Canonical Approximation of Fitness Landscapes

Robert Happel[a] and Peter F. Stadler[a,b,*]

[a]Theoretische Biochemie, Institut für Theoretische Chemie
Universität Wien, Vienna, Austria

[b]Santa Fe Institute, Santa Fe, NM

[*]Mailing Address:
Peter F Stadler, Inst. f. Theoretische Chemie, Univ. Wien
Währingerstr. 17, A-1090 Wien, Austria
Phone: [43] 1 40480 665 Fax: [43] 1 40480 660
E-Mail: `studla@tbi.univie.ac.at`

Keywords

Correlation Functions — Fourier Series — Landscapes — Laplace Operator — Random Walk — RNA Folding

Abstract

We present a method for approximating a fitness landscape as a superposition of "elementary" landscapes. Given a correlation function of the landscape in question we show that the relative amplitudes of contributions with p-ary interactions can be computed. We show an application to RNA free energy landscapes.

1. Fitness Landscapes

Since Sewall Wright's seminal paper [1] the notion of a *fitness landscape* underlying the dynamics of evolutionary optimization has proved to be one of the most powerful concepts in evolutionary theory. Implicit in this idea is a collection of genotypes arranged in an abstract metric space, with each genotype next to those other genotypes which can be reached by a single mutation, as well as a value assigned to each genotype. Such a construction is by no means restricted to the theory of biological evolution. Hamiltonians of disordered systems, such as spin glasses [2, 3], and the cost functions of combinatorial optimization problems [4] have the same mathematical structure. Eigen's [5] pioneering work on the molecular quasispecies has shown that the dynamics of evolutionary adaptation (optimization) on a landscape depends crucially on detailed structure of the landscapes itself. Extensive computer simulations, see, e.g., [6, 7, 8, 9, 10] have made it very clear that a complete understanding of the dynamics is impossible without a thorough investigation of the underlying landscape [11].

A theory of landscapes is based on three ingredients: the first two items are a *finite* (but very large) set V of *configurations* and a *fitness function* $f : V \to \mathbb{R}$. The third ingredient is a notion of neighborhood between the configurations, which allows us to interpret V as the vertex set of a graph Γ, with an edge set E defined by the neighborhood relations, i.e., two vertices are joined by an edge in Γ if and only if they are neighbors. We will refer to Γ as the *configuration space* of the landscape f. In this contribution we shall mostly consider configurations that are sequences of constant length n taken from an alphabet of α letters. Γ is called a *sequence space* [12] in this special case, and in case of a 2-letter alphabet one speaks of a boolean hypercube. We remark at this point that the theory outlined in section 2 applies also to more general classes of graphs. For the technical details we refer to [13, 14].

2. Approximation Theory for Landscapes

2.1. Fourier Expansions and Elementary Landscapes

In the following we shall need an algebraic description of the configuration space Γ. The most useful algebraic representation of a graph is its adjacency matrix $\mathbf{A}$ which has the following entries

$$\mathbf{A}_{xy} \stackrel{\text{def}}{=} \begin{cases} 1 & \text{if } \{x,y\} \in E \\ 0 & \text{otherise} \end{cases}, \tag{1}$$

i.e., $\mathbf{A}_{xy} = 1$ is and only if the vertices x and y are neighbors. The number of neighbors of vertex $x \in V$ is called the degree of x. Let $\mathbf{D}$ be the diagonal matrix of the vertex degrees. Sequence spaces are *regular*, i.e., all vertices have the same number of neighbors, namely $D = (\alpha - 1)n$. For regular graphs we have, of course, $\mathbf{D} = D\mathbf{I}$, where $\mathbf{I}$ is the identity matrix and D is the common degree of all vertices. Instead of the adjacency matrix $\mathbf{A}$, it is often convenient to characterize a graph Γ by its *Laplacian*

$$-\Delta \stackrel{\text{def}}{=} \mathbf{D} - \mathbf{A}. \tag{2}$$

For regular graphs this definition simplifies to $\Delta = \mathbf{A} - D\mathbf{I}$. The graph Laplacian Δ can be viewed as a generalization of the more familiar differential operator Δ in continuous spaces. For the details we refer to [15, 16, 17, 18]. The graph Laplacian $-\Delta$ is non-negative definite, and the smallest eigenvalue $\lambda_0 = 0$ has multiplicity 1 if and only if Γ is a connected graph. In what follows we will assume that Γ is connected. In this case an eigenvector with eigenvalue $\lambda = 0$ is always constant on V.

A series expansion in terms of a complete and orthonormal system of eigenfunctions of the Laplace operator is commonly termed a Fourier expansion. Following [19], we will adopt the same terminology here. Thus, let f be landscape on Γ and let $\{\varphi_i\}$ denote a complete orthonormal set of eigenvectors of the graph Laplacian[1]. Then we call the expansion

$$f(x) = \sum_{i=1}^{|V|} a_i \varphi_i(x) \tag{3}$$

Fourier expansion of the landscape. A landscape is called *elementary* if it is of the form $f(x) = c + \varphi(x)$, where c is an arbitrary constant and φ is an eigenvector of the graph-Laplacian belonging to an eigenvalue $\lambda > 0$, see [20, 14]. Elementary landscapes form an important class because the landscape of the most intensively studied combinatorial optimization problems, such as the travelling salesman problem [21], the graph bipartitioning problem, or the graph coloring problem, are of this type [20].

For boolean hypercubes defined on the alphabet $\{+1, -1\}$, a Fourier basis can easily be determined explicitly. Let $x \in \{+1, -1\}^n$. It is easy to verify then that each product of exactly p factors of the form

$$\varepsilon_{i_1 i_2 \ldots i_p}(x) \stackrel{\text{def}}{=} x_{i_1} x_{i_2} \ldots x_{i_p} \qquad \text{with} \quad i_1 < i_2 < \ldots < i_p \tag{4}$$

is an eigenvector of $-\Delta$ belonging to the eigenvalue $\lambda_p = 2p$. In particular, Derrida's p-spin models

$$\mathcal{H}_p(x) \stackrel{\text{def}}{=} \sum_{i_1 < i_2 < \ldots < i_p} J_{i_1 i_2 \ldots i_p} x_{i_1} x_{i_2} \ldots x_{i_p} = \sum_{i_1 < i_2 < \ldots < i_p} J_{i_1 i_2 \ldots i_p} \varepsilon_{i_1 i_2 \ldots i_p}(x) \tag{5}$$

[22, 23] are superpositions containing only contributions of one order of interactions, namely $p > 0$. Thus they are themselves eigenfunctions of $-\Delta$ for the boolean hypercube with eigenvalue $\lambda_p = 2p$; consequently, they are elementary. An example of an elementary landscape on sequence spaces with larger alphabets is graph coloring with α colors [20].

[1] We write $\varphi_i(x)$ to mean the x-component of the vector φ_i throughout this paper.

2.2. Correlation Functions for Landscapes

If a simple algebraic description, such as equ.(5) for the p-spin models, is not available for the landscape in question we need a condensed description of its salient features. This is because the extremely large number of configurations, 4^n for RNA and $n!$ for a n-city travelling salesman problem, renders a complete "listing" infeasible. Correlation measures relating the values of nearby configurations with each other seem to be a natural approach. First we define a mean and a variance

$$\overline{f} \stackrel{\text{def}}{=} \frac{1}{|V|}\sum_{x\in V} f(x) \qquad \text{and} \qquad \sigma_f^2 \stackrel{\text{def}}{=} \frac{1}{|V|}\sum_{x\in V}\left[f(x)-\overline{f}\right]^2 = \overline{f^2}-\overline{f}^2 \tag{6}$$

for each landscape $f: V \to \mathbb{R}$. Note that $\sigma_f^2 = 0$ if and only if f is constant, i.e., if the landscapes is *flat*. There is nothing "statistical" about $\overline{f}$ or σ_f^2. Both quantities are unambiguously defined numbers given f. They should not be mistaken for the averages over different instances that are commonly used in a statistical mechanics type analysis of what one might call statistical models of landscapes (random fields) [3].

Eigen and co-workers [11] have introduced correlation functions

$$\rho(d) \stackrel{\text{def}}{=} \frac{\langle f(x)f(y)\rangle_{d(x,y)=d} - \overline{f}^2}{\sigma_f^2} \tag{7}$$

that depend on the Hamming distance in sequence space as a measure of the local structure of fitness landscapes. The notation $\langle\,.\,\rangle_{d(x,y)=d}$ indicates the mean value is calculated from all pairs of sequences x, y with Hamming distance $d(x,y) = d$. We will call ρ the "direct" correlation function of the landscape f. An alternative approach has been explored by Weinberger [24]. A simple random walk $\{x_0, x_1, \ldots\}$ on the vertex set of Γ generates a "time series" $\{f(x_0), f(x_1), \ldots\}$. The autocorrelation function

$$r(s) \stackrel{\text{def}}{=} \frac{\langle f(x_t)f(x_{t+s})\rangle_{x_0,t} - \langle f(x_t)\rangle_{x_0,t}\,\langle f(x_{t+s})\rangle_{x_0,t}}{\sqrt{\left(\langle f(x_t)^2\rangle_{x_0,t} - \langle f(x_t)\rangle_{x_0,t}^2\right)\,\left(\langle f(x_{t+s})^2\rangle_{x_0,t} - \langle f(x_{t+s})\rangle_{x_0,t}^2\right)}} \tag{8}$$

of this time series can be used to describe the landscape f. The notation $\langle\,.\,\rangle_{x_0,t}$ emphasizes that the expectation is taken over all "times" t and all initial conditions x_0. We will refer to $r(s)$ as the *"random walk" correlation function* of the landscape f on Γ. A simple random walk [25] on a graph Γ has transition matrix $\mathbf{T} \stackrel{\text{def}}{=} \mathbf{D}^{-1}\mathbf{A}$. It can be shown [14] that equ.(8) can recast in the form

$$r(s) = \frac{1}{\sigma_f^2}\left[\frac{1}{|V|}\langle f, \mathbf{T}f\rangle - \overline{f}^2\right] \tag{9}$$

for any regular graph. The two correlation measures $r(s)$ and $\rho(d)$ are closely related to each other, since

$$r(s) = \sum_{d=0}^{n} \phi_{sd}\,\rho(d)\,, \tag{10}$$

where ϕ_{sd} is the probability that a simple random walks of s steps ends in distance d from its starting point [24]. In particular, the nearest neighbor correlation satisfies $\varrho = r(1) = \rho(1)$.

2.3. Characterization of Elementary Landscapes

It has been shown recently [14] that there is an intimate relationship between the Fourier expansion of a landscape and the form of its correlation functions $\rho(d)$ and $r(s)$. This observation is based on a result that we shall state here in the sequence space version, but which holds for all regular graphs provided the definition of ρ is appropriately modified.

Theorem 1. [14] Let f be a non-flat landscape on a sequence space (Hamming graph). Then the following statements are equivalent:

(i) f is elementary with $\lambda = p\alpha$.

(ii) The "random walk" correlation function is exponential,

$$r(s) = \varrho^s = (1 - \lambda/D)^s = (1 - \frac{\alpha}{\alpha - 1}\frac{p}{n})^s\,. \tag{11}$$

(iii) The "direct" correlation function is a Krawtchouk polynomial,

$$\rho(d) = \omega_p^{n,\alpha}(d) \stackrel{\text{def}}{=\!=} \frac{1}{\binom{n}{p}(\alpha-1)^p} \sum_{j=0}^{p} (-1)^j (\alpha-1)^{p-j} \binom{d}{j} \binom{n-d}{p-j}. \tag{12}$$

∎

The parameter p determines the order of interaction between the positions in the sequence. For configuration spaces different from sequence spaces there are other systems of orthogonal polynomials in item (iii) of theorem 1. In general these satisfy the orthogonality relation

$$\langle \omega_p ; \omega_q \rangle \stackrel{\text{def}}{=\!=} \sum_d \omega_p(d)\omega_q(d)N(d) = \frac{|V|}{m(\lambda_p)}\delta_{pq}\,, \tag{13}$$

where $N(d)$ is the number of pairs of configurations with mutual distance d and $m(\lambda_p)$ is the multiplicity of λ_p as an eigenvalue of $-\Delta$, see [26]. For sequence spaces we have the explicit relation

$$m(\lambda_p) = \frac{N(d)}{\alpha^n} = (\alpha-1)^d \binom{n}{d}. \tag{14}$$

Since any landscape on Γ is necessarily a superposition of elementary landscapes, so are their correlation functions. Let $f = \sum_j a_j \varphi_j$ be a Fourier expansion of f, and denote by λ_p the distinct eigenvalues of $-\Delta$. Furthermore, let I_p be the set of all indices k for which $\Delta\varphi_k + \lambda_p\varphi_k = 0$. The value $p = 0$ corresponds to the flat component of the landscape. Define the *amplitude* of the p-ary interactions as

$$B_p \stackrel{\text{def}}{=\!=} \frac{\sum_{k\in I_p} |a_k|^2}{\sum_{k\neq 0} |a_k|^2} \tag{15}$$

for all $p \neq 0$. Note that $B_p \geq 0$ and $\sum_p B_p = 1$. As a by-product of the proof of Theorem 1 one can also show [14] that the Fourier expansion of f translates into an expansion of the correlation functions of the landscape f:

Theorem 2. $r(s) = \sum_{p\neq 0} B_p (1-\lambda_p/D)^s$ and $\rho(d) = \sum_{p\neq 0} B_p \omega_p^{n,\alpha}(d)$. ∎

Given a particular landscape, the crucial information about its correlation structure is thus contained in the amplitudes B_p which describe the relative importance of the different elementary components. We may consider B_p as a "spectrum" of the p-ary interactions contributing to the fitness function f. If ρ is known exactly, then B_p can be computed using the scalar product $\langle\, ;\, \rangle$ defined in equ.(13):

$$B_p = \frac{m(\lambda_p)}{|V|} \langle \omega_p ; \rho \rangle \tag{16}$$

We now apply Theorem 2 to computer-generated landscapes of RNA folding.

3. Application: RNA Free Energy Landscapes

RNA sequences are strings over the alphabet {**G,C,A,U**}. The canonical distance measure between two sequences of equal length is the Hamming distance. As a consequence, the set of all RNA sequences of a given length, say n, are naturally arranged in the 4-letter sequence space $\mathcal{Q}_4^n$ of dimension n. The physico-chemical properties of RNA molecules, and, in particular, their free energies of folding, ΔG, depend crucially on the spatial structure of the molecule. In the case of RNA the process of folding the one-dimensional primary structure (sequence) into the three-dimensional tertiary structure can be decomposed into two steps:

1) Folding of the sequence into a planar secondary structure by formation of complementary Watson-Crick base pairs **G**≡**C** and **A**=**U** and the weaker **G**−**U** pairs.
2) Formation of the 3D tertiary structure from the planar pattern.

The reason for this decomposition is that the intramolecular forces stabilizing the secondary structures — base pairing and base pair stacking — are much stronger than those accounting for the particular spatial arrangement. Thus the free energy for the formation of the entire spatial structure can be estimated by the free energy for the formation of the secondary structure. The dominant role of the secondary structure is also well documented in nature by the conservation of secondary structure elements in evolution [27]. There are efficient algorithms for the

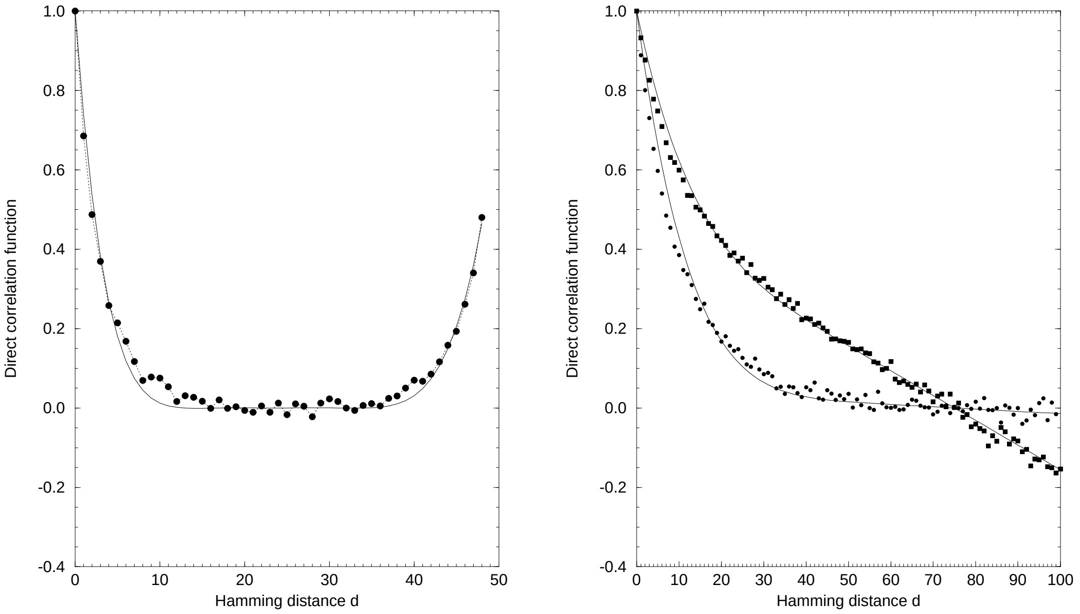

Figure 1: a) **GC** alphabet, chain length 50. Fitted curve is $0.73\omega_6^{100,2} + 0.27\omega_7^{100,2}$.
b) **GCAU** alphabet, □, and **GCXK** alphabet, •. The chain length is $n = 100$. The fitted curves are of the form $B_1\omega_1^{100,4} + B_6\omega_6^{100,4}$/ Numerical values of the amplitudes as compiled in table 1.
The parameter set [28] used in the folding algorithm contains an almost exact symmetry which causes a sequence and its complement to fold in general into closely related structures with very similar free energies. Consequently, the correlation functions of two-letter alphabets exhibit a somewhat distorted symmetry, i.e., a significant correlation between a sequence and its mutants in distance classes close to n. For alphabets with more than two letters this effect is obscured by the large number, $(\alpha - 1)^n$, of sequences in distance class n.

prediction of the secondary structure of RNA molecules [29, 30, 31], which allow for a detailed analysis of landscapes associated with folding process [32, 33, 34, 35]. The autocorrelation functions of RNA free energy landscapes discussed in here are taken from [34]. These data contain a noise level of approximately ± 0.05.

The amplitudes B_p for the RNA free energy landscapes cannot be computed from equation (16). This is due to the fact that the weight function $N(d)$ in the definition of the scalar product (13) emphasizes large values of d for which ρ vanished in the background noise. One has to resort therefore to a least-squares fitting procedure that makes explicit use of the non-negativity of the amplitudes B_p and that uses only a small number of non-zero coefficients. The same fitting procedure has been used to obtain estimates of B_p from independently generated "random walk" correlation functions. We find that two modes already yield reasonably good fits to the date. Using more than two modes increases the quality of the fits only slightly. Furthermore, fits with more than two coefficients do not compare very well between independent data sets. We conclude hence that the numerical estimates of the correlation functions $\rho(d)$ and $r(s)$ are not accurate enough to obtain a more detailed decomposition of the RNA free energy landscapes. Nevertheless, the data displayed in Table 1 suggest a number of interesting interpretations. Examples of "direct" correlation functions $\rho(d)$ and best fits in term of only two modes are shown in Figure 1.

Table 1. Fits to RNA Free Energy Landscapes.

n	B_6			B_1		B_7
	GCAU	**GCXK**	**GC**	**GCAU**	**GCXK**	**GC**
20	0.68	0.86		0.32	0.14	
30	0.65	0.88		0.35	0.12	
50	0.57	0.93	0.73	0.43	0.07	0.27
70	0.57	0.93		0.43	0.07	
100	0.53	0.96		0.47	0.04	

First of all, we find distinct differences between the natural **GCAU** alphabet and an artificial alphabet **GCXK** with two base pairs, **GC** and **XK**, of equal strength. While the latter is represented very well by the $p = 6$ mode, we obtain a superposition of the modes $p = 1$ and $p = 6$ for the natural alphabet. This fact can be explained by the unequal strength of the **AU** and **GC** base pairs. As shown in [36] there is an essentially linear increase of the free energy of folding with increasing **GC** content of the sequence. This accounts for the $p = 1$ mode which corresponds to the additive fitness model, or 'Fujijama' landscape, [37].

Correlation functions of **GC** and **AU** landscapes are quite similar [34]. For the **GC** case we a good fit in terms of $p = 6$ and $p = 7$. Of course we cannot expect the two-letter RNA landscapes to be elementary or to be superpositions of exactly two modes. Their spectrum seems to consist of a broad peak in the range $p = 5 - 8$, indicating that on average each nucleotide in the sequence interacts with some 5 or 6 other positions. This is a perfectly reasonable result when compared to the the energy model [29] implicit in the RNA folding algorithm. The major contribution of the folding energy comes from stacking of base pairs, i.e., a position within a stack will be influenced by its pairing partner and the four positions forming the adjacent base pairs. Since the folding procedure is inherently non-local we expect also small contributions with high interaction orders p.

The approximation technique described in this paper can be used to replace computationally expensive landscapes such as those of RNA folding by a superposition of computationally simpler model landscapes, such as p-spin models or Kauffman's NK models, while retaining the correlation structure of the landscapes. As a consequence, more extensive computer simulations of evolutionary adaptation on realistic landscapes are feasible. On the other hand, the amplitudes B_p provide a method of quantifying the correlation structure of a landscape allowing for a much easier interpretation than either one of the correlation functions $r(s)$ or $\rho(d)$. An analysis of Kauffman's NK models in terms of the amplitudes B_p will be published elsewhere [38].

References

[1] S. Wright. The roles of mutation, inbreeding, crossbreeeding and selection in evolution. In D. F. Jones, editor, *Int. Proceedings of the Sixth International Congress on Genetics*, volume 1, pages 356–366, 1932.

[2] K. Binder and A. P. Young. Spin glasses: Experimental facts, theoretical concepts, and open questions. *Rev.Mod.Phys.*, 58:801–976, 1986.

[3] M. Mézard, G. Parisi, and M. Virasoro. *Spin Glass Theory and Beyond.* World Scientific, Singapore, 1987.

[4] M. Garey and D. Johnson. *Computers and Intractability. A Guide to the Theory of $\mathcal{NP}$ Completeness.* Freeman, San Francisco, 1979.

[5] M. Eigen. Selforganization of matter and the evolution of biological macromolecules. *Die Naturwissenschaften*, 10:465–523, 1971.

[6] S. Bonhoeffer and P. F. Stadler. Errortreshold on complex fitness landscapes. *J. Theor. Biol.*, 164:359–372, 1993.

[7] W. Fontana and P. Schuster. A computer model of evolutionary optimization. *Biophysical Chemistry*, 26:123–147, 1987.

[8] W. Fontana, W. Schnabl, and P. Schuster. Physical aspects of evolutionary optimization and adaption. *Physical Review A*, 40(6):3301–3321, 1989.

[9] M. Huynen and P. Hogeweg. Pattern generation in molecular evolution. Exploitation of the variation in RNA landscapes. *J.Mol.Evol.*, 39:71–79, 1994.

[10] M. A. Huynen, P. F. Stadler, and W. Fontana. Evolution of RNA and the Neutral Theory. SFI Preprint # 95-01-006, 1995.

[11] M. Eigen, J. McCaskill, and P. Schuster. The molecular Quasispecies. *Adv. Chem. Phys.*, 75:149 – 263, 1989.

[12] M. Eigen and P. Schuster. *The Hypercycle.* Springer-Verlag, New York, Berlin, 1979.

[13] P. F. Stadler. Towards a theory of landscapes. In R. López Peña, editor, *Complex Systems and Binary Networks.* Springer-Verlag, New York, 1995. in press, Santa Fe Institute Preprint 95-03-30.

[14] P. Stadler. Landscapes and their correlation functions. Santa Fe Preprint, in preparation.

[15] N. L. Biggs. *Algebraic Graph Theory.* Cambridge University Press, Cambridge UK, 2nd edition, 1994.

[16] R. Grone, R. Merris, and V. Sunder. The laplacian spectrum of a graph. *SIAM J. Matrix Anal. Appl.*, 11:218–238, 1990.

[17] B. Mohar. The laplacian spectrum of graphs. In Y. Alavi, G. Chartrand, O. Ollermann, and A. Schwenk, editors, *Graph Theory, Combinatorics, and Applications*, pages 871–898, New York, 1991. John Wiley and Sons, Inc.

[18] P. M. Soardi. *Potential Theory on Infinite Networks*, volume 1590 of *Lecture Notes in Mathematics*. Springer-Verlag, Berlin, 1994.

[19] E. D. Weinberger. Local properties of Kauffman's N-k model: A tunably rugged energy landscape. *Phys. Rev. A*, 44(10):6399–6413, 1991.

[20] L. Grover. Local search and the local structure of NP-complete problems. *Oper.Res.Lett.*, 12:235–243, 1992.

[21] E. L. Lawler, J. K. Lenstra, A. H. G. R. Kan, and D. B. Shmoys. *The Traveling Salesman Problem. A Guided Tour of Combinatorial Optimization.* John Wiley & Sons, 1985.

[22] B. Derrida. Random energy model: Limit of a family of disordered models. *Phys.Rev.Lett.*, 45:79–82, 1980.

[23] B. Derrida. The random energy model. *Phys.Rep.*, 67:29–35, 1980.

[24] E. D. Weinberger. Correlated and uncorrelated fitness landscapes and how to tell the difference. *Biol.Cybern.*, 63:325–336, 1990.

[25] F. Spitzer. *Principles of Random Walks.* Springer-Verlag, New York, 1976.

[26] A. Brouwer, A. Cohen, and A. Neumaier. *Distance-regular Graphs.* Springer Verlag, Berlin, New York, 1989.

[27] T. R. Cech. Conserved sequences and structures of group I introns: building an active site for RNA catalysis — a review. *Gene*, 73:259–271, 1988.

[28] S. M. Freier, R. Kierzek, J. A. Jaeger, N. Sugimoto, M. H. Caruthers, T. Neilson, and D. H. Turner. Improved free-energy parameters for predictions of RNA duplex stability. *Proc. Natl. Acad. Sci., USA*, 83:9373–9377, 1986.

[29] M. Zuker and D. Sankoff. RNA secondary structures and their prediction. *Bull.Math.Biol.*, 46(4):591–621, 1984.

[30] J. S. McCaskill. The equilibrium partition function and base pair binding probabilities for RNA secondary structure. *Biopolymers*, 29:1105–1119, 1990.

[31] I. L. Hofacker, W. Fontana, P. F. Stadler, S. Bonhoeffer, M. Tacker, and P. Schuster. Fast folding and comparison of RNA secondary structures. *Monatsh. Chemie*, 125(2):167–188, 1994.

[32] S. Bonhoeffer, J. McCaskill, P. Stadler, and P. Schuster. Temperature dependent RNA landscapes, a study based on partition functions. *European Biophysics Journal*, 22, 1993.

[33] W. Fontana, T. Griesmacher, W. Schnabl, P. Stadler, and P. Schuster. Statistics of landscapes based on free energies, replication and degredation rate constants of RNA secondary structures. *Monatsh. Chemie*, 122:795–819, 1991.

[34] W. Fontana, P. F. Stadler, E. G. Bornberg-Bauer, T. Griesmacher, I. L. Hofacker, M. Tacker, P. Tarazona, E. D. Weinberger, and P. Schuster. RNA folding and combinatory landscapes. *Phys. Rev. E*, 47(3):2083 – 2099, 1993.

[35] M. Tacker, W. Fontana, P. Stadler, and P. Schuster. Statistics of RNA melting kinetics. *Eur. J. Biophys.*, 23:29–38, 1994.

[36] P. F. Stadler and W. Grüner. Anisotropy in fitness landscapes. *J. Theor. Biol.*, 165:373–388, 1993.

[37] S. Kauffman. *The Origin of Order.* Oxford University Press, New York, Oxford, 1993.

[38] P. Stadler and R. Happel. Random field models for landscapes. Santa Fe Preprint, in preparation.