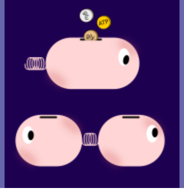

Optimal Cell Behavior in Time

Dafni Giannari, Hidde de Jong, Diego A. Oyarzún, Steffen Waldherr, Agustín G. Yabo

Outline of presentation

- Dynamic optimization: introduction and motivation
- Time-varying expression of enzymes in a metabolic pathway
- Teaser: time-varying resource allocation and cellular growth
- Conclusions and perspectives

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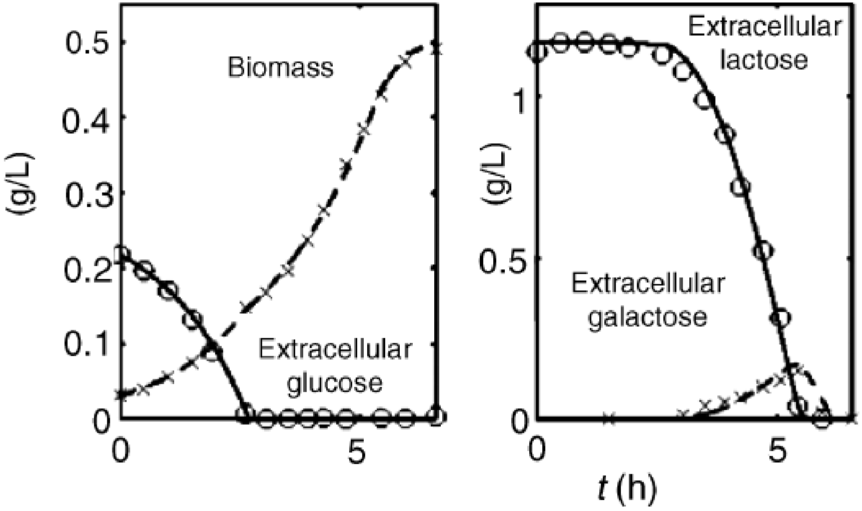
- Many links with other lectures
  - Optimization of metabolic fluxes
  - The enzyme cost of metabolic fluxes
  - Principles of cell growth
  - Growth balance analysis
  - Dynamic flux balance analysis
  - …

Bacterial adaptation

- Bacterial cells need to adapt to dynamically changing environments
  - Example: diauxic growth of *E. coli*

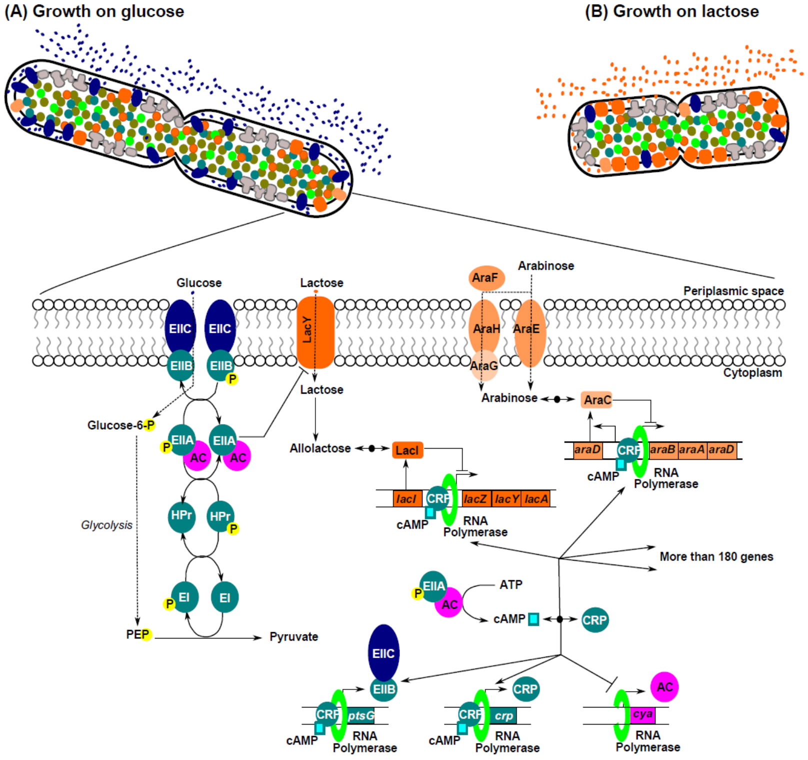


Bettenbrock *et al.* (2006), *J. Biol. Chem.*, 281:2578-84

Regulation of bacterial adaptation

- Bacterial cells have developed complex sensory and regulatory systems to realize adaptation

- Difficult to obtain quantitative, mechanistic models for these systems
  - Incompletely known mechanisms, unknown parameter values, …



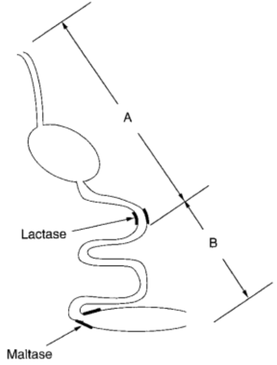
Kremling *et al.* (2015), *Trends Microbiol.*, 23:99-109

Dynamic optimization approach

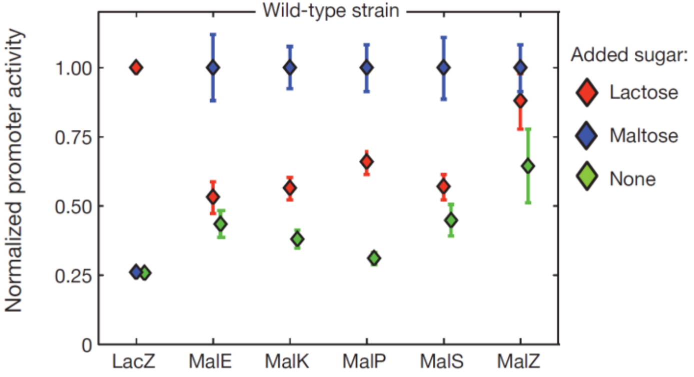
- Alternative: ignore regulatory mechanisms and assume that **cells perform (dynamic) optimization**
  - Limiting resources (proteins, fluxes, …)
  - … allocated to cellular processes (reactions)
  - … so as to maximize some objective (biomass synthesis, adaptation time, …)
  - … in a changing environment (nutrients, temperature, light, …)
  - … over a time-interval (response time, day/night cycle, …)
- Dynamic *vs* static optimization
  - Time-varying allocation of resources
  - Non-trivial features: resource buffers, anticipation of future changes, …
- **Assumption**: bacteria have evolved to (dynamically) optimize their functioning in competitive, changing environments

Evidence for dynamic optimization

- Microorganisms are capable of anticipating changes in their environment
  - Along digestive tract, exposure of *E. coli* to lactose precedes exposure to maltose
  - Expression of maltose genes when lactose is present



Savageau (1998), *Genetics*, 149:1677-91



Mitchell *et al.* (2008), *Nature*, 460:220-4

- But: assumption remains working hypothesis!

Dynamic optimization and optimal control

- Mathematical formulation of dynamic optimization yields **optimal control problem**:

$$\max_{u \in U} J(x, u, t_0, t_e),$$

such that

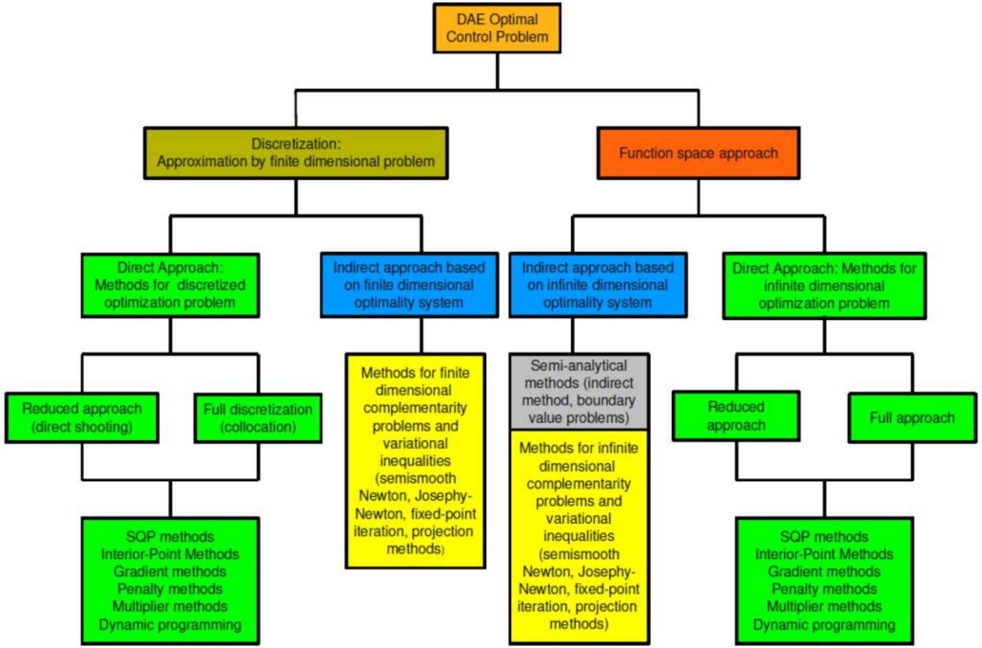
$$\frac{dx}{dt} = f(x(t), u(t)), \quad x(t_0) = x_0,$$
$$0 \geq c_1(x(t), u(t)),$$
$$0 \geq c_2(x(t_0), x(t_e)).$$

- Specification of optimal control problem:
  - Dynamical system with state x and dynamics f
  - Time-varying control u, over time-interval $[t_0, te]$
  - Objective function J, and path constraints c_1 and time-point constraints c_2

Tsiantis and Banga (2020), *BMC Bioinform*, 21:472

Dynamic optimization and optimal control

- Rich variety of mathematical techniques exist to **(numerically) solve optimal control problems**

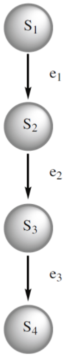


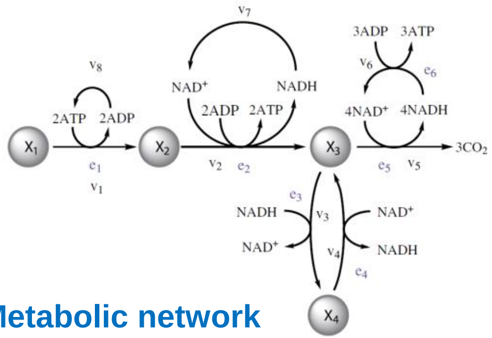
Gerdts (2013), OMPC Summer school Bayreuth, link
Ref. M. Köbis

Examples of dynamic optimization

- Dynamic optimization in two examples, increasingly larger scope:
  - Time-varying expression of enzymes in **metabolic pathways and networks**
  - Teaser: time-varying resource allocation and **cellular growth**

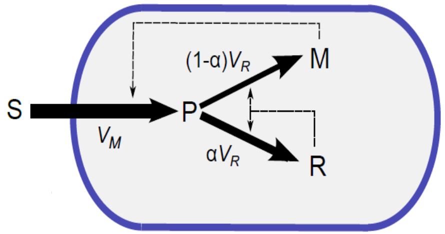
Metabolic pathway





Metabolic network

Cellular growth



Outline of presentation

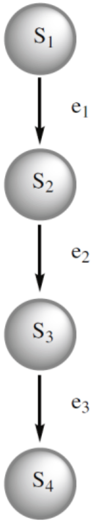
- Dynamic optimization: introduction and motivation
- **Time-varying expression of enzymes in a metabolic pathway**
- Teaser: time-varying resource allocation and cellular growth
- Conclusions and perspectives

Time-varying expression of enzymes

- **Metabolic pathway**: chain of enzymatic reactions converting substrate into product
- Allocation of enzyme capacity to reactions is resource allocation problem

Enzymes are limiting (costly) resource

S_1: substrate
$S_{2,3}$: intermediate metabolites
S_4: product
e_1, …, e_3: enzymes



Klipp *et al.* (2002), *Eur. J. Biochem.*, 269:5406–13
Bartl *et al.* (2010), *BioSystems*, 101:67-77
De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1

Time-varying expression of enzymes

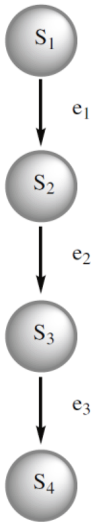
- Model describing dynamics of metabolic pathway

  Mass-action kinetics

$$\frac{ds}{dt} = N \cdot v(s(t), \boxed{e(t)}), \quad s(t_0) = [s_{10}, 0, 0, 0]',$$

$$N = \begin{bmatrix} 0 & 0 & 0 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{bmatrix},$$

$$v_1(s_i, e_i) = k_i \, e_i \, s_i, \quad i = 1, \ldots, 3,$$



Time-varying expression of enzymes

- **Assumption**: pathway has evolved so as to minimize transition time, that is, time to make a (certain amount of) product.
- **Dynamic optimization problem**: given an objective function

$$J(e) = t_e,$$

where $e(t)$ is a time-dependent function, find

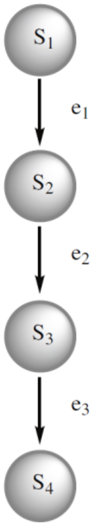
$$e_{opt} = \arg\min_{e} \; J(e)$$

under constraints

$$e_T \geq e_1 + e_2 + e_3,$$
$$s_4(t_e) = 0.9 \cdot s_{10}.$$

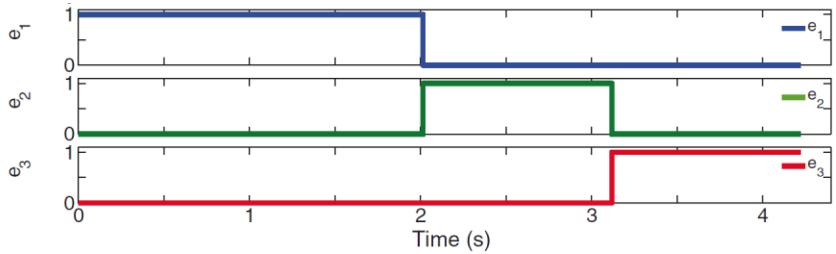
Time-varying expression of enzymes

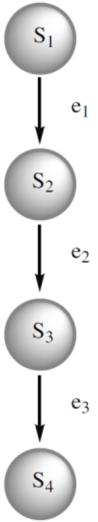
- What is the optimal enzyme expression pattern?



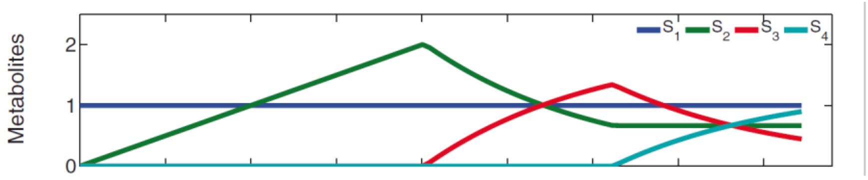
Time-varying expression of enzymes

- What is the optimal enzyme expression pattern?





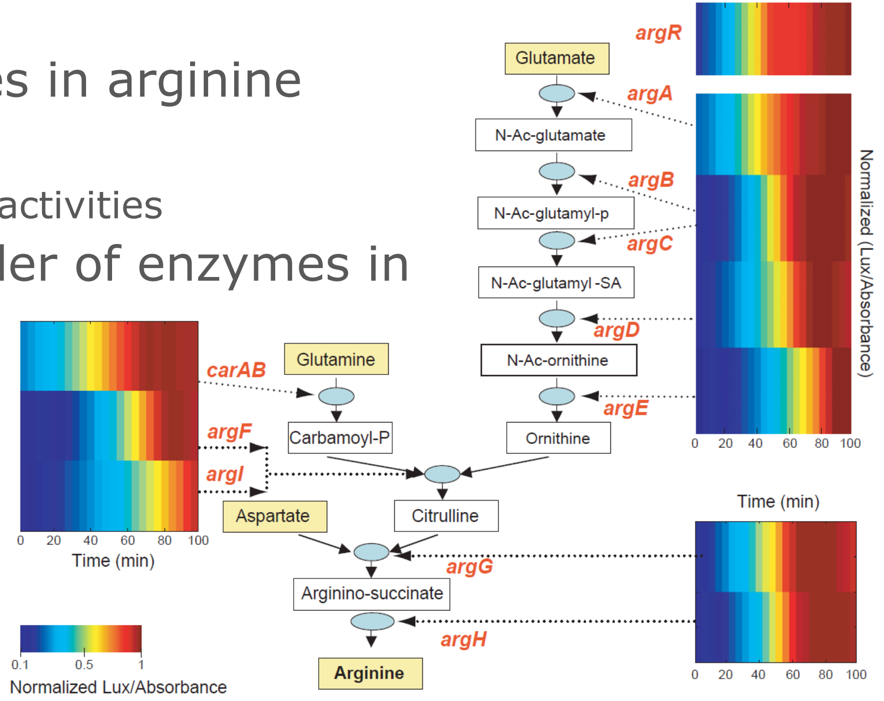
- Temporal ordering of expression of enzymes corresponding to ordering of reactions in pathway



De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1

Time-varying expression of enzymes

- Experimental evidence for temporal expression patterns of enzymes?
- Just-in-time expression of enzymes in arginine metabolism
  - Measurement of (normalized) promoter activities
- Temporal order corresponds to order of enzymes in unbranched pathways



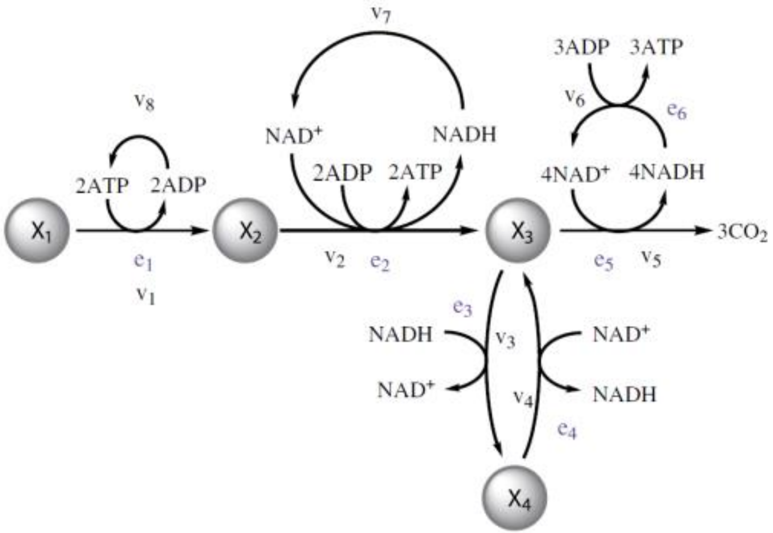
Zaslaver *et al.* (2004), *Nat. Genet.*, 36:486-91

Time-varying expression of enzymes

- Generalization from pathways to networks
  - Diauxic growth on glucose and ethanol in yeast

X_1: glucose
$X_{2,3}$: intermediate metabolites
X_4: ethanol

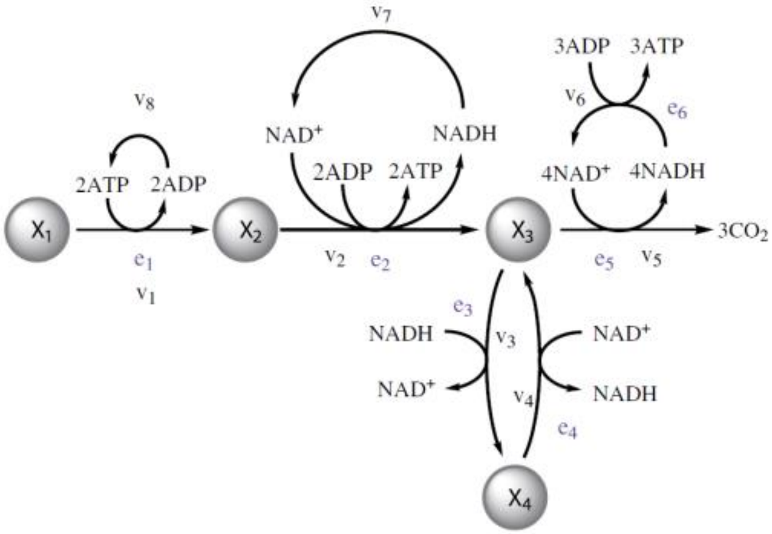
v_1 : upper glycolysis
v_2 : lower glycolysis
v_3 : ethanol production
v_4 : ethanol consumption
v_5 : TCA cycle
v_6 : respiratory chain
$v_{7\text{-}8}$: cofactor recycling



Klipp *et al.* (2002), *Eur. J. Biochem.*, 269:5406–13
De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1

Time-varying expression of enzymes

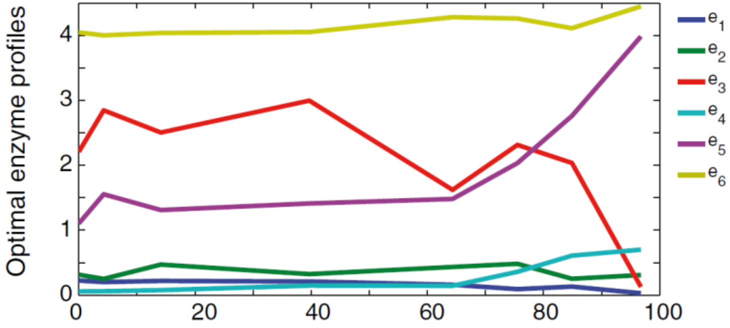
- Generalization from pathways to networks
  - Diauxic growth on glucose and ethanol in yeast
  - Mass-action model, constraint on total enzyme concentration
  - Maximization of survival time (quiescent state)



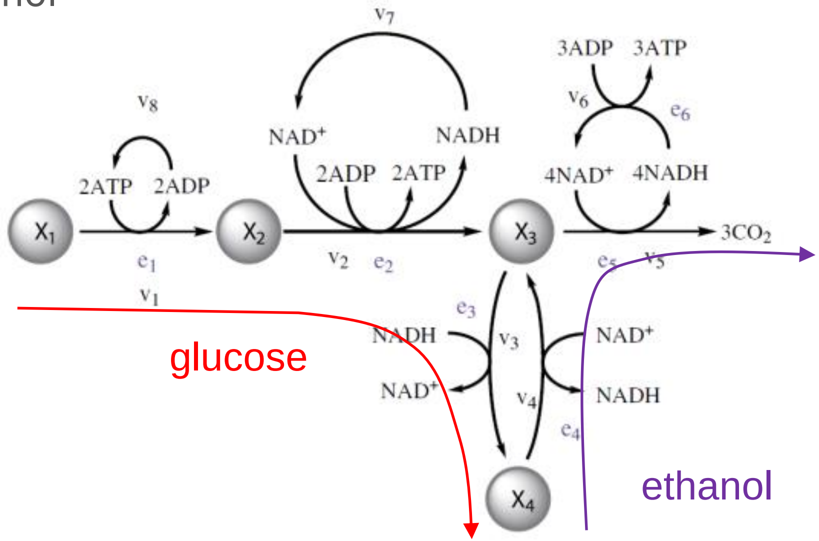
Klipp *et al.* (2002), *Eur. J. Biochem.*, 269:5406–13
De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1

Time-varying expression of enzymes

- Generalization from pathways to networks
  - Diauxic growth on glucose and ethanol in yeast
  - Mass-action model, constraint on total enzyme concentration
  - Maximization of survival time (quiescent state)
  - Predicted diauxic growth: glucose → ethanol



Klipp *et al.* (2002), *Eur. J. Biochem.*, 269:5406–13
De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1



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- **Teaser: time-varying resource allocation and cellular growth**
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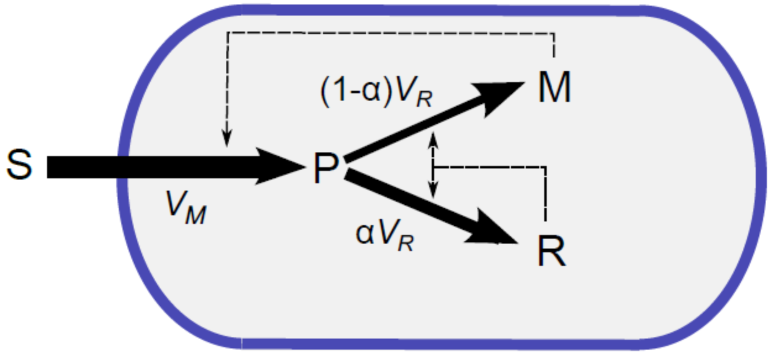
Time-varying resource allocation and growth

- Bacterial growth is fundamentally a **resource allocation problem**
  How does the cell distribute available resources over cellular functions?
- Resource allocation can be studied using **self-replicator models** of bacterial growth



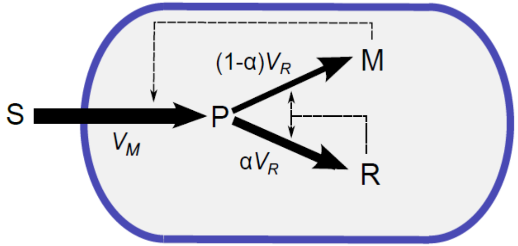
S: substrate (nutrient)
P: precursor
M: metabolic machinery
R: gene expression machinery
Biomass: M + R

α: resource allocation

Molenaar *et al.* (2009), *Mol. Syst. Biol.*, 5:323
Scott *et al.* (2014), *Mol. Syst. Biol.*, 10:747
Giordano *et al.* (2016), *PLoS Comput. Biol.,* 12:e1004802

Time-varying resource allocation and growth

- **Assumption**: bacteria have evolved to maximize growth, *i.e.*, total amount of biomass produced over time-interval
- Example **questions of interest**:
  - Which resource allocation strategy (choice of α) would optimize biomass in stable environment?
  - Which strategy would optimize biomass after a shift from poor to rich substrate?
  - Which strategy would optimize biomass in an environment with poor substrate with periodic pulses of rich substrate?



- See **"Optimal Cell Behavior in Time"** chapter and **MOOC** for more information!

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Conclusions

- **Pros** of dynamical optimization approach
  - Avoids modeling of (unknown) regulatory mechanisms
  - Allows for specification of constraints on solutions
  - Exploits availability of numerical tools for solving optimal control problems
  - Applies both to explaining observed behavior and designing desired behavior

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    - Avoids modeling of (unknown) regulatory mechanisms
    - Allows for specification of constraints on solutions
    - Exploits availability of numerical tools for solving optimal control problems
    - Applies both to explaining observed behavior and designing desired behavior

- **Cons** of dynamical optimization approach
    - Faces problems with numerical solvers: robustness, multiple solutions, …
    - Requires prior specification of plausible objective function(s): many possibilities…
    - Is based on (questionable) hypothesis that observed behavior has been optimized through natural selection

Perspectives

- **Multi-objective optimality** (Pareto optimality): system simultaneously optimizes several objectives, leading to trade-offs
- **Inverse optimality**: exploits huge amounts of available data to infer rather than assume objective function(s)
- **Experimental validation** of model predictions

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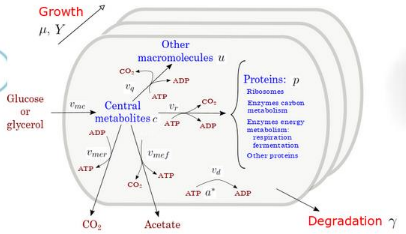
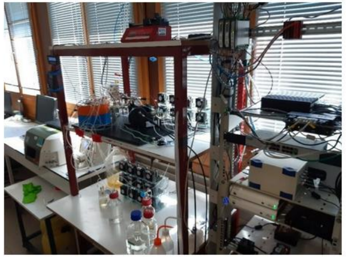
Open PhD position: Development and validation of small-scale models of bacterial growth and bioproduction





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