Tiling solutions for optimal biological sensing.

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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.

I. 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 widely 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 Gasper 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.

II. GENE REGULATION

An important question in developmental biology is how the symmetry at the early stages of the embryo is stably broken to create structured organisms given the inherent cellular stochasticity. Examples of symmetry breaking are observed in development where the mother lays the foundation for gradients that are later translated to cell fates through a noisy signaling network. During development cells differentiate and start expressing different sets of proteins. The fruit fly (Drosophila melanogaster) is a model organism to study early embryonic development and cell differentiation [28, 29]. The fly mother produces bicoid mRNAs, which are laid in the anterior of the egg. As the proteins translated from these mRNAs diffuse away from the pole they establish a decaying anterior-posterior protein gradient. Together with other maternal proteins (e.g. Nanos), Bicoid proteins locally regulate the expression a set of downstream "gap genes" (lunchback, kruppel, knirps and giant) to determine, among other features, the anterior-posterior (head to abdomen) axis. The gap genes control the expression of downstream genes (called pair-rule genes) that form very well defined stripes, which later lead to the formation of segments in the fly’s body. The precise positioning and width of these stripes is essential for correct development. One of the puzzles of biology is how the position of the stripes can be controlled so accurately. All the positional information the fly embryo has is contained in the profiles of the maternal proteins. This information must be transmitted accurately in the different steps of gene expression, or the developmental plan will fail.

The task of transmitting the information about the concentrations of the maternal gradients 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, which are probabilistic in nature. Furthermore the scarcity of the reaction products increases the intrinsic noise of the cell, requiring a stochastic framework [7, 30–37]. There is typically one active copy of DNA per cell, a few copies of mRNA and tens to hundreds copies of a protein of a given species. The stochastic nature of gene expression has been confirmed experimentally [31, 33, 38–40].

Many elements of the gene regulatory network that regulate the expression of stripes have been mapped out. Owing to the experimental and theoretical advances of the last decade, we now have a good understanding of the molecular details of the basic forms of gene regulation. At the same time, our understanding of the basic components of molecular noise has increased. We can use this knowledge to go beyond the simple characterization of gene regulatory networks and ask whether we can identify the physical principles that govern the observed behavior of circuits. Specifically, can we understand why the early steps of cell differentiation in the fly embryo follow this specific pattern? How do the specific regulatory elements come together in space and time, and which parts of the regulatory process control which observed features?

In this initial stage of development, the continuous Bicoid concentration gradient gets translated into localized expression patterns of the gap genes: lunchbck is only expressed in the first (anterior) part of the embryo, kruppel in the middle, giant and knirps in two sets of distinctly positioned stripes along the length of the embryo [41]. Inspired by the regulation of the gap genes in early fly development, Tkacik, Bialek and myself were interested in understanding the circumstances under which the expression of the target genes becomes localized [7, 24, 26]. Even these early stages of fly development include a number of complicated interactions between the target genes, so we started by studying a simplified system where one continuous input (inspired by Bicoid) regulates $L$ independent downstream genes, inspired by the $L = 4$ gap genes (see Fig. 1). We asked what are the regulatory interactions between the one input and $L$ output genes that maximizes the transmitted information between the input and outputs.

Information between the input and output is an intuitive concept that is also formally defined as mutual in-
The described input-output function is parametrized by optimizing the information with respect to the input concentration $c$ and the output concentration $\bar{c}$.

To make progress, we also need to characterize the regulatory network. We can assume that the conditional distribution of the output given the input that describes the regulation function is well approximated as a Gaussian with covariance $\Sigma(c)$ around the deterministic regulatory function. In general for $L$ interacting output genes $\Sigma(c)$ is the inverse covariance matrix of size $L \times L$ of the fluctuations in the expression levels $\{g\}$ at fixed input $c$. However in the specific case discussed in most of this review of $L$ non-interacting genes, $\Sigma(c)$ only has diagonal entries coming from the variance in its own output and the global input $c$, $\Sigma_{ii}(c) = \sigma_i^2(c) \delta_{ij}$. The Gaussian assumption effectively reduces the problem of describing the input and output probability distributions, $P(\{g\}) = \int dc P(\{g\}|c)P(c)$ to knowing the input distribution and the parameters of the $L$ dimensional Gaussian distribution, i.e. its mean $\{\bar{g}(c)\}$ and covariance matrix $\Sigma(c)$. Since this is rather repetitive to draw for $L$ non-interacting genes, Fig. 1 depicts the parametrization of the network for one output gene.

We can now use our knowledge of the regulatory interactions and noise properties in gene regulation and account for all the biophysical constraints by parametrizing the variance and the mean regulatory functions. We chose a basic thermodynamic Hill model for regulation (see below) and assumed that most of the noise comes from the random production of proteins (Poisson noise - first term in Eq. 2) and the diffusion limited switching of the genes (a Berg-Purcell cell [44] - second term in Eq. 2):

$$
\sigma_i^2(c) = \frac{1}{N_{\text{max}}} \left[ \bar{g}_i(c) + c c_0 \left( \frac{d\bar{g}_i(c)}{dc} \right)^2 \right],
$$

(2)

where $N_{\text{max}}$ is the maximum number of independent molecules that are made from gene $i$ and $c_0 = N_{\text{max}}/Da\tau$ is the characteristic concentration scale composed of the characteristic length and timescales for regulation (the diffusion constant $D$, the size of the target binding site $a$ and the input integration time $\tau$). By doing this we effectively parametrize the variance by the mean input-output relation, $\bar{g}_i(c)$. The Hill functions that describe $\bar{g}_i(c)$ are sigmoidal smooth monotonic functions of the input concentration

$$
\bar{g}_i(c) = \frac{e^{h_i}}{K_i^{h_i} + e^{h_i}},
$$

(3)

parametrized by the concentration which results in half-maximal expression of the gene, $K_i$, called the dissociation constant, and the steepness of the regulatory function $h_i$, which is linked to the cooperativity of the molecular reactions involved in regulation. The form of this expression can be derived from thermodynamic arguments with $K_i = \exp(-F/k_BT)$ where $F$ is the the free energy of binding per input molecule. The sign of the cooperatively parameter $h_i$ differentiates between activation...
(h_i > 0) and repression (h_i < 0) of the target gene by
the input, and its value extrapolates between linear reg-
ulation ((h_i = 1) and threshold switching (h_i → ∞).
Each gene responds by producing a differentiable output
in a limited input concentration range ~ K_i/h_i set by
the cooperativity coefficient and measured in units of K_i
around the concentration midpoint given by the dissociation
constant K_i. Below that range the gene is essentially
off, and above it has saturated its expression. More de-
tails of the parametrization can be found in [7, 24, 25].
In summary, this parametrization allows us to describe
the properties of the network in terms of two parame-
ters: the dissociation constant K_i, which
describes the positioning of the gene in the input concen-
tration range and the cooperatively function which sets
the range of inputs the gene is responsive to. To find the
optimal network we must find the optimal values of these
parameters.

Biological systems must obey a number of constraints,
including paying a cost for producing molecules. We can
now optimize mutual information with respect to the in-
distribution given this molecular constraint that we
include by limiting the range of input molecules (tech-
ically imposing an upper integration bound for input concen-
trations) and demanding the distribution is normal-
ized:

\[ \frac{1}{δP(c)} \left[ S[P(\{g\})] - \int dc P(c) S[P(\{g\}|c)] \right] \]
\[ + \lambda \int dc P(c) = 0. \]  

The expression is easily minimized, because we have
parametrized P(\{g\}|c) as a Gaussian defined explicitly
in terms of biophysical rates of the problem. The opti-
mal input distribution P^*(c) is expressed in terms of the
uncertainty of the input c given the outputs \{g\}, given
by the variance of the posterior \sigma_c^2(\{g\}):

\[ \frac{1}{\sigma_c^2(\{g\})} = \sum_{i,j=1}^L \left[ \frac{d\hat{g}_i(c)}{dc} \cdot (\Sigma(c)^{-1})_{ij} \frac{d\hat{g}_j(c)}{dc} \right] \]
\[ \left. \right|_{c=c^*(\{g\})} \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

\[ = \frac{1}{\mathcal{L}} \left[ \frac{\left( \sum_{i=1}^L \left( \frac{d\hat{g}_i(c)}{dc} \right)^2 \right)}{\sigma_0^2(c)} \right] \]  

The last line in Eq. 7 explicitly gives the expression for \mathcal{L}
non-interacting genes, whereas the other expression keep
the general form for possibly interacting genes. Given
the optimal input distributions we can calculate the the
optimal information of the system

\[ I^*(c; \{g\}) = \log Z. \]  

The details of this calculation can be found in [7].

The optimization problem requires finding the optimal
parameters of the regulatory functions (\{K_i, h_i\}_{i=1,...,L})
that maximize log Z, whose form is determined by the
noise. The optimal solutions are a result of the balance
between the two sources of noise in Eq. 2: the input
noise coming from fluctuations in regulatory protein concen-
trations (second term in Eq. 2), and the output noise
caused by the small number of produced proteins g_i (first
term in Eq. 2). At small input concentrations the fluc-
tuations from an unreliable readout of c dominate and
push the solutions to have higher values of K_i, whereas
the need to distinguish different levels of outputs reli-
ably decrease the steepness of the regulatory functions
and forces them to use also the smaller concentration
ranges, decreasing K_i and h_i. The actual parameters of
the regulation function need to be optimized numerically
and for large concentration ranges of input molecules we
obtained the characteristic optimal regulatory functions
as shown in panels B–E of Fig. 2. The different pan-
els show the solutions for increasing input concentration
ranges. In these solutions each gene is effectively regu-
lated in a finite localized input concentration regime. For
small concentrations the first gene is expressed and when it
saturates, the second gene is expressed. This trend
continues and the gene expression domains tile space.

The tiling solution is the most informative solution
when the concentration range of input molecules is large.
When the concentration range of the input molecules is small (see Fig. 2 A), the optimal solution consists of all
genes making the same readout of the input by having
exactly the same regulatory function. In this case the
genes no longer tile space, but repeat the same mea-
surement to minimize the error coming from reading out
small concentrations. The transition from one regime to
another is continuous as a function of input range concen-
tration and information. This can be explained in terms
of the dissociation constants of each gene, which give
the concentration value at which a gene is expressed at half
maximum. Either there is enough concentration range
to use the discrete gene readout —in this case the genes
have different values of the dissociation constants; or it
is better to attempt a reliable readout in one concen-
tration regime, and the dissociation constants collapse. The
transition from the non-tiling to tiling regimes in terms
of the dissociation constants is shown in Fig. 2 F. Fig-
ure 2 also shows that the tiling of genes is gradual and the
redundancy is lifted one gene at a time as the input
concentration range increases.
FIG. 2: The most informative regulatory functions \((g_1(c), \ldots, g_5(c))\) (shown in different colors) for a gene regulatory network with one input \(c\) regulating \(L = 5\) non-interacting output genes, for increasing ranges of the maximum input concentrations \(c_{\text{max}}\) (A–E). At very small values of \(c_{\text{max}}\) all \(L\) genes have the same regulatory function making the readout completely redundant. For increasing values of \(c_{\text{max}}\) the redundancy of the readout is lifted, as successive genes individually cover particular subranges of the input concentration. (F) The emergence of the tiling solution in terms of the gene dissociation constants \(K_{r1}, \ldots, K_{r5}\) as a function of \(c_{\text{max}}\). We assumed Hill regulatory functions and Berg-Purcell and small molecule noise dominate protein fluctuations, as described in [7].

III. IMMUNE RECEPTORS

Let me now leave gene regulation and turn to a completely different system - the adaptive immune repertoire. After this short presentation, I will return to the our information optimal gene regulatory network and compare the characteristics of these two very different biological systems.

The role of the immune system is to protect the organism from the many pathogenic threats it constantly encounters. To fulfill this role, it must be prepared to identify a great variety of unknown challenges, including ones it has never been exposed to. It must thus maintain a diversity of specialized cells, each specific to particular challenges, but which together cover the full array of potential threats. These cells are called B and T-cells and the particular receptors responsible for recognition on each of these specialized cells are generated in an essentially random manner [45]. Yet together these receptors form a diverse repertoire that allows the immune system to fulfill its function of recognizing pathogens exceptionally well. Since not all threats are equally likely, the immune repertoire adapts to the changing pathogenic environment, at the same time keeping a memory of past infections. The diversity of the composition of the immune repertoire emerges as a selforganized process, stimulated by interactions with the environment.

Receptor proteins on the surfaces of these cells interact with pathogens, recognize them through specific binding and initiate the immune response. The interaction between pathogen proteins and receptors is based on the binding of two polypeptides (one being part of the receptor, the other being part of the pathogenic protein) and is specific, yet degenerate: a single receptor is able to recognize more than one pathogen peptide (antigen) and, conversely one antigen can bind to more than one receptor. How the highly dimensional space of pathogenic peptides is covered by receptors is a particularly challenging example of a covering problem.

The immune response is controlled by many factors on many scales, however it is initiated when a B or T-cell receptor successful recognizes an element of a foreign pathogen, called an antigen. In our approach, presented in [27], we decided to focus on this part of the puzzle and ask how should immune receptors be distributed in order to minimize the harm from infections given a fixed, static antigenic environment. Additionally, antigens and receptors have a limited number of encounters, since it takes time for a receptor and antigen to meet given the finite concentrations of both and the size of the organism. This imposes a constraint on the efficiency of recognition. By formulating the problem in this way, we simplified it to a static version of a covering problem with limited resources. However even in this simple formulation the exact meaning of most of the used terms needs to made precise.

Since recognition is triggered by binding of receptors
and antigens, we can consider the problem in an effective recognition space. Both types of molecules (antigens and receptors) live in this space and they recognize each other if the distance between them in this space is small. The idea of recognition space is similar to shape space [46] which has been very useful for decades for describing effective antigen-receptor interactions. We do not need to further parametrize the space to describe this interaction (for example as has been done using string models, where both molecules are taken to be strings of effective amino acids with effective physical and biochemical properties and their similarity is measured in terms of a Hamming distance between the strings), however this specific picture is a helpful concrete example of the type of effective recognition space we have in mind. Since we are thinking about a static picture, the receptor repertoire is described by a probability distribution \( P_a \) and the fixed ensemble of antigens by \( Q_a \), as depicted in Fig. 3. A receptor and antigen can meet and recognize each other with a cross-reactive recognition probability \( f_{a,p} \). This function accounts for the fact that one receptor can recognize many pathogens and, conversely, one antigen can be recognized by many receptors. Given the recognition probability, the probability of an immune response from an encounter of a random receptor with a given antigen, \( a \), is \( P_a \cdot \sum_{r} f_{a,r} P_r \).

Since we are interested only in the consequences (recognition or not-recognition) of encounter events, we choose to measure time in the mean number of encounters \( m \). The recognition events are random and Poisson distributed in \( m \). The limitation on the number of encounters can also be understood in terms of finite sampling of the receptors by the antigen. As the number of encounters increases while the antigen remains unrecognized, the effective cost of the infection increases according to a function \( F_a(m) \), due to the damage caused by the potentially proliferating antigen to the tissues of the organism. Therefore to obtain the total harm caused by a given antigen we need to integrate the effective cost over the number of encounters weighted by the distribution of successful recognition encounters:

\[
F_a(P_r) = \int_{0}^{+\infty} dm \, F_a(m) \, P_r e^{-m \hat{P}_r}.
\]  

Finally, the overall cost to the organism needs to take into account the costs from all the antigens:

\[
\text{Cost}(\{P_r\}) = \sum_a Q_a F_a(P_r).
\]  

This cost accounts for the trade-off between a having to distribute many receptors given a finite number of encounters in such a way that the total harm caused by infections increases with time. Given a fixed antigen distribution, \( Q_a \) we find the optimal distribution \( P_r \) of receptors that minimizes this cost.

The details of this optimization, as well as some analytical intuition gained from limiting cases is discussed in detail in [27]. The interesting results for the purpose of the current discussion are best seen in the numerical results recounted in Fig. 4 A for a two dimensional random antigen distribution. We see the optimal receptor distribution tiles space in a random way: the distribution is discrete with receptors positioned as individual non-overlapping peaks in recognition space. To quantify this pattern in more detail we can look at the radial distribution function as a function of distance between the receptor positions (Fig. 4 C). We see a strongly repelling core at small distances, that forbids the placing receptors too close to one another and characteristic regular peaks at larger distances that indicate likely positions of the receptors. Analyzing the structure function, confirms our intuition that the precise placement of the receptor is not important (Fig. 4 D). The structure factor at long wavelengths corresponding to short inter-receptor distances goes to 1, as it does in a liquid or disordered glass. However at large scales the pattern is completely reproducible, as quantified by the structure factor going to zero at short wavelengths. Cross-reactivity allows one receptor to cover all the antigens within a given range and results in the hard core, whereas needing to protect against even the rare but potentially dangerous antigens requires a thorough coverage of the whole space.

A biological implication of this type of receptor distribution is the fact that two individuals seeing roughly the same antigen environment can have dramatically different optimal repertoires aimed at targeting this specific set of antigens, while both manage to attain complete covering of the antigens, as illustrated by Fig. 4 B. Two individuals can see two slightly different versions of the same environment simply due to sampling different antigens. Further discussion of the immunological implications can be found in the original paper [27].

The appearance of the tiling pattern in the optimal solution depends on the value of cross reactivity. This is most easily seen in the limiting case of taking both the antigenic environments and cross-reactivity to be Gaussian functions [27] - the localized peaked receptor distribution is optimal only when the variance of the cross-reactivity \( \sigma \) is more than \( \sqrt{2} \) times larger than the variance of the pathogen distribution \( \sigma > \sqrt{2} \sigma_Q \). The transition is continuous: the variance of the receptor distribution decreases until it becomes a delta function.

IV. CONNECTION TO REAL SYSTEMS

The reasoning presented above finds the form of idealized optimal regulatory networks and repertoires. The role of such an approach is not necessarily to explain the detailed form of a given biological design. In fact in both cases, as is especially clear in the case of the immune repertoire, we have greatly simplified the problem and not taken into account important signaling and spatial dependencies of the system. Our goal in both case was to learn some general properties and understand which
FIG. 4: Optimal receptor distribution \( P^*_r \) for two-dimensional random environments (A). The antigenic landscape \( Q_a \) is generated randomly from a log-normal distribution with coefficient of variation \( \kappa = 1 \). (B) A cartoon representation of the main characteristics of the optimal receptor distribution: locally the receptors are placed randomly and are non-overlapping, whereas at large distances they uniformly tile space in a way that two locally distinct patterns are indistinguishable on large scales. The lines guide the eye to compare the two patterns. These properties are well quantified by analyzing the tiling patterns using correlation functions (C-D). (C) The radial distribution function of \( P^*_r \), \( g(R) \), has an exclusion zone at small distances around each peak, with a periodic pattern at large distances characteristic of a local tiling pattern. (D) The normalized power spectral density \( S(q) \) of \( P^*_r \) for different values of the coefficient of variation of the distribution function of the environmental, \( \kappa \), quantifies the heterogeneity of the antigenic landscape at different scales. Fluctuations average out at large scales (small \( q \)) to uniformly cover space, whereas locally (large \( q \)) there are many possible placements for the receptors (non-zero \( S_q \)).

In the case of the two systems considered here, the initial formulation of the problem is very different. In both cases we looked for optimal solutions, however they are optimized for very different quantities. The gene regulatory network is optimized for information transmission between the input and output - a common assumption in studies of shared sequences between individuals show no more overlap than expected by chance [47–50]. Zebrafish B-cell repertoire studies also showed no correlation between the environment and repertoire [51, 52]. Another corollary of our predictions is that receptors should form well separated clusters. Analysis of the amino acid sequences of CDR3 regions in zebrafish B-cell repertoires showed that the sequences cluster into a relatively small number of attractors that are mostly different from the genetic templates [51]. This hints that a tiling solution in effective recognition space is not incompatible with the data.

V. DISCUSSION

In the case of the two systems considered here, the initial formulation of the problem is very different. In both cases we looked for optimal solutions, however they are optimized for very different quantities. The gene regulatory network is optimized for information transmission between the input and output - a common assumption in
many sensing systems [12, 23, 53, 54]. By contrast, the immune repertoire is optimized to guarantee the least costly response - to allow the immune system to respond to a diversity of antigens with the smallest delay weighted by the potential harm of not responding. Nevertheless in both problems there is a trade-off given by the limitations of the system. In gene regulation the cell does not have infinite input molecules at its disposal, forcing it to distribute its response genes. In the immune system the number of encounters between antigens and receptors is finite, limiting the number of potential recognition events. These two trade-offs lead to similar types of solutions that show the same kind of characteristic features on short and large scales.

Naturally the biological nature of the gene regulatory and repertoire problem is very different. Additionally even in terms of their formal theoretical description the systems are very different. The gene regulatory problem includes placing discrete genes in a continuous space, making the problem discrete from the beginning. In the case of the repertoire the space is continuous and the discrete distribution emerges by itself.

Despite these differences the gene regulatory and immune repertoire show very similar tiling structures at different scales (see Fig. 5 for a direct comparison). Locally we observe clustering in both cases. The optimal repertoire has the structure of discrete peaks although the probability of having the receptors at a given position in recognition space is a priori continuous. The receptors are discrete non-overlapping entities. Similarly the range of input concentrations in which a given gene is expressed, and in which we can discriminate the input concentration by measuring the output, is locally limited. Reducing that input concentration range results in the clustering of the regulatory properties of the output genes, and the overall range of inputs they respond to. In both systems we see this clustering of function on small scales: some areas of recognition space or input concentration are directly covered by a receptor or a given gene, whereas nearby areas are not. Yet on the large scale in both cases the whole space is nearly uniformly covered by genes or receptors, as seen explicitly from the close to uniform coverage of the antigens by the receptor distribution, \( \tilde{P}_a = \sum_r f_{r,a} P_r \) [27]. So at large scales we observe the characteristic tiling of all of space by the total distribution of receptors, which leaves no part of effective space uncovered.

The analogy depicted in Fig. 5 is made more explicit in terms of the parameters of the two problems. The specific placement of the receptor corresponds to the concentration at half maximum expression of the gene \( (K_i) \) - the placement of the gene in input concentration space. But just as cross-reactivity ensures that areas of recognition space where there are no receptors remain covered, \( \sim K_i/h_i \) sets the range of input for which a given gene differentially responds to input concentrations.

This structure of local clustering and global tiling of space depends on the ratio of cross-reactivity to the size of the space for immune receptors and the value of the maximum input concentration scaled in natural units of concentration for gene regulation. Natural units of concentration result from the characteristic physical timescales of regulation (diffusion constant \( D \), signal protein integration time \( \tau \), the maximum number of independent molecules of the output \( N_{max} \) and typical size of binding site \( a \) ), \( \ell_{opt} = N_{max}/Da\tau \). If we consider a relatively large effective space (whether it is the input concentration range or recognition space) the optimal solution will consist of \( L > 1 \) genes and \( L > 1 \) receptors that use cross-reactivity to cover the whole pathogenic space. If we now decrease this effective space, the optimal genetic solutions will reduce to one gene and similarly the whole recognition space can easily be covered by one receptor. The discrete structure of the optimal immune repertoire distribution depends on the small scale noise. If there was no intrinsic variability at small scales the optimal distributions would be continuous since nothing would differentiate between particular points in space. This effect can be seen in the limiting case of Gaussian antigen distributions where there is no small-scale noise at all and the optimal receptor distribution is also Gaussian (given a Gaussian cross-reactivity function).

The fact that solutions that optimize information in a finite space result in discrete solutions that tile space has been known for a long time [55, 56] and studied in a number of systems from neuroscience [57] to ecology [58]. The only way to obtain a continuous optimal distribution when optimizing information is to consider an unbounded space. However the tiling solution discussed here in terms of gene regulation is slightly different. The genes are already discrete, imposing the discrete structure on the problem. The input concentration range adds an additional layer of potential discreteness (clustering) that is different from the discreteness of the information optimal distributions discussed in other contexts. The discrete number of genes is separated in concentration space, which they tile, building a discrete structure from already discrete units. This type of solution is analogous to optimal tiling of the visual receptive range by retinal ganglion cells [59, 60] and linked to the hypothesis of efficient coding [22]. The pattern of expressing neurons that process visual stimuli in the retina ("lateral inhibition") has been proposed as a way to remove redundancy in the encoding of the signal that comes from correlations in the environment (visual stimulus) and the response (receptive field).

More generally, the appearance of discretized solutions in continuous systems, similar to the tiling patterns described here has been described in many different contexts. Many of these analogies, pointed out to me by Olivier Rivoire and Thierry Mora, are often linked to bet-hedging strategies [61] with applications ranging from phenotypic stability [62], competition of individuals for resources [63], ecology models of population regulation [64], neural coding [57] to portfolio risk management [65]. Of course discrete designs of components of
naturally occurring biological systems are very common. For example, in neuroscience both the visual system [66] and the olfactory system [67] use discrete receptors to respond to continuous or quasi-continuous inputs, whereas the existence of species is responsible for the interest of ecologists in this topic. The retina system has been characterized in great detail experimentally [68] and theoretical detailed predictions have been put forward based on the idea of efficient coding, which hypothesizes that signal processing has evolved to optimally encode natural stimulus while minimizing resources, to the extent that it is becoming possible to test these predictions against existing the neural circuitry [69–72].

Lastly, we can ask what is the link between these optimal solutions, which are obtained in a static setting, to real dynamical biological systems. How is the structure of non-overlapping genes and well separated receptors that nevertheless manage to completely cover space achieved in terms of the natural dynamics of the systems? As was explicitly shown in [27] a simple birth-death dynamics of receptor clones where receptors compete for interactions with antigens results in exactly the same optimal repertoire distributions as discussed above. There, mutual competitive exclusion is responsible for the characteristic tiling structure. In genes, the concentration ranges in which genes function are also mutually exclusive, as evidenced by their distinct dissociation constants. In our information optimization setup, the genes do not interact. Yet the system achieved this solution by means of long term evolution, which favored this non-overlapping state.

In fact, allowing two output genes to interact results in an optimal network where the gene with a higher dissociation constant represses the expression of the gene with a smaller dissociation constant. This further restricts the range of activity of the gene with a lower dissociation constant, since it gets turned completely off beyond a certain concentration. In this interacting gene example the exclusion is encoded both in the dissociation constants and the direct negative regulation. In general evolution can use either one of these methods to arrive at non-overlapping concentration ranges where these genes function, hence tiling solutions. Negative feedback or competition is essential for the dynamics to reach these locally clustered, globally tiled solutions also in other systems. Such behavior has been termed competitive exclusion in ecology [73] and evoked as a reason for the emergence of species, as well as lateral inhibition in neuroscience [74].

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[75] Mutual information is a symmetric quantity so it also can be defined as the difference of entropies of the input and the input given the output.