

Molecular Filters for Noise Reduction

Luca Laurenti², Attila Csikasz-Nagy^{3,4}, Marta Kwiatkowska², and Luca Cardelli^{1,2}

¹ Microsoft Research Cambridge, UK

² Department of Computer Science, University of Oxford, UK

³ King's College London

⁴ Pázmány Péter Catholic University

1 Extended Abstract

Biochemical processes such as gene expression are inherently stochastic and must control noise, which presents itself as stochastic fluctuations. These fluctuations can be extrinsic, arising from interactions occurring with other processes in the environment, or intrinsic, resulting from the random timing of the reactions themselves. Molecular processes transform noisy input signals from the environment into output signals through a number of stages, with signals represented by chemical species and each stage implemented by a molecular reaction network. Since each stage can compound the noise, in order to obtain a reliable final output natural systems must integrate mechanisms that, directly or indirectly, reduce noise or otherwise confine it. Examples include signaling cascades, which have been shown to reduce extrinsic fluctuations [4].

Inspired by the concept of low-pass filters in electronics, in this talk, we introduce the concept of *molecular filter* as a Chemical Reaction Network (CRN) that can reduce the noise of an input signal while still maintaining some of the features of its time evolution, and study noise reduction capabilities of molecular filters in a stochastic setting. We propose three fundamental filter modules and their implementation as stochastic chemical reaction networks. We account for intrinsic as well as extrinsic noise, and derive principles holding for filters when embedded in a general biochemical network, which may include multiple feed-forward and feedback loops. First, we consider *linear* filters (Figure 1A), implemented by means of at most uni-molecular reactions, and we show that, in case of positive correlation between the elements of the network, they are limited by Poisson levels, that is, the variance of the output signal is lower bounded by its mean. We then show how the presence of feedback loops may improve the performance of linear filters below Poisson levels. Specific models of linear filters have already been studied in the context of closed models of gene expression [3]. Here, while still providing exact analysis based on the solution of the Chemical Master Equation, we generalize the analysis in the referenced papers taking also into account the more general and common case where the dynamics of the other components of the networks are left unspecified, and possibly involving non-linearity and feedback loops. The limitations in the noise suppression capabilities of linear filters motivate us to consider *non-linear* filters. We introduce a *non-linear* filter mechanism given by the co-expression of two species that then

bind together, called the *annihilation module* (Figure 1B), which we demonstrate is able to reduce the noise to below Poisson levels. We then propose the *annihilation filter* (Figure 1C), which combines the properties of the linear filter and annihilation module. We show how the annihilation filter in particular can greatly reduce molecular noise. We observe that co-expression and non-linear degradation are key requirements for such noise reduction. This is important to be stressed as theoretical analysis is usually restricted to linear degradation [2].

Using analytical, numerical and stochastic simulation techniques we demonstrate how the different filters improve robustness of the systems in which they are embedded.

Finally, we discuss that the molecular filters we derive are prevalent in gene expression. For instance, the linear filter, implemented by simply producing and degrading a species at a slow enough rate is a low-pass filter mechanism widely deployed in gene expression to increase robustness, both at the transcription and translation level. Moreover, we find that the annihilation module and annihilation filter are sound models of microRNA regulated gene expression, in the case of correlated expression of microRNAs with the target gene. This supports the hypothesis that microRNA may play a role in increasing robustness and precision of gene expression.

We stress that the focus of this talk is not to offer new models of particular molecular processes, but to identify fundamental and general mechanisms that, at the molecular level, can reduce noise, and to understand their properties and limitations. Thus, our results provide new insight into how biochemical networks control noise.

The results of this talk have been published in [1].

References

1. L. Laurenti, A. Csikász-Nagy, M. Kwiatkowska, and L. Cardelli. Molecular filters for noise reduction. *Biophysical Journal*, 2018.
2. I. Lestas, G. Vinnicombe, and J. Paulsson. Fundamental limits on the suppression of molecular fluctuations. *Nature*, 467(7312):174–178, 2010.
3. B. Munsky, G. Neuert, and A. Van Oudenaarden. Using gene expression noise to understand gene regulation. *Science*, 336(6078):183–187, 2012.
4. M. Thattai and A. van Oudenaarden. Attenuation of noise in ultrasensitive signaling cascades. *Biophysical journal*, 82(6):2943–2950, 2002.

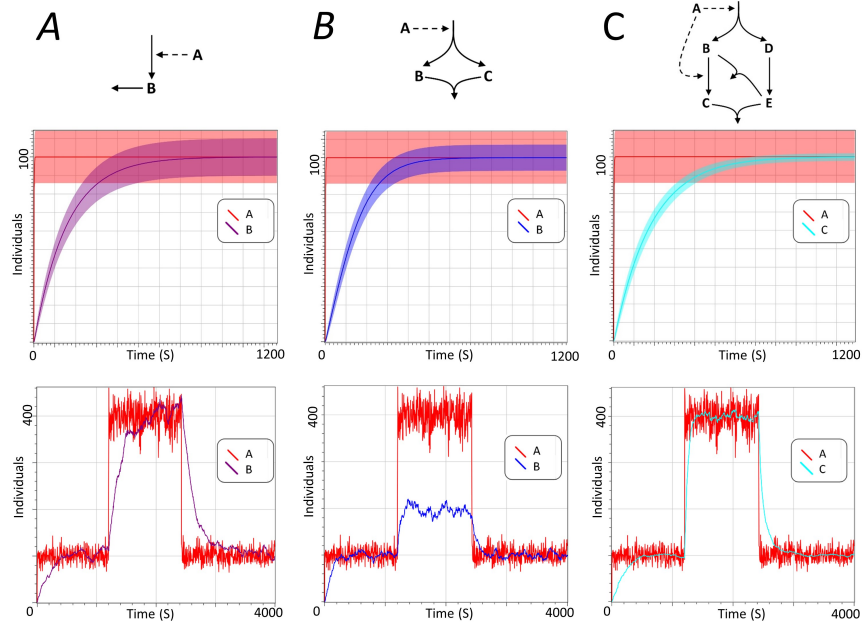


Fig. 1: Comparison of the actions of linear filter, \mathcal{M} annihilation module, and annihilation filter on noisy input A generated by reactions $\rightarrow^{50} A + A$; $A \rightarrow^1$. (Top row) Schematic representation of linear filter (A), annihilation module (B), and annihilation filter (C). (Middle row) Plots of expectation and standard deviation of input and output of each filter until time 1200, as estimated by the Linear Noise Approximation (LNA). (Bottom row) Plots of the effect of each filter obtained from a single stochastic simulation until time 4000. (A) The linear filter introduces a delay to buffer stochastic fluctuations and reduce the noise, but only to Poisson levels. (B) The annihilation module improves noise reduction performance but cannot proportionally follow changes in the input. (C) The annihilation filter not only improves the noise reduction capabilities compared to the other modules, but also proportionally follows changes in the input.