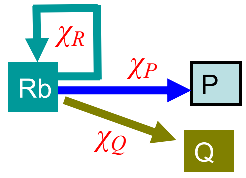
## Simple 3-component model of bacterial growth

let $\chi_R$ be the fraction of Rb synthesizing Rb



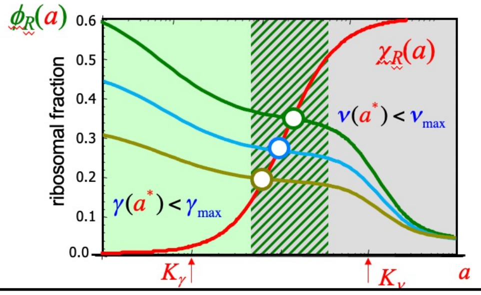
$$\lambda \cdot M_{Rb} = \chi_R \cdot \varepsilon \cdot N_{Rb}^{act} = \chi_R \cdot \overbrace{\left(\frac{\varepsilon}{m_{Rb}}\right) f_{act}}^{\gamma \text{ translational activity}} \cdot M_{Rb}$$

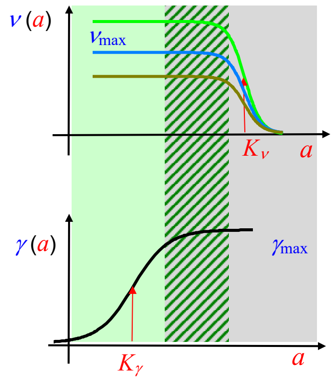
$$\Rightarrow \boxed{\lambda = \chi_R \cdot \gamma}$$

$$\rightarrow \phi_R = \chi_R(a^*)$$

$$\begin{cases} \phi_R = \phi_R^{\max} \cdot \dfrac{\nu(a^*)}{\nu(a^*) + \gamma(a^*)} \\ \lambda = \gamma(a^*) \cdot \phi_R \end{cases}$$

- maximal $\lambda$ if $\nu(a^*) \approx \nu_{max}$, $\gamma(a^*) \approx \gamma_{max}$; but observed $\gamma < \gamma_{max}$
- any AA could be growth-limiting; origin of the universality of GR-dependent response





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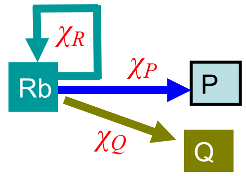

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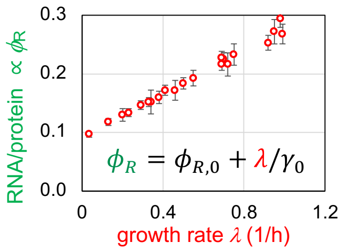
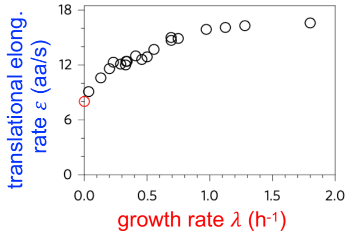
$$\frac{\gamma}{\gamma_0} = \frac{\lambda}{\lambda + \lambda_0}; \quad \lambda_0 \equiv \gamma_0 \phi_{R,0} \approx 0.35/h$$

➔ reduction in $\gamma$ for slow growth due to
-- reduction in $\varepsilon$: slow kinetics of TC
-- reduction in $f_{act}$: keep Rb reserve

➔ qualitative; difficult to move forward (due to the lack of additional constraint or optimality principle)





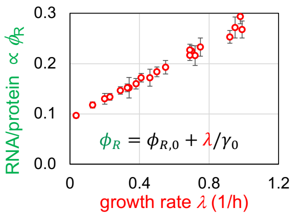
## ppGpp-mediated model of growth control:

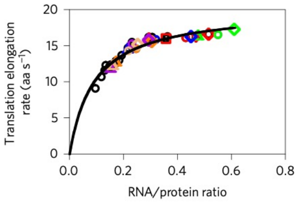
$\phi_R \cdot \phi_R^{inact} = \phi_{R,0}^2$

- ppGpp senses transl. elong. rate $g = \boxed{g_0} \cdot \left(\frac{\varepsilon_{max}}{\varepsilon} - 1\right)$
- ppGpp represses Rb synthesis $\phi_R(g) = \frac{\boxed{a}}{g} = \phi_{R,0} \cdot \left(\frac{g_0}{g}\right) = \phi_{R,0} \cdot (1 + \lambda/\lambda_0)$
- ppGpp activates Rb hibernation $\phi_R^{inact}(g) = \boxed{b} \cdot g = \phi_{R,0} \cdot \left(\frac{g}{g_0}\right) = \frac{\phi_{R,0}}{1 + \lambda/\lambda_0}$
- relation to growth rate: $\lambda = \varepsilon(g) \cdot [\phi_R(g) - \phi_R^{inact}(g)]$
  [cf flux sensing/control]
- linearity: $\varepsilon(\lambda \to 0) = \frac{1}{2}\varepsilon_{max}$ ⇨ $g(\lambda = 0) = g_0$
  $b = a/g_0^2$

**Recovers…**

- ribosome growth law: $\phi_R = \phi_{R,0} + \lambda/\gamma_0$
  with $\phi_{R,0} = a/g_0$ and $\gamma_0 = \varepsilon_{max}/m_{Rb}$
- Michaelis relation of ER on Rb abundance:
  $$\varepsilon = \varepsilon_{max}\frac{\phi_R}{\phi_R + \phi_{R,0}}$$
- inverse dependence of $g$ on GR:
  $$g = \frac{g_0}{1 + \lambda/\lambda_0} \qquad \lambda_0 = \gamma_0\phi_{R,0}$$
- GR-dependence of ER: $\varepsilon = \varepsilon_{max}\frac{1 + \lambda/\lambda_0}{2 + \lambda/\lambda_0}$





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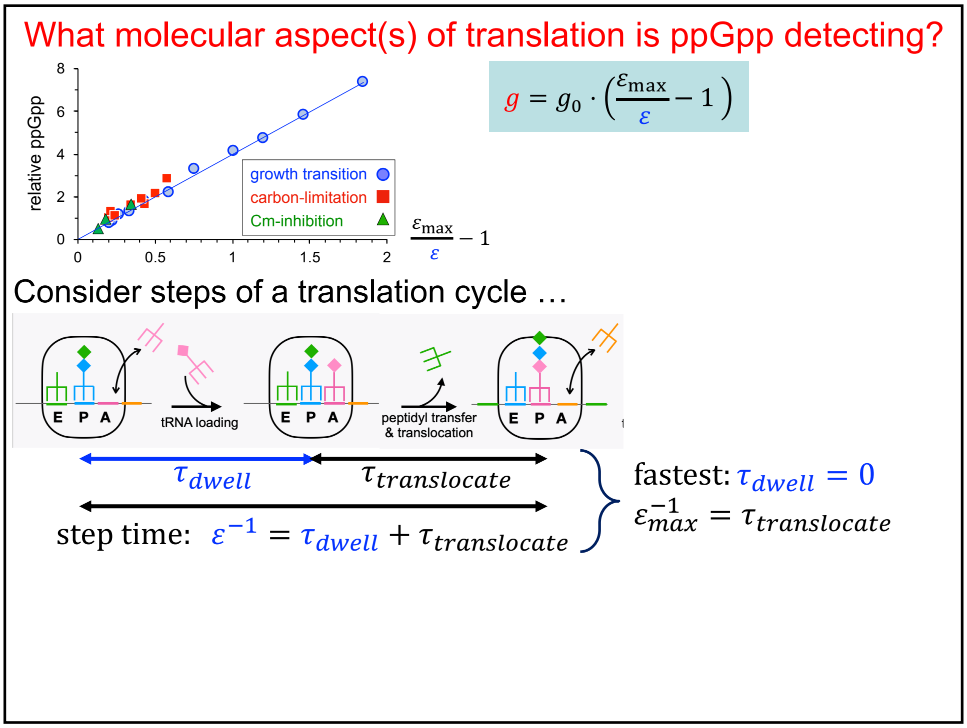
**Alternative formulation:**

- linear Rb law
- Michaelis ER-Rb relation
- $\varepsilon_0 = \frac{1}{2}\varepsilon_{max}$

**recovers**

- $\varepsilon(\lambda)$
- $\phi_R^{inact}(\lambda) \propto \phi_R(\lambda)$

- new constraint
- origin unknown
- but observed also for other bacteria examined



## What molecular aspect(s) of translation is ppGpp detecting?

$$g = g_0 \cdot \left(\frac{\varepsilon_{\max}}{\varepsilon} - 1\right)$$

Consider steps of a translation cycle …

$\tau_{dwell}$ $\tau_{translocate}$

step time: $\varepsilon^{-1} = \tau_{dwell} + \tau_{translocate}$

fastest: $\tau_{dwell} = 0$

$\varepsilon_{max}^{-1} = \tau_{translocate}$

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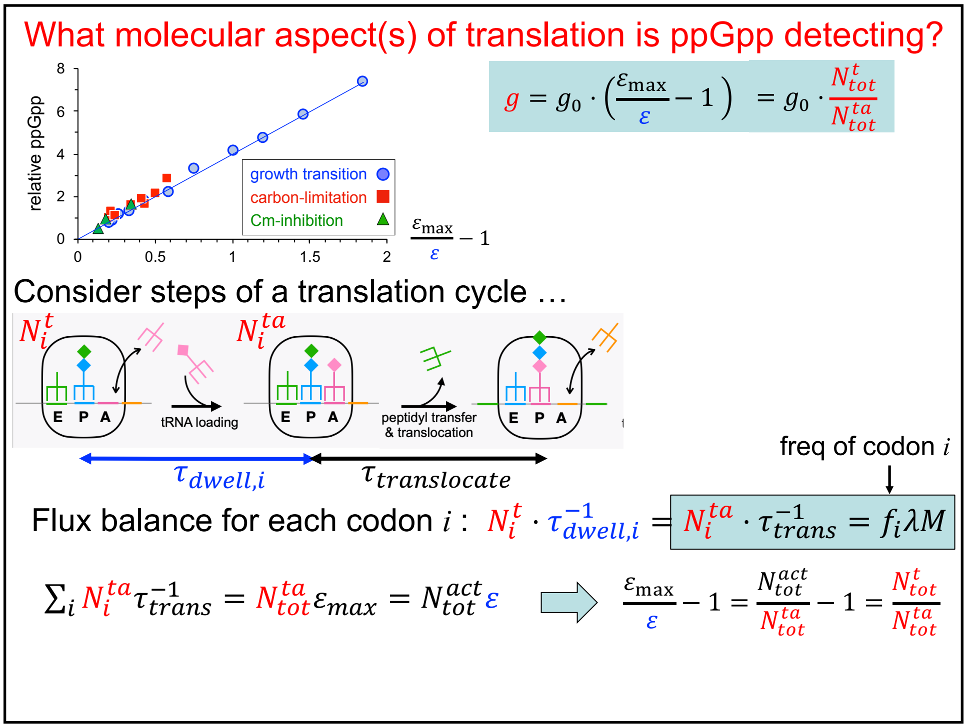

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$$g = g_0 \cdot \left(\frac{\varepsilon_{\max}}{\varepsilon} - 1\right) = g_0 \cdot \frac{N_{tot}^{t}}{N_{tot}^{ta}}$$

Consider steps of a translation cycle …

$\tau_{dwell,i}$ $\tau_{translocate}$

freq of codon $i$

Flux balance for each codon $i$ : $N_i^t \cdot \tau_{dwell,i}^{-1} = \boxed{N_i^{ta} \cdot \tau_{trans}^{-1} = f_i \lambda M}$

$$\sum_i N_i^{ta} \tau_{trans}^{-1} = N_{tot}^{ta} \varepsilon_{max} = N_{tot}^{act} \varepsilon \Rightarrow \frac{\varepsilon_{\max}}{\varepsilon} - 1 = \frac{N_{tot}^{act}}{N_{tot}^{ta}} - 1 = \frac{N_{tot}^{t}}{N_{tot}^{ta}}$$

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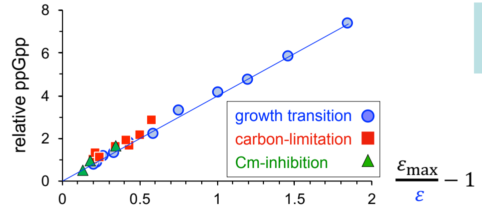
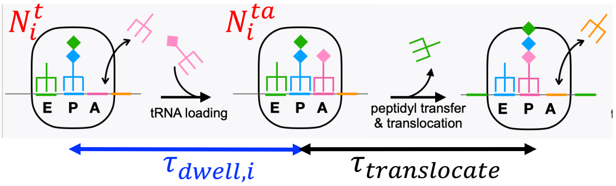


$$g = g_0 \cdot \left(\frac{\varepsilon_{\max}}{\varepsilon} - 1\right) = g_0 \cdot \frac{N_{tot}^{t}}{N_{tot}^{ta}}$$

$$g = g_0 \sum_i f_i \left(\frac{1}{\rho_i^{ta}} - 1\right) = g_0 \sum_i f_i \frac{\rho_i^{t}}{\rho_i^{ta}}$$

$$g = g_0 \sum_i f_i \frac{[t_i]/K_i^{t}}{[ta_i]/K_i^{ta}}$$

Consider steps of a translation cycle …



$$\rho_i^{ta} = \frac{[ta_i]}{K_i^{ta}} \bigg/ \left(\frac{[ta_i]}{K_i^{ta}} + \frac{[t_i]}{K_i^{t}}\right)$$

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$$\rho_i^{ta} \equiv N_i^{ta}/N_i^{act} \Rightarrow \rho_i^{ta} N_i^{act} \cdot \varepsilon_{max} = f_i \lambda M \Rightarrow \frac{\varepsilon_{max}}{\varepsilon} = \sum_i \frac{f_i}{\rho_i^{ta}}$$

$$\sum_i N_i^{act} = \frac{\lambda M}{\varepsilon_{max}} \sum_i \frac{f_i}{\rho_i^{ta}} = \frac{\varepsilon \cdot N_{tot}^{act}}{\varepsilon_{max}} \sum_i \frac{f_i}{\rho_i^{ta}}$$

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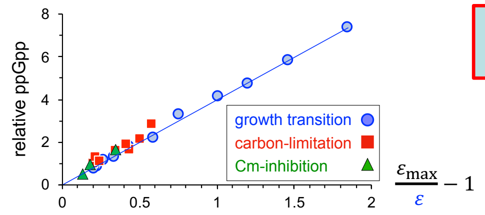

$$\boxed{g = g_0 \cdot \left(\frac{\varepsilon_{\max}}{\varepsilon} - 1\right) = g_0 \cdot \frac{N_{tot}^{t}}{N_{tot}^{ta}}}$$

-- a way for cell to “track” $\varepsilon$ ?

$$g = g_0 \sum_i f_i \frac{[t_i]/K_i^{t}}{[ta_i]/K_i^{ta}}$$

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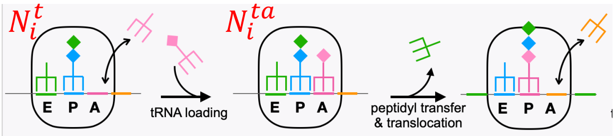
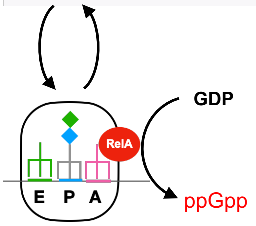
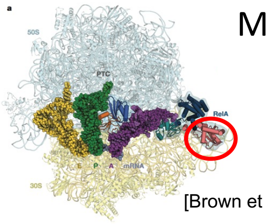






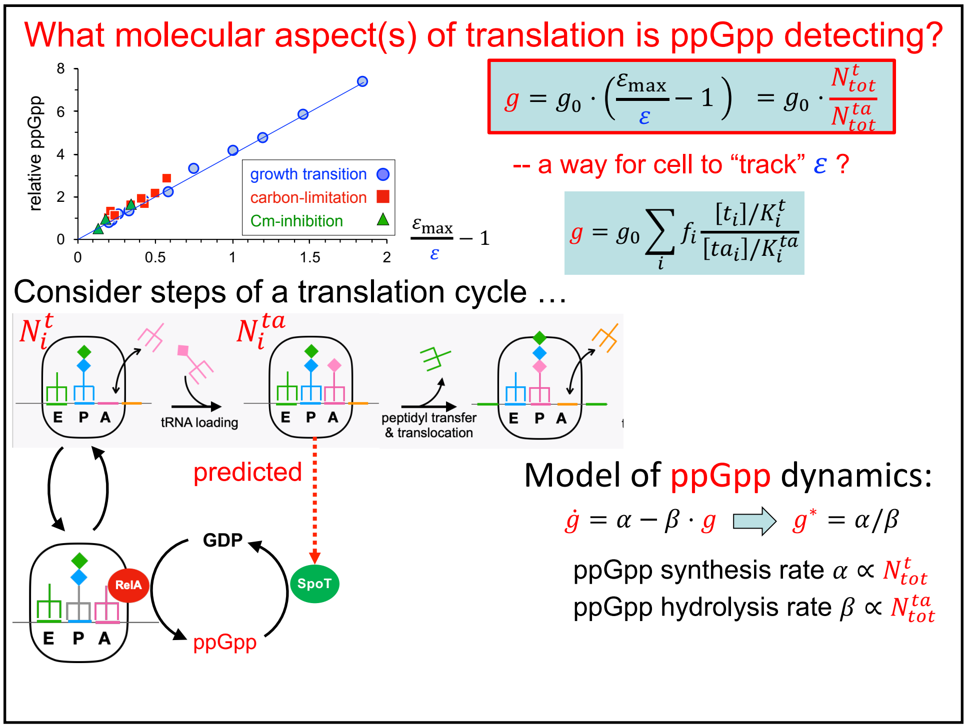
[Brown et al, Nature 2016]

### Model of ppGpp dynamics:

$$\dot{g} = \alpha - \beta \cdot g \Rightarrow g^* = \alpha/\beta$$

ppGpp synthesis rate $\alpha \propto N_{tot}^{t}$

ppGpp hydrolysis rate $\beta \propto N_{tot}^{ta}$



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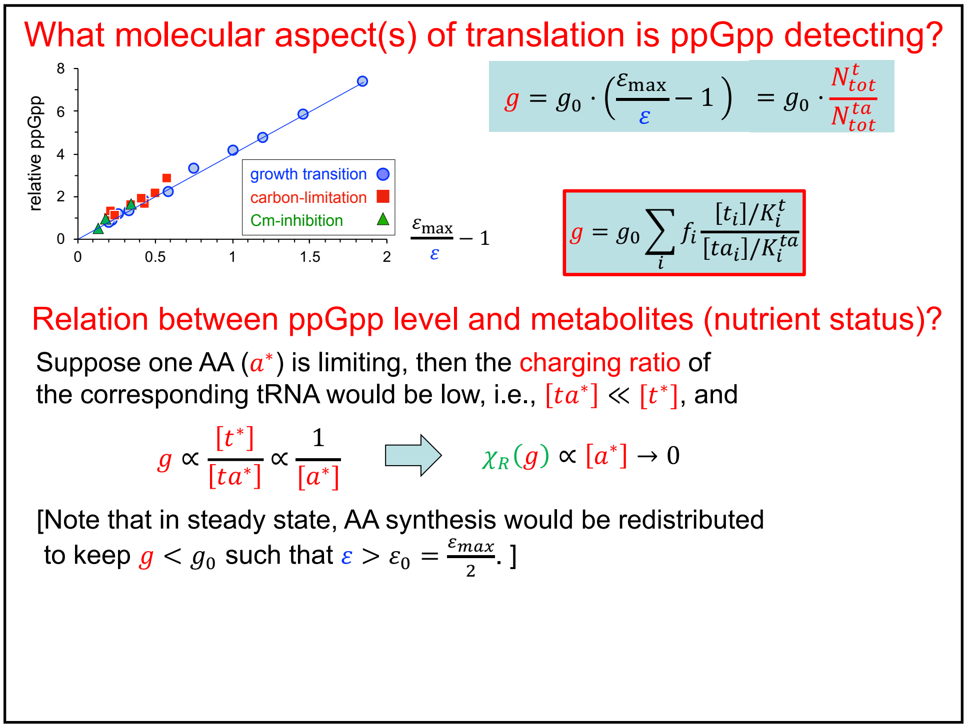

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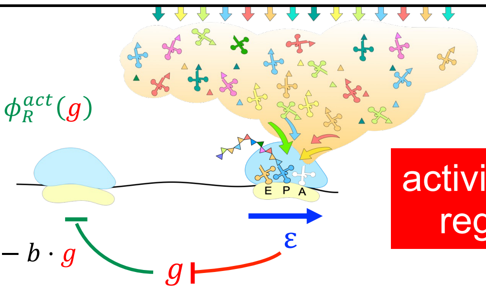
### Relation between ppGpp level and metabolites (nutrient status)?

Suppose one AA ($a^*$) is limiting, then the charging ratio of the corresponding tRNA would be low, i.e., $[ta^*] \ll [t^*]$, and

$$g \propto \frac{[t^*]}{[ta^*]} \propto \frac{1}{[a^*]} \Rightarrow \chi_R(g) \propto [a^*] \to 0$$

[Note that in steady state, AA synthesis would be redistributed to keep $g < g_0$ such that $\varepsilon > \varepsilon_0 = \frac{\varepsilon_{max}}{2}$. ]

$\lambda = \varepsilon(g) \cdot \phi_R^{act}(g)$



$\phi_R^{act}(g) = \frac{a}{g} - b \cdot g$

**activity-based regulation**

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➔ the "GR response" is dependent only on the relation between $\lambda$ and $g$, not on what nutrient components drives change in $g$

➔ senses flux rather than conc; essence of dimensional reduction by cells

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**use it or lose it !**