Suppression of Variation in Cell-Size: A Control Theoretic Approach

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October 3, 2014

Building over a recent work [1], we explored the possibility of creating networks of small networks which can be utilized for controlling cell size. We explored few topologies in direction of finding a control network which can keep the size of the cell fixed and put an upper bound on the size of the Endosome. Some progress has been made on building a simulator for these topologies in an event-driven simulation environment (SystemC library of C++) [1].

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

Background

- Inside the cell, randomizing and correcting statistical forces battle it out and create fluctuations - noise. Many control circuits have evolved to eliminate or exploit the noise.
- In this rotation project, we used a recent result [1] which establishes limits on 'controllability' in a feedback network to build control networks for controlling cell-size.
- To explore such network construct, we started building a simulation environment using C++ and event-driven simulation library **SystemC**.

A Feedback Network Studied in [1]

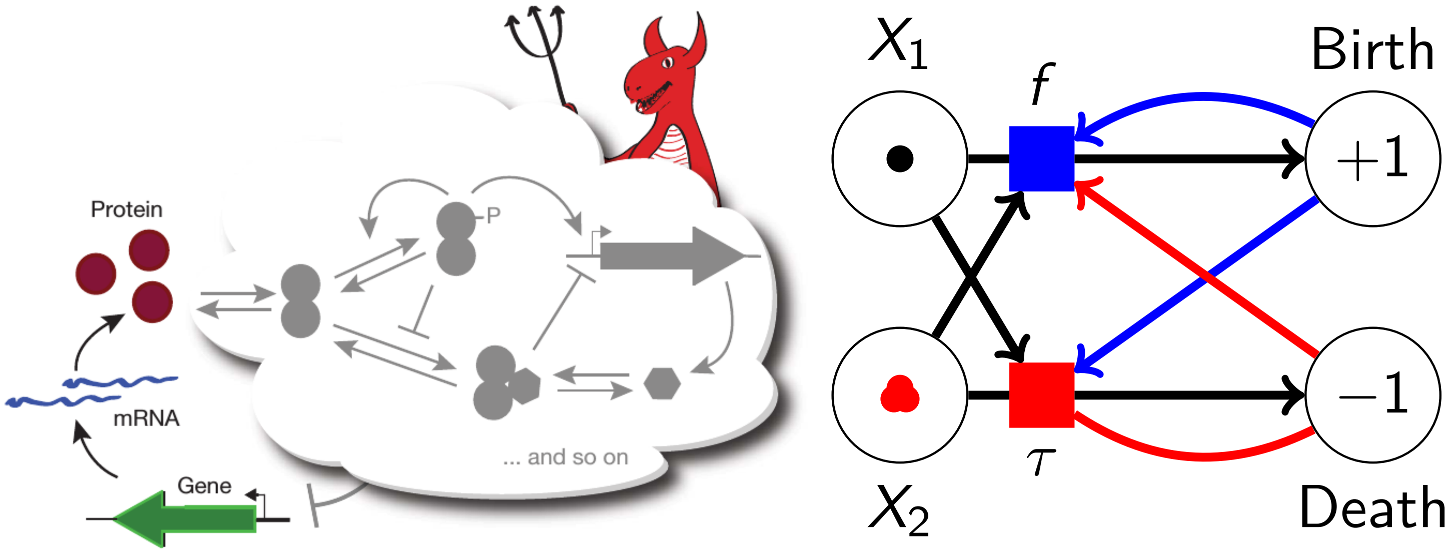


Figure : On left, mRNA/Protein network, from [1]. An equivalent description using Petri Nets on the right with X_1 as mRNA and X_2 as its protein. Signalling events are probabilistic.

Birth and Death in Network

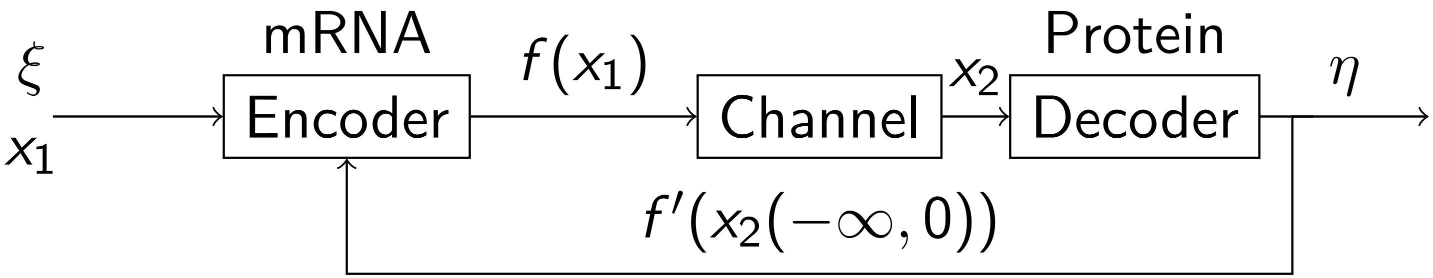
$$X_1 \xrightarrow{f'(x_2(-\infty,t))} X_1 + 1 \qquad X_1 \xrightarrow{\tau_{x_1}} X_1 - 1 \tag{1}$$

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

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 $x_1 \rightarrow$.
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

I'd like to thank Dr. Madan Rao for advice and discussions during the rotation; and Amit for walking me through the needed theory. And various Open Source Softwares especially LaTeX.