Noisy genes, noisy genomes, noisy cells: 
Recurring themes in biological organisation

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1 Introduction

Noise is the stuff that life is made of. From the thermal fluctuations that drive conformational changes in proteins, through the random interactions that occur due to the passive and active transport of finite species of molecules in the cellular and extra cellular environment, to the unpredictable nature of evolution, stochastic processes are responsible for the existence of the biosphere and for the survival of biological systems. Over the past decades and centuries, the forms that fluctuations take and their effects across all biological systems and across all scales are slowly being unravelled. The picture that emerges is astounding. Randomness is fundamental to biology, and to understand the wonders of biological systems, we must also understand the noise that underlies their existence and drives their function.

This perspective is to a large extent derived from Erwin Schrödinger’s legacy, which he laid out in his seminar manuscript, What is Life. Indeed, as is now well recognised, fluctuations are all pervasive and their effects cannot be dismissed as a high order correction. Foundational questions, such as how reliable functionality arises out of unreliable elements are of interest in understanding cell fate and embryonic development, in intracellular networks more generally, in the brain, and even in the heart.

In what follows, we outline a few examples, taken from a variety of model systems, that all appear linked by some unifying concepts in the description of fluctuations. Whether these commonalities underlie unifying principles in biological organisation remains to be discovered.

2 Noisy genes

By comparison to their constituent genes and proteins, cells are remarkably reliable. Gene networks turn on and off the production of the appropriate proteins at the right time and in response to appropriate cues. The patterns of interactions within complex intracellular networks, and across overlaid (metabolic, protein interaction and gene regulatory) networks are intricately coordinated to ensure the proper functioning of the cell. But how is this functionality attained in the presence of the many sources of intrinsic noise? For example, the first synthetic oscillating genetic network (the repressilator), successfully produced bursts of fluorescent proteins in E. coli, but these pulses were much less regular than would be expected by naturally occurring rhythms in the same organism (Elowitz & Leibler, 2000). In order to fully understand how cells are able to suppress undesired fluctuations, it is also important to characterise the noise to be suppressed.

To model protein population levels and fluctuations therein, it is possible to represent transcription and translation in some detail. Both of these processes involve base by base advancement of a molecular complex over an underlying DNA or mRNA strand. Such a process can be described in terms of a biased random walk, but this is often complicated by delays, obstacles, additional intervening factors (sometimes with a regulatory purpose) and so on. The resulting first passage problem is often nontrivial and can involve a number of competing time scales. In
fact, a recent model of transcription (Voliotis, 2007) predicts broad and heavy-tailed distributions of mRNA population levels and translation is likely to generate further variability. The results appear consistent with experimental observations of so-called transcriptional bursting (e.g., Golding et al., 2005).

3 Noisy genomes

If genes are the information carrying units on our genomes, then the organisation of DNA on the genome must be of considerable importance. Non-uniformity of nucleotide composition within genomes from a variety of taxa was revealed already several decades ago (e.g., Inman, 1966; Filipski, Thiery, & Bernardi, 1973). Of particular interest is the GC content (defined as the fraction of guanine, G, and cytosine, C, nucleotides along the DNA sequence). The human genome, for example, was described as a mosaic of regions with alternating low and high GC contents. Interestingly, these regions appeared particularly long (of the order of 300MB or longer), as compared to length scales of genes, or even gene clusters.

In a recent statistical study of GC-composition in the human genome (Cohen et al., 2005), it was demonstrated that such ‘long-range structures’ in fact lack any characteristic scale. Evolution is usually modelled as a combination of mutation, deletion, insertion and duplication events that occur randomly along the sequence. Thus, the existence of scale-free structures along the genome raises interesting questions about organisational processes, whether those correspond to evolutionary drift or to the effects of selective pressures.

4 Noisy cells

Cells are by and large the functional units of the body, and are often relied upon, even in very small numbers, to respond correctly to various internal and external cues. Cells of our immune system must respond promptly to invasion or infection to trigger a counter-attack. Neurons are relied upon for sensory integration, sometimes over weak and very noisy inputs. And our heart relies on cardiac myocytes to operate the beating of a never-resting pump. One may therefore ask what are the noise characteristics of single cells, and how do those scale up to higher (cell network) levels, where signatures of functionality can already be observed.

One perspective on such questions can be gleaned from controlled experiments on cultured cells in vitro. For instance, long-term non-invasive imaging experiments on primary cultures of cardiac cells monitored spontaneous contractions in isolated cells, groups of cells and large networks of cells (see Cohen, 2001, and Cohen, Soen & Braun, 1999). Surprisingly, inter-event interval statistics of single cell data clearly lacked any characteristic time scale. As myocytes aggregated into small groups, bursting dynamics could be observed, and only large networks exhibited the clock-like rhythms so characteristic of heart tissue. However, even in large networks, rhythm aberrations, skipped beats and other forms of fluctuations could still be described by scale-free fluctuations (Soen et al., 1999). Such single cell dynamics and the transition to large network rhythms can be described both in terms of biophysical ion channel models and from a nonlinear dynamical systems perspective (Cohen, 2001).

Our second example, of primary cultures of cortical neurons, reveal remarkably similar phenomena. Cells embedded in small networks exhibit heavy tailed (Lévy) inter-spike interval distributions (very similarly to those of isolated heart cells). As network size increases, network dynamics include globally-active time windows that are dubbed synchronised bursting events. The corresponding inter-burst interval statistics reveal a number of competing time scales. For
considerably larger networks, inter-burst interval statistics themselves mirror those of inter-spike intervals in small networks. Once again, we find that noise is ubiquitous at every level of organisation. If it manifests itself in the living brain, such noise raises significant difficulties to the computational neuroscience community. If however, the brain has devised mechanisms to regulate, suppress (and perhaps at times utilise and exploit) these fluctuations, it remains to be seen how such regulation (itself consisting of unreliable components) is achieved so reliably.

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References


