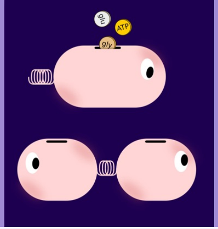
Economic Principles in Cell Biology

Paris, July 08-11, 2024



Principles of cell growth

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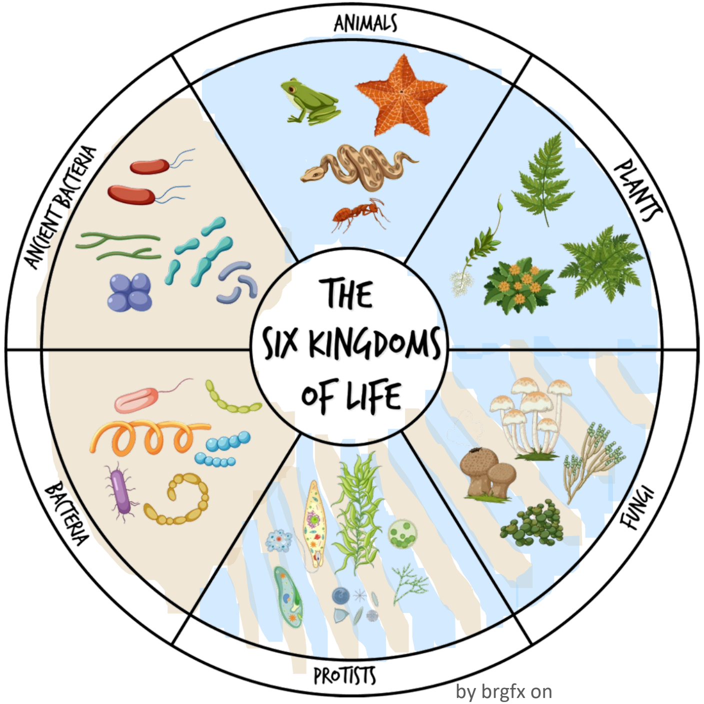
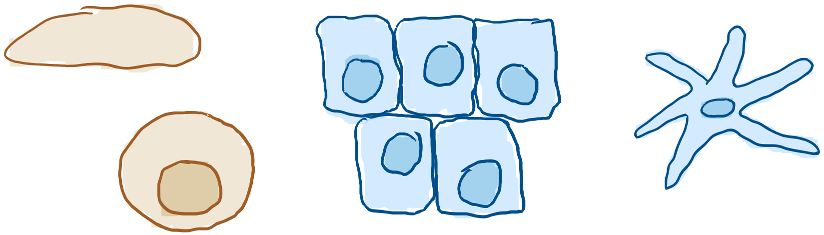
Self-replication is a hallmark of life

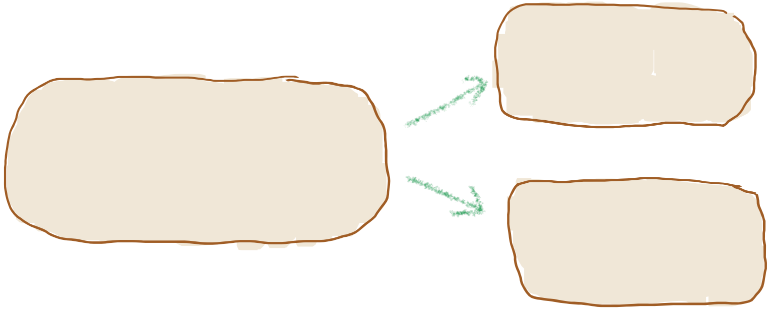


by brgfx on Freepik

Cells are building blocks of life



Cellular self-replication underpins reproduction of life



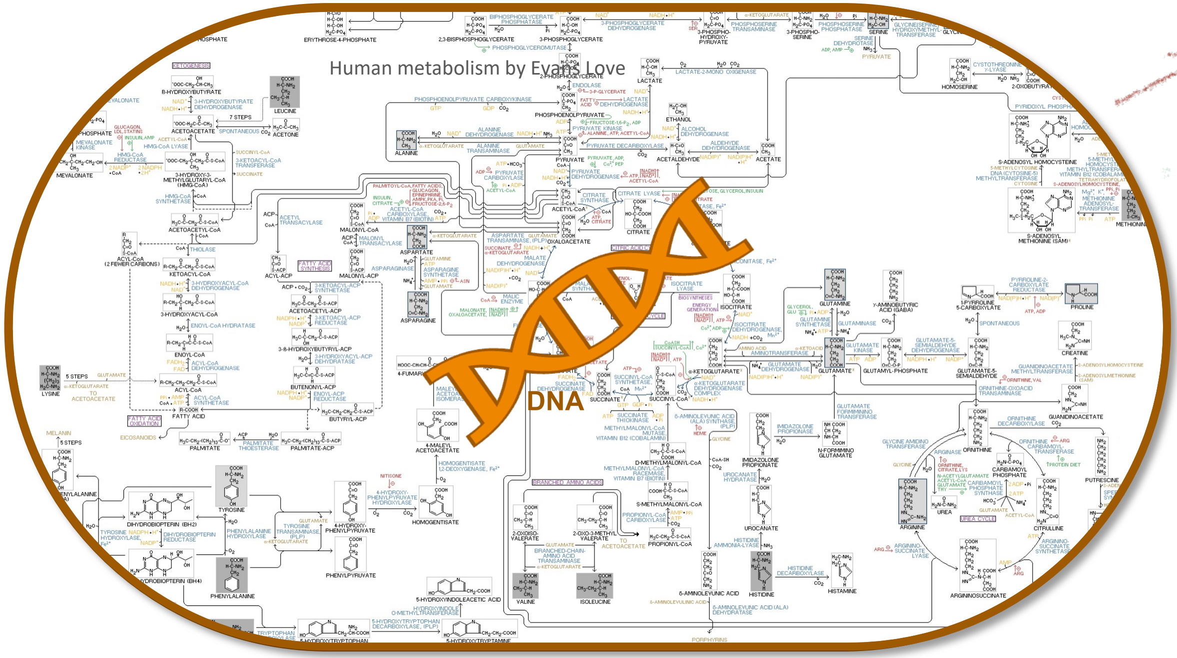
Self-replication is inherently coupled to growth

Cells absorb nutrients

C

N

P

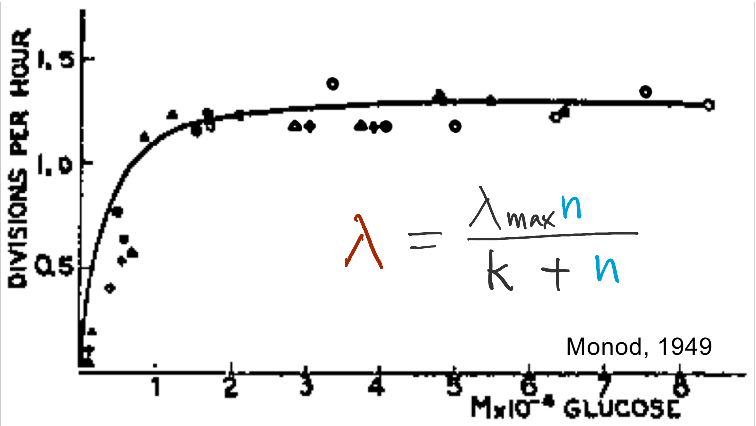


growth

replication

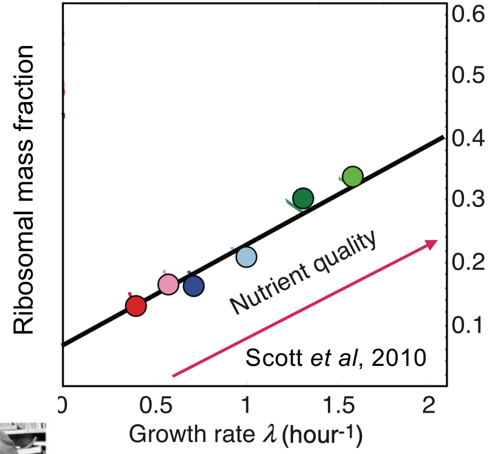
Growth laws govern the relation of growth with environmental & cellular features

Monod growth



$$\lambda = \frac{\lambda_{max} n}{k + n}$$

Ribosomal growth laws



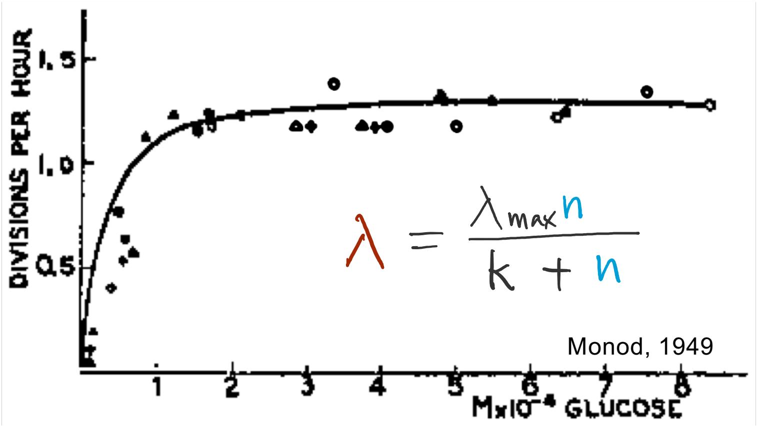
Monod | Schaechter | Maaløe and Kjeldgaard | Bremer and Dennis

1942 — 1949 — 1958 — 1966 — 1996

A brief history of bacterial growth physiology – Schaechter 2015

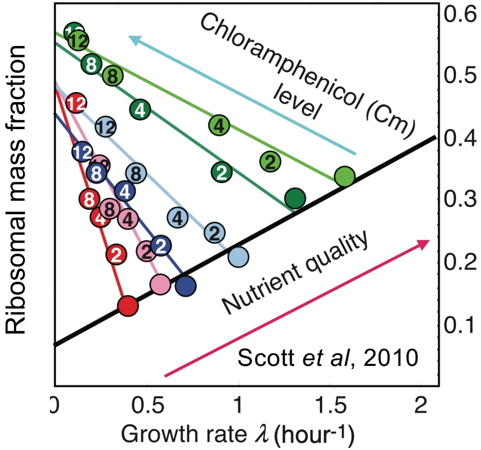
Growth laws govern the relation of growth with environmental & cellular features

Monod growth



$$\lambda = \frac{\lambda_{max} n}{k + n}$$

Ribosomal growth laws



① $\lambda \sim \phi_r$

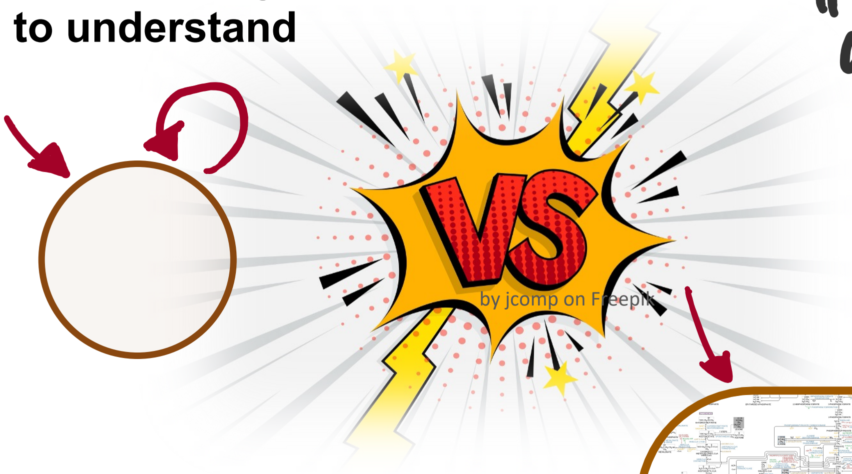
② $\lambda \sim -\phi_r$

Other growth laws:

- cell size
- cell surface
- nutrient influx…

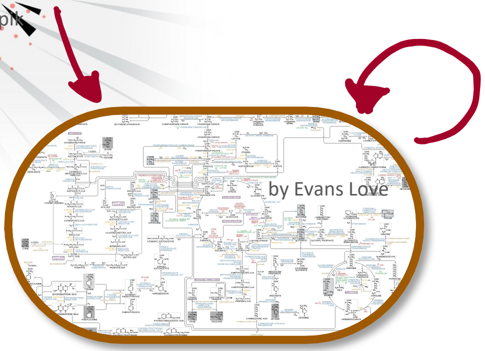
What model should we use?

Simple enough to understand



"All models are wrong but some are useful."

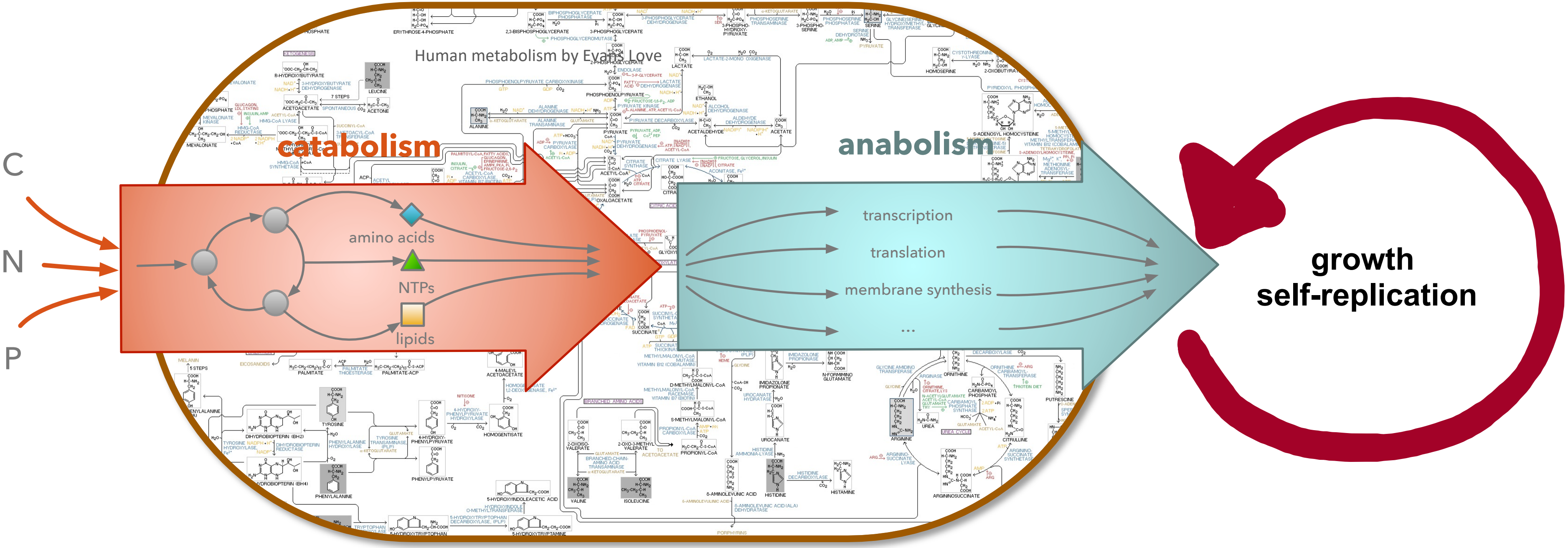
George E.P. Box



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

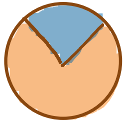


Let's start with a simple growth model

Two reactions: $n \xrightarrow{V_1} r \qquad r \xrightarrow{V_2} B$

Assumptions:

① Proteome dominates biomass



$P_{n\to r} + P_{r\to B} = B$

② Cell has constant density

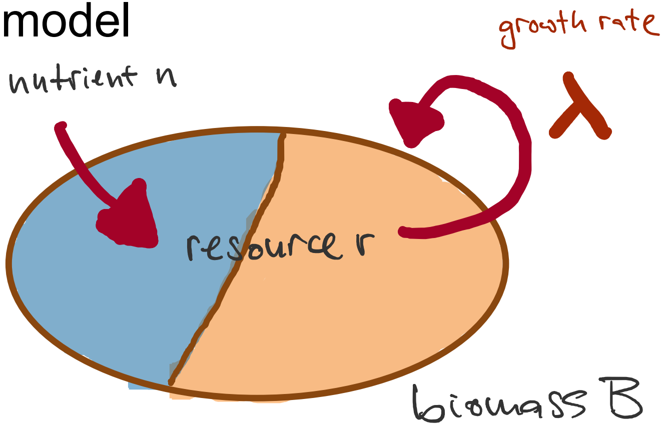
$B \sim V \Rightarrow \frac{Y}{B} \sim$ concentration of cell component y

③ Reaction rates are proportional to protein concentrations

$V_1 = \frac{P_{n\to r}}{B} \cdot \beta_{n\to r} \qquad V_2 = \frac{P_{r\to B}}{B} \cdot \beta_{r\to B}$

④ Steady-state assumption:

$\dot{r} = \frac{dr}{dt} = V_1 - V_2 = 0 \Leftrightarrow V_1 = V_2$



What determines the growth rate?

① - ④ : $\frac{(B - P_{r\to B})}{B} \beta_{n\to r} = \frac{P_{r\to B}}{B} \cdot \beta_{r\to B}$

$\Rightarrow P_{r\to B} = B \cdot \frac{\beta_{n\to r}}{\beta_{r\to B} + \beta_{n\to r}}$

$\dot{B} = \lambda \cdot B = V_2$

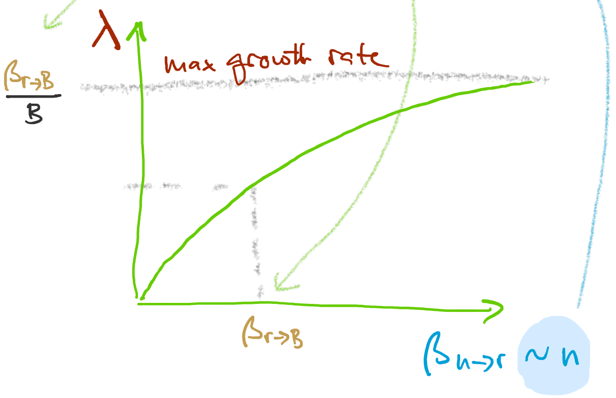
$\Rightarrow \lambda = \frac{V_2}{B} = \frac{1}{B} \cdot \frac{P_{r\to B}}{B} \beta_{r\to B}$

$= \frac{1}{B} \cdot \frac{\beta_{r\to B} \cdot \beta_{n\to r}}{\beta_{r\to B} + \beta_{n\to r}}$

The simple model gives insight on growth laws

at steady-state

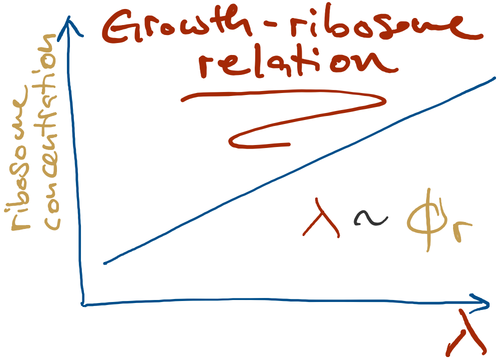
$$\lambda = \frac{\beta_{r\to B}}{B} \cdot \frac{\beta_{n\to r}}{\beta_{r\to B}+\beta_{n\to r}}$$

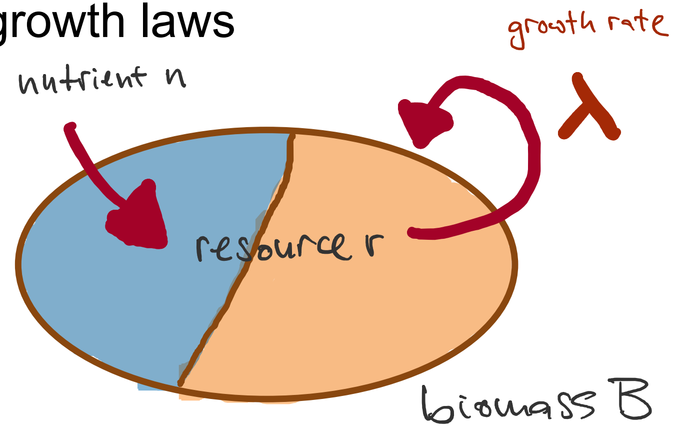


but also

$$\lambda = \frac{1}{B} \frac{P_{r\to B}}{B} \beta_{r\to B}$$

$$\Rightarrow \lambda \sim \frac{P_{r\to B}}{B}$$





What determines the growth rate?

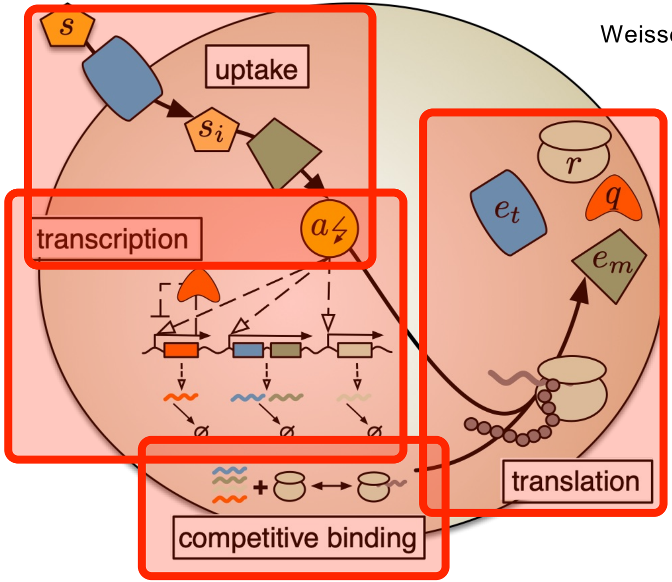
Further assume nutrient limiting

$$\Rightarrow \lambda \sim \frac{\lambda_{max}\, n}{k + n}$$ Monod-growth

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

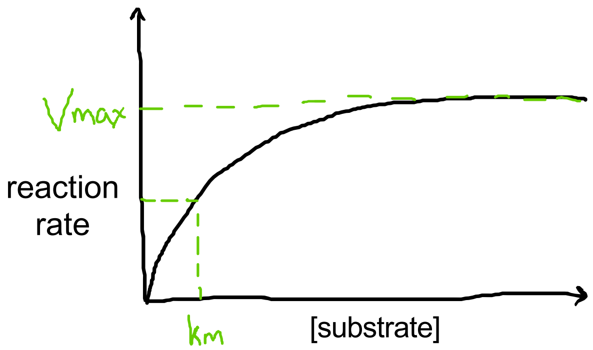
	dilution	transcription	dilution/degradation	ribosome binding	dilution	translation
ribosomes	$r \xrightarrow{\lambda} \varnothing$	$\varnothing \xrightarrow{\omega_r} m_r$	$m_r \xrightarrow{\lambda+d_m} \varnothing$	$r + m_r \xleftrightarrow{k_b,\, k_u} c_r$	$c_r \xrightarrow{\lambda} \varnothing$	$n_r\, a + c_r \xrightarrow{\nu_r} r + m_r + r$
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	$s_i \xrightarrow{\lambda} \varnothing$	$s \xrightarrow{\nu_{\text{imp}}} s_i$	$s_i \xrightarrow{\nu_{\text{cat}}} n_s\, a$			
ATP	$a \xrightarrow{\lambda} \varnothing$	nutrient import	metabolism			

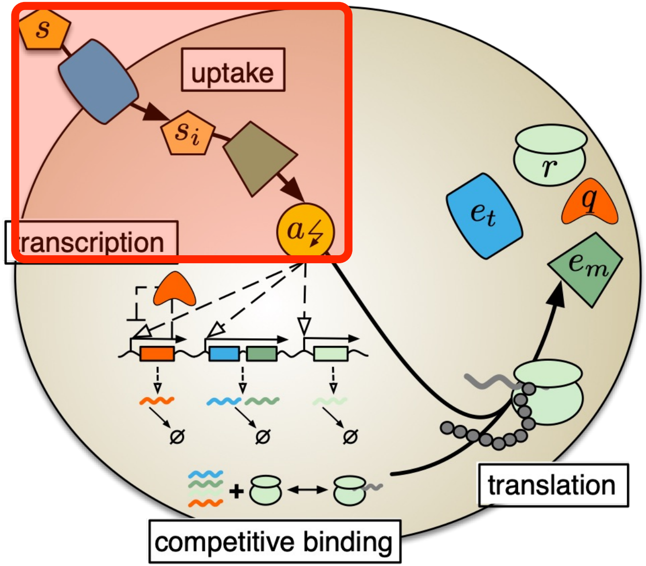
Enzymes catalyze nutrient uptake and metabolism.

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:

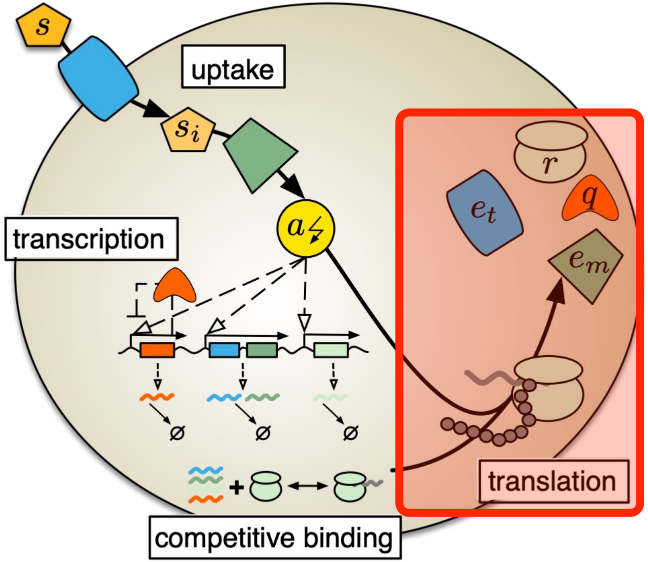
$$\nu_x = c_x \cdot \left(n_x \cdot \left(\frac{1}{K_p a} + \frac{1}{k_2} \right) + \frac{1}{k_p} \right)^{-1}$$

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

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

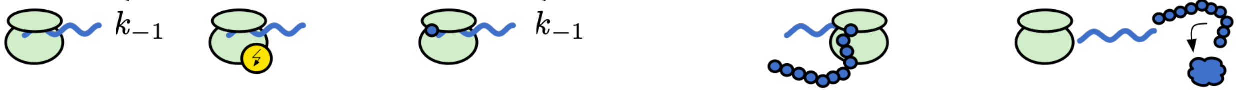
elongation rate

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



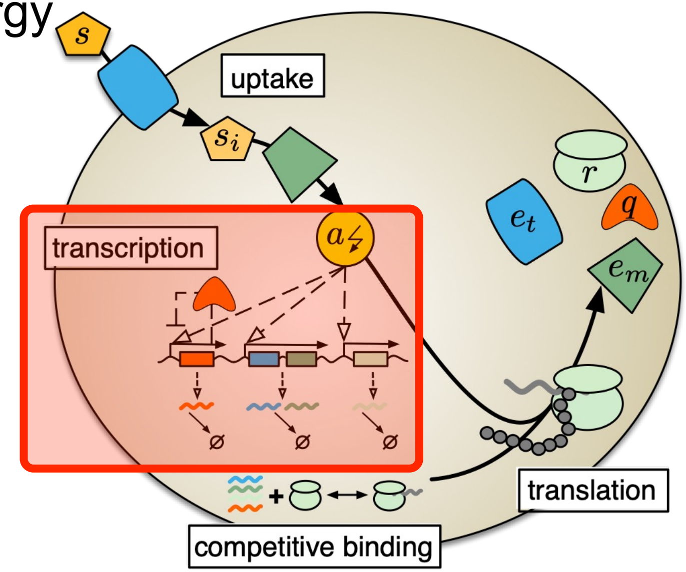
ATP consumption by translation ~2/3 of total consumption (Russel & Cook, 1995).
We assume a simplified mechanism where ATP directly binds the elongating complex:

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



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:

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

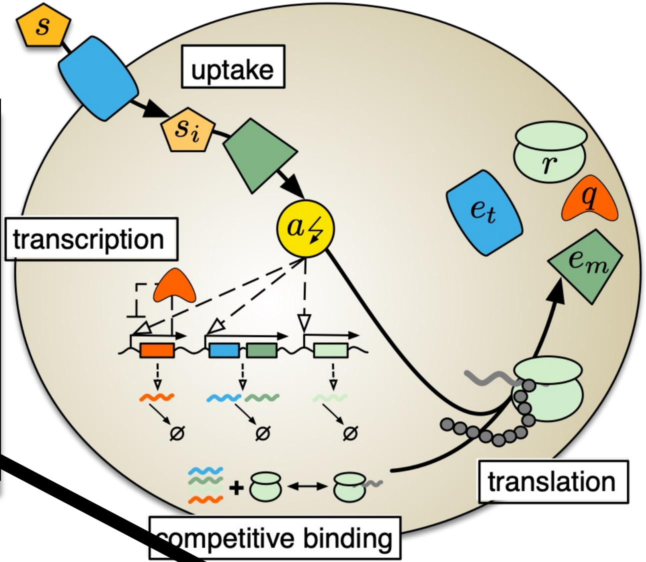
$$x \in \{e, \alpha, r, p\}$$

Translational activity determines growth.

From steady state follows

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

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



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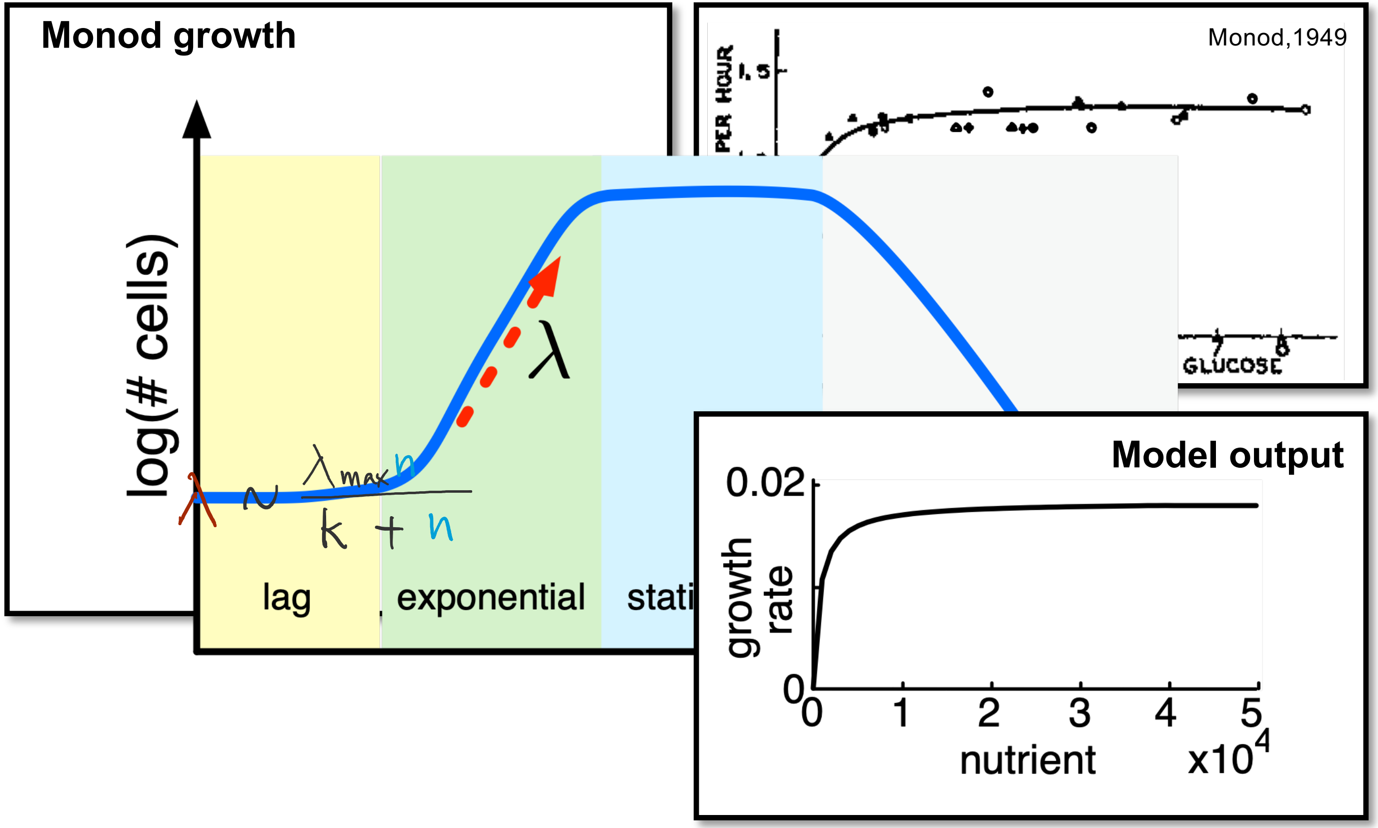
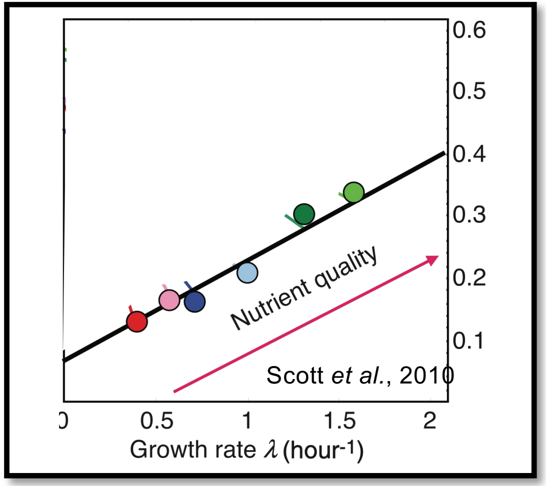
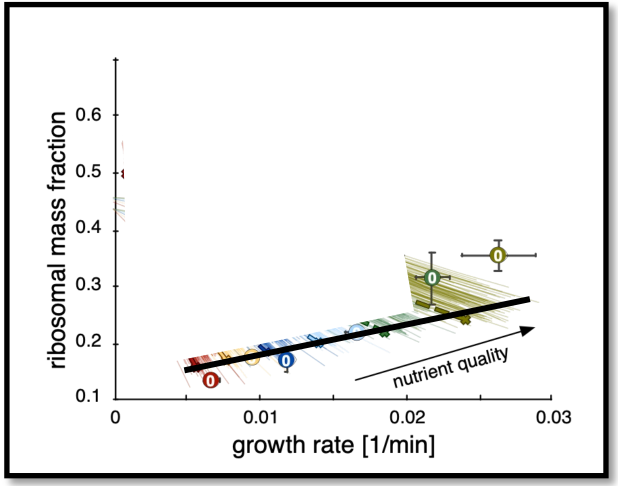
ATP	$a \xrightarrow{\lambda} \varnothing$					
		nutrient import	metabolism			

The model recovers Monod's growth law.

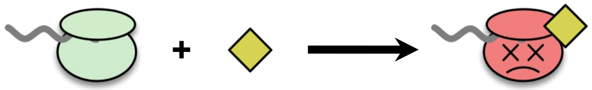


The model recovers the ribosomal growth laws.





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



c_x C_m z_x

$$s_i \xrightarrow{\nu_{\mathrm{cat}}} n_s a$$

nutrient quality = energy yield

We can derive the empirical growth relations analytically.

1. When varying nutrient conditions

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

mass fractions total & free ribosomes

time to translate one ribosome

2. When inhibiting translation

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

housekeeping load

total ribosomes

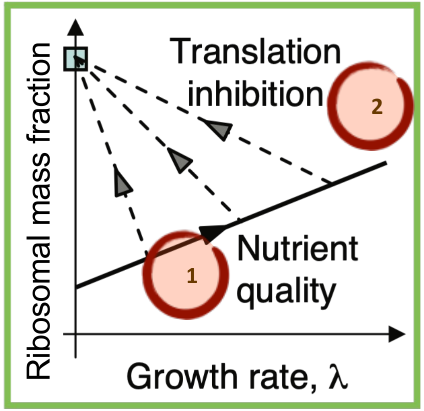
enzyme time

constant environment

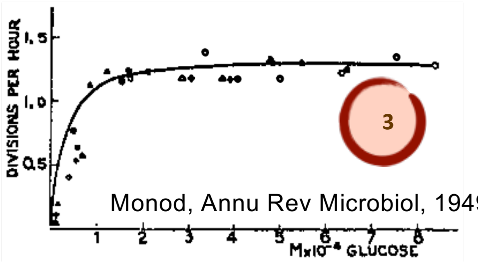
3. When changing amounts of external nutrient

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

import threshold



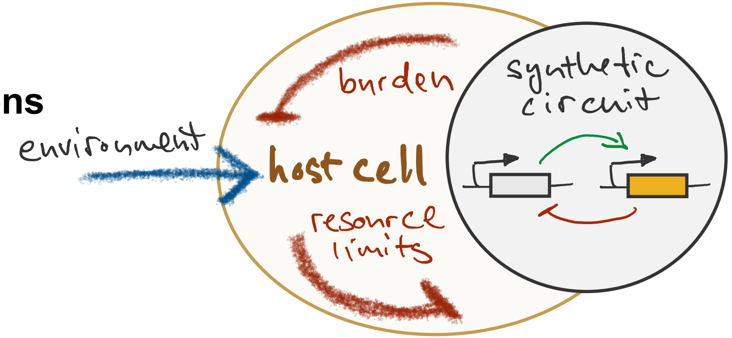
Scott & Hwa, Curr Opin Biotechnol, 2011



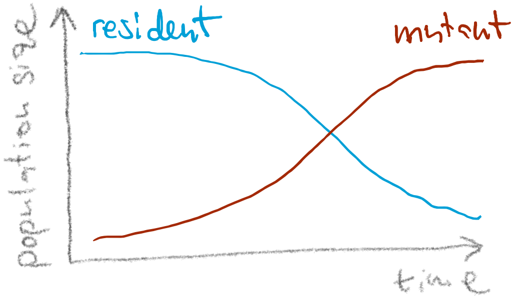
Monod, Annu Rev Microbiol, 1949

Other things we can investigate with such mechanistic model:

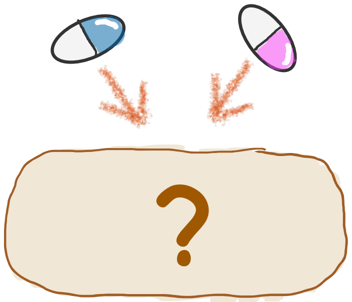
Host-circuit interactions



Evolutionary stability of cell mechanisms



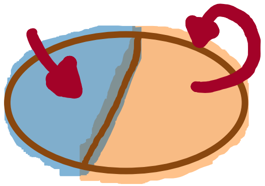
Antibiotic responses

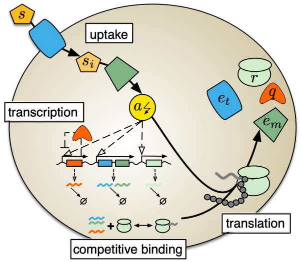


In summary

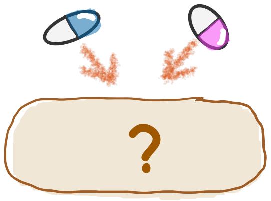
Cellular self-replication is inherently coupled with growth

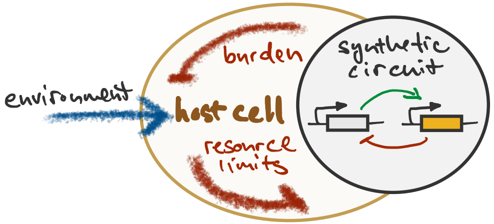
Small mechanistic models give insights on principles underpinning growth





Complexity comes at cost but can give versatility



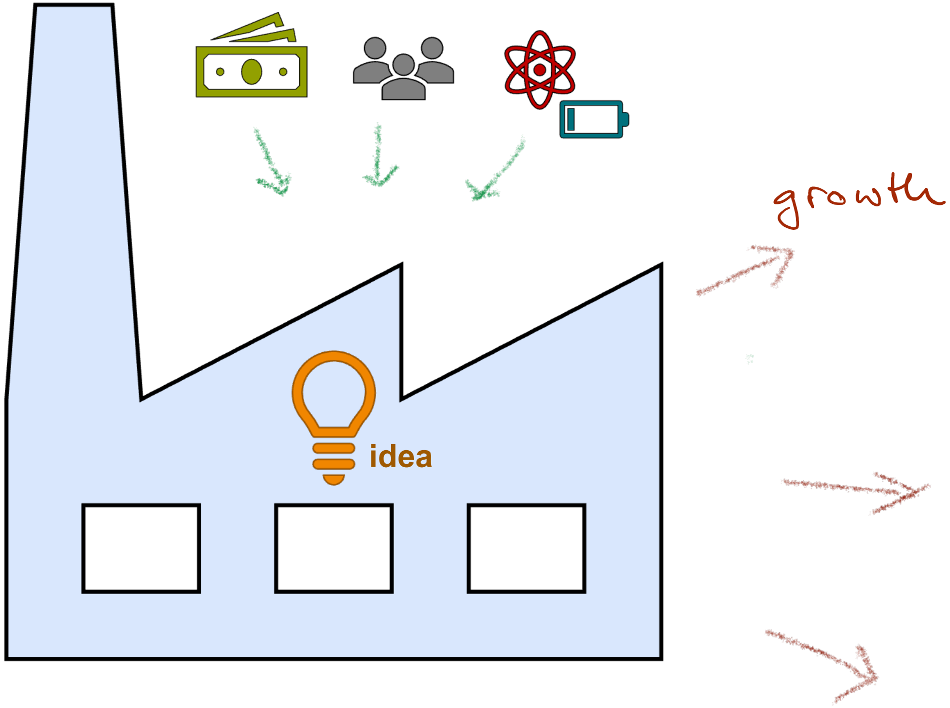


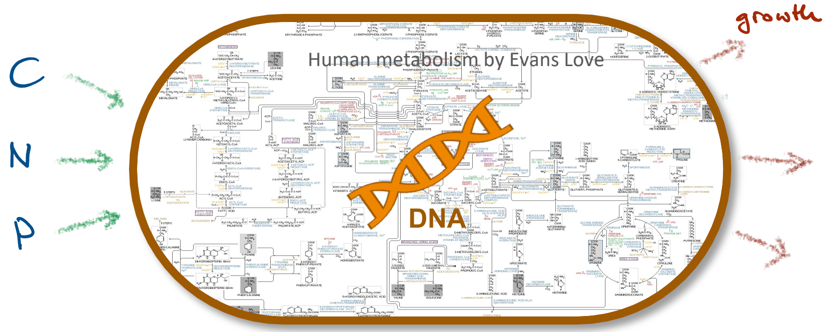
Further reading:

EPCP book chapter "Principles of growth"

Weiße *et al*, PNAS 2015

Economic principles?





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