

## Rate-Distortion Scenario for the Emergence and Evolution of Noisy Molecular Codes

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We discuss, in terms of rate-distortion theory, the fitness of molecular codes as the problem of designing an optimal information channel. The fitness is governed by an interplay between the cost and quality of the channel, which induces smoothness in the code. By incorporating this code fitness into population dynamics models, we suggest that the emergence and evolution of molecular codes may be explained by simple channel design considerations.

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Living systems store information in one form of a molecule (e.g., DNA) and use it to produce a different molecule (e.g., protein), usually relying on intermediary recognition processes by other molecules (e.g., tRNA). This information transfer is a code, albeit one that must perform in a noisy environment. Such noisy information channels are omnipresent in biology and analyzing them can highlight the engineering constraints on living systems and their impact on fitness. Several studies have examined the biophysical makeup of the transcription regulatory network (TRN) to scrutinize the effect of this information system on fitness [1–3].

In this work, we first introduce a measure for the fitness of molecular codes. The quality of the code is measured by the distortion of a typical message. The cost is the typical number of bits required to write one message. The overall fitness of the code is the weighed sum of cost and quality. This is similar to the basic problem of rate-distortion theory [4,5]—how to design an optimal information channel by balancing the cost against the required transmission quality. We find that the relevant control parameter is the derivative of cost with respect to quality, termed gain. The code appears at a phase transition in the information channel [5–11] with the gain playing a role of an inverse temperature. To examine the appearance of codes we then turn to models describing populations of information-processing systems, simplified “organisms”, which compete and evolve according to the fitness of their codes. We show that the coding transition can be induced by changing a number of parameters such as the accuracy of reading and the population size. Finally, we treat two realistic scenarios of deviations from the simplified ideal dynamics, which involve mutations and genetic drift (i.e., reproduction fluctuations). Mutations broaden the population to include systems with lower code fitness, creating a “quasispecies” with a reduced effective fitness. Genetic drift delays the coding transition to higher gains.

*The fitness of molecular codes.*—Molecular codes often relate two sets of molecules, which we may think of as *symbols* and their potential *meanings*. In the genetic code, for example, the symbols are the 64 DNA base-triplets

(codons) and their meanings are the 20 amino acids and the stop signal [12]. In the case of the TRN, DNA sites are the symbols and the meanings are the transcription factors that bind the sites [13,14]. Optimizing the quality and cost of a biological code can therefore be regarded as a semantic problem of wisely assigning meanings to symbols. To discuss this semantic problem, we consider an information channel that relates two spaces, one with  $s$  symbols and the other with  $m$  meanings (Fig. 1). The channel describes how meanings are stored in memory as molecular symbols, and how the symbols are read to reconstruct the meaning.

Molecular codes rely on error-prone binding and the channel is therefore described by a three-stage stochastic process [5,7,8,10]: (i) The storage of meanings in memory as symbols is represented by an encoder matrix  $e_{ai}$ , the probability that a meaning  $\alpha$  is encoded by a symbol  $i$ . (ii) The symbol is read as described by the reader matrix  $r_{ij}$ , the probability to read the symbol  $i$  as  $j$ , which accounts for possible misreading errors. (iii) Finally, the read symbol  $j$  is interpreted as carrying a meaning  $\omega$  according to a decoder matrix  $d_{j\omega}$ . The distortion between the original meaning  $\alpha$  and the reconstructed one  $\omega$  is measured by the distance  $c_{\alpha\omega}$ . In the genetic code, for example, amino-acid meanings are encoded as base-triplet symbols, which in turn are read by tRNAs at the ribosome.

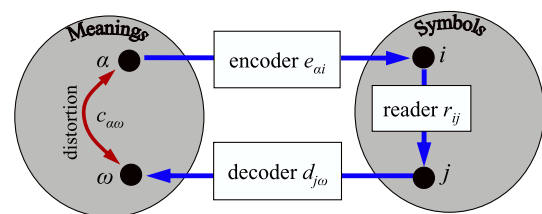


FIG. 1 (color online). Molecular codes as noisy information channels. The code relates the space of meanings (left) with that of symbols (right). The channel is a three-stage Markov process (blue arrows): (i) A meaning  $\alpha$  is encoded as a symbol  $i$  by the encoder  $e_{ai}$  (ii)  $i$  is read as  $j$  by the reader  $r_{ij}$  (iii)  $j$  is decoded as  $\omega$  by the decoder  $d_{j\omega}$ . The distance between the original and the reconstructed meanings is  $c_{\alpha\omega}$  (red arrow).

Finally, the decoded amino-acid carried by the tRNA is ligated to the synthesized protein.

To estimate the *quality* of the coding system one examines how well a reconstructed meaning preserves the original one. This is measured by the average *distortion*  $D$  [4,5] along all possible paths  $\alpha - i - j - \omega$  between original and reconstructed meanings [7,8,10]. The *demand* for each meaning  $\alpha$  is  $f_\alpha$ , which accounts for the possibility that some meanings are used more frequently than others. To calculate  $D$ , each path is weighed by its probability,  $f_\alpha e_{\alpha i} r_{ij} d_{j\omega}$ , and the summation yields

$$D = \langle c_{\alpha\omega} \rangle = \sum_{\alpha, i, j, \omega} f_\alpha e_{\alpha i} r_{ij} d_{j\omega} c_{\alpha\omega}. \quad (1)$$

The reader  $r_{ij}$  may be represented as a graph, in which the nodes are the symbols and edges connect symbols that are likely to be confused [e.g., Fig. 2(c)] [12,15]. If the reader was ideal ( $r_{ij} = \delta_{ij}$ ) then it would have been advantageous to decode as many meanings as there are available symbols. However, since the molecular reader is not perfect it is preferable to decode fewer meanings and thereby minimize the effect of misreading errors. Moreover, the preferable codes are *smooth*, that is symbols that are likely to be confused encode the same meaning or meanings that are close with respect to the distance  $c_{\alpha\omega}$  [12–15] [Fig. 2(d)].

A common measure for the *cost* of a coding system is the mutual information  $I$  that estimates the average number of bits required to encode one meaning [5],

$$I = \sum_{\alpha, i} f_\alpha e_{\alpha i} \ln \frac{e_{\alpha i}}{u_i}, \quad (2)$$

where  $u_i = \sum_{\alpha} f_\alpha e_{\alpha i}$  is the overall probability to use the symbol  $i$ . In molecular codes  $I$  is directly linked to fitness: The decoder  $e_{\alpha i}$  is the probability that the molecule carrying the meaning  $\alpha$  binds the molecular symbol  $i$ . In the TRN, for example,  $\alpha$  is a transcription factor and  $i$  is a prospective DNA binding site. The binding probability  $e_{\alpha i}$  scales like a Boltzmann exponent  $e_{\alpha i} \sim \exp \varepsilon_{\alpha i}$ , where the binding energy  $\varepsilon_{\alpha i}$  is in  $k_B T$  units. It follows that  $I$  is actually the average binding energy  $I = \sum_{\alpha, i} f_\alpha e_{\alpha i} (\varepsilon_{\alpha i} - \bar{\varepsilon}_i) = \langle \varepsilon_{\alpha i} - \bar{\varepsilon}_i \rangle$ , with the reference energies  $\bar{\varepsilon}_i = \ln \sum_{\beta} f_\beta \exp \varepsilon_{\beta i}$ . In several molecular codes (e.g., TRN) the binding energies  $\varepsilon_{\alpha i}$  are approximately linear in the size of the binding sites. The cost  $I$  is therefore proportional to the average size of the binding site [1–3]. The evolutionary cost to replicate, transcribe and translate the gene that encodes the binding site and the cost to correct mutations in this gene, are all expected to be linear in the binding site size [16].  $I$  is therefore proportional to the actual fitness cost.

To optimize the molecular coding apparatus, its cost and distortion must be balanced. We describe this interplay as the maximization of an overall *code fitness*,  $H = -D - \kappa^{-1}I$ . While  $I$  and  $D$  are to be minimized, the fitness  $H$  is driven by evolution towards maxima, as manifested by the minus signs in  $H$ . The *gain*  $\kappa = \partial I / \partial D$  measures the bits

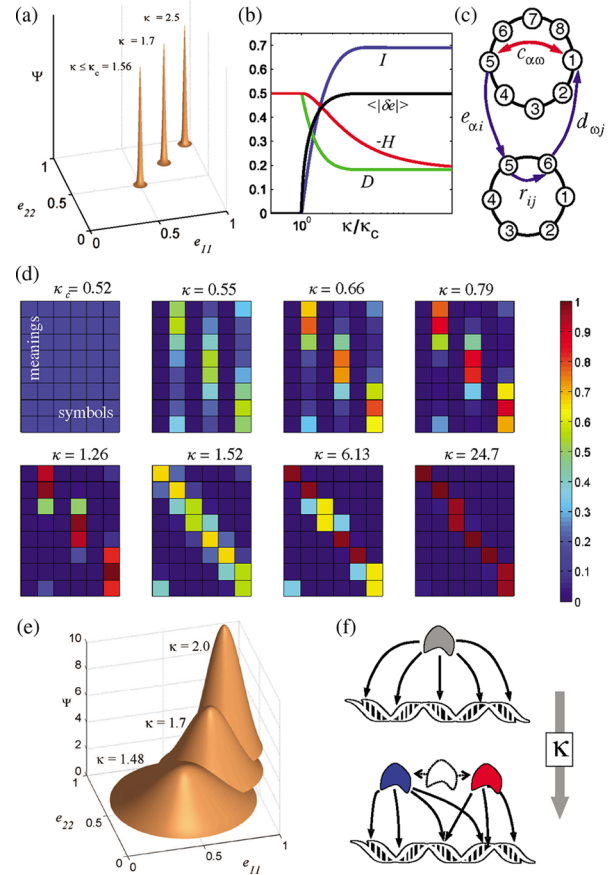


FIG. 2 (color online). Emergence and evolution of molecular codes. (a) A code relates  $m = 2$  meanings  $\{1, 2\}$  and  $s = 2$  symbols  $\{1, 2\}$ . The encoder  $e_{\alpha i}$  has 4 entries and is constrained to a 2D square by the 2 conservation relations  $e_{11} + e_{12} = e_{21} + e_{22} = 1$ . The reader is  $r_{ij} = (1 - 2\varepsilon)\delta_{ij} + \varepsilon$  with the misreading probability  $\varepsilon = 0.1$ . At low mutation rates the population peaks at the optimal encoder (illustrated as sharp peaks). Below the critical gain  $\kappa_c = 1.56$  the state is noncoding with  $e_{\alpha i} = \frac{1}{2}$ . Above  $\kappa_c$  a coding state evolves. (b) The channel cost  $I$  increases from 0 at the coding transition,  $\kappa = \kappa_c$ , while the distortion  $D$  decreases. The average order parameter  $\langle |\delta e| \rangle$  increases continuously from 0 at the second-order coding transition. The fitness  $H$  (plotted as  $-H$ ) increases to an asymptotic value. (c) A code that relates 8 meanings and 6 symbols. The distance is  $c_{\alpha\omega} = \min(|\alpha - \omega|, 8 - |\alpha - \omega|)$  and the reader is defined by a probability of 0.98 that  $i$  is read as  $i$  and 0.01 that it is read as one of its two neighbors on the symbol graph. (d) The optimal encoder  $e_{\alpha i}$  is plotted as color-coded  $6 \times 8$  arrays at increasing gains  $k$ . Below  $\kappa_c = 0.52$  (top left) the encoder is  $e_{\alpha i} = 1/6$  with uncorrelated symbols and meanings. A *coding* state emerges at  $\kappa_c$ . The symbol-meaning correlation increases with  $\kappa$  until every meaning  $\alpha$  is encoded by exactly one symbol  $i$  (bottom right). The optimal code is smooth; i.e., close meanings are encoded by close symbols, as manifested by the continuous diagonal shape of the encoder. (e) Quasispecies dynamics of the code from (a) with mutation rate  $\mu = 5 \times 10^{-5}$ . Below  $\kappa_c = 1.56$ , the population distribution  $\Psi$  is smeared around the noncoding optimum. Above  $\kappa_c$ , a coding state appears,  $\Psi$  sharpens and migrates towards the one-to-one code  $e_{11} = e_{22} = 1$ . (f) A coding transition in the TRN, when a universal transcription factor splits into distinct species when the gain  $\kappa$  increases.

of information required to increase the quality. The gain  $\kappa$  is expected to increase with the complexity the organism and its environment: The circuitry of a complex organism transmits more signals and reads a larger genome. It is therefore beneficial for this organism to pay a larger cost to improve the quality of its code, since it gains more from such an improvement. Similarly, the gain is larger in a richer environment.

*Population dynamics in the code space.*—To examine how codes evolve in response to changes in the gain, we consider a population of simplified organisms that compete according to the fitness of their codes. We imagine a scenario where—for a given demand  $f_\alpha$ , determined by the environment, and a given reader  $r_{ij}$ —each “organism” has a code specified by its encoder  $e_{\alpha i}$  and decoder  $d_{j\omega}$ . The optimal encoder and decoder are related through Bayes’ theorem [7–10],  $d_{j\omega} \sum_{\beta,i} f_\beta e_{\beta i} r_{ij} = f_\omega \sum_i e_{\omega i} r_{ij}$ , which states the intuitive notion that if an encoded meaning  $\omega$  tends to be read as the symbol  $j$  then it is likely that  $j$  is decoded as  $\omega$  [17]. Therefore, it suffices to identify every organism by its encoder  $e_{\alpha i}$  and one may describe the population as points in a “code space”, which is spanned by all possible encoders [Fig. 2(a)]. This space is an  $(m \times s)$ -dimensional unit cube  $0 \leq e_{\alpha i} \leq 1$  and each axis corresponds to an entry of the encoder  $e_{\alpha i}$ . An organism is represented by a point in the cube and the population is a “cloud” of such points of probability density  $\Psi(e_{\alpha i})$ . Since the encoder obeys the  $m$  conservation relations  $\sum_i e_{\alpha i} = 1$ , the effective dimension is reduced to  $m \times (s - 1)$ . In the following, we treat three limiting cases of population dynamics in the code space: first, a large population with negligible mutation-rate, next, a large population with significant mutation rate and, finally, a smaller population with considerable genetic drift.

*The coding transition.*—To find the coding transition we first look at simplified case of large populations with negligible mutation rate. These tend to peak at an optimal value of the encoder  $e_{\alpha i}^*$  and therefore may be approximated by a delta-function,  $\Psi(e_{\alpha i}) = \delta(e_{\alpha i} - e_{\alpha i}^*)$ . As a result, the dynamics in this regime amounts to tracing the evolution of the optimal code as the gain  $\kappa$  changes. The optimal code is found at the extremum,  $\partial H / \partial e_{\alpha i} = 0$  [17], which leads to

$$e_{\alpha i}^* = u_i e^{-\kappa \Omega_{\alpha i}} / \sum_j u_j e^{-\kappa \Omega_{\alpha j}}. \quad (3)$$

In this Boltzmann partition, the effective energies are  $\Omega_{\alpha i} = \sum_{j,\omega} r_{ij} d_{j\omega} (2c_{\alpha\omega} - \sum_\gamma d_{j\gamma} c_{\gamma\omega})$  and the gain  $\kappa$  plays the role of an inverse temperature; i.e., organisms with lower  $\kappa$  are “hotter” and their codes are noisier.

A simple example for the evolution of a code with increasing gain  $\kappa$  is graphed in Figs. 2(a) and 2(b). At low  $\kappa$ , the optimal encoder is  $e_{\alpha i} = u_i$  and  $I$  vanishes since the encoder is  $\alpha$ -independent and therefore conveys no information about the meanings [Eq. (2)]. For this reason this state is termed *noncoding*. To pinpoint the transition,

we examine the stability of the fitness with respect to small variations of the encoder  $\delta e_{\alpha i} = e_{\alpha i} - u_i$ . The variation  $\delta e_{\alpha i}$  is the order parameter that describes the emergence of a *coding* state,  $\delta e_{\alpha i} \neq 0$ , with correlated meanings and symbols. We find that the coding-nocoding transition takes place at a *critical gain*  $\kappa_c$  [17],

$$\kappa_c^{-1} = 2\lambda_R^* \lambda_C^*, \quad (4)$$

where  $\lambda_C^*$  is the maximal eigenvalue of the normalized distance,  $C_{\alpha\omega} = \sqrt{f_\alpha f_\omega} (\sum_\beta f_\beta c_{\beta\omega} + \sum_\gamma f_\gamma c_{\alpha\gamma} - \sum_{\beta\gamma} f_\beta f_\gamma c_{\beta\gamma} - c_{\alpha\omega})$ , and  $\lambda_R^*$  is the second-largest eigenvalue of the weighted square of the reader  $R_{ij} = \sqrt{u_i u_j} \sum_k (r_{ik} r_{kj} / \sum_t u_t r_{tk})$  [17].  $\lambda_R^*$  corresponds to the *smoothest* nonuniform eigenvector  $\delta e_{\alpha i}^* \neq 0$ , which represents a coding state [12,15,18]. This eigenvector, which emerges at the coding transition [Figs. 2(b)–2(d)], is the first-excited state of the system and measures the tendency of a meaning  $\alpha$  to be encoded by the symbol  $i$ . Boltzmann partitions and consequent phase transitions are common in rate-distortion theory and analogous optimization problems in the context of clustering, deterministic annealing, and self-organizing maps [4–11].

The critical gain [Eq. (4)] indicates three possible pathways from the random, noncoding state towards the emergence of a code: via increasing the gain  $\kappa$ , via increasing the reading accuracy (larger  $\lambda_R$ ) or via increasing the average distance between meanings (larger  $\lambda_C$ ). We suggest that such simple coding-noncoding transitions may describe the emergence of biological codes. In the case of TRN, for example, one imagines the primordial circumstances when a primitive organism had only one universal transcription factor that binds all DNA sites [Fig. 2(f)]. Then, as  $\kappa$  increases, for example, the environment becomes richer in information, the factor splits into several distinct factors, each binding to specific sites. In the case of the genetic code, a series of transitions [like those in Fig. 2(d)] is thought to describe the emergence and evolution of the code [12,15,18].

*Effects of mutations.*—Mutations add another kind of noise, smearing the population over a larger region of the code space. When the mutation rate  $\mu$  is significant one may model the population in terms of reaction-diffusion dynamics, in the spirit of the quasispecies model [19],

$$\frac{\partial \Psi}{\partial t} = [H(e_{\alpha i}) - \bar{H}] \Psi + \mu \sum_{\alpha,i} \frac{\partial^2 \Psi}{\partial e_{\alpha i}^2}. \quad (5)$$

In Eq. (5), each organism in the population reproduces at a rate equal to the fitness of its code  $H(e_{\alpha i})$  (the reaction term). However, codes may mutate at a rate  $\mu$ . This random walk in the code space is described by the diffusion term. The fitness  $H$  is normalized by the average fitness  $\bar{H} = \int \Psi(e_{\alpha i}) H(e_{\alpha i}) de_{\alpha i}$  to ensure conservation of the probability distribution. Typically,  $\Psi$  approaches a steady state, which corresponds to the eigenmode of maximal  $\bar{H}$  [19]. To find the steady state we approximate the fitness by

a quadratic expansion around an optimum  $H \approx H_* - \frac{1}{2} \sum_{\alpha,i,\omega,j} Q_{\alpha i \omega j} \delta e_{\alpha i} \delta e_{\omega j}$ . Assuming a Gaussian ansatz for  $\Psi$  we find the steady state [17],  $\Psi \sim \exp[-(8\mu)^{-1/2} \sum_{\alpha,i,\omega,j} \sqrt{Q_{\alpha i \omega j}} \delta e_{\alpha i} \delta e_{\omega j}]$ , where  $\sqrt{Q}$  is the square root of the Hessian  $Q_{\alpha i \omega j}$ .  $\Psi$  indicates that the mutations smear the population over a width that increases with the mutation-rate as  $\sim \mu^{1/4}$  [Fig. 2(e)], which may be significant even for relatively low mutation rates due to the small exponent. The leakage by mutations from the optimal code to lesser codes reduces the average fitness,  $\bar{H} = H_* - (\mu/2)^{1/2} \text{Tr} \sqrt{Q}$  [17]. At the coding transition [Eq. (4)], the Gaussian  $\Psi$  becomes infinitely wide in the direction of the emergent coding eigenvector  $\delta e_{\alpha i}^*$ , a precursor of the appearance of a coding state along this direction.

*Effects of genetic drift.*—The quasispecies dynamics is deterministic in the sense that it neglects random reproduction fluctuations, termed genetic drift, which are irrelevant in large populations. However, when the effective size of the population  $n$  is small,  $n\mu \ll 1$ —considered to be the relevant condition during the emergence of the genetic code, for example—genetic drift is a major determinant. The typical dynamics in this regime exhibits long periods of time when the population resides in the vicinity of a fitness optimum separated by short transients of diffusion by genetic drift to another optimum. For our purpose, it is convenient to coarse grain this dynamics in space and time and regard it as instantaneous random transitions between the optima. In this type of dynamics the distribution  $\Psi$  approaches asymptotically a Boltzmann partition  $\Psi \sim e^{nH}$ , with an “inverse temperature” that is equal to the population size  $n$ , up to a factor of order unity [3,20]. It is convenient to define a free energy [20],  $F = \langle -H \rangle - n^{-1}S$ , in which the fitness is minus the Hamiltonian and the entropy of the genetic drift is  $S = - \int \Psi \ln \Psi de_{\alpha i}$ . A mean-field treatment yields the approximation (akin to a mean-field Potts model) [17],

$$F = -H(\bar{e}_{\alpha i}) + n^{-1} \sum_{\alpha,i} f_{\alpha} \bar{e}_{\alpha i} \ln f_{\alpha} \bar{e}_{\alpha i}, \quad (6)$$

where  $\bar{e}_{\alpha i}$  is the average encoder  $\bar{e}_{\alpha i} = \int e_{\alpha i} \Psi(e_{\alpha i}) de_{\alpha i}$ . Equation (6) indicates that the genetic drift contribution  $S$  adds another source of randomness to that of the cost  $I$ ; both drive the system towards the random noncoding state.

From stability analysis of  $F$  it follows that the genetic drift shifts the critical transition to higher gains,  $\kappa_c^{-1} + n_c^{-1} = 2\lambda_R^* \lambda_C^*$  [17]. This also adds a fourth pathway towards the coding transition, via population growth, to the three pathways suggested by Eq. (4). To give an order-of-

magnitude estimate for  $\kappa_c$  and  $n_c$ , we notice that if the misreading probability is relatively small (the nondiagonal terms  $R_{ij} \ll 1$ ) then  $\lambda_R^* \approx 1$ . It follows that the smaller of  $\kappa_c$  and  $n_c$  is of the order of  $1/\lambda_C^*$ , which roughly scales like the  $1/(\text{fitness reduction by one reading error})$ . Such cost-quality considerations are generic [18,21] and may help to understand the evolution of other biological information-processing systems.

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