Cell-size and Variance in Endosome-size control in a Feedback Network

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Building over a recent work [1], we explored the possibility of creating networks of small networks which can be utilized for controlling the cell size . We explore possible topologies which can keep the size of the cell "fixed" and put an upper bound on the variance of the size of the Endosome. Only endocytosis and exocytosis events affect the cell- and endosome-size in this treatment. A simulator for exploring these topologies in an event-driven simulation environment (SystemC library of C++) has been written [1].

[1] https://github.com/dilawar/FeedbackSimulator/

Introduction

- Inside the cell, randomizing and correcting statistical forces create fluctuations - noise. Many control circuits are found in cell which eliminates, tolerates, or exploits the noise.
- In this rotation project, a recent result [1] which establishes fundamental bounds using information theory on noise-suppression in a feedback network is used to explore control networks for controlling cell-size.
- To analyze such possible networks, we have been building a simulation environment using C++ and event-driven simulation library **SystemC**.

A Feedback Network Studied in [1]

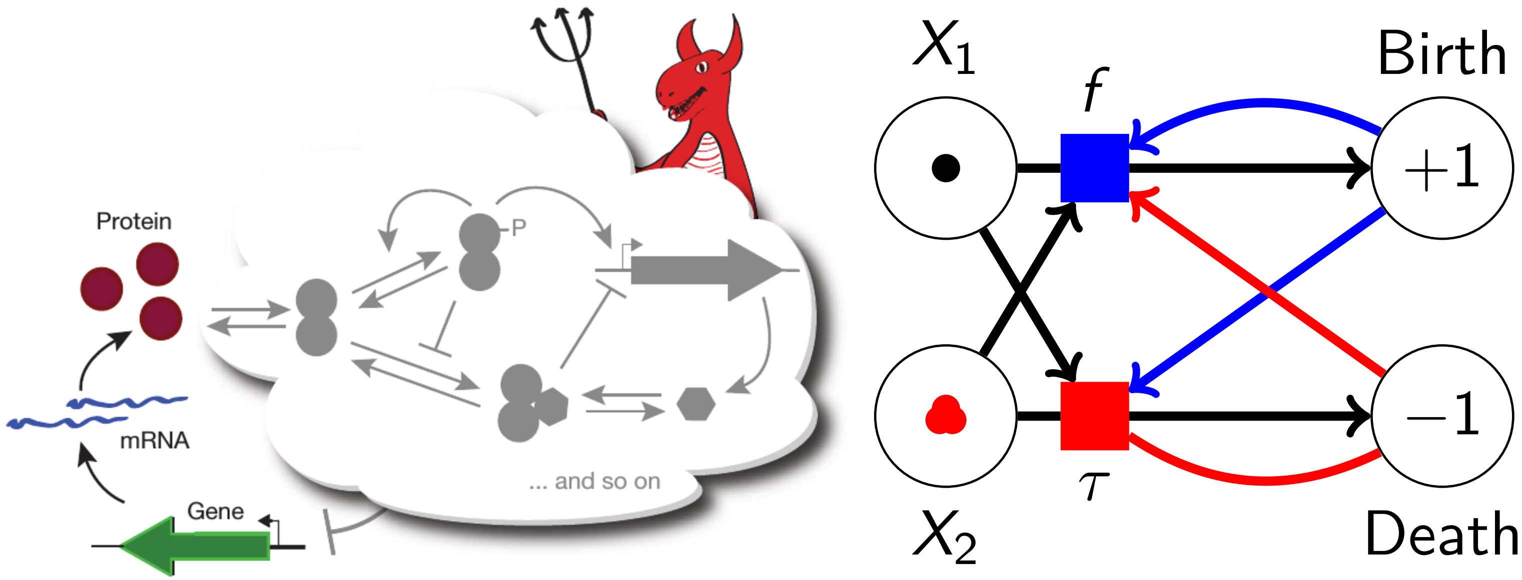


Figure : On left, mRNA/Protein network, from [1]. An equivalent description using Petri Nets on the right with X_1 as mRNA and X_2 as its protein. Signalling events are probabilistic.

Birth and Death in Network

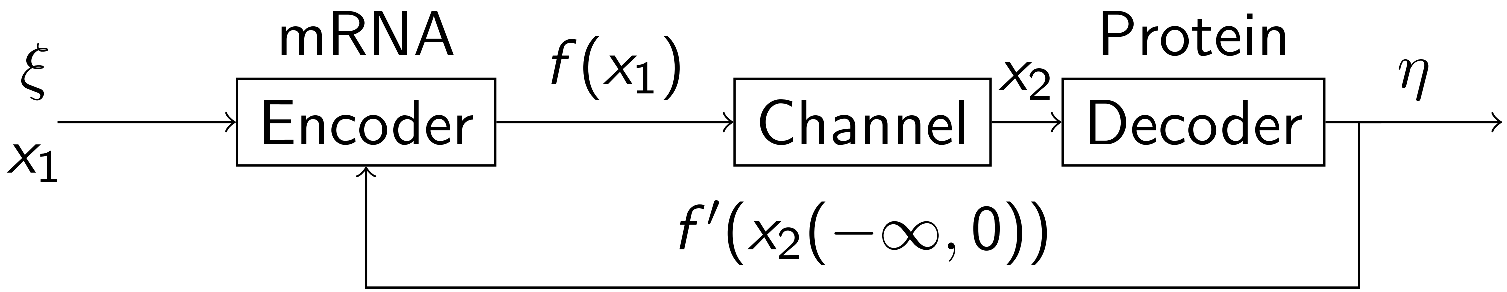
$$X_1 \xrightarrow{f'(x_2(-\infty,t))} X_1 + 1 \qquad X_1 \xrightarrow{\tau_{x_1}} X_1 - 1 \tag{1}$$

$$X_2 \xrightarrow{f(x_1)} X_2 + 1 \qquad X_2 \xrightarrow{\tau_{x_2}} X_2 - 1 \tag{2}$$

Information theoretic modelling

How much we can infer about X_1 by knowing the time-series of X_2?
The following stochastic equation describes x_1.

$$dx_1 = \frac{f' - x_1}{\tau_1} dt + \sqrt{\frac{2\langle x_1 \rangle}{\tau_1}} dw \tag{3}$$



Channel Capacity

$$C = \langle f \rangle \log(1 + \frac{\sigma_f^2}{\langle f \rangle^2}) \tag{4}$$

Information theoretical modelling

The bounds

1. There is bound on variance in x_1 whenever there is a bound on error with which x_1 can be measured.
2. To measure x_1 with small estimation error, a minimal capacity is required for channel $x_1 \to$.
3. To achieve a certain capacity, a minimal variance in the f is required.
4. If f depends on x_1, then high variance in x_1 is needed to increase the channel capacity C.

Reducing the variance reduces the channel capacity which in turn makes is harder to further reduce the variance.

$$\frac{\sigma_{x_1}^2}{\langle x_1 \rangle^2} \geq \frac{1}{\langle x_1 \rangle} \times \frac{2}{1 + \sqrt{1 + 4N_2/N_1}} \tag{5}$$

$$N_1 = \langle x_1 \rangle, N_2 = \langle f \rangle \tau_1 \tag{6}$$

Network of networks

Cascade of network

Put a figure here.

A linear cascade of networks causes information loss like the game of broken-telephone.

$$\frac{1}{N_{eff}} = \sum_{j=2}^{n+1} {N_j}^{-1} \tag{7}$$

Cell-Size control: endocytosis and exocytosis

- Size of cell: X_1. Size of the endosome: X_2.
- U is a controller which controls $X1$.

- **Endocytosis** $X_1 \xrightarrow{\tau_{x_1}} X_1 - 1$, and $X_2 \xrightarrow{f(x_1)} X_2 + 1$
- **Exocytosis** $X_1 \xrightarrow{U(x_2(-\infty,t))} X_1 + 1$, and $X_2 \xrightarrow{\tau_{x_2}} X_2 - 1$.

Questions considered

1. Assume U is most the optimum, what is the variance in X_2 when X_1 is kept at S_0?
2. Assume U is the most optimum, how well network controls X_1 under random fluctuations (simulation)?
3. For given benchmarks (fixed S_0 and variance in X_2), can U be designed?

References & Acknowledgements

Ioannin Lestas., Glenn Vinnicombe, Johan Paulsson
Fundamental limits on the suppression of molecular fluctuations
Nature, Vol 467, Sep 09, 2010

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Simulation Flow