Biochemical Reactions as Renewal Processes: the case of mRNA Degradation

Paolo Paradisi[1] and Davide Chiarugi[1]

Istituto di Scienza e Tecnologie dell'Informazione "A. Faedo" (ISTI-CNR),
Via Moruzzi 1, 56124 Pisa, Italy
(davide.chiarugi,paolo.paradisi)@isti.cnr.it

Background

In the last decade, the improvements of wet-lab techniques is making available novel experimental data about biochemical reactions occurring in single living cells. This information provides evidences that random events arising at the molecular level play important roles in determining the overall behaviour of biological organisms [2, 10]. As a consequence, new interest is rising towards stochastic models of biochemical systems. In this context, the Continuous Time Markov Chain (CTMC) is the most popular modeling approach and it is associated with the well-known Gillespie's Chemical Master Equation (CME) [8, 1]. CTMCs are characterised by two properties: (i) The probability of transition events (chemical reactions) towards the future states depend only on the current state (Markov property); (ii) Transition probabilities are time-independent and, thus, the process is time-invariant.
Importantly, the first property was proven to entail negative exponential distributions of the inter-event times or Waiting Times (WTs).
The aforementioned biological data show stochastic temporal dynamics which significantly deviates from those expected according to a CTMC process. In particular, in many cases, the WTs elapsing between subsequent chemical reactions are found to be distributed according to non-exponential distributions [6, 3–5], leading to the loss of both the Markov property and time-invariance. Therefore, modelling approaches grounding on CTMCs (and the CME) can result inadequate.

To address this issue, we propose an approach which grounds on the Renewal Theory (see below). Through our proposal we aim at providing a sound framework which allows us to model correctly a wide range of biochemical systems. We show the main features of our approach through a case-study represented by the mRNA degradation process.

1 Renewal Processes

A renewal process consists in a sequence of events occurring randomly in time and independently from each other. As a consequence, the WTs between two

subsequent events are mutually independent. Renewal processes are being used to describe the emergence of intermittency associated with "birth-death" events of self-organized, coherent, long living structures [7].

In the present case-study, events are defined by the occurrence of a (bio)chemical reaction and renewal processes represent the natural choice to take into account non-exponential decay of WT distributions in the modeling of biological data coming from single cell measurements.

2 A model for the mRNA degradation process

The mRNA degradation is a complex biochemical process occurring in the cell which eventually leads to the complete hydrolysis of mRNA. The temporal behaviour of this process can be non trivial, due to the fact that it is carried out by different enzymes operating in series. In [11] mRNA degradation has been characterised experimentally in *S. cerevisiae*. In many cases, as noticed also in [6], the time course observed in [11] follow a decay pattern that it is markedly non exponential. Thus, the degradation rate turns out to be time-dependent as well as the WTs between two subsequent degradation events. This scenario can hardly be described through a CTMC [9].

For providing an accurate representation of the time course of the various steps leading to mRNA degradation, we resort on renewal theory. Thus we describe mRNA degradation as a stochastic process with renewal events. In this case study, we assume waiting times distributed according to a inverse power-law:

$$\psi(\tau) \sim 1/\tau^{\mu}$$

In particular, we study the range $1 < \mu < 3$. We show that our approach provides an accurate description of the investigated system as a time-dependent stochastic process.

This work aims at paving the way towards a novel general approach towards the modeling of biochemical processes in general.

References

1. T. Ahn, Y. Cao, and L. T. Watson. Stochastic simulation algorithms for chemical reactions. In *Proceedings of the 2008 International Conference on Bioinformatics and Computational Biology, BIOCOMP 2008*, pages 431–436, 2008.
2. G. Balzsi, A. van Oudenaarden, and J.J Collins. Cellular decision making and biological noise: from microbes to mammals. *Cell*, (6):910–925, 2011.
3. J. A. Bernstein, A. B. Khodursky, P. Lin, S. Lin-Chao, and S. N. Cohen. Global analysis of mrna decay and abundance in escherichia coli at single-gene resolution using two-color fluorescent dna microarrays. *Proceedings of the National Academy of Sciences of the United States of America*, 99(15):9697–9702, 2002.
4. D. Colquhoun and A. G. Hawkes. On the stochastic properties of single ion channels. *Proceedings of the Royal Society of London - Biological Sciences*, 211(1183):205–235, 1981.

5. P. De Anna, T. Le Borgne, M. Dentz, D. Bolster, and P. Davy. Anomalous kinetics in diffusion limited reactions linked to non-gaussian concentration probability distribution function. *Journal of Chemical Physics*, 135(17), 2011.
6. C. Deneke, R. Lipowsky, and A. Valleriani. Complex degradation processes lead to non-exponential decay patterns and age-dependent decay rates of messenger rna. *PLoS ONE*, 8(2), 2013.
7. P. Paradisi *et al.* Scaling laws of diffusion and time intermittency generated by coherent structures in atmospheric turbulence. *Nonlinear Processes in Geophysics*, 19(1):113–126, 2012.
8. D. T. Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of computational physics*, (22):403–434, 1976.
9. I. Mura, D. Prandi, C. Priami, and A. Romanel. Exploiting non-markovian bioprocesses. *IET Systems Biology.*, (253):83–98, 2009.
10. A. Raj, S. A. Rifkin, E. Andersen, and A. van Oudenaarden. Variability in gene expression underlies incomplete penetrance. *Nature*, (463):913, 2010.
11. O. Shalem, O. Dahan, M. Levo, M. R. Martinez, I. Furman, E. Segal, and Y. Pilpel. Transient transcriptional responses to stress are generated by opposing effects of mrna production and degradation. *Molecular Systems Biology*, 4, 2008.