# A Mathematical Framework to Represent Input-Output Characteristics of A Single Gene Transcription-Translation Regulator

**Weekly Research Report #1**

October 20, 2013

## 1 Nomenclature

In this short report, we will consider a simple gene regulatory network which consist of one regulator, $X$, and one regulatee, $Y$. We will consider number of molecules (or concentrations) at the steady state. Those quantities modeled as sum of a constant and a zero-mean random variable. Explicitly,

$$\begin{aligned} X &= \bar{X} + \delta_X \\ Y &= \bar{Y} + \delta_Y \end{aligned}$$

where $\delta_X$, $\delta_Y$ are zero-mean random variables (perturbations), and $\bar{X}$, $\bar{Y}$ are the average values for the corresponding species.

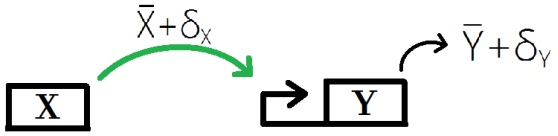


Figure 1: *The simple regulatory device*

## 2 Assumptions

The assumptions about the nature of this simple device are given below. (*Not complete*)

- Distribution of $\delta_X$ is unimodal and light tailed.
- Time scale of $X$ binding to the promoter (typically $\sim$ 1 sec for E.Coli) is much smaller than the time scale of transcription ($\sim$ 1 min) and translation ($\sim$ 2 min) of $Y$.

- (*Not very critical!* ) Half-life of the protein $Y$ ($\sim 2-5$ min) is much larger than associated mRNA molecule ($\sim 2-5$ min).
- Steady-state values for $X$ and $Y$ have ergodic distributions.
- ...

# 3 Mathematical Model

## 3.a Noiseless Model

This model assumes $\delta_X$ is zero, and there is not any noise that comes from either transcription or translation. Then the steady-state value of $Y = \bar{Y}$ can be calculated by the means of Michaelis-Menten equations [1], and the resulting relation can be given as:

$$Y \quad = \quad f(X) = \frac{\beta}{1 + \left(\frac{X}{K}\right)^n} \text{ where,}$$

$\beta$ : Maximum number of $Y$ molecules in the cell, roughly the maximum production rate (including all regulation, transcription and translation phases) times life-time of $Y$.

$K$ : The equilibrium constant for the regulation reactions, empirically equal to the input level to reach half of the maximum level at the output.

$n$ : Cooperativity coefficient for the binding of $X$ binding to the promoter. Typically, $|n| \sim 1-4$. Note if $|n| > 1$ then, $f(\cdot)$ becomes a s-shaped function which is the major motivation behind the digital analogy of the GRNs.

## 3.b Noisy Model

To investigate the input and output noise characteristic of the simple device discussed above, we will introduce following 2-step model.

1. First we will compute the expected value of $Y$, by adopting the noiseless model above. Note there are actually two kinds of noise we need to consider, the first is the fluctuations of $X$ in other words $\delta_X$, and the second is the inherent noise come from the discrete nature of the binding process. However, since the following transcription and translation processes are much slower the second noise will be averaged out. Then:

$$\begin{aligned} \bar{Y} &= E[Y] = E[f(X)] \\ &= E\left[f\left(\bar{X}\right) + f'\left(\bar{X}\right)\left(X-\bar{X}\right) + \frac{1}{2}f''\left(\bar{X}\right)\left(X-\bar{X}\right)^2 + \epsilon\right] \\ &\simeq f\left(\bar{X}\right) + \frac{1}{2}f''\left(\bar{X}\right)\left\langle\delta_X^2\right\rangle \end{aligned}$$

   Note that, at the second step, we expanded $f(\cdot)$ around $\bar{X}$ and neglected terms higher than second power via the assumption $X$ is light-tailed.

2. We calculated $\bar{Y}$ in the first step, as the second step we will calculate the variance of the output fluctuations: $\left\langle\delta_Y^2\right\rangle$. As mentioned before and experimentally demonstrated at [2], translational noise typically dominates other noise sources. Then

using the mathematical model from [2]:

$$\langle \delta_Y^2 \rangle \quad = \quad \bar{Y}\,(1+b)$$

where $b$ is roughly equal to the average number of proteins translated from one mRNA molecule and independent from the input noise.

The overall model is demonstrated in the figure below:

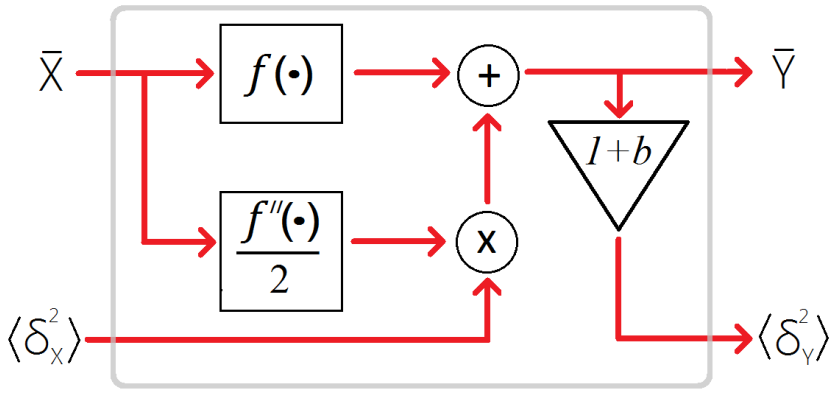


Figure 2: *Block diagram of the noisy model*

## 4 Discussion & Remarks

- Note that, noise on the input protein is reflected to the output mean value as a deterministic bias and for $|n| > 1$, this bias always decreases the difference $|\bar{Y} - \beta/2|$ (*safety margin*). Therefore, *if the circuits are designed using the traditional model* $f$, one can employ a failure condition as:

$$\langle \delta_X^2 \rangle \quad > \quad \frac{\beta - 2f\left(\bar{X}\right)}{f''\left(\bar{X}\right)}$$

  and if $X$ is also output of a similar device: $\langle \delta_X^2 \rangle = (1+b)$
- If $\bar{X} >> K$ or $\bar{X} << K$, then $f''\left(\bar{X}\right)$ is close to 0, and input noise practically has no effect.
- ...

## References


[1] Alon, Uri. "Introduction to Systems Biology: And the Design Principles of Biological Networks." Vol. 10. CRC press, 2007.

[2] Ozbudak, Ertugrul M., et al. "Regulation of noise in the expression of a single gene." Nature genetics 31.1 (2002): 69-73.