Kinetic modeling of biochemical reaction networks

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INRIA Grenoble - Rhône-Alpes and IBIS

- IBIS: systems biology group at INRIA/Université Grenoble-Alpes
  - Analysis of bacterial regulatory networks by means of models and experiments
  - Biologists, computer scientists, mathematicians, physicists, …

http://team.inria.fr/ibis

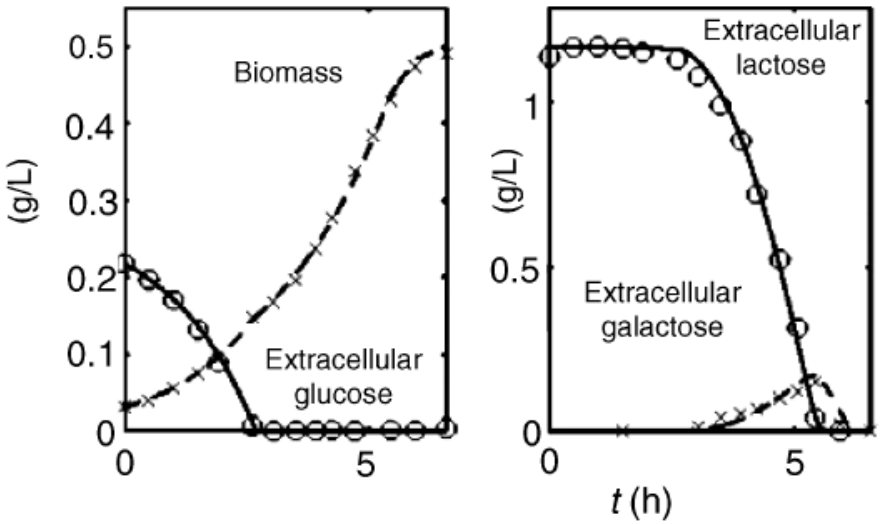
Overview

- Part 1. Systems biology and kinetic modeling
  - Introduction
  - **Kinetic modeling of biochemical reaction networks**
- Part 2. Metabolic network modeling
  - **Kinetic modeling of metabolism**
  - Metabolic control analysis (MCA)
  - Flux balance analysis (FBA)
  - Practical on flux balance analysis (COBRA)
- Part 3. Gene regulatory network modeling
- Part 4. Models and data

Bacterial growth and metabolism

- Bacterial metabolism is **flexible**, allowing cells to grow on different carbon sources

  Preferential utilisation: **diauxic growth** on glucose and lactose

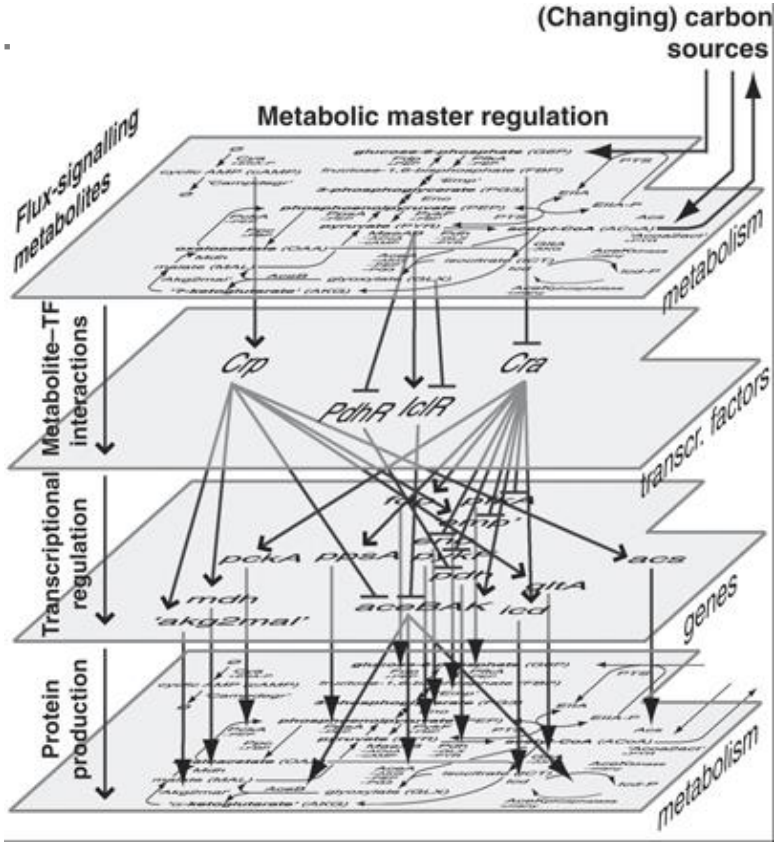


Bettenbrock *et al.* (2006), *J. Biol. Chem.*, 281(5):2578-84

- Adaptation of bacterial physiology to different carbon sources

Coordination of adaptative responses

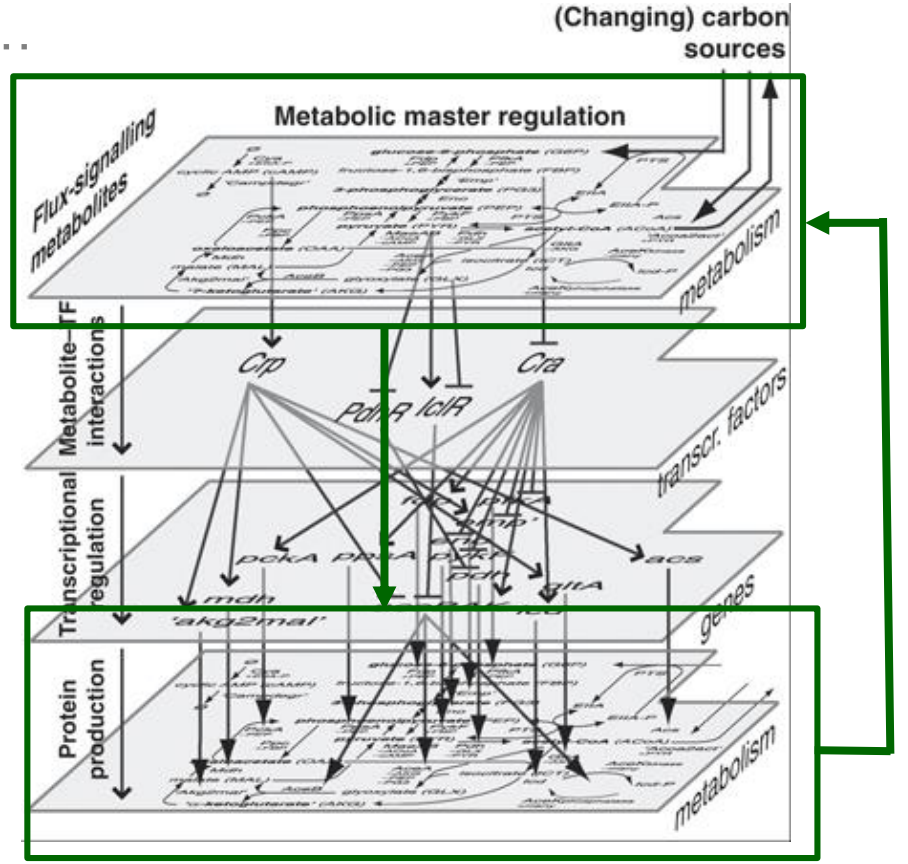
- Coordination of adaptative responses of bacterial cell achieved by **large and complex regulatory networks**
  - Variety of molecular mechanisms…
  - … operating on different time-scales…



Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

Coordination of adaptative responses

- Coordination of adaptative responses of bacterial cell achieved by **large and complex regulatory networks**
  - Variety of molecular mechanisms…
  - … operating on different time-scales…
  - … involving numerous feedback loops across levels



Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

No global view on network functioning

- Coordination of adaptative responses of bacterial cell achieved by large and complex regulatory networks
- Abundant knowledge on biochemical mechanisms underlying interactions between network components
- Accumulation of data on multi-level response of network to external perturbations

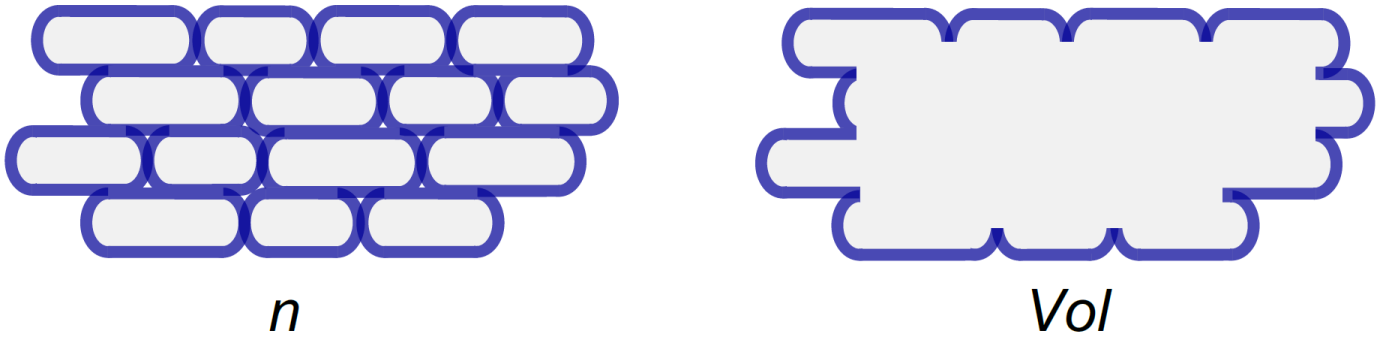
  Metabolic fluxes and cellular concentrations of metabolites, enzymes, transcription factors, signalling molecules, …
- However, **global view on functioning of entire network** is difficult to achieve and largely absent today
- Use of models to analyse and predict dynamical behaviour of system

  Emergence of new discipline: **systems biology**

Growth of microbial populations

- Growth can be considered on the level of number of **individual cells** or **aggregated volume of growing population** Vol [L]

  Segregated *vs* nonsegregated models



de Jong *et al.* (2017), *J. Roy. Soc. Interface*, 14(136):20170502

Growth of microbial populations

- Ordinary differential equation (ODE) model of the growth of a population of microorganisms

  Growth rate $\mu\ [\mathrm{h}^{-1}]$

$$\dot{Vol} = \mu \cdot Vol$$

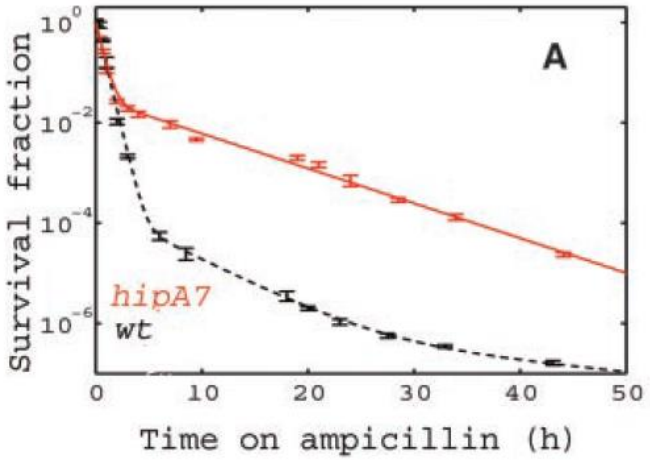
- Solution of growth model for constant growth rate $\mu = \mu^*$

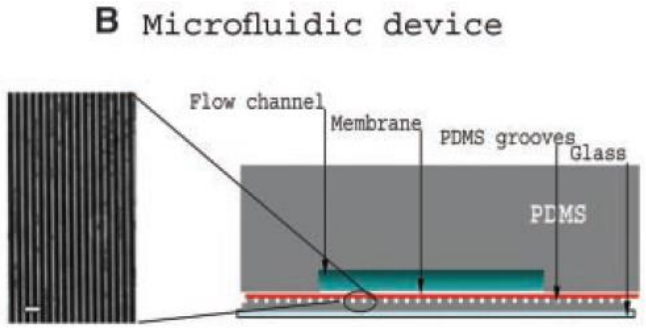
$$Vol(t) = Vol(0) \cdot e^{\mu^* \cdot t}$$

  Doubling time $t_{1/2} = \ln 2 / \mu^*$

Growth of microbial populations

- If all cells have same growth rate, segregated and nonsegregated models are identical
- But: growth rate of cells in population may be heterogeneous
  - Bacterial persistence after antibiotics treatment





Balaban *et al.* (2004), *Science*, 305(5690):1622-5

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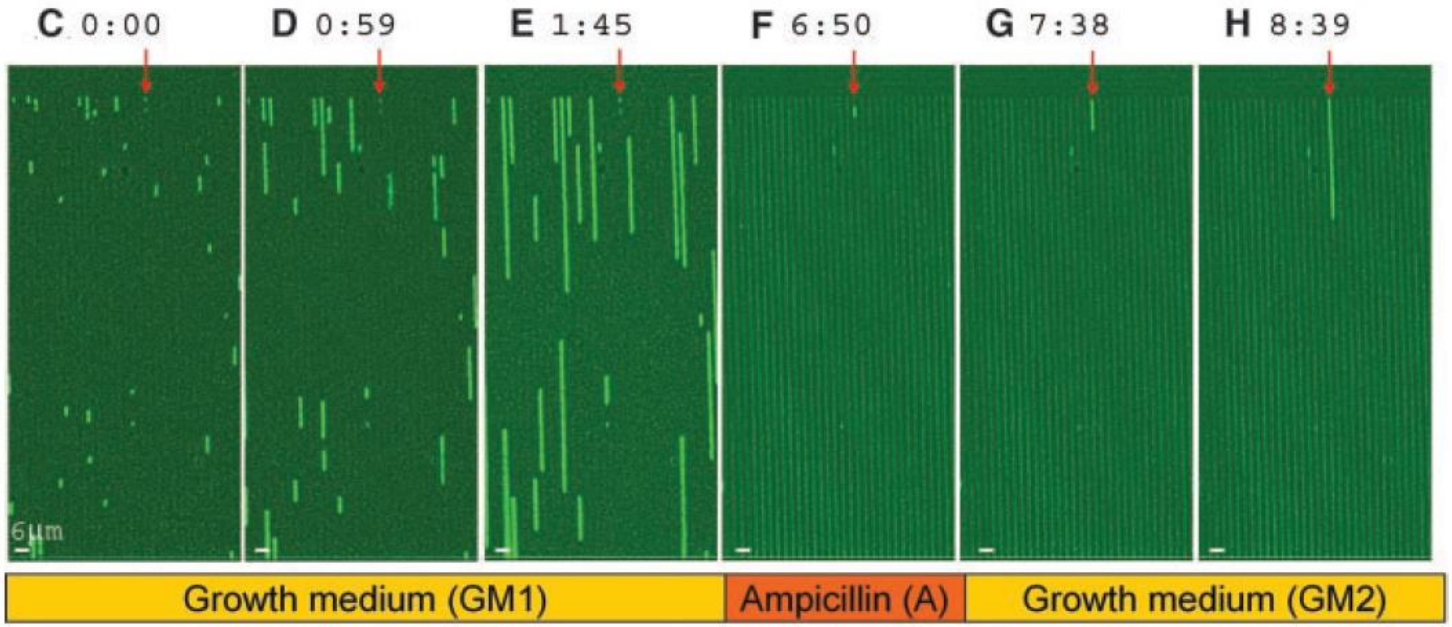

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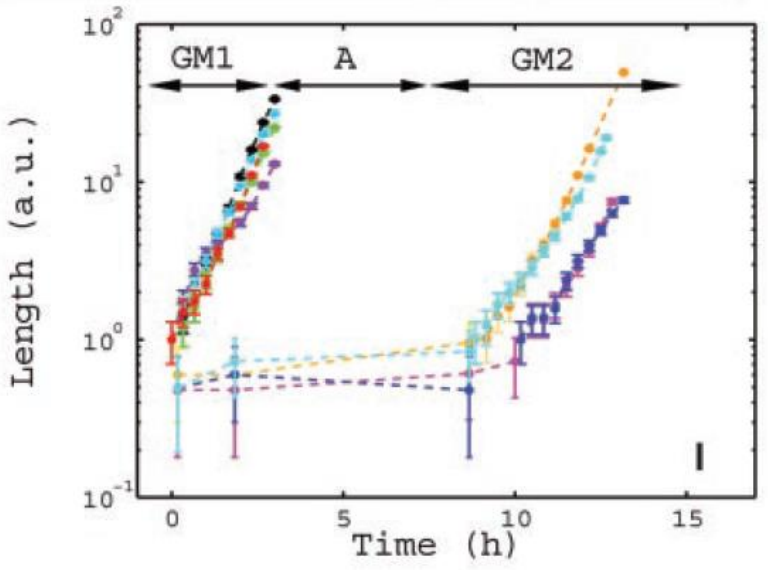
Growth of microbial populations

- If all cells have same growth rate, segregated and nonsegregated models are identical
- But: growth rate of cells in population may be heterogeneous
  - Bacterial persistence after antibiotics treatment
  - Persister cellss have lower growth rate before antibiotics treatment

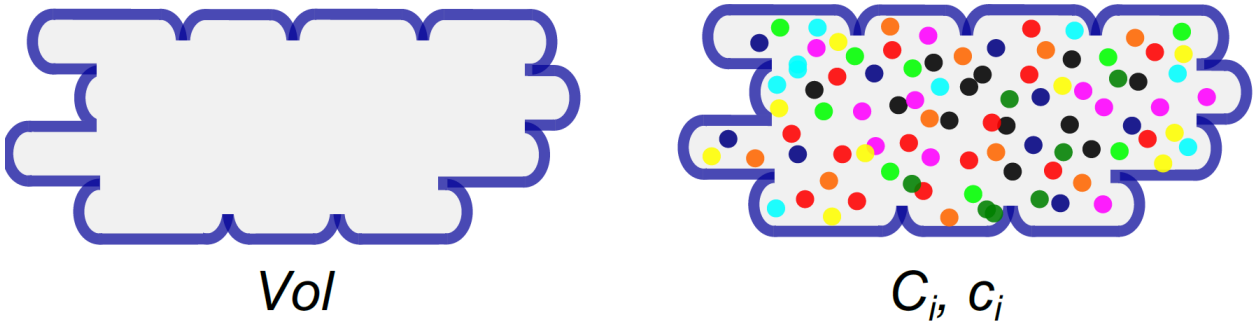


Balaban *et al.* (2004), *Science*, 305(5690):1622-5

Volume and macromolecular contents

- Growth is fueled by biochemical processes
- Models describing molecular constituents and biochemical reactions in which they are involved

  Structured *vs* unstructured models



Volume and macromolecular contents

- Basic assumption: volume proportional to biomass (total mass of molecular constituents in cells)

  Dry mass of constituent *i* C_i $[\mathrm{g}]$

  Biomass B $[\mathrm{g}]$

$$Vol \sim \sum_i C_i = B$$

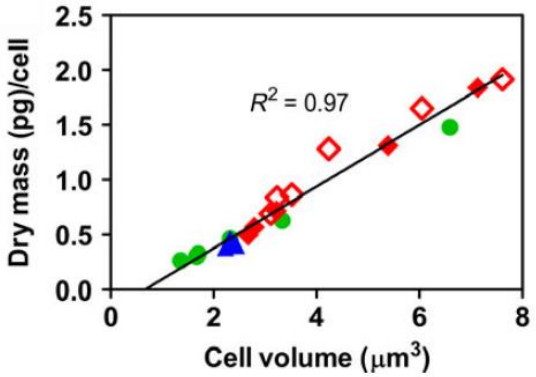
- In other words, biomass density $1/\delta$ $[\mathrm{g\,L^{-1}}]$ is constant:

$$Vol = \delta \cdot \sum_i C_i = \delta \cdot B$$

Volume and macromolecular contents

- Assumption of constant biomass density supported by experimental data

  Biomass density approximately $300\ \mathrm{g\ L^{-1}}$



Conditions	Strain	Description	Medium	Symbols
Nutrient limitation	NCM3722	Wild type	Various nutrient	●
Translation Inhibition with Cm	NCM3722	Wild type	Glucose with Cm	▲
Glucose LacZ OE	NQ1389	Titratable LacZ expression	Glucose with cTc	◆
Glucose +cAA LacZ OE	NQ1389	Titratable LacZ expression	Glucose+cAA with cTc	◇

Basan *et al.* (2015), *Mol. Syst. Biol.*, 11:836-5

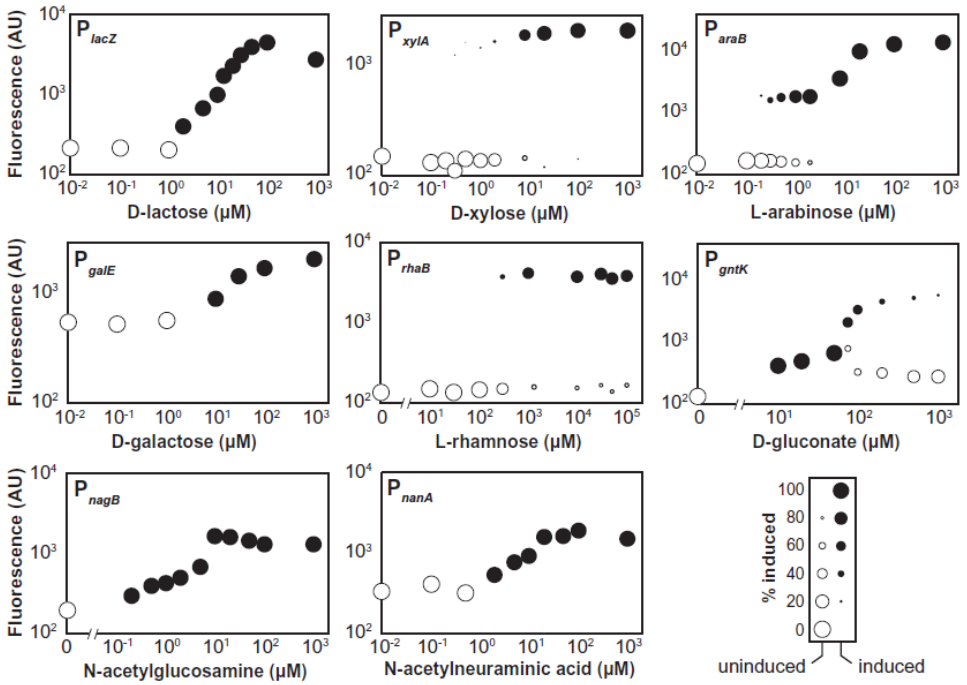
Volume and macromolecular contents

- Concentration c_i $[\mathrm{g\,L^{-1}}]$ of molecular constituent *i* in population:

$$c_i = C_i / Vol$$

- If all cells have same concentration, then c_i also applies to individual cells
- But: concentrations may be heterogeneous, leading to different growth phenotypes

  Enzymes for secondary carbon sources in *E. coli*



Afroz *et al.* (2014), *Mol. Microbiol.*, 93(6):1093-1103

Volume and macromolecular contents

- Concentration c_i $[\mathrm{g\,L^{-1}}]$ of molecular constituent *i* in population:

$$c_i = C_i / Vol$$

- If all cells have same concentration, then c_i also applies to individual cells
- Consequence of proportionality of mass and volume: total concentration is constant

$$\sum_i c_i = \sum_i C_i / Vol = B / Vol = 1/\delta$$

Volume and macromolecular contents

- ODE model of dynamics of molecular constituent *i* :

$$\dot{c}_i = \frac{\dot{C}_i \cdot Vol - C_i \cdot \dot{V}ol}{Vol^2} = \frac{\dot{C}_i}{Vol} - \frac{C_i}{Vol} \cdot \frac{\dot{V}ol}{Vol}$$

$$= \frac{\dot{C}_i}{Vol} - \mu \cdot c_i .$$

Appearance of term for **growth dilution** of individual constituents

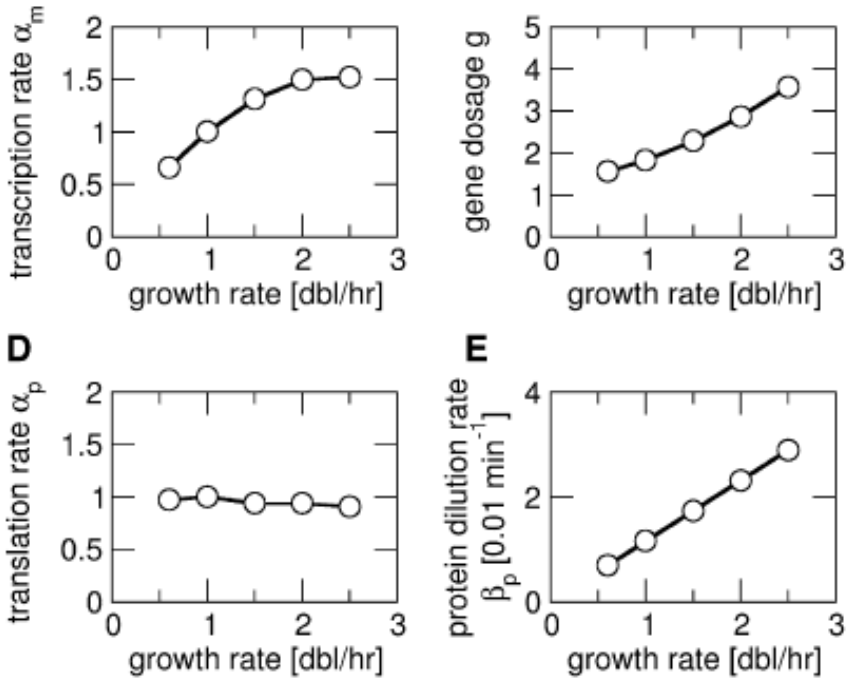
- Growth rate follows from dynamics of molecular constituents

$$\mu = \frac{\dot{V}ol}{Vol} = \delta \cdot \sum_i \frac{\dot{C}_i}{Vol} = \delta \cdot \frac{\dot{B}}{Vol}$$

No growth dilution if mass of all constituents remains constant

Volume and macromolecular contents

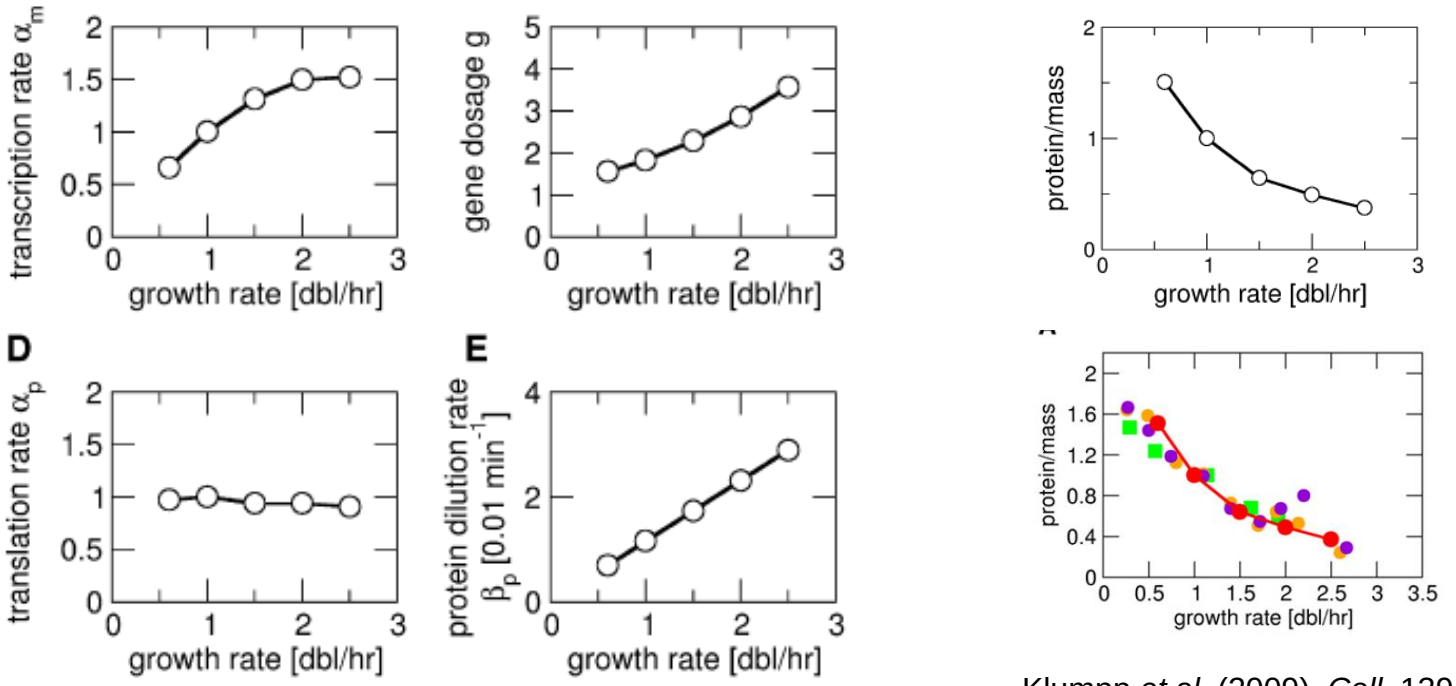
- Growth dilution may have an important effect on the concentration of cellular constituents
  - Changes in rate of protein synthesis and decay of **constitutive gene**



Klumpp *et al.* (2009), *Cell*, 139(7):1366-75

Volume and macromolecular contents

- Growth dilution may have an important effect on the concentration of cellular constituents
  - Changes in rate of protein synthesis and decay of **constitutive gene**
  - Concentration of gene product is growth-rate dependent



Klumpp *et al.* (2009), *Cell*, 139(7):1366-75

Biochemical reactions underlying growth

- Term $\dot{C}_i / Vol$ represents net effect of biochemical reactions on concentration of molecular constituent *i*
- Change of variables: $X_i = C_i / \alpha_i \ [\mathrm{mol}]$

  Rate of reactions based on physical encounters of molecules

$$x_i = X_i / Vol$$

- ODE model of dynamics of molecular constituent *i* :

$$\dot{x}_i = \frac{\dot{X}_i}{Vol} - \mu \cdot x_i$$

Biochemical reactions underlying growth

- Reformulation of reaction rates $\dot{X}_i / Vol$
  - Rate of reaction *j* : $v_j \quad [\mathrm{mol\ L^{-1}\ h^{-1}}]$
  - Stoichiometry of constituent *i* in reaction *j* : N_{ij}

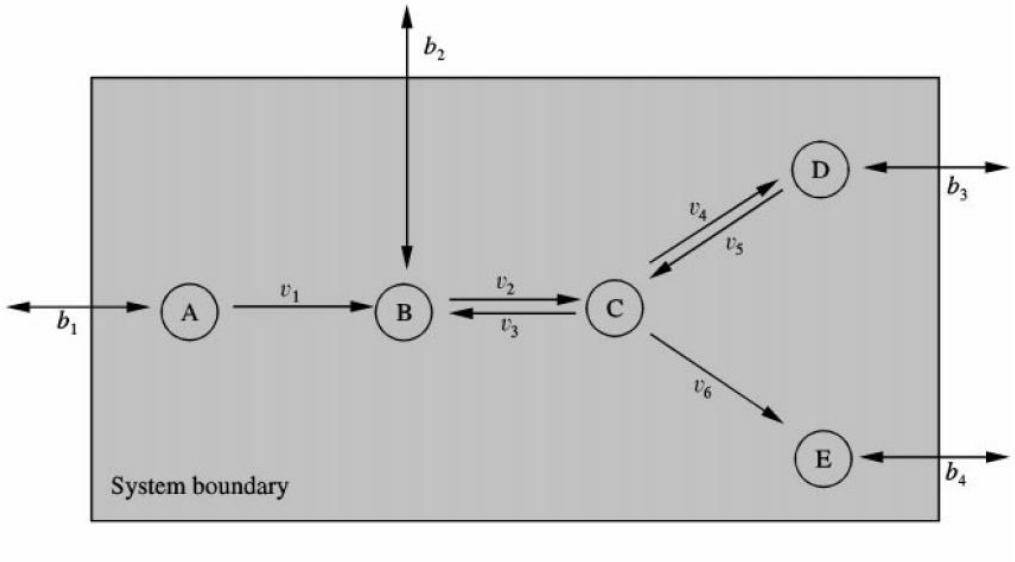
…- N_{ij} constituent *i* -… $\xrightarrow{v_j}$

$\xrightarrow{v_j}$ …+N_{ij} constituent *i* +…

Biochemical reactions underlying growth

- Stoichiometry matrix N describes structure of reaction network

  Internal reactions and exchange reactions, reversible and irreversible



$$N = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 1 & -1 & 1 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 \end{bmatrix} \quad v = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ b_1 \\ b_2 \\ b_3 \\ b_4 \end{bmatrix}$$

Schilling *et al.* (2000), *J. Theor. Biol.*, 203(3):229-48

Biochemical reactions underlying growth

- Reformulation of reaction rates $\dot{X}_i / Vol$
  - Vector of reaction rates: v
  - Stoichiometry of constituent *i* in reaction *j* : N_{ij}
  - Vector of concentrations of molecular constituents: x
- Stoichiometry model of biochemical reactions

$$\dot{x} = N \cdot v - \mu \cdot x$$

Biochemical reactions underlying growth

- Stoichiometry model of biochemical reactions

$$\dot{x} = N \cdot v - \mu \cdot x$$

- Expression of growth rate

$$\mu = \delta \cdot \sum_i \frac{\dot{C}_i}{Vol} = \delta \cdot \sum_i \alpha_i \cdot \frac{\dot{X}_i}{Vol}$$
$$= \delta \cdot \sum_i \alpha_i \cdot N_i \cdot v(x).$$

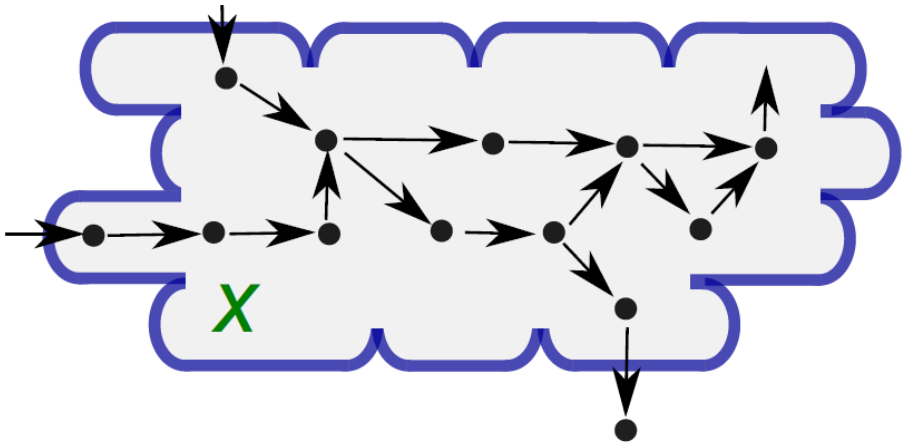
  - Rate of accumulation of (mass of) constituents (within unit volume per unit time) relative to total amount of constituents (within unit volume)
  - Not *ad-hoc* definition, but derived from basic assumptions

Biochemical reactions underlying growth

- ODE model for growth of microbial populations:

$$\dot{x} = N \cdot v(x) - \mu \cdot x,$$

$$\mu = \delta \cdot \sum_i \alpha_i \cdot N_i \cdot v(x).$$

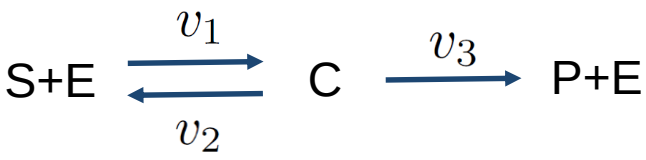


- Reaction rates depend on concentrations x of substrates, products, effectors

Enzyme kinetics

- **Mass-action kinetics** is based on fundamental law for rate of biochemical reactions

  Rates are proportional to concentrations of reactants



$$\dot{e}(t) = -v_1 + v_2 + v_3 = -k_f \cdot e(t) \cdot s(t) + k_r \cdot c(t) + k_{cat} \cdot c(t),$$
$$\dot{s}(t) = -v_1 + v_2 = -k_f \cdot e(t) \cdot s(t) + k_r \cdot c(t),$$
$$\dot{c}(t) = v_1 - v_2 - v_3 = k_f \cdot e(t) \cdot s(t) - k_r \cdot c(t) - k_{cat} \cdot c(t),$$
$$\dot{p}(t) = v_3 = k_{cat} \cdot c(t),$$

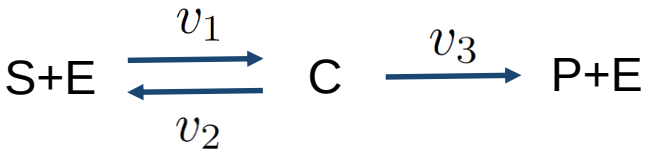
  where the following **conservation relations** hold:

$$e(t) + c(t) = e_0,$$
$$s(t) + c(t) + p(t) = s_0, \quad c(0) = 0, \quad p(0) = 0.$$

Enzyme kinetics

- **Mass-action kinetics** is based on fundamental law for rate of biochemical reactions

  Rates are proportional to concentrations of reactants



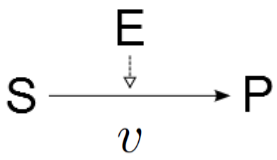
- **Question**: What is the stoichiometry matrix for this system?
- **Question**: What are the units of the parameters if concentrations are expressed in mol L^{-1}?
- **Question**: How can the equation system be simplified using the conservation relations? Hint: keep *s* and *c*

Enzyme kinetics

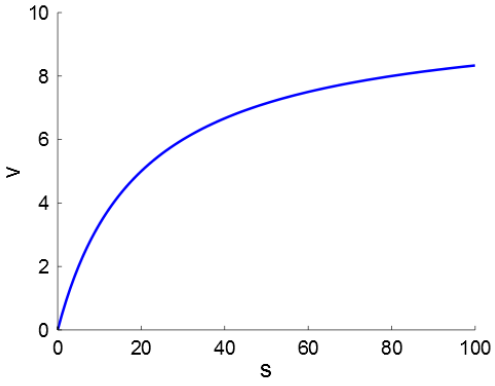
- Simplified equation system for enzymatic reaction:

$$\dot{s}(t) = -k_f \cdot (e_0 - c(t)) \cdot s(t) + k_r \cdot c(t),$$
$$\dot{c}(t) = k_f \cdot (e_0 - c(t)) \cdot s(t) - (k_r + k_{cat}) \cdot c(t).$$

- Quasi-steady state assumption: $\dot{c}(t) \approx 0$
- Quasi-steady state assumption leads to **Michaelis-Menten kinetics**:



$$\dot{s} = -v(s) = -V_m \cdot \frac{s}{K_m + s},$$
$$\dot{p} = v(s) = V_m \cdot \frac{s}{K_m + s},$$
$$K_m = \frac{k_r + k_{cat}}{k_f}, \quad V_m = k_{cat} \cdot e_0.$$



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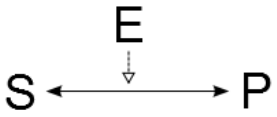
- Quasi-steady state assumption: $\dot{c}(t) \approx 0$
- Quasi-steady state assumption leads to **Michaelis-Menten kinetics**
- Quasi-steady state assumption valid under certain conditions on the parameters

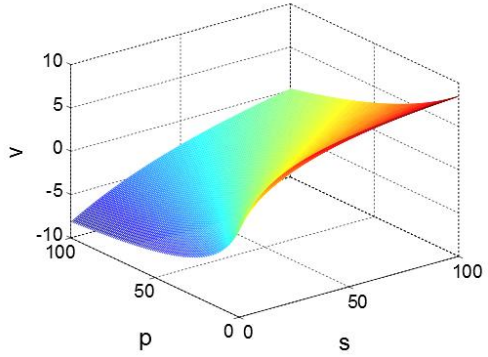
Chen *et al* (2010), *Genes Dev.*, 24(17):1861-75

Enzyme kinetics

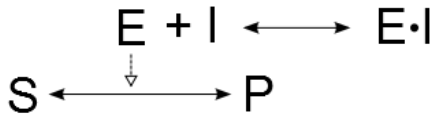
- Michaelis-Menten kinetics for **reversible enzymatic reaction**



$$v(s,p) = \frac{V_m^+ \cdot s/K_{m1} - V_m^- \cdot p/K_{m2}}{1 + s/K_{m1} + p/K_{m2}}$$

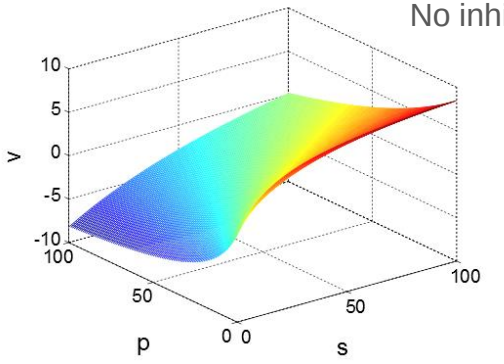


- Michaelis-Menten kinetics for reversible enzymatic reaction with **competitive enzyme inhibition**



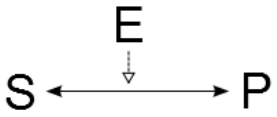
$$v(s,p,i) = \frac{V_m^+ \cdot s/K_{m1} - V_m^- \cdot p/K_{m2}}{1 + i/K_i + s/K_{m1} + p/K_{m2}}$$

No inhibitor



Enzyme kinetics

- Michaelis-Menten kinetics for **reversible enzymatic reaction**



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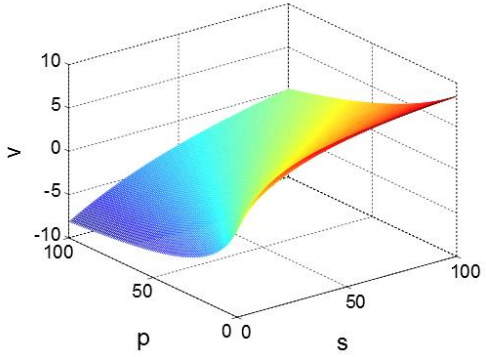
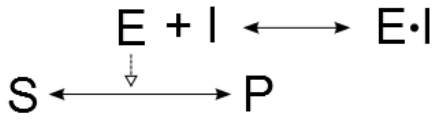


- Michaelis-Menten kinetics for reversible enzymatic reaction with **competitive enzyme inhibition**



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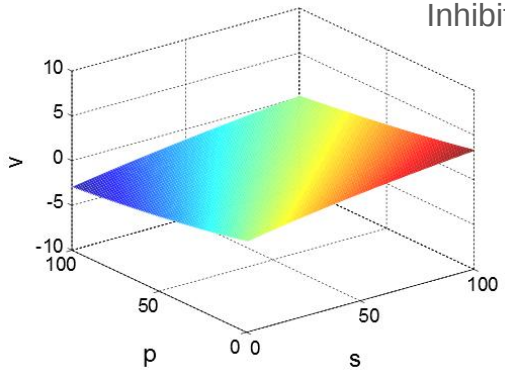


Enzyme kinetics

- Many other rate laws for enzyme kinetics have been proposed
  - Generalization to multiple substrates and products
  - Thermodynamic view, separating enzyme-dependent from enzyme-independent properties
  - Convenient mathematical approximations

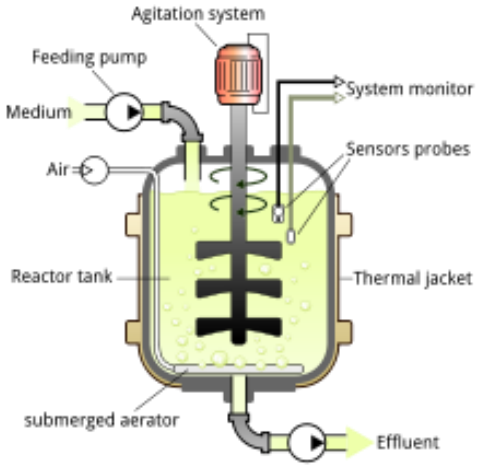
Heinrich and Schuster (1996), *The Regulation of Cellular Systems*, Chapman & Hall

Cornish-Bowden (2004), *Fundamentals of Enzyme Kinetics*, Portland Press

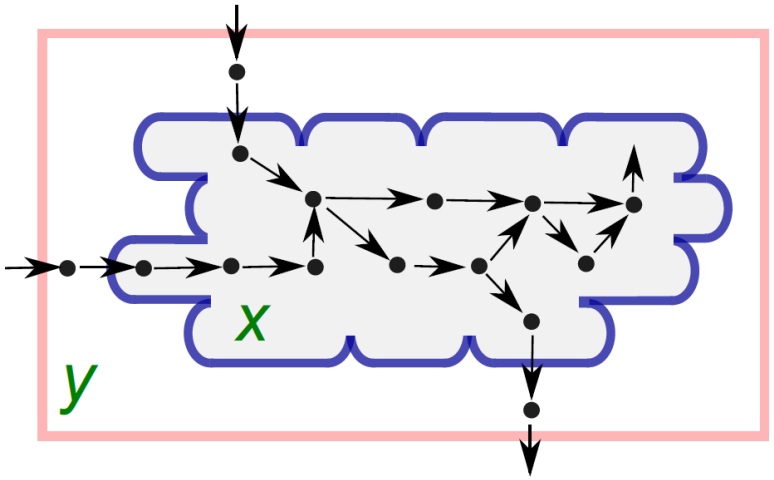
- Rate laws for gene expression kinetics and signal transduction kinetics introduced in later courses

Growth in a changing environment

- No explicit model of the environment
  - Some reactions in v correspond to uptake of substrates or secretion of products
- Environment modeled as bioreactor filled by liquid medium of fixed volume
  - Substrate/product concentrations in medium: $y \quad [\mathrm{g\ L^{-1}}]$
  - Volume of medium: $Vol_{medium} \quad [\mathrm{L}]$



Source: wikpedia



Growth in a changing environment

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  - Some reactions in v correspond to uptake of substrates or secretion of products
- Environment modeled as bioreactor filled by liquid medium of fixed volume
  - Substrate/product concentrations in medium: $y \quad [\mathrm{g\ L^{-1}}]$
  - Volume of medium: $Vol_{medium} \quad [\mathrm{L}]$
- ODE model for dynamics of substrate/product concentrations in medium

$$\dot{y} = \alpha_y \cdot E \cdot v(x, y) \cdot (\, Vol / \, Vol_{medium})$$

  - Stoichiometry matrix for exchange reactions: E
  - Diagonal matrix of molar mass coefficients: α_y

Growth in a changing environment

- No explicit model of the environment
  - Some reactions in v correspond to uptake of substrates or secretion of products
- Environment modeled as bioreactor filled by liquid medium of fixed volume
  - Substrate/product concentrations in medium: $y \quad [\mathrm{g\ L^{-1}}]$
  - Volume of medium: $Vol_{medium} \quad [\mathrm{L}]$
- ODE model for dynamics of substrate/product concentrations in medium

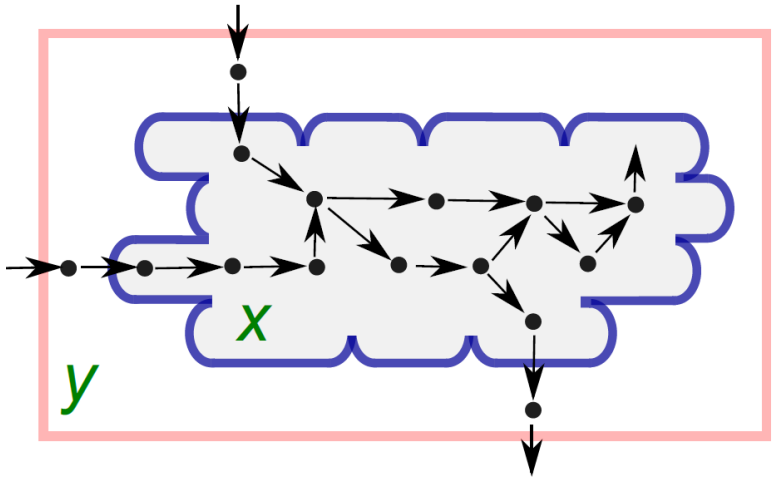
$$\frac{Vol}{Vol_{medium}} = \delta \cdot \frac{\sum_i C_i}{Vol_{medium}} = \delta \cdot b,$$

$$\dot{y} = \delta \cdot \alpha_y \cdot E \cdot v(x, y) \cdot b.$$

Growth in a changing environment

- ODE model for growth of microbial populations:

$$\dot{x} = N \cdot v(x,y) - \mu \cdot x,$$
$$\dot{y} = \delta \cdot \alpha_y \cdot E \cdot v(x,y) \cdot b,$$
$$\mu = \delta \cdot \sum_i \alpha_i \cdot N_i \cdot v(x,y),$$
$$\dot{b} = \mu \cdot b,$$



Growth in a changing environment

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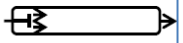
$$\mu = \delta \cdot \sum_i \alpha_i \cdot N_i \cdot v(x,y),$$
$$\dot{b} = \mu \cdot b,$$

- Model applies to batch cultivation, but can be easily adapted for continuous culture or fed-batch culture

Bastin and Dochin (1990), *On-Line Estimation and Adaptive Control of Bioreactors*, Elsevier, 1990

Growth in a changing environment

- Bioreactor models have been mostly used in context of biotechnological applications
- **But**: they also apply to complex natural environments, such as digestive tracts of vertebrates and insects

Organ shape and location in horse digestive tract	Example of organ names	Reactor shape	Modelized reactor	Scheme
	Stomach (human) Rumen (cow) Crop (hoazin) Saccular forestomach (kangaroo) Proctodeum P3 (termite)	Open sac-like reactor	Continuously stirred tank reactor (CSTR)	
	Caecum (rabbit)	Closed sac-like reactor	Batch reactor	
	Large intestine (human)	Large tubular reactor	CSTR in series	
	Small intestine (human) Tubiform forestomach (kangaroo)	Narrow tubular reactor	Plug-flow reactor	

Godon *et al.* (2013), *BioEnergy Res.*, 6(3):1063-81

Towards integrated models of the cell

- Integrated models of the cell are emerging, but some interesting precursors exist
  - Coarse-grained model of an *E. coli* cell

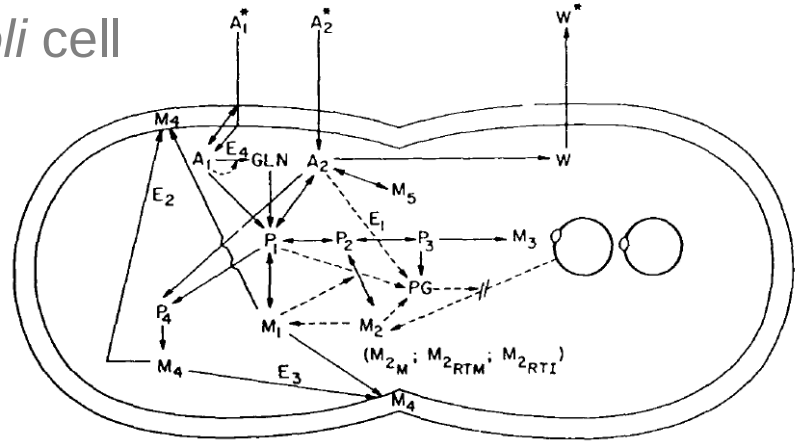


FIGURE 7 An idealized sketch of the model of *E. coli B/rA* growing in a glucose-ammonium salts medium with glucose or ammonia as the limiting nutrient. At the time shown the cell has just completed a round of DNA replication and initiated cross-wall formation and a new round of DNA replication. Solid lines indicate the flow of material, while dashed lines indicate flow of information. Reproduced with permission from Shuler and Domach, 1983.

A_1 = ammonium ion
A_2 = glucose (and associated compounds in the cell)
W = waste products (CO_2, H_2O, and acetate) formed from energy metabolism during aerobic growth
P_1 = amino acids
P_2 = ribonucleotides
P_3 = deoxyribonucleotides
P_4 = cell envelope precursors
M_1 = protein (both cytoplasmic and envelope)
$M_{2_{RTI}}$ = immature "stable" RNA
$M_{2_{RTM}}$ = mature "stable" RNA (*r*-RNA and *r*-RNA—assume 85% *r*-RNA throughout)
M_{2_M} = messenger RNA
M_3 = DNA
M_4 = non-protein part of cell envelope (assume 16.7% peptidoglycan, 47.6% lipid, and 35.7% polysaccharide)
M_5 = glycogen
PG = *ppGpp*
E_2, E_3 = molecules involved in directing cross-wall formation and cell envelope synthesis—the approach used in the prototype model was used here but more recent experimental support is available
GLN = glutamine
E_1 = glutamine synthetase
*—the material is present in the external environment.

Domach *et al.* (1984), *Biotechnol. Bioeng.*, 26(3):203-16

Towards integrated models of the cell

- Integrated models of the cell are emerging, but some interesting precursors exist

  Coarse-grained model of an *E. coli* cell

- Model has evolved into minimal, **functionally complete model** of chemoheterotrophic bacterium

Model structure	Count	Examples
Compartments	4	Cytoplasm, cell membrane, whole cell, medium
Chemical species	408	Glucose-6P, alanine, mRNAs, proteins
Reactions	570	Fructose-6P synthesis, CTP synthesis
Rate parameters	570	Mass action or Michaelis–Menten rate constants
Saturation parameters	581	Michaelis–Menten-like saturation parameters
Inhibition parameters	25	Michaelis–Menten-like inhibition parameters
Rate rules	1	Methylation state of chromosome
Algebraic rules	1	Cell width (CW)
Events	36	DNA replication initiation, cell division
Constraints	408	Each species must have mass >0
Genes	241	Protein and stable RNA coding genes
Single coding genes	102	*dnaB*, *pgi*, etc.
Gene clusters	19	*replisome*, etc.
Genes in clusters	139	Ribosomal proteins, *dnaE*, etc.

Shuler *et al.* (2012), *Methods Mol. Biol.*, 881:573-610

Towards integrated models of the cell

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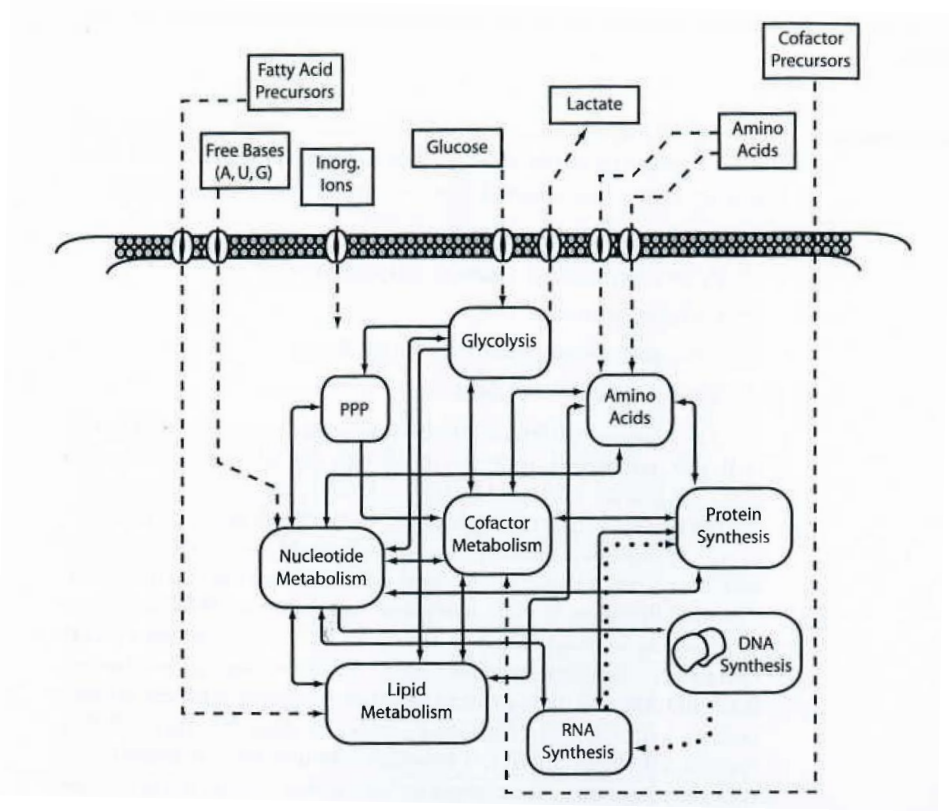
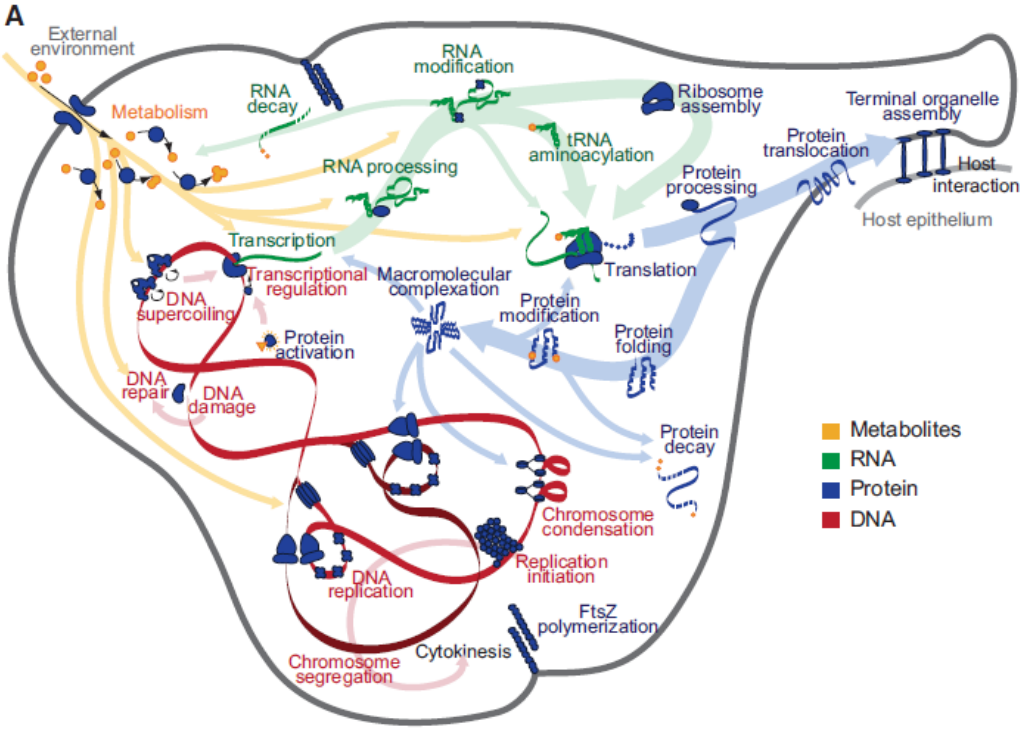


Shuler *et al.* (2012), *Methods Mol. Biol.*, 881:573-610

Whole-cell model *M. genitalium*

- Metabolic networks are integrated with gene networks and signalling networks
  - Complex multi-level system with feedback across different time-scales

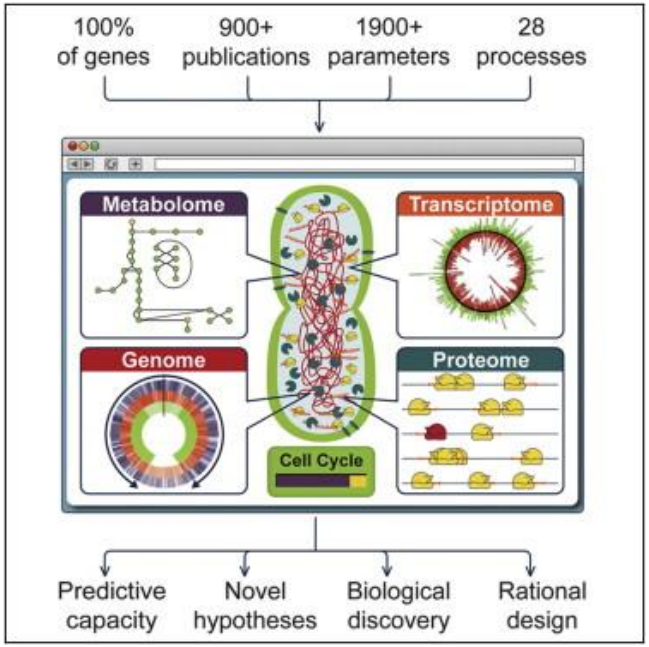


Whole-cell model of *Mycoplasma genitalium*

Karr *et al.* (2012), *Cell*, 150(2): 389-401

Whole-cell model *M. genitalium*

- Whole-cell model represents huge modelling effort:
  - Whole-genome model including **complete** known metabolic, gene, and signalling networks



Karr *et al.* (2012), *Cell*, 150(2): 389-401

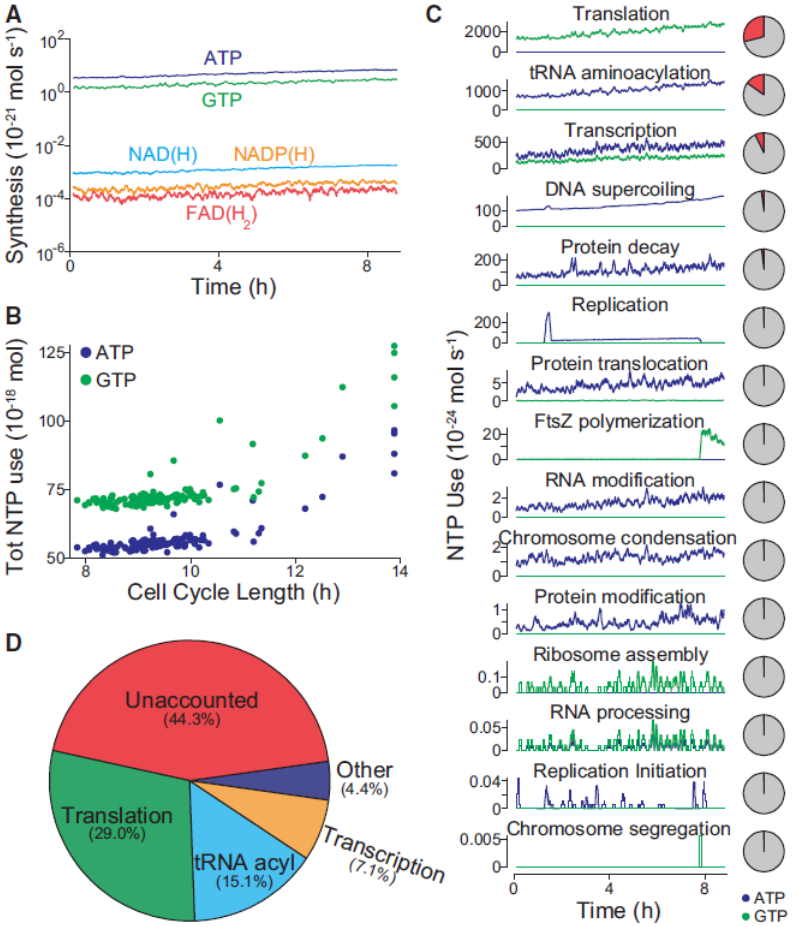
  - Variety of **formalisms** to model the 28 modules: FBA, kinetic ODE models, Boolean models, Markov chains, …
  - Cell cycle simulated for >100 cells, >30 mutants on 128-core machine

Whole-cell model *M. genitalium*

- Whole-cell simulation of *M. genitalium* cell cycle

Whole-cell model *M. genitalium*

- Whole-cell simulations have provided new insights into **global use and allocation of energy**
  - Transcription and translation most costly processes
  - Energy use largely independent of cell-cycle length
  - Usage of almost half of produced energy not accounted for!



Karr *et al.* (2012), *Cell*, 150(2): 389-401

Whole-cell models

- Whole-cell models help analyze the dynamics of interactions between multiple functions of the cell
  - Models allow predictions to be confronted with experimental data and performance of thought experiments
- But whole-cell models have problems as well!
  - Models **difficult to construct**, to debug and to maintain
  - Huge **number of parameters**, many unknown: parameter estimation is a difficult problem requiring many data of high quality
  - How do we **extract fundamental insights** on cell functioning from large, mechanistic models?

Whole-cell models

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  - Models allow predictions to be confronted with experimental data and performance of thought experiments
- But whole-cell models have problems as well!

On Exactitude in Science

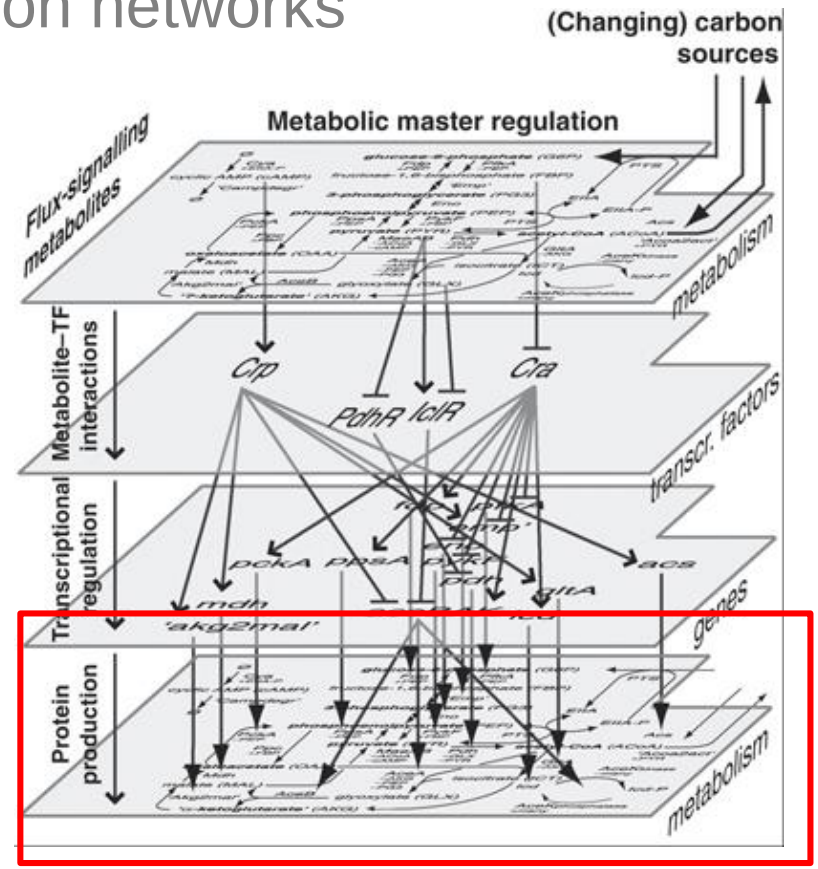
Jorge Luis Borges, *Collected Fictions*, translated by Andrew Hurley.

…In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and which coincided point for point with it. The following Generations, who were not so fond of the Study of Cartography as their Forebears had been, saw that that vast Map was Useless, and not without some Pitilessness was it, that they delivered it up to the Inclemencies of Sun and Winters. In the Deserts of the West, still today, there are Tattered Ruins of that Map, inhabited by Animals and Beggars; in all the Land there is no other Relic of the Disciplines of Geography.

—Suarez Miranda, *Viajes de varones prudentes*, Libro IV, Cap. XLV, Lerida, 1658

Alternatives to whole-cell models

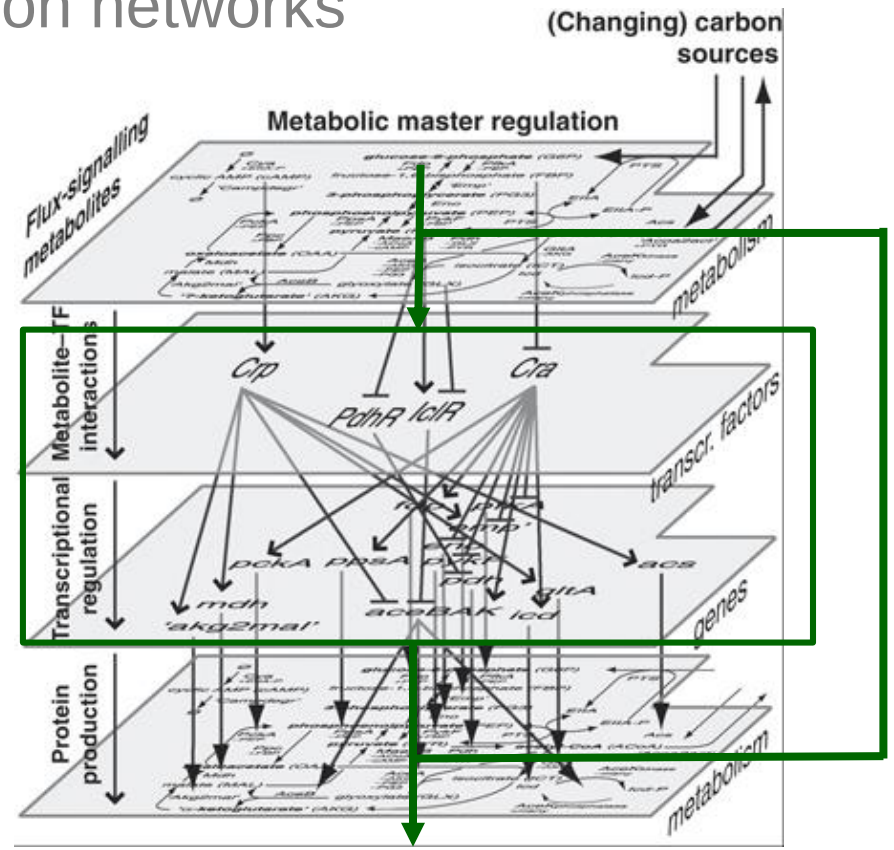
- Focus on **subsystems** that can be studied in isolation due to **modular structure** of reaction networks
  - Time-scale hierarchies
  - Connectivity structure
- **Metabolic networks**
  - Metabolites and enzymatic reactions
  - Short turn-over times of metabolite pools in comparison with enzyme pools



Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

Alternatives to whole-cell models

- Focus on **subsystems** that can be studied in isolation due to **modular structure** of reaction networks
  - Time-scale hierarchies
  - Connectivity structure
- **Gene regulatory networks**
  - Genes, proteins, and regulatory interactions
  - Limited number of indirect interactions mediated by (fast) metabolic networks



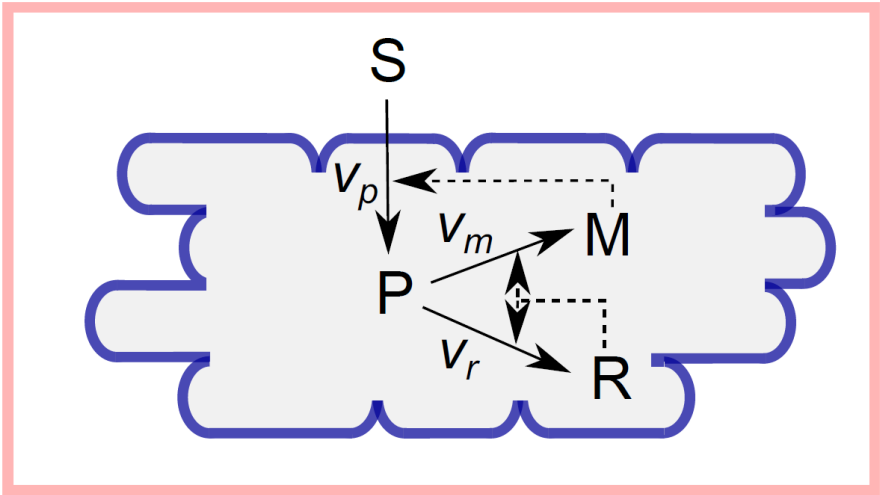
Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

Alternatives to whole-cell models

- Focus on **subsystems** that can be studied in isolation due to **modular structure** of reaction networks
  - Time-scale hierarchies
  - Connectivity structure
- **Coarse-grained models** that aggregate reactions into macroreactions of major functions

  Resource allocation models

Scott *et al.* (2014), *Mol. Syst. Biol.*, 10:747



S: substrate
P: precursor metabolites
M: metabolic machinery (enzymes)
R: gene expression machinery (ribosomes)

Conclusions

- Adaptation of bacteria to their environment involves reorganisation of cellular physiology
- Adaptation process achieved by large and complex regulatory networks
  - Nonlinear dynamical systems with feedback across different time-scales
- Fundamental questions on network functioning require integrated models of the cell
  - Metabolism, gene expression, growth, signalling, …
- Formal framework based on kinetic modeling
- Detailed whole-cell models vs models of modular subsystems and coarse-grained models
- Metabolic networks and gene regulatory networks

Merci !

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