Optimal switching behavior, Just-in-time production

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Temporal Optimality

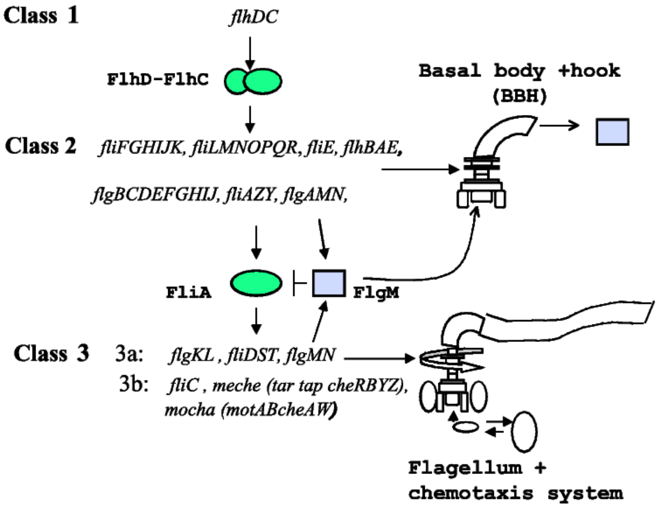
Maximizing a functional of a time-dependent function while respecting a given set of constraints.

Introduction

Observing temporal optimality

Kalir, S., McClure, J., Pabbaraju, K., Southward, C., Ronen, M., Leibler, S., Surette, M. G., and Alon, U. (2001).
Ordering genes in a flagella pathway by analysis of expression kinetics from living bacteria.
Science, 292(5524):2080–3.

Temporal optimality - can it be observed?



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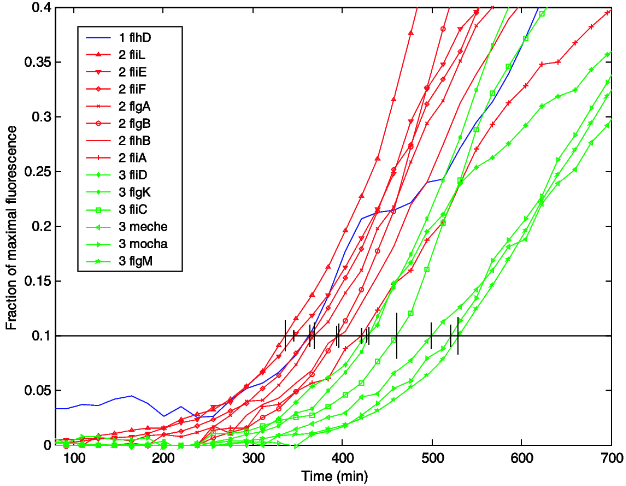

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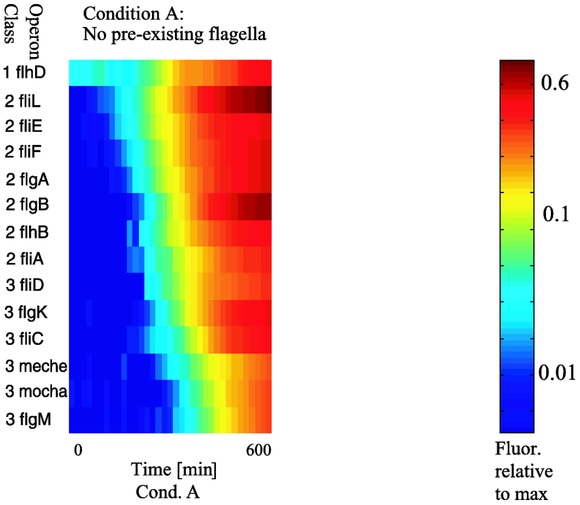

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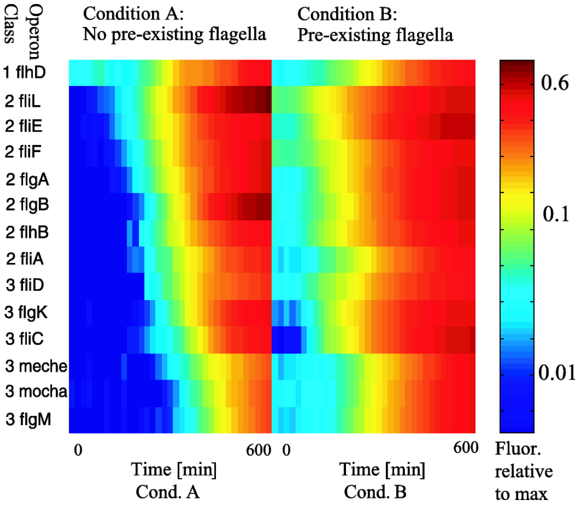

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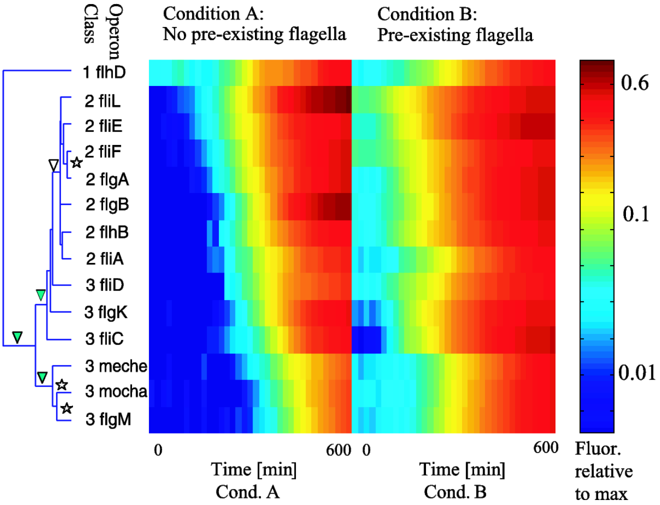

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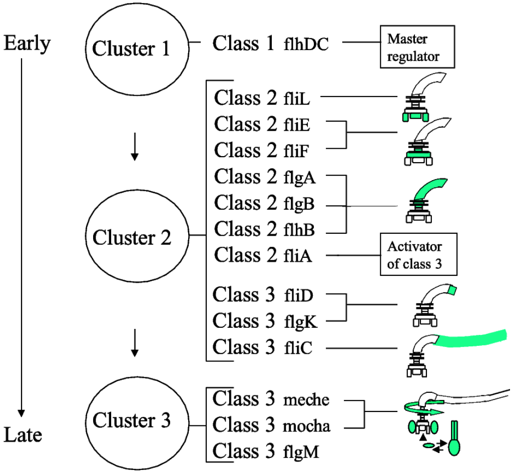
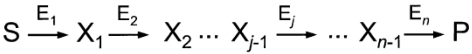


Linear kinetics

Theoretical foundation and application

Klipp, E., Heinrich, R., and Holzhütter, H.-G. (2002).
Prediction of temporal gene expression: Metabolic optimization by re-distribution of enzyme activities.
Eur J Biochem, 269(22):5406–5413.

Unbranched reaction chain, linear kinetics



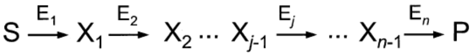
System equations

$$\frac{dS}{dt} = -k_1 \cdot E_1 \cdot S \quad (1)$$

$$\frac{dX_i}{dt} = k_i \cdot E_i \cdot X_{i-1} - k_{i+1} \cdot E_{i+1} \cdot X_i \quad (2)$$

$$\frac{dP}{dt} = k_n \cdot E_n \cdot X_{i-1} \quad (3)$$

Unbranched reaction chain, linear kinetics



Constraint

$$\sum_{i=1}^{n} E_i(t) = E_{\text{tot}} \tag{4}$$

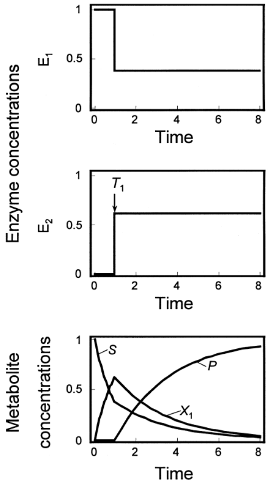
Performance

$$\tau = \frac{1}{C} \int_0^\infty (C - P(t))\, dt \tag{5}$$

$$C = S\big|_{t=0} \tag{6}$$

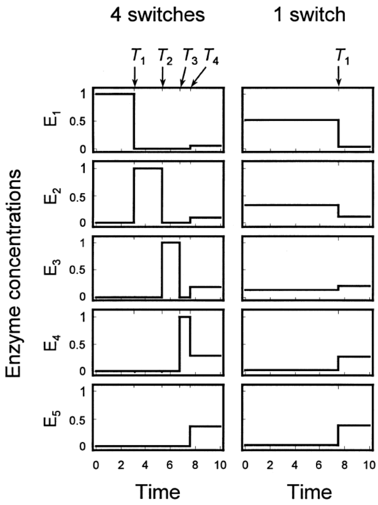
$$\tau \rightarrow \text{MINIMUM} \tag{7}$$

Unbranched reaction chain



- Optimize over the Banach-space of piecewise-constant functions
- One intermediary metabolite
- Solution for the optimization problem found explicitely

Unbranched reaction chain



- Four intermediary metabolites
- Numerical optimization of T_i and $E_i(j)$

1. Explicit solution of system equations for $P(t)$ depending on T_i and $E_i(j)$
2. Explicit calculation of the transition time τ
3. Minimization of τ by a steepest descent method

Unbranched reaction chain

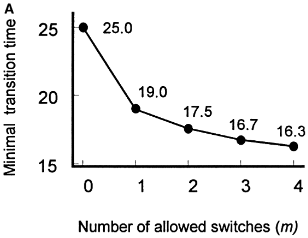
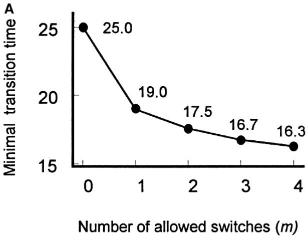


Figure A 4 intermediary metabolites

Figure B 0 to 9 intermediary metabolites

- Minimal transition time decreases with number of switches but only until # of switches reaches # of metabolites
- With increasing pathway length the payoff of time-dependent optimality increases

Unbranched reaction chain



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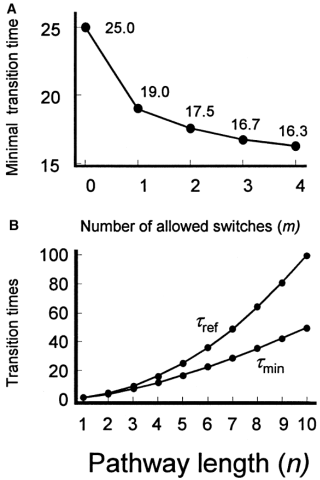

Figure **A** 4 intermediary metabolites

Figure **B** 0 to 9 intermediary metabolites

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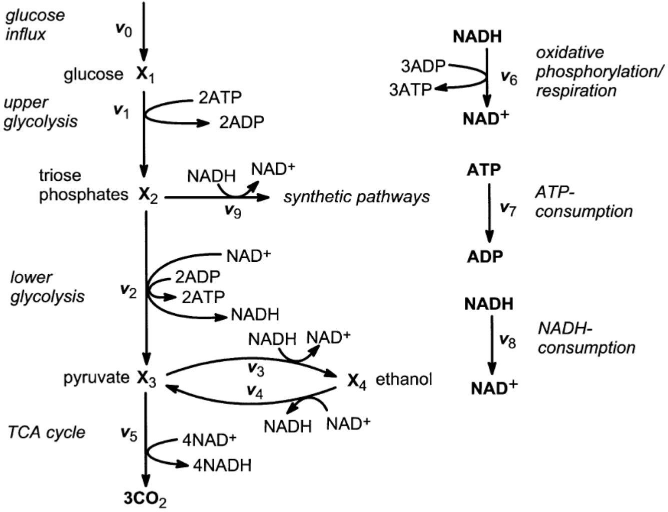
Central metabolism of yeast



Central metabolism of yeast - Mathematical formulation

System equations

...

Constraint

$$NADH + NAD^+ = const. \quad (8)$$

$$ATP + ADP = const. \quad (9)$$

$$\sum_{i=1}^{6} E_i(t) \leq E_{tot} \quad (10)$$

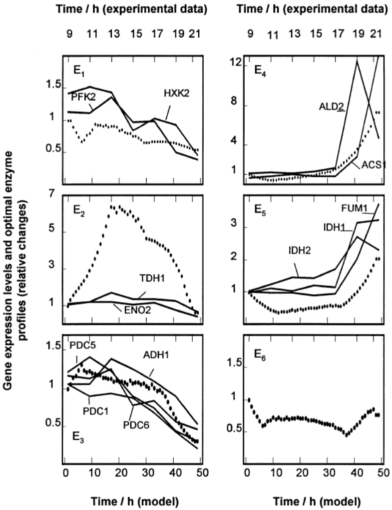
Performance

$$\vartheta = t\,\Theta\left(ATP - ATP_c\right)\Theta\left(NADH - NADH_c\right) \quad (11)$$

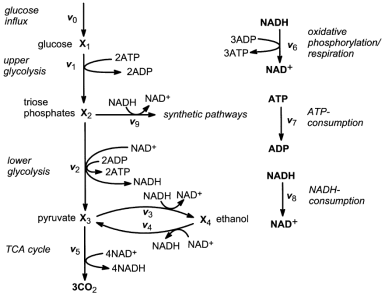
$$\Theta(x) = \begin{cases} 1 & \text{if} \quad x \geq 0 \\ 0 & \text{if} \quad x < 0 \end{cases} \quad (12)$$

$$\vartheta \rightarrow \text{MAXIMUM} \quad (13)$$

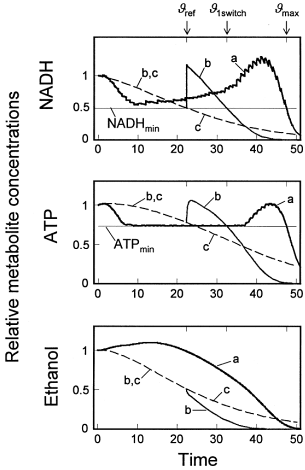
Central metabolism of yeast - Optimal enzyme profiles



- Optimal enzyme profiles: dotted curves
- Related gene expression profiles: solid curves
- Optimization performed with a genetic algorithm



Central metabolism of yeast - Time-courses of metabolites



Curves A optimal enzyme profiles

Curves B one optimal single switch of enzyme acitvities

Curves C time-independent enzyme concentrations

Towards a Michaelis-Menten kinetics modelling

R. Heinrich and E. Klipp, J. Theor. Biol. (1996), 182, 243-352
Control Analysis of Unbranched Enzymatic Chains in States of Maximal Activity.
Nat. Genet., 36(5):486–91.

Metabolic Control Analysis

MCA results for linear kinetics

- distributions of control coefficients and of enzyme concentrations correspond with eachother
- maximization of the steady-state flux leads to a decrease in enzyme concentrations and control coefficients along the pathway when equilibrium constants > 1

Extension to Michaelis Menten kinetics (Heinrich & Klipp, 1996)

- optimization performed also with respect to intrinsic kinetic parameters
- optimal results depend on external substrate concentrations

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Optimization in a Michaelis-Menten Pathway

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Unbranched reaction chain, Michaelis-Menten kinetics

$$\mathbf{S_0} \xrightarrow{\mathbf{E_1}} \mathbf{S_1} \xrightarrow{\mathbf{E_2}} \mathbf{S_2} \xrightarrow{\mathbf{E_3}} \mathbf{P}$$

metabolites: $$\frac{dS_i}{dt} = V_i E_i \frac{S_{i-1}}{S_{i-1} + Km_i} - V_{i+1} E_{i+1} \frac{S_i}{S_i + Km_{i+1}} - \alpha S_i$$

enzymes: $$\frac{dE_i}{dt} = \beta_i \frac{1}{1 + R(t)/k_i} - \alpha E_i$$

α cell division rate

β maximal promoter activity

$R(t)$ active repressor level

k_i repression coefficient

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Optimality with respect to a cost function to be minimized:

$$C = a \sum_i \int_0^T \beta_i \frac{1}{1 + R(t)/k_i} dt + \int_0^T \left| \frac{dP}{dt} - \frac{dP}{dt}_{\text{goal}} \right| dt$$

Goals:

- minimize the total enzyme concentration used
- as fast as possible substrate-product turnover

Unbranched reaction chain, Michaelis-Menten kinetics

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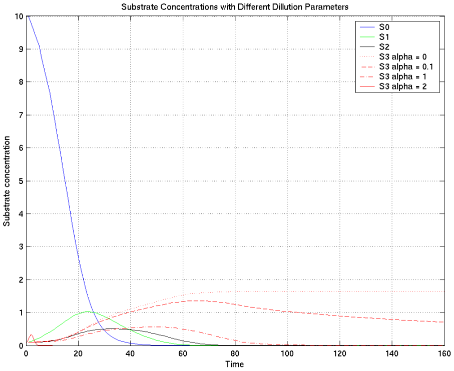
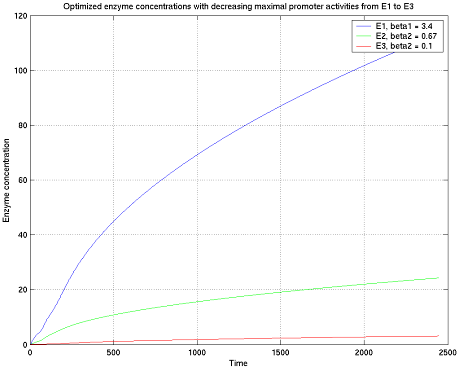
Results: Substrates in Time at Different Cell Division Rates



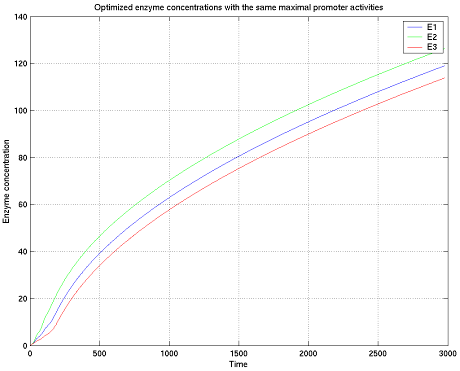
- dilution effects due to cell division determine the slope of the product concentration (red curves)

Results: Optimal Enzyme Concentrations



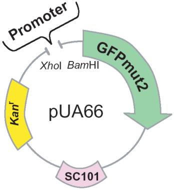
- optimal promoter activity levels are distributed through time in a hierarchical manner $\beta_1 > \beta_2 > \beta_3$ just as the respective enzyme concentrations

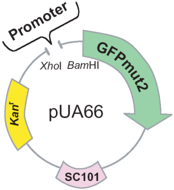
Results: Enzyme Concentrations at a Uniform Promoter Activity



- reference enzyme concentrations levels with the same promoter activity levels $\beta_1 = \beta_2 = \beta_3$

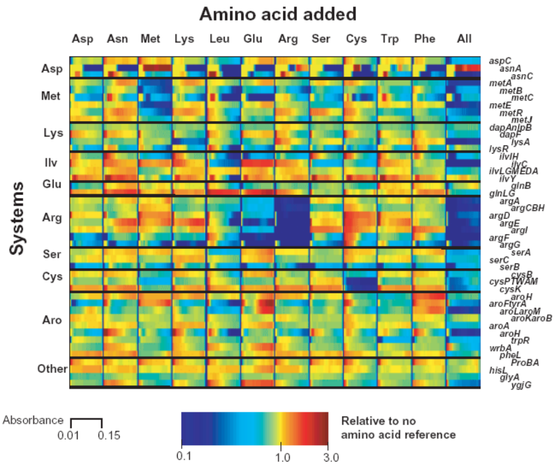
Aminonacid Biosynthesis Pathways





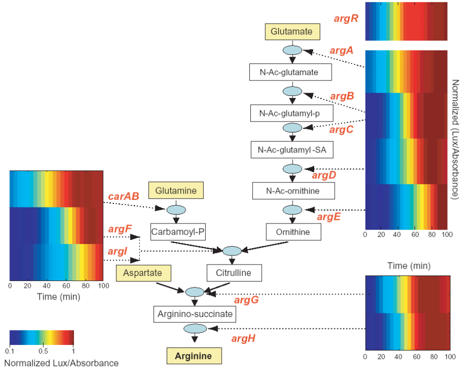
- time measurements of promoter activity of genes involved in aminoacid biosynthesis (AAB) using GFP and Lux Reporter genes (resolution: 8 minutes)
- activity of AAB-Promoters in a medium lacking all amino-acids vs. a medium with one aminoacid and all aminoacids

Aminonacid Biosynthesis Pathways



- decrease of AAB promoter activity of involved genes when adding the respective aminoacid to the medium
- decrease of activity of all promoters when adding all aminoacids

Temporal Order: Arginine Biosynthesis



- Observing temporal ordering in promoter activity profiles and in unnormalized expression kinetics

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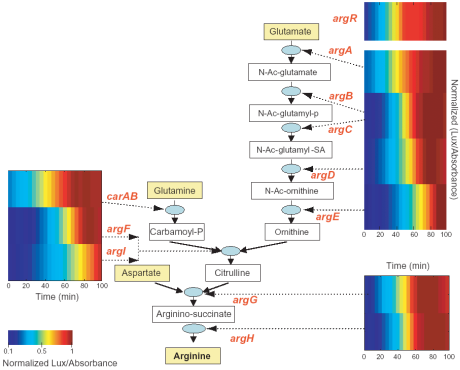

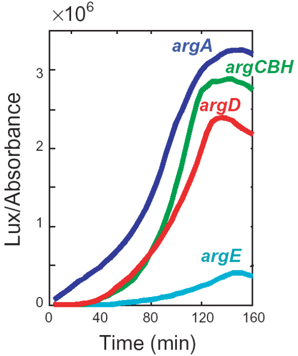

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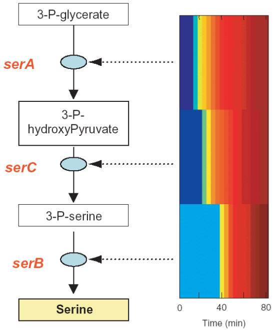
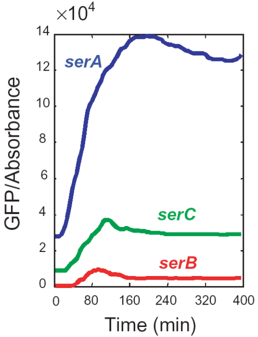
Temporal Order: Serine Biosynthesis





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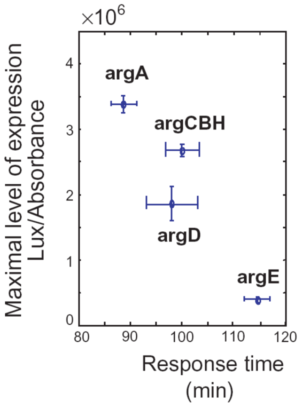
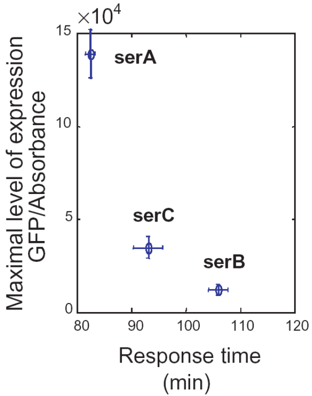
Early Pathway Appearence, a Higher Promoter Activity





- The maximal promotor activity level is higher and it is reached faster for enzymes appearing earlier in the pathway
(left: arginine, right: serine)

Discussion

- evolutionary development of biological systems implies a non-random distribution of parameters within pathways
- optimization is performed with respect to certain goal functions
- introduced optimality principles in unbranched linear and Michaelis-Menten kinetic pathways
  - temporal optimality
  - switching behaviour
  - just-in-time production

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Take-home messages

Principle of temporal optimality

Maximizing a functional of time dependent functions while respecting a given set of constraints

Just-in-time production

Producing enzymes right when they are needed is often optimal

Bibliography I

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