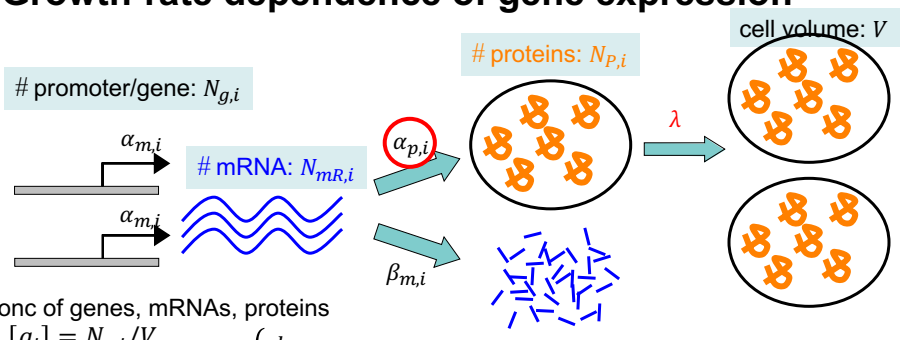
Growth-rate dependence of gene expression



conc of genes, mRNAs, proteins

$$[g_i] = N_{g,i}/V$$
$$[mR_i] = N_{mR,i}/V$$
$$[P_i] = N_{p,i}/V$$

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

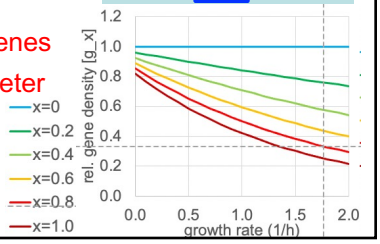
steady-state protein conc

$$[P_i]^* = [g_i]\frac{\alpha_{m,i}\alpha_{p,i}}{\beta_{m,i}\lambda}$$

➔ can't predict the GR dependence of unreg. genes

➔ follow the growth dependence of each parameter

$$[g_i] = (\rho_0/m_0)\, e^{-x_i\lambda T_c} \propto e^{-x_i(2/3)(0.3+\lambda T_0)}$$



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C. translational efficiency ($\alpha_{p,i}$)

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

steady state:

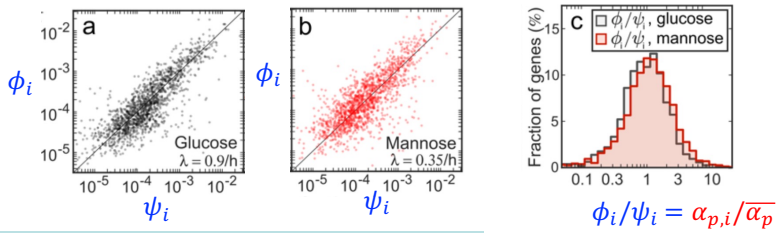
$$\sum_i \begin{cases} \alpha_{p,i}[mR_i]^* = \lambda[P_i]^* \\ \overline{\alpha_p}\,[mR]^* = \lambda[P]^* \end{cases} \Rightarrow \frac{\alpha_{p,i}}{\overline{\alpha_p}} = \frac{\phi_i}{\psi_i}$$

with mean $\overline{\alpha_p} \equiv \sum_i \alpha_{p,i}\psi_i$

strategy (for culture in steady state):

- obtain "proteome fraction" by mass spec: $\phi_i = [P_i]^*/[P]^*$
- obtain "transcriptome fraction" by RNA-seq: $\psi_i = [mR_i]^*/[mR]^*$

R. Balakrishnan, M. Mori et al, Science (2022)



$$\phi_i/\psi_i = \alpha_{p,i}/\overline{\alpha_p}$$

➔ $\phi_i \approx \psi_i$ for different conditions!

➔ $\alpha_{p,i} \approx \overline{\alpha_p}$, i.e., similar translation efficiency for most genes!!

➔ majority of mRNAs look alike to ribosomes

27

C. translational efficiency ($\alpha_{p,i}$)

steady state:

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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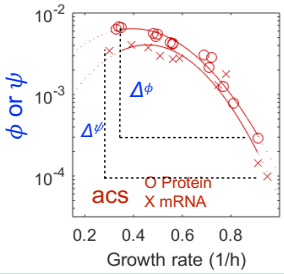

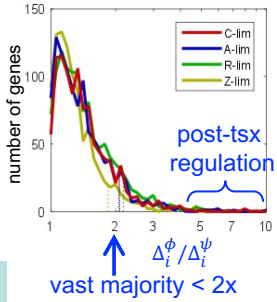

➔ $\phi_i \approx \psi_i$ for <u>different</u> conditions!

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➔ majority of mRNAs look alike to ribosomes

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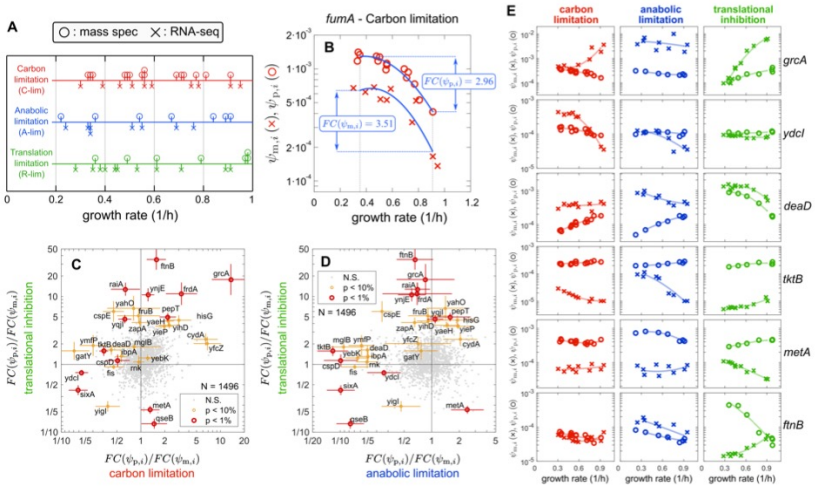
genes showing differential regulation of mRNA and proteins



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➔ $\alpha_{p,i} \approx \overline{\alpha_p}$, i.e., similar translation efficiency for most genes!!

➔ majority of mRNAs look alike to ribosomes

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Topic 5: Global effects of gene expression

Description of individual genes:

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

$\alpha_{m,i}$ = mRNA synthesis rate/promoter
$\beta_{m,i}$ = mRNA degradation rate
$\alpha_{p,i}$ = protein synthesis rate/mRNA
λ = cell growth rate (proteins stable)

transcriptional regulation

$$\alpha_{m,i} = \alpha_{m,0} \cdot \mathcal{P}_i(\dots) = \alpha_{m,0} \frac{[RNAP]_{av}}{K_{P,i}} \cdot \mathcal{R}_i(\dots)$$

$$\frac{d}{dt}[mR_i] = 0 \;\Rightarrow\; [mR_i]^* = \frac{\alpha_{m,i}}{\beta_{m,i}}[g_i]$$

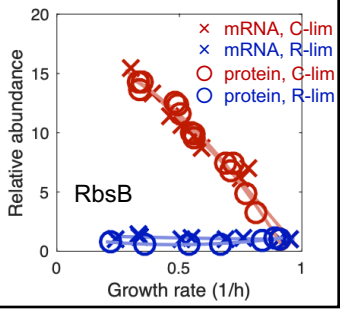
$$\Rightarrow \frac{d}{dt}[P_i] = \underbrace{\alpha_{p,i} \cdot [mR_i]^*}_{\alpha_i} - \lambda \cdot [P_i]$$

α_i protein synth. flux (aka "promoter activity")

Puzzles:

- mRNA level is thought to reflect "promoter activity"; why not??
- where did the dilution effect go?

➔ much simpler job for gene regulation if true
➔ how does E. coli do it?



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C. translational efficiency ($\alpha_{p,i}$)

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

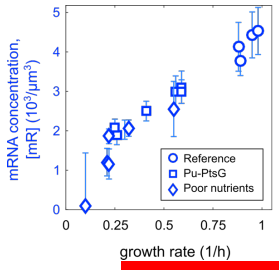
steady state:

$$\sum_i \begin{cases} \alpha_{p,i}[mR_i]^* = \lambda[P_i]^* \\ \overline{\alpha_p}\,[mR]^* = \lambda[P]^* \end{cases} \Rightarrow \frac{\alpha_{p,i}}{\overline{\alpha_p}} = \frac{\phi_i}{\psi_i}$$

with mean $\overline{\alpha_p} \equiv \sum_i \alpha_{p,i}\psi_i$

Q: source of constraint on the total flux of protein synthesis $\overline{\alpha_p}\,[mR]^*$?

➔ mRNA abundance nearly matched to the growth rate
➔ translational initiation rate $\overline{\alpha_p}$ nearly growth independent



➔ $[mR]^* \sim \lambda$ $\quad \overline{\alpha_p} \sim [P]^* \approx \text{const}$

reexamine protein synth flux ('promoter activity')

$$\cancel{\lambda[P_i]^*} = \alpha_{p,i}[mR_i]^* \approx \overline{\alpha_p} \cdot \psi_i \cdot \cancel{[mR]^*}$$

since $\alpha_{p,i} \approx \overline{\alpha_p}$ for typical genes

➔ protein synth flux does not give promoter activity (dominated by GR itself)

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C. translational efficiency ($\alpha_{p,i}$)

steady state:

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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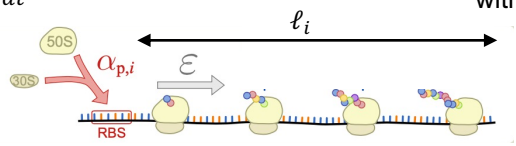
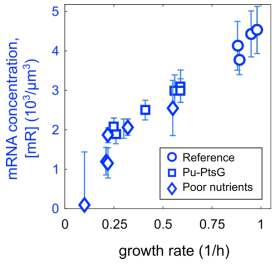


protein synthesis flux:

$\lambda[P_i]^* \cdot \ell_i = \varepsilon \cdot [Rb]^*_{act}$



total flux of protein synthesis: [avg protein length: $\ell \equiv \sum_i \ell_i \phi_i$]

$$\lambda[P]^* \cdot \bar{\ell} = \varepsilon \cdot [Rb]^*_{act} \Rightarrow \overline{\alpha_p}\,[mR]^* \cdot \bar{\ell} = \varepsilon\,[Rb]^*_{act} \Rightarrow \frac{\overline{\alpha_p} \cdot \bar{\ell}}{\varepsilon} = \frac{[Rb]^*_{act}}{[mR]^*}$$

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C. translational efficiency ($\alpha_{p,i}$)

steady state:

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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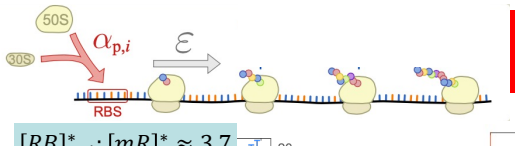
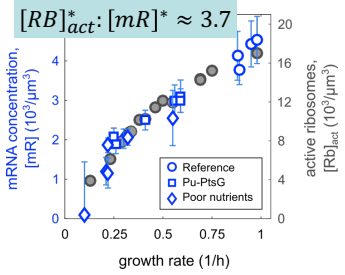
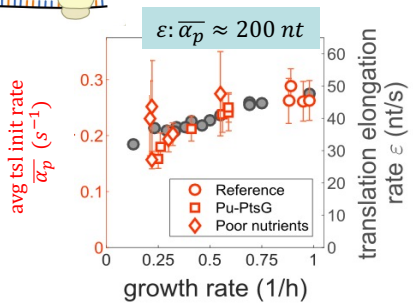


➔ const Rb density on mRNA (across conditions & mRNAs)

$[RB]^*_{act}$: $[mR]^* \approx 3.7$



ε: $\overline{\alpha_p} \approx 200\ nt$



[Dai et al, Nat Microb. (2017)]

total flux of protein synthesis:

$$\lambda[P]^* \cdot \bar{\ell} = \varepsilon \cdot [Rb]^*_{act} \Rightarrow \overline{\alpha_p}\,[mR]^* \cdot \bar{\ell} = \varepsilon\,[Rb]^*_{act} \Rightarrow \frac{\overline{\alpha_p} \cdot \bar{\ell}}{\varepsilon} = \frac{[Rb]^*_{act}}{[mR]^*}$$

33

C. translational efficiency ($\alpha_{p,i}$)

steady state:

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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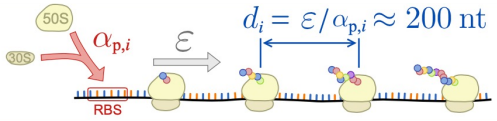

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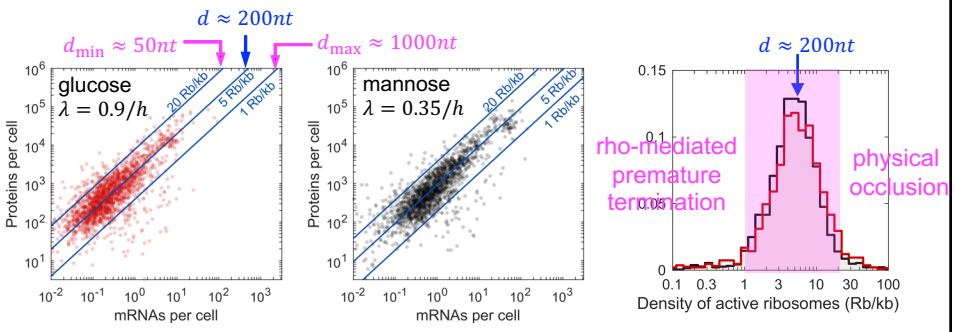

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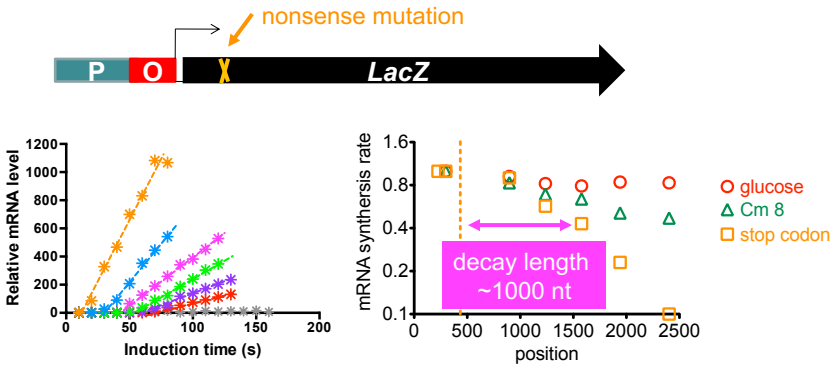
Quantitative study of tsx processivity

Dai et al, Nature Microb. (2019)



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with mean $\overline{\alpha_p} \equiv \sum_i \alpha_{p,i}\psi_i$

Q: source of constraint on the total flux of protein synthesis $\overline{\alpha_p}\,[mR]^*$?

➔ mRNA abundance nearly matched to the growth rate

➔ translational initiation rate $\overline{\alpha_p}$ nearly growth independent

Next: how is mRNA abundance set?

$$[mR_i]^* = \alpha_{m,i}[g_i]/\beta_{m,i}$$ (via synthesis or turnover?)

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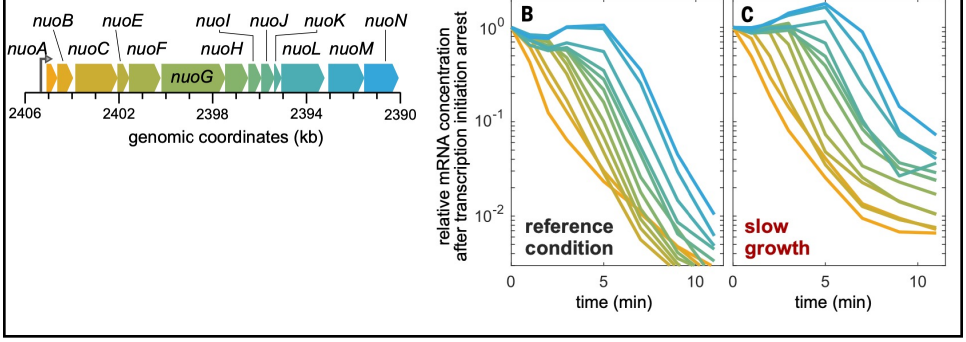
mRNA turnover ($\beta_{m,i}$)

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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

$$[mR_i](t) = [mR_i](0) \cdot e^{-\beta_{m,i}\cdot(t-t_{0,i})}$$



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mRNA turnover ($\beta_{m,i}$) weakly dependent on gene and condition

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

➔ $\beta_{m,i} \approx \bar{\beta}_{m,i} \equiv \sum_i \beta_{m,i}\psi_i \approx 0.5/\text{min}$

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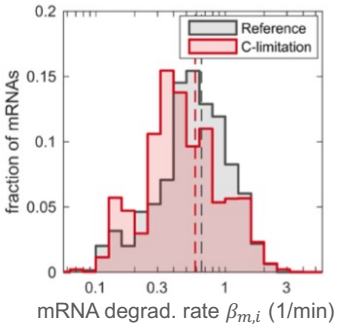

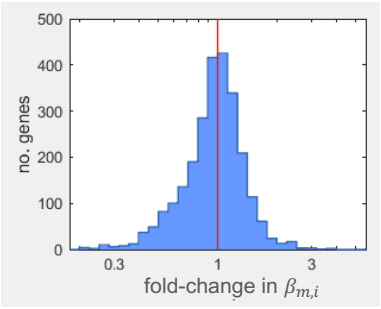

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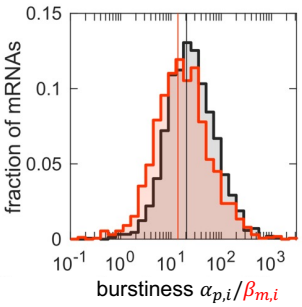
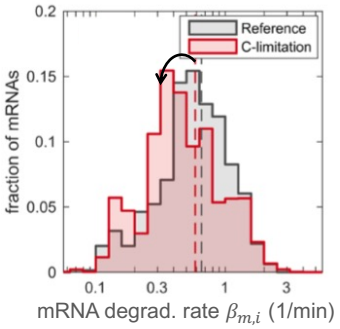
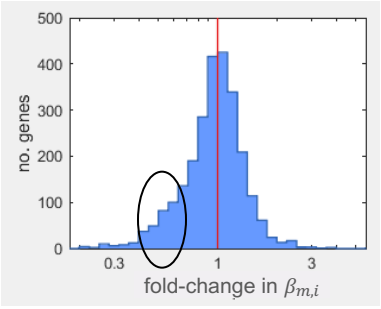


detour:

- huge burstiness typical: $\alpha_{p,i}/\beta_{m,i} \sim 20$
- post-tsx regulation
  (change in mRNA turnover: signature of sRNA and protein regulation)





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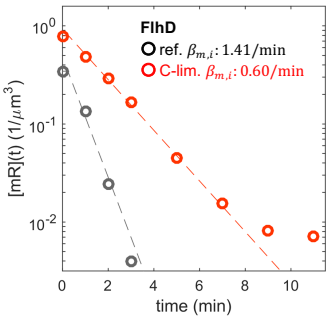

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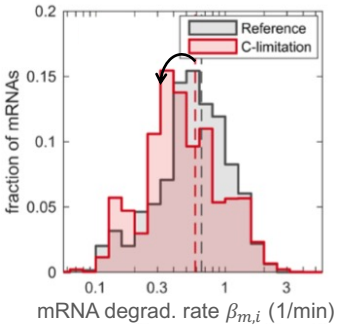

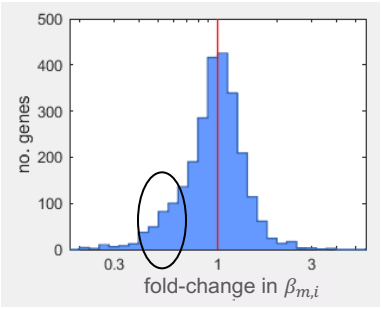

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mRNA turnover ($\beta_{m,i}$) weakly dependent on gene and condition

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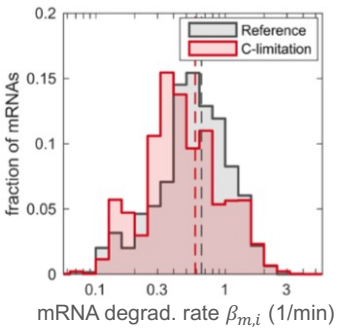
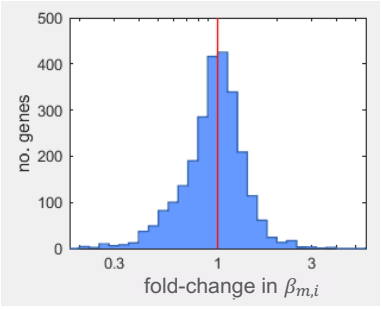
➔ $\beta_{m,i} \approx \bar{\beta}_{m,i} \equiv \sum_i \beta_{m,i}\psi_i \approx 0.5/\text{min}$

➔ GR-dependence of total mRNA abundance must come from mRNA synthesis ($\alpha_{m,i}$)

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





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focus on mRNA synthesis ($\alpha_{m,i}$):

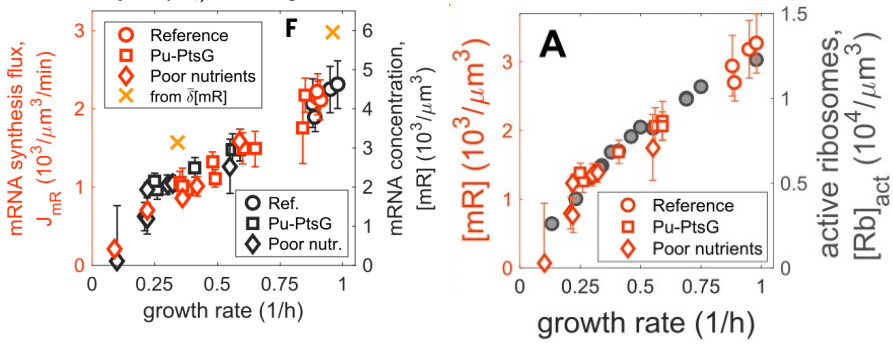
$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

steady-state: $\alpha_{m,i}[g_i] - \beta_{m,i}[mR_i]^*$

total mRNA synthesis flux:

$J_{mR} \equiv \sum_i \alpha_{m,i}[g_i] = \bar{\beta}_m \cdot [mR]^*$

constancy of $\bar{\beta}_{m,i}$: change in total mRNA abundance $[mR]^*$ from J_{mR}



➔ total mRNA synthesis flux tuned to match the translational capacity

42

focus on mRNA synthesis ($\alpha_{m,i}$):

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

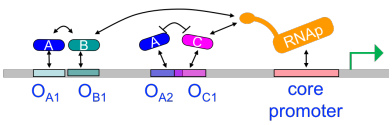
steady-state: $\alpha_{m,i}[g_i] - \beta_{m,i}[mR_i]^*$

total mRNA synthesis flux:

$J_{mR} \equiv \sum_i \alpha_{m,i}[g_i] = \bar{\beta}_m \cdot [mR]^*$

model of transcriptional regulation:

$$\mathcal{R}_i([A],[B],\dots)\frac{[RNAP]_{av}}{K_{p,i}}\,\alpha_{m,0}$$



$$\alpha_{m,i} = [RNAP]_{av} \cdot \underbrace{\alpha_{m,0}\mathcal{R}_i([A],[B],\dots)/K_{p,i}}$$

promoter on-rate → $k_i([A],[B],\dots)$

$$J_{mR} = \sum_i \alpha_{p,i}[g_i] = [RNAP]_{av} \cdot \sum_i [g_i]\,k_i$$

43

focus on mRNA synthesis ($\alpha_{m,i}$):

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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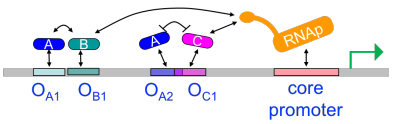
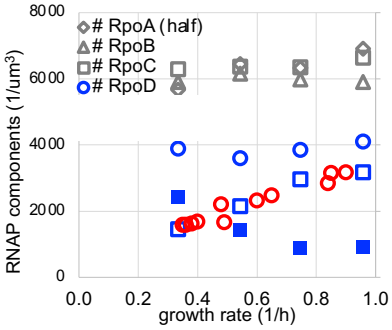


$$\alpha_{m,i} = [RNAP]_{av} \cdot \alpha_{m,0}\mathcal{R}_i([A],[B],\ldots)/K$$

promoter on-rate → $k_i([A],[B],\ldots)$

$$J_{mR} = \sum_i \alpha_{p,i}[g_i] = [RNAP]_{av} \cdot \sum_i [g_i]\,k_i$$



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

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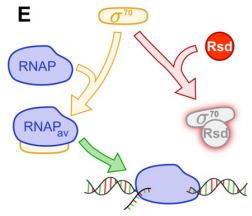
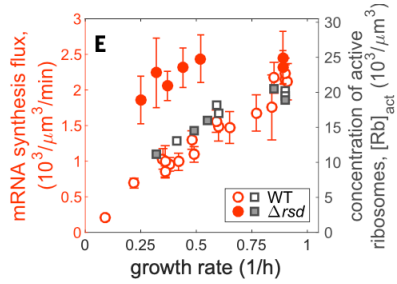
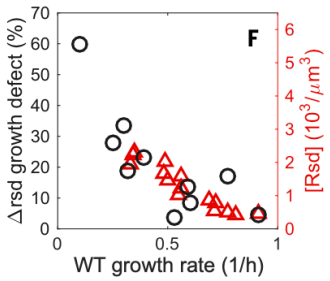
➔ Rsd titrates the pool of available RNAP to match tsx output with tsl capacity



➔ Rsd expression significantly affects the rate of total mRNA synthesis



➔ Δrsd strain exhibits growth defect in proportion to its expression level in WT



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focus on mRNA synthesis ($\alpha_{m,i}$):

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

Summary

$\alpha_{m,i}[g_i] = \cancel{[RNAP]_{av}}\,[g_i]k_i = \bar{\beta}_{m,i}\,\psi_i\cancel{[mR]}$

➔ $\psi_i \propto [g_i] \cdot k_i$

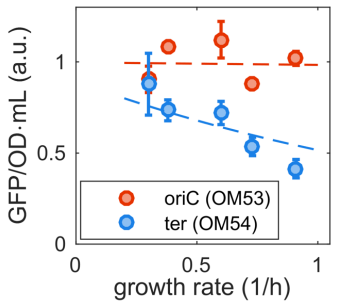
➔ $\phi_i \approx \psi_i \propto [g_i] \cdot k_i$

➔ $[P_i] \propto [g_i] \cdot k_i$

i.e., protein conc set "directly" by transcriptional regulation, approximately independent of changes in growth rate

constitutive expression (k_i=const)

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



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

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

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focus on mRNA synthesis ($\alpha_{m,i}$):

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➔ $\phi_i \approx \psi_i \propto [g_i] \cdot k_i$

➔ $[P_i] \propto [g_i] \cdot k_i$

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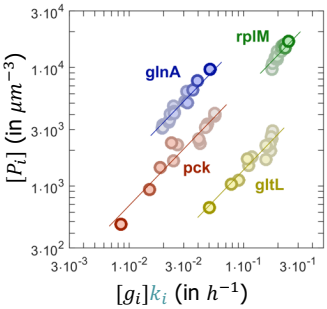
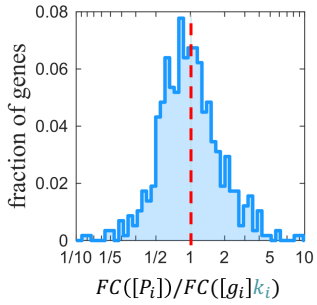
Global survey of relation between $[P_i]$ and k_i





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focus on mRNA synthesis ($\alpha_{m,i}$):

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{m,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$

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$\alpha_{m,i}[g_i] = \cancel{[RNAP]_{av}}\,[g_i]k_i = \bar{\beta}_{m,i}\,\psi_i\cancel{[mR]}$

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i.e., protein conc set "
by transcriptional regu
approximately indepe
changes in growth rate

In general,

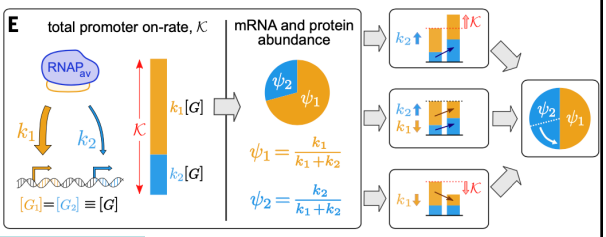
$$\phi_i \approx \psi_i \approx \frac{[g_i]\cdot k_i}{\sum_i [g_i]\cdot k_i}$$

"quantitative central dogma"

➔ $[P_i] \propto [g_i]\cdot k_i$ from fixed $\sum_i [g_i]k_i$

➔ approx. obtained for WT cells

➔ not always true for mutants



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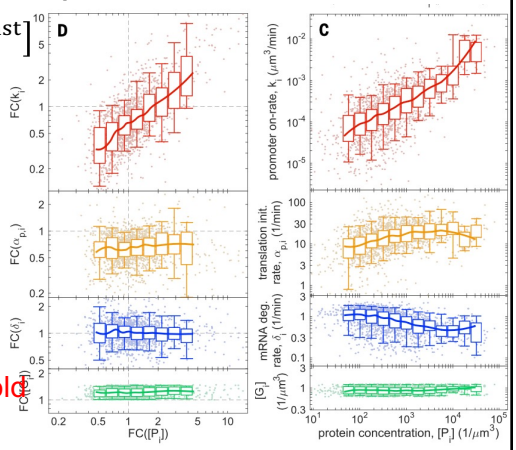
Factors affecting protein concentrations (steady state carbon limitation)

variation in $FC(\mathrm{P_i}) = [\mathrm{P_i^{slow}}]:[\mathrm{P_i^{fast}}]$

- gene dose: negligible
- mRNA stability: negligible
- translational efficiency: 30%
- promoter on-rate: 10-fold

variation in $[\mathrm{P_i}]$

- gene dose: negligible
- mRNA stability: 2-fold
- translational efficiency: 3-fold
- promoter on-rate: 100-1000 fold



➔ genes "born" into different expression classes

➔ expression level set largely by basal promoter on-rate k_i
(with help from translation eff and mRNA stability for the highest expression class)

➔ range in basal rates >> tsx regulation >> post-tsx regulation

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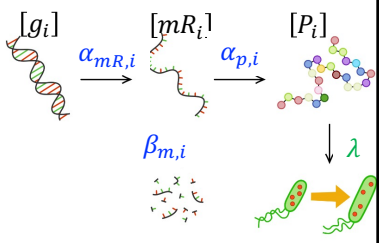
Summary: from DNA to protein

Canonical model for gene expression

$$\begin{cases} \frac{d}{dt}[mR_i] = \alpha_{mR,i}[g_i] - \beta_{m,i}[mR_i] \\ \frac{d}{dt}[P_i] = \alpha_{p,i}[mR_i] - \lambda\,[P_i] \end{cases}$$



steady-state:

$$[P_i] = \frac{\alpha_{p,i}}{\beta_{m,i}}\frac{[g_i]\alpha_{mR,i}}{\lambda} = \frac{\alpha_{p,i}}{\beta_{m,i}}\frac{[RNAP]_{av}[g_i]k_i}{\lambda}$$

Principles of gene expression (*E. coli*)
0) predominance of basal tsx level in defining expression classes
1) uniformity and constancy of mRNAs in translation and degradation
2) coordination of total mRNA synthesis flux with translational capacity

➔ connection from promoter to protein conc: $\frac{[P_i]}{[P]} \approx \frac{[mR_i]}{[mR]} \approx \frac{k_i[g_i]}{\sum_j k_j[g_j]}$

- general promoter entanglement thru GR dependence of $\sum_j k_j[g_j]$
- Rsd as coordinator of transcription and translation
- mRNA as proxy for protein (~200nt per ribosome)
- extremely high burstiness (~20 for typical genes) [cf: Hausser et al, 2020]

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