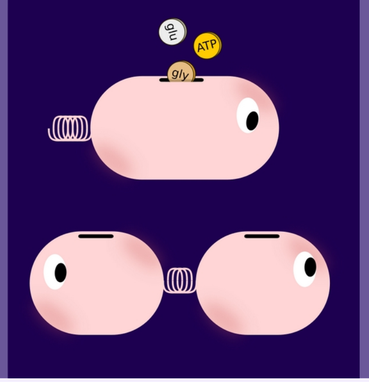
Economic Principles in Cell Physiology

Paris, July 4-6, 2022



Balanced Growth and Steady-state Metabolism

Experiments, Concepts, Principles, and Theory
Some of the fundaments, not their usage or open questions in the field

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Bruggeman, Planque, Molenaar, Teusink, Searching for principles of microbial physiology, FEMS Reviews, 44(6), 821-844 ,2020

You are the next generation, if you ask me, this generation should make the link with the experimentalists.

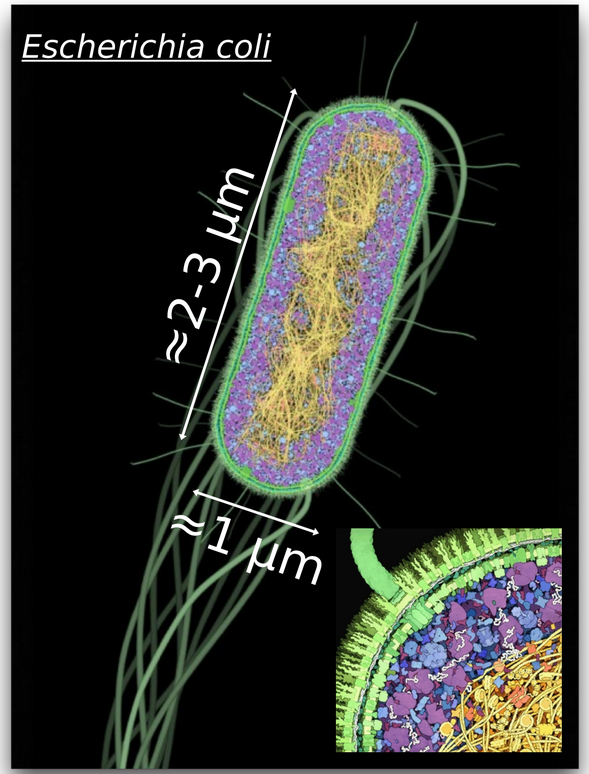
The challenge is no longer to only develop new theory, we need to test this.

We need to start to resemble the theoretical physics field more.

You also need to understand quantitative experimentation and microbial physiology.

This is possible now, and not 15 years ago when the resource-allocation “field” started.

Cell Composition and Dimensions



Two, single-copy molecules collide every 3 seconds. One molecule travels *E. coli*'s length in 0.2 seconds.

Property	Value
Volume (V)	~ 1fl =10^{-15} l
# proteins/cell	10^6
Protein diameter (R)	5 nm
Protein-protein distance	5 nm
Protein diffusion coefficient (D)	~ 5 μm^2/s
#amino acids/protein	~350
Elemental composition	$CH_{1.8}O_{0.5}N_{0.2}$

Time for two molecules to find each other (each occurring at 1 copy/cell):

$$\tau = \frac{V}{4\pi(R_A + R_B)(D_A + D_B)}$$

Time to travel distance *L*

$$t = \frac{L^2}{6D}$$

Growth Medium and Cell Composition

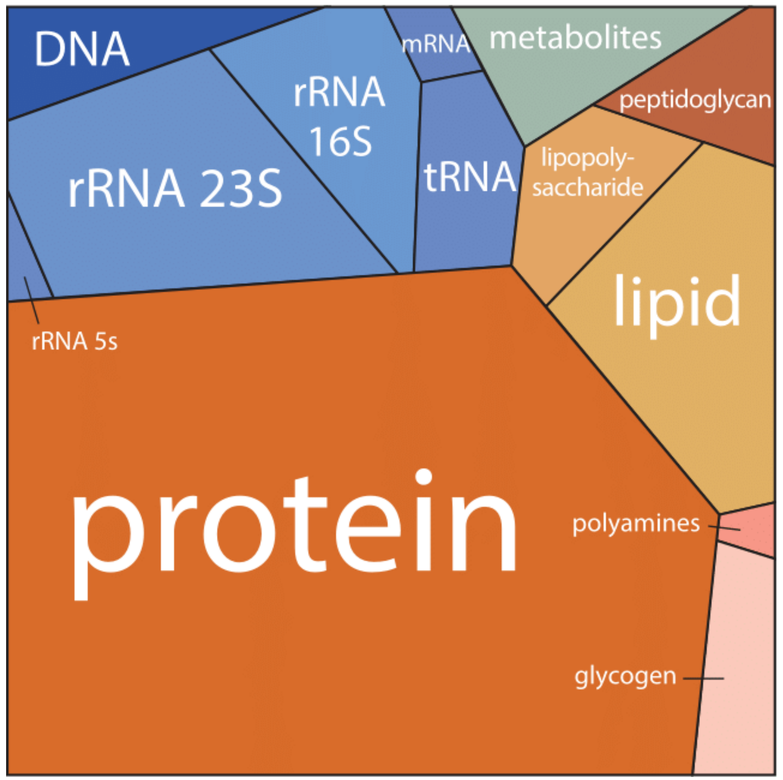
Example of a growth medium

1.	970 ml basic solution (anhydrous salts, autoclaved)	per 970 ml
	KH_2PO_4	13.0 g
	K_2HPO_4	10.0 g
	Na_2HPO_4	9.0 g
	K_2SO_4	2.4 g
	NH_4Cl	Varies (see text)
2.	10 ml trace element solution (sterile filtered)[a]	per 100 ml
	$FeSO_4$ ($7H_2O$)	0.60 g
	$CaCl_2$ ($2H_2O$)	0.60 g
	$MnCl_2$ ($4H_2O$)	0.12 g
	$CoCl_2$ ($6H_2O$)	0.08 g
	$ZnSO_4$($7H_2O$)	0.07 g
	$CuCl_2$ ($2H_2O$)	0.03 g
	H_3BO_3	2 mg
	$(NH_4)_6Mo_7O_{24}$ ($4H_2O$)	0.025 g
	EDTA	0.50 g
3.	10 ml 1 M $MgCl_2$ (sterile filtered)	
4.	6 ml thiamine (5 mg/ml, sterile filtered)[b]	
5.	1 ml ampicillin (100 mg/ml, sterile filtered)	
6.	D-Glucose (varies, see text for details)	
7.	10 µl 10% yeast extract (sterile filtered)[c]	

[a] The addition of the trace element solution ensures that the large number of metal ion containing enzymes in *E. coli* can function optimally.

[b] Thiamine (vitamin B_1) is provided since many commercial strains of *E. coli* are vitamin B_1 deficient.

[c] The addition of trace amounts of yeast extract seems to provide vitamins and cofactors that will allow for a reduced lag phase in the growth curve, although it is generally not essential.



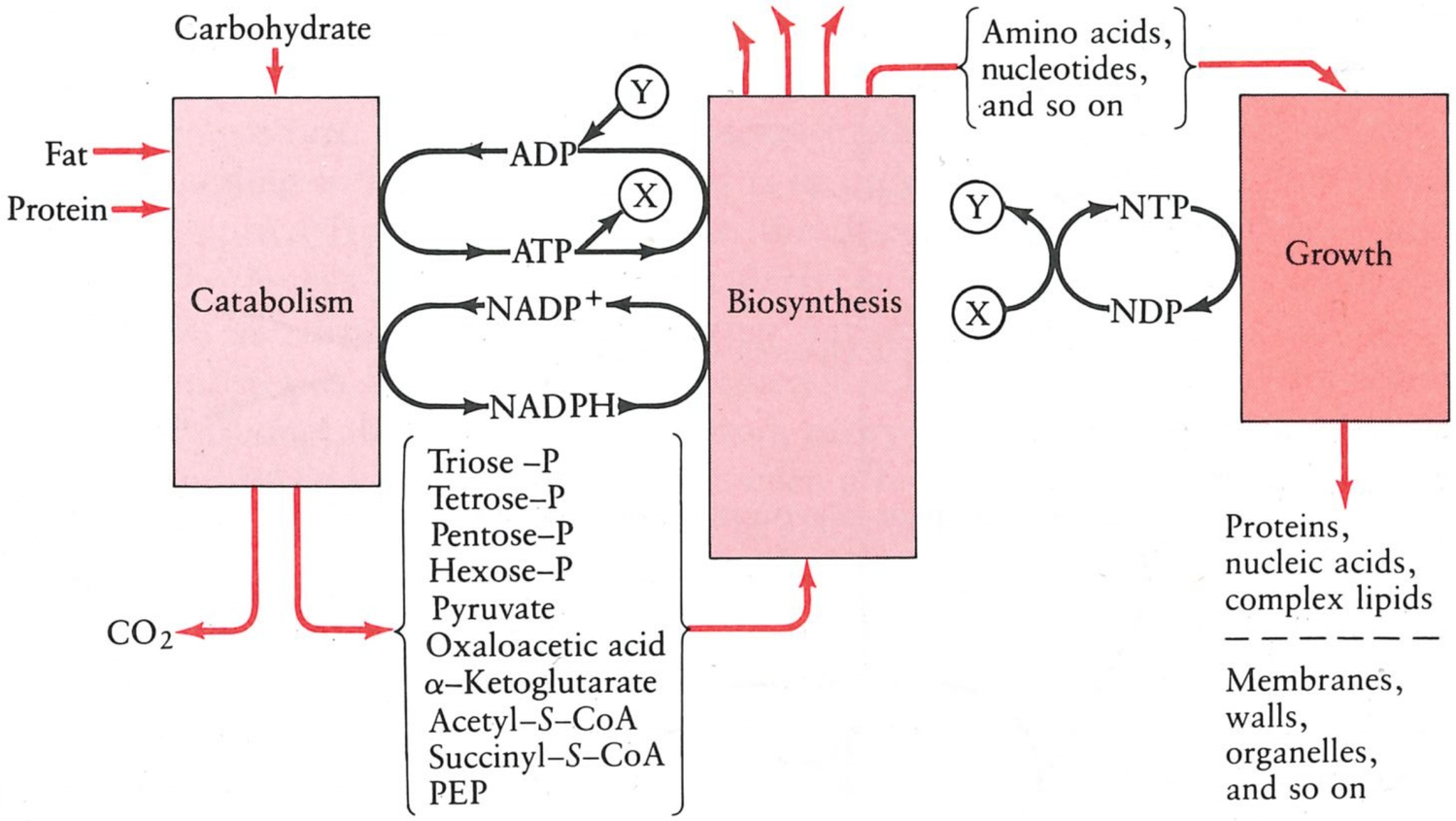
macromolecule	percentage of total dry weight	weight per cell (fg)	characteristic molecular weight (Da)	number of molecules per cell
protein	55	165	3×10^4	3,000,000
RNA	20	60		
23 S rRNA		32	1×10^6	20,000
16 S rRNA		16	5×10^5	20,000
5 S rRNA		1	4×10^4	20,000
transfer		9	2×10^4	200,000
messenger		2	1×10^6	1,400
DNA	3	9	3×10^9	2
lipid	9	27	800	20,000,000
lipopolysaccharide	3	9	8000	1,000,000
peptidoglycan	3	9	$(1000)_n$	1
glycogen	3	9	1×10^6	4,000
metabolites and cofactors pool	3	9		
inorganic ions	1	3		
total dry weight	100	300		
water (70% of cell)		700		
total cell weight		1000		

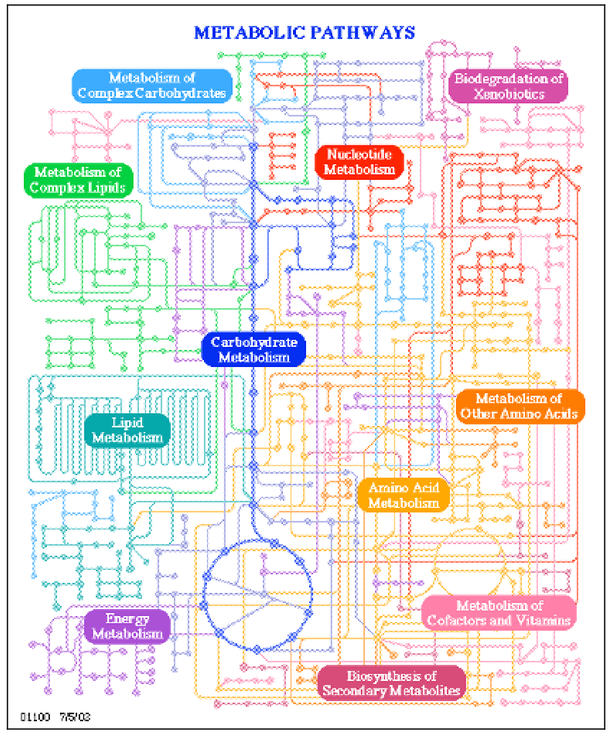
composition rules of thumb

- carbon atoms ~10^{10}
- 1 molecule per cell gives ~1 nM conc.
- ATP required to build and maintain cell over a cell cycle ~10^{10}
- glucose molecules needed per cell cycle ~3×10^9 (2/3 of carbons used for biomass and 1/3 used for ATP)

http://book.bionumbers.org/what-is-the-macromolecular-composition-of-the-cell/

Basic Organisation of Metabolism





Basic Organisation of Metabolism

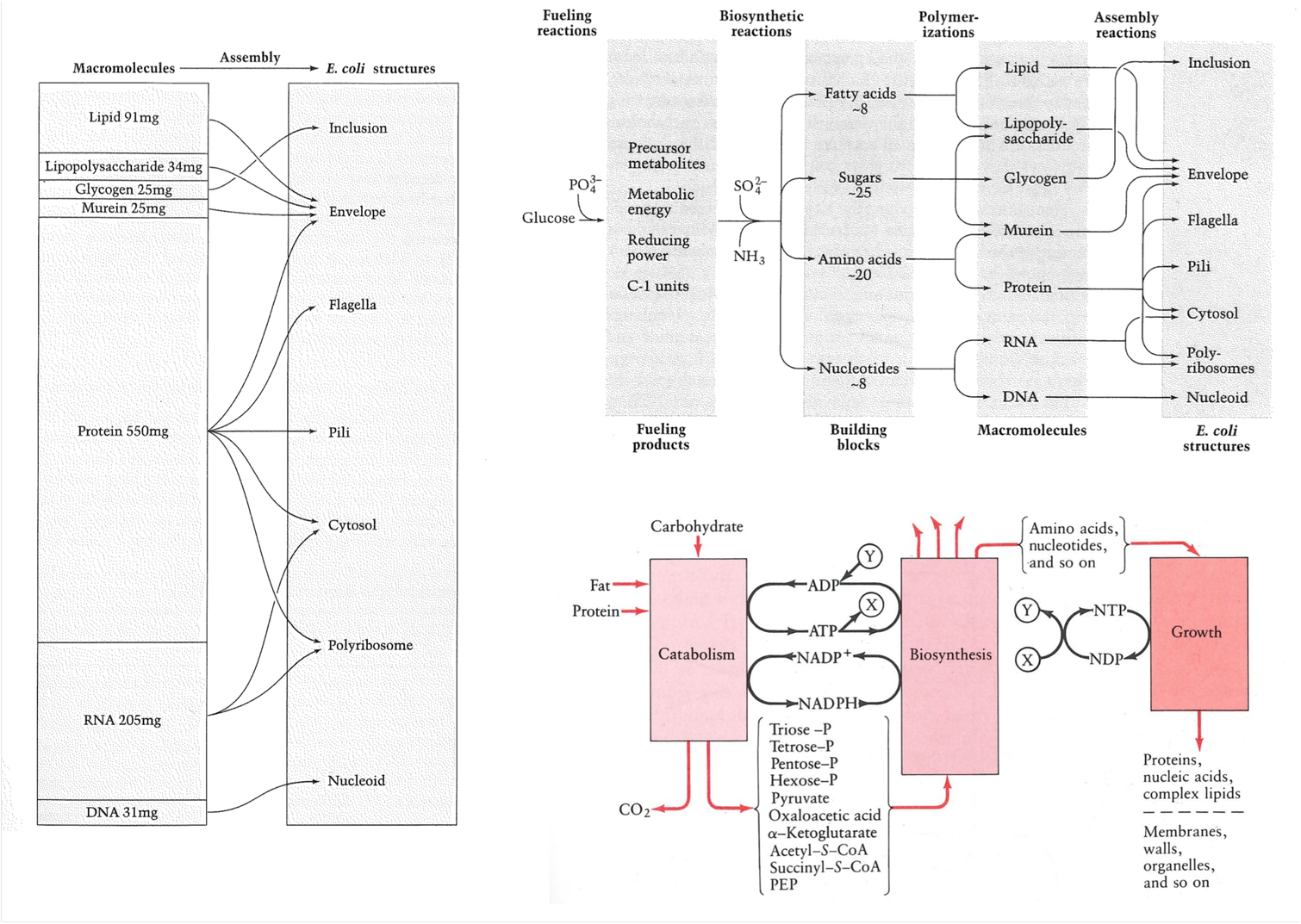
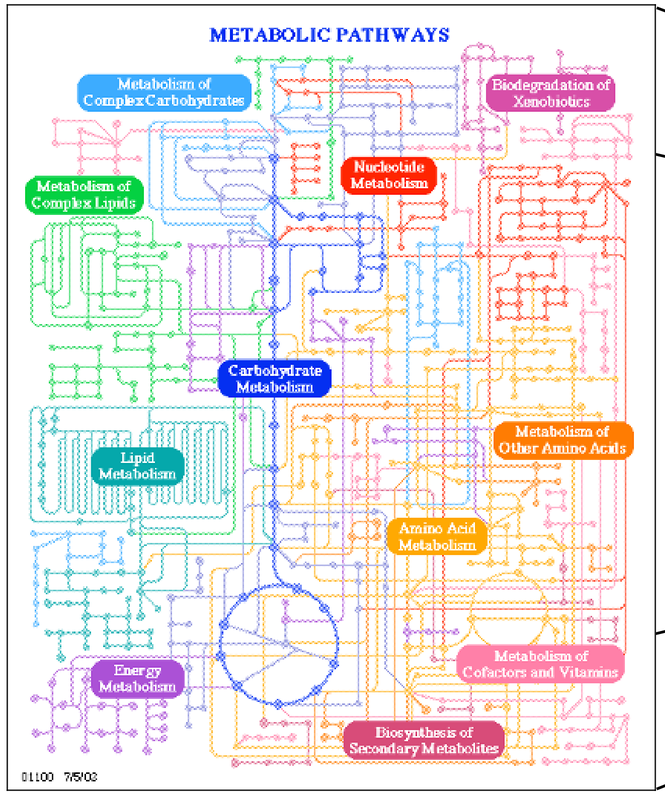
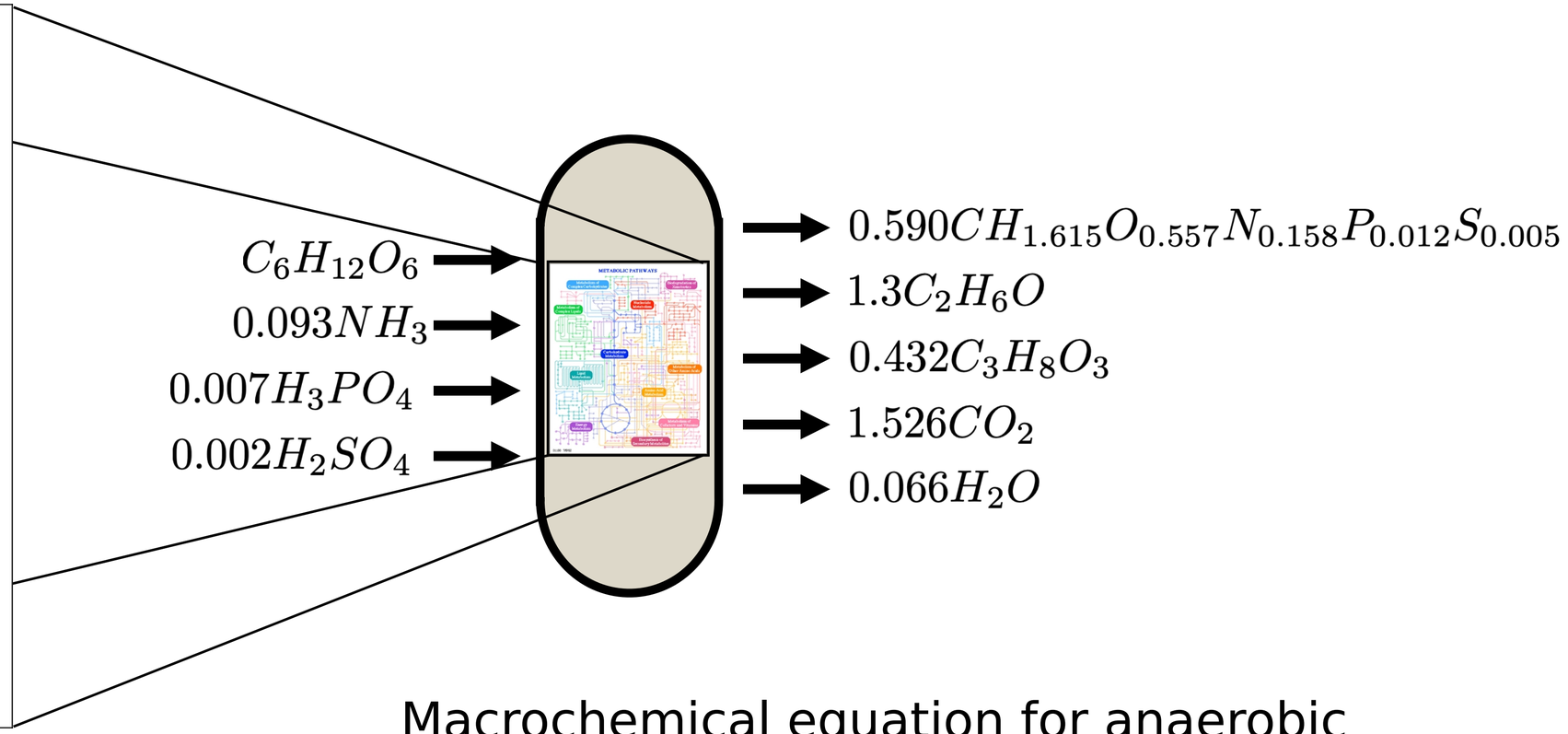


FIG. 1: Coarse-grained overviews of metabolism.

Nutrient Needs and Macrochemical Equation





- 1000 of genes encode metabolic proteins
- In rich media, about 300 proteins are minimally needed for growth
- Generally, about 600 proteins are minimally needed

Macrochemical equation for anaerobic growth of *S. cerevisiae* on glucose

(Trace Elements (vitamins, metals, etc.) are omitted!)
Coefficients are “yields”, 1 mol C6H12O6 gives 0.59 mol of cells

Understanding biomass yields from whole-cell stoichiometry

Macrochemical growth equation, Ω (FBA outcome of *E. coli* stoic model)

$$11.40glc + 25.2358O_2 + 0.964Pi + 0.25SO4 \rightarrow 1 \text{ gram biomass} + 9.2H + 53.7H_2O + 27.37CO_2$$

Stoichiometric coefficient are inverse yields.

$$Y_{X/S} = \frac{\mu}{q_s} = \frac{\frac{\text{gram cells}}{\text{gram cells}} \times \text{hr}}{\frac{\text{mol S}}{\text{gram cells} \times \text{hr}}} = \frac{\text{gram cells}}{\text{mol S}}$$

Can be calculated from stoichiometry only

Flux vector, e.g. an EFM

$$\Omega = \mathbf{m}^T_{1\times m}\mathbf{N}_{m\times r}\mathbf{q}_{r\times 1}$$

Vector of metabolite names

Stoich matrix with external metabolites

With FBA maximal yields can be computed

Heijnen and Kleerebezem, Bioenergetics of Microbial Growth, Encyclopedia of Industrial Biotechnology, 2010

Lag phase, Exponential Growth and Stationary Phase

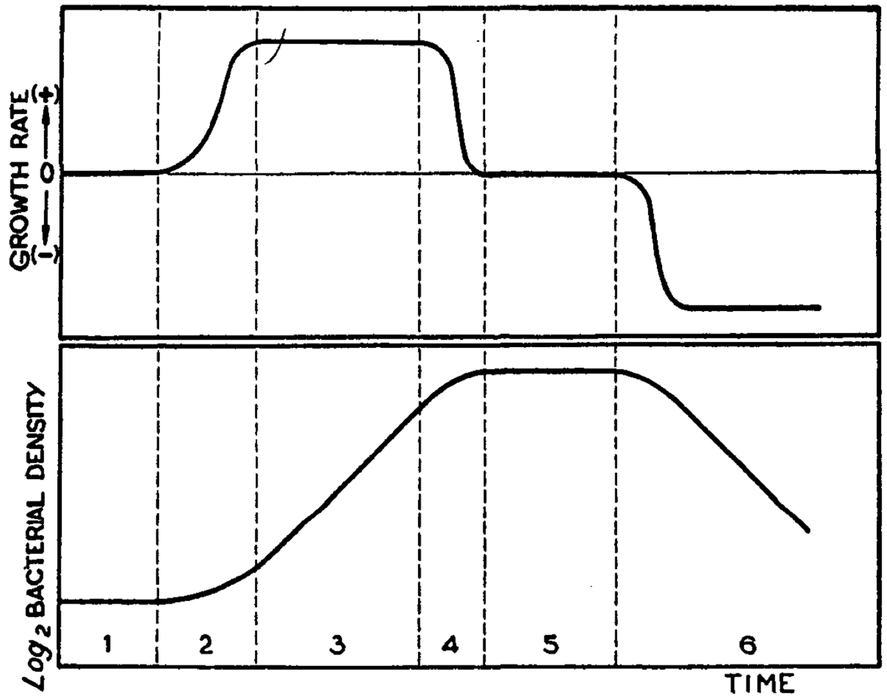


FIG. 1.—Phases of growth. Lower curve: log bacterial density. Upper curve: variations of growth rate. Vertical dotted lines mark the limits of phases. Figures refer to phases as defined in text (see p. 373).

1. lag phase: growth rate null;
2. acceleration phase: growth rate increases;
3. exponential phase: growth rate constant;
4. retardation phase: growth rate decreases;
5. stationary phase: growth rate null;
6. phase of decline: growth rate negative.

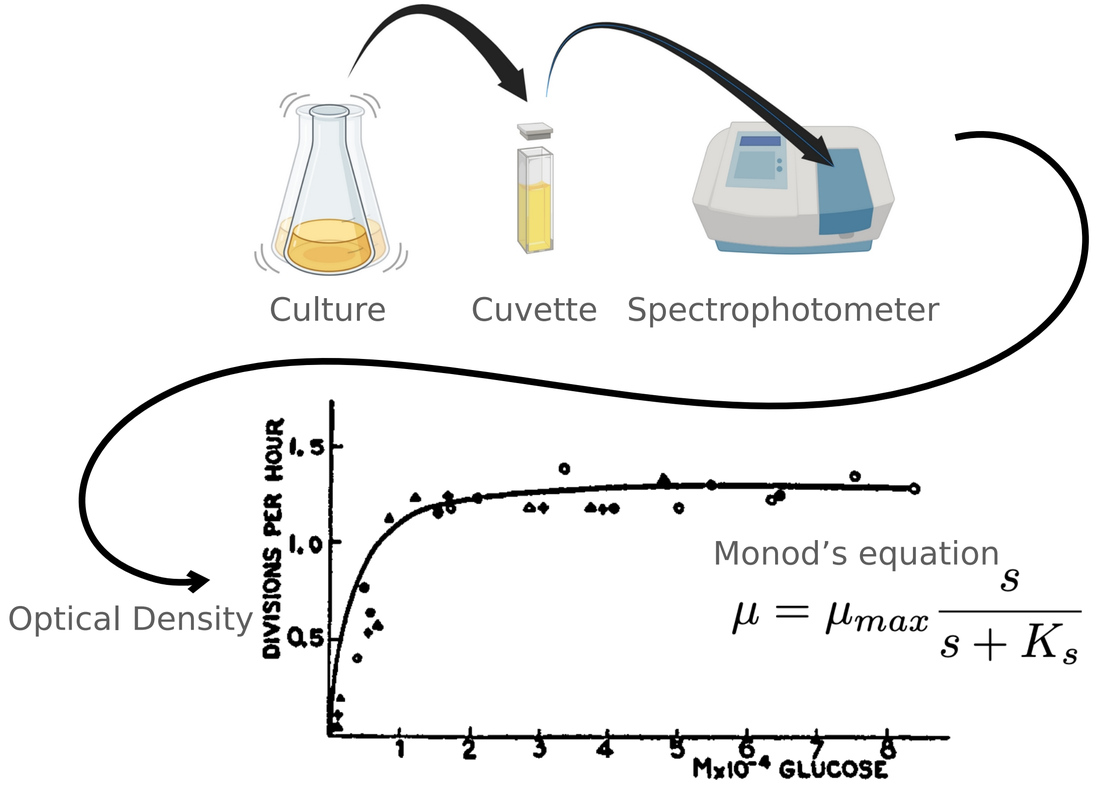
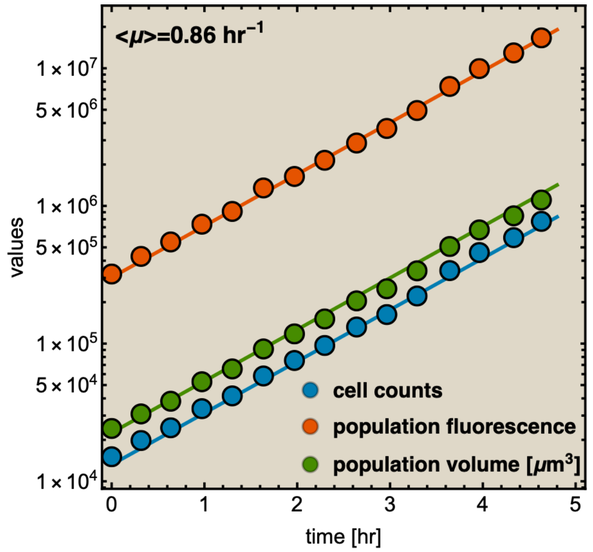


FIG. 4.—Growth rate of *E. coli* in synthetic medium as a function of glucose concentration. Solid line is drawn to equation (2) with $R_K = 1.35$ divisions per hour, and $C_1 = 0.22\ \text{M} \times 10^{-4}$ (11). Temperature 37° C.

J. Monod, The Growth of Bacterial Cultures, Annu Rev Microbial, 3:371-394, 1949

Balanced growth conditions

Applies to the average cell in a population, an abstract concept



Average cell properties:

Number of molecules of type *i* $n_i = \frac{N_i}{N_C}$

Cell volume $v = \frac{V}{N} = \sum_{\text{Molecules}} \hat{v}_i n_i$

Average cell properties are constant:

$$\frac{dn_i}{dt} = 0$$

$$\frac{dv}{dt} = 0$$

During Balanced Growth: All extrinsic properties rise exponentially in time.

$$\mu := \frac{1}{N_C}\frac{dN_C}{dt} = \frac{1}{V}\frac{dV}{dt} = \frac{1}{M}\frac{dM}{dt} = \frac{1}{N_i}\frac{dN_i}{dt}$$

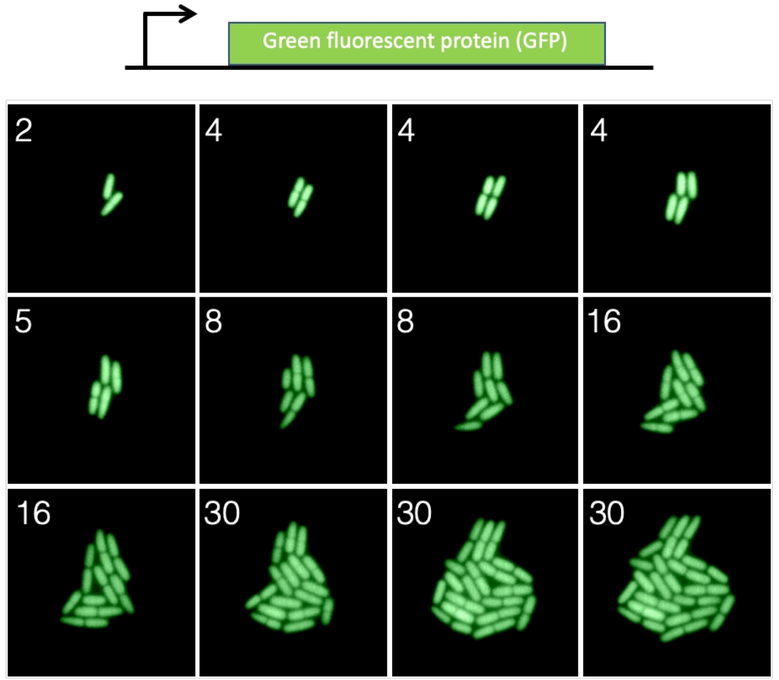
N_C: number of cells
V: culture volume
M: dry cell mass
N_i: number of molecule of type *i*

Note: $\frac{1}{x}\frac{dx}{dt} = \frac{d\ln x}{dt}, \quad \frac{d}{dt}\frac{y(t)}{x(t)} = \frac{y(t)}{x(t)}\left(\frac{d\ln y}{dt} - \frac{d\ln x}{dt}\right)$

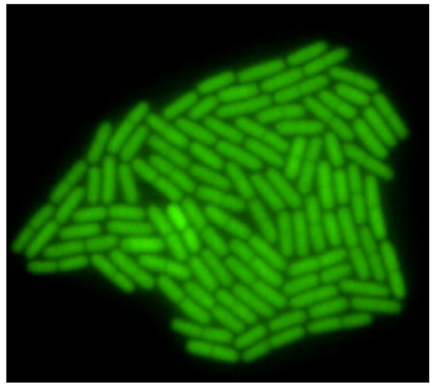
Extrinsic properties are proportional to mass (e.g. number cells, volume, number of molecules) and intrinsic properties are ratios of extrinsic properties (e.g. concentrations)

Frederick Neidhart, Constant obsession with dN/dt, J Bacteriol, 181(24): 7405-7408, 1999; Campbell, Synchronisation of cell division, Bacteriol Rev, 21, 263-272, 1957

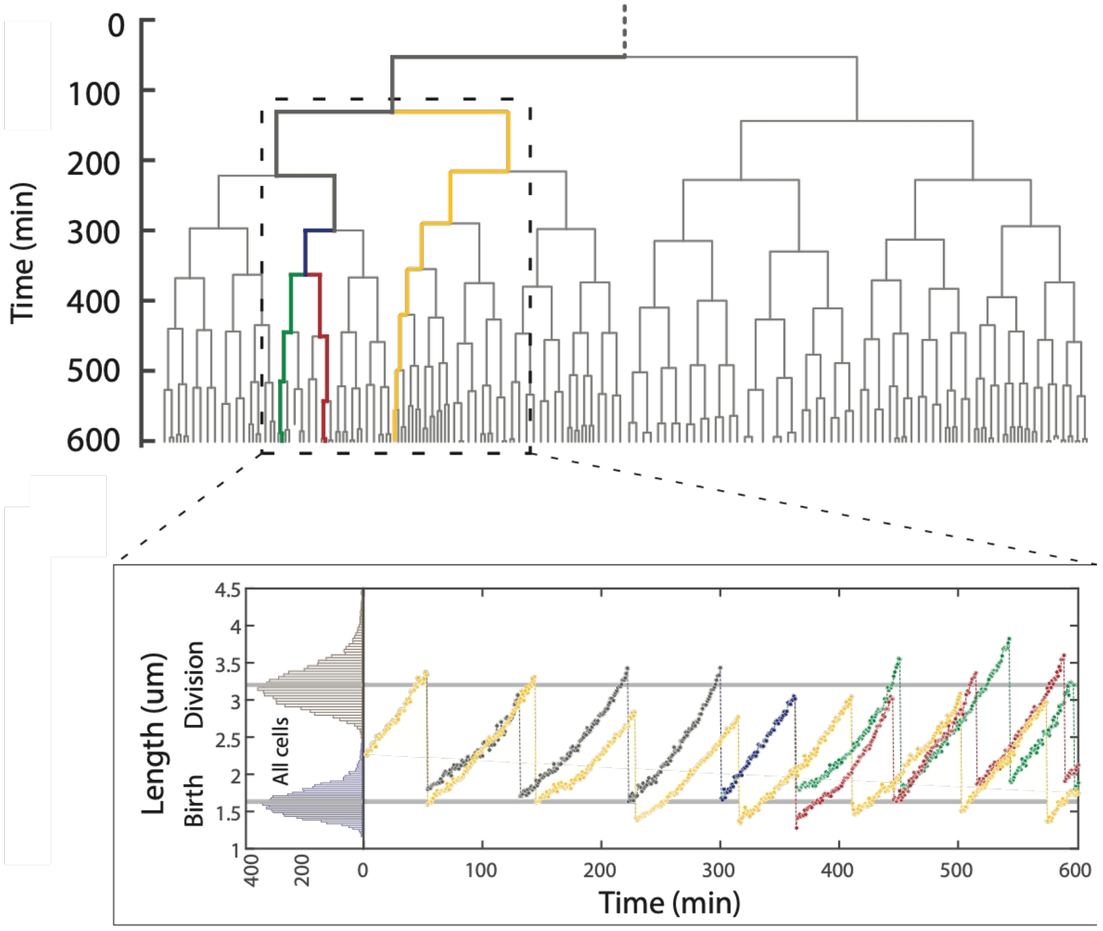
The average cell of this growth process



Growth of the bacterium *B. subtilis* on an agar pad, measured with fluorescence microscopy. The bacterium expresses a fluorescent protein.



Quantitative analysis from *E. coli* microcolony formation



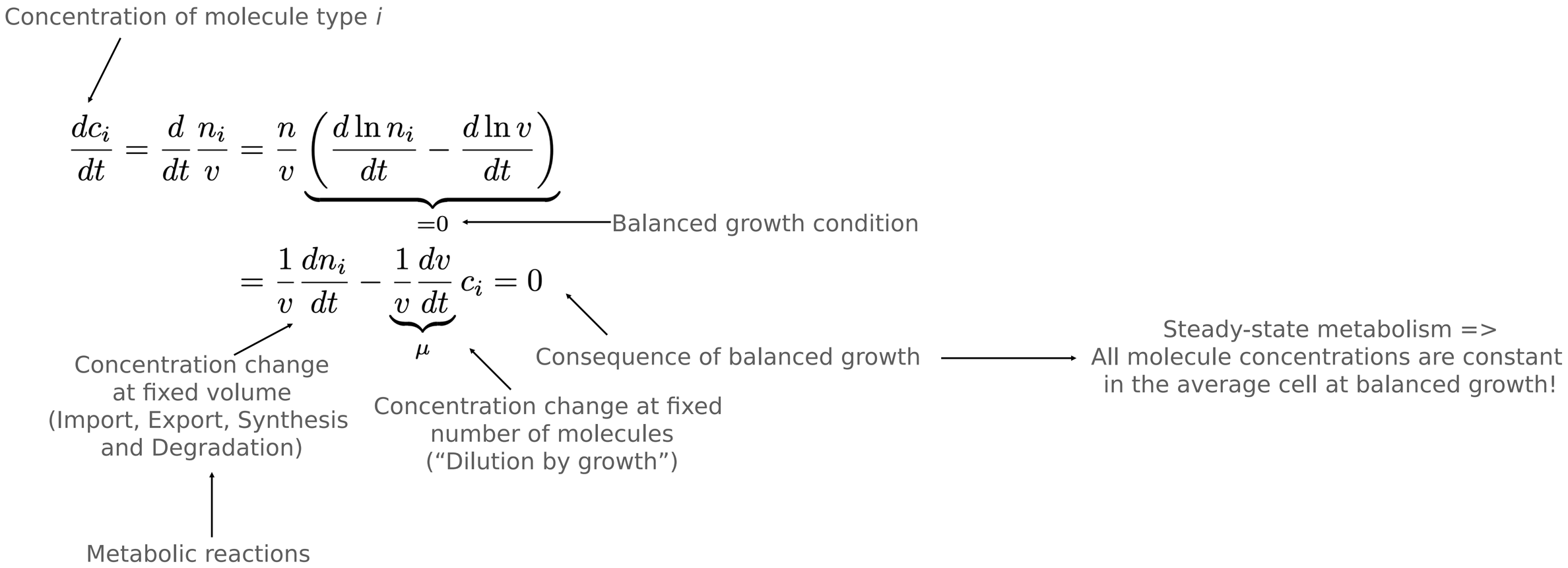
The average does not need to exist, can be an abstraction

Maybe a single cell does not visit the average cell state during its cell cycle

The average value of a dice is 3.5 after all.

Balanced growth studies are about the average cell

Which has a time-invariant, steady-state metabolism



So, at balanced growth, a steady-state metabolism

When concentration is constant then:

$$\frac{1}{v}\frac{dn_i}{dt} = \mu c_i$$

Net biosynthesis compensates for dilution

Reaction rate *j*

Stoichiometric matrix

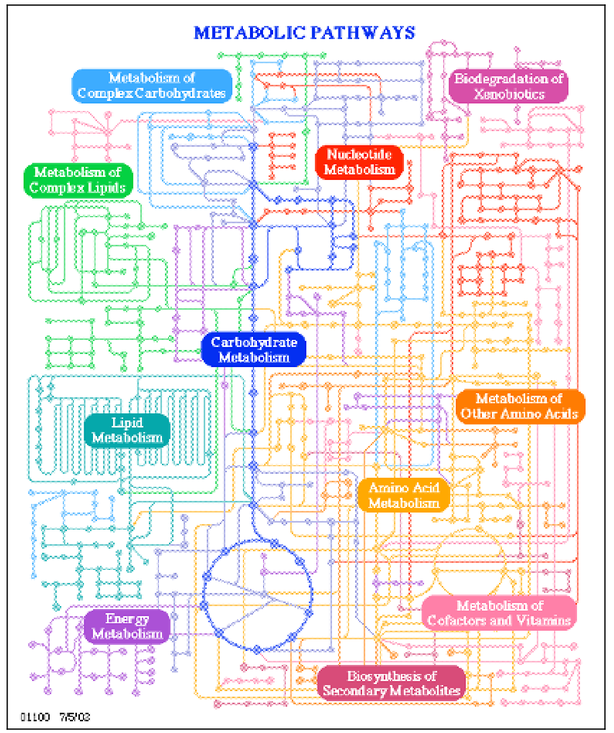
$$\frac{1}{v}\frac{dn_i}{dt} = \sum_j s_{ij} v_j(\mathbf{c};\mathbf{p}) \quad \Rightarrow \quad \frac{1}{v}\frac{d\mathbf{n}}{dt} = \mathbf{S}\mathbf{v}$$

Stoichiometric coefficient of metabolite *i* in reaction *j*

When the v's are much bigger than the growth rate μ, which applies for metabolism (but not for translation!)

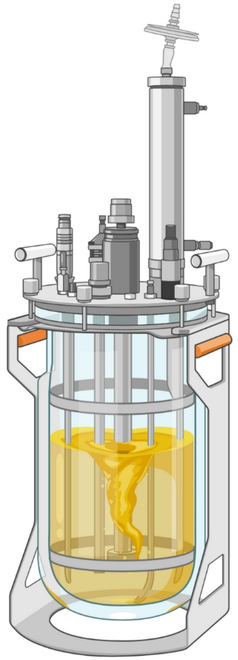
$$\sum_j s_{ij} v_j(\mathbf{c};\mathbf{p}) = 0, \ \mathbf{S}\mathbf{v} = \mathbf{0}$$

Stoichiometric matrix of metabolism



Cultivation methods for Balanced Growth

- Shake flask, Erlenmeyer, Greiner Tube
- Temperate constant, pH-buffered medium
- Excess nutrient conditions
- Uncontrolled, batch cultivation
- Transient balanced growth state
- Lag phase, exponential growth, stationary
- Growth until one nutrient depletes

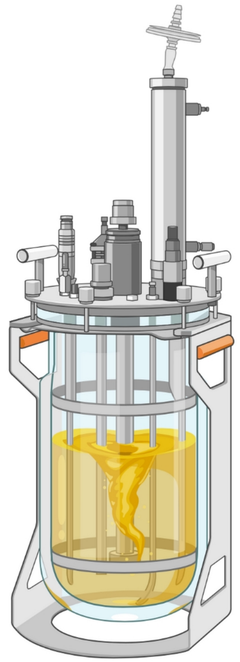


- Bioreactor
- pH, temperature controlled
- Inflow and outflow of medium and biomass (not necessarily)
- Steady-state is reached, at balanced growth conditions
- In case of chemostat, cells have to grow equally fast as medium is removed
- Growth rate = Dilution rate (D; F = flow rate, V = Volume, D=F/V), is set by experimentalist

Novick, Szilard, Description of the chemostat, Science, 112(2920):715-16, 1950

The chemostat

Also read up on the auxostat, turbidostat, and the retentostat



Biomass Growth Outflow

$$\frac{dX}{dt} = \mu(s)X - DX$$

Nutrient outflow

$$\frac{ds}{dt} = Ds_r - Ds - \frac{\mu(s)}{Y_{X/S}}X$$

Nutrient inflow

$$\mu(s) = \mu_{max}\frac{s}{K_s + s}$$

Monod's rate law

Nutrient consumption

Steady state

$$\mu(s) = D$$

$$s = \frac{DK_s}{\mu_{max} - D}$$

$$X = Y_{X/S}(s_r - s)$$

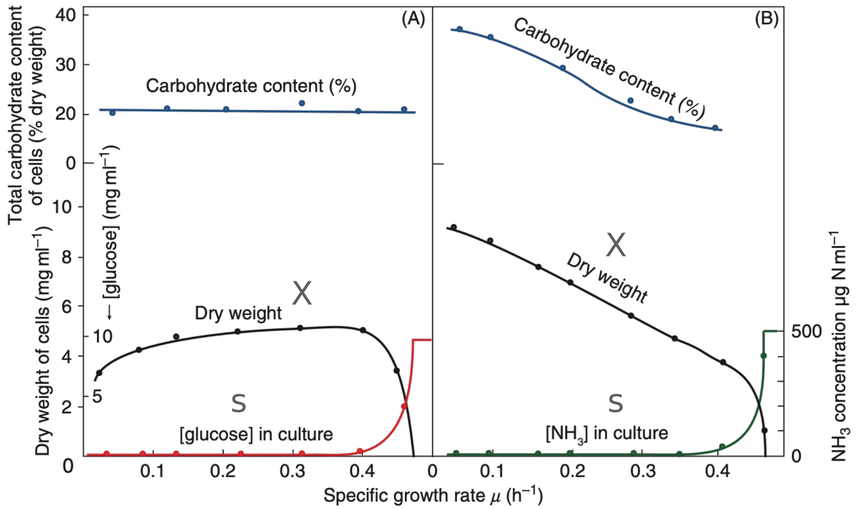


Fig. 5 Carbohydrate content of *Torula utilis* as a function of growth rate and limiting nutrient (unpublished data of Herbert and Tempest). The organism was grown in a continuous culture at a number of different growth rates in a glucose-NH_3-salts medium (A) with glucose as limiting nutrient, and (B) with NH_3 as limiting nutrient. Dry weight of cells in the culture and their total carbohydrate content (anthrone method), as well as steady-state levels of glucose and NH_3 in the culture, are plotted against growth rate. Reproduced from Herbert, D. (1961). The chemical composition of microorganism as a function of their environment. In: Meynell, G. G. and Gooder, H. (eds.) *Microbial reaction to environment: 11th symposium*, pp. 391–416. Reading: Society of General Microbiology: Cambridge University Press.

Experimental illustration

- pH and temperature controlled
- Flow rate F (liter/hour), volume V (liter), dilution rate D=F/V (hour)
- Inflow rate = Outflow rate
- Inflow of nutrients, outflow of culture medium, incl. cells
- Steady-state is possible then biomass, fluxes, and all concentrations are constant
- D = growth rate < maximal growth rate
- Medium is prepared in such a way that one nutrient becomes limited

Novick, Szilard, Description of the chemostat, Science, 112(2920):715-16, 1950
Kuenen, Continuous cultures (chemostats), Encyclopedia of Microbiology, 4th edition, 2019

Monod’s law, diauxic shifts, shifts in metabolism

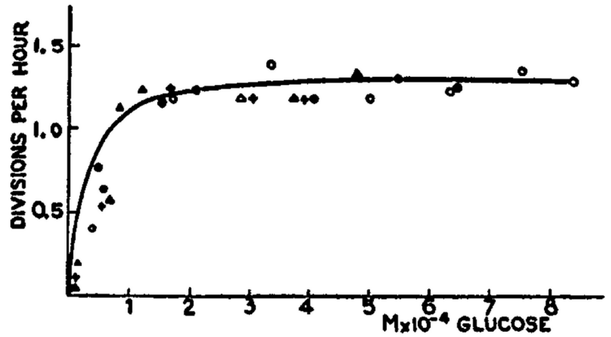


FIG. 4.—Growth rate of *E. coli* in synthetic medium as a function of glucose concentration. Solid line is drawn to equation (2) with $R_K = 1.35$ divisions per hour, and $C_1 = 0.22$ M $\times 10^{-4}$ (11). Temperature 37° C.

Growth rate depends on the concentration of the limiting nutrient (when no single single is limiting then maximal growth)

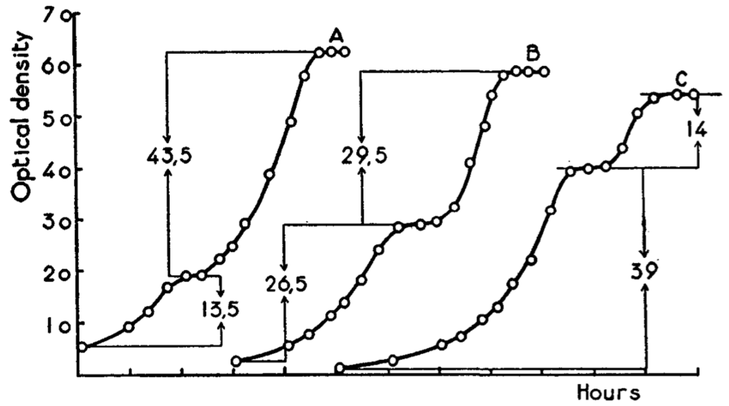
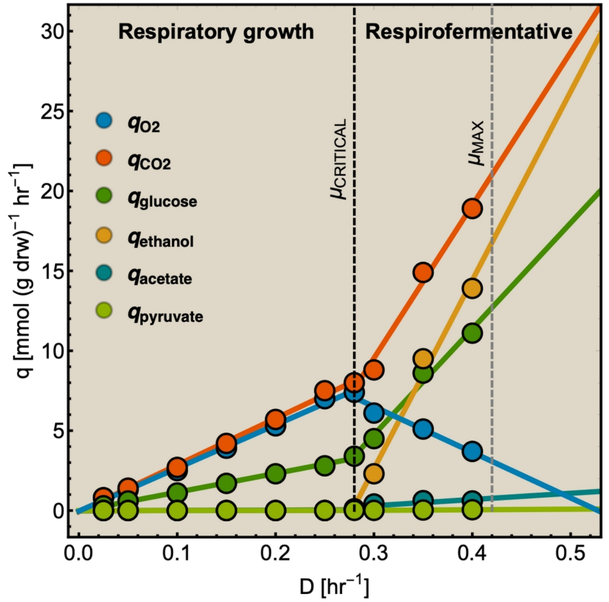


FIG. 9.—Diauxie. Growth of *E. coli* in synthetic medium with glucose+sorbitol as carbon source.
The figures between arrows indicate total growth corresponding to each cycle.
(*a*) Glucose 50 μg. per ml.; sorbitol 150 μg. per ml.
(*b*) Glucose 100 μg. per ml.; sorbitol 100 μg. per ml.
(*c*) Glucose 150 μg. per ml.; sorbitol 50 μg. per ml.
Total growth corresponding to first cycle is proportional to glucose concentration. Total growth of second cycle is proportional to sorbitol concentration (11).

Some carbon sources are consumed in a sequence, others are co-consumed.

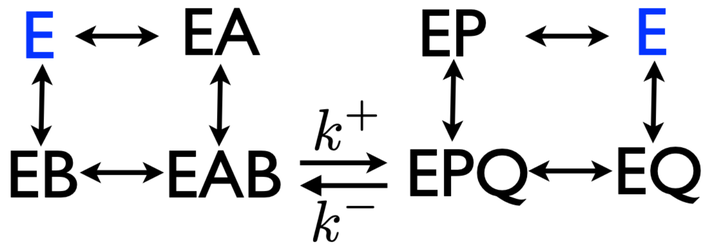


At constant conditions, the expressed metabolism can shift as function of growth rate

J. Monod, The Growth of Bacterial Cultures, Annu Rev Microbial, 3:371-394, 1949

Enzyme kinetics/catalysis

A



B

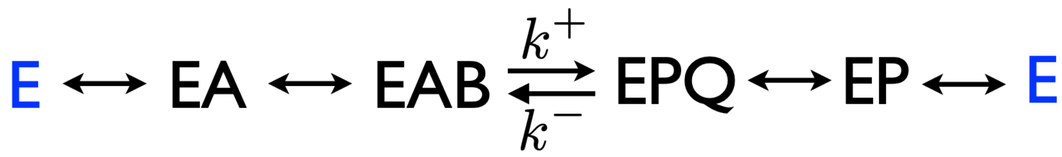
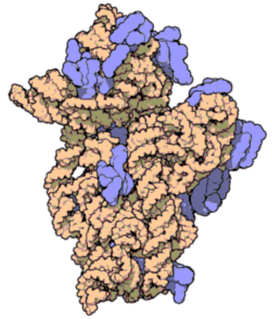


FIG. 3: **Two different enzyme mechanisms for the same reaction:** $A + B \rightleftharpoons P + Q$.

Reactions occurring in the active site



Rate equation

$$v = \frac{V^+ \frac{ab}{K_A K_B} - V^- \frac{pq}{K_P K_Q}}{1 + \frac{a}{K_A} + \frac{b}{K_B} + \frac{ab}{K_A K_B} + \frac{p}{K_P} + \frac{q}{K_Q} + \frac{pq}{K_P K_Q}}$$

$$v = \frac{V^+ \frac{ab}{K_A K_B} - V^- \frac{pq}{K_P K_Q}}{1 + \frac{a}{K_A} + \frac{ab}{K_A K_B} + \frac{p}{K_P} + \frac{pq}{K_P K_Q}},$$

From: Bruggeman, unpublished.
Segel, Enzyme Kinetics: Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems, Wiley, 1993

General rate law for enzyme kinetics/catalysis

Reaction: $s_1 + s_2 \rightleftarrows p_1 + p_2$

$$v = \underbrace{k_{cat}^{+} e}_{V_{max}^{+}} \underbrace{\frac{\frac{s_1 s_2}{K_{s_1} K_{s_2}}}{\left(1 + \frac{s_1}{K_{s_1}} + \frac{p_1}{K_{p,1}}\right)\left(1 + \frac{s_2}{K_{s,2}} + \frac{p_2}{K_{p_2}}\right)}}_{f^{+}(\mathbf{c};\mathbf{p})} \underbrace{\left(1 - \frac{p_1 p_2}{s_1 s_2 K_{eq}}\right)}_{1 - e^{\frac{\Delta\mu}{RT}}}$$

Maximal forward rate

Substrate saturation function

Deviation from thermodynamic equilibrium

General rate law

$$v = k e f^{+} \left(1 - e^{\frac{\Delta\mu}{RT}}\right)$$

Thermodynamic driving force (Gibbs free energy potential) $\Delta\mu$

Equilibrium constant $K_{eq} = e^{-\frac{\Delta\mu^{0'}}{RT}}$

Standard Gibbs free energy potential $\Delta\mu^{0'}$

A useful Growth Rate definition at Balanced Growth

In terms of the protein synthesis rate / cellular protein content

Earlier we concluded that (and that μ cannot be neglected metabolic rates are comparable)

$$\frac{dc_i}{dt} = \frac{1}{v}\frac{dn_i}{dt} - \mu c_i = 0$$

Now consider a protein,

$$\frac{dp_i}{dt} = \alpha_i k_r r f_r(\mathbf{c};\mathbf{p}) - \mu p_i$$

Ribosome fraction allocation to protein *i* α_i

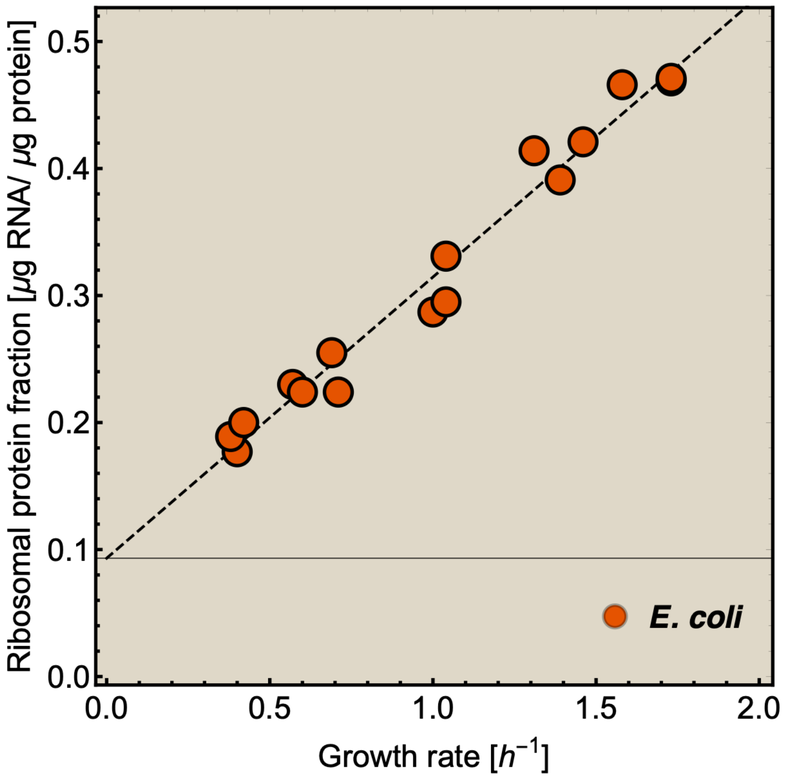
Now consider all proteins and balanced growth,

$$k_r r f_r(\mathbf{c};\mathbf{p}) - \mu \sum_i p_i = 0$$

$$\mu = k_r f_r \frac{r}{p_T} = \frac{\text{protein synthesis rate}}{\text{cellular protein content}}$$

Ribosomal protein fraction

Ribosome fraction as function of Growth Rate



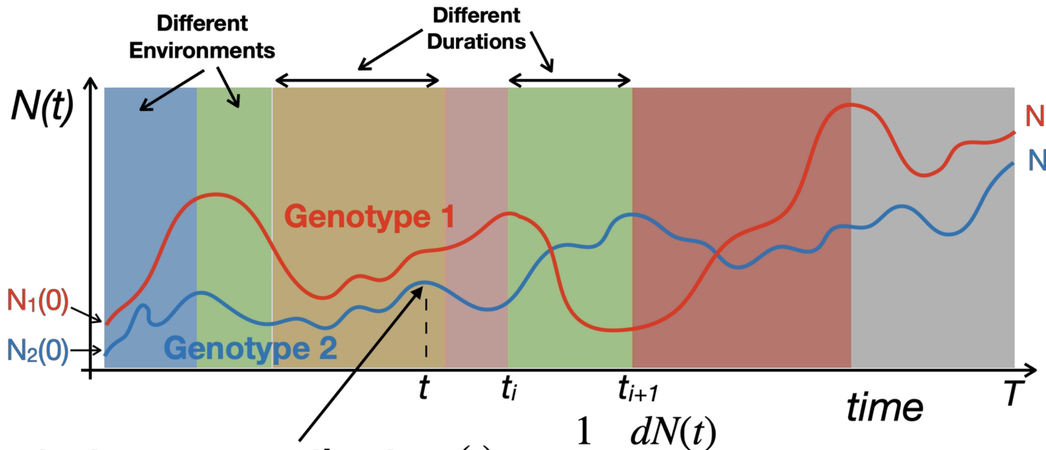
Finding agrees with theory:

$$\mu = k_r f_r \frac{r}{p_T} = k_r f_r \frac{r_T - r^i}{p_T} \quad \Rightarrow \quad \phi_r = \frac{\mu}{k_r f_r} + \phi_0$$

So, in this regime f_r is fixed.
(This is done by ppGpp's regulation of ribosome expression)

Scott, et al., Interdependence of cell growth and gene expression: origins and consequences, Science, 330(6007): 1099-102, 2010;
Schaechter, et al., Dependency of medium and temperature of cell size and chemical composition during balanced growth of Salmonella typhimurium, J Gen Microbiol, 19(3): 562-606, 1958

Instantaneous versus Long-term Growth Rate



Long-term fitness

Fitness $F = \frac{1}{T} \ln \frac{N(T)}{N(0)}$

Instantaneous growth rate $\mu(t) = \frac{1}{N(t)} \frac{dN(t)}{dt}$

Instantaneous/short-term fitness

$$F = \frac{1}{T} \ln \frac{N(T)}{N(0)} = \text{average growth rate} = \langle \mu \rangle$$

Instantaneous growth rate and metabolic enzyme kinetics

Identification of Optimisation Variables

Growth rate definition:

$$\mu = \frac{\text{protein synthesis rate}}{\text{cellular protein content}} = \frac{v_r}{p_T} = \frac{v_r}{\sum_{i=1}^{N} p_i} = \frac{v_r}{\sum_{i=1}^{N} \frac{v_i}{k_i f_i(\mathbf{c})}} = \frac{1}{\sum_{i=1}^{N} \frac{v_i / v_r}{k_i f_i(\mathbf{c})}}$$

Enzyme rate over translation rate
(If only independent flux then constants!)

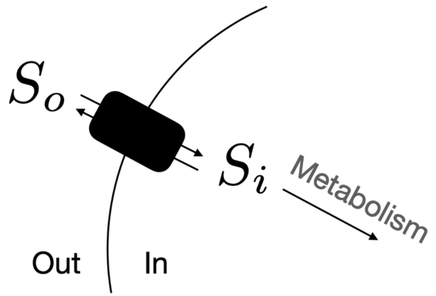
Enzyme saturation

Maximisation of growth rate
- saturation of enzymes
- N small
- High v_i/v_r

Enzyme Kinetic Constraints

Reactant concentrations
Diffusion constants of reactants
Organic chemistry in catalytic site
Physicochemical conditions in catalytic site
Temperature
Thermodynamic Driving Force
Equilibrium constant
Haldane relationship (relates equilibrium constant to enzyme-kinetic parameters)

Note on permeases:

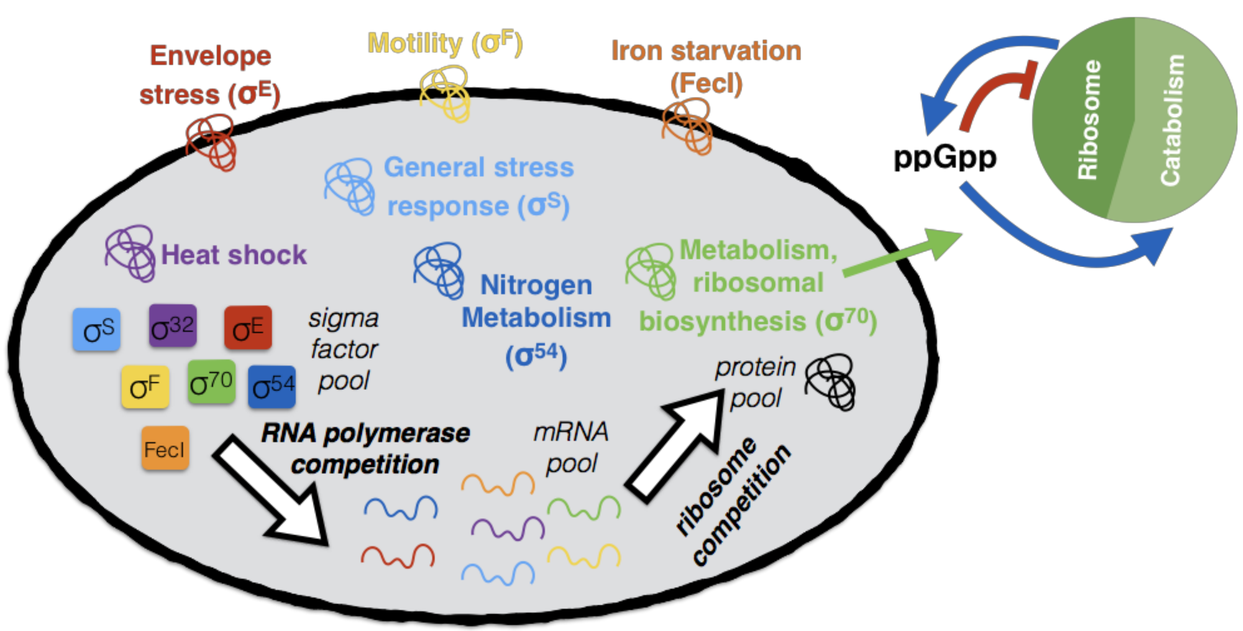


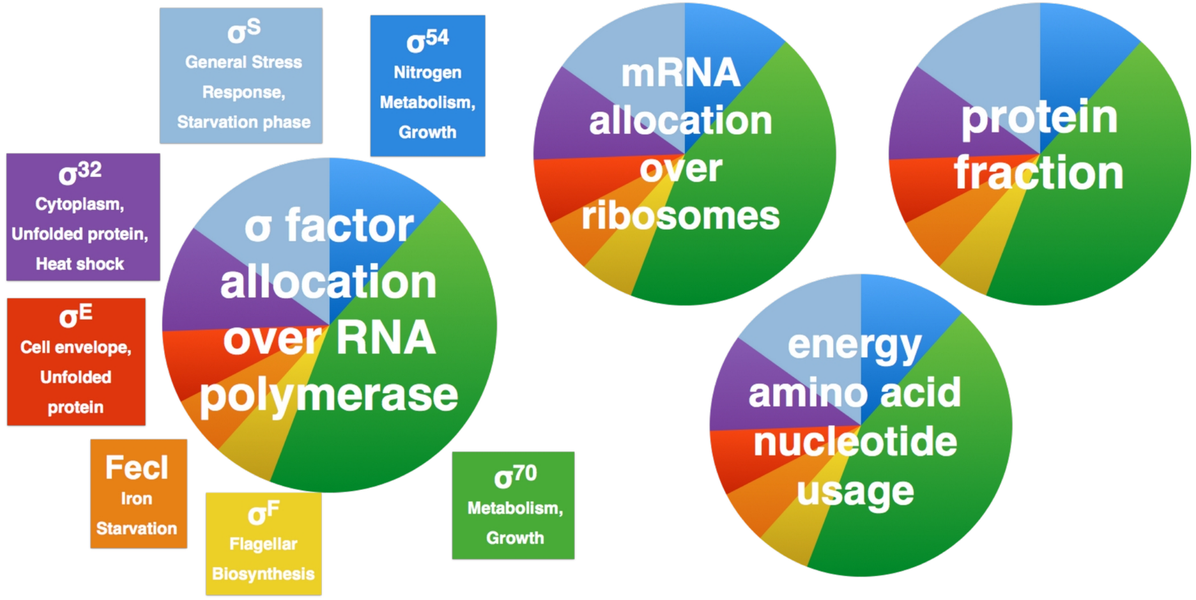
Nutrient uptake

Haldane's relationship (Biochemical law):

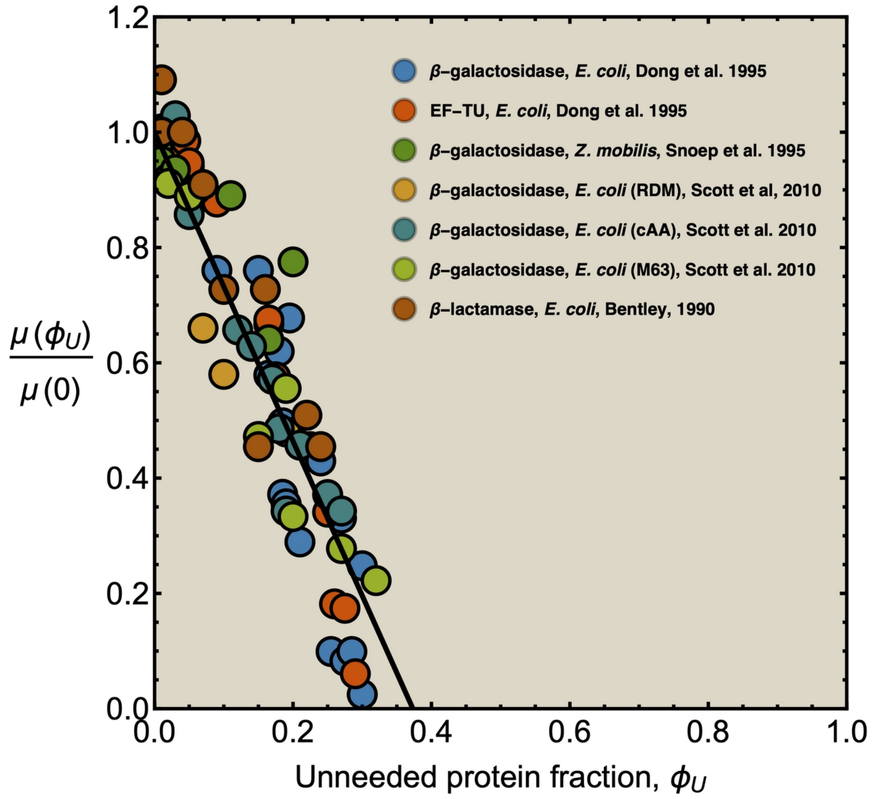
$$\text{Maximal Uptake Rate} \times \text{Affinity for } S_o = \text{Maximal Export Rate} \times \text{Affinity for } S_i$$

Protein expression constraints: finite biosynthetic resources



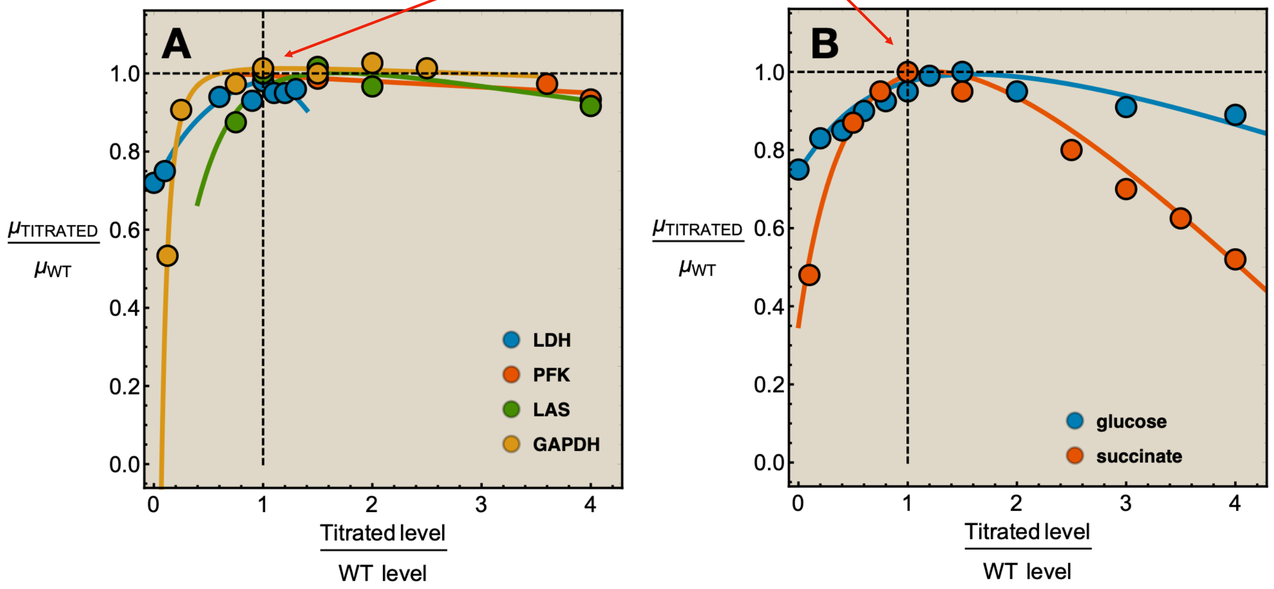


Growth rate vs (un)needed protein levels



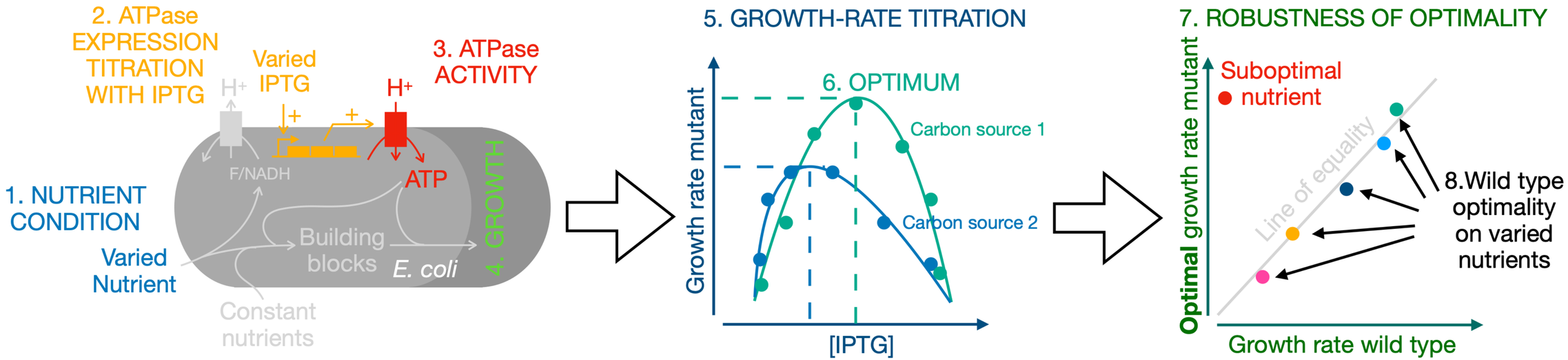
Consequence of
unneeded protein expression

Optimal protein expression!

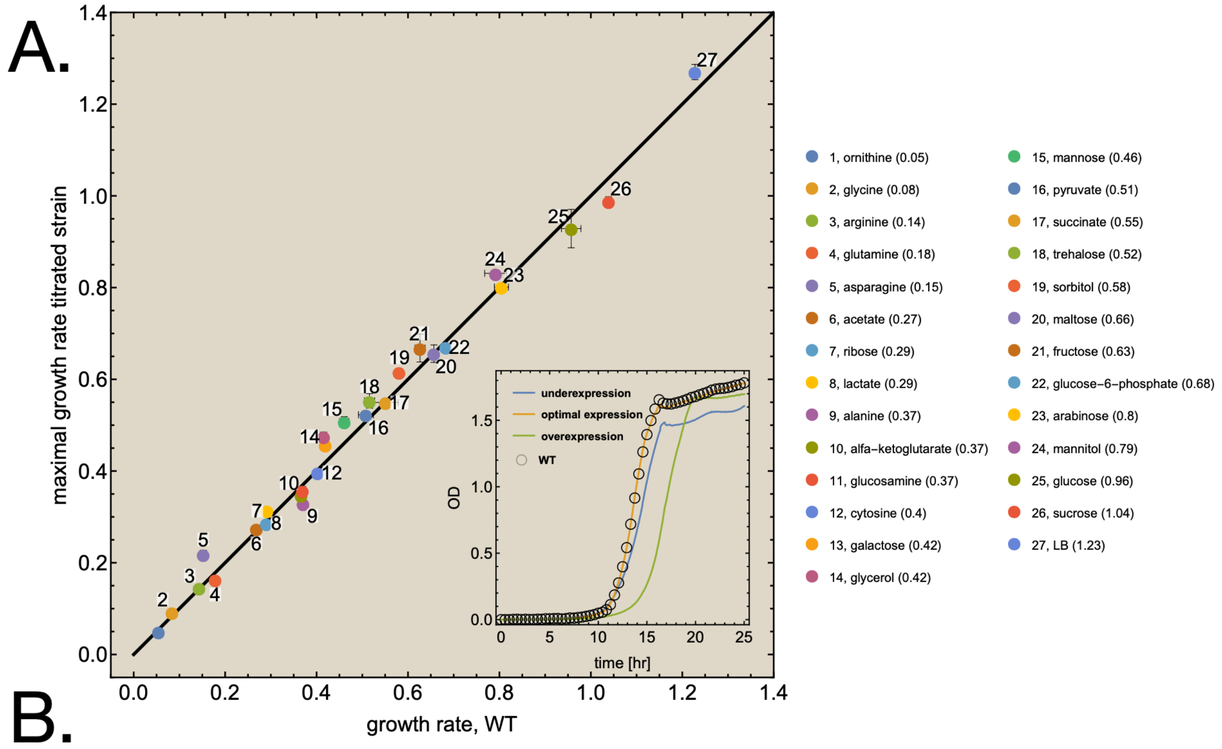


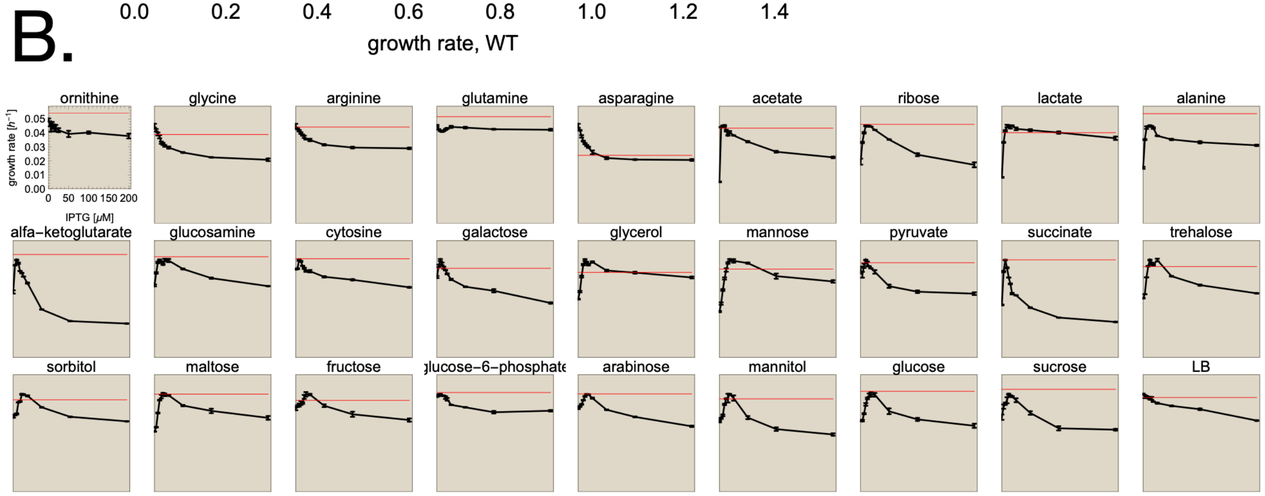
Consequence of
needed protein expression

Growth rate vs needed protein levels: experiments



Growth rate vs needed protein levels: H-ATPase in *E. coli*





- Within 5% of optimal protein expression across 27 conditions
- ATP synthesis rate is proportional to the growth rate $v_{ATP} \propto \mu$

Rabbers, Bruggeman, Escherichia coli robustly expresses ATP synthase at growth rate-maximizing concentrations, FEBS Jr, https://doi.org/10.1111/febs.16401, 2022

Metabolic Fluxes and Whole-cell Enzyme Content

Proportionality relation, scaling, growth vs stress trade off

$$e_T(e_1..e_N) = \sum_{i=1}^{N} e_i, \;\; \Rightarrow \;\; \lambda e_T(e_1..e_N) = e_T(\lambda e_1..\lambda e_N) = \sum_{i=1}^{N} \lambda e_i$$

$$v(e) = k \times e \times f(\mathbf{c}), \;\; \Rightarrow \;\; \lambda v(e) = v(\lambda e) = k \times \lambda e \times f(\mathbf{c})$$

$$\mathbf{Sv}(\lambda \mathbf{e}) = \mathbf{S}\lambda\mathbf{v}(\mathbf{e}) = \mathbf{0}$$

Thus, when all metabolic enzyme are multiplied by ƛ in concentration then all steady-state rates (fluxes) increase in concentration. And metabolite concentrations stay constant.

$$\mu = \frac{v_r}{e_T} = \frac{v_r(e_G)}{e_G + e_{NG}} = \frac{v_r(e_T - e_N G)}{e_G + e_{NG}} = \frac{v_r(e_T(1 - e_{NG}/e_T))}{e_G + e_{NG}} = \frac{v_r(e_T)}{e_G + e_{NG}} \left(1 - \frac{e_{NG}}{e_T}\right)$$

Non-growth associated protein content

Growth associated protein content

$$\mu \propto \frac{e_G}{e_T} \propto 1 - \frac{e_{NG}}{e_T}$$

Growth rate versus non-growth associated process (e.g. stress) trade off

Optimal Allocation of Resources

Growth rate definition:

$$\mu = \frac{\text{protein synthesis rate}}{\text{cellular protein content}} = \frac{v_r}{p_T} = \frac{v_r}{\sum_{i=1}^{N} p_i} = \frac{v_r}{\sum_{i=1}^{N} \frac{v_i}{k_i f_i(\mathbf{c})}} = \frac{1}{\sum_{i=1}^{N} \frac{v_i/v_r}{k_i f_i(\mathbf{c})}}$$

Enzyme rate over translation rate
(If only independent flux then constants!)

Enzyme saturation

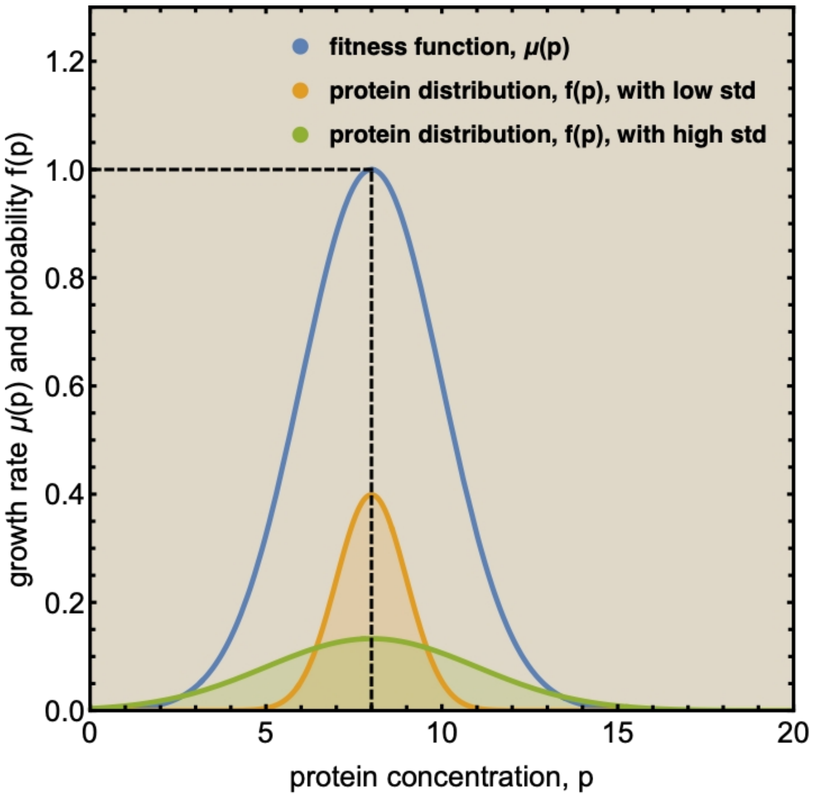
Maximisation of growth rate
- saturation of enzymes
- N small
- High v_i/v_r

Constraints
1. **Finite protein pool sizes**
2. **Fixed boundary concentrations (thermodynamic driving force)**
3. **Stoichiometry**
4. **General enzyme rate law**

1. Optimise metabolite concentrations (Meike's talk)
2. Calculate enzyme concentrations from optimal metabolite concentrations

Wortel, et al., Metabolic states with maximal specific rate carry flux through an elementary flux mode, FEBS Jr, https://doi.org/10.1111/febs.12722, 2014
Berkhout, et al., Gene network requirements for regulation of metabolic gene expression to a desired state, Scientific Reports, 3, 1417, 2013

Instantaneous vs long-term growth rate and bet-hedging



The net growth rate of a genotype is the average growth rate of all its phenotypes,

$$\mu = \int_0^\infty \underbrace{\mu(p)}\underbrace{f(p)dp} \approx \sum_p \mu(p) Prob(p)$$

Probability of protein concentration *p*

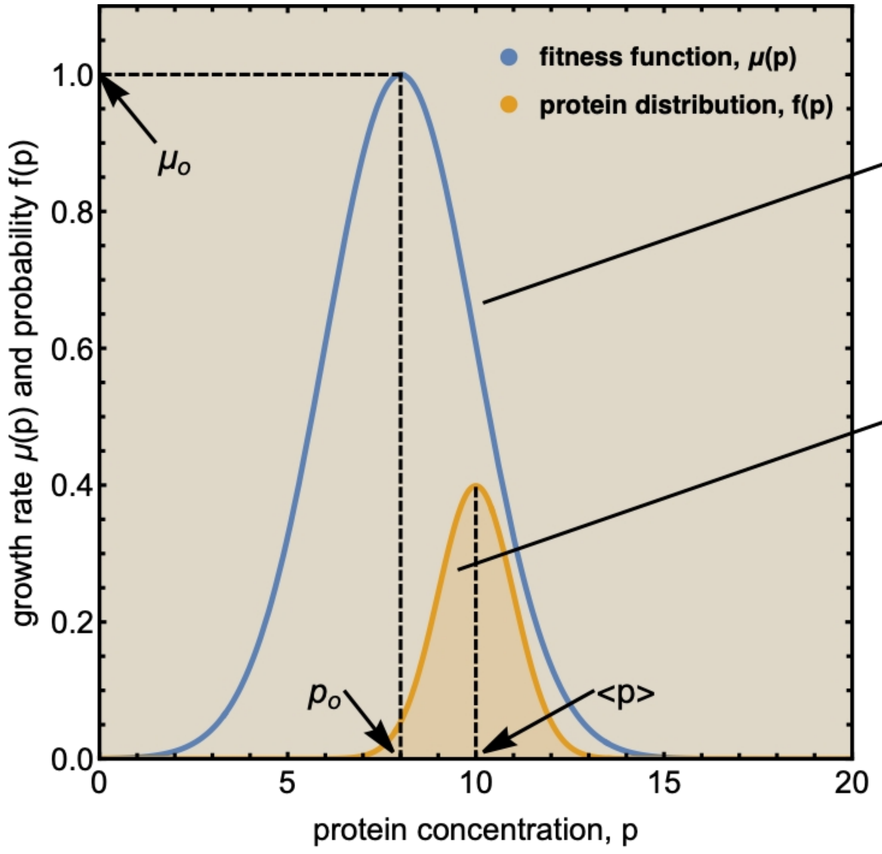
Growth rate of phenotype with concentration *p*

Thus, the growth rate of the orange genotype is higher than of the green genotype because the orange genotype displays higher growth rates with a higher probability such that its net growth rate is higher.

$$\mu_{green} = 0.55, \quad \mu_{orange} = 0.9 \quad (\mu < 1)$$

(Bruggeman, unpublished)

Instantaneous vs long-term growth rate and bet-hedging



$$\mu(p) = \mu_o e^{-\frac{(p-p_o)^2}{2w^2}}$$

$$p \sim \frac{e^{-\frac{(p-\langle p\rangle)^2}{2\sigma_p^2}}}{\sqrt{2\pi}\sigma_p} = f(p)$$

(*p* ~ means “p is distributed as”.)

$$\overline{\mu}(\langle p\rangle, \sigma_p) = \int_{-\infty}^{\infty} \mu(p) f(p) dp = \mu_o \frac{we^{-\frac{(p_o-\langle p\rangle)^2}{2(w^2+\sigma_p^2)}}}{\sqrt{w^2+\sigma_p^2}} = \mu_o \frac{e^{-\frac{(p_o-\langle p\rangle)^2}{2w^2\left(1+\frac{\sigma_p^2}{w^2}\right)}}}{\sqrt{1+\frac{\sigma_p^2}{w^2}}}$$

(Bruggeman, unpublished)

Instantaneous vs long-term growth rate and bet-hedging

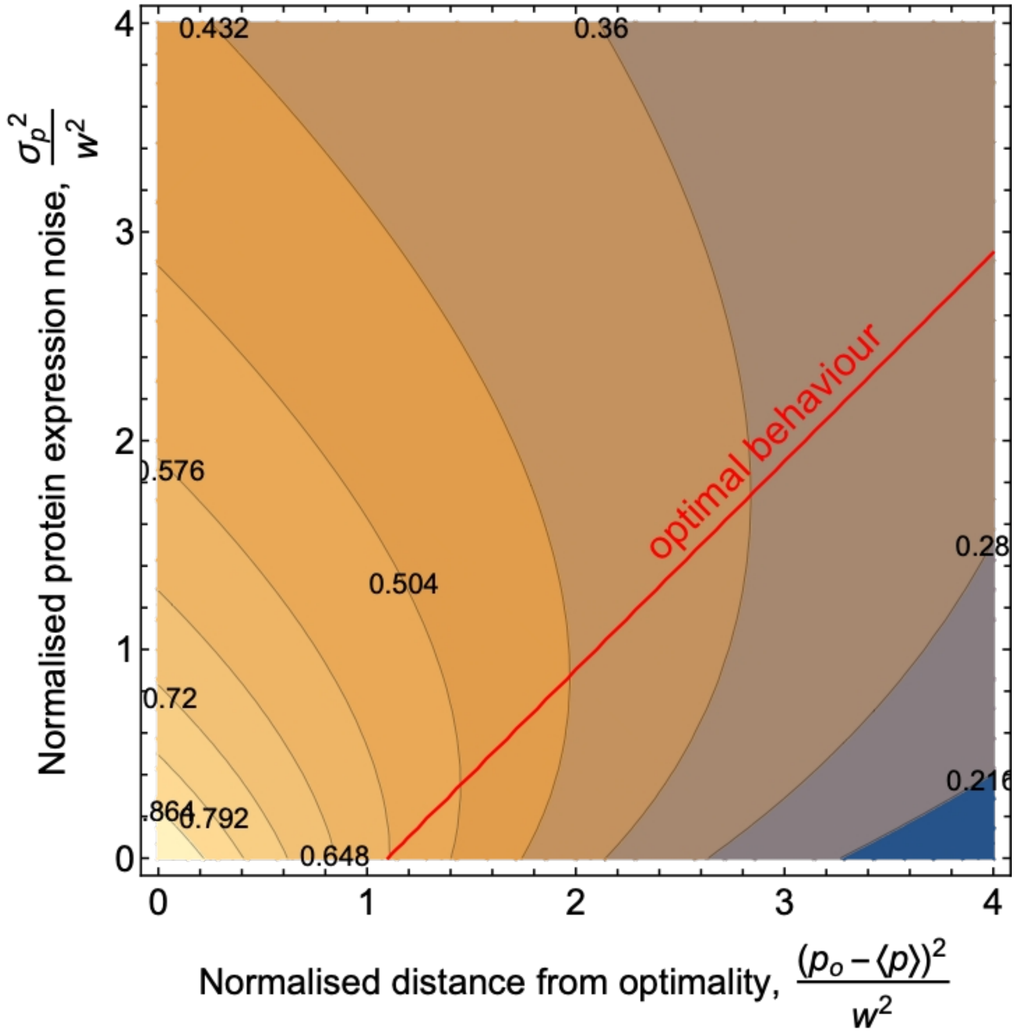
Now, we consider that
the environment changes,

$$p_o = \alpha s + \beta$$

$$\mu(p,s) = \mu_o e^{-\frac{(p-(\alpha s+\beta))^2}{2w^2}}$$

with *s* as the changing
environmental parameter.

Is it still true that noise in protein
concentration is fitness enhancing
when the mean expression concentration
is far from the optimal concentration?



(Bruggeman, unpublished)

Conclusions

- When conditions are constant, a population generally converges to a balanced growth state, which allows us to study the average cell properties quantitatively (concepts: originate from the 1950’s)
- During balanced growth, metabolism is at steady state.
- Growth by dilution can be neglected for fast changing metabolism, not for macromolecule synthesis
- Long-term fitness equals the average instantaneous growth rate over a time period
- Instantaneous growth rate can be shown to equal the protein synthesis rate per unit cellular protein
- The growth rate can be equated into the general rate law for enzyme kinetics, relating growth rate to metabolic activity and the expression strategy, allowing for optimisation and experimental predictions
- All of this considered deterministic processes, i.e. the average cell, in reality this is an abstraction and cell-to-cell heterogeneity plays a role.