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Stochastic noise reduction upon complexification: Positively correlated birth-death type systems

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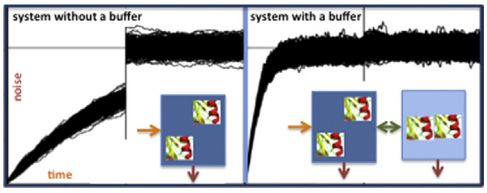
HIGHLIGHTS

- Noise in biological systems is studied by discrete stochastic differential equations.
- Biological systems are modeled by birth-death type systems with or without a buffer.
- Noise is described by the variance of the number of molecules at constant mean.
- Noise is increased or decreased according to the type of system/buffer correlation.
- In general noise is reduced upon connecting positively correlated birth-death systems.

GRAPHICAL ABSTRACT



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ABSTRACT

Cell systems consist of a huge number of various molecules that display specific patterns of interactions, which have a determining influence on the cell's functioning. In general, such complexity is seen to increase with the complexity of the organism, with a concomitant increase of the accuracy and specificity of the cellular processes. The question thus arises how the complexification of systems – modeled here by simple interacting birth-death type processes – can lead to a reduction of the noise – described by the variance of the number of molecules. To gain understanding of this issue, we investigated the difference between a single system containing molecules that are produced and degraded, and the same system – with the same average number of molecules – connected to a buffer. We modeled these systems using Itō stochastic differential equations in discrete time, as they allow straightforward analytical developments. In general, when the molecules in the system and the buffer are positively correlated, the variance on the number of molecules in the system is found to decrease compared to the equivalent system without a buffer. Only buffers that are too noisy themselves tend to increase the noise in the main system. We tested this result on two model cases, in which the system and the buffer contain proteins in their active and inactive state, or protein monomers and homodimers. We found that in the second test case, where the interconversion terms are non-linear in the number of molecules, the noise reduction is much more pronounced; it reaches up to 20% reduction of the Fano factor with the parameter values tested in numerical simulations on an unperturbed birth-death model. We extended our analysis to two arbitrary interconnected systems, and found that the sum of the noise levels in the two systems generally decreases upon interconnection if the molecules they contain are positively correlated.

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1. Introduction

Biological systems involve large amounts of different molecules that are closely packed in a relatively small area—the cell and the intercellular medium. These molecules are located in some specific regions of space—inside or outside the cell, inside or outside the nucleus, etc—or move from one region to another. They interact in a specific manner to form transient or permanent complexes that perform the biological activity. These highly complex systems are moreover very sensitive to the environment (presence of other molecules) and external conditions (temperature, pH, salt concentration, etc). It is obviously impossible to take all these degrees of freedom into account. Therefore deterministic models can only reproduce the average of variables involved in biological processes. To gain insight into the actual time evolution of an individual process, stochastic models must be used, such as stochastic differential equations (SDE) or the master equation formalism.

In spite of their highly complex and stochastic behavior, biological systems work very precisely and efficiently and perform their activity quite specifically, with a surprisingly low level of error. A striking observation is that while the overall complexity of the cellular processes (for example the transcription machinery) tends to increase with the complexity of the organisms (for example prokaryotes versus higher eukaryotes), the specificity and accuracy of these processes appear in general to increase too. In other words, the noise at the molecular and cellular levels tends to decrease when the number of degrees of freedom and thus the complexity of the organism increases.

Note however that this overall tendency is not always true: some noise is not detrimental to biological systems. Sometimes it can create the diversity needed for cellular adaptation to, for example, different environments thereby generating new gene expression patterns or phenotypes (Samoilov et al., 2006; Thattai and van Oudenaarden, 2004). Also, cell differentiation has been suggested to be noise-driven (Hoffmann et al., 2008; Forde, 2009).

Intrinsic noise reduction in biological systems has been investigated earlier by combinations of analytical and numerical approaches. In particular, in the framework of gene expression networks, it has been shown that negative feedback can dramatically reduce the variability in gene expression (Gardner and Collins, 2000; Becskei and Serrano, 2000; Paulsson, 2004; Yi et al., 2008). Actually, negative translational feedback appears to have a much greater efficiency at reducing stochasticity than negative transcriptional feedback (Swain, 2004). Also, complex promotor architectures are suggested to make gene expression regulation more precise (Müller and Stelling, 2009). In contrast, in a genetic switch model consisting of a single gene with positive autoregulation, larger numbers of activator sites appear to lead to less accurate delays (Albert and Rooman, 2012); the effect of cooperative binding of activators has also been studied and the level of noise seems to increase with the interaction energy (Gutierrez et al., 2009). Furthermore, cell–cell communication appears to lead in some (but not all) cases to decreased noise, due to the summation of the effects of all cells of the population (Tanouchi et al., 2008; Weber and Buceta, 2011; Koseska et al., 2009). Finally, at the protein level, noise control is achieved through oligomerization (Ghim and Almaas, 2008; Bundschuh et al., 2003) or through the interaction between proteins and background molecules (Morishita and Aihara, 2004).

To gain understanding of these issues, which are central for elucidating the basis of biological evolution but also for engineering novel cells in the framework of synthetic biology, we studied analytically a simple system containing molecules that are produced and degraded and compared it with the slightly more complex system in which the original system is connected to a second system—called buffer. The system-buffer pair may be viewed as representing molecules that go from one region to the other, for example, from the cytoplasm to the nucleus and back. Also, molecules in the main system can be considered as being in their inactive state and those in the buffer in their active state due to their binding to a ligand. Alternatively, the molecules in the main buffer can be protein monomers and those in the buffer homomultimers.

Our goal here is to compare the variance of the number of molecules—that represents the noise—of a system with and without a buffer. We would like to emphasize that this comparison is performed for an equal average number of molecules in the main system (excluding the buffer). We indeed assume that a biological system needs a fixed mean number of molecules to function correctly, whether or not a buffer is present.

We modeled the systems using discrete-time stochastic differential equations (SDE), in which the stochasticity is reproduced through Wiener processes. This formalism has the advantage of allowing easy analytical developments, which allow gaining basic understanding of the reasons underlying the noise reduction upon increase of complexity. For the sake of completeness, the link between this type of formalism and the Fokker–Planck equation and with the master equation is recalled explicitly. This clarifies the significance of the parameters that enter in the two approaches.

2. Stochastic system without a buffer

Consider first a simple biological system consisting of molecules of type $\tilde{y}$ which are produced at some rate $\tilde{P}$ and eliminated at some other rate $\tilde{D}$ (see Fig. 1(a)). These molecules may for example be viewed as proteins that enter the system after translation from RNA and leave it due to degradation, transformation or interaction with other biomolecules. They may also be seen as proteins that enter and leave a given cell or cell compartment. As biological processes are inherently stochastic, the amount of molecules, denoted by $\tilde{Y}$, and their production and degradation rates are taken as stochastic processes, defined on some probability space and indexed by a parameter t that represents the time and varies over the interval $[0, T]$. A natural model for the time evolution of such a system consists of an Itō stochastic differential equation in continuous time of the following form (see for example Allen, 2007):

$$d\tilde{Y}(t) = d\tilde{P}(t) - d\tilde{D}(t), \tag{1}$$

where we assume that the production and degradation rates are each expressed as the sum of a deterministic term with drift coefficient denoted by $p^{(m)}$ and $d^{(m)}$, respectively, and of a stochastic term with diffusion coefficient $\sqrt{p^{(v)}}$ and $\sqrt{d^{(v)}}$ (where the superscripts m and v stand for "mean" and "variance"):

$$\begin{aligned} d\tilde{P}(t) &= \tilde{p}^{(m)}(t,\tilde{Y})\,dt + \sqrt{\tilde{p}^{(v)}(t,\tilde{Y})}\,d\tilde{\eta}(t), \\ d\tilde{D}(t) &= \tilde{d}^{(m)}(t,\tilde{Y})\,dt + \sqrt{\tilde{d}^{(v)}(t,\tilde{Y})}\,d\tilde{\chi}(t); \end{aligned} \tag{2}$$

$\tilde{\eta}(t)$ and $\tilde{\chi}(t)$ stand for two independent Wiener processes. Remember that, by definition, $\tilde{\eta}(0) = 0$ and $\tilde{\chi}(0) = 0$, and that both $\tilde{\eta}(t) - \tilde{\eta}(t')$ and $\tilde{\chi}(t) - \tilde{\chi}(t')$ follow a $\mathcal{N}(0, t-t')$ distribution for all t, t'. Note also that the Wiener process has continuous-valued

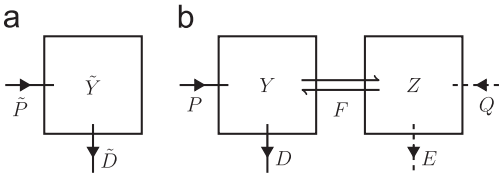

Fig. 1. Representation of a system without a buffer (*a*), and with a buffer (*b*).