b + C \]
  S: substrate
  b: component (e.g., CH\(_3\), NH\(_2\), e\(^-\))
  C: co-enzyme
  (needed for difficult reactions)

> but many organisms use fermentation even with oxygen (Crabtree effect); why?

> metabolic control via coordinated regulation of enzyme abundance/activity
Feedback inhibition by end-product

- 1st reaction of pathway often inhibited by product
- same enzymes used for synthesis of valine and isoleucine
- must have enzymes responding differently to different products (isozymes)
- in E. coli K-12, ilvG is defective
  ➔ valine sensitivity in minimal media
  ➔ α-ketobutyrate toxicity (repressed by isoleucine)

Also: negative feedback regulation of enzyme expression in response to end-product accumulation

Protein = defined sequence of 20 amino acids

Protein synthesis: ribosomes

- tRNA charging
- aa-tRNA
- aaRS
- ATP
- free AA & uncharged tRNAs
protein = defined sequence of 20 amino acids

protein synthesis: ribosomes

\[ J_i = k_i [RS_i] \frac{[a_i]}{K_{a,i} + [a_i]} \cdot \frac{[tR_i]}{K_{tR,i} + [tR_i]} \]

~100 variables
~500 parameters

free AA & uncharged tRNAs

~100 variables
~500 parameters

regulation: when and how much proteins to make
dependence on temp, pH, osmolarity, …

~500 enzymes
~500 metabolites
~5000 parameters
~10000 parameters

~500 enzymes
~500 metabolites
~5000 parameters
~10000 parameters

amino acid synthesis: ~20 AA

~10000 parameters

dependence on temp, pH, osmolarity, …

glucose (6C)

parameter explosion
How to deal with exploding no. of parameters?

Newtonian Mechanics $\vec{r}'_i(t) = \vec{a}_ii (\vec{r}_i - \vec{r}_j)$

Need moles of parameters:
$\vec{r}_i(t = 0) = \ldots$
$\vec{v}_i(t = 0) = \ldots$

$PV = nRT$

Statistical Mechanics $\rho(\hat{q}_i, \hat{p}_i; t) \xrightarrow{t \to \infty} \rho_{eq}(\mathcal{H}(\hat{q}_i, \hat{p}_i))$
Microbial growth law [Ole Maaloe et al, 1960s, 70s]
Orthogonal perturbations [Scott et al, Science 2010]

Model of bacterial growth
• assume all ribosomes efficiently engaged in protein synthesis

\[
\dot{M}_{\text{tot}} = \lambda \cdot M_{\text{tot}} \quad \gamma \cdot M_{Rb}
\]

\[
\phi_R = \frac{M_{Rb}}{M_{\text{tot}}} = \frac{\lambda}{\gamma}
\]

most ribosomes are engaged in translation

rate protein mass accum. = rate Rb elongation

\[
\dot{M}_{\text{tot}} = \frac{M_{Rb}}{M_{\text{tot}}} = \frac{\lambda}{\gamma}
\]

(\sim 20 \text{ aa/s or } 10 \text{ Rb/hr})
Microbial growth law [Ole Maaloe et al, 1960s, 70s]

Orthogonal perturbations [Scott et al, Science 2010]

Theory of proteome allocation

Electrical circuit analogy:

bacterial cells perform dimensional reduction – how?

Molecular Biology

protein synthesis: ribosomes

> 2/3 of biomass: proteins

- protein synthesis:
  20 aa; 60+ tRNA
  ~500 parameters

- aa biosynthesis:
  500 enzymes; 1000 metabolites
  5000 parameters

- regulation

- dependence on temp, pH, ...

How to does a cell diagnose its own state of growth?
Perception of cellular growth rate not by measuring concentrations but through sensing the translational speed of the ribosomes

\[
growth \text{ rate } \lambda = C_{Rb}(g) \cdot \gamma(g)
\]

→ quantitatively accounts for growth laws

Figure 3

"quantitatively accounts for growth laws"