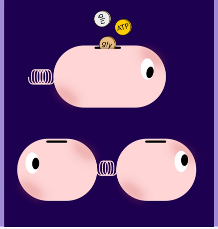
Economic Principles in Cell Biology

Paris, July 10-14, 2023




# Self-replicator cell models

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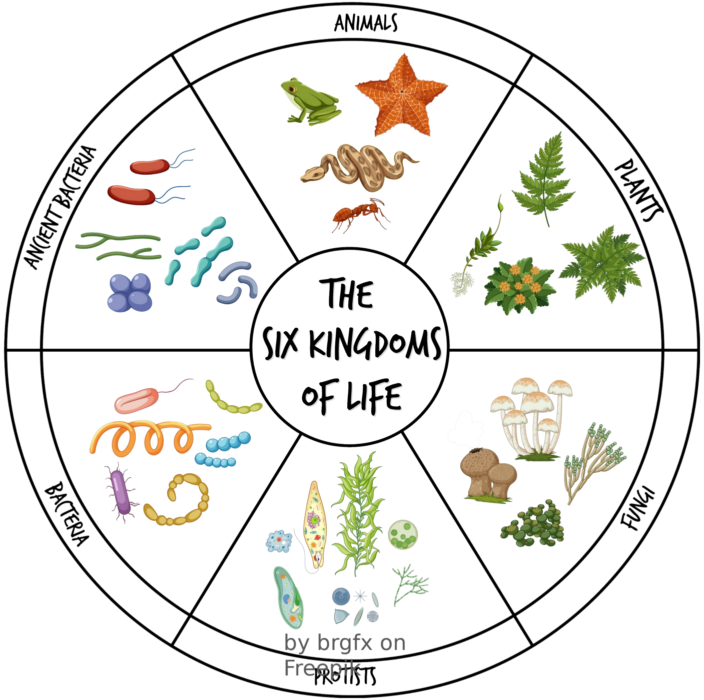
# Self-replication is a hallmark of life

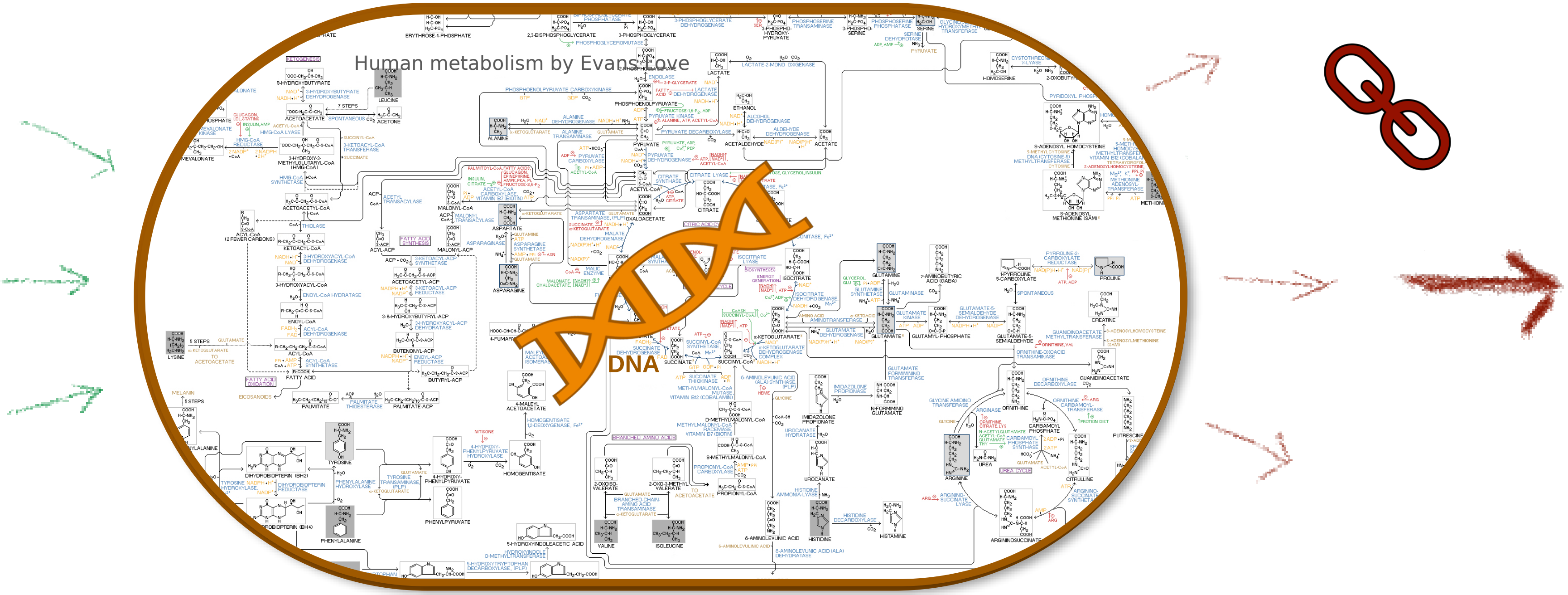


by brgfx on Freepik

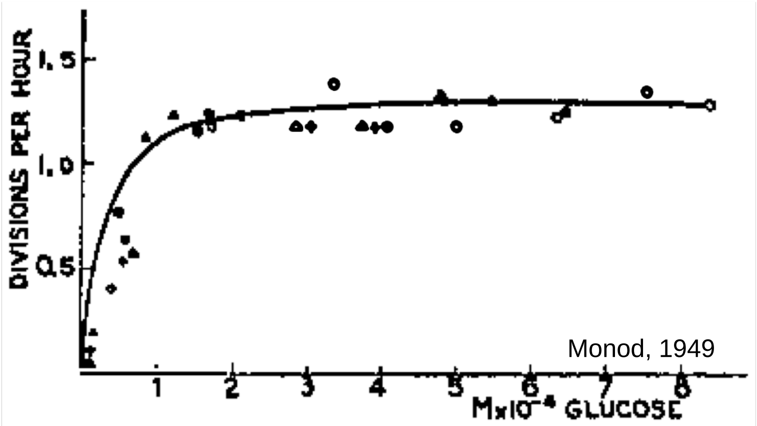
Cells are building blocks of life

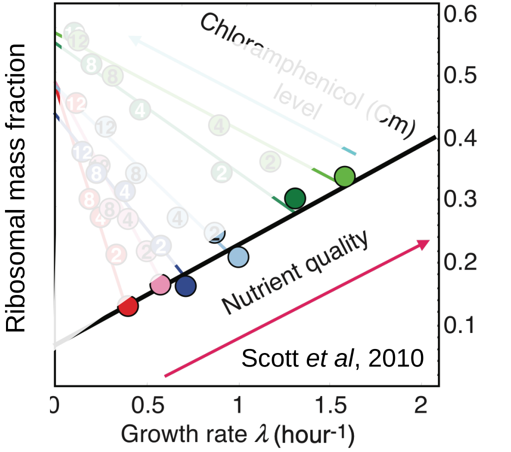
Cellular self-replication underpins reproduction of life

# Self-replication is inherently coupled to growth



# Growth laws govern the relation of growth with environmental & cellular features




**Other growth laws:**

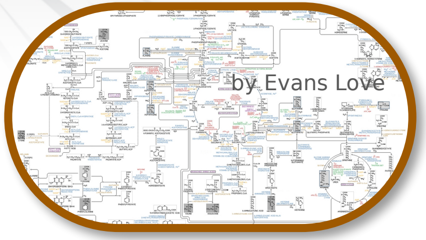
- cell size
- cell surface
- nutrient influx…

# What model should we use?

**Simple enough to understand**

by jcomp on Freepik

**George E.P. Box**

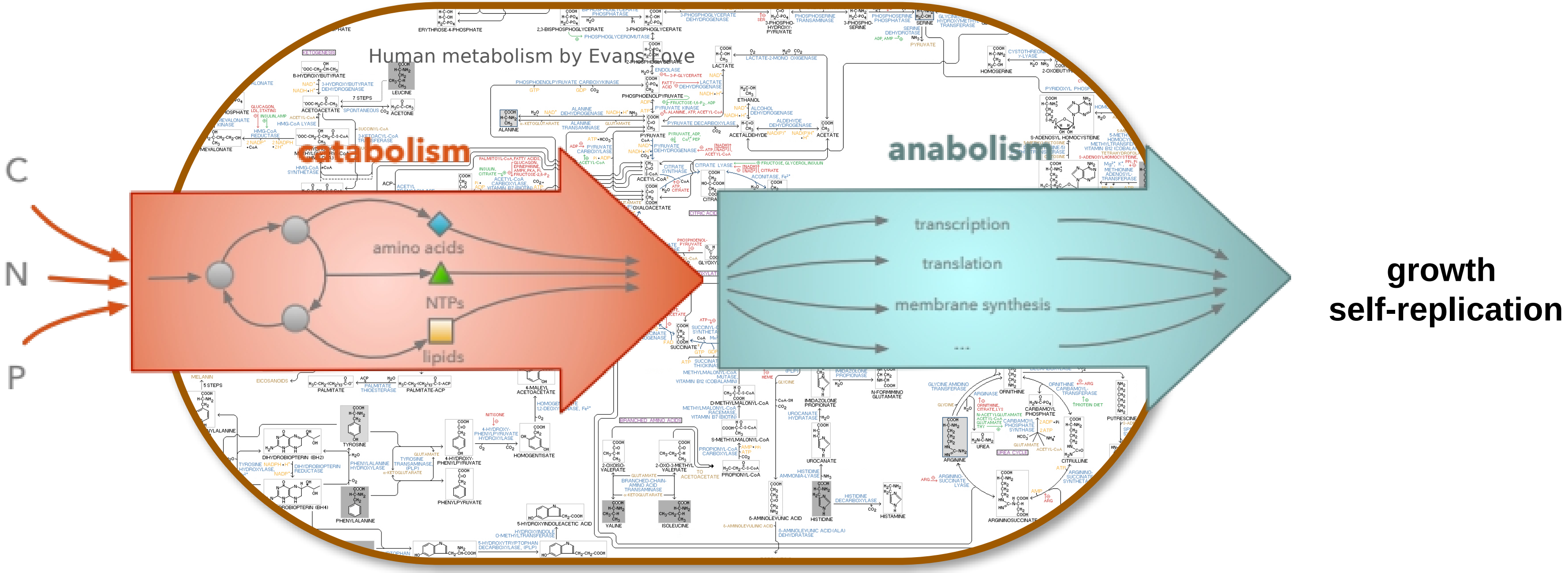


by Evans Love

**Complex enough to explain**

1. There is no one model.
2. What’s the purpose of the model?

# Many cell models share a common structure



# Let’s start with a simple growth model

Two reactions:

Assumptions:

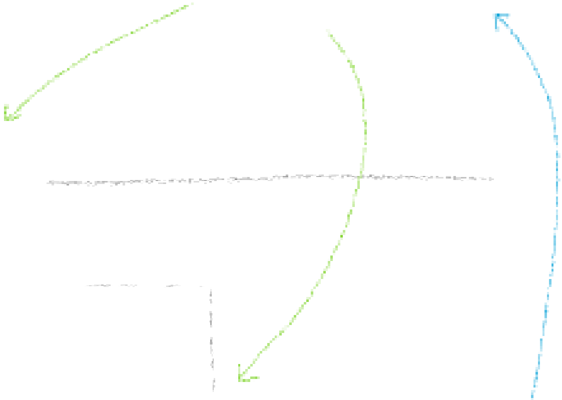
- Proteome dominates biomass
- Cell has constant density

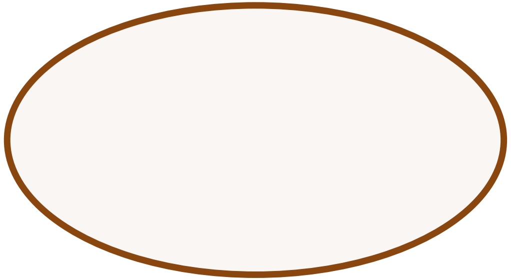
concentration of cell component y

- Reaction rates are proportional to protein concentrations
- Steady-state assumption:

**What determines the growth rate?**

# The simple model gives insight on growth laws



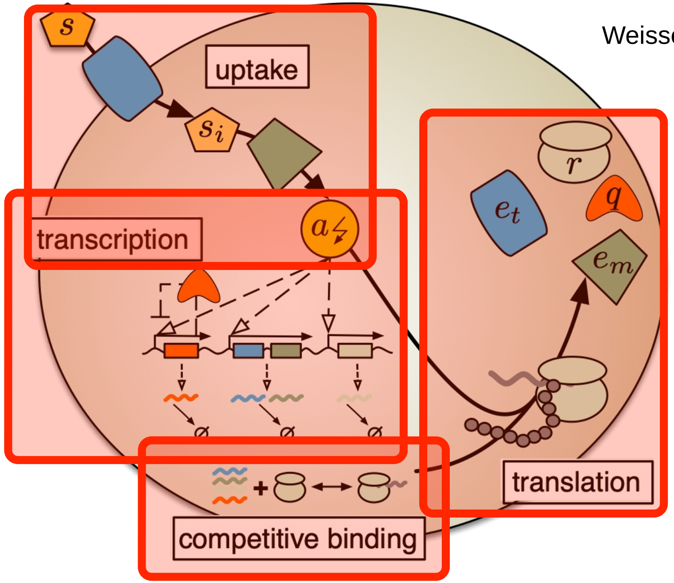


**What determines the growth rate?**

**Basic mechanistic assumptions explain growth laws.**

# What can a more complex model teach us?

Weisse *et al*, PNAS 2015




**We focus on key mechanisms:**

- nutrient uptake
- gene expression
- dilution

## 14 species

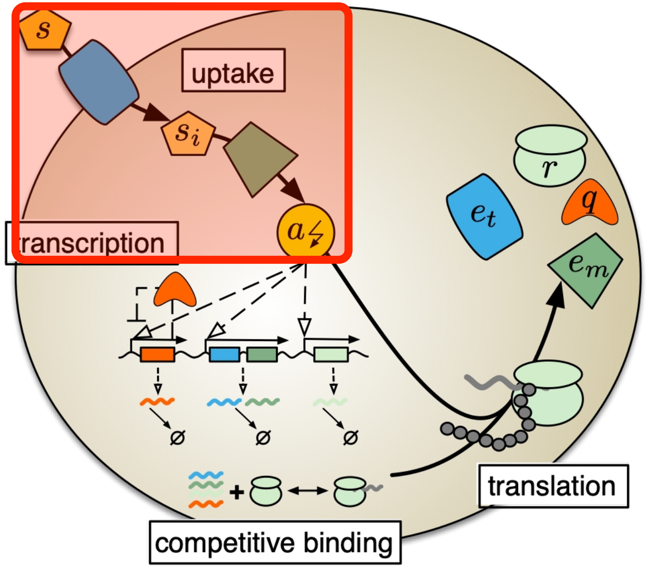
| | dilution | transcription | dilution/degradation | ribosome binding | dilution | translation |
|---|---|---|---|---|---|---|
| ribosomes | $r \xrightarrow{\lambda} \varnothing$ | $\varnothing \xrightarrow{\omega_r} m_r$ | $m_r \xrightarrow{\lambda+d_m} \varnothing$ | $r + m_r \xleftrightarrow{k_b,\,k_u} c_r$ | $c_r \xrightarrow{\lambda} \varnothing$ | $n_r\, a + c_r \xrightarrow{\nu_r} r + m_r + r$ |
| transporter enzyme | $e_t \xrightarrow{\lambda} \varnothing$ | $\varnothing \xrightarrow{\omega_t} m_t$ | $m_t \xrightarrow{\lambda+d_m} \varnothing$ | $r + m_t \xleftrightarrow{k_b,\,k_u} c_t$ | $c_t \xrightarrow{\lambda} \varnothing$ | $n_t\, a + c_t \xrightarrow{\nu_t} r + m_t + e_t$ |
| metabolic enzyme | $e_m \xrightarrow{\lambda} \varnothing$ | $\varnothing \xrightarrow{\omega_m} m_m$ | $m_m \xrightarrow{\lambda+d_m} \varnothing$ | $r + m_m \xleftrightarrow{k_b,\,k_u} c_m$ | $c_m \xrightarrow{\lambda} \varnothing$ | $n_m\, a + c_m \xrightarrow{\nu_m} r + m_m + e_m$ |
| growth-independent proteins | $q \xrightarrow{\lambda} \varnothing$ | $\varnothing \xrightarrow{\omega_q} m_q$ | $m_q \xrightarrow{\lambda+d_m} \varnothing$ | $r + m_q \xleftrightarrow{k_b,\,k_u} c_q$ | $c_q \xrightarrow{\lambda} \varnothing$ | $n_q\, a + c_q \xrightarrow{\nu_q} r + m_q + q$ |
| internal nutrient | $s_i \xrightarrow{\lambda} \varnothing$ | $s \xrightarrow{\nu_{\mathrm{imp}}} s_i$ | $s_i \xrightarrow{\nu_{\mathrm{cat}}} n_s\, a$ | | | |
| ATP | $a \xrightarrow{\lambda} \varnothing$ | nutrient import | metabolism | | | |

# Enzymes catalyze nutrient uptake and metabolism.

Nutrient import & catabolism modelled as saturable enzymatic reactions:

$$s \xrightarrow{\nu_t} s_i \qquad \nu_t = v_t \frac{e_t \cdot s}{K_t + s}$$

$$s_i \xrightarrow{\nu_m} n_s\, a \qquad \nu_m = v_m \frac{e_m \cdot s_i}{K_m + s_i}$$



# Translation is an ATP-consuming process.

Repeated binding and elongation with subsequent release occur with net rate:

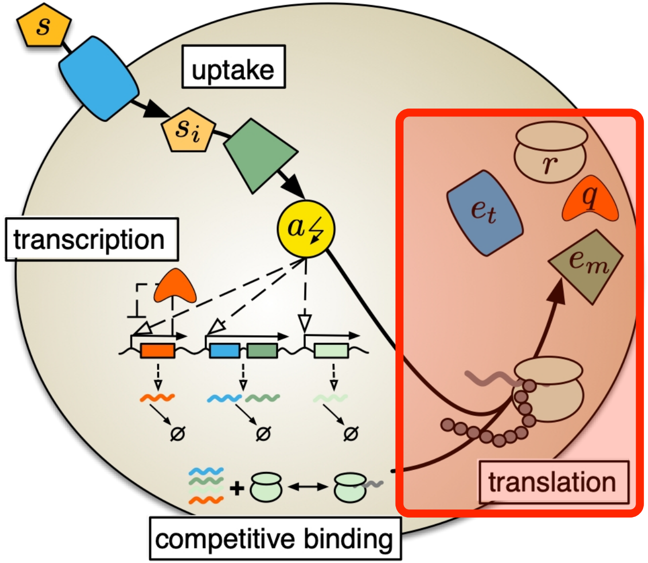
$$\nu_x = \overline{rm}_x \cdot \left(n_x \cdot \left(\frac{1}{K_p a} + \frac{1}{k_2}\right) + \frac{1}{k_p}\right)^{-1}$$

Assuming that release is fast, we can write this as:

$$\overset{k_p \gg 1}{\Rightarrow} \nu_x = \frac{\overline{rm}_x}{n_x} \cdot \boxed{\underbrace{\frac{\gamma_{\max} \cdot a}{\frac{\gamma_{\max}}{K_p} + a}}_{=:\gamma(a)}}$$

elongation rate

$$K_p := \frac{k_1 k_2}{k_{-1} + k_2}, \qquad \gamma_{\max} := k_2$$

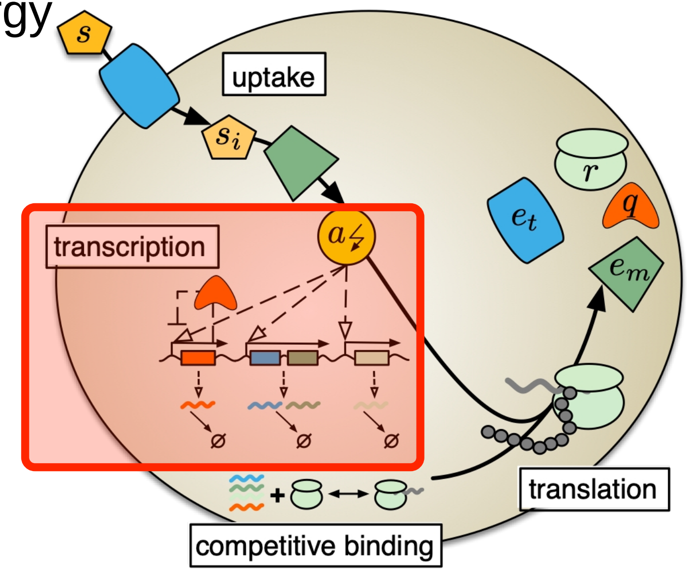



ATP consumption by translation ~2/3 of total consumption (Russel & Cook, 1995).
We assume a simplified mechanism where ATP directly binds the elongating complex:

$$R_0M \underset{k_{-1}}{\overset{k_1 A}{\rightleftharpoons}} R_0MA \xrightarrow{k_2} R_1M \underset{k_{-1}}{\overset{k_1 A}{\rightleftharpoons}} \cdots \xrightarrow{k_2} R_{n_x}M \xrightarrow{k_p} R_0 + M + P$$

**Literature**: Cleland, *Biochemistry*, 14(14):3220–3224, 1975. **Books on enzyme kinetics**: Cornish-Bowden or Fersht.

# Transcription has a low contribution to energy consumption.




We model transcription as an energy-dependent process but ignore its ATP-consumption:

$$\nu_{m,x} = \frac{c_x}{3n_x} \cdot \frac{\rho_{\max} a}{\theta_x + a}$$

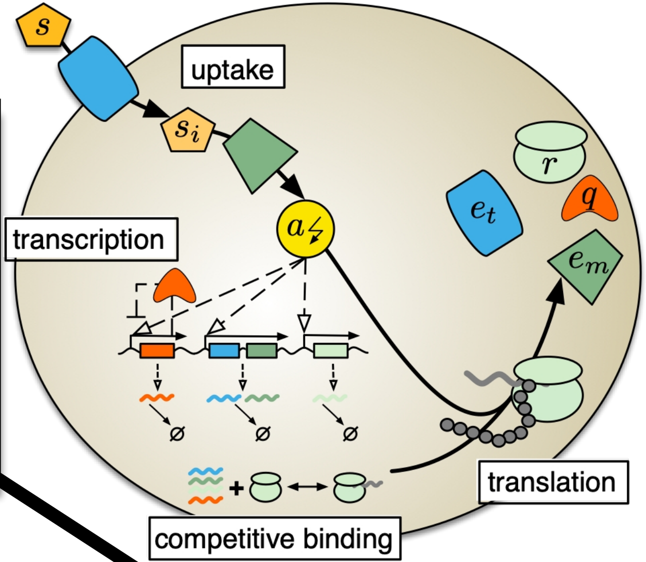
$$x \in \{e, \alpha, r, p\}$$

# Translational activity determines growth.

From steady state follows

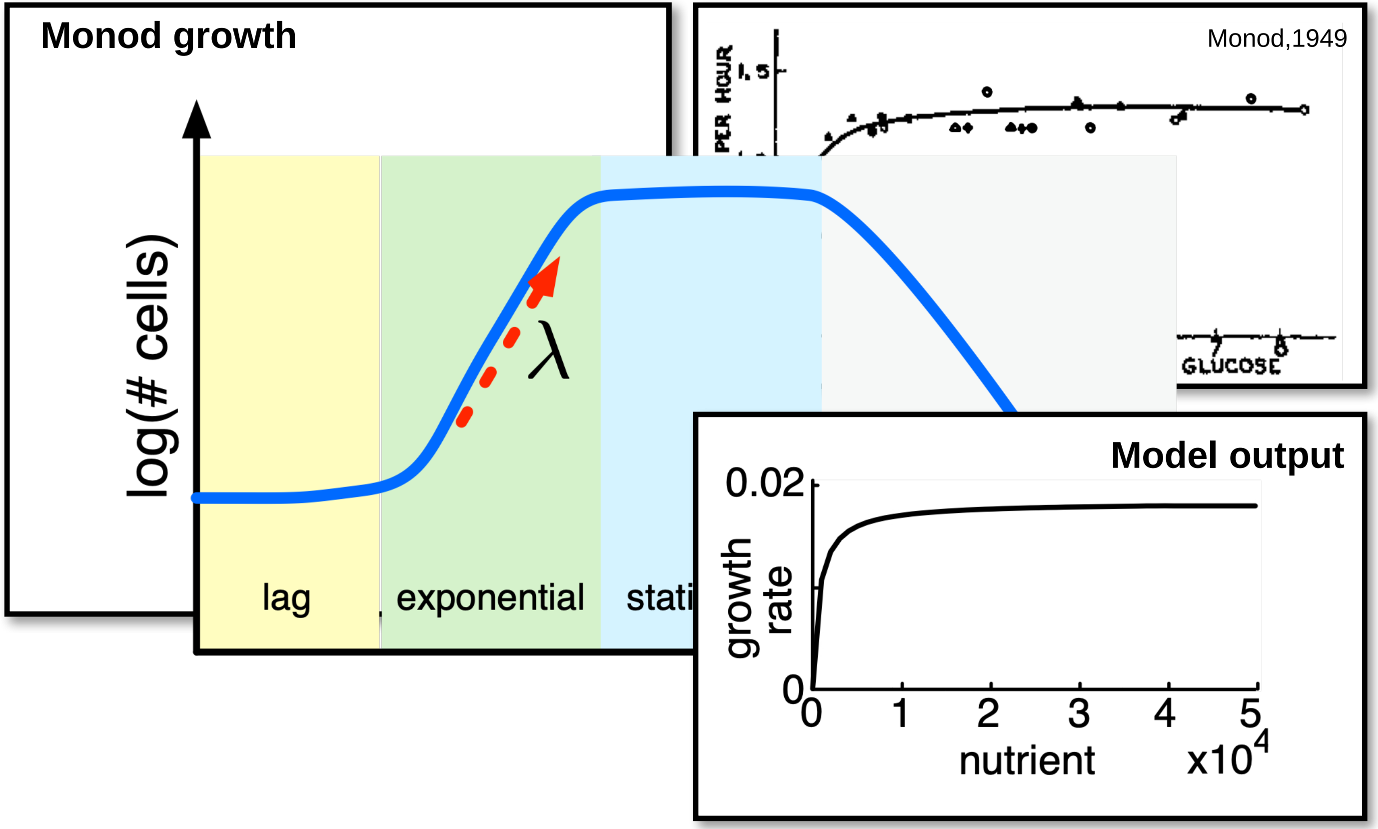
$$\lambda \propto \text{protein synthesis}$$

$$= \frac{1}{M} \sum_x \boxed{c_x} \cdot \boxed{\gamma(a)}$$

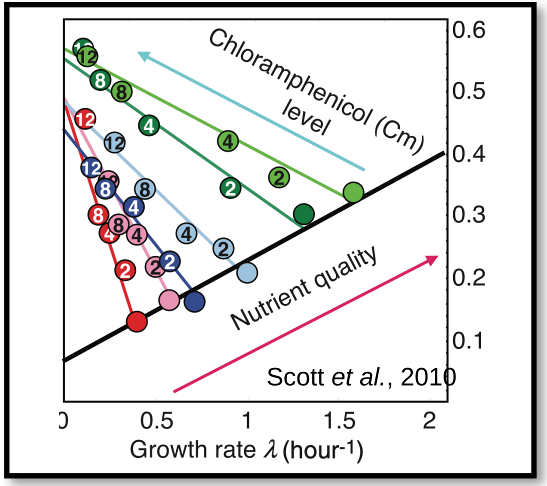


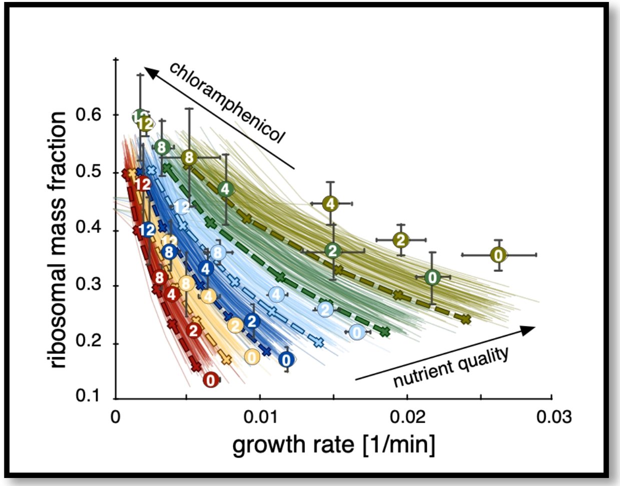

| | dilution/degradation | **transcription** | dilution/degradation | **binding** ribosome-mRNA binding | **translation** translation |
|---|---|---|---|---|---|
| ribosomes | $r \xrightarrow{\lambda} \varnothing$ | $\varnothing \xrightarrow{\nu_{m,r}} m_r$ | $m_r \xrightarrow{\lambda+d_{m,r}} \varnothing$ | $r + m_r \xleftrightarrow{k_b,k_{u,r}} \overline{rm}_r$ | $n_r \cdot a + \overline{rm}_r \xrightarrow{\nu_r} r + m_r + r$ |
| ATP | $a \xrightarrow{\lambda} \varnothing$ | | | | |
| enzymes | $e_{t/m} \xrightarrow{\lambda+d_e} \varnothing$ | $\varnothing \xrightarrow{\nu_{m,e}} m_e$ | $m_e \xrightarrow{\lambda+d_{m,e}} \varnothing$ | $r + m_e \xleftrightarrow{k_b,k_{u,e}} \overline{rm}_e$ | $n_e \cdot a + \overline{rm}_e \xrightarrow{\nu_e} r + m_e + e_{t/m}$ |
| transcription factor | $\alpha \xrightarrow{\lambda+d_\alpha} \varnothing$ | $\varnothing \xrightarrow{\nu_{m,\alpha}} m_\alpha$ | $m_\alpha \xrightarrow{\lambda+d_{m,\alpha}} \varnothing$ | $r + m_\alpha \xleftrightarrow{k_b,k_{u,\alpha}} \overline{rm}_\alpha$ | $n_\alpha \cdot a + \overline{rm}_\alpha \xrightarrow{\nu_\alpha} r + m_\alpha + \alpha$ |
| other growth dependent proteins | $p \xrightarrow{\lambda+d_p} \varnothing$ | $\varnothing \xrightarrow{\nu_{m,p}} m_p$ | $m_p \xrightarrow{\lambda+d_{m,p}} \varnothing$ | $r + m_p \xleftrightarrow{k_b,k_{u,p}} \overline{rm}_p$ | $n_p \cdot a + \overline{rm}_p \xrightarrow{\nu_p} r + m_p + p$ |
| internal sugar | $s_i \xrightarrow{\lambda} \varnothing$ | | | | |

# The model recovers Monod’s growth law.

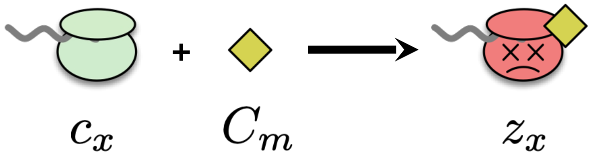


# The model recovers the ribosomal growth laws.




Translational inhibition assuming chloramphenicol binds the mRNA-ribosome complexes, which then can't be translated anymore:




$$s_i \xrightarrow{\nu_{\text{cat}}} \boxed{n_s} a$$

nutrient quality = energy yield

# We can derive the empirical growth relations analytically.

1. When varying nutrient conditions

mass fractions
total & free ribosomes

$$\lambda = \frac{1}{\tau_\gamma}(\phi_R - \phi_r)$$

time to translate one ribosome

2. When inhibiting translation

housekeeping load

free ribosomes

$$\lambda \simeq \frac{1}{\tau_e}(1 - \phi_q - \phi_R) \cdot \frac{s}{K_t + s}$$

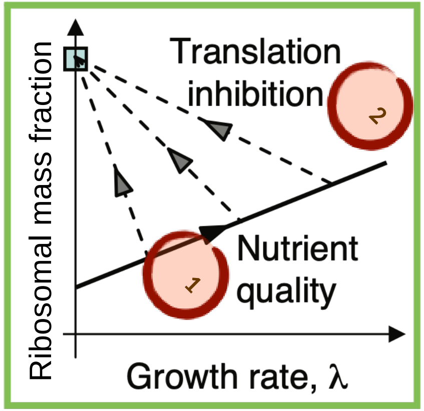
enzyme time

constant environment

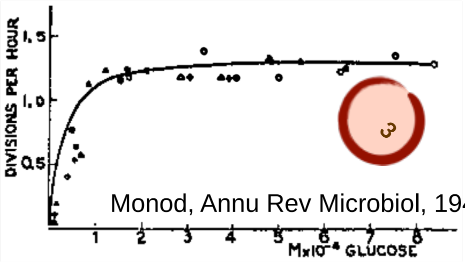
3. When changing amounts of external nutrient

$$\lambda \simeq \frac{(1-\phi_q)s}{K_t\tau_e + (\tau_e + \tau_\gamma)s}$$

import threshold



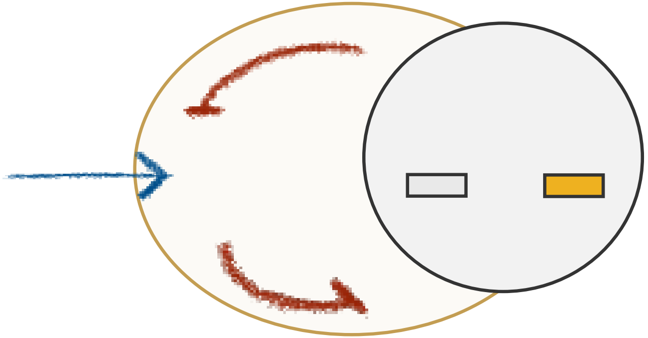

Scott & Hwa, Curr Opin Biotechnol, 2011




Monod, Annu Rev Microbiol, 1949

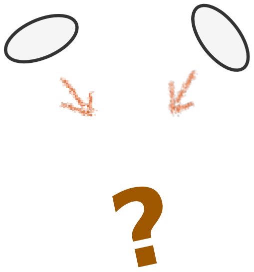
# Other things we can investigate with such mechanistic model:

**Host-circuit interactions**



**Evolutionary stability of cell mechanisms**

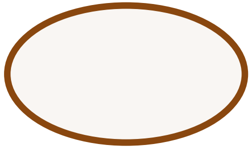

**Antibiotic responses**

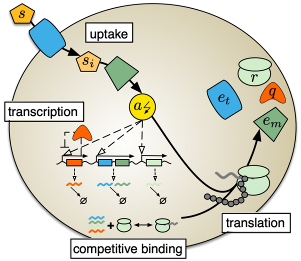


# In summary

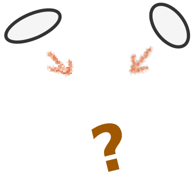
**Cellular self-replication is inherently coupled with growth**

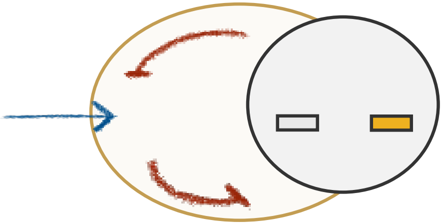
***Small* mechanistic models give insights on principles underpinning growth**






**Complexity comes at cost but can give versatility**



**Further reading:**

EPCP book chapter “Models of growing cells”

Weiße *et al*, PNAS 2015

# Economic principles?