



Prediction of temporal gene expression
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Dynamic optimisation

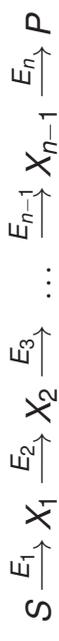
Find **time-dependent** enzyme concentrations that minimize the **transition time** τ needed to convert S into P.

Performance

$$\tau = \frac{1}{C} \int_0^{\infty} (C - P(t)) dt, \quad C = S|_{t=0}, \quad \tau \rightarrow \min$$

Constraint

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



Differential equations

$$\begin{aligned} \frac{dS}{dt} &= -k_1 E_1 S \\ \frac{dX_i}{dt} &= k_i E_i X_{i-1} - k_{i+1} E_{i+1} X_i \\ \frac{dP}{dt} &= k_n E_n X_{n-1} \end{aligned}$$

(with $X_0 = S$)



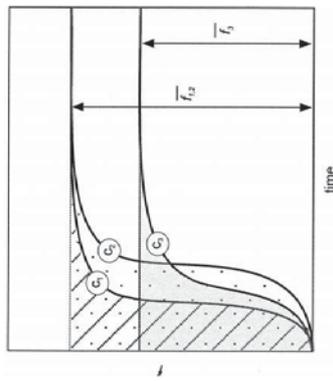
Transition time

Llorens et al. 1999

- ▷ Time taken by $f(t)$ to reach steady-state value.
- ▷ Quotient of the area enclosed by the final state and the curve, and the overall variation of f :

$$\tau = \frac{1}{\bar{f}} \int_0^{\infty} (\bar{f} - f(t)) dt$$

- ▷ $\tau_{c(1)} < \tau_{c(3)} < \tau_{c(2)}$

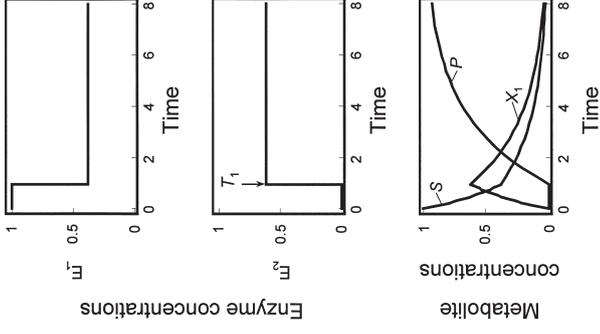




Case: $n = 2$

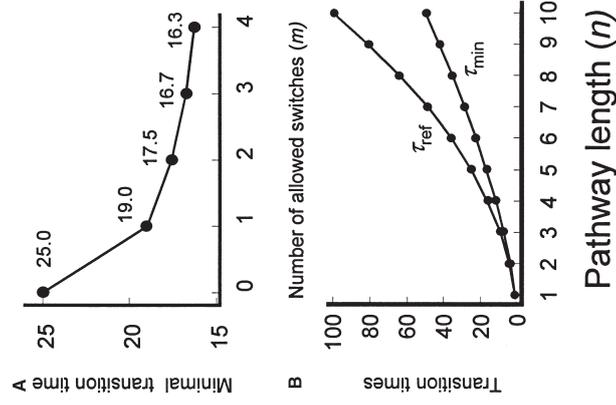


- ▷ Two time intervals
- ▷ Switching time $T_1 = \ln(2/(3 - \sqrt{5}))$
- ▷ First interval ($t \leq T_1$):
 $E_1 = 1, E_2 = 0 \quad [E_{tot}]$
- ▷ Second interval ($t > T_1$):
 $E_1 = (3 - \sqrt{5})/2,$
 $E_2 = \ln(\sqrt{5} - 1)/2$
- ▷ Optimal transition time:
 $\tau_{min} = 1 + T_1 + (1 - e^{-T_1})^{-1} [(k \cdot E_{tot})^{-1}]$



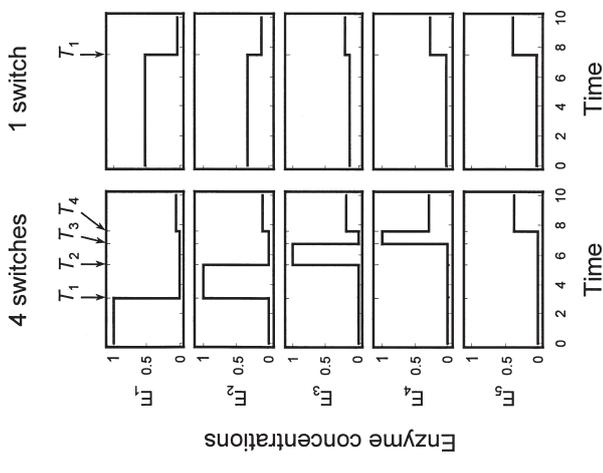
Minimal transition times

- ▷ For $n = 5$, the minimal transition time is achieved for $m = 4$.
- ▷ In general, the transition time seems to decrease with the number of switches, until $m = n - 1$.

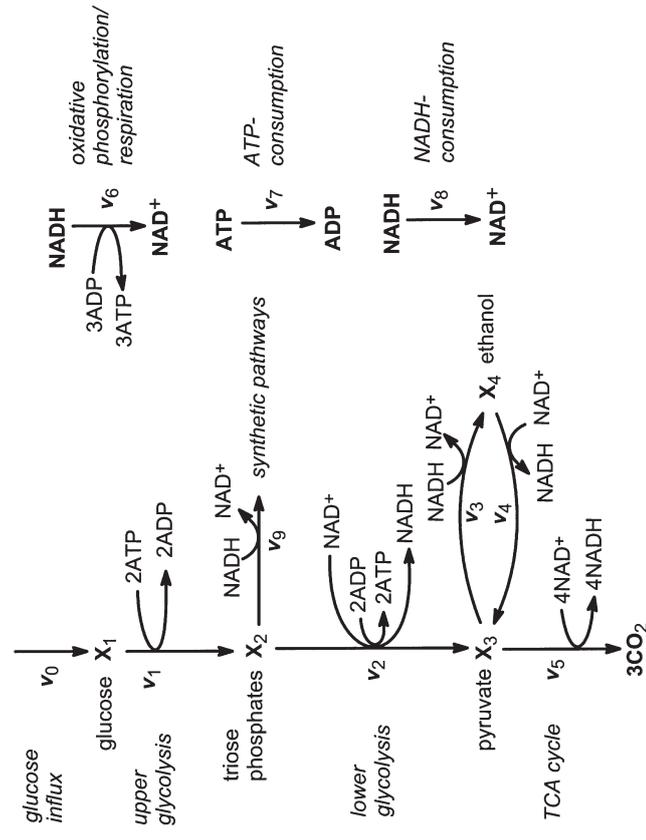


Case: $n > 2$

- ▷ Numerical solution
- ▷ Divide time horizon into $m + 1$ intervals and assume $E_i(t)$ constant on each interval.
- ▷ Compute switching times and enzyme concentrations minimizing the transition time τ .
- ▷ Except the last interval, only 1 enzyme is active at a time.



Central metabolism of yeast





Differential equations

$$\begin{aligned}
 dX_1/dt &= v_0 - v_1 \\
 dX_2/dt &= 2v_1 - v_2 - v_9 \\
 dX_3/dt &= v_2 - v_3 + v_4 - v_5 \\
 dX_4/dt &= v_3 - v_4 \\
 dNADH/dt &= v_2 - v_3 + v_4 + 4v_5 - v_6 - v_8 - v_9 \\
 dATP/dt &= -2v_1 + 2v_2 + 3v_6 - v_7
 \end{aligned}$$

Rate laws

$$\begin{aligned}
 v_1 &= E_1 \cdot k_1 \cdot X_1 \cdot ATP \\
 v_2 &= E_2 \cdot k_2 \cdot X_2 \cdot NAD^+ \cdot ATP \\
 v_3 &= E_3 \cdot k_3 \cdot X_3 \cdot NADH \\
 v_4 &= E_4 \cdot k_4 \cdot X_4 \cdot NAD^+ \\
 v_5 &= E_5 \cdot k_5 \cdot X_3 \cdot NAD^+ \\
 v_6 &= E_6 \cdot k_6 \cdot NADH \cdot ADP \\
 v_7 &= k_7 \cdot ATP \\
 v_8 &= k_8 \cdot NADH \\
 v_9 &= k_9 \cdot X_2 \cdot NADH
 \end{aligned}$$

Constraints

$$\begin{aligned}
 NADH + NAD^+ &= \text{const} \\
 ATP + ADP &= \text{const} \\
 \sum_{i=1}^6 E_i(t) &\leq E_{\text{tot}}
 \end{aligned}$$

Performance

$$\theta = t \cdot \frac{\Theta(ATP - ATP_{\text{crit}})}{\Theta(NADH - NADH_{\text{crit}})}$$

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

$$\theta \rightarrow \max$$

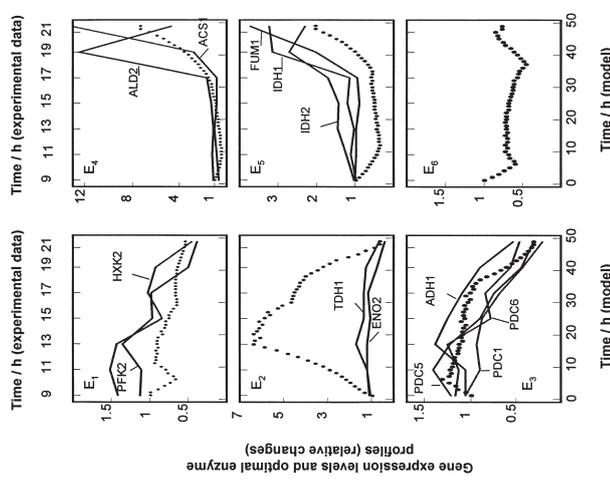
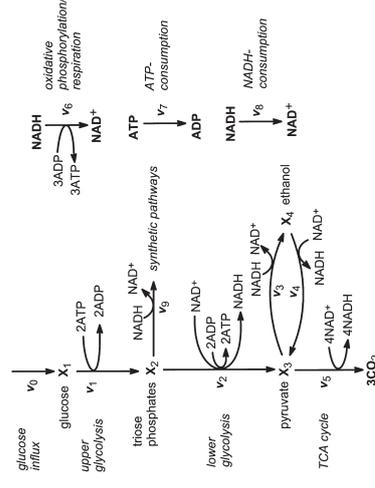
→ survival time



- ▷ Start in steady-state ($t < 0$), at $t = 0$ turn off glucose supply ($v_0 = 0$).
- ▷ Maximise survival time θ .
- ▷ Use genetic algorithm to compute optimal enzyme concentrations (for equidistant switching times).
- ▷ Compare with experimental results.

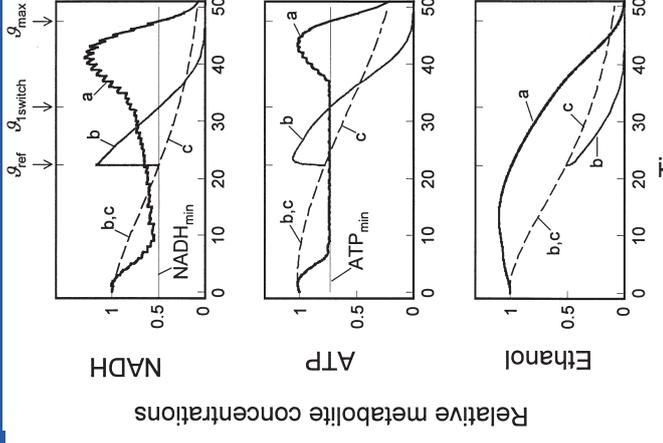


- ▷ Depletion of glucose.
- ▷ Utilize ethanol to maintain NADH/NAD⁺ and ATP levels.
- ▷ Switch from fermentation to respiration.
- ▷ Down-regulation of glycolysis, up-regulation of TCA cycle and gluconeogenesis.
- ▷ Survive over longer periods of starvation.





- ▷ NADH, ATP, ethanol concentrations
- ▷ **Three scenarios**
 - a) Optimal time-dependent enzyme profiles
 - b) Single switch
 - c) Time-independent enzyme profiles
- ▷ Calculated survival times $\theta_{\max}, \theta_{1\text{switch}}, \theta_{\text{ref}}$



- ▷ Evolutionary optimisation of gene expression in mathematical terms.
- ▷ Turning on/off enzyme activities may significantly improve metabolic efficiency.
- ▷ Limited resources force the cell to concentrate protein synthesing capacities to enzymes that are currently needed.
- ▷ Optimal long-term strategy is not optimal regarding short-term behavior (cf. lag phase in unbranched pathway, intermediate storage of ethanol in yeast).