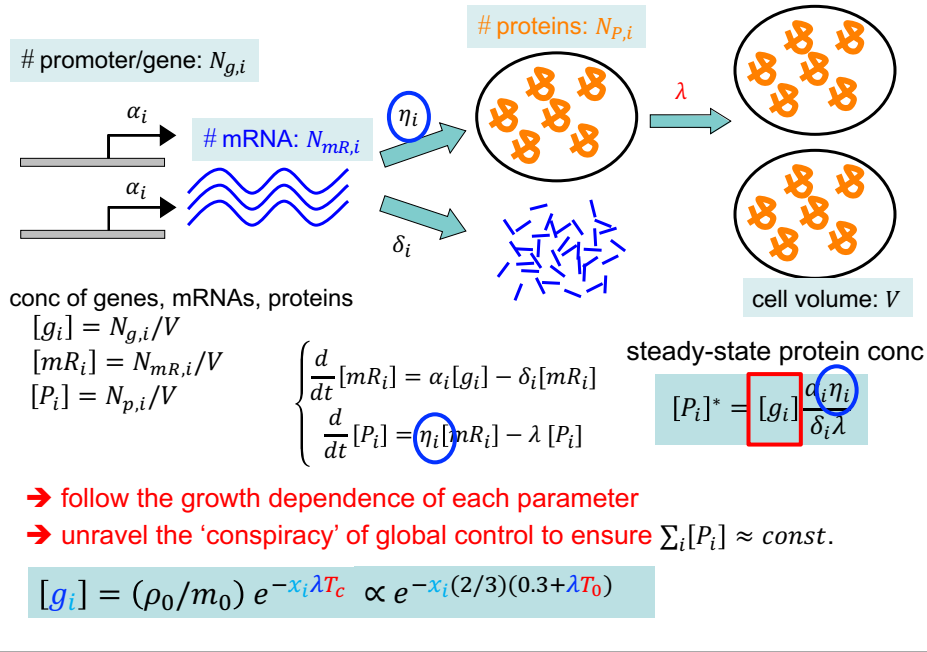
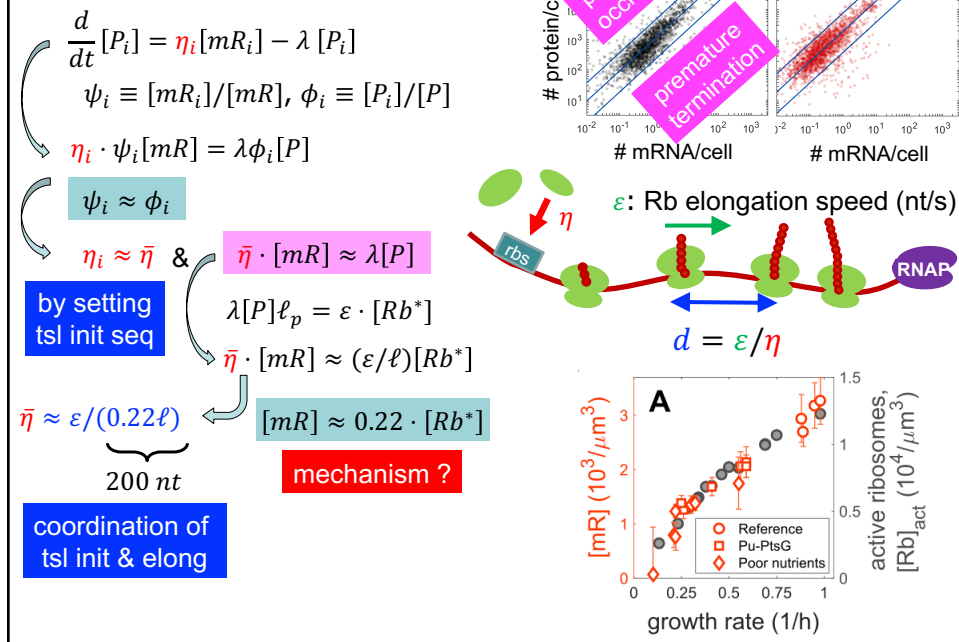


Growth-rate dependence of gene expression



30

Summary:



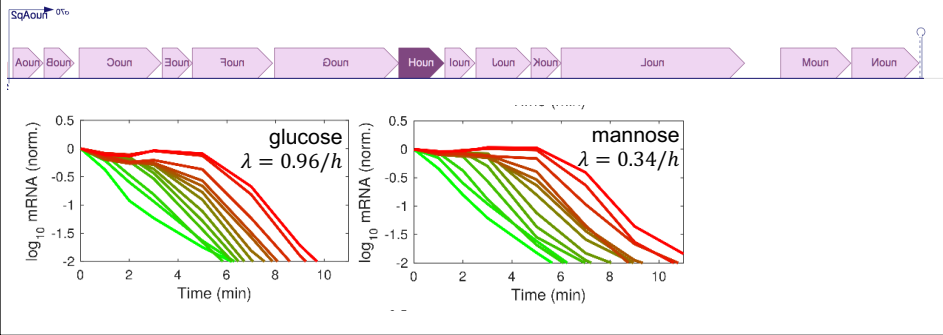
31

mRNA turnover (δ_i)

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

- stop initiation of transcription at 't = 0' (rifampicin)
- measure mRNA abundance for t > 0 (RNA-seq)
- fit to delayed exponential decay:

$$[mR_i](t) = [mR_i](0) \cdot e^{-\delta_i \cdot (t-t_{0,i})}$$
- note that only relative abundance required



33

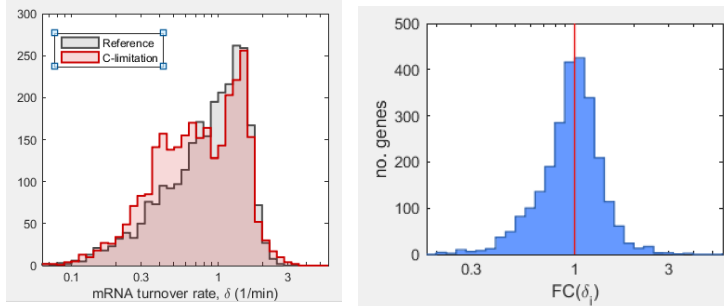
mRNA turnover (δ_i) weakly dependent on gene and condition

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

$\rightarrow \delta_i \approx \bar{\delta} \equiv \sum_i \delta_i \psi_i \approx 0.5/\text{min}$
 \rightarrow GR-dependence of total mRNA abundance must come from mRNA synthesis (α_i)

- stop initiation of transcription at 't = 0' (rifampicin)
- measure mRNA abundance for t > 0 (RNA-seq)
- fit to exponential decay:

$$[mR_i](t) = [mR_i](0) \cdot e^{-\delta_i t}$$
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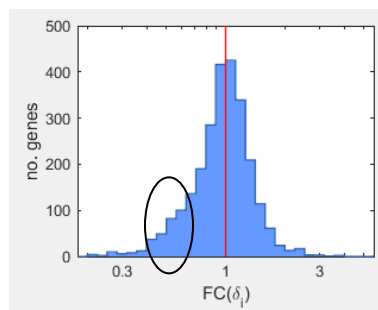
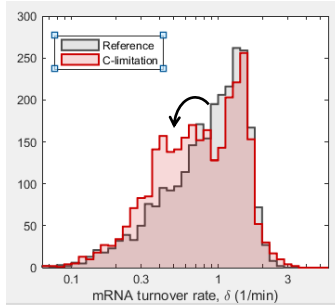
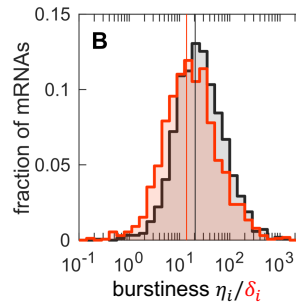
34

mRNA turnover (δ_i)

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

detour:

- huge burstiness typical: $\eta_i/\delta_i \sim 20$
- post-tsx regulation
(change in mRNA turnover: signature of sRNA and protein regulation)



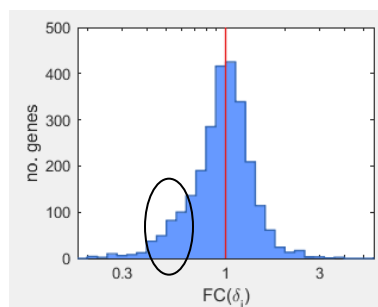
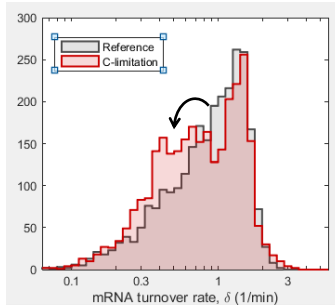
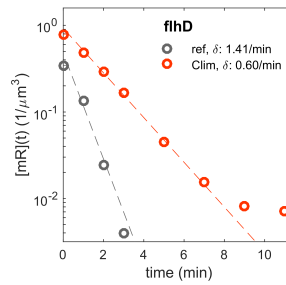
35

mRNA turnover (δ_i)

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

detour:

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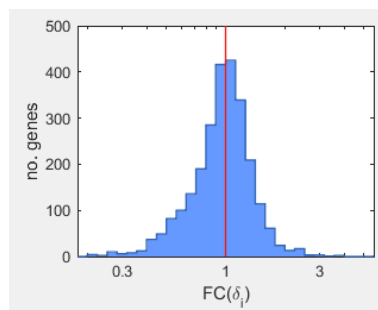
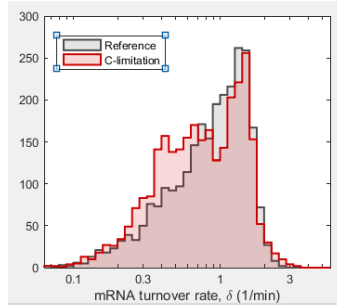
36

mRNA turnover (δ_i) weakly dependent on gene and condition

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_i[g_i] - \delta_i[mR_i] \\ \frac{d}{dt}[P_i] = \eta_i[mR_i] - \lambda[P_i] \end{cases} \begin{array}{l} \rightarrow \delta_i \approx \bar{\delta} \equiv \sum_i \delta_i \psi_i \approx 0.5/\text{min} \\ \rightarrow \text{GR-dependence of total mRNA abundance} \\ \text{must come from mRNA synthesis } (\alpha_i) \end{array}$$

- 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



37

focus on mRNA synthesis (α_i):

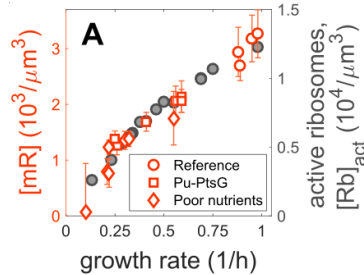
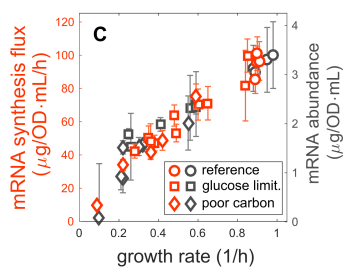
$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_i[g_i] - \delta_i[mR_i] \\ \frac{d}{dt}[P_i] = \eta_i[mR_i] - \lambda[P_i] \end{cases}$$

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

total mRNA synthesis flux:

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

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



\rightarrow total mRNA synthesis flux tuned to match the translational capacity

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focus on mRNA synthesis (α_i):

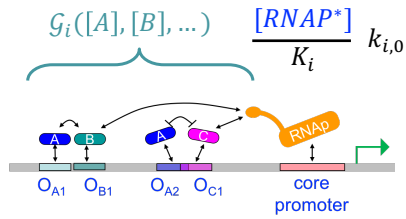
$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_i[g_i] - \delta_i[mR_i] \\ \frac{d}{dt}[P_i] = \eta_i[mR_i] - \lambda[P_i] \end{cases}$$

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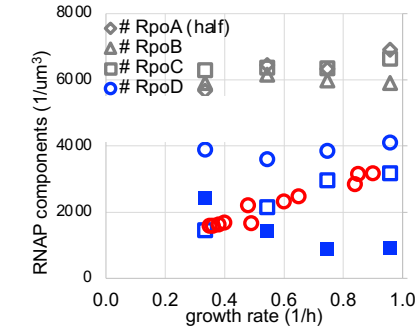
model of transcriptional regulation:



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

RNAP recruitment rate $\rightarrow \mathcal{R}_i([A], [B], \dots)$

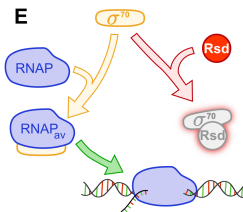
$$J_{mR} = \sum_i \alpha_i[g_i] = [RNAP^*] \sum_i [g_i] \mathcal{R}_i$$



- RNAP components GR-independent
- anti- σ^D factor Rsd upregulated as growth slows down

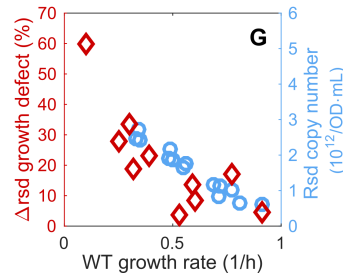
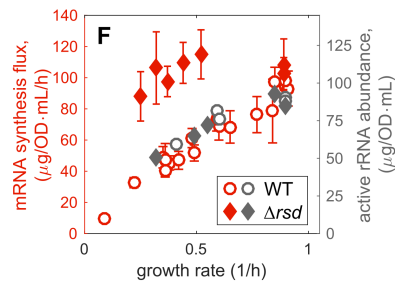
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\rightarrow Rsd titrates the pool of available RNAP to match tsx output with tsl capacity



\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



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focus on mRNA synthesis (α_i):

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

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

Summary

$$\alpha_i[g_i] = \cancel{[RNAP^*]}[g_i]\mathcal{R}_i = \delta_i \cancel{\psi_i[mR]}$$

$$\rightarrow \psi_i \propto [g_i] \cdot \mathcal{R}_i$$

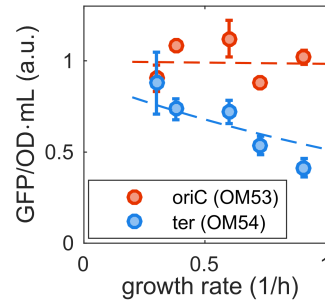
$$\rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot \mathcal{R}_i$$

$$\rightarrow [P_i] \propto [g_i] \cdot \mathcal{R}_i$$

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

constitutive expression ($\mathcal{R}_i = \text{const}$)

\rightarrow expect $[P_i] \propto [g_i] \propto e^{-x_i \lambda T_c}$



- *Ptet:gfp* at *oriC* ($x_i = 0$)
 - *Ptet:gfp* at *terC* ($x_i = 1$)
- $$\lambda T_c \approx \frac{2}{3} \cdot (0.3 + \lambda T_0), T_0 \approx 1 \text{ h}$$

44

focus on mRNA synthesis (α_i):

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

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

Summary

$$\alpha_i[g_i] = \cancel{[RNAP^*]}[g_i]\mathcal{R}_i = \delta_i \cancel{\psi_i[mR]}$$

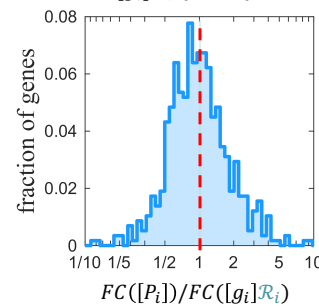
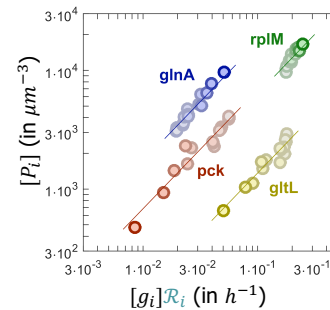
$$\rightarrow \psi_i \propto [g_i] \cdot \mathcal{R}_i$$

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by transcriptional regulation
(weighted by gene copy #)
independent of growth changes

Global survey of relation
between $[P_i]$ and \mathcal{R}_i



46

focus on mRNA synthesis (α_i):

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

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

Summary

$$\alpha_i[g_i] = \cancel{[RNAP^*]}[g_i]\mathcal{R}_i = \delta_i \cancel{\psi_i[mR]}$$

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$$\rightarrow \phi_i \approx \psi_i \propto [g_i] \cdot \mathcal{R}_i$$

$$\rightarrow [P_i] \propto [g_i] \cdot \mathcal{R}_i$$

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

In general,

$$\phi_i \approx \psi_i \approx \frac{[g_i] \cdot \mathcal{R}_i}{\sum_i [g_i] \mathcal{R}_i}$$

“quantitative central dogma”

→ $[P_i] \propto [g_i] \cdot \mathcal{R}_i$ requires fixed $\sum_i [g_i] \mathcal{R}_i$

→ approximately obtained for WT cells

→ not always true for mutants

