**Growth-rate dependence of gene expression**

- # promoter/gene: $N_{g,i}$
- # mRNA: $N_{mR,i}$
- # proteins: $N_{P,i}$
- steady-state protein conc

- follow the growth dependence of each parameter
- unravel the ‘conspiracy’ of global control to ensure $\sum_i [P_i] \approx \text{const.}$

$$[g_i] = \frac{N_{g,i}}{V}$$
$$[mR_i] = \frac{N_{mR,i}}{V}$$
$$[P_i] = \frac{N_{P,i}}{V}$$

\[ \frac{d}{dt}[mR_i] = \alpha_i [g_i] - \delta_i [mR_i] \]
\[ \frac{d}{dt}[P_i] = \eta_i [mR_i] - \lambda [P_i] \]

**Summary:**

\[ \frac{d}{dt}[P_i] = \eta_i [mR_i] - \lambda [P_i] \]
\[ \psi_i \equiv [mR_i]/[mR], \phi_i \equiv [P_i]/[P] \]
\[ \eta_i \cdot \psi_i [mR] = \lambda \phi_i [P] \]
\[ \psi_i \approx \phi_i \]
\[ \eta_i \approx \bar{\eta} \quad \text{&} \quad \bar{\eta} \cdot [mR] \approx \lambda [P] \]

by setting tsl init seq

\[ \bar{\eta} \approx \frac{\epsilon}{0.22 \ell} \quad \text{or} \quad 200 \text{ nt} \]

- coordination of tsl init & elong

\[ \lambda [P] \ell_p = \epsilon \cdot [Rb^*] \]
\[ \bar{\eta} \cdot [mR] \approx \frac{\epsilon}{\ell_p} [Rb^*] \]

\[ [mR] \approx 0.22 \cdot [Rb^*] \]

- mechanism ?

\[ \ell_p \approx \frac{\epsilon}{0.22 \ell} \]

- \[ \bar{\eta} \approx \frac{\epsilon}{0.22 \ell} \]

- Rb elongation speed (nt/s)

\[ \epsilon = - \frac{\text{Rb elongation speed}}{\text{cell volume}} \]

\[ d = \frac{\epsilon}{\bar{\eta}} \]

**Graph A:**

- [mRNA] vs. growth rate (1/h)
- [Rb] vs. active ribosomes
- [Rb] vs. [Rb]_ext
mRNA turnover ($\delta_i$)

\[
\begin{align*}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{align*}
\]

- stop initiation of transcription at 't = 0' (rifampicin)
- measure mRNA abundance for $t > 0$ (RNA-seq)
- fit to delayed exponential decay:
  \[ [mR_i](t) = [mR_i](0) \cdot e^{-\delta_i(t-t_0)} \]
- note that only relative abundance required

\[
\begin{align*}
\text{glucose} &\quad \lambda = 0.96/h \\
\text{mannose} &\quad \lambda = 0.34/h
\end{align*}
\]

mRNA turnover ($\delta_i$) weakly dependent on gene and condition

\[
\begin{align*}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{align*}
\]

\[
\begin{align*}
\delta_i &\approx \bar{\delta} \equiv \sum \psi_i \approx 0.5/min \\
\Rightarrow &\quad \text{GR-dependence of total mRNA abundance must come from mRNA synthesis ($\alpha_i$)}
\end{align*}
\]

- stop initiation of transcription at 't = 0' (rifampicin)
- measure mRNA abundance for $t > 0$ (RNA-seq)
- fit to exponential decay:
  \[ [mR_i](t) = [mR_i](0) \cdot e^{-\delta_i t} \]
- note that only relative abundance required
mRNA turnover ($\delta_i$)

$$\begin{align*}
\frac{d}{dt} [mR_i] &= \alpha_i [g_i] - \delta_i [mR_i] \\
\frac{d}{dt} [P_i] &= \eta_i [mR_i] - \lambda [P_i]
\end{align*}$$

detour:

- huge burstiness typical: $\eta_i/\delta_i \sim 20$
- post-tsx regulation

(change in mRNA turnover: signature of sRNA and protein regulation)
mRNA turnover ($\delta_i$) weakly dependent on gene and condition

\[
\begin{align*}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{align*}
\]

- stop initiation of transcription at $t = 0$ (rifampicin)
- measure mRNA abundance for $t > 0$ (RNA-seq)
- fit to exponential decay:
  \[ [mR_i](t) = [mR_i](0) \cdot e^{-\delta_i t} \]
- note that only relative abundance required

focus on mRNA synthesis ($\alpha_i$):

\[
\begin{align*}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{align*}
\]

steady-state: $\alpha_i[g_i] = \delta_i[mR_i]$  

total mRNA synthesis flux:

\[ J_{mR} \equiv \Sigma_i \alpha_i[g_i] = \bar{\delta} \cdot [mR] \]

constancy of $\bar{\delta}$: change in $[mR]$ from $J_{mR}$

\[ \text{total mRNA synthesis flux tuned to match the translational capacity} \]
focus on mRNA synthesis ($\alpha_i$):

$$\frac{d}{dt}[mR_i] = \alpha_i[g_i] - \delta_i[mR_i]$$

$$\frac{d}{dt}[P_i] = \eta_i[mR_i] - \lambda [P_i]$$

steady-state: $\alpha_i g_i = \delta_i mR_i$

total mRNA synthesis flux:

$$J_{mR} = \sum_i \alpha_i g_i = \delta \cdot [mR]$$

model of transcriptional regulation:

$$G_i([A], [B], ...) \frac{[RNAP^*]}{K_i} k_{i,0}$$

RNAP recruitment rate $\rightarrow R_i([A], [B], ...)$

$$J_{mR} = \sum_i \alpha_i g_i = [RNAP^*] \sum_i g_i R_i$$

- RNAP components GR-independent
- anti-$\sigma^D$ factor Rsd upregulated as growth slows down

$\Rightarrow$ Rsd titrates the pool of available RNAP to match tsx output with tsl capacity

$\Rightarrow$ Rsd expression significantly affects the rate of total mRNA synthesis

$\Rightarrow$ $\Delta rsd$ strain exhibits growth defect in proportion to its expression level in WT
focus on mRNA synthesis ($\alpha_i$):
\[
\begin{aligned}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{aligned}
\]
steady-state: $\alpha_i[g_i] = \delta_i[mR_i]$

Summary
$\alpha_i[g_i] = [RNA反应][g_i]\cdot R_i = \bar{\delta} \psi_i[mR_i]$
\[
\Rightarrow \psi_i \propto [g_i] \cdot R_i
\]
\[
\Rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot R_i
\]
\[
\Rightarrow [P_i] \propto [g_i] \cdot R_i
\]

i.e., protein conc set “directly” by transcriptional regulation (weighted by gene copy #)
independent of growth changes

constitutive expression ($R_i=$const)
\[
\Rightarrow \text{expect } [P_i] \propto [g_i] \propto e^{-x\cdot \lambda T_c}
\]

\[
\begin{array}{c}
\text{growth rate (1/h)} \\
0 & 0.5 & 1
\end{array}
\]
\[
\begin{array}{c}
P_i \text{ (in mL)} \\
0 & 0.5 & 1
\end{array}
\]

- $Ptet:gfp$ at oriC ($x_i = 0$)
- $Ptet:gfp$ at terC ($x_i = 1$)

$\lambda T_c \approx \frac{2}{3} \cdot (0.3 + \lambda T_0)$, $T_0 \approx 1$ h

focus on mRNA synthesis ($\alpha_i$):
\[
\begin{aligned}
\frac{d}{dt}[mR_i] &= \alpha_i[g_i] - \delta_i[mR_i] \\
\frac{d}{dt}[P_i] &= \eta_i[mR_i] - \lambda [P_i]
\end{aligned}
\]
steady-state: $\alpha_i[g_i] = \delta_i[mR_i]$

Summary
$\alpha_i[g_i] = [RNA反应][g_i]\cdot R_i = \bar{\delta} \psi_i[mR_i]$
\[
\Rightarrow \psi_i \propto [g_i] \cdot R_i
\]
\[
\Rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot R_i
\]
\[
\Rightarrow [P_i] \propto [g_i] \cdot R_i
\]

i.e., protein conc set “directly” by transcriptional regulation (weighted by gene copy #)
independent of growth changes

Global survey of relation between $[P_i]$ and $R_i$
focus on mRNA synthesis ($\alpha_i$):

$$
\begin{align*}
\frac{d}{dt}[m_{R_i}] &= \alpha_i[g_i] - \delta_i[m_{R_i}] \\
\frac{d}{dt}[p_i] &= \eta_i[m_{R_i}] - \lambda [p_i]
\end{align*}
$$

steady-state: $\alpha_i[g_i] = \delta_i[m_{R_i}]$

Summary

$$
\alpha_i[g_i] = [RNA^{\ast}][g_i]R_i = \delta \psi_i[m_{R_i}]
\Rightarrow \psi_i \propto [g_i] \cdot R_i
\Rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot R_i
\Rightarrow [p_i] \propto [g_i] \cdot R_i
$$

i.e., protein conc set “directly” by transcriptional regulation 
(weighted by gene copy #) independent of growth changes

In general,

$$
\phi_i \approx \psi_i \approx \frac{[g_i] \cdot R_i}{\sum_i [g_i] R_i}
$$

“quantitative central dogma”

$\Rightarrow [p_i] \propto [g_i] \cdot R_i$ requires fixed $\sum_i [g_i] R_i$

$\Rightarrow$ approximately obtained for WT cells

$\Rightarrow$ not always true for mutants

Summary

$\alpha_i[g_i] = [RNA^{\ast}][g_i]R_i = \delta \psi_i[m_{R_i}]
\Rightarrow \psi_i \propto [g_i] \cdot R_i
\Rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot R_i
\Rightarrow [p_i] \propto [g_i] \cdot R_i
$

i.e., protein conc set “directly” by transcriptional regulation 
(weighted by gene copy #) independent of growth changes

Carbon limitation

```
carbon source -> keto acids <- amino acids
```

```
cAMP <- ppGpp
```

Other genes catabolic genes ribosomal genes

47