Prediction of temporal gene expression

by E. Klipp, R. Heinrich, H.G. Holzhütter, Eur. J. Biochem. 269, 5406-13, (2002)

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Mathematics for key technologies

Unbranched pathway

$$S \xrightarrow{E_1} X_1 \xrightarrow{E_2} X_2 \xrightarrow{E_3} \ \dots \ \xrightarrow{E_{n-1}} X_{n-1} \xrightarrow{E_n} P$$

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 $X_0 = S$)

Dynamic optimisation

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

Performance

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

Constraint

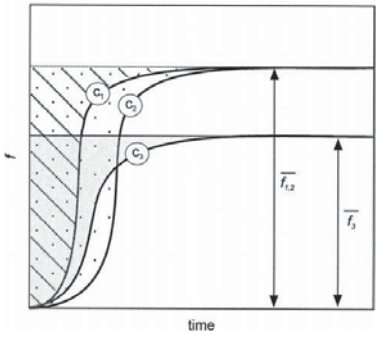
$$\sum_{i=1}^{n} E_i(t) \leq E_{tot}$$

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:

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



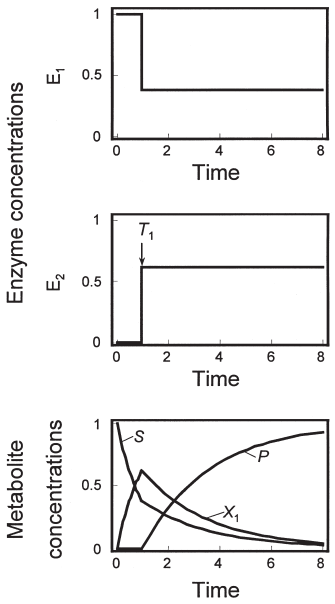
- $\tau_{c(1)} < \tau_{c(3)} < \tau_{c(2)}$

Case: n = 2

$S \xrightarrow{E_1} X \xrightarrow{E_2} P$

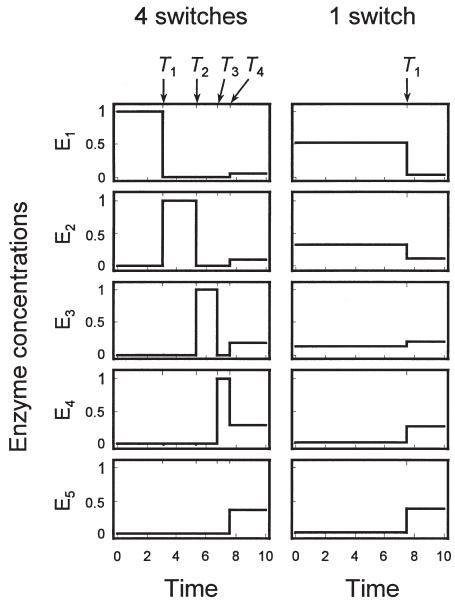
⇝ analytic solution

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



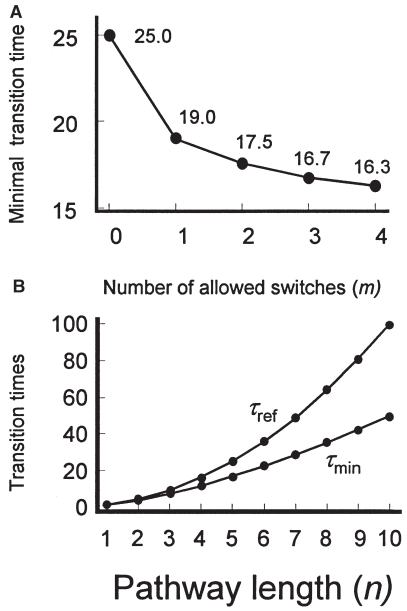
Case: n > 2

- 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.

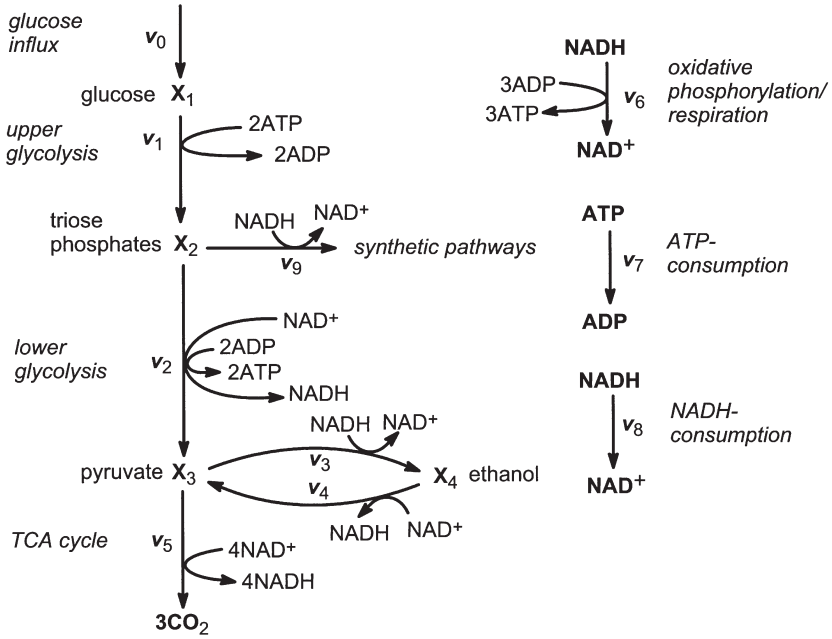


Minimal transition times

- 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 $m = n-1$.



Central metabolism of yeast



Mathematical model

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

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

Performance

$$
\begin{aligned}
\theta &= t \cdot \Theta(ATP - ATP_{crit}) \cdot \Theta(NADH - NADH_{crit}) \\
\Theta(x) &= \begin{cases} 1, \text{ if } x \geq 0 \\ 0, \text{ if } x < 0 \end{cases} \\
\theta &\rightarrow \max
\end{aligned}
$$

$\rightsquigarrow$ survival time

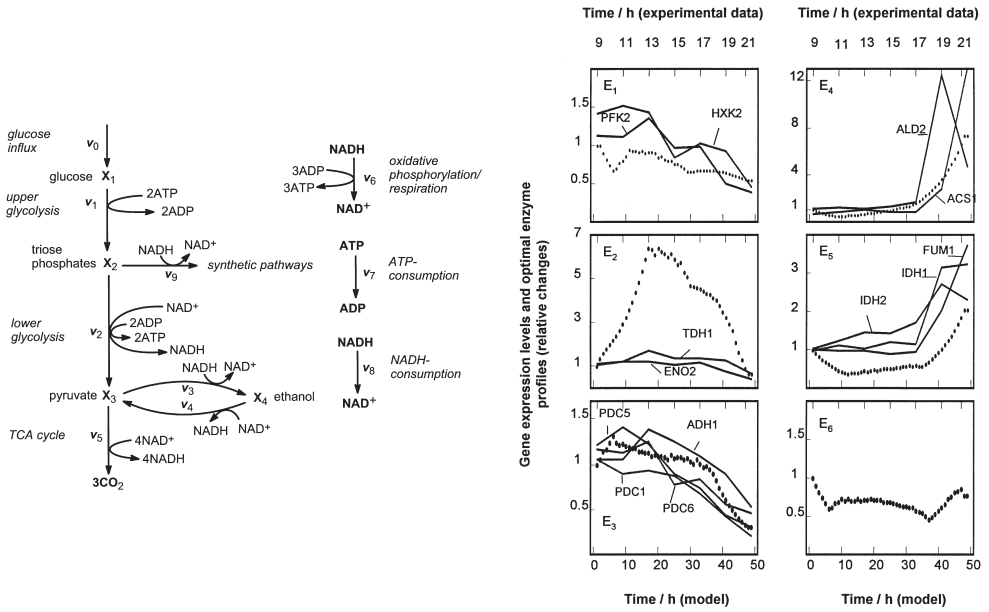
Diauxic switch

- 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.

Computational Set-up

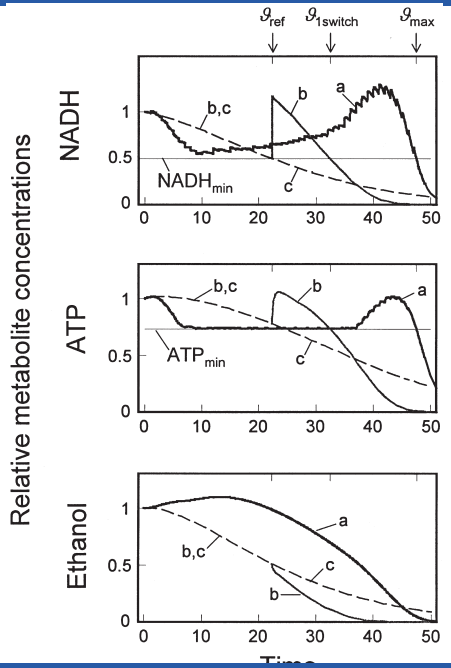
- Start in steady-state ($t < 0$), at $t = 0$ turn off glucose supply ($v_0 = 0$).
- Maximise survival time θ.
- Use genetic algorithm to compute optimal enzyme concentrations (for equidistant switching times).
- Compare with experimental results.

Diauxic switch



Metabolite concentrations

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



Discussion

- 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).