Gene regulation by a protein translation factor at the single-cell level

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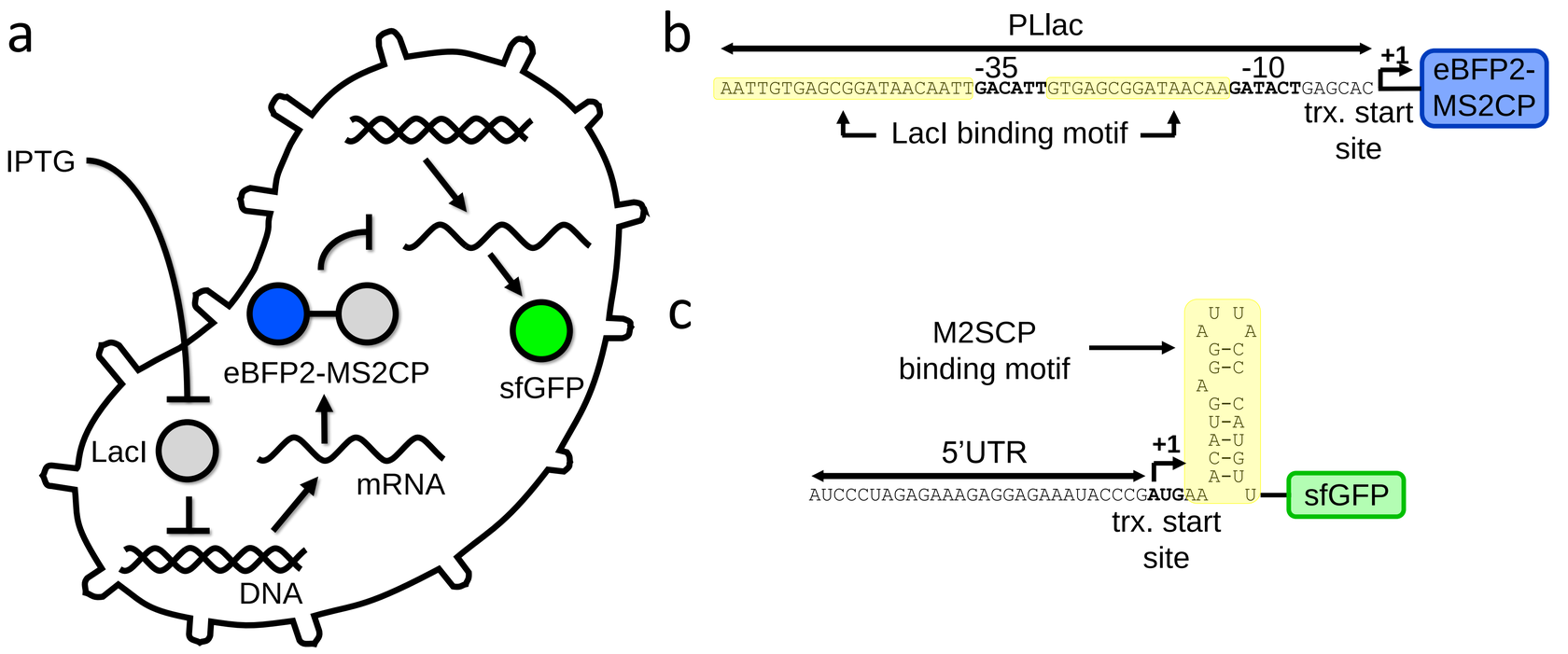
Summary

- Gene expression is inherently **stochastic** and pervasively regulated. Unlike transcriptional regulation, the stochastic behavior of genes regulated at the level of **translation** is poorly **understood**.
- We engineered a **synthetic** genetic system in which a target gene is down-regulated by a **protein translation factor**, which in turn is regulated transcriptionally.
- We found that **noise propagation** from gene to gene is **buffered**, the regulated gene is sensitive in a nonlinear way to reductions in cell growth rate, and that a **Gamma** distribution provides a deep analytical explanation about cell-to-cell **variability** in the population.

System Details



a. General overview of the system. **b. & c.** Nucleic acid sequences of the system's implementation. **d.** Histograms of single-cell fluorescence for sfGFP (the regulated protein) for different induction conditions with IPTG. **e.** Mean and noise of expression for sfGFP as a function of IPTG.

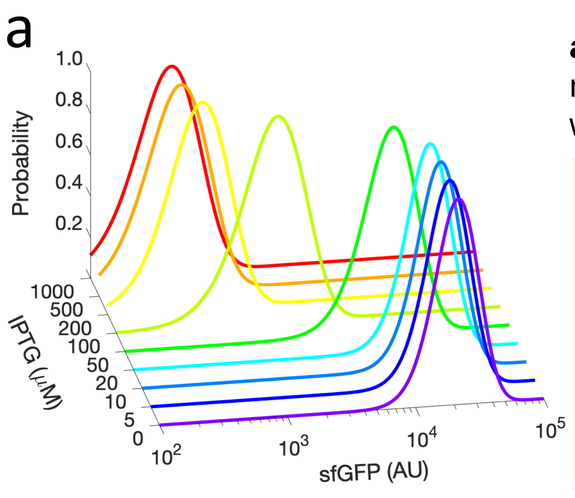
Deterministic and Stochastic Modeling

*The **deterministic** model arises from **ODEs** solved under steady-state conditions. The stochastic model follows **Langevin's formalism**.*

$$\langle \mathrm{sfGFP} \rangle = \alpha_y \frac{1 + \rho_y \left(\frac{\langle \mathrm{eBFP2} \rangle}{\theta_x} \right)^{n_x}}{1 + \left(\frac{\langle \mathrm{eBFP2} \rangle}{\theta_x} \right)^{n_x}}$$

$$\mathrm{CV}^2_{\mathrm{sfGFP}} = \underbrace{\eta_y^2}_{\text{extrinsic}} + \underbrace{\frac{\beta_y}{\langle \mathrm{sfGFP} \rangle}}_{\text{intrinsic}} + \underbrace{\frac{1}{2} \left(\frac{\alpha_y (1-\rho_y) n_x \left(\frac{\langle \mathrm{eBFP2} \rangle}{\theta_x} \right)^{n_x - 1}}{\theta_x \left(1 + \left(\frac{\langle \mathrm{eBFP2} \rangle}{\theta_x} \right)^{n_x} \right)^2} \right)^2 \frac{\gamma_y \langle \mathrm{eBFP2} \rangle^2}{\langle \mathrm{sfGFP} \rangle^2} \mathrm{CV}^2_{\mathrm{eBFP2}}}_{\text{regulation}}$$

Expressions for $\langle \mathrm{eBFP2} \rangle$ *and* $\mathrm{CV}^2_{\mathrm{eBFP2}}$ *are omitted for the sake of space.*



a. Gamma distributions predicted by the model for different induction conditions with IPTG.

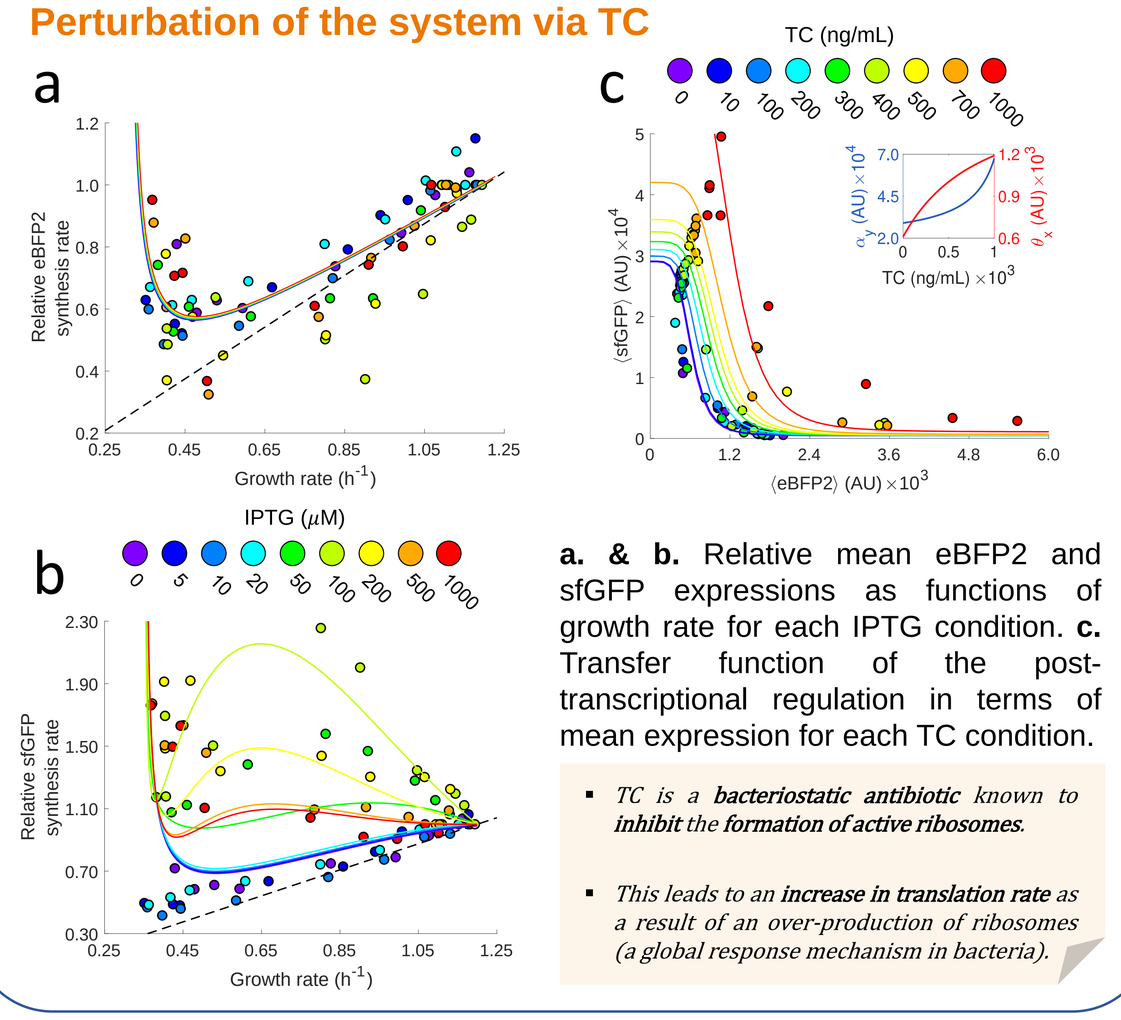
*Note that Gamma distribution shape parameters **a** and **b** follow the relationship:*

$$a = \frac{1}{\mathrm{CV}^2_{\mathrm{sfGFP}}}$$

$$b = \langle \mathrm{sfGFP} \rangle \mathrm{CV}^2_{\mathrm{sfGFP}}$$

Thus, both can be easily computed by the model.

Perturbation of the system via TC



a. & b. Relative mean eBFP2 and sfGFP expressions as functions of growth rate for each IPTG condition. **c.** Transfer function of the post-transcriptional regulation in terms of mean expression for each TC condition.

- *TC is a **bacteriostatic antibiotic** known to **inhibit** the **formation of active ribosomes**.*
- *This leads to an **increase in translation rate** as a result of an over-production of ribosomes (a global response mechanism in bacteria).*

Conclusions

- The **protein-RNA interaction** leads to a **down-regulation** in expression by blocking the progression of the ribosome on the target mRNA.
- A general **mathematical framework** was suitable to describe the **stochastic behavior** in regulations exerted by both **transcription and translation factors**.
- An **interplay** between **global** and **local regulatory mechanisms** that affects both the mean expression and noise levels has been reported.
- The mathematical model is **general enough** to describe different RNA-binding protein implementations of this regulatory system.

Main references

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