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Tiling solutions for optimal biological sensing

Structures de pavage pour optimiser la sensibilité biologique

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ABSTRACT

Biological systems, from cells to organisms, must respond to the ever-changing environment in order to survive and function. This is not a simple task given the often random nature of the signals they receive, as well as the intrinsically stochastic, many-body and often self-organized nature of the processes that control their sensing and response and limited resources. Despite a wide range of scales and functions that can be observed in the living world, some common principles that govern the behavior of biological systems emerge. Here I review two examples of very different biological problems: information transmission in gene regulatory networks and diversity of adaptive immune receptor repertoires that protect us from pathogens. I discuss the trade-offs that physical laws impose on these systems and show that the optimal designs of both immune repertoires and gene regulatory networks display similar discrete tiling structures. These solutions rely on locally non-overlapping placements of the responding elements (genes and receptors) that, overall, cover space nearly uniformly.

RÉSUMÉ

Les systèmes biologiques, depuis la cellule jusqu'à l'organisme, ne peuvent survivre et fonctionner que s'ils s'adaptent aux changements continuels de l'environnement. Ce n'est pas une tâche aisée, à cause de la nature aléatoire des signaux qu'ils reçoivent, de la nature collective et souvent autoorganisée des phénomènes qui contrôlent leur réponse, et aussi en raison de la limitation des ressources. Malgré la diversité des échelles et des fonctions qu'on observe dans le monde vivant, on peut faire apparaître quelques principes généraux qui gouvernent le comportement des systèmes biologiques. Je considère ici deux exemples très différents de problèmes biologiques : la transmission de l'information dans les réseaux de régulation des gènes et le système immunitaire adaptatif qui nous protège des agents pathogènes. Je discute les compromis que les lois physiques imposent à ces systèmes, et je montre que la structure optimale des systèmes immunitaires comme des réseaux de régulation des gènes est organisée de façon semblable, en forme de pavage discret. Ces solutions correspondent à des dispositions sans recouvrement des unités de réponse (gènes et récepteurs) qui remplissent l'espace de façon presque uniforme.

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1. Introduction

A fascinating aspect of biological systems is the emergence of large-scale reproducible function from the small-scale molecular interactions between cellular elements (proteins, genes). Living systems, both whole organisms and molecular units, amaze us by the precision of their performance. How is this precision achieved under the physical constraints that biology must obey? One way to approach this question is to note that many biological systems display emergent behavior: macroscopic, stereotyped phenomena that cannot be explained merely by composing the properties of the system's underlying elementary, and intrinsically noisy, units. As we know from physics, nontrivial emergent behavior often results from interactions on different length, time, or energy scales. These effects are also ubiquitous in biological systems, for example in single cells expressing certain subsets of genes, in highly orchestrated multi-cellular programs such as development or the reliable response of the adaptive immune system against attacking pathogens. Examples of correlated phenomena have been extensively studied in statistical physics for the past century, leading to increasing our understanding of many-body interactions in condensed matter systems, as well as technological advances.

Concurrently, recent advances in experimental technologies give us great insight into the functioning of biological systems both at the molecular, inner-cellular level, as well as the level of large scale functional systems in the organism and the behavior of large scale groups of animals. These technical developments allow us to make quantitative measurements of their constitutive elements and link it to their function. Trying to understand the functioning of these various systems, we see the emergence of common principles governing their behavior, despite the large biological differences, their functioning at different scales, and their fulfilling very different functions. In recent years physicists have become more interested in how physical principles are realized in cells. In the last decade, such an approach of taking inspiration from different biological systems (such as vertebrate development, chemotaxis, fly development, olfaction, visual processing) has proven very fruitful in proposing potential design principles (e.g. error correction [1,2], noise minimization [3,4], information transmission [5–11], acquiring information [12], speed and accuracy of decision making [13], minimax strategies [14], evolvability [15–18], optimization of resources [19–21]) that govern how physical laws are realized in living organisms. The lessons learned from these theoretical ideas have pushed the limits of experiments in concrete systems and often questioned our understanding of basic physical and biological processes.

Biological systems perform a function, limited both by the physical laws they must obey, as well as limited resources in the environment they find themselves in. Functioning efficiently and reliably in a given environment requires the matching of the statistical properties of the system to those of the environment, as has been discussed in the context of neuroscience [22,23]. If infinite sensing elements were available, the environment could be sensed up to the limits imposed by intrinsic physical noise. Of course this is not the reality of any biological system, where sensing and response must be fast and reliable and natural trade-offs appear in the design of these systems. If we assume that the structure of biological systems makes it possible for them to reliably interact with their environment, we can attempt to understand which elements of form are linked to certain functions.

Here I will discuss two very different systems that perform two very different functions: genes and their regulatory proteins, inspired by regulation in developmental systems and the ensemble (called repertoire) of receptors expressed on the surface of immune cells. Generally, the goal when sensing is to cover the whole input space in such a way that each part of this space is well covered, given the constraints of limited resources. The detailed description and formulation of the goals of these two systems is very different, but similar trade-offs appear in these two different contexts. As we shall see, the optimal solutions that these two systems find are very similar, although they are solutions to very different problems that involve an adequate, yet different in their nature, response to their environments. In short, they both involve tiling the input space, be it the input concentration of a developmental gradient or the current distribution of antigens (elements of pathogens), with their sensory elements. I will concentrate on these two examples coming from my own work. However the idea of tiling by sensory systems has been wildly explored in neuroscience (where it is termed "lateral inhibition") and comes about naturally in information theory. I will mention briefly these two cases in the discussion. I will start by explaining the problem of interest in each of the systems and show how tiling solutions emerge in both cases before discussing the differences and similarities between them.

The work presented here is a review of work I did with different collaborators, all of whom have been exploring how sensory systems function. The gene regulatory system inspired by fly development was done in collaboration with Gašper Tkacik and William Bialek [7,24–26]. I considered the question of optimal immune repertoires with Andreas Mayer, Vijay Balasubramanian and Thierry Mora [27]. In this review I chose to present only one aspect of the results obtained for these two systems – one that is common to both – tiling. The analysis in the original papers has many different perspectives that I do not discuss here.

2. Gene regulation

Differential expression of genes in cells is controlled by gene regulatory networks that respond to changes in protein concentrations indicative of internal and environmental signals and accordingly modify the expression levels of downstream genes. These regulatory elements thus process the information about the current state of the cell and its surroundings. The task of transmitting the information about input concentrations is made more difficult by the fact that gene expression is a noisy process. On the molecular level, the interactions between genes and proteins occur by means of chemical reactions,