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Supplemental Information

Architectural Principles for Characterizing the Performance of Antithetic Integral Feedback Networks

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Supporting Information

Analysis of Stochastic Systems

In this section we derive the approximate expression for the Fano factor of the output species in a stochastic antithetic integral feedback system with two process species. In the following we start from the chemical reaction network description of the antithetic integral feedback system (Gillespie (1977, 2000); Munsky and Khammash (2006)), write down the chemical master equation for the stochastic system, and perform approximations with justifications to obtain an expression for the Fano factor of the output species. The approximation used is mathematically the same as the so-called linear noise approximation or first order system size expansion (Paulsson (2005)).

We describe the biochemical reactions of anthithetic integral feedback system with two process species:

$$\emptyset \xrightarrow{\mu} Z_1 \qquad Z_1 \xrightarrow{\theta_1} Z_1 + X_1 \qquad X_1 \xrightarrow{k} X_1 + X_2 \qquad X_2 \xrightarrow{\theta_2} X_2 + Z_2$$
$$X_1 \xrightarrow{\gamma_p} \emptyset \qquad X_2 \xrightarrow{\gamma_p} \emptyset$$
$$Z_1 + Z_2 \xrightarrow{\eta} \emptyset.$$

If we assume infinitely strong binding of the anthithetic integral reaction, then limit $\eta \to \infty$ holds. Hence, at any time, only one of species Z_1 and Z_2 can be non-zero. If both species are non-zero, then they sequester each other infinitely fast through reaction $Z_1 + Z_2 \to \emptyset$ until one of them becomes zero. Therefore, we can define variable $Z = Z_1 - Z_2$, which has a one-to-one correspondence to species Z_1 and Z_2 counts, where positive Z indicates counts of Z_1, and negative Z indicates counts of Z_2.

With this simplification, the dynamics of the stochastic anthithetic integral feedback system can be described by a continuous-time Markov chain (CTMC) over the counts of species Z, X_1 and X_2 using the following master equation dynamics Del Vecchio and Murray (2015):

$$\begin{aligned}
\dot{p}(x_1, x_2, z) = &\ \mu(p(x_1, x_2, z-1) - p(x_1, x_2, z)) \\
&+ \theta_1 \max\{z, 0\}[p(x_1 - 1, x_2, z) - p(x_1, x_2, z)] \\
&+ k x_1 [p(x_1, x_2 - 1, z) - p(x_1, x_2, z)] \\
&+ \theta_2 x_2 [p(x_1, x_2, z+1) - p(x_1, x_2, z)] \\
&+ \gamma_p [(x_1 + 1) p(x_1 + 1, x_2, z) - x_1 p(x_1, x_2, z)] \\
&+ \gamma_p [(x_2 + 1) p(x_1, x_2 + 1, z) - x_2 p(x_1, x_2, z)],
\end{aligned} \tag{1}$$

where $p(x_1, x_2, z; t)$ denotes the probability for the system to have $Z = z$, $X_1 = x_1$, and $X_2 = x_2$ at time t. Here we use the convention that $p(x_1, x_2, z) = 0$ whenever $x_1 < 0$ or $x_2 < 0$. Note that z denote the difference between count of species Z_1 and Z_2, so it can take negative values.

We observe that all the terms on the right hand side of equation (1) are linear, except for the $\max\{z, 0\}$ term. We can see this more clearly if we consider the first moment equation.

If we consider the steady state master equation, we set the left hand side to 0 and we apply $\sum_{x_1,x_2,z} x_1$ with the sum over all $x_1, x_2 \in \mathbb{N}, z \in \mathbb{Z}$, then we obtain that

$$\theta_1 \mathbb{E}(Z|Z \geq 0)\mathbb{P}(Z \geq 0) = \gamma_p \mathbb{E}X_1$$

Similarly, if we apply $\sum_{x_1,x_2,z} x_2$, and $\sum_{x_1,x_2,z} z$, we get

$$k\mathbb{E}X_1 = \gamma_p \mathbb{E}X_2 \qquad \mu = \theta_2 \mathbb{E}X_2.$$

The term that prevents us from solving this set of linear equations for the first moments is the $\max\{z, 0\}$ term, which results in the probability for Z to be non-negative in the moment equations.

Therefore, we make a second assumption that $Z \geq 0$ with probability 1 at steady state. This means Z_2 is zero with probability 1 and this represents a good approximation if the system is stable, without Z_1 oscillating to a very low count.

Under this assumption, we then obtain the linear equation:

$$\theta_1 \mathbb{E}Z = \gamma_p \mathbb{E}X_1.$$

Similarly, if we apply sum $\sum_{x_1,x_2,z} x_1 z$ to the master equation, we obtain a system of linear equations for steady-state moments of both the first and the second order terms. As the system of equations becomes cumbersome to solve by hand, a Mathematica script was written to automatically derive and solve the moment equations. Solution gives the Fano factor of x_2 as the following:

$$\frac{\operatorname{Var} X_2}{\mathbb{E}X_2} = \frac{\gamma_p(2\theta_1 k + k\gamma_p + 2\gamma_p^2)}{2\gamma_p^3 - \theta_1\theta_2 k}. \tag{2}$$

As $\gamma_p \to \infty$, we obtain an additional simplification

$$\frac{\operatorname{Var} X_2}{\mathbb{E}X_2} \sim 1 + \frac{k}{2\gamma_p}.$$

It should be noted that while the Fano factor result derived above are the same as the recent results in Briat et al. (2018), the method of derivation and the insights that can be obtained are different. Where Briat et al. (2018) derived results using moment invariants from the chemical master equation of the full system without the large η assumption to highlight the invariant properties of the antithetic integral feedback system, we used the large η assumption to derive a simplified chemical master equation equation (1) that highlights the almost-linear property of the system. It further suggests that the only nonlinearity, $\max\{z, 0\}$, which acts like a saturation effect, is the central nonlinearity that differentiates the full model of antithetic integral feedback from its linearization. We mean this in the sense that, when the system is far from saturation, the linear and nonlinear models exhibit the same behavior. The linearization appears to break down when Z frequently becomes negative.

On a more philosophical level, we note that both our result here and the result in Briat et al. (2018) can be calculated by brute-force using the linear noise approximation Paulsson (2005), however the specific derivations and arguments here and in Briat et al. (2018) provide insight about the system beyond the resulting equation.

References

Briat, C., Gupta, A., Khammash, M., 2018. Antithetic proportional-integral feedback for reduced variance and improved control performance of stochastic reaction networks. Journal of The Royal Society Interface 15 (143), 20180079.

Del Vecchio, D., Murray, R. M., 2015. Biomolecular feedback systems. Princeton University Press Princeton, NJ.

Gillespie, D. T., 1977. Exact stochastic simulation of coupled chemical reactions. The journal of physical chemistry 81 (25), 2340–2361.

Gillespie, D. T., 2000. The chemical langevin equation. The Journal of Chemical Physics 113 (1), 297–306.

Munsky, B., Khammash, M., 2006. The finite state projection algorithm for the solution of the chemical master equation. The Journal of chemical physics 124 (4), 044104.

Paulsson, J., 2005. Models of stochastic gene expression. Physics of life reviews 2 (2), 157–175.