The nk Model and Population Genetics

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Abstract

The nk model of fitness interactions is examined. This model has been used by previous authors to investigate the effects of fitness epistasis on substitution dynamics in molecular evolution, and to make broader claims about the importance of epistasis. To examine these claims, an infinite-allele approximation is introduced. In this limit, it is shown that the nk model is, at an appropriate level of description, formally identical to the non-epistatic House-of-Cards model; a well-studied model in theoretical population genetics. It is further shown that in many parameter regimes, the analytical results obtained from this infinite-allele approximation are very close to results from the full nk model (with a finite number of alleles per locus). The findings presented shed light on a number of previous results.

1 Introduction

When the fitness effect of an allele varies with the genetic background in which the allele is present, we say there is epistasis for fitness. When the fittest allele in one genetic background is not the fittest allele in another background, then we have 'rank-order' or 'reverse-sign' epistasis. The effects of such epistasis are most prominent when highly divergent individuals hybridise - causing post-zygotic reproductive isolation, or its within-population analogue, outbreeding depression (Barton 2001; Edmands 2002). However, the suggestion that such epistasis might play a role in the adaptive evolution of single populations has been far more controversial (Whitlock et al. 1995; Coyne et al. 1997; Wolf et al. 2000). A key question is whether segregating alleles often encounter genetic backgrounds that are sufficiently different for significant epistasis to be manifest - i.e. whether genetic variation of the appropriate kind is present.

These issues aside, it is clear that fitness epistasis might have important evolutionary consequences even when little genetic variation of any kind is present. One of these consequences is the existence of multiple genotypes with higher fitness than all of their one-mutant neighbours (the one mutant neighbours of a given genotype are those genotypes that may be reached by a single mutational event). Since these locally-optimal genotypes may have lower fitness than the best possible combination of alleles (the global optimum), and double mutations are rare, populations may become 'trapped' at globally suboptimal states (Wright 1932; Maynard Smith 1970; Kauffman and Levin 1987; Whitlock et al. 1995). In addition, when multiple local optima exist, the stochastic appearance of mutations may be an important diversifying force in evolution - bringing about the evolutionary divergence of isolated populations subject to identical selection pressures (e.g., Mani and Clarke 1990).

A second possible consequence of fitness epistasis is the occurrence of non - independent substitution events. This stems from the fact that the fixation of a particular allele may alter the selective context for other alleles, actively inducing further substitutions, or preventing them from taking place. When substitutions induce further substitutions, molecular evolution may be characterised by concerted bursts of change. This is one possible explanation for the overdispersal of the molecular clock - the empirical finding that the variance in the number of non-synonymous substitutions in a lineage may greatly exceed the mean number (Maynard Smith 1970; Fitch and Markowitz 1970; Gillespie 1984; Kimura 1985; Stephan and Kirby 1993; Ohta 1997a, 1997b).

These, and other effects of fitness epistasis have been invoked to explain an increasing range of empirical results (e.g., Lenski and Travisiano 1994; Korona 1996;

Schrag et al. 1997; Elena et al. 1998; Burch and Chao 1999; Moore et al. 2000; Elena and Lenski 2001; Jeong et al. 2001; Kondrashov et al. 2002; Fraser et al. 2002). Despite this, however, there has been a relative dearth of quantitative theoretical predictions. A possible explanation is the sometimes baroque complexity of the models used to study genetic interactions. An exception, in this respect, is the "nk model" introduced by Kauffman and Levin (1987; c.f. Felsenstein 2000; Barton and Keightley 2002). The nk model has the advantage that the level of fitness epistasis may be tuned by adjusting a single parameter, denoted k; but despite this simplicity, it is able to account for a rich variety of empirically observed phenomena (see below). In addition, the adequacy with which the nk model represents a particular biological system is, in theory, open to empirical test (e.g., Kauffman and Weinberger 1989; Fontana et al. 1993; Jeong et al. 2001; Fraser et al. 2002).

Previously, the nk model has been used to investigate both the properties of local optima, and substitution dynamics in molecular evolution. In particular, Kauffman and Levin (1987) and others (Weinberger 1991; Macken and Perelson 1989; Kauffman 1993; Perelson and Macken 1995) investigated statistics concerning the number and fitness values associated with locally-optimal genotypes. Kauffman (1993) showed that increasing the epistasis parameter, k, causes the number of local optima to increase, but their expected fitness to decrease. As such, he suggested that when an equilibrium was reached, populations characterised by a high value of k would tend to be at a severe selective disadvantage compared with populations characterised by a smaller value of k. He dubbed this finding "the crisis of complexity" (Kauffman 1993). Ohta (1997a, 1997b, 1998) used individual-based simulation to investigate the substitution process under the nk model. Choosing parameters so that both natural selection and genetic drift played an important role in substitutions, Ohta showed that overdispersal of the substitution process could result. With this in mind, the nk model was described as a generalisation of Gillespie's (1984) 'mutational landscape model,' which was introduced to model coordinated bursts of selectively-driven substitutions. Furthermore, and in seeming contradiction to Kauffman (1993), Ohta showed that the equilibrium level of fitness attained in the simulations was relatively independent of k.

The present study introduces a slightly modified version of the nk model that allows us to shed light on the results of Kauffman and Ohta. Though our model is still technically epistatic in the sense above, it is also formally identical to a standard population genetics model that contains no epistasis (for reasons given below). As such, the modified model is capable of generating neither local optima, nor substitutions that induce further substitutions. Despite this fact, we show that the modified model is able to qualitatively reproduce some of the key results of the

previous authors. Let us begin by introducing the nk model in something close to its conventional form.

2 The nk model

The nk framework can be used to model fitness interactions at various levels of organisation (such as interactions between different proteins, or among different sites within a protein). With suitable parameterisation, the treatment given below is broadly consistent with all of these scenarios. However, for concreteness, and following most previous treatments, we will use the terminology of 'loci' and 'alleles' throughout. With this in mind, consider a sequence of n haploid loci, each with a possible alleles. In this case, a^n distinct haploid genotypes may be formed. The logarithm of the fitness associated with each of these genotypes is determined from the sum of n "fitness-contributions," - one contribution arising from each locus. Denoting the fitness of a given genotype by W, and the fitness contribution of locus i by h_i, we have

$$\ln(W) = \sum_{i=1}^{n} h_i. \tag{1}$$

The use of log fitness in this equation gives us a multiplicative model of fitness (since $W = e^{h_1} \times e^{h_2} \times \cdots \times e^{h_n}$). This is a minor departure from Kauffman (1993) and others, who used an additive nk model. However most previous results depend exclusively on the rank ordering of the fitness values, and so will be identical for additive and multiplicative models. Furthermore, for several reasons, a multiplicative model is the natural choice in population genetics (see, e.g., Phillips et al. 2000).

The key to the model is understanding how the h_i are calculated. Rather than assign these values in a formulaic way to facilitate the analysis, the nk model assumes that each possible h_i is a random number that is drawn, at the outset, from a particular probability distribution. This distribution, denoted $f(h)$, is termed the landscape distribution, since it determines the statistical properties of the fitness landscape. In all of the work below, we assume that the landscape distribution is normal, with mean 0 and variance σ^2:

$$f(h) = \left(2\pi\sigma^2\right)^{-1/2} \exp\left\{-h^2/\left(2\sigma^2\right)\right\}. \tag{2}$$

We note that Kauffman (1993) and others, have used a uniform distribution for $f(h)$. However, a normal distribution has some advantages (as will become clear below), and again, the exact form of $f(h)$ makes little difference to the rank-order statistics considered by most previous authors.

So far, we have not made clear exactly how many h values must be generated in order to determine the fitness values of all possible genotypes. The answer to this question depends on how genotype relates to fitness, and this depends crucially on the value of the epistasis parameter, k.

Consider first the nk model when there is no epistasis (this corresponds to setting $k = 0$ in the general description given below). In this case the fitness contribution of locus i, namely h_i, is independent of the alleles carried at other loci and depends only on the allele carried at locus i. Since a alleles are available at locus i, h_i may take one of a distinct values in any given individual. For each particular realisation of the model, each of these a values must be independently generated from $f(h)$ and then stored in a lookup table. Following this procedure for each of the n loci, we end up with a table containing a total of $n \times a$ independently-generated random numbers. The fitness values of all possible genotypes can then be calculated using the appropriate numbers from the table.

To incorporate epistasis, the nk model allows the fitness contribution of locus i to depend not only on the allele carried at locus i, but also on the alleles carried at k other loci. We say these k loci epistatically influence locus i, such that the value of h_i will change whenever a mutation occurs at any of $k + 1$ loci, namely locus i and the k other loci that epistatically influence this locus. Since each locus has a possible alleles, considered together, locus i and the k loci that epistatically influence locus i may form a total of a^{k+1} distinct combinations of alleles. Under the assumptions of the nk model, each of these a^{k+1} combinations leads to a distinct, independently-generated value of h_i. As such, to specify the fitness of all genotypes, we need a lookup table that contains a total of $n \times a^{k+1}$ random numbers, each generated from the landscape distribution, $f(h)$.

An additional complication that arises when there is epistasis (i.e., when $k > 0$), is that we must specify the pattern of epistatic connections. In other words, we must decide exactly which k loci epistatically influence each locus. Kauffman (1993) calls this the specification of the "k-amongst-the-n". A variety of methods have been used to assign the epistatic connections, three of which are depicted in Figure 1.

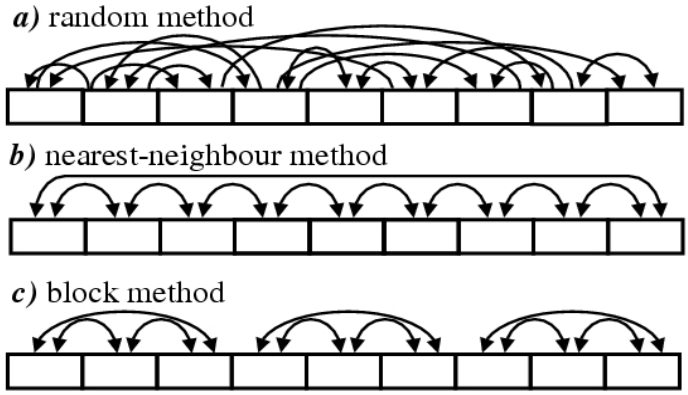


Figure 1

Possible patterns of epistatic connectivity under the nk model are depicted. In each case, $n = 9$ loci are shown, and each locus is epistatically influenced by $k = 2$ other loci. Connections of epistatic influence are denoted with arrows; so the loci that epistatically influence a given locus have arrows leading from them, and terminating at that locus. Because $k = 2$, exactly two arrows terminate at each locus in all cases. Each diagram represents the results of assigning the epistatic connections via a different method. Fig. 1a represents a possible outcome when the connections are assigned at random (so each locus is epistatically influenced by $k = 2$ loci chosen at random from the remaining $n - 1$ loci). Note that, in this case, a variable number of arrows stem from each locus. Fig. 1b shows the pattern when each locus is influenced by its k nearest-neighbour loci, with the loci on the ends of line connected to each other. Fig 1c shows epistatic connections arranged in blocks of $k + 1$ reciprocally interacting loci.

Kauffman investigated assigning the connections at random (Fig. 1a), and connecting each locus to its k nearest neighbours in the sequence (Fig. 1b). The latter method was adopted by Ohta (1997a). A third possibility, the 'block method', was introduced by Perelson and Macken (1995), and was motivated by the observation that molecular sequences have natural partitions - such as protein domains. To implement the block method, the n loci are divided into a series of equally-sized blocks, each containing $k+1$ loci - thus n must be exactly divisible by $k+1$. (The generalisation to blocks of variable size is trivial.) Each locus within a given block is epistatically influenced by every other locus within that block, but by no locus outside the block (Fig. 1c).

Kauffman (1993) suggested that the way in which the epistatic connections are assigned makes little difference to the statistics of the nk landscapes. Below, we confirm, via simulation, that the three methods depicted in Figure 1 yield very similar results. There are, however, important differences as regards analytical tractability. In particular, with the random and nearest neighbour methods (Figs. 1a and 1b), difficulties stem from the fact that the sets of epistatic connections overlap, so a single locus may be connected to every other locus via a chain of connections. For this reason, the analytical results which follow apply strictly to the block method (Fig. 1c).

3 Optima results

We have already noted that the earliest analytical work on the nk model focussed on the statistics of the locally optimal genotypes - genotypes with higher fitness than all of their single-mutant neighbours. When $k = 0$, natural selection can, in theory, 'optimise' each locus independently, and so there is only one optimal genotype - which is by definition the global optimum. As k increases, and loci become increasingly interdependent, the number of local optima increases rapidly (Kauffman 1993). Perelson and Macken (1995) have shown that under the block method, the expected number of local optima is approximately $a^n \left[(a-1)(k+1)\right]^{-n/(k+1)}$ (the approximation assumes that k is reasonably large).

We can also calculate the expected fitness of the globally optimal genotype, which we denote W_{glo}, and that of a randomly chosen locally-optimal genotype, denoted W_{opt}. These are extreme value statistics (e.g., Gumbel 1958), and so follow from standard results. However, to express the statistics of interest in a helpful form, our choice of landscape distribution, eq. (2), requires that we make some rather crude

approximations (described in Appendix 1). These lead to

$$E\left[\ln W_{glo}\right] \approx n\sigma\left[2\ln(a)\right]^{1/2}, \qquad \mathrm{Var}\left[\ln W_{glo}\right] \approx \frac{0.82n\sigma^2}{(k+1)\ln(a)} \tag{3}$$

$$E\left[\ln W_{opt}\right] \approx n\sigma\left[\frac{2D}{k+1}\right]^{1/2}, \qquad \mathrm{Var}\left[\ln W_{opt}\right] \approx \frac{0.82n\sigma^2}{D} \tag{4}$$

where $D = \ln\left[(a-1)(k+1)+1\right]-1$. Note that the expected log fitness of the global optimum, $E\left[\ln W_{glo}\right]$, is entirely independent of k (to the level of approximation adopted). However, the equivalent statistic for a randomly chosen optimum declines rapidly with k. Indeed, as k become very large, $E\left[\ln W_{opt}\right]$ approaches zero - which is the mean of the landscape distribution, and so the value expected for a genotype chosen entirely at random. This is one of Kauffman's (1993) key results.

4 How is the model epistatic?

So far, we have presented results that are largely within a conventional nk framework. However, it is revealing to relate the all-important parameter k to the conventional population genetics notion of epistasis. This will, in turn, help us to understand the population dynamics of the nk model under natural selection. With this in mind, consider a mutation occurring at locus i. This mutation may described by its selection coefficient, s_i, defined by $W' = W \times (1+s_i)$, where W denotes the denotes the fitness of an individual not carrying the mutation, and W' the fitness of the mutant. A mutation at a second locus, j, might be described in a similar way, and have a fitness $W' = W \times (1+s_j)$. If there is no epistasis, then the fitness of the double mutant (the genotype with mutations at loci i and j) would be $W'' = W \times (1+s_i) \times (1+s_j)$. The extent of epistasis is usually measured by the magnitude of the deviation from this multiplicative result. Denoting this epistatic deviation by ε_{ij}, we have $W'' = W \times (1+s_i) \times (1+s_j) \times (1+\varepsilon_{ij})$.

Let us now calculate the relevant quantities for the nk model. Under the model, the mutation at locus i will alter a certain number of fitness contributions - that of locus i itself, and all of those loci that are epistatically influenced by locus i (these would be the loci whose arrows terminated at locus i, in Figure 1). The fitness contribution of all other loci will remain unchanged. From eq. (1), we have

$$\ln(1+s_i) = \ln W' - \ln W = \sum_l \left(h_l^* - h_l\right) \tag{5}$$

where the sum is over all loci that are epistatically influenced by locus i, and h_l and h_l^* denote the fitness contribution of locus l before and after the mutation has occurred. According to the specification of the model, both h_l and h_l^* are random numbers drawn from the landscape distribution, $f(h)$.

We can gain important insights into the nk model merely by noting the number of terms that appear in the sum in eq. (5), and in the equivalent sum needed to specify the epistatic deviation, ε_{ij}. To see this, consider the two loci i and j, when $k = 1$. In this case, there are three possible patterns of connection, and these are depicted in the left hand column of Table 1.

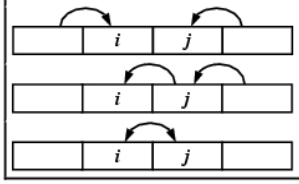
	$\ln(1+s_i)$	$\ln(1+s_j)$	$\ln(1+\varepsilon_{ij})$
	$h_i^* - h_i$	$h_j^* - h_j$	0
	$h_i^* - h_i$	$h_i^{**} - h_i + h_j^* - h_j$	$h_i^{***} - h_i^{**} - h_i^* + h_i$
	$h_i^* - h_i + h_j^* - h_j$	$h_i^{**} - h_i + h_j^{**} - h_j$	$h_i^{***} - h_i^{**} - h_i^* + h_i + h_j^{***} - h_j^{**} - h_j^* + h_j$

Table 1

The quantities needed to represent selection acting on a pair of loci are shown, under the assumptions of the nk model (see text, eqs. (1) and (5)). Each row of the table shows results for a different arrangement of epistatic connectivity between the loci. Within a row, each differently-notated h value is simply a distinct random number, independently generated from the landscape distribution, $f(h)$.

The other columns give the quantities relevant for calculating the effects of selection, and the epistatic deviation, in each of the three cases. There are three things to notice about Table 1, all of which reveal important properties of the nk model. Firstly (and of least significance), as the interconnectivity of the loci increases, we require more independently generated h values to describe the situation (the three cases require 4, 6 and 8 values respectively). Since increasing the value of the parameter k increases the connectivity, this shows why more h values are required to specify the fitness of every possible genotype as k increases.

Secondly, the number of terms in the epistatic deviation increases with the connectivity. This means that the selective effect of the double mutant will become increasingly unpredictable from those of the two single mutants. It is this property that is commonly meant by epistasis. As a result, increasing k will increase the amount of epistasis, in this commonly-used sense.

Thirdly, it is clear from Table 1 that the number of terms needed to specify the selective effects of the single mutants will also increase with the connectivity. In nk papers, this is usually expressed by saying that increasing k decreases the correlation of the fitness landscape. Less formally, we can say that increasing k will lead, on average, to mutations causing larger changes in fitness. As a result, mutations occurring at loci with more epistatic connections will tend to be under stronger selection, but, as pointed out by Fisher (1930, Ch. 2), these large-effect mutations are also more likely to be deleterious.

It is important to note that the close relation of the three properties mentioned above, is not typical of epistatic models in theoretical population genetics. For example, it is easy to imagine a model in which the distribution of the epistatic parameter, ε_{ij}, changes, while the distributions of the single-mutant selection coefficients, s_i and s_j, remain fixed. However, the three properties are intimately linked in the nk framework, and each of them stems from the fact that a given substitution will alter, on average, $k+1$ distinct h values. As a result of this, any increase in fitness epistasis (the unpredictability of the double mutant fitness from the single mutant fitnesses) will also be accompanied by a decrease in the correlation of the fitness landscape - or an increase in the expected "size" of single mutants. This will prove crucial for understanding the dynamics of the nk model.

5 Infinite alleles approximation

A major problem with analysing the nk model is the fact that evolution may revisit previously-tested combinations of interacting alleles - a fact which leads to some intractable mathematics. Previously published analyses have avoided this problem

by assuming that the number of genotypes is very large (e.g., Macken and Perelson 1989; Weinberger 1991; Perelson and Macken 1995). Here, we also make this assumption, but in a novel way. Specifically, we treat the nk model in the limit where the number of alleles, a, becomes very large and effectively infinite. In this case, rather than choosing our mutant values from a lookup table of limited size, we can, when a mutation occurs, simply generate a new random number directly from the landscape distribution. As a result, a mutation at any locus may generate the complete spectrum of mutant effects, regardless of the allele present before the mutation; thus, in principle, all possible fitness values are reachable via a single mutation from all possible genotypes.

Technically, employing the infinite-allele limit does not alter the epistatic nature of the nk model. The effects of a particular allele may still be background-dependent, and so all of the properties described in the previous section will still apply. However, because the mutational opportunities available are now background-independent, the large a approximation does nullify two of the most important consequences of fitness epistasis. In particular, regardless of the value of k, substitutions can never induce further bursts of substitutions, and populations will never become trapped at local optima. Indeed local optima will cease to exist - a fact which exemplifies their general irrelevance in fitness landscapes of high-dimensionality (see Provine 1986; Gavrilets 1997). Furthermore, it can be shown that in the infinite-allele limit, the nk model becomes formally identical to an entirely non-epistatic model familiar from population genetics. This model is the "fixed" or "House-of-Cards" model that has been widely studied in the context of molecular evolution (Ohta and Tachida 1990; Tachida 1991, 1996; Gillespie 1994, 1995). We clarify the relationship between the House-of-Cards model and the nk model below.

The above considerations show that employing the infinite-allele limit alters the nk model in a fundamental respect. Nevertheless, we show below that the analytical results obtained in this limit are often very close to simulation results from the original nk model with a small number of alleles.

6 Dynamics with infinite alleles

Let us now consider the dynamics of a population evolving according to the nk model in the infinite-allele limit. Our overall aim is to calculate the probability distribution of population fitnesses as they change over time. This distribution characterises the evolution of a large number of replicate populations with an identical initial state, and incorporates the stochastic processes of drift and mutation as well as natural selection.

Consider a single population of stable size N. We assume that the per locus mutation rate, u, is sufficiently small that mutations appear in the population very rarely. That is, we assume $unN \ll 1$. In this low mutation rate limit, it follows that the loss or fixation of a newly-arisen mutation occurs very rapidly when compared with the typical interval between the appearance of mutations. Hence the population is genetically monomorphic, at the relevant loci, for the majority of the time, and the fixation of loss of a mutation is approximated as an instantaneous process. It also follows that the mode of reproduction (i.e., whether sexual or asexual) makes little difference to the evolutionary outcome. Assumptions similar to the above have been used by many previous authors (e.g., Maynard Smith 1970; Gillespie 1983, 1984; Tachida 1991; Orr 1998; Barton 2001; Welch and Waxman 2003), and in most previous nk work (Kauffman and Levin 1987; Weinberger 1991; Macken and Perelson 1989) - although this work has not often taken natural selection explicitly into account (see Fontana et al. 1993 and Orr 2002). Clearly, a crucial quantity in the analysis is the probability that a newly arisen mutation reaches fixation. If the mutation has selection coefficient s, this probability is given by

$$\Pi(s) = \frac{1 - e^{-2s}}{1 - e^{-2Ns}} \tag{6}$$

(Kimura 1957). Since all analytic work in this section is restricted to the block method of assigning epistatic connections (Fig. 1C), we consider the evolution of a single block of loci. Given the infinite-allele assumption, the loci within the block are fully interchangeable. As such, we need only consider the sum of their fitness contributions. With this in mind, we introduce the notation $X = \sum_j h_j$ where the sum is over all loci in the block under consideration. Since each block contains $k+1$ loci, the sum contains $k+1$ terms. Now consider a mutation taking place at any one of the loci within the block. From eq. (5), we have $s = e^{X^* - X} - 1$, where X^* is the fitness contribution of the block after the mutation. This result for s shows that the dynamics of the fitness contribution of the block can be expressed solely in terms of the random variables X^* and X. We now describe the probability densities of these variables. We begin with the post-mutation quantity, X^*, whose probability density we will denote $q(x)$. It follows from the discussion of mutation given above, that X^* is simply the sum of $k+1$ independent draws from the landscape distribution. Since we have assumed that the landscape distribution is normal, eq. (2), it follows that $q(x)$ will also be normal, with a mean 0 and a variance $(k+1)\sigma^2$.

$$q(x) = \left[2\pi(k+1)\sigma^2\right]^{-1/2} \exp\left\{-x^2 / \left[2(k+1)\sigma^2\right]\right\}. \tag{7}$$

Furthermore, it follows from the Central Limit Theorem, that for *all* landscape

distributions with finite variance, a sufficiently large value of k will lead to an approximately normal $q(x)$. Our choice of a normal $f(h)$ yields an exactly normal $q(x)$ for arbitrary k.

The variable X describes the fitness contribution of a block at a given time. Since its value will change cumulatively as the result of selection, mutation and drift, its probability density will also be time-dependent. Accordingly, we denote the probability density of X at time t by $p(x,t)$. In Appendix 2, we derive the following equation which determines how $p(x,t)$ changes over time.

$$\frac{\partial p(x,t)}{\partial t} = (k+1)\,uN \left\{ q(x) \int \Pi(e^{x-y}-1)\; p(y,t)dy \right.$$

$$\left. -p(x,t) \int \Pi(e^{y-x}-1)\; q(y)dy \right\} \tag{8}$$

Equation (8) is virtually identical to an equation given by Tachida (1991) for describing the House-of-Cards model (his eq. (A4)), and this clarifies the relationship between the two models. When the number of alleles is infinite, the nk model remains epistatic at the level of single loci, but each block of loci evolves according to the non-epistatic House-of-Cards model. This is reasonable, since while there is epistasis within blocks, there is no epistasis between blocks (Fig. 1).

Due to this formal identity, we can make use of previously available results to understand the nk model. For example, Tachida (1991) shows that eq. (8) has a stable equilibrium, which can be approximated by

$$\lim_{t\to\infty} p(x,t) \simeq q(x-\Lambda) \tag{9}$$

$$\text{where } \Lambda = 2(N-1)(k+1)\sigma^2 \tag{10}$$

(see Appendix 2; Zeng et al. 1989; Tachida 1991). Thus the approximate equilibrium distribution of the fitness contribution of a block of loci is simply the normal distribution, $q(x)$, with a shifted mean. Using this result, we can find the expected value of log fitness at equilibrium; this is simply the sum of the expected values for each block. The same applies approximately to the equilibrium variance in log fitness. Since, by assumption, there are $n/(k+1)$ blocks in total, we have

$$E\left[\ln \widehat{W}\right] \simeq 2(N-1)n\sigma^2, \qquad \text{Var}\left[\ln \widehat{W}\right] \simeq n\sigma^2 \tag{11}$$

(see also Gillespie 1994). Remarkably, both results in eq. (11) are wholly independent of k.

7 Simulation results

How well, then, do the infinite-allele results approximate the dynamics of the nk model when a is finite and the epistatic connections are, e.g., randomly assigned? To answer this question, we have carried out simulations. The simulation procedure is designed to match the assumptions behind the preceding analysis in all respects other than the infinite-allele approximation. As such, we assume that mutations are very rare, and so enter a homogeneous population one at a time, and then either reach fixation or are lost. (Simulations carried out in this way were used by Tachida 1991, and a comparison with results obtained by more sophisticated simulation methods was undertaken by Gillespie 1994.) To initialise each simulation trial, we populated fitness lookup tables using the landscape distribution, and chose an initial genotype at random (note that the results changed little if the initial conditions were retained for whole sets of simulation trials). After initialisation, the simulation procedure can be described by the following algorithm: i) to determine the interval of time before the appearance of a mutation, a random Poisson waiting time was generated from a distribution with mean $1/(Nnu)$; ii) the mutating locus was chosen at random, and its allele was replaced with one of the $a-1$ alternative alleles, also chosen at random; iii) the mutant fitness was calculated using the lookup tables, and the mutation either reached fixation or was lost with a probability determined by eq. (6). These three steps were then repeated for the next mutation, and the trial terminated after evolution had proceeded for a certain length of time. For each set of parameter values, we carried out 1000 replicate trials, and then averaged over the results.

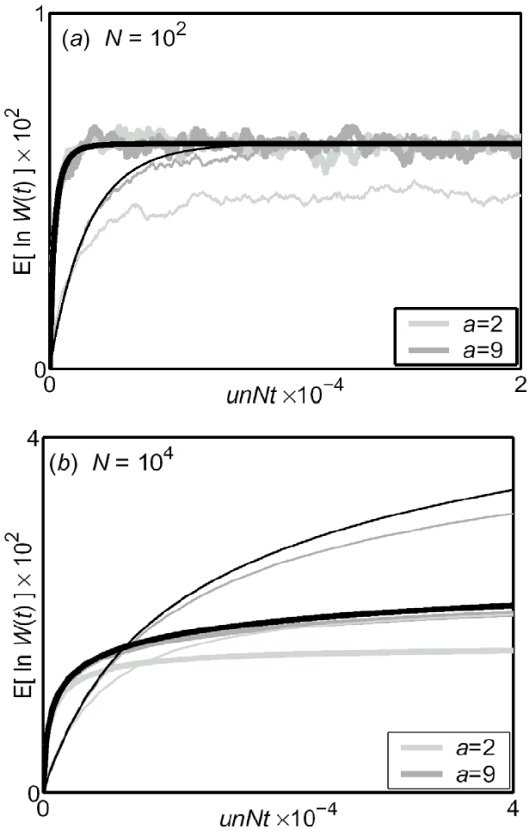


Figure 2

The expected logarithm of fitness, $E\left[\ln W(t)\right]$, is plotted as a function of time, measured in units of $unNt$. Simulation results (the grey curves) are compared to the numerical integration of eq. (8) (the black curves). In all cases, $n = 32$ loci were used, and $\sigma = 10^{-3}$ was the standard deviation of the landscape distribution, eq. (2). Each plot shows two different values of k (the level of gene interaction): $k = 1$ (thinner lines) and $k = 15$ (thicker lines). Simulation results are presented for $a = 2$ alleles and $a = 9$ alleles, and the block method of assigning epistatic connection was used.

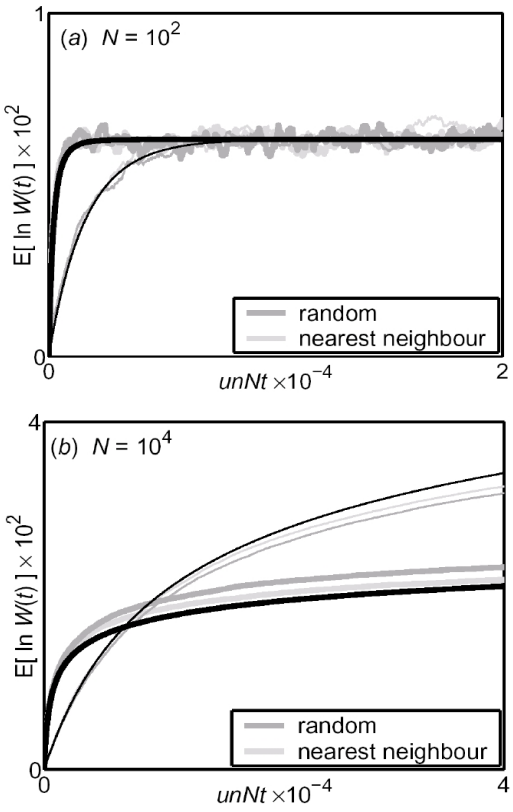


Figure 3

The results shown are identical to those in Figure 2, with the exception that the simulation results shown use the random method, and the nearest-neighbour method of assigning epistatic connections (see Fig. 1). In each case $a = 9$ alleles were used.

Figures 2 and 3 show simulation results generated in the manner described above. Also shown, for comparison, are infinite-allele results obtained by the numerical integration of eq. (8) with $p(x,0) = q(x)$ as the initial condition (this is equivalent to choosing the initial genotype at random). For the fixed parameters, previous work on the House-of-Cards model has shown that its behaviour depends crucially on the strength of selection, measured by the product of the population size and the standard deviation of the mutant distribution, $q(x)$; this product is $N\sqrt{k+1}\sigma$ in our notation. In contrast, the genomic mutation rate un - which we have assumed is small - simply acts as an overall scaling factor of time. We choose to vary N and k in the results presented. In particular, pairs of plots show results for weak selection: $N\sigma = 1/10$; and for strong selection: $N\sigma = 10$. Each plot then includes results for two values of k, namely $k = 1$ (the thinner line of each pair) and $k = 15$ (the thicker lines).

Figure 2 shows simulation results using the block method of assigning epistatic connections (Fig. 1c), and different numbers of alleles. Results are presented for $a = 2$ alleles, since biallelic loci are common to most nk work, and deviate most from the infinite-allele approximation. Results are also presented for $a = 9$ alleles, since this value was used by Ohta (1997a, 1997b, 1998). Figure 2a shows the weak selection results. In all cases, the population is shown to rapidly reach a dynamic equilibrium. The continued fluctuation of the curves after this point shows that substitutions are still occurring, it is just that weakly beneficial and weakly deleterious substitutions occur with roughly equal frequency (see also Gillespie 1994, 1995). For the curve representing $a = 2$, $k = 15$, and for both curves using $a = 9$, the equilibrium is given very accurately by eq. (11). In these cases, the agreement between the analytical results and the simulation is excellent - and so the infinite-allele House-of-Cards model accurately approximates the dynamical behaviour of the nk model. The exceptional case is the curve representing the case $a = 2$, $k = 1$; here the curve reaches an equilibrium not treated analytically, where genetic drift, and the scarcity of alleles affect the outcome (we return to this case in the discussion).

Figure 2b shows equivalent results with strong selection. In this case, quantitative agreement with the infinite-allele results is good only at small times when $a = 9$, and is poor when $a = 2$. This is because selection was strong enough for the finite-allele populations to reach a fitness optimum, rather than a drift-influenced equilibrium. The fitness level reached lay between the values predicted by the optimum equations, (3) and (4), rather than the higher value predicted by eq. (11). By comparing equation (3) and eq. (11), we can say that, in general, an optimum is likely to be reached if $N\sigma \gg \sqrt{\ln(a)/2}$.

Figure 3 shows simulation results using different methods of assigning the epistatic connections, namely the random method (Fig. 1a) and the nearest-neighbour method (Fig. 1b). In both cases, $a = 9$ alleles were used. Comparing Figures 2 and 3, it is clear that altering the pattern of epistatic connections makes rather little difference to the results (Kauffman 1993). However, systematic differences are apparent, particularly when connections are randomly assigned and selection is strong (Fig. 3b). These differences seem to stem from the fact that a new mutation may alter the fitness contribution of a variable number of loci (depending on how many loci are epistatically affected by the locus at which the mutation occurs.) Compared to the cases where each mutation alters a fixed number of fitness contributions, this variation in size acts as a mildly retarding force when k is small, but accelerates the rate of adaptation when k is larger.

8 Dynamics with infinite alleles and strong selection

We have seen in the previous section that the nk model can be very accurately approximated by the House-of-Cards model when selection is weak (as measured by small values of the compound parameter $N\sqrt{k+1}\sigma$). When selection is strong, however, the agreement is typically poor. Nevertheless, in the following section, we further explore the behaviour of the infinite-alleles model with strong selection. We show that, in spite of the poor quantitative agreement in this regime, the influence of k on the outcome of evolution is remarkably similar to that under the standard nk model.

Simulation results for the House-of-cards model with strong selection were reported by Gillespie (1994, 1995). He showed that, after a relatively short period of time, substitutions become increasingly rare and effectively stop occurring. This means that when selection is strong, the equilibrium represented by eqs. (11), is simply never reached. (In general, the relevance of equilibrium quantities depends on the relative timescales of equilibration and environmental change, after which the fitness effects associated with different allelic combinations are likely to change; e.g., Gillespie 1983, 1995; Tachida 1991.) The reason for the absence of equilibration in the House-of-Cards model with strong selection is clear. In order for a block of loci to approach its expected equilibrium fitness, mutations of value $\Lambda = 2(N-1)(k+1)\sigma^2$ must be generated from $q(x)$ (see eqs. (7) and (10)). Since these mutations are a distance of $2(N-1)\sqrt{k+1}\sigma$ standard deviations from the mean of $q(x)$, it follows that if $N\sqrt{k+1}\sigma \gg 1$, such mutations will be extremely rare. Gillespie (1994, 1995)

made a similar point using the theory of records.

Although we know that eqs. (11) will not apply when selection is strong, no previous results tell us the level of fitness that *will* be attained. We now derive this result. The calculation uses an approximation for the fixation probability of eq. (6). This approximation relies on the fact that when selection is strong, only beneficial mutations are capable of fixing, i.e., $\Pi(s) \simeq 0$ for $s < 0$. In addition, we assume that the selection coefficients of beneficial mutations are small. In this case, we have

$$\Pi(s) \simeq \begin{cases} 2\ln(1+s), & s > 0 \\ \\ 0, & s \leq 0. \end{cases} \tag{12}$$

This approximate fixation probability allows us to obtain a major simplification. By scaling time and other quantities, we can eliminate all parameters from eq. (8). As a consequence, if all blocks of loci are identically distributed initially, then we can write the expected log fitness in terms of a single function, $F(\bullet)$, and just two combinations of parameters:

$$E\left[\ln W(t)\right] = \frac{n\sigma}{\sqrt{k+1}} \times F\left(2\left(k+1\right)^{3/2} uN\sigma t\right). \tag{13}$$

This equation is derived in Appendix 2. If, as in Figures 2 and 3, the population begins with a randomly chosen genotype (which means that $p(x,0) = q(x)$), an exact form of the function $F(\bullet)$ can be found (see eq. (20) Appendix 2), and has the approximation

$$F\left(T\right) \simeq \begin{cases} T, & T \ll 1 \\ \\ 2.36 \times T^{0.05}, & 1 \ll T < 10^7. \end{cases} \tag{14}$$

A number of interesting conclusions follow from considering eqs. (13) and (14) together. Firstly, at large times, where the second line of eq. (14) will apply, the expected log fitness of a population will be proportional to $(k+1)^{-0.425}$, a rate of decline that is slightly less rapid than the reciprocal of the square root: $(k+1)^{-1/2}$. This result is remarkably similar to the outcome of evolution when a is finite. In that case, as can be seen from Figs. 2b and 3b, and from eq. (4), strong selection takes populations to optima whose expected log fitness also declines slightly less rapidly than $(k+1)^{-1/2}$ (the small positive contribution comes from the term denoted D in eq. (4)). In other words, the influence of k on the outcome of evolution is very similar in both the infinite-a House-of-Cards model and in the conventional nk model.

A similar conclusion follows from comparing the small and large argument versions of eq. (14). These can be thought of as applying to poorly-adapted and well-adapted populations respectively. In the former case, when t is small and the population is poorly-adapted, $E[\ln W(t)]$ is proportional to $(k+1)\,t$, so large k leads to the most rapid rate of increase in fitness. At large times, when significant adaptation has already occurred, we have seen that $E[\ln W(t)]$ is proportional to $(k+1)^{-0.425}t^{0.05}$, so small k leads to the most rapid rate of adaptation. Although these results apply strictly to the infinite-allele model, an identical trade-off between different values of k can be seen clearly in the finite-allele simulation curves shown in Figures 2b and 3b (where it leads to a crossing of the trajectories of populations characterised by different values of k).

This trade-off is inherently a multi-locus phenomenon, and so has not been previously reported for the House-of-cards model. However, very similar results have been reported for a model of optimising selection acting on multiple quantitative traits, that was first introduced by Fisher (1930, Ch.2) to advocate micromutationalism (Hartl and Taubes 1998; Orr 1998, 2000; Welch and Waxman 2003; see also Hansen 2003 for more general results). The parallel between the two models helps to reiterate the fact that the effects of k on the correlation of the fitness landscape can also be understood in terms of the "size" of new mutations.

9 Discussion

The present study has examined the nk model introduced by Kauffman and Levin (1987). We have shown that when epistatic connections are arranged according to the block method of Perelson and Macken (1995), and the number of alleles, a, is assumed to be effectively infinite, the nk model becomes formally identical to the non-epistatic House-of-Cards model (Ohta and Tachida 1990; Tachida 1991, 1996; Gillespie 1994, 1995).

We further showed that when selection is weak, the House-of-Cards model accurately approximates the nk model even in the more general case - that is, when the number of alleles is limited, and epistatic connections are, e.g., randomly assigned (Fig. 3). The dynamical similarity of these models under weak selection has important implications for interpreting the simulation results of Ohta (1997a, 1997b, 1998). In particular, it suggests that they should not be explained by invoking those properties of the nk model that disappear in the infinite-allele limit. Such properties include the existence of multiple local optima, and the ability of substitutions to selectively induce further substitutions, neither of which may occur under the House-of-Cards model. This point has particular relevance for understanding the

overdispersion of the substitution process in Ohta's simulations. Although epistatic models can lead to the clustering of substitutions (e.g., Fitch and Markovitz 1970), so can the House-of-Cards model (Tachida 1991). As a result, rather than attribute the overdispersion demonstrated by the nk model to fitness epistasis, it is more plausibly attributed to the similarity of the nk model to the House-of-Cards model. Indeed, Ohta (1997b) remarked that the behaviour of the index of dispersion under the nk model closely resembles results from the House-of-Cards model; we have shown why this is to be expected.

Kauffman (1993) used the nk model to show how, as k increased, the ability of populations to reach states of high fitness was compromised by the existence of multiple locally optimal genotypes of low fitness. This can be thought of as restating and quantifying Wright's (1932) claim that the lack of fit intermediates may be an important obstacle to natural selection when fitness epistasis is widespread. In response to Wright, it has been argued that local optima become increasingly irrelevant in fitness landscapes of high dimensionality (e.g., Provine 1986; Gavrilets 1997). Here, however, we have shown that, when selection is strong, a near-identical fitness penalty is paid by high-k populations, even when the number of alleles available is infinite, and so no local optima exist (see eqs. (13)-(14)). The fact that this result was obtained with the House-of-Cards model, and that similar results have been reported with Fisher's quantitative trait model (e.g., Hartl and Taubes 1996; Orr 2000; Hansen 2003; Welch and Waxman 2003), suggest that this result can be best explained by the effect of the parameter k on the expected size of mutations - a property that is inextricably linked with the level of fitness epistasis in the nk framework. We have also shown that Kauffman's result is conditional on strong selection acting on at all loci. When selection is weak, increasing k may have no effect on the equilibrium fitness (e.g., eq. (11); Fig. 2a, Fig. 3a, Ohta 1997a), and in some cases, will lead to a fitness increase (Fig. 2a). Further caveats will apply when, as in real genetic systems, the strength of selection varies between sites (see, e.g., Solow et al. 1999).

Finally, and more broadly, we have stressed that adjusting parameter k within the nk framework, has variety of effects on evolutionary dynamics. As such, it should not be assumed that the "level of epistasis" can be adjusted without also adjusting other quantities of crucial importance (e.g., the strength of selection acting on each site). This should be borne in mind when interpreting the results of simulation studies using the nk model in which k is an important parameter (e.g., Bergman et al. 1995; Peck 2004).

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Appendix 1

In this appendix we briefly derive equations (3) and (4), for the expectation and variance of the log fitness of the globally-optimal genotype and of a randomly-chosen locally optimal genotype. These are extreme value statistics and the following relies heavily on Gumbel (1958) throughout. Consider a probability density $g(x)$ with associated cumulative distribution $G(x)$. We now make a number, Z, of independent draws from $g(x)$, and denote the largest value drawn by X_1. The cumulative distribution of X_1 is simply $G(x)^Z$. When Z is large, and $g(x)$ is normal, this distribution approaches a Gumbel distribution with expectation and variance $E[X_1] \simeq \alpha + \gamma\beta$, and $\mathrm{Var}[X_1] \simeq \pi^2\beta^2/6$, with α defined by $1-G(\alpha) = 1/Z$, β defined by $1/\beta = Zf(\alpha)$, and $\gamma = 0.5772...$ is Euler's constant. To give a clearer indication of the parameter-dependence, in the text we make the rougher approximations:

$$\begin{aligned} E[X_1] &\approx \sigma_g \left(2\left[\ln(Z) - 1\right]\right)^{1/2}, \\ \mathrm{Var}[X_1] &\simeq \pi^2 \sigma_g^{-2} \ln\left(Z^2/2\pi\right)/6. \end{aligned} \tag{15}$$

where σ_g is the standard deviation of $g(x)$. To derive the equations in the text, consider a single block of loci. The fitness contribution of this block will be the sum of $k+1$ independent random numbers each drawn from the landscape distribution, eq. (2). Given our choice of distribution, this is equivalent to taking a single draw from a normal distribution with mean zero and standard deviation $\sigma_g = (k+1)^{1/2}\sigma$; i.e., the relevant $g(x)$ is the distribution $q(x)$ of eq. (7). The globally optimal fitness value of a block of loci will be the maximum of $Z = a^{(k+1)}$ draws, since this is total number of allelic combinations that may be formed in that block. A randomly-chosen optimal block will be the maximum of $Z = (a-1)(k+1)+1$ draws, which includes the locally-optimal sequence and all of its one-mutant neighbours. The equations in the text relate to the log fitness of a complete genotype, and so are found by multiplying by expectation and variance of an optimal block, by the number of blocks, $n/(k+1)$.

Appendix 2

In this Appendix, we derive the equation determining the dynamics of the probability distribution, $p(x,t)$, eq. (8), and some of its properties. We begin with a stochastic process where time is measured in "events," and an event is the loss or

fixation of a mutation that is newly arisen in a given block of loci. After $\tau+1$ events the log fitness contribution of block α, namely X_α, obeys

$$X_\alpha(\tau+1) = X_\alpha(\tau) + I\left(X'_\alpha - X_\alpha(\tau)\right)\left(X'_\alpha - X_\alpha(\tau)\right)\delta_{r,\alpha}. \tag{16}$$

Here, X'_α is the mutant value of X_α and I is an indicator variable which depends on the fixation probability of eq. (6). At every event, $I(x)$, takes the value 1 with probability $\Pi\left(e^x-1\right)$, when fixation of a mutation occurs and it takes the value 0, with probability $1-\Pi\left(e^x-1\right)$, when loss of a mutation occurs. Additionally $\delta_{r,\alpha}$ denotes a Kronecker delta and r takes one of the values $1,2,...,n/(k+1)$ with the probability that a mutation occurs in block r, namely $(k+1)/n$.

From eq. (16), a difference equation for the probability density of $X_\alpha(\tau)$ can be obtained. Equation (8) closely resembles this difference equation, and follows from (i) treating τ as a continuously varying quantity, governed by a differential equation (an approximation which follows from the small probability of fixation associated with each event); and (ii) averaging over an infinite number of replicate populations, allowing us to replace τ by the expected number of events in time t, namely unN. The equilibrium result, eq. (9), can be found by using an approximate form of the fixation probability eq. (6). Specifically, we assume selection coefficients are small, and replace $\Pi\left(e^{x-y}-1\right)$ by $\Pi\left(x-y\right)$. From this follows

$$\lim_{t\to\infty} p(x,t) \simeq \frac{q(x)\exp\left[2(N-1)x\right]}{\int q(y)\exp\left[2(N-1)y\right]dy} \tag{17}$$

(Tachida 1991) which can be confirmed, numerically, to be stable. Equation (9) follows from using eq. (7) in eq. (17).

We now derive results for the scaling leading to eq. (13), when the approximation of eq. (12) applies. In terms of $\theta = x\left[(k+1)\sigma^2\right]^{-1/2}$, $T = 2\left(k+1\right)^{3/2}uN\sigma t$, $Q\left(\theta\right) = \exp\left(-\theta^2/2\right)/\sqrt{2\pi}$ and $P(\theta,T) = \sqrt{(k+1)\sigma^2}p(x,t)$, the dynamical equation, eq. (8), takes the form $\partial P(\theta,T)/\partial T = Q\left(\theta\right)\int_{-\infty}^{\theta}(\theta-\phi)P(\phi,T)d\phi - P(\theta,T)\int_{\theta}^{\infty}(\phi-\theta)Q\left(\phi\right)d\phi$. This equation contains no parameters. Assuming $P(\theta,0)$ is independent of parameters, it follows that the mean value of θ is only a function of T, which we write as $F(T)$:

$$F(T) = \int \theta P(\theta,T)d\theta. \tag{18}$$

This is the function appearing in eq. (13) of the main text. For the special case $P(\theta,0) = Q(\theta)$ corresponding to $p(x,0) = q(x)$, we have determined the exact solution for $P(\theta,T)$:

$$P(\theta,T) = TQ(\theta)\int_{-\infty}^{\theta}\exp\left(-\eta(\phi)T\right)d\phi \tag{19}$$

where $\eta(\theta) = \int_\theta^\infty (\phi - \theta)\, Q(\phi)\, d\phi = Q(\theta) - (\theta/2)\,\mathrm{erfc}\left(\theta/\sqrt{2}\right)$. In this case, the function $F(T)$ follows by noting that $\theta Q(\theta) = -dQ(\theta)/d\theta$, allowing us to obtain

$$F(T) = T \int Q(\theta) \exp\left(-\eta(\theta) T\right) d\theta. \tag{20}$$

From this result, it follows that $\lim_{T\to 0} F(T)/T = 1$ (eq. (14)). An approximation to $F(T)$ for larger T may be derived as follows. First, noting that $Q(\theta) = d^2\eta(\theta)/d\theta^2$ and integrating by parts in eq. (20) yields $F(T) = T^2 \int \left[d\eta(\theta)/d\theta\right]^2 e^{-\eta(\theta)T} d\theta$. Changing variable of integration from θ to η leads to

$$F(T) = T^2 \int_0^\infty \left(-[d\eta(x)/dx]_{x=\theta(\eta)}\right) e^{-\eta T} d\eta. \tag{21}$$

Since T appears only in the exponential, large T results in only small η contributing to the integral and that for small η, $\left(-[d\eta(x)/dx]_{x=\theta(\eta)}\right)$ approximately depends on η as a power of η. Using $\theta(\eta)$ in the range 2 to 6, corresponding to η in the range 1.5×10^{-10} to 8.5×10^{-3}, we fitted a straight line to $\log(\left(-[d\eta(x)/dx]_{x=\theta(\eta)}\right))$ as a function of $\log(\eta)$: $\log(\left(-[d\eta(x)/dx]_{x=\theta(\eta)}\right)) \simeq a + (B-1)\log(\eta)$ and found $a \simeq 0.88$, $B \simeq 1.95$ so $-[d\eta(x)/dx]_{x=\theta(\eta)} \simeq e^a \eta^{B-1}$. Substitution of this into eq. (21) yields $F(T) \simeq e^a \Gamma(B) T^{2-B}$ where $\Gamma(\cdot)$ denotes Euler's Gamma function and corresponds to eq. (14) of the main text.

More generally, we expect that $F(T) \simeq e^{a(T)} \Gamma(B(T)) T^{2-B(T)}$ where $a(T)$ and $B(T)$ are, on the scale of $T = 10^6$, slowly varying functions of T.