Dimension Reduction by Bacteria

Conference on Theory & Biology
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Tenet of classical molecular biology (bottom-up): molecular knowledge $\rightarrow$ biological function

Biocomplexity at the molecular scale:
- predictive understanding requires “moles” of parameters
- most success models: few-component systems
Newtonian Mechanics \[ \frac{d^2 \vec{r}_i}{dt^2} = \vec{f}_{ij}(\vec{r}_i - \vec{r}_j) \]

Thermodynamics

\[ PV = nRT \]

Need many parameters:
\[ \vec{r}_i(t = 0) = \ldots \]
\[ \vec{v}_i(t = 0) = \ldots \]
Molecular Biology  dimension reduction?  Physiology
Start with quantitative physiology

simple perturbation $\rightarrow$ simple responses
$=$ phenomenological laws

$\rightarrow$ quantitative predictions of responses to new perturbations
$\rightarrow$ connect to molecular network by coarse-graining
$\rightarrow$ insight on regulatory strategies and organizing principles

Biology’s own dimension reduction via regulation
Microbial growth law [Ole Maaloe et al, 1950-70]

Orthogonal perturbations

\[ \text{RNA} \propto R_b \text{conc} \text{ [Scott et al, Science 2010]} \]

translational limitation

carbon limitation

Model of bacterial growth

• assume all ribosomes efficiently engaged in protein synthesis

rate protein mass accum. = rate Rb elongation

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

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

\[ \lambda : \text{specific growth rate} \]
\[ \gamma : \text{Rb elongation rate} \]

(~20 aa/s or 10 Rb/hr)
Microbial growth law [Ole Maaloe et al, 1960-70]

Orthogonal perturbations

**Theory of proteome allocation**

- protein synthesis: \( \lambda = \gamma \cdot \phi_R \)
- biosynthesis: \( \lambda = \nu_A \cdot \phi_A \)
- carbon uptake: \( \lambda = \nu_C \cdot \phi_C \)

Constraint: \( \phi_R + \phi_A + \phi_C = 1 - \phi_Q \approx 45\% \)

**Electrical circuit analogy:**

- \( J = \lambda \)
- \( V_{\text{total}} = 1 - \phi_Q \)

Environmental parameters: \( \nu_C, \nu_A \)
Genetic parameters: \( \gamma, \phi_Q \)
Theory of proteome allocation

- protein synthesis: \( \lambda = \gamma \cdot \phi_R \)
- biosynthesis: \( \lambda = v_A \cdot \phi_A \)
- carbon uptake: \( \lambda = v_C \cdot \phi_C \)

constraint: \( \phi_R + \phi_A + \phi_C = 1 - \phi_Q \approx 45\% \)

Electrical circuit analogy:

\[
\begin{align*}
J &= \lambda \\
V_{\text{total}} &= 1 - \phi_Q \\
\Delta V &= \phi_C \\
\Delta V &= \phi_A \\
\Delta V &= \phi_R \\
\end{align*}
\]

environmental parameters: \( v_C, v_A \)
genetic parameters: \( \gamma, \phi_Q \)
Quantitative Proteomics
in collaboration with Jamie Williamson lab (TSRI)

![Graphs showing the fraction of proteome under different conditions](image)

- **Catabolic**
  - C-lim
  - N,R-lim

- **AA synthesis**
  - N-lim
  - C,R-lim
  - C,N-lim

- **Starvation**
  - C,N-lim
  - R-lim

- **Others**
  - nucleotides, ...

[Hui et al, Mol Sys Biol. (2015)]
Acetate overflow (bacterial Warburg effect)

[Basan et al, Nature (2015)]

Acetate line

- Various carbons
- Reducing glucose uptake
- Reducing lactose uptake
- Increasing glycerol uptake
- Amino acids

possible problems:
- limited O$_2$ uptake
- cofactor recycling
- competition with other microbes, …

Carbon constraint:
$$J_{C,f} + J_{C,r} = J_{C,in} - \beta \lambda$$

Energy balance:
$$J_{E,f} + J_{E,r} = \sigma \lambda$$
$$J_{E,f} = e_f \cdot J_{C,f}$$
$$J_{E,r} = e_r \cdot J_{C,r}$$
Acetate overflow (bacterial Warburg effect)

Assume Ohms’ law

\[ J_{E,f} = \epsilon_f \cdot \phi_f \]
\[ J_{E,r} = \epsilon_r \cdot \phi_r \]

Proteome constraint:

\[ \phi_f + \phi_r = 1 - (\phi_0 + b\lambda) \]

Carbon constraint:

\[ J_{C,f} + J_{C,r} = J_{C,in} - \beta\lambda \]

Energy balance:

\[ J_{E,f} + J_{E,r} = \sigma\lambda \]
\[ J_{E,f} = e_f \cdot J_{C,f} \]
\[ J_{E,r} = e_r \cdot J_{C,r} \]
Tradeoff between growth and adaptation

preshift: glycolytic (e.g., glucose)
postshift: gluconeogenic (e.g., acetate)

[Basan et al, in submission]
growth defect due to (hyper osmolarity) stress

normal osmolarity

transient

adaptation to hyper osmolarity

possible problems:
• potassium, glutamate
• macromolecular crowding
• smaller turgor pressure
• ...

Dai et al (in prep)
Strategy of growth control

\[ n(t) \quad J_C = k_C(n) \cdot [C] \quad \{m_i(t)\} \quad J_P = \sigma(t) \cdot [R] \quad \{p_i(t)\} \]

- external nutrient
- nutrient influx
- metabolites (aa, ATP, ...)
- protein synthesis

avg translation rate
Strategy of growth control

\[ n(t) \]

external nutrient

\[ J_C = k_C(n) \cdot [C] \]

nutrient influx

\{m_i(t)\}

metabolites (aa, ATP, ...)

\[ J_P = \sigma(t) \cdot [R] \]

protein synthesis

\[ ppGpp \]

\[ \chi_C(t) \]

\[ \chi_R(t) \]

\{\chi_i\}

\{p_i(t)\}

regulation of ribosome synthesis: \( \chi_R \)

RelA

uncharged tRNAs \( \rightarrow \) ppGpp \( \rightarrow \) \( \chi_R \)

but hundreds of variables/parameters!
(difference for the cell and for quantitative bio)

what info does the cell use to decide how fast to grow?

\( \rightarrow \) by monitoring the translation rate:

\[ \sigma^{-1} = \sigma_{\text{trans}}^{-1} + \sigma_{\text{charge}}^{-1}(\{m_i(t)\}) \]
Strategy of growth control

\[ n(t) \]
\[ J_C = k_C(n) \cdot [C] \]

**external nutrient**

**nutrient influx**

\[ \text{metabolites (aa, ATP,...)} \]

**protein synthesis**

**regulation of ribosome synthesis:** \( \chi_R(\{m_i(t)\}) \)

RelA

uncharged tRNAs \( \rightarrow \) ppGpp \( \rightarrow \) \( \chi_R \)

**but hundreds of variables/parameters!**

(difficulty for the cell and for quant bio)

what info does the cell use to decide how fast to grow?

\[ \sigma^{-1} = \sigma_{\text{trans}}^{-1} + \sigma_{\text{charge}}^{-1}(\{m_i(t)\}) \]

[Brown et al, Nature 2016]
Strategy of growth control

\[ n(t) \quad J_C = k_C(n) \cdot [C] \quad \{m_i(t)\} \quad J_P = \sigma(t) \cdot [R] \]

nutrient influx
metabolites (aa, ATP, …)
protein synthesis

\[ \chi_C(t) \quad \chi_R(t) \quad \{\chi_i\} \quad \{p_i(t)\} \]

regulation of ribosome synthesis: \( \chi_R(\{m_i(t)\}) \leftarrow \hat{\chi}_R(\sigma(\{m_i(t)\})) \)

[Ericksen et al, Nature (2017)]

\[
\begin{align*}
\frac{d}{dt}[R] &= \hat{\chi}_R(\sigma(t)) J_P - \lambda(t) [R] \\
\frac{d}{dt}[C] &= \hat{\chi}_C(\sigma(t)) J_P - \lambda(t) [C]
\end{align*}
\]

eq of motion for \( \sigma(t) = k_C[C]/[R] \)

\[
\frac{d}{dt} \sigma = \sigma \cdot [k_C \hat{\chi}_C(\sigma) - \sigma \hat{\chi}_R(\sigma)]
\]

⇒ from soln for \( \sigma(t) \), get \([R](t), [C](t), \lambda(t)\)
Growth transition kinetics

[Erickson et al, Nature (2017)]

\[
\frac{d}{dt} \sigma = \sigma \cdot [k_C \hat{\chi}_C(\sigma) - \sigma \hat{\chi}_R(\sigma)]
\]

proteome-wide responses
Strategy of growth control

\[ J_C = k_C(n) \cdot [C] \]

\[ \{ m_i(t) \} \]

\[ \sigma(\{ m_i(t) \}) \rightarrow \chi_R(t) \]

hypothesized strategy of growth control

\[ \rightarrow \text{via monitoring the translation rate:} \]

\[ \sigma(\{ m_i(t) \}) \rightarrow \chi_R(t) \]

\[ \sigma(\{ m_i(t) \}) \rightarrow \chi_R(t) \]

\[ \rightarrow \text{a “activity-based” mode of regulation} \]
Given $\mathcal{H}(\vec{q}_i, \vec{p}_i)$, find $\rho(\vec{q}_i, \vec{p}_i, t)$ with $\partial_t \rho = -\{\rho, \mathcal{H}\}$

$\rho(\vec{q}_i, \vec{p}_i, t) \xrightarrow{t \to \infty} \hat{\rho}(\mathcal{H}(\vec{q}_i, \vec{p}_i))$

**Newtonian Mechanics**

**Thermodynamics**

$PV = nRT$
protein synthesis

external nutrient

\( n(t) \)

nutrient influx

\( J_C = k_C(n) \cdot [C] \)

metabolites (aa, ATP, …)

\( \{m_i(t)\} \)

protein synthesis

\( J_P = \sigma(t) \cdot [R] \)

regulation of ribosome synthesis:

\( \chi_R(\{m_i(t)\}) \leftarrow \hat{\chi}_R(\sigma(\{m_i(t)\})) \)

⇒ “dimensional reduction” is built into the regulatory functions.

Newtonian Mechanics

Given \( \mathcal{H}(\tilde{q}_i, \tilde{p}_i) \), find \( \rho(\tilde{q}_i, \tilde{p}_i, t) \) with \( \partial_t \rho = -\{\rho, \mathcal{H}\} \)

\( \rho(\tilde{q}_i, \tilde{p}_i, t) \xrightarrow{t \to \infty} \hat{\rho}(\mathcal{H}(\tilde{q}_i, \tilde{p}_i)) \)

Thermodynamics

\( PV = nRT \)
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Nothing in (molecular) biology makes sense except in the light of physiology.