Active Degradation Allows for Increased Information Transmission Rate in Genetic Control

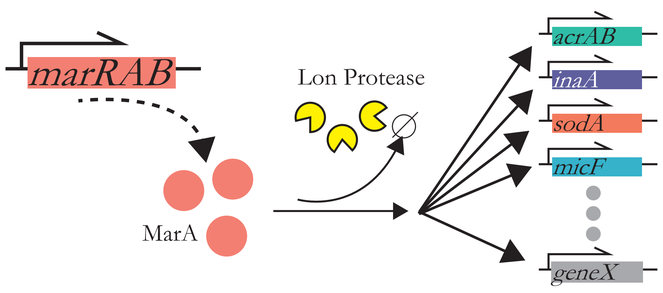
Nicholas Rossi[1], Aleksandra Walczak[2], Thierry Mora[2], Mary Dunlop[3]

(1)Molecular Biology, Cell Biology and Biochemistry Program, Boston University (2)Laboratoire de Physique Theorique, Ecole Normale Superieure,(3)Department of Biomedical Engineering, Boston University

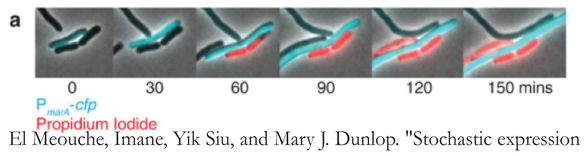
Introduction

As there is a cost implicit to replacing degraded proteins, decreasing the half-life of transcription factors through active degradation is a rare feature in bacteria. However, analytic and computational results reveal utility in short half-life regulatory molecules as they can rapidly transmit information to downstream targets. This can quickly generate well-correlated, yet diverse responses among multi-component regulons. This coordinated diversity has particular relevance to bet-hedging phenotypes, in which isogenic populations show varying susceptibility to stress in an effort to balance the guaranteed cost of resistance machinery against the potential danger of a changing environment. Using the multi-antibiotic resistance regulon as a case study, we show that an actively degraded regulator transmits information faster to downstream genes than a regulator that is slowly removed through dilution. Conversely, the maximum information transmitted decreases with a shorter half-life. This is the result of a rapidly changing signal being filtered by downstream targets. The balance between fidelity of signal transmission and information transmission rate demonstrates a trade-off in bacterial regulatory networks. Favoring information rate over fidelity may be favorable in rapidly changing environments.

The multiple antibiotic resistance activator MarA is actively degraded by Lon protease



Stochastic fluctuations in MarA concentration are linked to transient antibiotic resistance at the single cell level

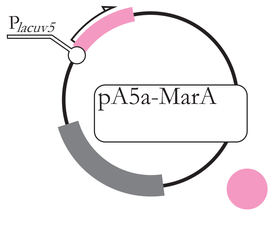


El Meouche, Imane, Yik Siu, and Mary J. Dunlop. "Stochastic expression of a multiple antibiotic resistance activator confers transient resistance in single cells." Scientific reports 6 (2016).

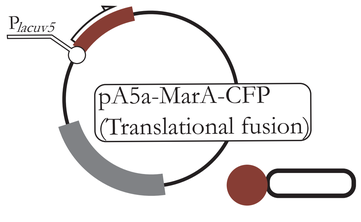
Methods

Modified the endogenous MarA protein to extend its half-life

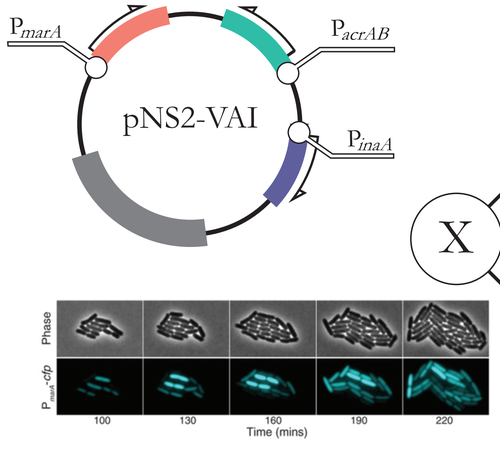
Wild type



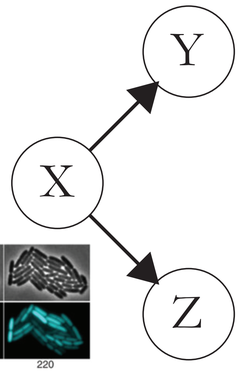
Extended half-life



Created a synthetic three color reporter plasmid to monitor dynamic promoter activity of MarA and two downstream genes



Modeled system with a set of stochastic differential equations that were evaluated computationally and solved analytically for a variety of statistics.



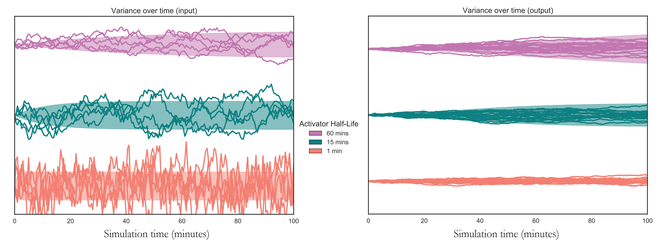
$$\dot{x} = \frac{-x}{\tau_x} + \sqrt{\frac{2}{\tau_x}}\eta_x$$

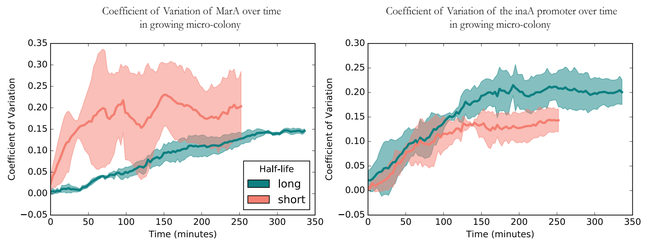
$$\dot{y} = g_y x - \frac{y}{\tau_y} + \sqrt{\frac{2}{\tau_y}}\eta_y$$

$$\dot{z} = g_z x - \frac{z}{\tau_z} + \sqrt{\frac{2}{\tau_z}}\eta_z$$

Results

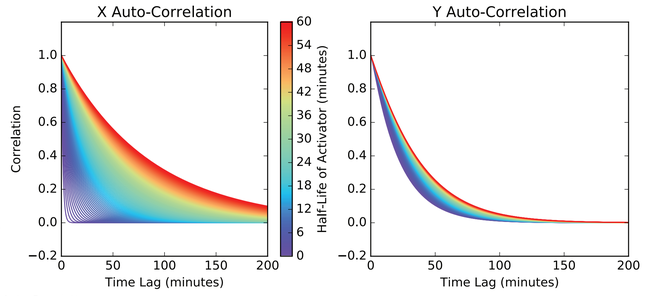
Modeling indicates that active degradation decreases memory causing cells to become less correlated over time providing increased variability over time.

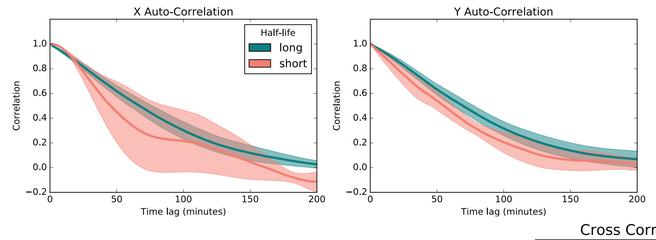




Experimental results show faster diversity in both an the activator and downstream genes.

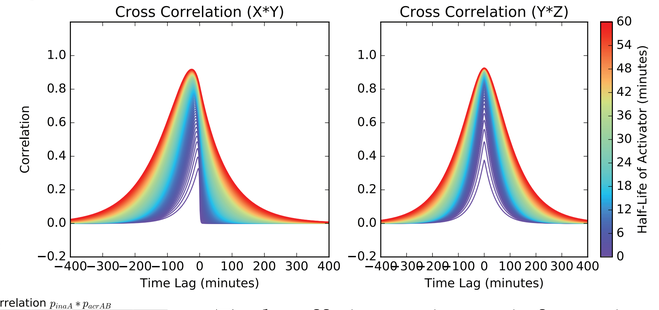
Analytic solutions to differential equations suggest a sharper drop in auto-correlation as active degradation increases

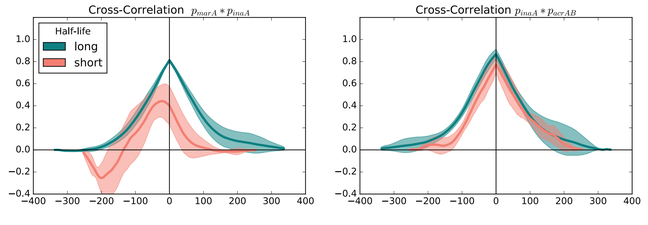




Experimental results confirm analytical auto-correlation solutions

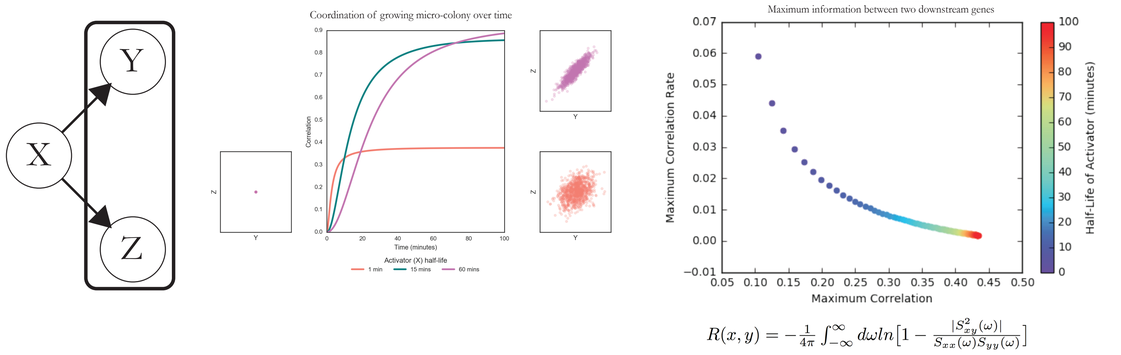
Cross-correlation solutions between input and output show time delay for maximum correlation, as well as lower maximum correlation as a function of decreased half-life





Trade-offs in maximum information and information transmission rate.

Active degradation can coordinated diversity quickly, but it decreases the maximum coordination possible.



$$R(x,y) = -\frac{1}{4\pi}\int_{-\infty}^{\infty} d\omega ln\left[1 - \frac{|S^2_{xy}(\omega)|}{S_{xx}(\omega)S_{yy}(\omega)}\right]$$