20251119 CCBS. Lecture 11. Growth Machine.

① Biomachine perspective — possibly in reverse!

② Growth Law of bacteria. 1970s to today.

③ Growth in Economics.

④ Dynamics of a growing and deciding cell.
— the vast frontier

① Growth biomachine perspective.

- Recall - the biomachine perspective.
  - Cells need to perform functions. eg. adaptation. computation.
    We have built/engineered machines that achieve such functions.
    So principles of engineered machines achieving this function can be used to understand principles of how biological systems are designed.
    - of course. specific tasks and physical constraints can be drastically different
  - But. for the function of growth this is actually better understood/ more thoroughly studied in biology!

So. this gives a chance to go in reverse. or at least back and forth.

[Quantitative studies of biological growth
  started in 1800s (Malthus. Volka-Voltera)
  more principled in 1940s. (Monod. growth law)
  Quantitative studies of economic growth
  started in 1800s. (Malthus. etc.)
  more principled in 1940s. (von Neumann etc.)

- So let's start in biology - this time.

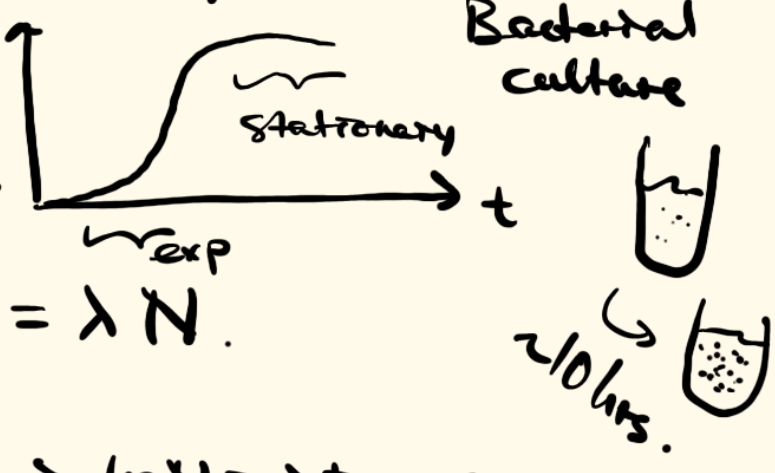
② Growth Law of Bacteria.

- We want a mechanistic model of bacterial growth.

  So. we know the key mechanisms

  and how to control / perturb growth.

- let's restrict our attention to steady state exponential growth (defined by growth curve).



(1). Exponential growth. $\frac{dN}{dt} = \lambda N$.

Explicitly solve: $\frac{d \log N}{dt} = \lambda. \Rightarrow \log N = \lambda t + c_0$

$\Rightarrow N = N_0 e^{\lambda t}$.

But this is rather phenomenological.

It's literally just "fit the curve".

Q: How is the growth rate determined?

(2). When limited by nutrient conc. (external limitation).

1940s. Monod. to 1970s. chemostat. still active in fermentation & metabolic engineering!

- Chemostat model.

  continuous flow. v. (vol/time).

  tank volume. V.

If c is concentration of nutrient in tank.

c_0 is conc. of nutrient influx.

Then $c(t+\Delta t) = \frac{1}{V}\left(c(t) V + c_0 v \Delta t - c v \Delta t\right)$

$\Rightarrow \frac{c(t+\Delta t) - c(t)}{\Delta t} = (c_0 - c)\frac{v}{V}$. (e.g. $\frac{1\,mL/min}{1\,mL} = 1/min$)

$\Rightarrow \frac{dc}{dt} = (c_0 - c)\delta$. $\delta = \frac{v}{V}$ = dilution rate.

Control c by c_0

- Growth in chemostat (gDW) ⌐ gram dry weight (mass)

Let M denote cell dry mass. $\rho = \frac{M}{V}$ denote cell density. (gDW/mL).

Since influx has no cells.

if M is produced at rate $\mu_M M$. (μ_M per cell mass)

Then. $\rho(t+\Delta t) = \frac{M(t+\Delta t)}{V} = \frac{M(t) + \mu_M M(t)\Delta t - V\rho(t)\Delta t}{V}$

$= \rho(t) + \underbrace{\frac{\mu_M}{V}}_{\mu} \rho(t)\Delta t - \delta\rho(t)\Delta t$

$\frac{d\ln\rho}{dt} = \mu - \delta$ $\Rightarrow$ $\underline{\frac{d\rho}{dt} = (\mu - \delta)\rho(t)}$. (not stable by itself).

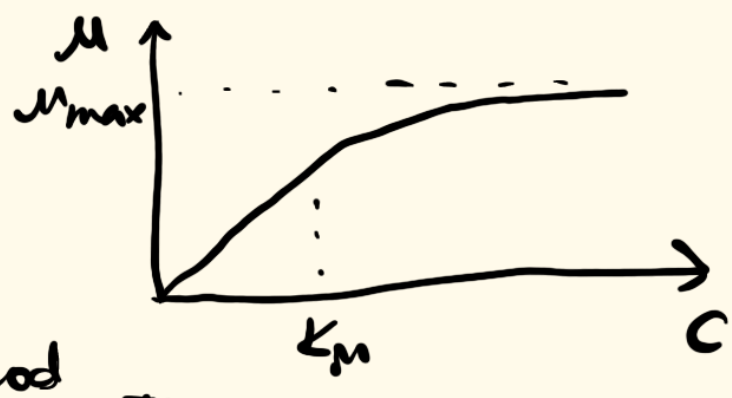
So if μ is const. we need to adjust δ to fit μ....

- Resource consumption limits cell growth.

when c is low enough. it dictates cell growth rate.

often has this phenomenological relation:

$\mu = \mu(c) = \mu_{max}\frac{c}{c+K_M}$. } Monod growth rate



- Consumer Resource Model"

$$\Rightarrow \begin{cases} \frac{d\rho}{dt} = \left(\mu_{max}\frac{c}{c+K_M} - \delta\right)\rho \\ \frac{dc}{dt} = (c_0 - c)\delta - \frac{1}{Y}\mu_{max}\frac{c}{c+K_M}\rho \end{cases}$$

($yield = \frac{\text{biomass}}{\text{nutrient mass consumed}}$ (const. if cell has constant composition.)

- From here on, such (phenomenological) models concerning nutrient resource $\leftrightarrow$ population growth can be used to analyze / reason about many scenarios.

- Ecology / population interaction.
  or fermentation / growth.

  - under one nutrient. how do different populations compete?
  - what about multiple nutrients / niches?
  - cross-feeding (some pop produce nutrients).
  - Cooperation vs competition

- Microbiome / microbial consortia.
  - Serial dilution vs continuous chemostat
  - dynamic niches.

- But... This explains how growth rate λ changes with c when nutrient conc. is limiting.
  But. what determines λ_{max}?
  ↳ The growth rate not under limiting nutrient conc?

Also. changing nutrient type. (e.g. carbon source quality)
glucose vs glycerol
cells' growth rate also changes.

⇒. Limitation is internal

(3). Growth Law.

1970s. Netherlands. Maaløe. etc.

then.
2010. Terry Hwa. (Scott et.al. Terry Hwa. Science. 2010)

- Experimentally. RNA vs protein in dry weight can be quantified. ⇒ Most dry weight is protein.

RNA mass / protein mass

Most RNA mass are ribosomes

⇓

⇐ changing nutrient { measure λ. / measure $\frac{M_R}{M_P}$

- This means. $\phi_R = \frac{M_R}{M_{tot}}$ fraction of ribosomes (ribosomal mass / (mass)) change with growth rate.
  ↳ total protein mass.

But how can this be?

- Cell growth is ribosomes making ribosomes!

– R ↻ If all proteins are just ribosomes.

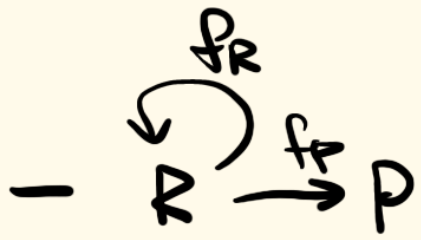
each ribosome produces proteins at a rate σ. (per ribosome mass.)

$$\frac{d M_R}{dt} = \sigma M_R.$$

growth rate is $\lambda = \sigma$

But ... λ should change with ϕ_R!

Idea: There are proteins other than ribosomes!



f_R: fraction of ribosomes used to produce R.

If there are proteins other than ribosomes!

P: proteins other than ribosomes R.

$$\frac{dM_R}{dt} = \sigma f_R M_R.$$

$$\frac{dM_P}{dt} = \sigma f_P M_R.$$

$$\Rightarrow \frac{d}{dt}\phi_R = \frac{d}{dt}\frac{M_R}{M_{tot}} = \frac{dM_R}{dt}\frac{1}{M_{tot}} - \frac{M_R}{M_{tot}^2}\frac{dM_{tot}}{dt}.$$

$$\left(\phi_R = \frac{M_R}{M_{tot}}\right). \qquad = \sigma f_R \frac{M_R}{M_{tot}} - \sigma \frac{M_R^2}{M_{tot}^2}.$$

$$= \sigma \phi_R (f_R - \phi_R).$$

So. if steady state is reached. then. $\phi_R = f_R$.

$\Rightarrow$. growth rate is $\lambda = \sigma \phi_R$.

Great! λ is linear with ϕ_R!

(what about P? Is ϕ_P constant?

$$\frac{d}{dt}\phi_P = \frac{d}{dt}\frac{M_P}{M_{tot}} = \frac{dM_P}{dt}\frac{1}{M_{tot}} - \frac{M_P}{M_{tot}^2}\frac{dM_{tot}}{dt} = \sigma f_P \frac{M_R}{M_{tot}} - \sigma \frac{M_P M_R}{M_{tot}^2}$$

$$= \sigma \phi_R (f_P - \phi_P)$$

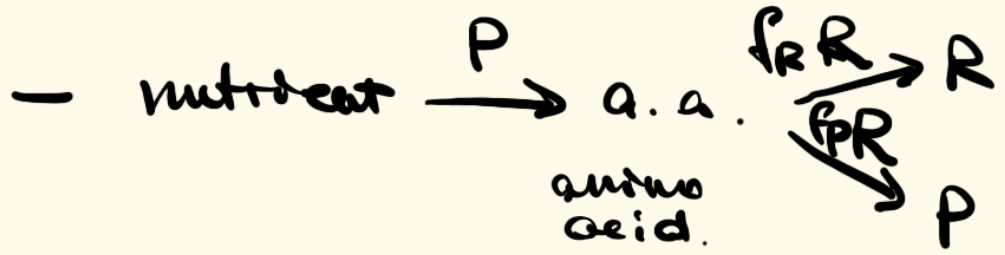
)

But... why does λ change under different nutrient quality?

That's what caused λ to change (e.g. glucose vs glycerol) in the first place in experiments...

Idea: nutrient quality $\downarrow$. more enzymes are needed to metabolize nutrients! (more steps etc.)

So. $\phi_P = \frac{M_P}{M_{tot}}$ $\uparrow$. (causing ϕ_R $\downarrow$)

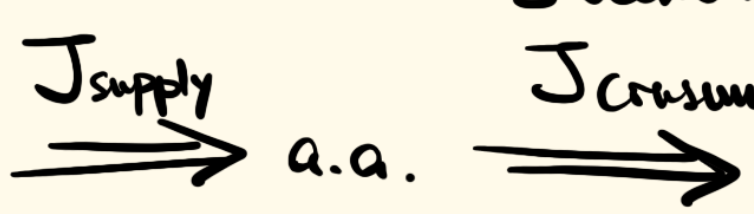


k = rate a.a. is produced per P mass.

$$\Rightarrow \frac{d M_{aa}}{dt} = k M_P - \sigma M_R = M_{tot}(k\phi_P - \sigma\phi_R).$$

↖ But this may not hold! (M_{aa} can't go negative!)

Look at the fluxes:



$J_{supply} = kP = \bar{k}\phi_P$. $J_{consume} = \sigma R = \bar{\sigma}\phi_R$.

Now. what if $J_{supply} < J_{consume}$?

will $\frac{M_{aa}}{M_{tot}}$ go to zero? go negative? No.

So. $J_{demand} = \sigma R = \bar{\sigma}\phi_R$ is the <u>capacity</u> of consumption. (<u>demand</u>)

If $J_{supply} < J_{demand}$ then <u>actual consumption</u> is J_{supply}! $J_{consumption} = \min(J_{supply}, J_{demand})$.

In fact. it will be slightly less than J_{supply}. since a bit extra of a.a. needs to be supply for growth. when $\phi_{a.a.}$ can't be approx. as roughly zero.

$$\frac{d\phi_{a.a}}{dt} = \frac{d}{dt}\frac{M_{aa}}{M_{tot}} = \frac{d M_{aa}}{dt}\frac{1}{M_{tot}} - \frac{M_{aa}}{M_{tot}^2}\frac{d}{dt}M_{tot}$$

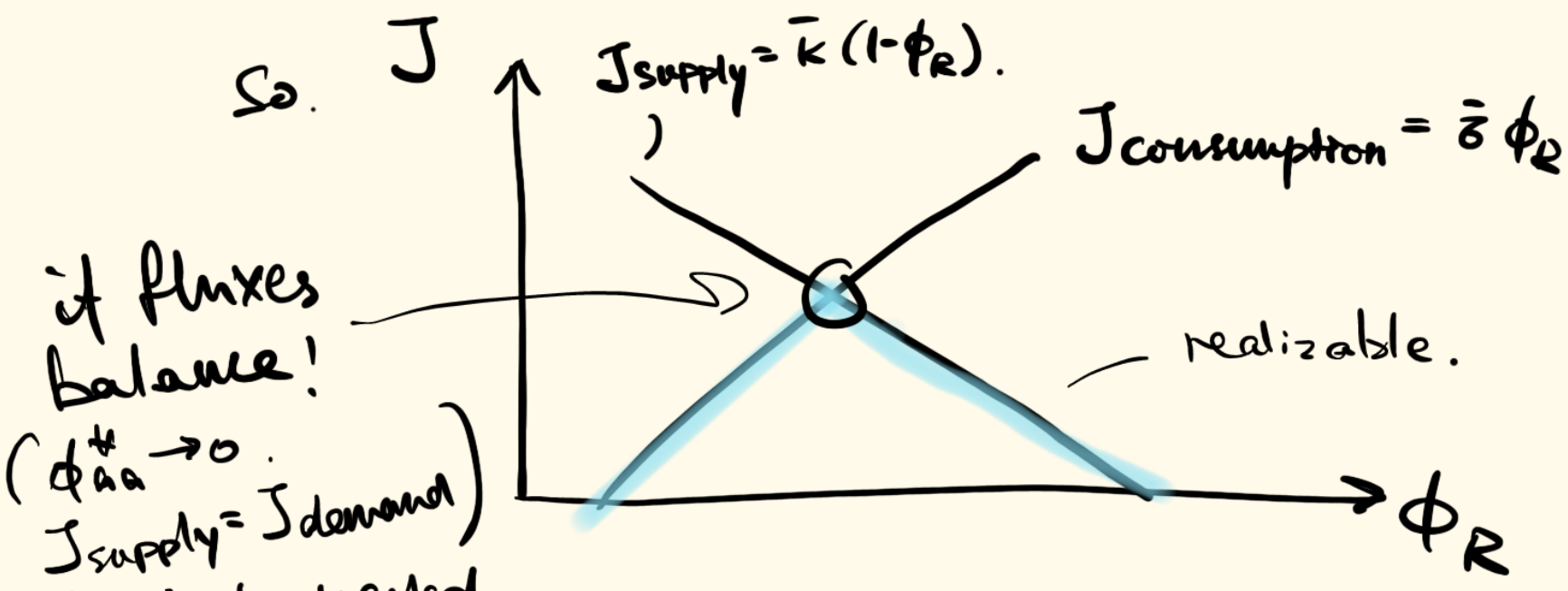
$$= k\phi_P - \sigma\phi_R - \phi_{aa}\sigma\phi_R$$

$$\Rightarrow \text{at s.s. } k\phi_P = (1+\phi_{aa})\sigma\phi_R.$$

$$\Rightarrow \phi_{aa} = \frac{k\phi_P}{\sigma\phi_R} - 1 = \frac{k\phi_P - \sigma\phi_R}{\sigma\phi_R}$$

Also cohole cell proteome is finite. $\phi_P + \phi_R = 1$.

So.



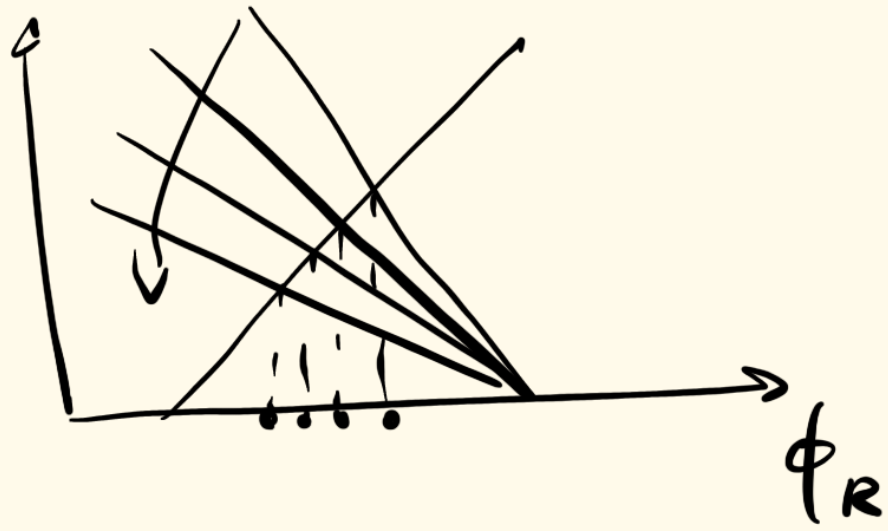
if fluxes balance!

($\phi_{aa}^* \to 0$.
$J_{supply} = J_{demand}$)

Nothing is wasted.

Growth is maximized! (over ϕ_R).

This can be used to explain the experimental observations!



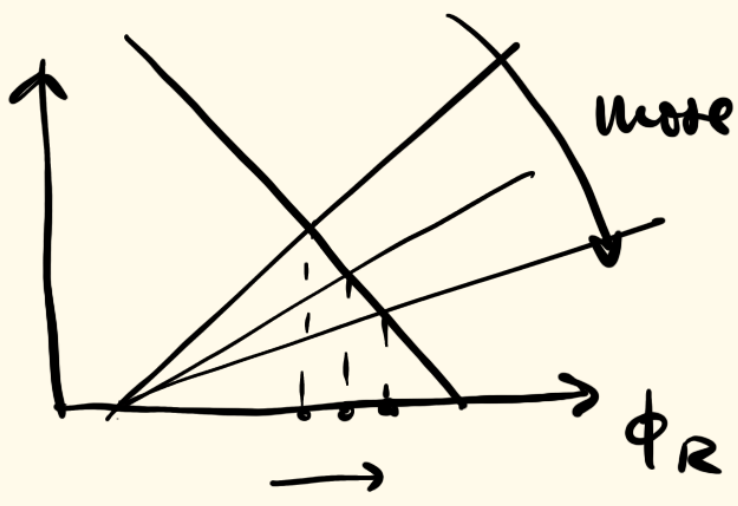
nutrient quality ↘

k ↘

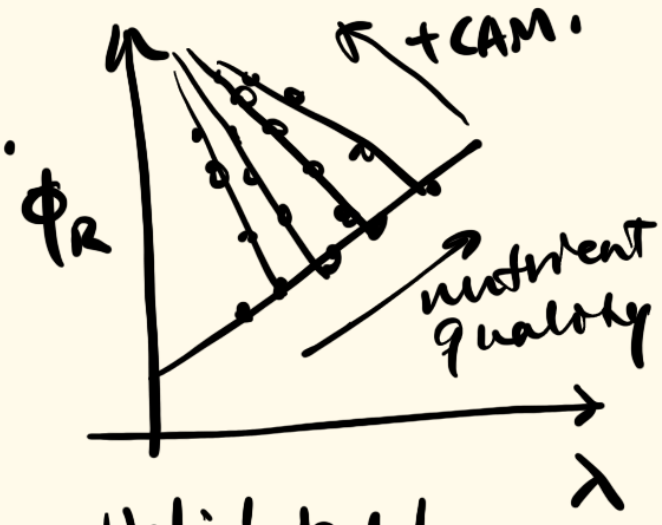
Prediction: if chloramphenicol (CAM) is added.

(it blocks ribosomal activity). then σ ↘

(or makes a fraction of ribosomes non-active)



ϕ_R increases!



Validated by Exp.

What's the growth rate?

— This is a chemical reaction network or dynamical system that is growing (not at steady state).

$$\left.\begin{aligned} \frac{dM_{aa}}{dt} &= kM_P - \sigma M_R \\ \frac{dM_P}{dt} &= \sigma f_P M_R \\ \frac{dM_R}{dt} &= \sigma f_R M_R \end{aligned}\right\} \Rightarrow \left\{ \frac{d}{dt}\begin{bmatrix} M_{aa} \\ M_P \\ M_R \end{bmatrix} = \begin{bmatrix} 0 & k & -\sigma \\ 0 & 0 & \sigma f_P \\ 0 & 0 & \sigma f_R \end{bmatrix} \begin{bmatrix} M_{aa} \\ M_P \\ M_R \end{bmatrix} \right.$$

This is linear. $\frac{dx}{dt} = Ax$.

recall. along eigenvector v. eigenvalue λ.

$x(0) = v$ $y(0)$ then $\frac{dx}{dt} = \lambda x(0)$.

$\Rightarrow$. $x(t) = e^{\lambda t} v\ y(0)$.

So. growth rate is <u>largest eigenvalue</u> of A.

In this case. A is upper triangular. eigenvalues are diagonal.

$\Rightarrow$. growth rate $\lambda = \sigma f_R$.

(Cell composition? Eigenvector of λ.

In this case. it's. $\begin{bmatrix} kf_P - \sigma f_R \\ \sigma f_P f_R \\ \sigma f_R^2 \end{bmatrix} \Rightarrow \begin{bmatrix} \frac{kf_P}{\sigma f_R} - 1 \\ f_P \\ f_R \end{bmatrix}$.)

Let $\alpha = \frac{k f_P}{\sigma f_R}$. then. $\phi_{aa} = \frac{\alpha - 1}{\alpha}$.

$\left(\frac{\alpha > 1.}{f_P + f_R = 1}\right)$.

$\phi_P = \frac{f_P}{\alpha}$

$\phi_R = \frac{f_R}{\alpha}$.

(3) Growth in economy. (macro)

- Now we have a good understanding of growth in bacteria.
  how is it related to growth in other fields?
  - This could enhance our understanding of bio growth with a different lens.

- One field concerning growth is Economy.
  - Micro Economy concerns growth of individual agents in the economy (e.g. supply or demand) such as households, workers, businesses specific markets. affected by fixed gov. regulations etc.
  - Macro Economy concerns the growth of economy as a whole and could suggest govt. regulations. e.g. labor interest rate. etc.
  - Both could be related to biological growth.
    but micro → has interactions among agents etc. (like one niche)
    our bacterial growth model considered just one species.
    but proteome divided into different sectors.
    So this is more like a Macro-Economic model.

- Macro Economy models. — a simple two-sector model.

How does an economy has sustained growth?

K↻ - Capital is re-invested and produces more capital.

- But labor (human capital) is needed to use capital for production.

↻ F(L,K)
L → K

1920s. quantitative production functions (Cobb-Douglass)

(Constant return to scale: multiply all inputs by λ. production changes proportionally. $F(\lambda K, \lambda L) = \lambda F(K,L)$)

$$\underbrace{Y}_{\text{production}} = F(K,L) = \underbrace{A K^{\alpha} L^{1-\alpha}}_{\text{activity.}}$$

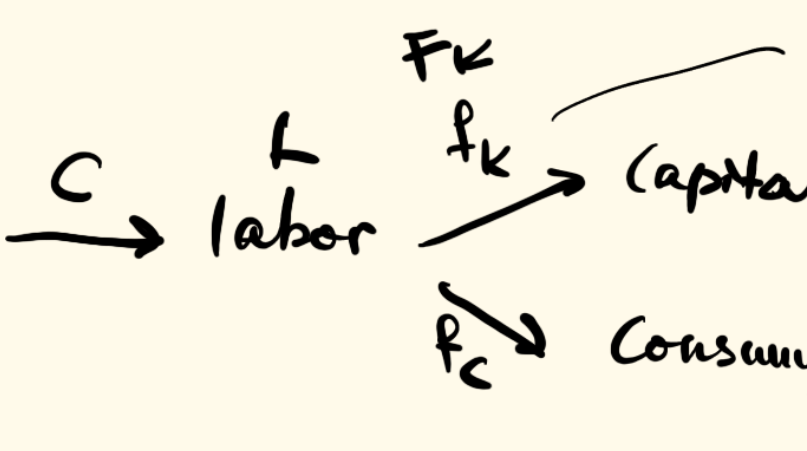
1956. Solow - Swan model. (neoclassical growth)

But how labor grows is not considered.

$$\dot{K} = Y - \delta K.$$

δ: depreciation rate.

- In order for Labor to grow. (technology. knowledge. Food. ...)
  Labor also consumes certain goods produced.
  ⇒. Two sectors.



: Tractors and Corn made by Tractors and Labor".

1960s. Uzawa.

1980s. Lucas. (C is like human capital)

- Analogy between macro economic growth and bacterial growth.

  Labor — amino acids

  Capital — ribosomes

- Dynamics. $Y_c = F_c(K_c, L_c) = A_c K_c^{\alpha_c} L_c^{1-\alpha_c}$

  $Y_k = F_k(K_k, L_k) = A_k K_k^{\alpha_k} L_k^{1-\alpha_k}$

  $L = L_c + L_k$. $f_k = \frac{L_k}{L}$. $\phi_k = \frac{K_k}{K}$.

  $K = K_c + K_k$. (fraction of labor) (fraction of capital.)

  - If $\alpha_c, \alpha_k = 1$. then it's exactly our bacterial growth model.

- Policy tradeoff in Economic growth:

  Key is in adjusting (f_k, f_c)

  $f_c \uparrow$. larger investment into human capital. / consumption goods

  can lead to less growth now, but more growth later.

  Pick f_c, f_k for balanced growth.

- Now let's learn an economic lesson from biology!

- Nutrient quality $\uparrow$ so. $k \uparrow$. ($J_{supply} = \bar{k} \phi_p$).

  This is like technology for consumption goods improved $\uparrow$.

  So. should increase ϕ_R (not ϕ_p). for max growth.

  $\Rightarrow$. More are spent on capital growth.

- CAM shock. ribosome productivity $\bar{\sigma}$ ↘.

($J_{demand} = \bar{\sigma}\phi_R$).

This is like technology for capital production ↘.

labor doesn't produce as much capital goods anymore.

(e.g. technology bottleneck?)

Then. ϕ_R ↗. More labor is spent on capital good production.

it growth is maximized.

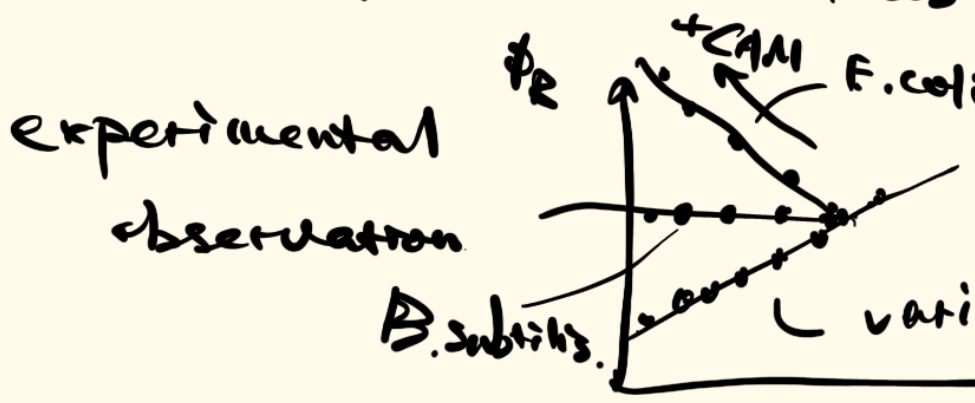
- But the above biological observation is

from <u>E.coli</u> which lives in human gut for growth.

mostly constant environment.

So. instantaneous growth is like long term growth.

B. subtilis. lives in soil. faces much more <u>uncertainty</u>.



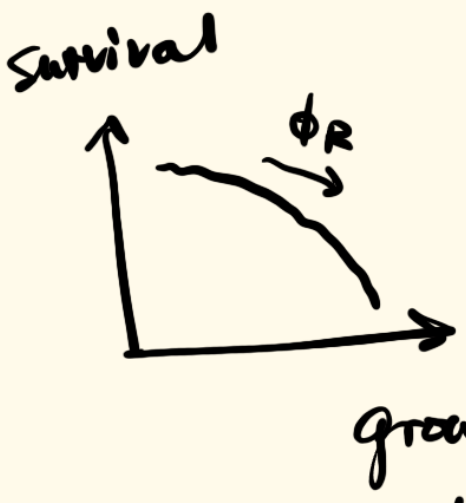
So. B. subtilis doesn't increase ϕ_R↗ under CAM shock!

Why? (Ryan Thiermann. Sackpace Jun. 2025 (Hopefully)).

For <u>survival</u>. <u>Growth-Survival tradeoff</u>.

— if ϕ_P doesn't decrease. more non-growth sector can be used to prepare for survival etc.

e.g. larger antibiotic shocks to come.



Trades off short-term growth for

Surviving through hardship

and then return to growth later.

WARNING: interpretation of experimental observation.

Mechanism is yet to be understood.

— What does this mean for Economy?

Under a sudden shock on capital productivity?

E. coli strategy: expects things will stay this way.

(capital productivity stays low.) for quite a while.

So. we should increase ϕ_R.

More investment into capital prod.

B. subtilis strategy: expects things could get a lot worse before improving a gain.

So. prepare for survival.

So. keep ϕ_R roughly the same.

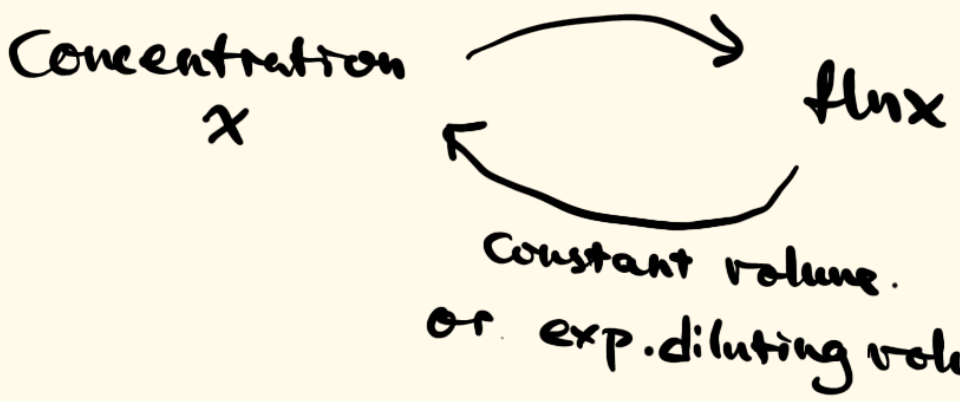
bet ϕ_P stay large. (investment into consumption/human capital or stabilization.

and. after survival. go for larger long term growth.

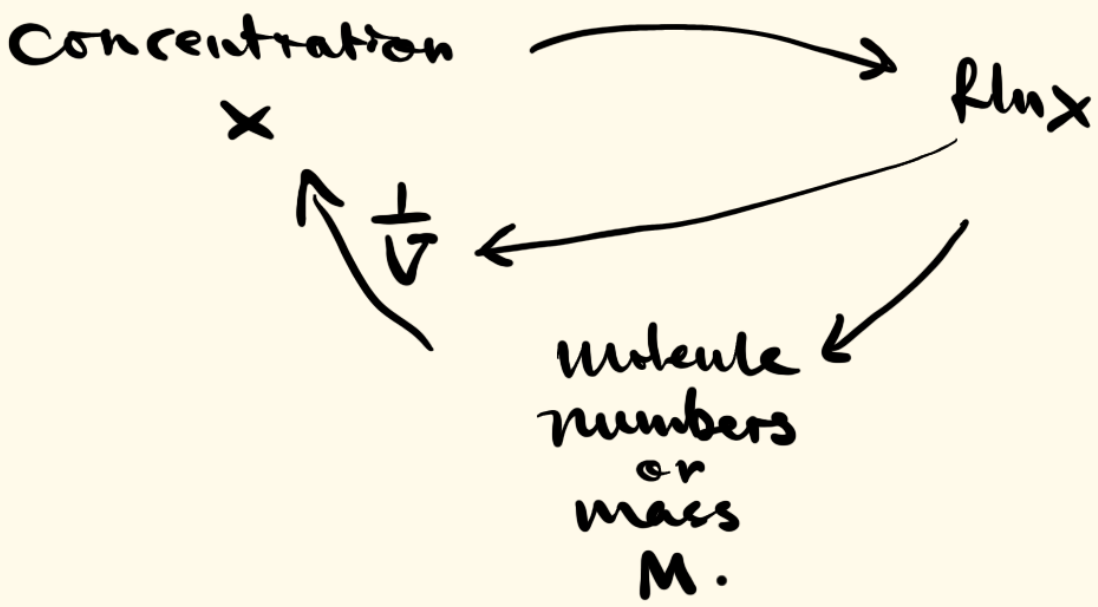
④. Wide frontier at a growing and deciding cell.

- This proteome partitioning idea bridges
  internal biochemical regulations
  and external cell growth / adaptation / nutrient consumption.

Go from "cell as a chemical reaction network
in a μm^3 testtube"

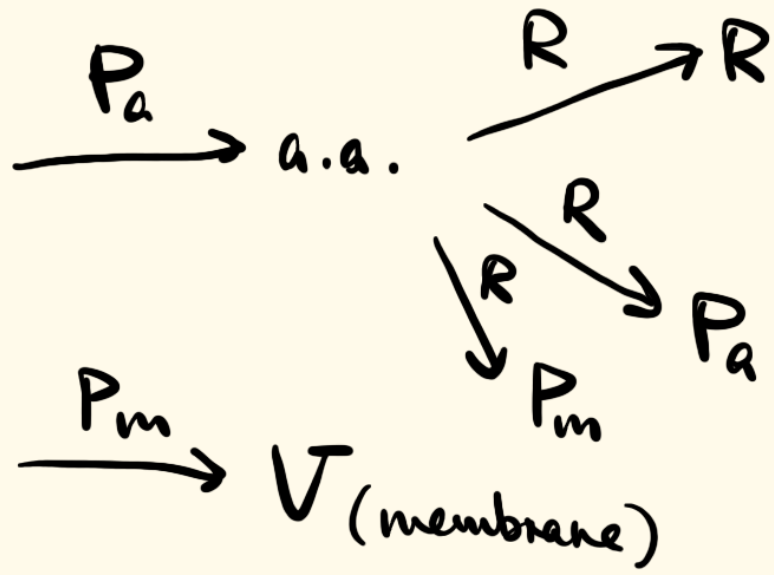


to "cell as a system growing and deciding
with biochemical reactions."



Volume increases by flux. as well!
and volume in turn regulates flux by
diluting concentrations!

e.g.



and write this system as a chemical reaction network with changing volume.

$$\mathring{V} = \lambda(x)\, V$$

$$\mathring{M}_x = F^+(x) - F^-(x) \quad \Big\} \text{ prod. consumption fluxes.}$$

$$\Rightarrow \quad x_i = \frac{M_{x,i}}{V}.$$

$$\frac{dx_i}{dt} = \frac{\mathring{M}_{x,i}}{V} - \frac{M_{x,i}}{V^2}\,\mathring{V}$$

$$= \frac{F^+(x)}{V} - \frac{F^-(x)}{V} - x_i \lambda(x)$$

$$= f^+(x,V) - f^-(x,V) - x_i \lambda(x)$$

where. $f^+(x,V) = \frac{F^+(x)}{V}$.

$$\begin{cases} \frac{dx_i}{dt} = f^+(x,V) - f^-(x,V) - x_i \lambda(x) \\ \frac{dV}{dt} = \lambda(x)\, V. \end{cases}$$

Lots of cool questions.

- How does dynamics of volume growth influence reactions inside?
- The fact that $A \propto V^{2/3}$?
- Decisions on growth arrest facing changing environments?
- Mechanics / ion homeostasis?
- Dynamic strategies on competition.
  e.g. storing up nutrients? etc...
- What would be an optimal strategy?
  How are cells implementing it?

A wide open frontier!