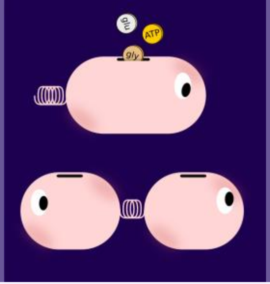
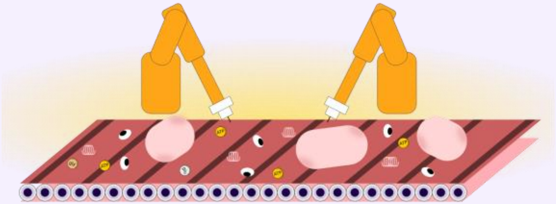
Economic Principles in Cell Physiology

Paris, July 4-6, 2022



Optimal Cell Behavior in Time

Hidde de Jong, Markus Köbis



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Outline of book chapter

- Dynamic optimization: introduction and motivation
- Time-varying expression of enzymes in a metabolic pathway
- Time-varying flux distribution in a metabolic network
  - Dynamic flux balance analysis (dFBA)
- Time-varying flux distribution in a metabolic network with enzyme costs
  - Dynamic enzyme-cost flux balance analysis (deFBA)
- Time-varying resource allocation and cellular growth
- Conclusions and perspectives

- Authors: Steffen Waldherr, Markus Köbis, Diego Oyarzun, Hidde de Jong, …

Outline of presentation

- Dynamic optimization: introduction and motivation
- Time-varying expression of enzymes in a metabolic pathway
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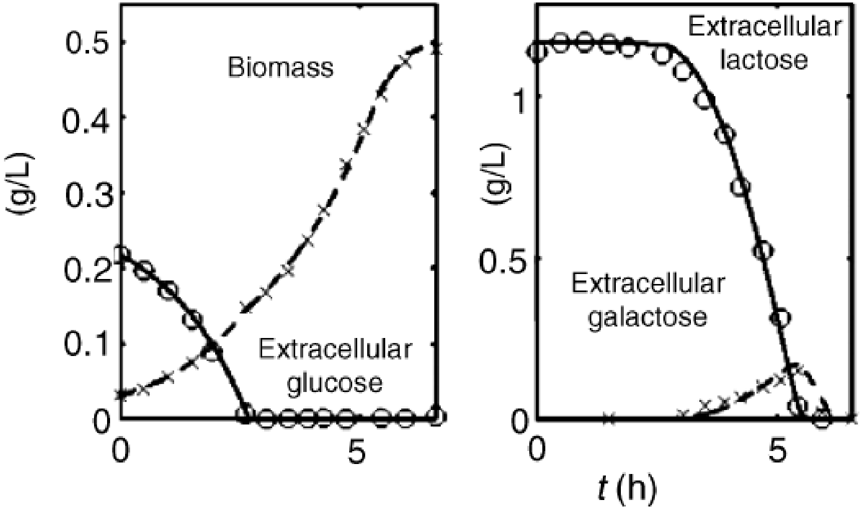
- Many links with previous lectures

Bacterial adaptation

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

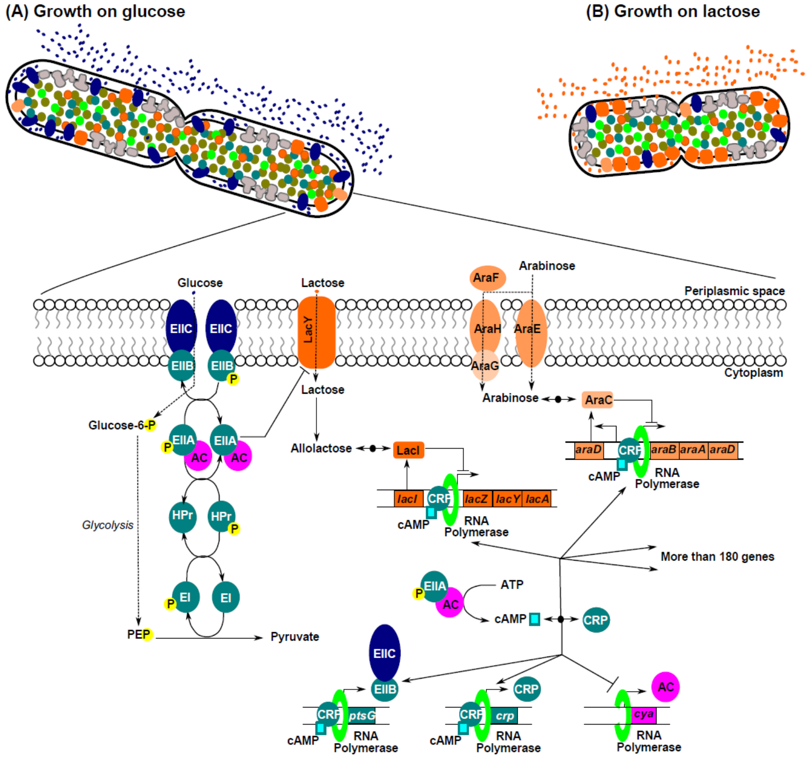


Bettenbrock *et al.* (2006), *J. Biol. Chem.*, 281:2578-84

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, …



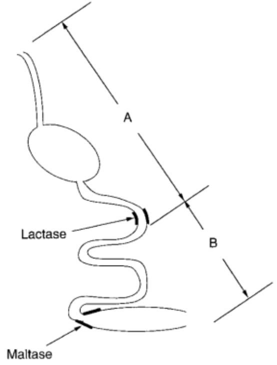
Kremling *et al.* (2015), *Trends Microbiol.*, 23:99-109

Dynamic optimization approach

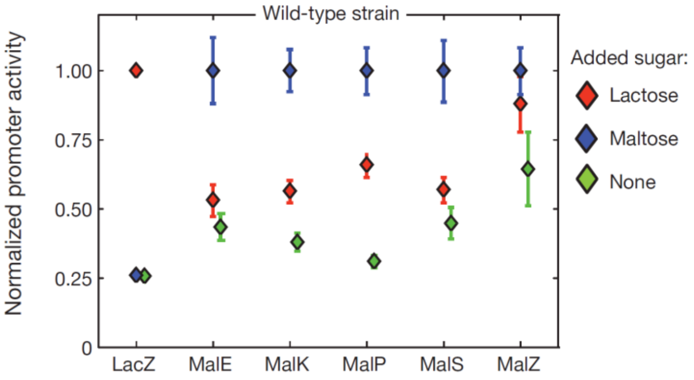
- Alternative: ignore regulatory mechanisms and assume that **cells perform (dynamic) optimization**
  - Limiting resources (proteins, fluxes, …)
  - … allocated to cellular processes (reactions)
  - … so as to maximize some objective (biomass synthesis, adaptation time, …)
  - … in a changing environment (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

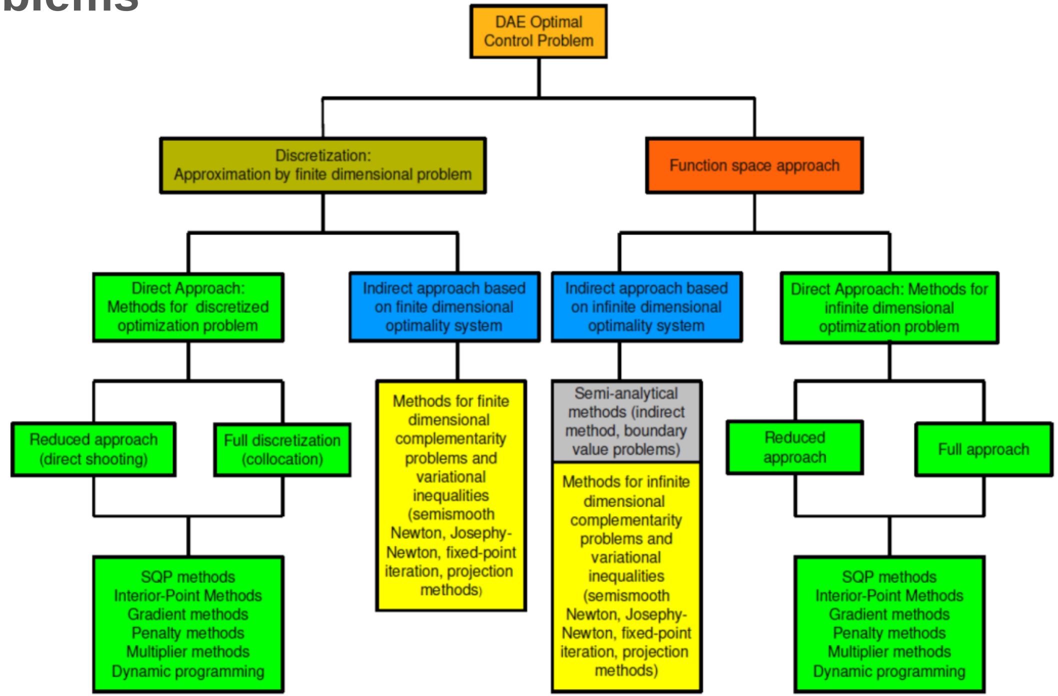
$$\frac{dx}{dt} = f(x(t), u(t)), \quad x(t_0) = x_0,$$
$$0 \geq c_1(x(t), u(t)),$$
$$0 \geq c_2(x(t_0), x(t_e)).$$

- 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**

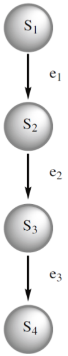


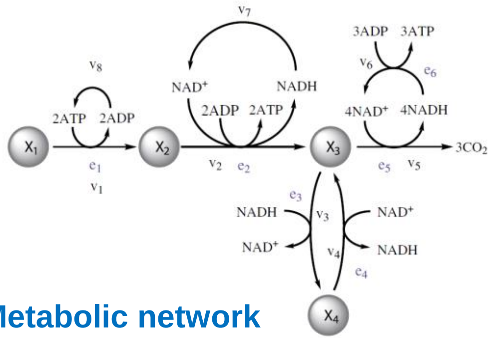
Gerdts (2013), OMPC Summer school Bayreuth, link

Examples of dynamic optimization

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

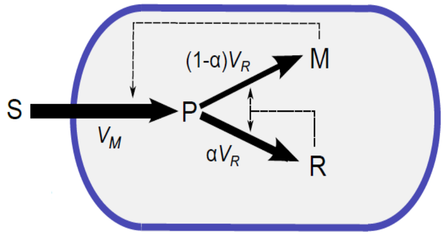
Metabolic pathway





Metabolic network

Cellular growth

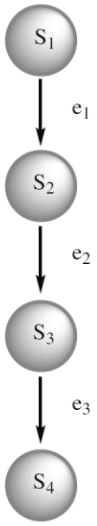


Outline of presentation

- Dynamic optimization: introduction and motivation
- **Time-varying expression of enzymes in metabolic pathways and networks**
- 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

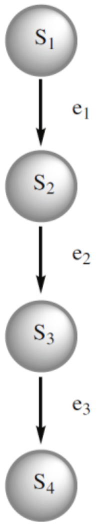
- Model describing dynamics of metabolic pathway

  Mass-action kinetics

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

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

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



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

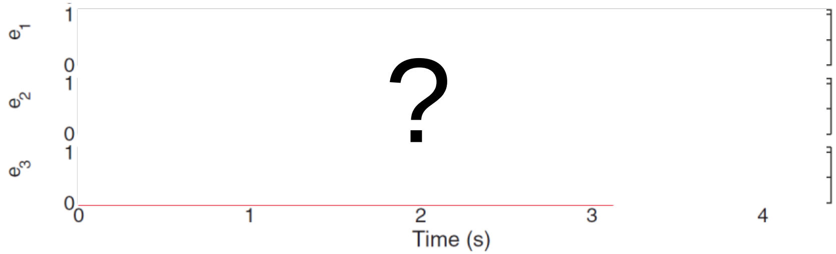
$$e_{opt} = \arg\min_{e} \ J(e)$$

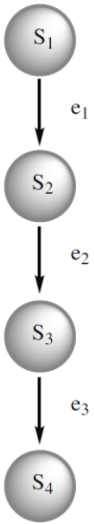
under constraints

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

Time-varying expression of enzymes

- What is the optimal enzyme expression pattern?





Time-varying expression of enzymes

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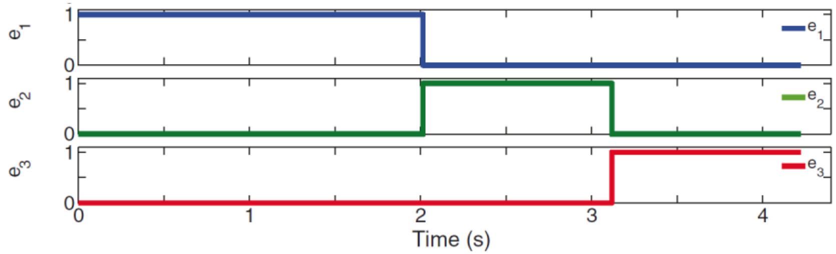
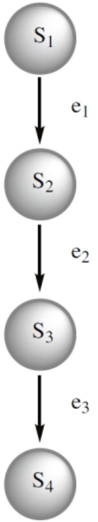
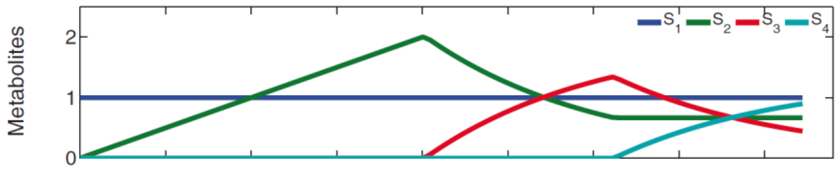




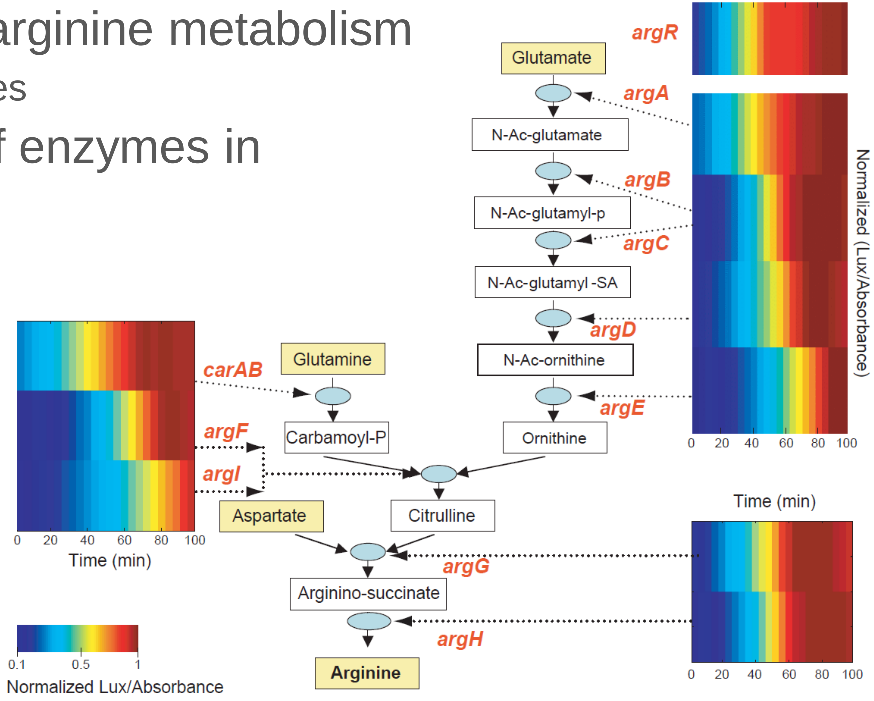
- Temporal ordering of expression of enzymes corresponding to ordering of reactions in pathway



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



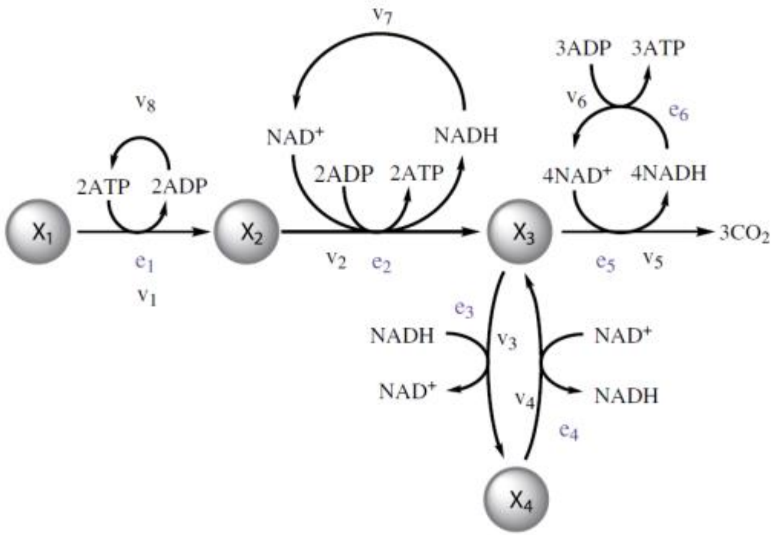
Zaslaver *et al.* (2004), *Nat. Genet.*, 36:486-91

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

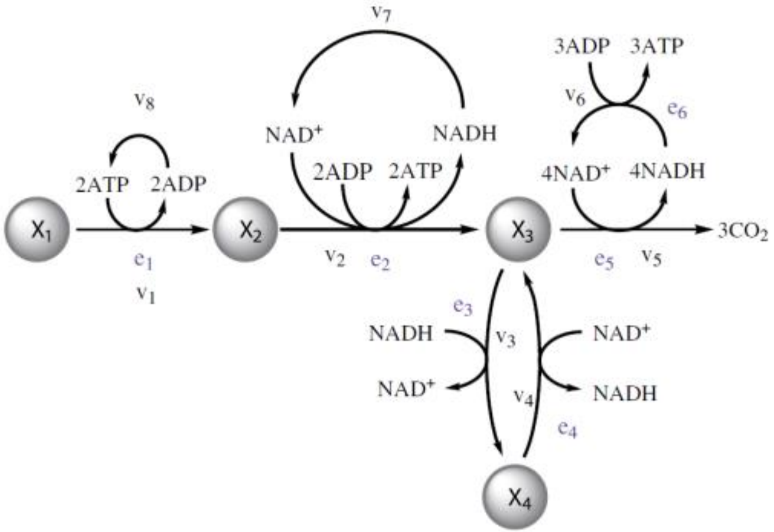
v_1 : upper glycolysis
v_2 : lower glycolysis
v_3 : ethanol production
v_4 : ethanol consumption
v_5 : TCA cycle
v_6 : respiratory chain
$v_{7\text{-}8}$: cofactor recycling



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

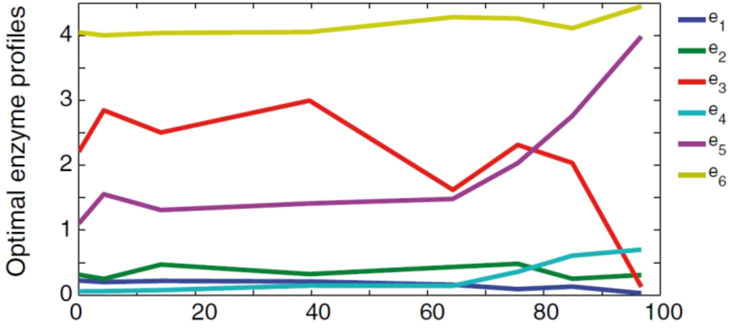
- Generalization from pathways to networks
  - Diauxic growth on glucose and ethanol in yeast
  - Mass-action model, constraint on total enzyme concentration
  - Maximization of survival time (quiescent state)



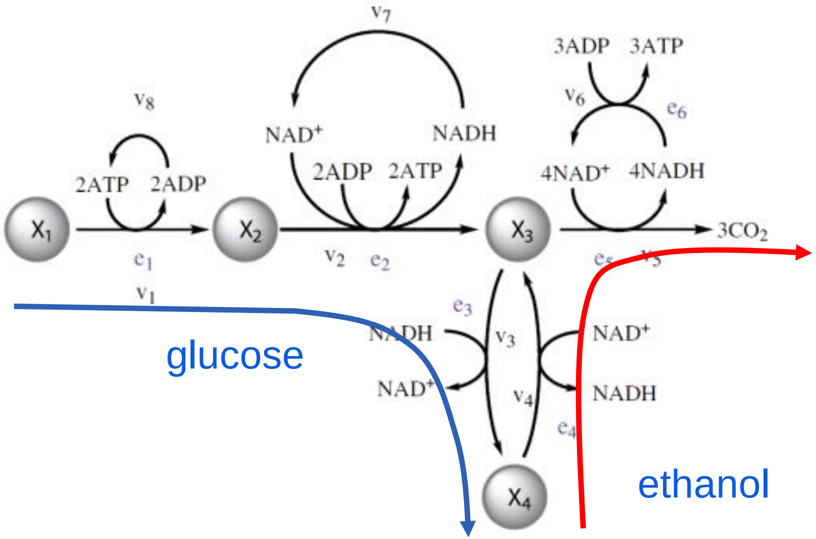
Klipp *et al.* (2002), *Eur. J. Biochem.*, 269:5406–13
De Hijas-Liste *et al.* (2014), *BMC Syst. Biol.*, 8:1

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



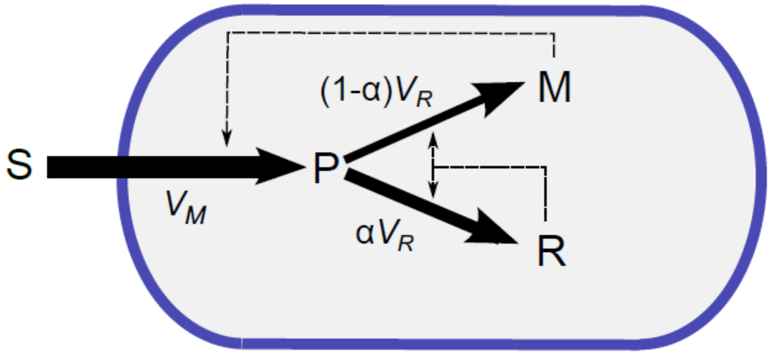
Outline of presentation

- Dynamic optimization: introduction and motivation
- Time-varying expression of enzymes in metabolic pathways and networks
- **Time-varying resource allocation and cellular growth**
- Conclusions and perspectives

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

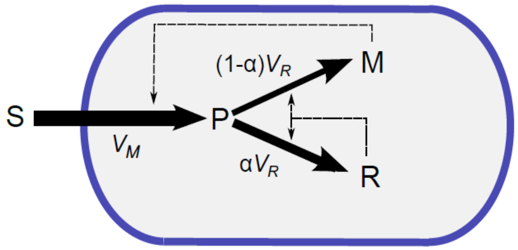
- Resource allocation can be studied using **self-replicator models** of bacterial growth

$$\frac{dp}{dt} = v_m(s,m) - v_r(p,r) - \mu\, p$$

$$\frac{dr}{dt} = \boxed{\alpha(t)}\, v_r(p,r) - \mu\, r$$

$$1/\beta = m + r$$

$$\mu = \beta\, v_r(p,r)$$



$$v_m(s,m) = k_m\, m\, \frac{s}{s+K_m} = k_m\,(1/\beta - r)\,\frac{s}{s+K_m}$$

$$v_r(p,r) = k_r\, r\, \frac{p}{p+K_r}$$

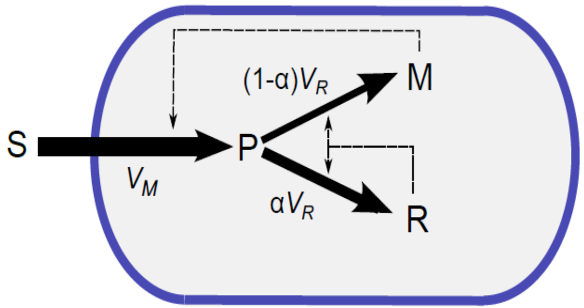
Time-varying resource allocation and growth

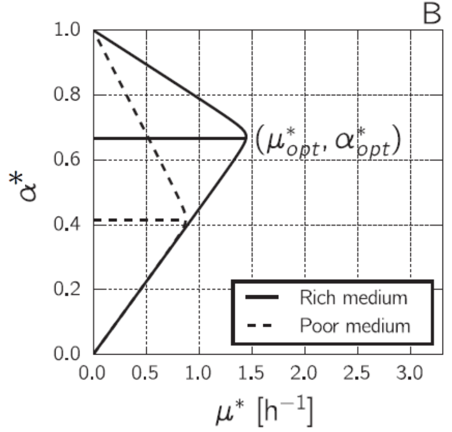
- **Assumption**: resource allocation has evolved to maximize growth
- **Static optimization problem**: given an objective function

$$J(\alpha^*) = \mu^* = \beta\, v_r(p^*, r^*)$$

find

$$\alpha^*_{opt} = \arg \max_{\alpha^* \in U} J(\alpha^*)$$





Time-varying resource allocation and growth

- **Assumption**: resource allocation has evolved to maximize growth
- **Dynamic optimization problem**: given an objective function

$$J(\alpha) = \int_0^{\tau} \mu(t)\, dt = \int_0^{\tau} \beta\, v_R(p,r)\, dt,$$

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

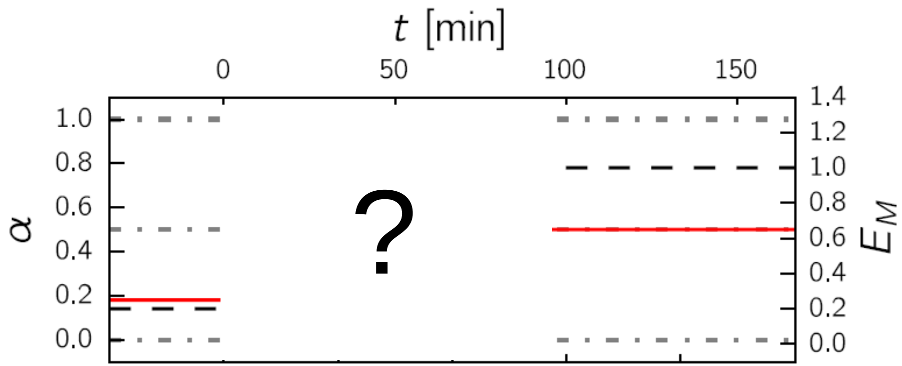
$$\alpha_{opt} = \arg\max_{\alpha \in \mathcal{U}} \; J(\alpha)$$

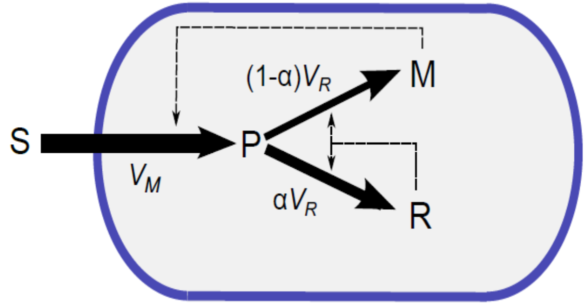
- Compute analytical or numerical solution using optimal control methods/tools

Giordano *et al.* (2016), *PLoS Comput. Biol.,* 12:e1004802
Yabo *et al.* (2022), *SIAM J. Appl. Dyn. Syst*., 21:137-165

Time-varying resource allocation and growth

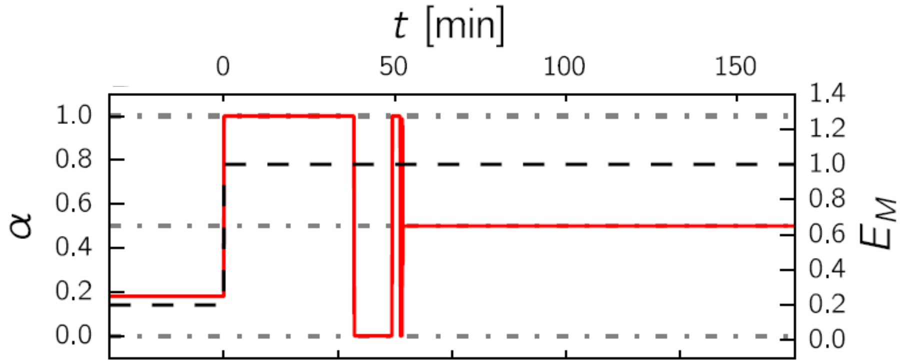
- What is the optimal resource allocation scheme for switch from poor to rich carbon source?

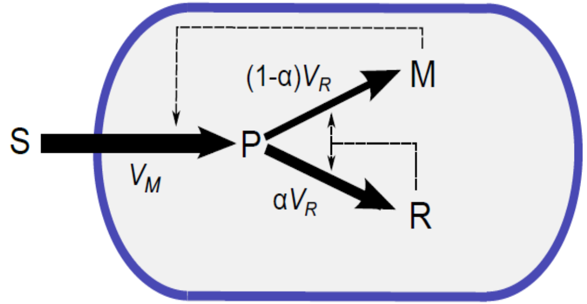




Time-varying resource allocation and growth

- Optimal resource allocation scheme is **bang-bang singular**
  - Sequence of switches between $\alpha = 1$ (maximal synthesis of gene expression machinery) and $\alpha = 0$ (maximal synthesis of metabolic machinery)
  - α is then set to α^*_{opt}, value leading to maximal growth rate in new medium

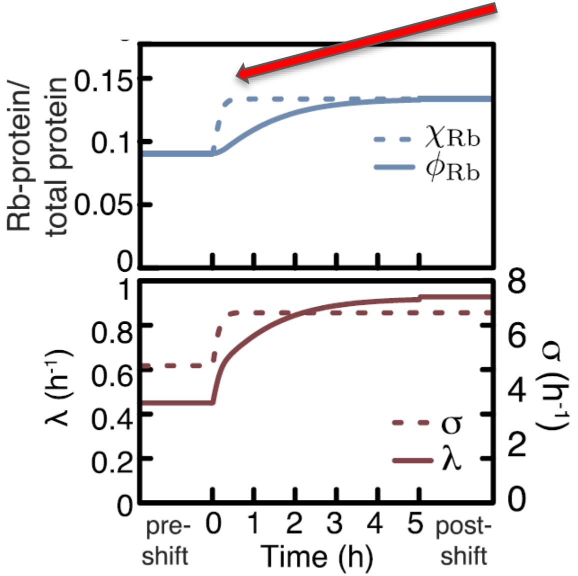




Time-varying resource allocation and growth

- Experimental evidence for oscillatory patterns in ribosome synthesis?

  No support from model based on population-level data

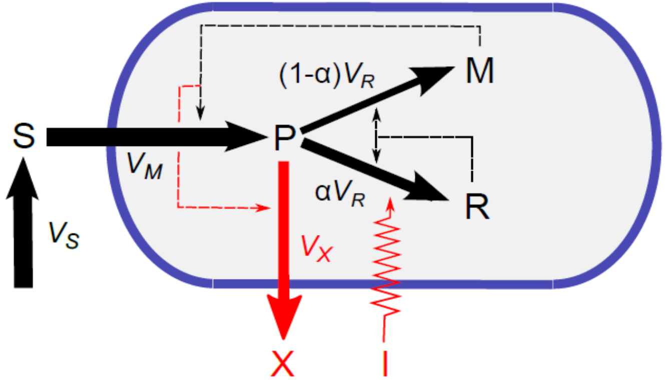


Upshift: succ → succ + gluc

Erickson *et al*. (2017), *Nature*, 551:119-23

Time-varying resource allocation and growth

- For biotechnological applications, one would like to **change** the natural resource allocation strategies of the cell
- Which external control I would **optimize production of X** over a given time interval?
- Optimal control problem with human-defined instead of naturally-evolved objective
- Optimal solution: first growth, then production



Izard, Gomez Balderas *et al.* (2015), *Mol. Syst. Biol.*, 11:840

Yegorov *et al.* (2019), *J. Math. Biol.*, 78:985-1032

Outline of presentation

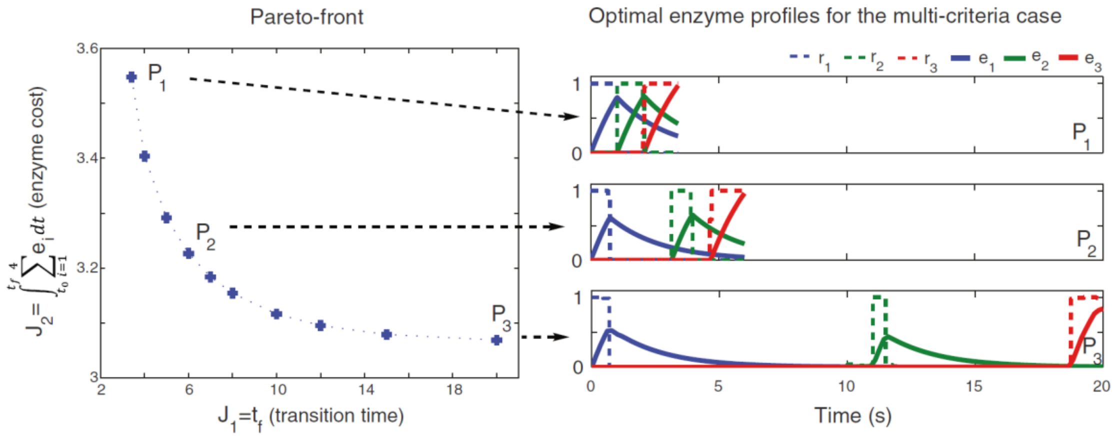
- Dynamic optimization: introduction and motivation
- Time-varying expression of enzymes in metabolic pathways and networks
- Time-varying resource allocation and cellular growth
- **Conclusions and perspectives**

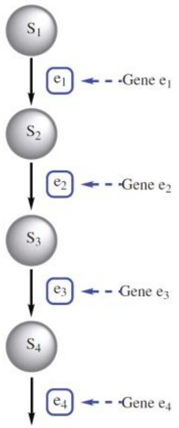
Conclusions

- **Pros** of dynamical optimization approach
  - Avoids modeling of (unknown) regulatory mechanisms
  - Allows specifications 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





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

- **Inverse optimality**: exploits huge amounts of available data to infer rather than assume objective function(s)
- **Experimental validation** of model predictions

Zhao *et al.* (2016), *Genome Biol.*, 17:109
Tsiantis *et al.* (2018), *Bioinformatics* 34:2433–40

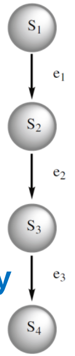
Economic metaphor

- Dynamic optimization perspective draws comparison between biological and economical processes
- Bacterial cells can be seen as economic agents
  - … with limited resources
  - … assigned to productive activities
  - … so as maximize their profits (or minimize their costs)
  - … in a changing, competitive market environment
  - … over a period of time
- Attractiveness of economic metaphor: provides intuitively plausible language to speak about cellular process

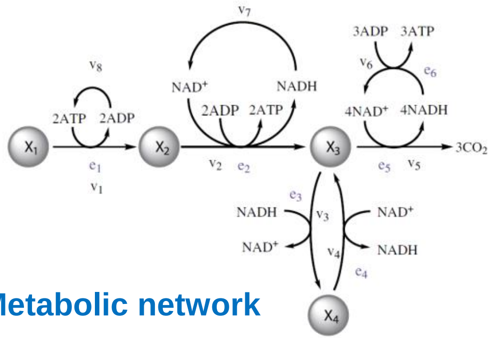
  Costs, investment, resource allocation, just-in-time, …

Economic metaphor

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

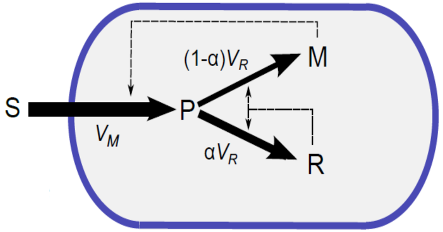


Metabolic pathway



Metabolic network

Cellular growth



Economic metaphor

- Dynamic optimization in two examples, increasingly larger scope:
  - Time-varying expression of enzymes in **metabolic pathways and networks**
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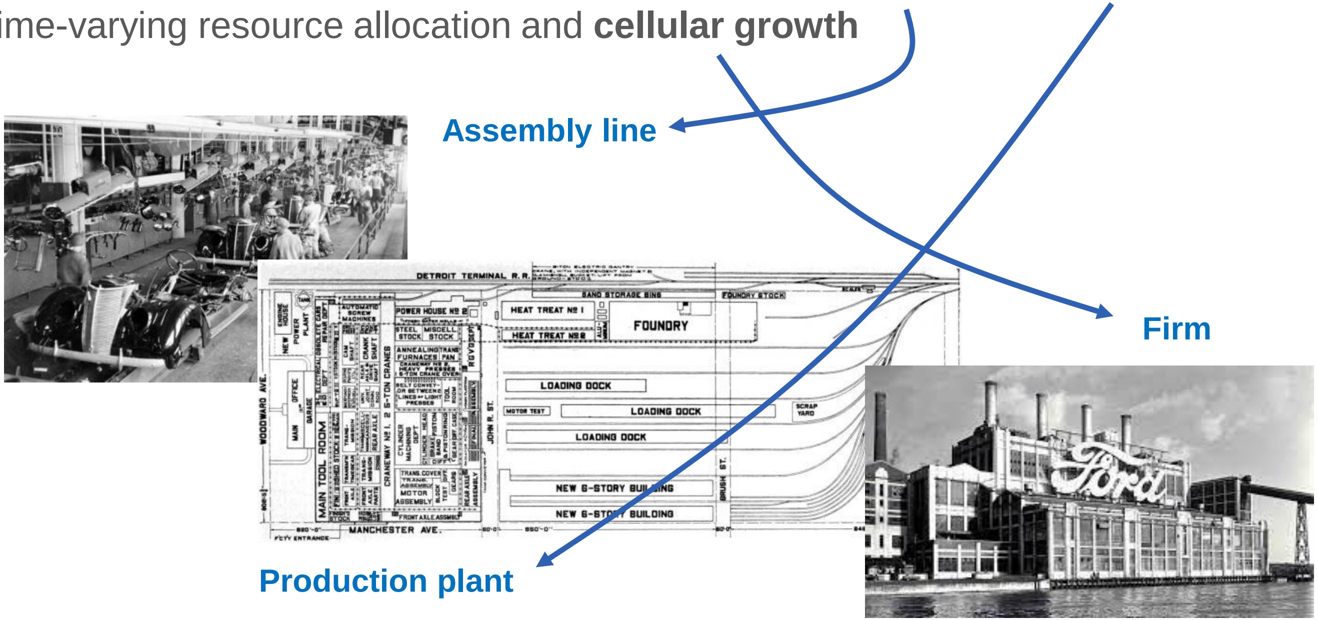

Economic metaphor

- Economists have developed **evolutionary economics**
  - Routines (capacities and rules of decision, investment strategies) shape behavior of firm
  - Routines are transmitted within the firm and gradually modified
  - Success of firm determined by ability to adapt routines to changing environment

Nelson and Winter (1982), *An Evolutionary Theory of Economic Change*, Belknap Press of Harvard University Press
Gayon (2011), *Biol. Theor.*, 6(4):320–5
https://en.wikipedia.org/wiki/Evolutionary_economics

- Limits to the evolutionary metaphor in economy
  - Firms grow and survive, but do not reproduce
  - Routines are transmitted, but within same evolving firm
  - Economic agents display (bounded) rationality and behavioral learning, rather than blind variation

- This also poses limits on the economic metaphor in biology!

Optimal Cell Behavior in Time – Thank You!