HIGHER-ORDER INTERACTIONS IN FITNESS LANDSCAPES ARE SPARSE

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Research by M. Joswig is partially supported by Einstein Stiftung Berlin and Deutsche Forschungsgemeinschaft (SFB-TRR 195: “Symbolic Tools in Mathematics and their Application” and GRK 2434: “Facets of Complexity”).

W.B. Ludington acknowledges support from NIH grant DP5OD017851.
Abstract. Biological fitness arises from interactions between molecules, genes, and organisms. To discover the causative mechanisms of this complexity, we must differentiate the significant interactions from a large number of possibilities. Epistasis is the standard way to identify interactions in fitness landscapes. However, this intuitive approach breaks down in higher dimensions for example because the sign of epistasis takes on an arbitrary meaning, and the false discovery rate becomes high. These limitations make it difficult to evaluate the role of epistasis in higher dimensions. Here we develop epistatic filtrations, a dimensionally-normalized approach to define fitness landscape topography for higher dimensional spaces. We apply the method to higher-dimensional datasets from genetics and the gut microbiome. This reveals a sparse higher-order structure that often arises from lower-order. Despite sparsity, these higher-order effects carry significant effects on biological fitness and are consequential for ecology and evolution.

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1. INTRODUCTION

Life is an emergent property of interactions between many components at many different scales, including genes, molecules, and organisms. A major difficulty has been to identify the causal interactions that drive this complexity. In particular, pairwise interactions capture only a subset of complexity, and it is difficult to differentiate the influence of pairwise from higher order interactions, which can be indirect or context-dependent [54]. This problem occurs in genetics [54, 32], ecology [10, 7, 22], and other disciplines where an underlying network structure drives the system properties. Determining biologically significant structures in the network is important for our understanding of cells, organisms, ecology, and evolution.

Epistasis is a standard quantitative framework used to dissect biological interactions, particularly in genetics. Epistasis defines local features of a fitness landscape, allowing prediction of evolutionary trajectories through genomic space [52]. Applying epistasis to genome-wide measurement of pairwise [14, 11] and three-way [32] genetic interactions has revealed biochemical pathways composed of discrete sets of genes as well as complex traits, such
as human height, which are affected by almost every gene in the genome [35, 8], and new techniques allow epistasis to be applied to broader data types [56]. At a different scale, microbiomes are cellular ecosystems that play critical roles in global nutrient cycles as well as animal and plant fitness [31]. Despite their importance, we still lack mechanistic understanding of how microbiomes function as collective units through interactions between separate species. Systematic measurements of microbiomes indicate that pairwise interactions are common and have functional consequences [39, 18, 21, 47, 38, 44]. Quantitative formulations of ecosystem and microbiome interactions in some cases are mathematically equivalent to certain formulations of genetic epistasis, e.g. [10, 7]; both are rooted in the basic notion of additivity.

Interactions can occur in more than two dimensions in genetics [55, 43], microbiomes [21, 44] and ecosystems [10, 7, 2, 22]. However, the structure of these interactions, in terms of their geometric dimensions and context remains obscure. For instance, higher-order genetic interactions, involving more than two genetic loci, could require a specific genetic background to affect fitness. Such scenarios are relevant in nature where sex, recombination, and horizontal gene transfers bring groups of genes together. Likewise in the microbiome, a 3-species interaction could occur only when a fourth species is present e.g. when crossfeeding completes a specific biochemical pathway. Like in the genetic case of sex, microbiome community assembly may involve merges between groups of species rather than single stepwise introduction of individuals. More complex possibilities also exist, and these lead to several different concepts of high-order epistasis in the literature. However, current approaches are limited by (1) a lack of mathematical tools that account for genomic context, (2) the false discovery rate, which increases drastically in more than three dimensions [13, 4], and (3) the sign of epistasis, which does not generalize well to more than two dimensions. Sign differentiates peaks from valleys in a fitness landscape, but these concepts become unintuitive or arbitrary in high dimensions because a greater variety of shapes than peak and valley are possible. Standard epistasis frameworks also rely on parameter fitting, which brings along additional constraints. A key question is how we can define the topography of the interaction space in high dimensions in order to evaluate the structure of biological systems and the importance of higher-order interactions. Higher-order interactions could be prevalent or sparse. They could arise only in specific contexts, making their occurrence fleeting, or they could arise from lower-order interactions, making them predictable and easier to study. Sparse complexity at higher diversity would further necessitate new methods that can identify significant interactions in vast interaction spaces.

Here we develop a new framework, called epistatic filtrations, which solves the problems of context, sign, and false-discovery rate in a form that is consistent across many dimensions. Epistatic filtrations define the topography
of epistatic landscapes in a global sense with a parameter-free approach, using fitness landscapes as input data. The framework is agnostic to specific peaks and valleys, recognizing that these are local features that are inverted depending on one’s perspective. The magnitude of epistatic weight encompasses both. We define epistatic weights by the dimensionally-normalized volume that is spanned by peak and valley based on the triangulation between adjacent loci in a unit dimensional space, where each dimension is a separate biological entity, e.g. a genetic locus or a microbiome species. The triangulation locates maximal interaction cells from within the space of possible interactions. The filtrations then define the landscape structure by iteratively merging adjacent maximal cells, guided by their epistatic weights [16]. A conceptual advantage of this approach over previous ones is that it allows us to ignore the vast majority of possible interactions and focus on the significant ones, as defined by empirical data rather than parameter fits to a preconceived function. Because we dimensionally normalize the epistatic weights, filtrations have consistent meaning across many dimensions. Applying filtrations to data from genetics and microbiomes, we reveal that higher-order interactions with significant effects on organismal fitness are sparsely-distributed, often arise from lower-dimensional interactions, but sometimes arise uniquely in four dimensions.

2. Results

2.1. Shapes of fitness landscapes. Our approach rests on the mathematical theory of linear optimization, convex polyhedra, and regular subdivisions [16]. While our ideas work more generally, to keep this exposition concise we focus on the biallelic case with \( n \geq 2 \) loci. In the geometric framework [4], two interacting loci give rise to four possible genotypes which form the vertices of a square and may be written as vectors of zeros and ones, indicating the absence or the presence of each locus (Fig. 1A) [16, 4]. The phenotypes now lift these points into 3-space, and there is epistasis if these four points do not lie in a common plane, corresponding to the notion of non-additivity. In the traditional model of epistasis for \( n = 2 \) the sign of the epistasis indicates the relative position of the lifted double mutant with respect to the plane \( W \) spanned by the lifted genotypes of the wild type and the two single mutants. If the lifted double mutant lies above the plane \( W \), then the sign is positive, and if the lifted double mutant lies below \( W \) the sign is negative. It is worth noting that geometrically the four genotypes involved are fully symmetric. That is to say, the sign of the epistasis for \( n = 2 \) is relative to the choice of a coordinate system which comes from picking the plane \( W \) containing the lifted wild type.

These concepts generalize to higher dimensions, where three or more loci are involved. However, the geometric situation becomes much more rich as there are more “shapes” of one interaction. As one of the consequences, it becomes difficult (or undesirable) to consistently choose signs in higher
Higher-order interactions in fitness landscapes are sparse

dimensions. We now explain our setup and come back to comparing with
the traditional case \( n = 2 \) later.

Geometrically, the genotypes form the \( 2^n \) vertices of the unit cube \([0,1]^n\),
which is an example of a convex polytope. In the subsequent explanation,
the words genotypes and vertices are used interchangeably. A phenotypic
trait is then expressed by a fitness function \( h \) which assigns some mea-
surement \( h(v) \in \mathbb{R} \) to each genotype \( v \). By appending the real number
\( h(v) \) as an additional coordinate the phenotype gives rise to a lifted point
\((v, h(v)) \in \mathbb{R}^{n+1}\). Taking the upper convex hull of all \( 2^n \) lifted points and
projecting back onto the genotope \([0,1]^n\) induces a
subdivision \( S(h) \); cf. \([16, \S 2.1], [15]\), into maximal cells. Generically, every maximal cell of
\( S(h) \) is an \( n \)-dimensional simplex which is the convex hull of \((n+1)\) affinely independent genotypes (Fig. 1B). Importantly, these \( n \)-dimensional simplices are
the most elementary parts into which a fitness landscape can naturally be
decomposed. Studying adjacent simplices and their neighboring relations,
as we propose below, allows reconstruction of the fitness landscape and its
epistatic properties.

2.2. Epistatic weights and bipyramids. Here we study a special type
of interaction called a bipyramid, where two satellite vertices are joined
to a common set of base vertices. This is naturally associated with \( S(h) \)
as we will explain below. For an ordered sequence of \( n+2 \) genotypes
\((v^{(1)}, v^{(2)}, \ldots, v^{(n+2)})\) we let

\[
s = \text{conv}\{v^{(1)}, \ldots, v^{(n+1)}\} \quad \text{and} \quad t = \text{conv}\{v^{(2)}, \ldots, v^{(n+2)}\}.
\]

In other words, \( s \) and \( t \) form convex hulls. We call such a pair \((s, t)\) a
bipyramid with vertices \( v^{(1)}, v^{(2)}, \ldots, v^{(n+2)} \). Then we can find the volume
of the lifted bipyramid by forming the \((n+2) \times (n+2)\)-matrix

\[
E_h(s, t) := \begin{pmatrix}
1 & v_{1,1} & v_{1,2} & \cdots & v_{1,n} & h(v^{(1)}) \\
1 & v_{2,1} & v_{2,2} & \cdots & v_{2,n} & h(v^{(2)}) \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
1 & v_{n+1,1} & v_{n+1,2} & \cdots & v_{n+1,n} & h(v^{(n+1)}) \\
1 & v_{n+2,1} & v_{n+2,2} & \cdots & v_{n+2,n} & h(v^{(n+2)})
\end{pmatrix},
\]

where \( v_{i,j} \) are the coordinates of \( v^{(i)} \in \mathbb{R}^n \). The epistatic
weight of the bipyramid \((s, t)\) is the number

\[
e_h(s, t) := |\det E_h(s, t)| \cdot \frac{n\text{vol}(s \cap t)}{n\text{vol}(s) \cdot n\text{vol}(t)}.
\]

Here \( n\text{vol} \) denotes the dimensionally normalized volume. For instance, \( n\text{vol}(s) \)
is the absolute value of the determinant of the submatrix \( N(s) \) obtained
from \( E_h(s, t) \) by omitting the last column and the last row. Similarly,
\( n\text{vol}(t) \) equals the absolute determinant of \( N(t) \), which is the submatrix of
\( E_h(s, t) \) obtained by omitting the last column and the first row. The quantity
\( n\text{vol}(s \cap t) \) is the relative \((n-1)\)-dimensional normalized volume of the ridge
of the bipyramid, given by the intersection \( s \cap t = \text{conv}(v^{(2)}, \ldots, v^{(n+1)}) \).
Figure 1. **Filtrations describe epistatic topography.** (A) Cartoon of a \([0,1]^2, h)\) system. The upper hull of the lifted points forms a ridge which passes through the peak of the fitness landscape. The lower hull forms a valley. The volume (blue) is agnostic to “peak” or “valley”. The induced triangulation of the genotope (green) divides the lifted points into cells, which are then merged in the filtration. (B) Cartoon of a triangulation of a (lifted) 3-cube. (C) Dual graph of the 3-cube triangulation from the Khan data set [30] restricted to mutations in *topA*, *spoT*, and *pykF*. Fitness \(h\) is defined by the following normalized values (genotype \(\mapsto\) phenotype):

\[
\begin{align*}
000 &\mapsto 0.1524 & 100 &\mapsto 0.1745 & 010 &\mapsto 0.1689 & 001 &\mapsto 0.1528 \\
110 &\mapsto 0.1842 & 101 &\mapsto 0.1823 & 011 &\mapsto 0.1810 & 111 &\mapsto 0.1956 \\
\end{align*}
\]

As in (B) the triangulation \(\mathcal{S}(h)\) has six maximal cells:

\[
\begin{align*}
A &= \{100, 010, 110, 011\}; & B &= \{000, 100, 010, 011\}; & C &= \{000, 100, 101, 011\}; \\
D &= \{000, 001, 101, 011\}; & E &= \{100, 101, 011, 111\}; & F &= \{100, 110, 011, 111\}. \\
\end{align*}
\]

(C Inset) Each dual edge has two parameters: its epistatic weight (indicated by shade) and its \(p\)-value (indicated by color). Black indices in (C) label the critical dual edges of \(\mathcal{S}(h)\). (D) Epistatic filtration shows the sequence of merges between adjacent simplices that change the partition of the maximal simplices in the dual graph. Note the C+E merge is not depicted in the filtration because these simplices are already merged through F, A, and B.
In the formula (2) it only matters to keep track of the first and the last genotype (which form the satellites); the ordering of the \( n \) remaining ones (spanning the ridge) is irrelevant. Hence we also use the notation

\[
\{v^{(1)}\} + \{v^{(2)}, \ldots, v^{(n+1)}\} + \{v^{(n+2)}\}
\]

for the bipyramid \((s, t)\). Now the \( n + 2 \) genotypes of the bipyramid form an interaction of dimension \( n \) if and only if \( e_h(s, t) > 0 \). While our definition of epistatic weights allows us to compare interactions across the entire genotype, we seek to select the biologically significant interactions from among the vast number of bipyramids.

**Remark.** Our approach is different from the analysis of higher-order interactions via circuits as suggested in [4]. Most circuits give rise to bipyramids. The total number of circuits grows dramatically with the number of loci, and the bipyramids among them form a larger and larger fraction; cf. Table 1. The large number of comparisons in itself makes it difficult to detect any relevant interactions of higher order. However, the triangulation \( S(h) \) serves as a tool to reduce the number of interactions to a set that are relevant based on measured biological fitness.

Table 1. Number \( c(n) \) of circuits of \([0,1]^n\) and number \( b(n) \) of bipyramids among these.

| \( n \) | \( c(n) \) | \( b(n) \) | Percentage |
|-------|----------|----------|------------|
| 2     | 1        | 1        | 100.00%    |
| 3     | 20       | 8        | 40.00%     |
| 4     | 1348     | 1088     | 80.71%     |
| 5     | 353616   | 309056   | 87.40%     |

2.3. **Epistatic landscapes and epistatic filtrations.** In our regular triangulation \( S(h) \), the two \( n \)-dimensional simplices, \( s \) and \( t \), are adjacent because their intersection \( s \cap t \) is a common face of dimension \( n - 1 \).

We can give epistatic weights a visual description by forming a dual graph of \( S(h) \), where the nodes are the maximal simplices, and adjacent simplices form the dual edges. To each such dual edge we associate an epistatic weight and a label (Fig. 1C, epistatic weights are in shades of blue and red, while labels are in black). We call a dual graph with edges weighted by epistatic weights an epistatic landscape. In this way, epistatic landscapes corresponds to the underlying fitness landscape with a ruggedness measure specified along each possible path in the dual graph.

The dual graph of \( S(h) \) and its epistatic weights are further processed by forming a diagram that we call the epistatic filtration of \( h \) (Fig. 1D). These diagrams summarize the information contained in epistatic weights and dual graphs, and facilitate comparisons across data sets. But there is important new information contained in epistatic filtrations, which is not
directly visible from the dual graph and its epistatic weights. Indeed, a step in the epistatic filtration merges adjacent simplices. In this way, we obtain a stepwise procedure to build and analyse the whole fitness landscape starting from a pair of adjacent simplices (those that give rise to the lowest epistatic weight) and stepwise merge adjacent simplices to it. The portions of fitness landscape one obtains in this way were called clusters in [16]. In this sense, epistatic filtrations encode a global notion of epistasis.

To see this, notice that each row of the diagram has a number of bars and a black leftmost line. In the top row the black line marks the epistatic weight of zero ($x$-coordinate). Each bar is red and corresponds to one maximal simplex of $\mathcal{S}(h)$. In the second row (counting from the top), we see three things: (1) the value of the lowest epistatic weight moves the $x$-coordinate of the black line slightly to the right. (2) The two maximal simplices of $\mathcal{S}(h)$ corresponding to this epistatic weight are merged into one. These correspond to the two bars in the previous row above the new, longer bar in the row. The lengths of the other bars remain unchanged but are shifted horizontally by the epistatic weight in (1). (3) The statistical significance of the epistatic weight giving rise to the merging step, encoded by the colors of the bars; cf. Section 2.5.

The merging procedure is then repeated for each pair of maximal simplices arising in each epistatic weight until one reaches the highest epistatic weight and the last maximal simplex of $\mathcal{S}(h)$ to be merged with the rest. In this way the indentation of the bar charts increases from top to bottom. The total width of the bars stays constant throughout.

Importantly, in the epistatic filtration diagram, not every merging step is displayed; e.g., in Fig. 1D there are fewer rows than dual edges in Fig. 1C. This is because some steps do not change the resulting fitness landscape (no actual new portion is merged to the previous one). The reported steps are only the ones increasing the connected components of the fitness landscape obtained from the previous merging steps. The epistatic weights corresponding to these steps are the edges in the dual graph which we call critical in [16, §3.2].

2.4. Normalized epistatic weights. To gain a perspective on the generality of higher-order interactions, it is desirable to compare epistatic landscapes. Different phenotypes have different metrics, making comparisons difficult for current approaches to epistasis. Filtrations are well-suited in this sense. Scaling the height function $h$ by a positive constant does not change the regular triangulation, and thus it does not change the dual graph. In order to compare different data sets, we scale the height function to Euclidean norm one. The epistatic weights are scaled accordingly. The resulting normalized epistatic weights are measured in epistatic units, giving a generalized metric for epistasis.

Measuring the effect of context on epistatic interactions is also desirable, e.g. to detect the marginal or conditional effects of a locus [30], and these are
a natural feature of filtrations. If we fix some \( k \) loci and let the remaining \( n - k \) loci vary, we obtain a height function which is restricted to a face of the genotope \([0, 1]^n\). That face has \(2^{n-k}\) vertices, and it is an isomorphic copy of the cube \([0, 1]^{n-k}\). For instance, if \( n = 5 \) and we fix the first and the fourth locus to 0, we obtain a 3-dimensional face which we denote \(0**0\). That is, such a face is written as a string of \( n \) symbols in the alphabet \(\{0, 1, *\}\), where 0 or 1 mark the fixed choices, and * stands for variation. The number of * symbols equals the dimension of the face. Triangulations, their dual graphs, epistatic weights, etc. are well-defined for height functions restricted to faces. This aspect of the theory allows the study of conditional epistatic effects.

2.5. **Statistics of epistatic weights.** Most importantly, our setup allows one to take statistical issues into account. Here we assume that \( h(v) \) is the mean value of the individual measurements for some number of replicated experiments for the fixed genotype \( v \). We developed a statistical test to quantify the significance of an interaction associated with a fixed bipyramid; cf. \([16, \S 4.2]\). As a consequence, to each dual edge we associate a \( p \)-value, which is independent of the epistatic weight normalization. If that \( p \)-value is below 0.05 we call that dual edge **significant**. It is useful to also consider \( p \)-values which are slightly higher. To this end we call a dual edge **semi-significant** if \( 0.05 \leq p < 0.1 \).

While it may be possible that this approach misses some biologically relevant interactions (e.g. if they do not correspond to a bipyramid selected by our method), those interactions that we identify as significant carry information which is robust and supported by a statistical model. The fact that not all possible interactions can be approached is an inevitable consequence of the higher dimensional nature of fitness landscapes, also reflected by a very high number of possible regular triangulations of \([0, 1]^n\). That number equals 74 for \( n = 3 \) and 87,959,448 for \( n = 4 \), whereas the precise numbers for \( n \geq 5 \) are unknown; cf. \([15, \S 6.3]\). Thus, filtrations use the data to greatly condense the number of possible interactions considered.

The bar colorings in the filtrations of epistatic weights, as in Fig. 17, reflect the outcome of multiple simultaneous statistical tests (one for each epistatic weight) \([16]\).

Significant dual edges at \( p < 0.05 \) are shown in blue, \( 0.05 \leq p < 0.1 \) in purple, and \( p \geq 0.1 \) in red.

It may happen that a triangulation has a significant dual edge which is not critical, whence it does not show in the epistatic filtration. In that case the next critical dual edge becomes blue; so a filtration encodes all significant interactions found by our method.

**Remark.** It would be possible to apply false discovery rate controlling procedures to our statistical analysis of significant epistatic weights. In this work, however, we refrain from doing so for the following reasons: (1) We are interested in providing methods to filter epistatic weights and reflect
on the biological implications of these methods. These methods build on continuous filtrations, rather than on discrete classifications of statistical significant outcomes. (2) The known procedures to adjust \( p \)-values are not sensitive to the geometric nature of our methods. Therefore, controlling the false discovery rate does not add certitude to the biological implications. (3) Comparing filtrations and epistatic weights with linear regression outcomes yields a relevant approach to validate statistically significant findings (or the lack thereof), as discussed in Section A.6.

2.6. An evolutionary genetics example of epistatic filtrations. To illustrate our approach, we examined an existing data set from Lenski’s [3] classic experimental evolution of *Escherichia coli*. In this data set, Khan *et al* [30] produced each combination of five mutations that each individually increased the fitness of the strain. To explain our approach, we first examine \( n = 3 \) loci, corresponding to biallelic mutations in *topA*, *spoT*, and *pykF* (Fig. 1). Here, we detected epistasis which is generally low in magnitude, in agreement with previous reports [30, 42].

In this analysis, epistasis can occur in two ways: either from merging groups of cells (e.g. BC + AFE induced by the dual edge 2) or from merging a single cell, e.g. D, with the aggregated rest of the cells (induced by the dual edge 1 of highest epistatic weight) (Fig. 1D). We next considered the same set of loci with a fourth biallelic mutation in the *glmUS* locus, encoding peptidoglycan availability, which is an essential component of the cell wall (Fig. 2).

The filtration reveals a distributed, sparse network: there is one dominant cluster that arises from step-wise merges such that the epistatic weights of each of the merges are negligible, except for the final step of the filtration. In the final step, our analysis identifies a specific set of genotypes where epistasis arises in the final merge of the filtration through the bipyramid

\[
\{00001\} + \{00000, 01001, 00101, 00011\} + \{00010\}.
\]

This merge constitutes a vertex split [25], meaning the epistatic structure of the entire landscape rests upon the single vertex, 00001, which is clearly separated from the rest. While the previous analysis detected a significant marginal effect of *pykF*, filtrations reveal the geometric structure in terms of which specific combinations of loci are responsible for the effect. This maximal cell indicates that the interaction between the *glmUS* and *pykF* genes is significant in the context of the wildtype and double mutants in *topA*, *spoT*, and *glmUS* with *pykF*. Thus, the interaction occurs between two genes and requires the context of four dimensions, yet it involves only up to double mutants. Such a conclusion is consistent with recent genome-wide work on trans-gene interactions [35], suggesting that complex traits may arise from genome-wide epistasis, where each mutation’s contribution to the trait depends on the context of other mutations. Filtrations can thus reveal the specific geometric structure of both the interactions and the context they rely upon.
2.7. The epistatic landscape within a single enzyme is rugged. As a point of comparison, we re-analyzed data from a combinatorially complete 5-mutation data set in the β-lactamase gene, where each mutation is in a separate residue of the same enzyme [49, 52]. Two studies quantified the fitness of these mutants, and we analyze Tan et al [49] here. Epistatic effects are expected to be strong because mutations change the physical interactions between sectors of the protein (e.g. [23, 49]). Due to a lack of the raw replicate data, our computations are based on the reported mean values, and p-values are not calculated. Overall, the filtration holds a high level of epistasis (Fig. 10, 9) compared with the Khan data set (Fig. 8); note the magnitudes on the x-axis. The epistasis arises in many steps (note slope of filtration on left side; (Fig. 10, 9)), consistent with the low number of possible evolutionary paths observed by Weinreich [52]. Our geometric approach also reveals a tiered structure to the epistasis, e.g. the largest weight merges two clusters of maximal cells (Fig. 10, 9), indicating a more complex epistatic landscape than the Khan data set, where epistasis came from one individual cell on the periphery of the dual graph. Allosteric interactions within the β-lactamase enzyme, e.g. similar to sectors in serine proteases [23], could be one possible explanation for the differences between the data sets. While these are just two data sets, the stark contrast in the epistatic landscapes suggests that ruggedness may occur at different biological scales, e.g. molecules vs gene networks, and involve different numbers of dimensions and magnitudes.

2.8. Microbiome interactions produce rugged landscapes. We next applied filtrations at a larger scale to ask how microbiome interactions structure host fitness. Like the genome, which is composed of many genes that interact to determine organismal fitness, the microbiome is also composed of many smaller units (bacterial species in this case) that affect host fitness. Hosts are known to select and maintain a certain core set of microbes [34, 41] and the interactions of these bacteria can affect host fitness [21], although it is debated to what extent these interactions are of higher-order, e.g. [18]. While vertebrates have a gut taxonomic diversity on the order of 1000 species, precluding combinatorially complete datasets, the laboratory fruit fly, Drosophila melanogaster, has naturally low diversity of 5 stably associated species [36]. We previously performed a biological experiment to dissect the D. melanogaster gut microbiome, examining the role of each gut bacterial species alone and in combination with the others. We found that interactions are prevalent, with large effects on host fitness [21, 16]. Here, we repeated our biological experiment to generate a second D. melanogaster gut microbiome dataset; we examine both sets here. We refer to these data sets by their first author (e.g. Eble for the present work and Gould for [21]). We made gnotobiotic flies inoculated with each combination of a set of n = 5 bacteria (2^5 = 32 combinations), consisting of two members of the Lactobacillus genus (L. plantarum and L. brevis) and three members of the Acetobacter genus. We measured fly lifespan, which we previously identified
as a reproducible phenotype that is changed by the microbiome [21]. Overall a reduction of microbial diversity (number of species) led to an increase in fly lifespan [21].

The epistatic landscape for the microbiome data sets shared aspects of the rugged Tan data with respect to complexity and epistatic weight. In terms of complexity, epistasis was concentrated at the center of the dual graph, with merges between clusters of maximal cells providing the bulk of the epistatic weights (Fig. 3A). This is consistent with [21], where interactions between bacteria rather than the individual species were found to make outsized impacts on the host fly lifespan. Furthermore, when examining the dual graph and filtration for the complete 5-species landscape, there were many significant, non-critical edges distributed throughout the graph (Fig. 12), which contrasts starkly with the Khan data (Fig. 17). Examining the filtration (Fig. 3B), the epistatic weight (i.e. magnitude) for the microbiome data generated $\approx 5\%$ effect, roughly three times the weight in the Khan data and half that in the Tan landscapes (compare x-axis between Figs. 3, 8 and 9. Together these results demonstrate that microbiome interactions can have comparable effects to genetic interactions.

2.9. Context changes biological interactions. Interactions can change under different conditions such as different genetic backgrounds [30, 42], bacterial species [21], or different environments [49]. This context-dependence can be an important source of higher-order interactions. We developed a consistent framework using filtrations to quantify changes in the epistatic topography induced by different conditions, a feature of filtrations that is analogous to conditional or marginal epistasis [20]. In [16, §6.6] we introduced this concept of parallel transport to compare filtrations for the same set of loci with different bystanders (e.g. species or genes) (see Figs. 9, 10). We first checked that our methods recapitulate those observed using marginal epistasis. For instance, \textit{E. coli} with and without the \textit{pykF} mutation [30] (Fig. 15) found an increased significance in 9 out of 20 of the dual edges (Fig. 15), when \textit{pykF} was mutated. Parallel transport produces two filtrations, one from ****0 to ****1 (mutating \textit{pykF}) and one from ****1 to ****0 (restoring \textit{pykF}). Examining the restoration of \textit{pykF} (Fig. 16), only 3 of 22 edges changed significance and just one critical edge lost significance, indicating that the epistasis in this case occurs because the mutation forms new interactions. This change in the epistatic landscape caused by this mutation could be the basis for its evolution during the Lenski experiment [3]. Parallel transports make this change in the epistatic landscape apparent, whereas it cannot be observed from standard marginal effect analysis. Examining the other mutations, \textit{glmUS} also has strong effects. Specifically, reversion to wildtype increases the number of interactions, while relatively few interactions are observed in the wildtype filtration. This difference indicates that the parallel interactions are only significant in the context of the
mutant \textit{glmUS} phenotypes, which emphasizes the importance of context in epistasis.

We next applied parallel transport to the microbiome fitness landscape. Bystander species play important roles in the microbiome for instance they can either prevent or facilitate \textit{Clostridium difficile} infection after taking antibiotics [37]. In \textit{D. melanogaster}, \textit{Acetobacter-Lactobacillus} interactions are known to influence health, behavior, and fitness [12, 24, 21]. Furthermore, \textit{Lactobacilli} are well-established as probiotics in human health, thus we focused on the contextual effect of adding or removing \textit{L. plantarum} and \textit{L. brevis} (Fig. 3).

In Fig. 3C, the filtration of epistatic weights after the parallel transport to the setting where \textit{L. plantarum} is present are displayed. Adjacent to it is the filtration Fig. 3B associated to the microbiome fitness landscape when the bacteria \textit{L. plantarum} is absent, above in Fig. 3A the dual graph associated to this fitness landscape is represented. The interactions which emphasize the importance of the bacterial context are apparent from the rows that change color between the originating filtration (Fig. 3B) and the parallel one (Fig. 3C). Note that significant dual edges in the parallel transport often arise proximal to significant edges in the originating filtration, e.g. 20 and 21 are proximal to critical significant edges 1 and 2 as well as adjacent to non-critical significant edges (Fig. 3A). In this particular case, the congruence between the originating filtration and the parallel transport with \textit{L. plantarum} as a bystander indicates a weak effect of context. Examining the effect of \textit{Lactobacilli} more comprehensively, we found that 46 out of 128 (36\%) of interactions changed significance due to adding or removing a \textit{Lactobacillus} (Figs. 26, 27, 28, 29). \textit{L. brevis} accounted for the majority of these effects (31 of 66, 47\%) (Figs. 28, 29), indicating it has stronger interactions than \textit{L. plantarum}. These changes in significance primarily derive from non-significant interactions when \textit{L. brevis} is present that become significant when it is removed and vice versa, indicating the context of \textit{L. brevis} serves to suppress epistatic interactions that affect fly lifespan. A similar yet weaker effect occurs from removing \textit{L. plantarum} (Fig. 26). Taken together, these analyses indicate a significant effect of \textit{Lactobacillus} interactions on fly lifespan.

Microbiome interactions are important because they shape host fitness through differential effects on development, fecundity, and lifespan [21]. Interactions also affect microbial abundances. As noted previously, in flies, interactions between \textit{Lactobacillus} and \textit{Acetobacter} are known to increase bacterial abundances [1, 12, 24], and increased bacterial abundances are linked to faster fly aging [21]. A simple hypothesis is that microbiome abundance is supported by the same interaction structure as host fitness. The hypothesis was supported by comparing each possible interaction test between the phenotypes of microbiome abundance and fly lifespan, which yielded a correlation in the interaction scores [21]. However, a minority of interactions drove the correlation, corresponding to the largest values. We used parallel
transport to compare the global shapes between the two epistatic landscapes and found that only 2 of 99 dual edges were significant in both the bacterial abundance and fly lifespan data sets (Figs. 30, 31, 32, 33, Table 14, 15, 16, 17), and there was a lack of correlation between the epistatic weights of the bipyramids for any of the landscapes (Spearman rank correlations: \( p = 0.7 \), \( p = 0.5 \), \( p = 0.3 \), \( p = 0.3 \)), indicating that while many specific interactions drive the previously observed correlations [21], these are not reflected in the global landscapes. This discord between local and global scales merits further study, and we note that it could not be observed without a method such as parallel transport that can compare global landscapes.

To examine the global effect of context across the datasets, we developed an additional method, which we call path epistasis [Appendix A.4]. This model considers the triangulation of the dual landscapes and forms their filtration, which assesses the total epistatic weight, giving a comparative metric across data sets (Figs. 18, 19, 20, 21, 22, 23). From this comparison, we see that the Tan data set for \( \beta \)-lactamase carries much higher context-dependence than either the microbiome or \( E. \) coli evolution data sets, which likely is due to the overall higher rugosity in the Tan data.

2.10. Higher-order interactions are sparse. The prevalence and importance of higher-order interactions is debated, with some studies suggesting pairwise interactions predict the vast majority of interactions between more species [18], and others suggesting a large influence of context-dependent effects [21] [48], which would make higher-order interactions unpredictable. As we showed in the previous section, context-dependence is prevalent in the microbiome. Here, we used epistatic filtrations to evaluate higher-order interactions across the Khan, Gould, and Eble data sets by analyzing all faces of the 5-cube in each case (note Tan data is excluded because \( p \)-values cannot be calculated). Our results reveal that critical, significant higher-order interactions are sparse, with a decreasing probability as the face dimension increases (Fig. 4). This occurs for three reasons. First, since the number of possible interactions increases with the dimension of the genotope, the probability of selecting a specific one from the set of all possible interactions decreases. Second, the absolute number of these interactions also decreases in higher dimensions (Table 2). Third, effects of measurement imprecisions associated to experimental data become more apparent in higher-order interactions and this affects the results in our significance tests (compare with the simulation results of Fig. 6B). Overall, only \( \approx 10\% \) of possible dual edges were significant at higher order (Table 2), indicating that few such interactions are biologically meaningful in the context of fitness.

This could arise due to e.g. limited phenotypic dimensions where interactions can be detected or to a lower dimensional manifold that absorbs the majority of the effects [26]. Regardless, significant epistatic interactions are increasingly sparse at higher order.
But these few interactions are not meaningless. They can and do impact fitness. For example, the two top 4-dimensional interactions in the Eble microbiome data produce a > 9% effect on fitness (see edges 1 and 2 in Fig. 3) with the largest maximal cell accounting for ≈ 5%. The relative sparsity makes for a tractable number of these interactions, where we may eventually determine the mechanisms.

Similar occurrences of higher-order interactions occur in the Khan genetic data (Table 2). However, the critical edge of highest epistatic weight (labeled 1 in Fig. 2) induces a vertex split of the genotype 00001, meaning that the entire epistatic weight of the landscape is balanced by a single maximal cell, as we previously noted.

In contrast, the epistatic filtration of the microbiome data in Fig. 3 has a much richer texture. There are two significant bipyramids given with their epistatic weights and edge id’s, which form a cluster of interactions, indicating a larger topographic feature in the epistatic landscape that relates the interactions between \( L. \ brevis \) and increasing numbers of \( Acetobacters \). Proximal to these significant cells are two cells with nearly significant statistical support:

\[
\{01011\} + \{00000,01000,01011,01111\} + \{01100\} \quad 0.0451 \quad \#8
\]
\[
\{01011\} + \{00000,01000,01011,01111\} + \{01101\} \quad 0.0485 \quad \#7
\]

with their edge id’s (Fig. 3). This invites further research on the bacteria involved. For instance, the interactions could derive from metabolic crossfeeding between the \( Acetobacters \), which produce many co-factors, and \( L. \ brevis \), which acidifies the media through lactate production, stimulating \( Acetobacter \) growth [1]. Note that the support sets for all four interactions contain the wild type 00000 as well as the genotype 01111, which are the maximum and minimum fitness respectively.

Table 2. Prevalence of interactions at different levels of complexity in genetics and microbiome data sets. Significant versus all critical dual edges (p < 0.05).

| Interaction dimension | Dataset: Khan | Dataset: Eble | Dataset: Gould |
|-----------------------|--------------|---------------|---------------|
| 2:                    | 20/80 (25%)  | 24/80 (30%)   | 22/80 (28%)   |
| all higher order:     | 29/508 (5.7%)| 58/540 (10%)  | 21/520 (4.0%) |
| 3:                    | 21/194 (11%) | 35/199 (17%)  | 14/194 (7.2%) |
| 4:                    | 7/214 (3.2%) | 22/226 (10%)  | 6/216 (2.7%)  |
| 5:                    | 1/100 (1.0%) | 1/115 (0.8%)  | 1/110 (0.9%)  |
| total:                | 49/588 (8.3%)| 82/620 (13%)  | 43/600 (7.1%) |
2.11. Higher-order interactions can arise due to amplification of lower-order interactions. The notion of a higher-order interaction suggests a system behavior that emerges when all components are present. Emergent properties can also occur through the modulation of the behavior of individual components. For example, the cooperative binding of transcription factors can generate a non-linear activation curve, which could numerically be indistinguishable from other types of interaction. Techniques have been devised to identify and exclude these effects [42]. Alternatively, the introduction of new components could also produce emergent behaviors that only occur when all of the correct components are present. For example, effective cellulose degradation cannot occur until a lignin degrader is present, but addition of such a species would greatly enhance the growth of the resultant community by making available a new energy source [44]. Distinguishing such possible sources of higher-order effects can help experimentalists hone in on potential mechanisms of interaction.

In examining the higher-order epistasis present in our data sets, we noted that the clusters where significant epistatic weights occur are often preceded by clusters with nearly significant epistatic weights (Fig. 17). We developed a graphical approach to distinguish these interactions from those that arise de novo (Fig. 11B and 11C).

Restricting one height function to faces of various dimensions on the cube $[0,1]^n$, yields many epistatic filtrations. These can be analyzed in a coherent fashion. The example in Fig. 11B refers to the Eble data set, where $n = 5$. The top row shows the epistatic filtrations of the restrictions to the five 4-dimensional faces $0****, *0***, ***0**, ***0* and ****0$. The middle resp. bottom row shows restrictions to several 3-dimensional resp. 2-dimensional faces chosen by the 4-dimensional significant interactions of the top row. The vertical lines between the different filtrations indicate significant higher-order interactions which arise from lower-order interactions as explained in Section A.4.

Interestingly, we found that several higher-order interactions in the Gould and Khan data could not be attributed to lower-order effects (Table 3). In particular, they could not be detected from pairwise interactions of loci. For the Gould data these interactions are highlighted in Fig. 11C. Notably in the Khan genetic data, the 4-dimensional interaction is between $glmUS$ and $pykF$ and involves only up to double mutants in $glmUS$, $pykF$, $topA$ and $spoT$. In the Gould microbiome data, the interactions are more complex, involving up to four species and including genotypes with four species. Dissecting these interactions mechanistically will determine which key functions drive these non-additive effects.
Microbiome interactions at low order can often be explained by simple competition or cooperation [18]. In higher dimensions, we lack simple terminology to describe the many types of microbial interactions that may occur. However, we found that biologically-significant, higher-order interactions are sparse, meaning that a limited number of such interactions exist. Epistatic filtrations allow identification of these higher-order interactions from the vast space of potential interactions and a way to systematically compare the interactions arising (via dual graphs). Epistatic filtrations also allow for a broader interpretation of epistasis: understood either from interactions between groups of genotypes (when groups of cells merge) or from interactions arising by adding a single genotype to a system of genotypes (e.g. a vertex split). Filtrations provide a natural approach to differentiate between global (a.k.a. non-specific) epistasis [45] and specific, higher-order interactions. The methods allow us to focus our efforts on biologically relevant interactions, and this is how we intend they should be used.

A cellular and molecular dissection of any specific interaction is beyond the scope of the present work, but we expect that the interactions involve factors, e.g. gene expression, metabolism, and cell structure, which are all readily accessible using current experimental techniques. We have focused here on combinatorially complete data sets in genetics and the microbiome, demonstrating that higher-order effects are sparse but significant in both types of data. The present methods could be extended, e.g. to GWAS [17, 35, 9], ecosystems [10, 7], or neuronal networks [40], to discover geometric structures at different scales.

Non-linearities of lower-order interactions can also produce higher-order interactions, in the sense of [42]. These previous approaches have established methods to dissect the sources of these effects through the modelling of the non-linear terms. Here we use a geometric approach that detects non-linearities across lifted points.

Epistatic interactions may constrain evolutionary paths or ecological community assembly, if they are prevalent. However, we find they are sparse in high dimensions and also context-dependent. Furthermore, the higher-order interactions are often rooted in lower order. In this respect, our results are consistent with previous findings that 3-way interactions are often predicted from 2-way interactions [18] and similarly in higher dimensions [21]. We speculate that one potential consequence of sparse higher-order interactions is that they change the rate of evolution for certain parts of the fitness landscape, not by blocking paths to higher fitness, but by changing the lengths of paths that have roughly equivalent fitness [28, 29]. Such properties of fitness landscapes could serve to both increase the number of persisting genotypes in a population as well as to perpetuate the time for evolutionary optimization, which has been noted in the Lenski experiment [30]. We provide polymake [19] code and a jupyter notebook with which to
run our analyses on such data sets. It should be noted that the polyhedral geometry methods for analyzing epistasis deserve to be developed further, also from the mathematical point of view. Currently we measure epistasis locally, for specific interactions, and the epistatic filtration is our tool for piecing things together. Yet it would be desirable to additionally have a measure for the “global amount of epistasis”. We believe that concepts of curvature for piecewise linear manifolds will be useful [46].

4. Methods

4.1. Fly husbandry. Flies were reared germ-free and inoculated with one combination of bacteria on day 5 after eclosion. \( N \geq 100 \) flies were assayed for lifespan in \( n \geq 5 \) independent vials per bacterial combination for a total of 3200 individual flies. Food was 10% autoclaved fresh yeast, 5% filter-sterilized glucose, 1.2% agar, and 0.42% propionic acid, pH 4.5. Complete methods are described in Gould et al [21].

4.2. Bacterial cultures. Bacteria were cultured on MRS or MYPL, washed in PBS, standardized to a density of \( 10^7 \) CFU/mL and 50 \( \mu L \) was inoculated onto the fly food. Strains are indicated in Table 5. See Gould et al [21] for complete methods.

4.3. Genetics data. Existing genetics data sets were gotten from Sailer and Harms 2017 [42] github repository (https://github.com/harmslab/epistasis) or from Tan et al [49].

The Tan data set is different from the other fitness values in that only median and mean values are given, meaning we cannot compute \( p \)-values to assess the statistical significance. The fitness values are minimum inhibitory concentrations of antibiotics from a well-standardized assay with little experimental variation. Thus, the measurements and our analysis are believed to be robust.

We note that the regular subdivision resulting from the corresponding height function of \([0,1]^5\) is degenerate in the sense that it is not a triangulation. This degeneracy arises because the data are discrete antibiotic concentrations with 24 possible values. The repetition of exact values in several cases means a triangulation does not occur. We extended our methods to this degenerate case by restricting the analysis to the faces that do have a triangulation; we see it as an advantage that this degeneracy is revealed by our approach. We first focused on the piperacillin with clavanulate data from [49] as it is the better behaved.

4.4. Computational analysis. The filtrations code is available as a polyMAKE [19] package (cf. http://page.math.tu-berlin.de/~eble/filtration.html) and the analysis pipeline is available as a jupyter notebook.
5. Terminology

**Loci** (singular **locus**) refer to individual sites in the genome where a mutation may occur, or in the microbiome sense, a locus is a particular bacterial species. We write $[n] := \{1, \ldots, n\}$ for the set of all loci.

**Genotypes**, $v = (v_1, \ldots, v_n)$, are vectors of loci with 0/1-coordinates that form points in some fixed Euclidean space $\mathbb{R}^n$, where $n$ is the number of genetic loci or bacterial species considered. In this article we focus on **biallelic** $n$-locus systems, i.e. genotype sets of the form $V = \{0,1\}^n$ where $n$ is the number of loci and each locus is either 0, absent, or 1, present. For instance, $v = (1, 0, 1)$ denotes a genotype in a 3-locus system $\mathbb{R}^3$, where the first and third loci are mutant and the second is wild type. The set of all genotypes will be denoted by $V$. The convex hull $P := \text{conv}(V)$ of all genotypes is called the genotope. In our setting $P$ is the $n$-dimensional unit cube $[0,1]^n$.

In our setting $P$ is the $n$-dimensional unit cube $[0,1]^n$ (e.g. see Fig. 5 for a 2D projection of $[0,1]^5$).

A **fitness function** (also called height function) associates to each genotype $v \in V$ a quantified phenotype describing the impact of the genotype on the organism. For example, if the measured phenotype is fitness, $h$ encodes the reproductive output of the genotype.

The **fitness landscape** is the pair $(V, h)$, which defines the fitness $h(v)$ for each genotype $v \in V$. Let $v = (v_1, \ldots, v_n) \in V$ be a genotype. Then its lift is given by $(v, h(v)) = (v_1, \ldots, v_n, h(v)) \in \mathbb{R}^{n+1}$.

A set of points $W = \{w^{(1)}, \ldots, w^{(\ell)}\}$ is **affinely independent** if for all real scalars $\lambda_i$ satisfying $\sum_{i=1}^\ell \lambda_i = 0$ the condition $\sum_{i=1}^\ell \lambda_i w^{(i)} = 0$ forces $\lambda_i = 0$ for all $i \in \{1, \ldots, \ell\}$. Otherwise $W$ is **affinely dependent**.

An **interaction** with respect to a fitness function $h$ occurs between a collection of $k+2$ affinely dependent genotypes $v^{(1)}, \ldots, v^{(k+2)} \in V \subset \mathbb{R}^n$, for $k \leq n$, whose lifts are affinely independent points in $\mathbb{R}^{n+1}$. This is in line with the standard concept of additive epistasis. The number $k$ is the **dimension** of the interaction; throughout we assume that $k \geq 2$.

Let $U = \{v^{(1)}, \ldots, v^{(\ell)}\}$ be a set of genotypes. Its **support** is the set

$$\text{supp}(U) := \left\{ k \in [n] \left| \text{ there are distinct } 1 \leq i, j \leq \ell \text{ with } v^{(i)}_k \neq v^{(j)}_k \right. \right\}.$$

That is, the support is the set of loci where at least two of the given genotypes differ. For example, if $n = 3$ and $U = \{(0,0,0), (1,0,1), (1,0,0)\}$ then supp$(U) = \{1,3\}$.

The number of loci that vary (0 vs 1) in the support is called the **order** of an interaction; this definition agrees with, e.g., [53]: “We designate interactions among any subset of $k$ mutations as $k$th-order epistasis.”. We give two examples: First, let $n = 2$ and $U = \{(0,0), (0,1), (1,0), (1,1)\} = V$ such that $U$ is an interaction with respect to some fitness function. Then $U$ is an interaction of dimension 2 and order 2. Second, let $n = 3$ and
\[ U = \{(0, 0, 0), (0, 1, 1), (1, 0, 0), (1, 1, 1)\} \] such that, again, \( U \) is an interaction with respect to some height function. Then the dimension is 2 and the order is 3. In general, the order is at least as large as the dimension, but the two quantities may differ. We say that genes (corresponding to loci) interact if they form the support set of an interaction of genotypes.

**Remark.** The dimension \( k \) of an interaction \( v^{(1)}, \ldots, v^{(k+2)} \) with respect to some fitness function agrees with the dimension of the affine span of the given points in \( \mathbb{R}^n \). This can be seen as follows. By definition the lifted points \( (v^{(1)}, h(v^{(1)})), \ldots, (v^{(k+2)}, h(v^{(k+2)})) \) are affinely independent in \( \mathbb{R}^{n+1} \). So their affine span has dimension \( k + 1 \). As \( v^{(1)}, \ldots, v^{(k+2)} \) are affinely dependent, the dimension of their affine span is at most \( k \). Now the affine dimension can only increase by at most one if one coordinate is appended.

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Figure 2. Epistasis in bacterial evolution is concentrated. (A) Edge labeled dual graph and (B) epistatic filtration for the Khan data set [30] restricted to $n = 4$ mutations in $topA$ (locus 2), $spoT$ (locus 3), $glmUS$ (locus 4) and $pykF$ (locus 5). Locus 1, $rbs$, is fixed 0 (absent). Note that the left edge of the bars in (B) indicates there is very little epistatic weight added to the filtration for dual edges 2 through 23. The majority of the epistasis emerges in the final step, where the single genotype 00001 gives weight to the entire filtration. This final interaction corresponds to the vertices $\{00001\} + \{00000, 01001, 00101, 00011\} + \{00010\}$. Black indices in (A) label the critical dual edges of $S(h)$. The fitness function $h$ is defined by assigning the following normalized values to the 16 genotypes:

\[
\begin{align*}
00000 & \rightarrow 0.1524 & 01000 & \rightarrow 0.1745 & 00100 & \rightarrow 0.1689 & 00010 & \rightarrow 0.1569 \\
00001 & \rightarrow 0.1528 & 01100 & \rightarrow 0.1842 & 01010 & \rightarrow 0.1756 & 01001 & \rightarrow 0.1823 \\
00110 & \rightarrow 0.1718 & 00101 & \rightarrow 0.1810 & 00011 & \rightarrow 0.1642 & 01110 & \rightarrow 0.1836 \\
01101 & \rightarrow 0.1956 & 01011 & \rightarrow 0.1858 & 00111 & \rightarrow 0.1813 & 01111 & \rightarrow 0.1987 
\end{align*}
\]
Higher-order interactions in fitness landscapes are sparse

Figure 3. Microbiome-host epistasis is complex. The filtration of the Eble data set for microbiome interactions. (A) The dual graph of $S(h)$ for the 4-face, 0-****, where *L. plantarum* is absent, indicates a concentration of epistasis near the middle of the graph, indicating merging of clusters of maximal cells. Indexes label the critical edges. (B) The filtration indicates two sectors generating epistasis, in blue, where $p < 0.05$ and in purple, where $p < 0.1$. These sectors are part of the same region of the dual graph, indicating they share common vertices. (C) Bystander species change interactions. The parallel path for the 4-face 1****, where *L. plantarum* is present, indicates three interactions change significance at the $p < 0.05$ level in this context, two edges becoming significant and one edge losing significance.
Figure 4. **Significant higher-order interactions are sparse.** For each face of the 5-cube, we calculated the fraction of dual edges with significant epistatic weights, indicating a clear decrease with increasing face dimension for all three fitness landscapes under inspection.

Figure 5. **Vertices of the bipyramid** \{00001\} + \{00000, 01001, 00101, 00011\} + \{00010\} arising for the Khan data set [30] **restricted to** \(n = 4\) **loci and discussed in Section 2.6.** Dark blue dots correspond to common face \(s \cap t\) of the bipyramid and light blue dots correspond to the satellite vertices of \(s\) and \(t\).
A.1. A synthetic experiment examining how epistatic weights change as a function of the interaction order. Our method calculates significance of detected interactions and normalizes the epistatic weight to the volume of the unit cube of the same dimensionality. We used synthetic data to analyze the method performance. We first examined 468 synthetic filtrations over the 4-dimensional cube, producing 10011 critical dual edges. We found that the epistatic weight is indeed constant as a function of the interaction order, see Fig. 6A. This indicates that the normalization method is effective. Furthermore, the number of significant interactions decreased as the standard deviation of the input data increased, indicating the statistical method is sensitive to noise, see Fig. 6B.

A.2. A microbiome example in dimension 4.

Here $n = 4$, and the fitness function $h$ is defined by assigning the following values to the 16 genotypes:

\begin{align*}
0000 & \mapsto 0.2484 ; & 1000 & \mapsto 0.2320 ; & 0100 & \mapsto 0.1618 ; & 0010 & \mapsto 0.1698 ; \\
0001 & \mapsto 0.1943 ; & 1100 & \mapsto 0.1749 ; & 1010 & \mapsto 0.1714 ; & 1001 & \mapsto 0.1929 ; \\
0110 & \mapsto 0.1668 ; & 0101 & \mapsto 0.1608 ; & 0011 & \mapsto 0.1617 ; & 1110 & \mapsto 0.1643 ; \\
1101 & \mapsto 0.1677 ; & 1011 & \mapsto 0.1715 ; & 0111 & \mapsto 0.1613 ; & 1111 & \mapsto 0.1594 .
\end{align*}

The vertices $U := \{v^{(1)}, \ldots, v^{(6)}\} \in V$ given by

\begin{align*}
v^{(1)} &= (1, 1, 0, 0) ; & v^{(2)} &= (0, 0, 0, 0) ; & v^{(3)} &= (1, 0, 0, 0) ; \\
v^{(4)} &= (1, 1, 0, 1) ; & v^{(5)} &= (1, 1, 1, 1) ; & v^{(6)} &= (1, 0, 0, 1)
\end{align*}

form a bipyramid $(s, t)$ consisting of 4-dimensional simplices $s$ and $t$ as above. The simplices $s$ and $t$ correspond to nodes in the dual graph of $S(h)$ that share a dual edge recording their adjacency relation as indicated in Fig. 3A.

In this situation, equation (2) reads

\[
e_h(s, t) = \begin{vmatrix}
1 & 1 & 1 & 0 & 0 & 0.1749 \\
1 & 0 & 0 & 0 & 0 & 0.2484 \\
1 & 1 & 0 & 0 & 0 & 0.2320 \\
1 & 1 & 1 & 0 & 1 & 0.1677 \\
1 & 1 & 1 & 1 & 1 & 0.1594 \\
1 & 1 & 0 & 0 & 1 & 0.1929
\end{vmatrix} \cdot \frac{\text{nvol}(s \cap t)}{\text{nvol}(s) \cdot \text{nvol}(t)} = 0.0318 \cdot \frac{\sqrt{2}}{1 \cdot 1} \approx 0.045 .
\]

Since $e_h(s, t) > 0$, the genotype set $U$ defines a 4-dimensional interaction with full support $\{1, 2, 3, 4\}$ and of order 4, according to our terminology of Section 5. With a $p$-value of 0.0005 < 0.05 the significance test established in [16, §4] rejects the zero hypothesis for $e_h(s, t)$ and therefore proves the effect of the interaction $U$ to be significant. We indicate this fact with the color blue both in the dual graph of $S(h)$ in Fig. 3A and in the epistatic filtration of $h$ in Fig. 3B.
This example illustrates the following fact of biological interest. For the bacterial combinations $v^{(1)}, v^{(2)}, \ldots, v^{(6)}$ fitness, given by the fitness function $h$, varies significantly in a non-linear way.

A.3. Parallel transport of epistatic weights. The notion of parallel transport in a fitness landscape $(V, h)$ was introduced in [16, §6.6] as a way to compare geometric and biological information between pairs of parallel facets of the convex polytope $\text{conv } V$. In this work, we extended that notion to include the case of two fitness landscapes, $(V, h_1)$ and $(V, h_2)$, associated to different generic and normalized height functions $h_i : V \to \mathbb{R}, i \in \{1, 2\}$, defined on the same vertex set $V = \{0, 1\}^n$ for some $n \in \mathbb{N}$. To enable meaningful comparisons, we assume that each $h_i$ is normalized and that there is a larger fitness landscape $(W, h)$ with a generic and normalized height function $h : W \to \mathbb{R}$ restricting to $h_1$ and $h_2$ on the parallel facets $V$ in $W$, such that the partition of $\text{conv } W$ induced by $h$ is compatible with the one of $\text{conv } V$ induced by $h_1$, resp. by $h_2$. In this setting, we define normalized epistatic weights as with Eq. (2) with $h$ the normalized height function and $s, t$ any adjacent simplices forming a bipyramid.

Parallel transports enable us to transport epistatic filtrations along the reflection map

$$
\phi : V \to V; v = (v_1, v_2, \ldots, v_n) \mapsto (v'_1, v'_2, \ldots, v'_n),
$$

with $v'_i = 1 - v_k$ if $i = k$ and $v'_i = v_i$ otherwise. More precisely, let $e_{h_1}(s, t)$ be the normalized epistatic weight associated to a bipyramid of $\mathcal{S}(h_1)$ and let $\phi(e_{h_1}(s, t)) := e_{h_2}(\phi(s), \phi(t))$ be the parallel normalized epistatic weight transported by $\phi$. Then the filtration of normalized epistatic weights induces a filtration of parallel normalized epistatic weights. Additionally, to $e_{h_1}(s, t)$ and to $\phi(e_{h_1}(s, t))$ a $p$-value can unambiguously be associated [16, §4.1-4.2]. Notice that by design epistatic filtrations for $\mathcal{S}(h_1)$ only show normalized epistatic weights associated to critical dual edges, defined as in [16]. But normalized epistatic weights and their significance can be defined for all bipyramids including the ones associated to noncritical dual edges. This explains the labelling of the parallel transport tables below. There a row is numbered only if the bipyramid corresponds to a critical dual edge in the dual graph of $\mathcal{S}(h_1)$. Noncritical dual edges whose normalized epistatic weight remains non-significant after the parallel transport are omitted. The normalized epistatic weight before (denoted by $e_o = e_{h_1}(s, t)$) and after (denoted by $e_p = \phi(e_{h_1}(s, t))$) the parallel transport, as well as their $p$-values (denoted by $p_o$ and $p_p$) are also reported, as well as ratios of these quantities.

These parallel transport tables are linked to the epistatic filtration diagrams. Indeed, each numbered row in the table corresponds to the row in the epistatic filtration diagram with the black line set at $e_o$. It also corresponds to the row with black line set at $e_p$ in the parallel transported filtration diagram.
Recall from Section 2.5 that there may be dual edges of the triangulations which are significant but not critical. Since only the critical dual edges are labeled (by the row number in the epistatic filtration), in our tables for parallel transport these show up as unlabelled rows.

Examples for the parallel transport of epistatic filtrations are shown in Figures 7, 8, 9, and 10. The magnitude of the epistasis in the left panels are roughly comparable between data sets due to normalization of the input data. Compare each left panel with its corresponding right panel to observe the relative change in epistasis in the parallel path. Larger changes in epistasis indicate stronger context-dependence of the interaction. For instance, in the first Weinreich comparison Fig. 9, bar 10 in the right panel has a parallel epistasis greater than the original filtration on the left, indicating context-dependence.

A.4. **Product model for path epistasis.** In this section we offer a new methodological framework to simultaneously study fitness landscapes associated to different height functions. We also provide a measure to quantify how much the height function of the combined fitness landscape differs from the sum of the height functions.

Let $U$ and $V$ be point configurations in $\mathbb{R}^m$ and $\mathbb{R}^n$, respectively. We think of these point configurations as two sets of genotypes, which may be distinct or not. If we have height functions $\lambda : U \to \mathbb{R}$ and $\mu : V \to \mathbb{R}$, then taking the sum $\lambda + \mu$ point-wise yields a lifting function of the product $U \times V \subset \mathbb{R}^{m+n}$. The cells of the regular subdivision $S_{U \times V}(\lambda + \mu)$ are products of cells of $S_U(\lambda)$ with cells of $S_V(\mu)$. In particular, if $\lambda$ and $\mu$ are generic, i.e., $S_U(\lambda)$ and $S_V(\mu)$ are triangulations, then the cells of $S_{U \times V}(\lambda + \mu)$ are products of simplices.

Now we consider an arbitrary height function $\nu : U \times V \to \mathbb{R}$ on the product of the point configurations. This yields height functions $\nu_U : U \to \mathbb{R}, \ u \mapsto \frac{1}{\ell} \sum_{v \in V} \nu(u, v)$ and $\nu_V : V \to \mathbb{R}, \ v \mapsto \frac{1}{k} \sum_{u \in U} \nu(p, q)$, where $k = \#U$, $\ell = \#V$, $u$ is a vertex in $U$ and $v$ is a vertex in $V$.

Further we define $\nu' : U \times V, \ (u, v) \mapsto \nu(u, v) - \nu_U(u) - \nu_V(v)$.

Observe that $(\lambda + \mu)_U(u) = \lambda(u) + \frac{1}{\ell} \sum_{v \in V} \mu(v)$ and $(\lambda + \mu)_V(q) = \mu(v) + \frac{1}{k} \sum_{u \in U} \lambda(u)$, and $(\lambda + \mu)'$ is the height function with constant value $-(\frac{1}{\ell} \sum_{u \in U} \lambda(u) + \frac{1}{k} \sum_{v \in V} \lambda(v))$. Thus $\lambda + \mu$ and $(\lambda + \mu)_U + (\lambda + \mu)_V$ induce the same regular subdivision of $U \times V$. Therefore, we propose to analyze the height function $\nu'$ to measure how much $\nu$ deviates from the sum of two height functions. We can use the techniques from our previous paper [16] and apply (all of) them to $S_{U \times V}(\nu')$ for any given $\nu$. For instance, this allows to measure how
independent two different height functions are on the same point set (this is the case $U = V$). We say that $\nu$ \textbf{decomposes as a product} if $\nu' = 0$.

\textbf{Example 1.} If $U = V = \{0, 1\}$ are the vertices of the unit interval then $U \times V$ are the vertices of the unit square $[0, 1]^2$. Analyzing $\mathcal{S}(\nu')$ for any given height function $\nu$ on the four points $(0, 0), (0, 1), (1, 0)$ and $(1, 1)$ gives back the standard basic example of additive epistasis.

\textbf{Remark.} Two observations are in order: In \cite[§6.6]{16} we considered a version of parallel transport to compare epistatic effects, see also Section A.3. The connection to the product model approach is as follows. Let $V = \{0, 1\}^n$, i.e., the vertex set of the $n$-dimensional unit cube, be embedded twice, into a pair of parallel facets of the unit $(n+1)$-cube $[0, 1] \times [0, 1]^n$. This occurs in the product model with $U = \{0, 1\}$. If a height function $\nu$ on $\{0, 1\} \times U$ decomposes as a product then the parallel transport (in both directions) is trivial. Note that the number of dimensions is greater for the product model than for the parallel transport.

Additionally, observe that the product model differs from the marginal epistasis framework, which would produce a single number testing if the mutant changes one specific interaction between the genes.

\textbf{A.4.1. Product model for the Khan data.} To illustrate the product model consider the following example from the Khan data. We are interested in detecting if interactions between the $topA$, $spoT$, and $pykF$ genes change when the $rbs$ gene is mutated. To answer this question we let $U$ and $V$ be 3-cubes inside $[0, 1]^5$ defined by three mutable loci, one for each of the above genes and indicated by $*$, and two fixed loci. The first fixed locus represents the $rbs$ gene. It is not mutated in $U$ and mutated in $V$. The height functions are compared over the three variable loci. Thus the filtration over the product model for $U$ and $V$ has four dimensions in this case. A computation reveals that there are no significant dual edges in the epistatic filtration on product model, see Fig. 18. This indicates that the $rbs$ mutant does not affect the interaction landscape.

\textbf{A.5. Meta-epistatic chart.} This section deals with the question to which extent higher order epistatic effects are induced by lower dimensional ones or, put in other terms, which lower dimension epistatic effects can be seen in higher dimension. The \textbf{meta-epistatic chart} is a diagram drawn on top of the induced epistatic filtrations for some selection of faces of a fixed cube; higher-order interactions induced by lower order interactions are marked as corresponding.

In Fig. 11B and Fig. 11C we exhibit an example for the Eble data set, with 5 loci, where we take the five 4-dimensional faces $0****, *0***, **0***, ***0* and ****0 into consideration. Mathematically, these five 4-faces constitute the face figure of the wild type. Fix one 4-face, say $0****$. The induced epistatic filtration on this face shows two blue bars corresponding to dual edges labeled 1 and 2. Each of them refers to the ridge of a bipyramid
Table 3. Significant 4-dimensional interactions which cannot be seen in lower dimensions, cf. Fig. 11. The value $p^\uparrow$ refers to the $p$-value of the 4-dimensional bipyramid in question whereas $p^\downarrow$ is the $p$-value of its ridge intersected with the $\cap$-face, cf. Fig. 11C for the Gould data.

| Data     | significant bipyramid | $\cap$-face | $p^\uparrow$ | $p^\downarrow$ |
|----------|-----------------------|-------------|---------------|----------------|
| Eble     | -                     | -           | -             | -              |
| Gould    | **0**                 | **01**      | 0.041         | 0.270          |
|          | **0**                 | **01**      | 0.041         | 0.149          |
|          | **00**                | **01**      | 0.041         | 0.076          |
|          | **00**                | **01**      | 0.041         | 0.063          |
| Khan     | 0**1**                | 0**1**      | 0.009         | 0.052          |

which is a 3-dimensional simplex in this case. These two ridges may intersect certain 3-dimensional faces in the right dimension and thus may or may not descend to significant ridges within certain 3-dimensional filtrations. In case of an incidence with a lower dimensional significant ridge, the significant 4-dimensional effect is induced by a lower dimensional effect and one may picture this fact as a directed assignment pointing from the lower towards the higher dimensional interaction.

A.6. Comparison with a simple linear regression approach. In the theory of fitness landscapes many linear regression approaches have been proposed to study higher-order interactions, see e.g. [6, 50, 56, 42]. In this section, we compare our epistatic weight method to an elementary regression approach using an example from the data.

The regression analysis we have in mind assumes that there is a linear relationship between the predictors $X_1, X_2, \ldots, X_n$ (one associated to each locus/dimension of the genotope) and response, or dependent, variables $Y$ (associated to the biological measurements). That is, one assumes that $Y = f(X_1, X_2, \ldots, X_n) + \epsilon$ where $f : \mathbb{R}^n \rightarrow \mathbb{R}; (X_1, X_2, \ldots, X_n) \mapsto \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$ and where $\epsilon$ is a random error term. The coefficients $\beta_1, \beta_2, \ldots, \beta_n$ are unknown but can be estimated by minimizing the sum of squared residuals associated to the observations pairs $(x, y)$. These observations pairs consisting of a genotype and a measurement associated to it. Notice that more than one measurements are typically associated to a single genotype. With the coefficient estimates one can make predictions for the dependent variable via

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1 x_1 + \hat{\beta}_2 x_2 + \cdots + \hat{\beta}_n x_n.$$  

The hat symbol $\hat{}$ indicates a prediction, for instance of $Y$ on the basis of $x_i = X_i$, or an estimate for an unknown coefficient.
Below, we are interested in the differences between the observed measurements $y$ associated to the genotypes of $[0,1]^n$, expressed in terms of $x_1, x_2, \ldots, x_n$ and the predicated values $\hat{y}$ on the regression hyperplane (4). Notice that the regression analysis remains unchanged after normalizing the height function to Euclidean norm one. Additionally, computing residues for all replicated measurements (when provided) and then take averages builds on the assumption that measurements associated to different genotypes are statistically independent from each other. This assumption is consistent with the one underlying the computation of statistical significances for epistatic weights, following [16, §4.2-4.3].

**Remark.** In the regression setting of (4) there are hypothesis tests (like the $F$-statistic, $t$-statistics and $p$-value) to answer if at least one regression coefficient $\beta_j, 1 \leq j \leq n$ is nonzero, see for example [27]. Such statistical approaches are different from the one in [16, §4.2-4.3], where other hypothesis tests for each epistatic weight were proposed.

A.6.1. *Regression for Eble data.* In the following, we perform a regression analysis focusing on the replicated measurements for the lifespan fitness landscape on $[0,1]^5$ obtained from Eble and subspaces thereof. Numerical measures of model fit ($F$-statistic: 2357, with $p$-value essentially zero, and for 3840 observations and 5 predictors) show that the multiple linear regression model can be considered to be appropriated for this data. Since the epistatic weights of the dual edges are close to zero ($\leq 0.02$) and are mostly not significant, the above regression analysis conclusion is in line with what we see from the filtration of epistatic weights associated to the same fitness landscapes, see Fig. 12.

From this example we see that the regression approach provides some general information on higher-order interactions. However, without further assumptions, only one interaction formula is given in terms of a regression hyperplane (4) while the epistatic weight approach gives more fine grained information. This example also illustrate that when the regression model fits the data well (essentially the higher the $F$-statistics and the more coefficients in the hyperplane equation are significantly non-zero) the epistatic filtration has little horizontal shifts and few significant epistatic weights.

We now proceed repeating the above analysis on some of the bipyramids considered in the parallel analysis for the normalized lifespan Eble data. Regressing over bipyramid 23 in Table 10

$\{0001\} + \{0000, 1001, 1011, 0111\} + \{1111\}$

in $0^{**\ast\ast\ast\ast}$ and $1^{**\ast\ast\ast\ast}$ reveals that only two average residues over $0^{**\ast\ast\ast\ast}$ are non-zero (associated to the microbiomes 00000 and 00001), and only one is non-zero over $1^{**\ast\ast\ast\ast}$ (associated to the microbiome 10000). This confirms the two non significant epistatic weights over bipyramid 23 in Table 10.

**Remark.** If minimally dependent sets of points in the genotopoe are fixed, as in the epistatic weight approach, and one regresses above these points,
then the corresponding regression hyperplanes equations are learned from data and the equations generally differ from the epistatic weights given as in (2), but similar biological and geometric conclusions can be drawn. This idea could then be taken further by considering smoothing splines, instead of linear regression, and their relation to epistatic filtrations. From an application point of view, one would obtain an interesting new extension of the concept of epistasis because intermediate genotypes could be assessed, which would correspond to the case of genetically heterogeneous populations of organisms as occur in nature.

Other numerical results for the above regressions are summarized in Table 4. Over \(0^{****}\) two coefficients are significantly non-zero (for \(x_1\) and \(x_4\)), see top part of Table 4. Similarly, over \(1^{****}\) four coefficients are significantly non-zero \((x_1, x_2, x_3, x_4)\), see bottom part of Table 4. The fit of the linear regression models is confirmed by the relatively high values of the \(F\)-statistic. Over \(0^{****}\) the \(F\)-statistics is 459.1 for a \(p\)-value essentially of zero and 720 observations. Over \(1^{****}\) the \(F\)-statistics is 52.61 for a \(p\)-value essentially of zero and 720 observations.

A.7. Comparison with other approaches. Currently the main lines of research to investigate higher-order epistasis in computational biology and related disciplines include the present methods, inspired from discrete polyhedral geometry [16, 21, 4, 5]; linear regression approaches, e.g. [56]; methods originating from harmonic analysis, e.g. [51, 42, 53]; and using correlations between the effects of pairwise mutations, discussed in [16].

In a 2-locus, biallelic system, all these methods can easily be recovered from one another; some of them even agree. This is true also for some ecological approaches, including the generalized Lotka-Volterra equations, which yield a mathematically equivalent form to epistasis for certain situations.

|        | Coefficient | Std. error | \(t\)-statistic | \(p\)-value |
|--------|-------------|------------|-----------------|-------------|
| \(\beta_0\) | 0.2320 | 0.005 | 44.642 | 0.000 |
| \(x_1\) | 0.0310 | 0.005 | 5.957 | 0.000 |
| \(x_2\) | 0.0610 | 0.007 | 8.874 | 0.000 |
| \(x_3\) | -0.0185 | 0.007 | -2.692 | 0.007 |
| \(x_4\) | -0.0861 | 0.007 | -12.518 | 0.000 |
e.g. see equation 9 of [10]. In higher dimensional systems, these methods remain conceptually closely related but they generally yield different insights about the problem, such as whether the interactions are significant, what their magnitude is, and what their sign is. Because these previous methods make specific, a priori assumptions about the forms of interactions, they are limited by these assumptions. Epistatic filtrations add a global perspective, determining the structure of interactions from the shape of the fitness landscape.

A.8. **Microbiome data sets.** In this work, *Drosophila* microbiome fitness landscapes consist of experimental measurements on germ-free *Drosophila* flies inoculated with different bacterial species. The lifespan of approximately 100 individual flies were measured for each combination of bacterial species, giving roughly 3,200 individual fly lifespans for each of the two data sets presented. The experimental methods are described in [21, 33]. The first data set is the exact data presented in [21, 33]. The second data set is the second set of species with exactly the same methods used in [21, 33]. The bacterial compositions considered consist of all possible combinations of five species. The species considered can all occur naturally in the gut of wild flies: *Lactobacillus plantarum* (LP), *Lactobacillus brevis* (LB), *Acetobacter pasteurianus* (APa), *Acetobacter tropicalis* (AT), *Acetobacter orientalis* (AO), *Acetobacter cerevisiae* (AC), *Acetobacter malorum* (AM). The 5-member communities both stably persist in the fly gut. For the purposes of this work, we define **stable** as maintaining colonization of the gut when ≤ 20 flies are co-housed in a standard fly vial and transferred daily to fresh food containing 10% glucose, 5% live yeast that has subsequently been autoclaved, 1.2% agar, and 0.42% propionic acid, with a pH of 4.5. The total number of species found stably associated with an individual fly is typically between 3 and 8. Consistently, *Lactobacillus plantarum* and *Lactobacillus brevis*, are found with two to three *Acetobacter* species. Less consistently, species of *Enterobacteria* and *Enterococci* occur, and these have been described as pathogens. While more strains may be present, for each of the two data sets in the present work, a set of five non pathogen species was chosen, including the two *Lactobacilli* and three *Acetobacter* species. The combinations of species are shown in Table 5. Different strains of the same species were used in the two data sets.
Table 5. Species considered in the two microbiome datasets.

| Species  | Gould data set | Eble data set |
|----------|----------------|---------------|
| 1        | *L. plantarum* | *L. plantarum* |
| 2        | *L. brevis*    | *L. brevis*   |
| 3        | *A. pasteurianus* | *A. cerevisiae* |
| 4        | *A. tropicalis* | *A. malorum*  |
| 5        | *A. orientalis* | *A. orientalis* |
Figure 6. Synthetic data demonstrate method performance. Synthetic height functions over the 4-dimensional cube are generated with 100 replicates each and standard deviation as indicated. The heights of the wild type 0000 and 0001 are sampled with mean 53, all the other vertices with mean 50. (A) The distribution of log_{10} transformed epistatic weights is roughly constant as a function of interaction order, indicating the dimensional normalization is effective. (B) The number of significant interactions decreases as the standard deviation of the input data for each genotype increases. A blue dot is drawn if the interaction is significant and a red dot is drawn otherwise.
HIGHER-ORDER INTERACTIONS IN FITNESS LANDSCAPES ARE SPARSE

Figure 7. Parallel transport from $0^{**0*}$ to $1^{**0*}$ within the Khan dataset, cf. Example 2.6. (A) Filtration based on the triangulation of $0^{**0*}$. (B) Parallel epistatic weights computed from $1^{***0*}$ for the triangulation based on $0^{**0*}$. (C) The two parallel triangulations (and exploded copies) are depicted. The partitions in the node set are transferred from the cube on the middle left to the cube on the middle right. Exploded versions of these same triangulations on the far left and far right demonstrate the geometry of the simplices generated by the triangulations.

Figure 8. Epistatic filtration and parallel epistatic units for transport from $0^{****}$ to $1^{****}$ within the Khan data.
Figure 9. Parallel transport from $0^{****}$ to $1^{****}$ within the Weinreich data. Analysis based on mean values only; hence there is no color coding for the significance.

Figure 10. Parallel transport from the face $**0**$ to the face $**1**$ within the Weinreich data. Analysis based on mean values only; hence there is no color coding for the significance.
Figure 11. Meta-epistatic charts illustrate whether or not higher-order interactions arise from lower-order interactions. (A) Cartoon of the principle underlying meta-epistatic charts. The important loci in the interaction are depicted as black dots in a hyperplane through the genotypes, where the true dimensions of the genotypes are flattened onto the cartoon plane (pink). Higher-order interactions that derive from lower-order interactions occur in a new hyperplane (blue), which magnifies the weights of a subset of the landscape. In contrast, novel higher-order interactions that only arise in higher dimensions do not lie in a single additional hyperplane but instead require at least two additional hyperplanes (green). In (B) and (C) two meta-epistatic charts are represented. In each chart we identify the source of a higher-order interaction for the Eble and Gould data respectively. The results are compiled in Table 3.
Figure 12. Complete filtration of the Eble fitness landscape over the whole 5-cube.
Figure 13. Dual graph for the Eble data set. (A) Entire dual graph. The degree edge distribution in the format (degree, number of edges) is 
(1, 0), (2, 5), (3, 30), (4, 45), (5, 36), (6, 0)). (B) The dual graph with only critical edges shown. The degree-edge distribution is ((1, 31), (2, 61), (3, 19), (4, 5), (5, 0), (6, 0)).
Figure 14. Dual graph for the complete Khan data set. (A) Complete dual graph. The degree edge distribution in the format (degree, number of edges) is ((1, 1), (2, 11), (3, 28), (4, 35), (5, 21), (6, 5)). (B) The dual graph with only critical edges shown. The degree-edge distribution is ((1, 27), (2, 50), (3, 23), (4, 1), (5, 0), (6, 0)). The degree edge distributions are not different between the Khan and Eble data sets (Kolmogorov-Smirnov test). However, the significant edges are more central in the Eble graphs.
Higher-order interactions in fitness landscapes are sparse

Figure 15. Epistatic filtration and parallel epistatic units for transport from ****0 to ****1 within the Khan data.

Figure 16. Epistatic filtration and parallel epistatic units for transport from ****1 to ****0 within the Khan data.
Table 6. Parallel analysis Khan ****0 → ****1, non-critical red/red-case omitted.

| No. | bipyramid | type          | $c_x$ | $c_y$ | $c_z$/$c_x$ | $p_x$ | $p_z$ | $p_x/p_z$ |
|-----|-----------|---------------|-------|-------|-------------|-------|-------|-----------|
| 20  | {00000}+{01000,01000,00100,10010,10001} | red/red | 0.000 | 0.001 | 0.753       | 0.900 | 0.894 | 1.007     |
| 19  | {01000}+{01000,01000,00110,11010} | red/red | 0.001 | 0.009 | 0.111       | 0.768 | 0.142 | 5.408     |
| 18  | {01000}+{01000,00110,11010,11110}+{01010} | red/red | 0.001 | 0.009 | 0.111       | 0.768 | 0.142 | 5.408     |
| 17  | {01000}+{00000,01000,00100,10010}+{00000} | red/red | 0.001 | 0.006 | 0.166       | 0.703 | 0.125 | 5.624     |
| 16  | {00100}+{01000,10100,01100,00110}+{11110} | red/red | 0.001 | 0.003 | 0.351       | 0.712 | 0.445 | 1.600     |
| 15  | {01100}+{01000,10100,00110,11110}+{11010} | red/red | 0.001 | 0.010 | 0.131       | 0.766 | 0.068 | 11.348    |
| 14  | {01100}+{01000,10100,11100,11110}+{11010} | red/red | 0.001 | 0.011 | 0.131       | 0.766 | 0.068 | 11.348    |
| 13  | {01000}+{01100,01000,01100,11010}+{10110} | red/red | 0.001 | 0.005 | 0.290       | 0.740 | 0.191 | 3.874     |
| 12  | {01000}+{01100,00110,11010,11110}+{10110} | red/red | 0.001 | 0.005 | 0.290       | 0.740 | 0.191 | 3.874     |
| 11  | {00100}+{01000,00100,11010,10110}+{11110} | red/blue | 0.002 | 0.011 | 0.144       | 0.731 | 0.035 | 21.188    |
| 10  | {01100}+{01000,01010,01100,11110}+{11010} | red/red | 0.002 | 0.013 | 0.131       | 0.766 | 0.068 | 11.348    |
| 9   | {00010}+{01000,00010,10010,01110}+{10100} | red/red | 0.002 | 0.009 | 0.211       | 0.672 | 0.145 | 4.634     |
| 8   | {01000}+{01000,01100,10100,11010}+{11110} | red/blue | 0.002 | 0.020 | 0.123       | 0.512 | 0.000 | \infty   |
| 7   | {00100}+{01000,00010,01010,00110}+{10100} | red/red | 0.003 | 0.005 | 0.549       | 0.498 | 0.443 | 1.124     |
| 6   | {00000}+{01000,00100,00010,10010}+{00110} | red/blue | 0.003 | 0.019 | 0.139       | 0.469 | 0.001 | 551.765   |
| 5   | {01100}+{01000,00110,01100,11010}+{11110} | red/blue | 0.003 | 0.015 | 0.183       | 0.581 | 0.018 | 31.923    |
| 4   | {00100}+{01000,01010,00110,11110}+{10110} | red/blue | 0.003 | 0.021 | 0.142       | 0.533 | 0.007 | 72.124    |
| 3   | {00100}+{01100,01010,00110,11110}+{00110} | red/red | 0.004 | 0.004 | 3.986       | 0.615 | 0.924 | 0.666     |
| 2   | {11000}+{01000,01000,10100,11010}+{10010} | red/blue | 0.004 | 0.023 | 0.160       | 0.568 | 0.011 | 50.265    |
| 1   | {10000}+{01000,10100,10010,11100}+{00010} | red/blue | 0.004 | 0.027 | 0.147       | 0.275 | 0.000 | \infty   |

Note: The table continues with similar entries for each row, indicating the type of analysis and various parameters for each case.
**Table 7.** Parallel analysis Khan $****1 \rightarrow ****0$, non-critical red/red-case omitted.

| No. | bipyramid | type   | $e_x$ | $e_y$ | $e_x/e_y$ | $p_x$ | $p_y$ | $p_x/p_y$ |
|-----|-----------|--------|-------|-------|-----------|-------|-------|-----------|
| 22  | {10011}+{00011,01011,00111,10111}+{11111} | red/red | 0.000 | 0.000 | 0.122     | 0.995 | 0.956 | 1.041     |
| 21  | {00111}+{00011,01001,01101,10111}+{11111} | red/red | 0.000 | 0.000 | 0.122     | 0.995 | 0.956 | 1.041     |
| 20  | {11001}+{01001,01101,10111,11111}+{01101} | red/red | 0.000 | 0.007 | 0.020     | 0.982 | 0.130 | 7.554     |
| 19  | {10111}+{00011,01011,00111,11111}+{01111} | red/red | 0.000 | 0.007 | 0.045     | 0.962 | 0.241 | 3.992     |
| 18  | {00001}+{00001,01001,00101,10011}+{10101} | red/red | 0.001 | 0.000 | 1.328     | 0.894 | 0.904 | 0.993     |
| 17  | {01001}+{00011,01101,10111,11111}+{01111} | red/red | 0.001 | 0.003 | 0.251     | 0.924 | 0.615 | 1.502     |
| 16  | {10101}+{01001,00101,11011,11111}+{01011} | red/red | 0.001 | 0.001 | 2.098     | 0.881 | 0.919 | 0.959     |
| 15  | {10101}+{00101,00011,10111,11111}+{10011} | red/red | 0.001 | 0.001 | 2.098     | 0.881 | 0.919 | 0.959     |
| 14  | {10101}+{00011,01011,10111,11111}+{01011} | red/red | 0.001 | 0.003 | 0.556     | 0.836 | 0.612 | 1.366     |
| 13  | {10011}+{01001,01101,01011,11011}+{11111} | red/red | 0.002 | 0.003 | 0.585     | 0.874 | 0.654 | 1.336     |
| 12  | {01001}+{00101,10101,01011,00111}+{11111} | red/red | 0.002 | 0.003 | 0.585     | 0.874 | 0.654 | 1.336     |
| 11  | {00101}+{00101,10011,01011,00111}+{11111} | red/red | 0.002 | 0.003 | 0.585     | 0.874 | 0.654 | 1.336     |
| 10  | {01011}+{01001,10101,01111,11111}+{10111} | red/red | 0.002 | 0.003 | 0.556     | 0.836 | 0.612 | 1.366     |
| 9   | {10111}+{01001,11001,10111,11111}+{01011} | red/red | 0.002 | 0.005 | 0.394     | 0.762 | 0.231 | 3.299     |
| 8   | {11001}+{01001,10101,01111,11111}+{01101} | red/red | 0.003 | 0.008 | 0.394     | 0.762 | 0.231 | 3.299     |
| 7   | {01001}+{00101,00011,10011,01011}+{00111} | red/red | 0.005 | 0.003 | 1.821     | 0.443 | 0.498 | 0.890     |
| 6   | {00101}+{00001,01001,10011,01011}+{11101} | red/blue | 0.005 | 0.011 | 0.444     | 0.300 | 0.006 | 49.180    |
| 5   | {10011}+{01001,11001,10111,11111}+{11101} | red/red | 0.005 | 0.001 | 4.686     | 0.375 | 0.752 | 0.499     |
| 4   | {10001}+{00011,01001,10011,01011}+{00111} | red/red | 0.006 | 0.001 | 6.035     | 0.125 | 0.703 | 0.178     |
| 3   | {01001}+{11001,10011,01011,11111}+{11011} | red/blue | 0.007 | 0.015 | 0.462     | 0.447 | 0.018 | 24.162    |
| 2   | {00111}+{00111,01101,01011,00111}+{10111} | red/red | 0.007 | 0.005 | 1.271     | 0.233 | 0.253 | 0.921     |
| 1   | {00011}+{01001,00101,00011,10011}+{01011} | blue/red | 0.014 | 0.006 | 2.376     | 0.052 | 0.188 | 0.276     |

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Figure 17. Complete filtration of the Khan 5-cube.
Figure 18. Product model associated to the parallel transport $0**0* \rightarrow 1**0*$ within the Khan evolution data, cf. Fig. 7.
Figure 19. Non-generic product model associated to the parallel transport $\ast\ast0\ast\ast \rightarrow \ast\ast1\ast\ast$ within the Weinreich data. Its unique non-simplicial maximal cell has 7 vertices and is split into a bipyramid by a slight perturbation of its height values, cf. Theorem 8 of [16]. The corresponding artificial dual edge has edge label 111 and is indicated by a horizontal line.
Figure 20. Non-generic product model associated to the parallel transport $0\star\star\star\star \rightarrow 1\star\star\star\star$ within the Weinreich data. There are two non-simplicial maximal cells, both of cardinality 7. As in Fig. 19 they are split into a bipyramid each at the beginning of the filtration process.
Figure 21. Product model for the parallel transport Khan $\ast\ast\ast0\ast \rightarrow \ast\ast\ast1\ast$. The semisignificant bipyramid labeled 2 reads $\{(1000)_{o}\} + \{(0000)_{o}, (1010)_{o}, (0110)_{o}, (1011)_{p}, (0011)_{p}\}$ and the semisignificant bipyramid labeled 1 reads $\{(1100)_{o}\} + \{(1011)_{o}, (1010)_{p}, (1001)_{p}, (0011)_{p}, (1111)_{p}\} + \{(1011)_{p}\}$. 

epistatic units
dual edges
Figure 22. Product model for the parallel transport $Eble \, 0^{****} \to 1^{****}$. The unique significant bipyramid reads $\{0001\}_o + \{(0000)_o, (1001)_o, (0101)_o, (0011)_o, (0001)_p\} + \{(0101)_p\}$. 
Figure 23. Product model for the parallel transport Eble $*0\leftrightarrow*1\leftrightarrow*$. 
Figure 24. ***0*(Khan) to ***1*(Khan).

Figure 25. ***1*(Khan) to ***0*(Khan).

Figure 26. 1*(*Eble) to 0*(*Eble).
Figure 27. 0***(Eble) to 1***(Eble).

Figure 28. 1****(Eble) to 0****(Eble).

Figure 29. *0****(Eble) to *1****(Eble).
Table 8. Parallel analysis Khan ***0* → ***1*, non-critical red/red-case omitted.

| No. | bipyr. | type   | $e_u$ | $e_p$ | $e_u/e_p$ | $p_u$ | $p_p$ | $p_u/p_p$ |
|-----|--------|--------|-------|-------|-----------|-------|-------|-----------|
| 23  | {11001}+{01000,00101,10101,11101}+{01011} | red/red | 0.000 | 0.012 | 0.012     | 0.982 | 0.098 | 10.000    |
| 22  | {11000}+{01000,10100,11100,11001}+{01011} | red/blue | 0.000 | 0.015 | 0.016     | 0.964 | 0.021 | 46.570    |
| 21  | {11000}+{10000,01000,10100,11001}+{01011} | red/blue | 0.000 | 0.015 | 0.016     | 0.964 | 0.021 | 46.570    |
| 20  | {00000}+{01000,00100,10101,10101}+{01010} | red/red | 0.001 | 0.006 | 0.092     | 0.900 | 0.253 | 3.557     |
| 19  | {00001}+{00000,10001,01001,00101}+{01011} | red/red | 0.001 | 0.008 | 0.096     | 0.894 | 0.233 | 3.837     |
| 18  | {10000}+{00000,01000,00101,10101}+{00101} | red/red | 0.001 | 0.001 | 0.704     | 0.809 | 0.735 | 1.101     |
| 17  | {10000}+{00000,01000,01001,10101}+{00111} | red/red | 0.001 | 0.001 | 0.704     | 0.809 | 0.735 | 1.101     |
| 16  | {00100}+{00100,01000,01001,10101}+{01101} | red/red | 0.001 | 0.008 | 0.114     | 0.849 | 0.139 | 6.108     |
| 15  | {11100}+{01000,01001,10101,11101}+{01111} | red/red | 0.001 | 0.000 | 85.893    | 0.864 | 0.998 | 0.866     |
| 14  | {10000}+{00000,10001,01001,11001}+{01111} | red/red | 0.001 | 0.002 | 0.704     | 0.809 | 0.735 | 1.101     |
| 13  | {10100}+{01000,01100,11001,11101}+{01111} | red/red | 0.001 | 0.002 | 0.504     | 0.828 | 0.646 | 1.282     |
| 12  | {10100}+{01000,01000,11010,11101}+{01111} | red/red | 0.001 | 0.006 | 0.231     | 0.759 | 0.196 | 3.872     |
| 11  | {10100}+{10000,11001,10101,11101}+{01111} | red/red | 0.002 | 0.003 | 0.504     | 0.828 | 0.646 | 1.282     |
| 10  | {10100}+{10000,11000,10100,11101}+{01111} | red/red | 0.002 | 0.002 | 1.536     | 0.512 | 0.731 | 0.700     |
| 9   | {00000}+{10000,00100,01001,10101}+{11101} | red/red | 0.004 | 0.010 | 0.412     | 0.298 | 0.078 | 3.840     |
| 8   | {00000}+{01000,01000,01001,10101}+{11011} | red/red | 0.004 | 0.010 | 0.412     | 0.298 | 0.078 | 3.840     |
| 7   | {00100}+{01000,10100,10010,11010}+{11100} | red/red | 0.005 | 0.006 | 0.779     | 0.268 | 0.241 | 1.112     |
| 6   | {00101}+{01000,01001,10100,11011}+{11101} | red/red | 0.005 | 0.000 | 18.429    | 0.419 | 0.962 | 0.436     |
| 5   | {01100}+{00001,01001,01100,10110}+{11011} | red/red | 0.005 | 0.007 | 0.736     | 0.308 | 0.272 | 1.132     |
| 4   | {01100}+{01000,11001,10100,11101}+{11011} | red/blue | 0.005 | 0.019 | 0.286     | 0.367 | 0.002 | 244.667   |
| 3   | {00100}+{00000,00100,01001,10101}+{10101} | red/red | 0.006 | 0.001 | 6.251     | 0.186 | 0.853 | 0.218     |
| 2   | {10000}+{00000,00100,10100,10101}+{10100} | blue/red | 0.009 | 0.006 | 1.661     | 0.025 | 0.252 | 0.100     |
| 1   | {00000}+{01000,00100,01010,10100}+{01100} | blue/blue | 0.010 | 0.010 | 0.969     | 0.015 | 0.019 | 0.786     |
|     | {00000}+{01000,00100,01101,10101}+{01110} | blue/red | 0.011 | 0.002 | 5.570     | 0.025 | 0.691 | 0.036     |
|     | {01000}+{00000,10000,00101,10101}+{10001} | blue/red | 0.011 | 0.004 | 3.146     | 0.031 | 0.576 | 0.054     |
|     | {01000}+{10000,01001,11001,10101}+{10001} | blue/red | 0.011 | 0.004 | 3.146     | 0.031 | 0.576 | 0.054     |
|     | {00100}+{10000,01000,10101,10101}+{11001} | blue/blue | 0.011 | 0.010 | 1.080     | 0.015 | 0.013 | 1.159     |
Table 9. Parallel analysis Khan $\star \star \star 1* \rightarrow \star \star \star 0*$, non-critical red/red-case omitted.

| No. | bipyramid$_i$ | type    | $c_o$ | $c_p$ | $c_o/c_p$ | $p_o$ | $p_p$ | $p_o/p_p$ |
|-----|----------------|---------|------|------|----------|------|------|----------|
| 21  | (11110)+{01010,00110,01111,10111,11111}+{01111} | red/red | 0.000 | 0.001 | 0.012    | 0.998 | 0.864 | 1.155    |
| 20  | (10011)+{00110,01011,00111,10111}+{11111}    | red/blue| 0.000 | 0.025 | 0.002    | 0.995 | 0.000 | $\infty$ |
| 19  | (00111)+{00110,10011,01011,10111}+{11111}    | red/blue| 0.000 | 0.031 | 0.002    | 0.995 | 0.000 | $\infty$ |
|     | (10011)+{00110,01011,10111,11111}+{01111}    | red/blue| 0.000 | 0.031 | 0.002    | 0.995 | 0.000 | $\infty$ |
| 18  | (10111)+{01010,01011,00111,11111}+{01111}    | red/red | 0.000 | 0.006 | 0.054    | 0.962 | 0.419 | 2.296    |
| 17  | (00110)+{10010,01010,10011,11111}+{11010}    | red/blue| 0.000 | 0.015 | 0.025    | 0.937 | 0.001 | 1050.448 |
| 16  | (11010)+{10010,01010,00110,11111}+{10011}    | red/blue| 0.001 | 0.022 | 0.025    | 0.937 | 0.001 | 1050.448 |
| 15  | (01010)+{10010,00110,10111,11111}+{10111}    | red/blue| 0.001 | 0.019 | 0.030    | 0.868 | 0.000 | $\infty$ |
|     | (00110)+{10010,01010,11010,11111}+{10011}    | red/blue| 0.001 | 0.024 | 0.025    | 0.937 | 0.001 | 1050.448 |
| 14  | (11010)+{10010,00110,10111,11111}+{10111}    | red/red | 0.001 | 0.004 | 0.207    | 0.874 | 0.481 | 1.817    |
| 13  | (01010)+{00110,10011,01011,11111}+{10111}    | red/blue| 0.001 | 0.029 | 0.030    | 0.868 | 0.000 | $\infty$ |
| 12  | (10011)+{01010,00110,01011,11111}+{01111}    | red/red | 0.001 | 0.006 | 0.164    | 0.892 | 0.316 | 2.823    |
| 11  | (01010)+{00010,00110,10011,01011}+{00111}    | red/red | 0.001 | 0.007 | 0.160    | 0.853 | 0.186 | 4.586    |
| 10  | (01010)+{00110,11010,11110,11111}+{10110}    | red/blue| 0.002 | 0.011 | 0.175    | 0.654 | 0.006 | 107.213  |
| 9   | (10010)+{01010,10110,10111,11111}+{10110}    | red/blue| 0.002 | 0.003 | 0.651    | 0.731 | 0.512 | 1.428    |
| 8   | (10110)+{10010,00110,11111,11111}+{10110}    | red/blue| 0.002 | 0.020 | 0.111    | 0.663 | 0.000 | $\infty$ |
|     | (01010)+{10010,00110,11010,11111}+{10110}    | red/blue| 0.002 | 0.014 | 0.175    | 0.654 | 0.006 | 107.213  |
| 7   | (00010)+{01010,00110,10011,01011}+{11111}    | red/red | 0.003 | 0.000 | 7.106    | 0.454 | 0.920 | 0.493    |
| 6   | (00010)+{10010,01010,00110,10011}+{11111}    | red/red | 0.003 | 0.000 | 7.106    | 0.454 | 0.920 | 0.493    |
| 5   | (10010)+{00010,01010,00110,10011}+{10110}    | red/blue| 0.003 | 0.009 | 0.318    | 0.576 | 0.031 | 18.521   |
|     | (10010)+{01010,00110,10111,11111}+{10110}    | red/blue| 0.003 | 0.009 | 0.318    | 0.576 | 0.031 | 18.521   |
|     | (00010)+{00110,10111,01011,00111}+{01111}    | red/blue| 0.003 | 0.020 | 0.160    | 0.458 | 0.000 | $\infty$ |
| 4   | (10110)+{10010,11010,11110,11111}+{10110}    | red/blue| 0.004 | 0.011 | 0.318    | 0.576 | 0.031 | 18.521   |
|     | (10110)+{01010,11011,11111,11111}+{10110}    | red/blue| 0.004 | 0.010 | 0.040    | 0.627 | 0.000 | $\infty$ |
| 3   | (00110)+{00010,10110,01011,01011}+{01110}    | red/blue| 0.004 | 0.023 | 0.181    | 0.491 | 0.000 | $\infty$ |
| 2   | (11100)+{01010,00110,11011,11111}+{01110}    | red/red | 0.005 | 0.008 | 0.584    | 0.436 | 0.130 | 3.354    |
| 1   | (01010)+{11010,10011,01011,11111}+{11111}    | red/red | 0.011 | 0.011 | 1.001    | 0.211 | 0.108 | 1.954    |
Table 10. Parallel analysis Eble $0^{****} \rightarrow 1^{****}$, non-critical red/red-case omitted.

| No. | bipyramid $\delta_4$ | type          | $e_o$ | $e_p$ | $e_o/e_p$ | $p_o$ | $p_p$ | $p_o/p_p$ |
|-----|----------------------|---------------|-------|-------|-----------|-------|-------|-----------|
| 23  | {00001} + {00000,01001,01010,01111} + {01111} | red/red       | 0.001 | 0.012 | 0.066     | 0.953 | 0.390 | 2.444     |
| 22  | {00001} + {00000,01001,01100,01111} + {01111} | red/red       | 0.001 | 0.012 | 0.066     | 0.953 | 0.390 | 2.444     |
| 21  | {01110} + {00000,01101,01111} + {01111}     | red/blue      | 0.001 | 0.025 | 0.041     | 0.923 | 0.038 | 24.226    |
| 20  | {01110} + {00000,01100,01110,01111} + {01111} | red/blue      | 0.001 | 0.035 | 0.041     | 0.923 | 0.038 | 24.226    |
| 19  | {00110} + {00000,01100,01111} + {01101}     | red/red       | 0.002 | 0.012 | 0.201     | 0.827 | 0.303 | 2.729     |
| 18  | {00110} + {00000,01100,01111} + {01101}     | red/red       | 0.003 | 0.014 | 0.201     | 0.827 | 0.303 | 2.729     |
| 17  | {01110} + {00000,01000,01101,01111} + {01101} | red/red       | 0.003 | 0.013 | 0.264     | 0.742 | 0.251 | 2.956     |
| 16  | {00110} + {00000,01100,01110,01111} + {00011} | red/red       | 0.004 | 0.003 | 1.568     | 0.755 | 0.843 | 0.896     |
| 15  | {00010} + {00000,01010,01110,01101} + {01110} | red/red       | 0.007 | 0.010 | 0.748     | 0.606 | 0.488 | 1.242     |
| 14  | {01010} + {00000,01010,01110,01101} + {00111} | red/red       | 0.008 | 0.005 | 1.583     | 0.443 | 0.639 | 0.693     |
| 13  | {01010} + {00000,01110,01111} + {01111}     | red/red       | 0.009 | 0.024 | 0.359     | 0.475 | 0.062 | 7.686     |
| 12  | {01010} + {00000,01000,01110,01101} + {01111} | red/red       | 0.009 | 0.024 | 0.359     | 0.475 | 0.062 | 7.686     |
| 11  | {00010} + {00000,01100,01110,01101} + {00111} | red/red       | 0.009 | 0.018 | 0.498     | 0.531 | 0.269 | 1.981     |
| 10  | {01010} + {00000,01100,01111} + {00111}     | red/red       | 0.014 | 0.014 | 1.018     | 0.288 | 0.313 | 0.929     |
| 9   | {00110} + {00000,01010,01110,01111} + {01111} | red/red       | 0.015 | 0.026 | 0.584     | 0.228 | 0.062 | 3.695     |
| 8   | {01110} + {00000,01001,01111} + {01111}     | red/blue      | 0.018 | 0.040 | 0.446     | 0.321 | 0.035 | 9.119     |
| 7   | {01110} + {00000,01001,01111} + {01111}     | red/red       | 0.019 | 0.003 | 6.623     | 0.668 | 0.800 | 0.085     |
| 6   | {01010} + {00000,01000,01111} + {01111}     | red/red       | 0.019 | 0.003 | 6.623     | 0.668 | 0.800 | 0.085     |
| 5   | {01000} + {00000,01000,01101,01111} + {01110} | red/red       | 0.020 | 0.011 | 1.750     | 0.169 | 0.443 | 0.381     |
| 4   | {01000} + {00000,01100,01110,01111} + {01110} | red/red       | 0.020 | 0.011 | 1.750     | 0.169 | 0.443 | 0.381     |
| 3   | {01000} + {00000,01001,01111} + {01111}     | red/red       | 0.021 | 0.013 | 1.535     | 0.140 | 0.339 | 0.413     |
| 2   | {01110} + {00000,01010,01111} + {01111}     | blue/blue     | 0.045 | 0.037 | 1.215     | 0.000 | 0.003 | 0.176     |
| 1   | {01010} + {00000,01000,01111} + {01110}     | blue/red      | 0.048 | 0.024 | 1.993     | 0.000 | 0.056 | 0.002     |
|     | {01100} + {00000,01000,01110,01111} + {01011} | blue/blue     | 0.064 | 0.034 | 1.855     | 0.000 | 0.005 | 0.000     |
|     | {00010} + {00000,01101,01111} + {00011}     | blue/blue     | 0.065 | 0.043 | 1.518     | 0.000 | 0.001 | 0.001     |
|     | {01100} + {00000,01010,01111} + {01011}     | blue/red      | 0.066 | 0.024 | 2.775     | 0.000 | 0.105 | 0.000     |
|     | {00011} + {00000,01011,01111} + {01011}     | blue/blue     | 0.066 | 0.033 | 1.989     | 0.000 | 0.009 | 0.000     |
|     | {01011} + {00000,01011,01111} + {00110}     | blue/blue     | 0.068 | 0.036 | 1.917     | 0.000 | 0.007 | 0.000     |
|     | {01101} + {00000,01110,01111} + {01011}     | blue/blue     | 0.083 | 0.045 | 1.829     | 0.000 | 0.002 | 0.000     |
|     | {01110} + {00000,01110,01111} + {01101}     | blue/red      | 0.084 | 0.021 | 4.035     | 0.000 | 0.210 | 0.000     |
Table 11. Parallel analysis Eble $1^{****} \rightarrow 0^{****}$, non-critical red/red-case omitted.

| No. | bipyramid$_i$ | type     | $\epsilon_o$ | $\epsilon_p$ | $\epsilon_o/\epsilon_p$ | $p_o$ | $p_p$ | $p_o/p_p$ |
|-----|---------------|----------|---------------|---------------|--------------------------|-------|-------|-----------|
| 23  | [1000]+[1100,11100,11110,10111]+[11101] | red/red  | 0.001 0.017 0.037 0.968 | 0.283 3.420 |
| 22  | [1000]+[1100,11100,11101,10111]+[11110] | red/red  | 0.001 0.017 0.037 0.968 | 0.283 3.420 |
| 21  | [1100]+[1000,11010,11110,11011]+[10011] | red/blue | 0.001 0.037 0.019 0.961 | 0.009 109.081 |
| 20  | [1100]+[1000,1001,11011,11111]+[10011] | red/blue | 0.001 0.045 0.019 0.961 | 0.009 109.081 |
| 19  | [1100]+[1000,11110,11011,11111]+[10011] | red/blue | 0.001 0.069 0.019 0.961 | 0.009 109.081 |
| 18  | [11100]+[1000,10100,11011,10111]+[10101] | red/red  | 0.001 0.112 0.126 0.919 | 0.387 2.375 |
| 17  | [10110]+[1000,10010,11110,11011]+[10011] | red/red  | 0.003 0.004 0.638 0.843 | 0.755 1.117 |
| 16  | [10010]+[1000,1001,10011,11110]+[10110] | red/red  | 0.003 0.014 0.235 0.789 | 0.295 2.675 |
| 15  | [1101]+[1100,11101,11011,10111]+[11111] | red/red  | 0.004 0.026 0.151 0.800 | 0.068 11.799 |
| 14  | [1000]+[1100,1001,11101,10111]+[11001] | red/red  | 0.005 0.030 0.177 0.790 | 0.144 5.486 |
| 13  | [1000]+[1100,1001,11101,10111]+[11010] | red/red  | 0.005 0.030 0.177 0.790 | 0.144 5.486 |
| 12  | [1101]+[1000,10100,11011,11111]+[10110] | red/red  | 0.005 0.009 0.575 0.607 | 0.378 1.606 |
| 11  | [1100]+[1100,10100,11011,11111]+[11010] | red/blue | 0.006 0.027 0.205 0.694 | 0.033 21.354 |
| 10  | [1101]+[1100,10100,11110,11011]+[10110] | red/red  | 0.007 0.012 0.575 0.607 | 0.378 1.606 |
| 9   | [1101]+[1100,10100,11011,11110]+[10110] | red/red  | 0.007 0.019 0.358 0.654 | 0.212 3.085 |
| 8   | [1000]+[1100,11001,11011,10111]+[11011] | red/red  | 0.007 0.019 0.358 0.654 | 0.212 3.085 |
| 7   | [1110]+[1100,10100,11010,11111]+[11011] | red/red  | 0.007 0.025 0.297 0.620 | 0.095 6.499 |
| 6   | [1100]+[1100,11010,11101,10111]+[10100] | red/blue | 0.008 0.051 0.159 0.628 | 0.003 234.328 |
| 5   | [1100]+[1000,11010,11110,11011]+[11001] | red/blue | 0.008 0.051 0.159 0.628 | 0.003 234.328 |
| 4   | [1100]+[1100,10010,11101,11011]+[11101] | red/red  | 0.010 0.040 0.236 0.583 | 0.020 29.745 |
| 3   | [1100]+[1100,11110,11011,10111]+[11110] | red/red  | 0.018 0.005 3.781 0.251 | 0.742 0.338 |
| 2   | [1110]+[1100,11110,11011,11110]+[11111] | red/red  | 0.019 0.029 0.651 0.339 | 0.140 2.421 |
| 1   | [1111]+[1100,11110,11111,11111]+[11101] | blue/blue | 0.022 0.067 0.321 0.212 | 0.000 ∞ |
|     | [1111]+[1100,11110,11111,11111]+[11101] | red/blue | 0.022 0.067 0.321 0.212 | 0.000 ∞ |
|     | [1110]+[1100,11010,11101,11111]+[10100] | blue/blue | 0.032 0.075 0.429 0.013 | 0.000 ∞ |
|     | [1100]+[1100,11010,11101,11111]+[11001] | blue/blue | 0.033 0.066 0.503 0.009 | 0.000 ∞ |
|     | [1100]+[1000,11000,11010,11110]+[11100] | blue/blue | 0.034 0.049 0.692 0.009 | 0.000 ∞ |
|     | [1000]+[11000,11010,11101,11110]+[11101] | blue/blue | 0.035 0.086 0.402 0.021 | 0.000 ∞ |
|     | [1110]+[1100,11000,11101,11111]+[11001] | blue/blue | 0.048 0.043 1.109 0.019 | 0.045 0.421 |
|     | [1010]+[11000,10110,11110,11111]+[11010] | blue/blue | 0.053 0.118 0.446 0.000 | 0.000 ∞ |
Table 12. Parallel analysis Eble *0*** → *1***, non-critical red/red-case omitted.

| No. | bipyramid | type         | $e_n$ | $e_p$ | $e_n/e_p$ | $p_n$ | $p_p$ | $p_n/p_p$ |
|-----|-----------|--------------|-------|-------|-----------|-------|-------|-----------|
| 23  | {01110}†+{00000,10000,10010,10111}†+{00111} | red/red  | 0.002 | 0.020 | 0.119     | 0.843 | 0.062 | 13.641    |
| 22  | {01110}†+{00000,10010,00110,11011}†+{00111} | red/red  | 0.003 | 0.028 | 0.119     | 0.843 | 0.062 | 13.641    |
| 21  | {01010}†+{00000,00110,00111,10011}†+{00101} | red/red  | 0.003 | 0.031 | 0.251     | 0.750 | 0.216 | 3.472     |
| 20  | {00110}†+{00000,00110,10011,01111}†+{00111} | red/red  | 0.004 | 0.009 | 0.519     | 0.755 | 0.475 | 1.589     |
| 19  | {00101}†+{00000,00011,10101,01111}†+{01111} | red/red  | 0.005 | 0.016 | 0.318     | 0.697 | 0.240 | 2.904     |
| 18  | {00101}†+{00000,00110,10110,01111}†+{01111} | red/red  | 0.005 | 0.016 | 0.318     | 0.697 | 0.240 | 2.904     |
| 17  | {00100}†+{00000,00110,10111,10101}†+{00111} | red/red  | 0.008 | 0.004 | 1.906     | 0.533 | 0.742 | 0.718     |
| 16  | {00010}†+{00000,10001,00111,01111}†+{01111} | red/red  | 0.009 | 0.019 | 0.464     | 0.538 | 0.144 | 3.736     |
| 15  | {00010}†+{00000,10010,00110,10011}†+{01111} | red/red  | 0.009 | 0.019 | 0.464     | 0.538 | 0.144 | 3.736     |
| 14  | {00010}†+{00000,00001,10111,01111}†+{00111} | red/red  | 0.009 | 0.000 | 170.000   | 0.436 | 0.996 | 0.438     |
| 13  | {00010}†+{00000,00110,10111,10111}†+{00111} | red/red  | 0.009 | 0.000 | 170.000   | 0.436 | 0.996 | 0.438     |
| 12  | {10100}†+{00000,00110,10101,11011}†+{00111} | red/red  | 0.010 | 0.010 | 0.989     | 0.380 | 0.336 | 1.131     |
| 11  | {10110}†+{00000,10000,10101,01111}†+{01010} | red/red  | 0.013 | 0.013 | 1.012     | 0.269 | 0.251 | 1.072     |
| 10  | {00011}†+{00000,00001,10011,01111}†+{01111} | red/red  | 0.013 | 0.010 | 1.281     | 0.331 | 0.405 | 0.817     |
| 9   | {00101}†+{00000,10100,10111,01111}†+{01111} | red/red  | 0.018 | 0.018 | 1.012     | 0.269 | 0.251 | 1.072     |
| 8   | {10010}†+{00000,00010,00110,10111}†+{00111} | red/red  | 0.020 | 0.017 | 1.225     | 0.067 | 0.081 | 0.823     |
| 7   | {10101}†+{00000,00001,10001,11011}†+{00111} | blue/red | 0.023 | 0.003 | 8.151     | 0.045 | 0.800 | 0.056     |
| 6   | {10110}†+{00000,10000,10011,11011}†+{00111} | blue/red | 0.023 | 0.003 | 8.151     | 0.045 | 0.800 | 0.056     |
| 5   | {10100}†+{00000,10000,10101,11111}†+{00001} | blue/blue | 0.032 | 0.003 | 11.148    | 0.042 | 0.856 | 0.049     |
| 4   | {10000}†+{00000,10010,10101,11111}†+{01000} | blue/red | 0.032 | 0.024 | 1.349     | 0.025 | 0.094 | 0.266     |
| 3   | {10000}†+{00000,10100,10110,11111}†+{01010} | blue/red | 0.032 | 0.024 | 1.349     | 0.025 | 0.094 | 0.266     |
| 2   | {10000}†+{00000,10001,10011,11111}†+{01001} | blue/blue | 0.043 | 0.044 | 0.977     | 0.001 | 0.000 | 4.886     |
| 1   | {10000}†+{00000,10001,10111,11011}†+{01001} | blue/red | 0.045 | 0.011 | 4.019     | 0.004 | 0.487 | 0.009     |

**Notes:**
- $e_n$ and $e_p$ are the probabilities of non-parallel and parallel mutations, respectively.
- $p_n$ and $p_p$ are the probabilities of non-parallel and parallel adaptations, respectively.
- $p_n/p_p$ is the ratio of non-parallel to parallel adaptation probabilities.

**References:**
- Eble, J. H. (2000). Higher-order interactions in fitness landscapes are sparse. *Evolution*, 54(2), 453-463.
Table 13. Parallel analysis Eble $1^{***} \rightarrow 0^{***}$, non-critical red/red-case omitted.

| No. | bipyramid$_j$ | type         | $e_u$ | $e_p$ | $e_u/e_p$ | $p_u$ | $p_p$ | $p_u/p_p$ |
|-----|---------------|--------------|-------|-------|-----------|-------|-------|----------|
| 22  | (11001) + {01000,01010,11011,11101,11111} + {01111} | red/red     | 0.002 | 0.008 | 0.198     | 0.853 | 0.408 | 2.091    |
| 21  | (01001) + {01000,11101,11011,01111} + {01111} | red/blue    | 0.003 | 0.030 | 0.090     | 0.856 | 0.042 | 20.381   |
| 20  | (11001) + {01000,11000,11101,11111} + {01111} | red/blue    | 0.003 | 0.028 | 0.123     | 0.800 | 0.045 | 17.738   |
| 19  | (11100) + {01000,01100,11110,11101} + {01110} | red/blue    | 0.004 | 0.029 | 0.137     | 0.757 | 0.041 | 18.554   |
| 18  | (01110) + {01000,01100,11101,01111} + {01110} | red/red     | 0.004 | 0.008 | 0.525     | 0.742 | 0.533 | 1.392    |
| 17  | (11100) + {01000,01010,11101,11011} + {01110} | red/red     | 0.005 | 0.012 | 0.428     | 0.689 | 0.436 | 1.580    |
| 16  | (01110) + {01000,11110,11011,01111} + {11111} | red/red     | 0.005 | 0.043 | 0.128     | 0.786 | 0.051 | 15.534   |
| 15  | (01111) + {01000,11110,11101,11111} + {11111} | red/red     | 0.005 | 0.043 | 0.128     | 0.786 | 0.051 | 15.534   |
| 14  | (01111) + {01000,01111,01110,01111} + {11110} | red/blue    | 0.006 | 0.034 | 0.165     | 0.592 | 0.005 | 112.121  |
| 13  | (11110) + {01000,01100,01111,11111} + {01111} | red/blue    | 0.007 | 0.033 | 0.200     | 0.656 | 0.037 | 17.730   |
| 12  | (01111) + {01000,11110,11110,01111} + {01111} | red/blue    | 0.007 | 0.041 | 0.165     | 0.592 | 0.005 | 112.121  |
| 11  | (01100) + {01000,01110,11110,11011} + {01111} | red/blue    | 0.008 | 0.041 | 0.200     | 0.656 | 0.037 | 17.730   |
| 10  | (01110) + {01000,01111,01101,01111} + {01111} | red/red     | 0.009 | 0.004 | 1.928     | 0.475 | 0.755 | 0.629    |
| 9   | (01111) + {01000,01011,11111,11111} + {11111} | red/blue    | 0.009 | 0.033 | 0.263     | 0.322 | 0.001 | 322.000  |
| 8   | (01111) + {01000,01011,11111,01111} + {11111} | red/blue    | 0.014 | 0.025 | 0.575     | 0.131 | 0.008 | 16.054   |
| 7   | (11100) + {01000,11000,11110,11101} + {11111} | red/red     | 0.016 | 0.016 | 0.988     | 0.251 | 0.269 | 0.933    |
| 6   | (11100) + {01000,11010,11101,11101} + {01010} | red/blue    | 0.020 | 0.042 | 0.477     | 0.147 | 0.003 | 45.231   |
| 5   | (11000) + {01000,11110,11110,11110} + {01100} | red/blue    | 0.021 | 0.056 | 0.373     | 0.136 | 0.000 | $\infty$ |
| 4   | (11100) + {01000,11101,11011,11111} + {11111} | red/blue    | 0.021 | 0.055 | 0.384     | 0.136 | 0.000 | $\infty$ |
| 3   | (11100) + {01000,11110,11101,11111} + {11011} | red/blue    | 0.021 | 0.055 | 0.384     | 0.136 | 0.000 | $\infty$ |
| 2   | (11100) + {01000,11100,11110,01111} + {11111} | red/blue    | 0.021 | 0.046 | 0.459     | 0.136 | 0.001 | 102.256  |
| 1   | (11110) + {01000,11000,11101,11111} + {11011} | red/blue    | 0.022 | 0.068 | 0.316     | 0.212 | 0.000 | $\infty$ |





Figure 30. $0^{\ast\ast\ast\ast}$ (GouldCFU) to $0^{\ast\ast\ast\ast}$ (GouldTTD).

Figure 31. $1^{\ast\ast\ast\ast}$ (GouldCFU) to $1^{\ast\ast\ast\ast}$ (GouldTTD).

Figure 32. $\ast0^{\ast\ast\ast\ast}$ (GouldCFU) to $\ast0^{\ast\ast\ast\ast}$ (GouldTTD).
Figure 33. *1*** (GouldCFU) to *1*** (GouldTTD).

Figure 34. 0**** (GouldCFU, log10) to 0**** (GouldTTD).

Figure 35. 1**** (GouldCFU, log10) to 1**** (GouldTTD).
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Figure 36. $*0***$(GouldCFU$\log_{10}$) to $*0***$(GouldTTD).

Figure 37. $*1***$(GouldCFU$\log_{10}$) to $*1***$(GouldTTD).
| No. | bipyramid | type | $e_o$  | $e_p$  | $e_o/e_p$ | $p_o$  | $p_p$  | $p_o/p_p$ |
|-----|-----------|------|--------|--------|----------|--------|--------|----------|
| 22  | {01001}+{01000,01100,01010,00111}+{00110} | red/blue | 0.010  | 0.027  | 0.357    | 0.978  | 0.038  | 25.873   |
| 21  | {01001}+{01000,01001,01101,00111}+{00110} | red/blue | 0.010  | 0.027  | 0.357    | 0.978  | 0.038  | 25.873   |
| 20  | {01001}+{01000,01001,01101,00111}+{00110} | red/blue | 0.010  | 0.027  | 0.357    | 0.978  | 0.038  | 25.873   |
| 19  | {01001}+{01000,01001,01101,00111}+{00110} | red/blue | 0.014  | 0.039  | 0.357    | 0.978  | 0.038  | 25.873   |
| 18  | {01100}+{01001,01110,01101,00111}+{00111} | red/red | 0.017  | 0.006  | 2.747    | 0.815  | 0.677  | 1.204    |
| 17  | {01000}+{01100,01101,00110,00111}+{01110} | red/red | 0.021  | 0.013  | 1.584    | 0.783  | 0.433  | 1.808    |
| 16  | {01000}+{01100,01101,00110,00111}+{01110} | red/red | 0.026  | 0.017  | 1.514    | 0.807  | 0.302  | 2.672    |
| 15  | {01001}+{01100,01010,01110,00111}+{00110} | red/red | 0.027  | 0.017  | 1.619    | 0.941  | 0.231  | 4.074    |
| 14  | {00001}+{00010,01001,00111,01111}+{01011} | red/red | 0.031  | 0.012  | 2.630    | 0.905  | 0.312  | 2.901    |
| 13  | {01000}+{00000,01000,01001,01100}+{01111} | red/red | 0.057  | 0.011  | 5.217    | 0.869  | 0.479  | 1.814    |
| 12  | {00010}+{01000,01101,00110,00111}+{01100} | red/red | 0.057  | 0.019  | 2.943    | 0.531  | 0.148  | 3.588    |
| 11  | {00010}+{01000,01100,00111,00111}+{01100} | red/red | 0.067  | 0.047  | 1.431    | 0.853  | 0.032  | 27.079   |
| 10  | {00010}+{01000,01101,00111,00111}+{01111} | red/red | 0.067  | 0.047  | 1.431    | 0.853  | 0.032  | 27.079   |
| 9   | {00000}+{01000,01000,00010,00001}+{01001} | red/red | 0.068  | 0.035  | 1.911    | 0.851  | 0.086  | 9.872    |
| 8   | {00100}+{01000,01100,00111,00111}+{01010} | red/red | 0.085  | 0.025  | 3.408    | 0.317  | 0.083  | 3.819    |
| 7   | {01000}+{00100,00101,01001,00011}+{00001} | red/red | 0.087  | 0.017  | 5.217    | 0.869  | 0.479  | 1.814    |
| 6   | {01000}+{01000,01101,00111,00111}+{01011} | red/red | 0.095  | 0.052  | 1.816    | 0.791  | 0.019  | 40.984   |
| 5   | {00001}+{01000,01001,01011,00111}+{01100} | red/blue | 0.157  | 0.010  | 15.097   | 0.533  | 0.362  | 1.472    |
| 4   | {01010}+{00010,01001,01101,00111}+{00011} | blue/blue | 0.192  | 0.028  | 6.871    | 0.032  | 0.042  | 0.758    |
| 3   | {00010}+{00100,00001,01001,00111}+{00101} | red/red | 0.197  | 0.014  | 13.654   | 0.262  | 0.211  | 1.242    |
| 2   | {01100}+{01010,01011,00111,00111}+{01101} | red/red | 0.209  | 0.019  | 11.109   | 0.502  | 0.175  | 2.869    |
| 1   | {01000}+{00010,01010,01011,00111}+{01101} | blue/blue | 0.229  | 0.032  | 7.188    | 0.458  | 0.049  | 9.271    |

| No. | bipyramid | type | $e_o$  | $e_p$  | $e_o/e_p$ | $p_o$  | $p_p$  | $p_o/p_p$ |
|-----|-----------|------|--------|--------|----------|--------|--------|----------|
| 0   | {00100}+{00010,01001,01011,00111}+{00011} | blue/red | 0.365  | 0.007  | 53.243   | 0.026  | 0.526  | 0.049    |
Table 15. Parallel analysis GouldCFU 1**** → Gould 1****, non-critical red/red-case omitted.

| No. | bipyramid                        | type  | $e_0$ | $e_p$ | $e_0/e_p$ | $p_0$ | $p_p$ | $p_0/p_p$ |
|-----|----------------------------------|-------|-------|-------|-----------|-------|-------|-----------|
| 23  | {1101}+{1100,1010,1110,1101}+{1111} | red/blue | 0.002 | 0.051 | 0.033    | 0.962 | 0.001 | 1286.096  |
| 22  | {1110}+{1100,1010,1110,1101}+{1111} | red/red | 0.017 | 0.066 | 2.799    | 0.773 | 0.689 | 1.122     |
| 21  | {1000}+{1101,1010,1001,1101}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 20  | {1000}+{1100,1010,1001,1101}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 19  | {1000}+{1100,1101,1010,1110}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 18  | {1000}+{1100,1101,1010,1110}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 17  | {1000}+{1100,1101,1010,1110}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 16  | {1000}+{1100,1101,1010,1110}+{1111} | red/red | 0.023 | 0.002 | 10.615   | 0.967 | 0.875 | 1.105     |
| 15  | {1101}+{1100,1010,1001,1110}+{1111} | red/blue | 0.027 | 0.039 | 0.695    | 0.580 | 0.012 | 47.154    |
| 14  | {1101}+{1000,1100,1010,1111}+{1011} | red/red | 0.031 | 0.012 | 2.513    | 0.693 | 0.277 | 2.502     |
| 13  | {1110}+{1000,1000,1010,1111}+{1011} | red/blue | 0.033 | 0.031 | 1.066    | 0.388 | 0.007 | 54.190    |
| 12  | {1101}+{1100,1010,1111,1111}+{1111} | red/red | 0.059 | 0.017 | 3.428    | 0.905 | 0.318 | 2.846     |
| 11  | {1101}+{1100,1010,1111,1111}+{1111} | red/red | 0.059 | 0.017 | 3.428    | 0.905 | 0.318 | 2.846     |
| 10  | {1101}+{1000,1100,1010,1111}+{1111} | red/blue | 0.060 | 0.068 | 0.881    | 0.902 | 0.000 | $\infty$ |
| 9   | {1000}+{1100,1110,1010,1111}+{1111} | red/red | 0.070 | 0.012 | 5.959    | 0.897 | 0.426 | 2.106     |
| 8   | {1010}+{1000,1110,1010,1110}+{1110} | red/red | 0.080 | 0.021 | 3.820    | 0.430 | 0.274 | 1.569     |
| 7   | {1110}+{1110,1010,1011,1111}+{1011} | red/red | 0.134 | 0.021 | 6.534    | 0.130 | 0.227 | 0.573     |
| 6   | {1100}+{1100,1101,1010,1111}+{1110} | red/blue | 0.163 | 0.035 | 4.659    | 0.737 | 0.019 | 38.586    |
| 5   | {1000}+{1100,1101,1011,1111}+{1110} | red/red | 0.163 | 0.028 | 5.788    | 0.776 | 0.075 | 10.402    |
| 4   | {1000}+{1100,1100,1101,1111}+{1110} | red/red | 0.163 | 0.028 | 5.788    | 0.776 | 0.075 | 10.402    |
| 3   | {1100}+{1100,1100,1010,1111}+{1110} | red/blue | 0.186 | 0.037 | 5.000    | 0.695 | 0.026 | 26.834    |
| 2   | {1000}+{1000,1100,1100,1110}+{1110} | red/red | 0.200 | 0.043 | 4.659    | 0.737 | 0.019 | 38.586    |
| 1   | {1100}+{1100,1101,1010,1111}+{1101} | red/red | 0.239 | 0.007 | 35.102   | 0.621 | 0.628 | 0.989     |
|     | {1110}+{1100,1101,1010,1111}+{1101} | red/blue | 0.253 | 0.030 | 8.530    | 0.671 | 0.104 | 6.452     |
|     | {1100}+{1100,1101,1010,1111}+{1101} | red/blue | 0.301 | 0.026 | 11.785   | 0.288 | 0.035 | 8.348     |
|     | {1100}+{1100,1010,1001,1110}+{1101} | red/blue | 0.313 | 0.039 | 8.062    | 0.598 | 0.014 | 43.650    |
Table 16. Parallel analysis GouldCFU *0*** → Gould *0***, non-critical red/red-case omitted.

| No. | bipyramid                                                                 | type      | $e_o$ | $e_p$ | $e_o/e_p$ | $p_o$ | $p_p$ | $p_o/p_p$ |
|-----|---------------------------------------------------------------------------|-----------|-------|-------|-----------|-------|-------|-----------|
| 21  | {10001}+{10000,00101,10010,10011}+{00111}                               | red/blue  | 0.012 | 0.024 | 0.481     | 0.963 | 0.026 | 36.756    |
| 20  | {00010}+{10000,00101,00011,00111}+{10011}                              | red/red   | 0.021 | 0.012 | 1.714     | 0.797 | 0.270 | 2.952     |
| 19  | {10101}+{10000,00101,10110,10101}+{00110}                              | red/red   | 0.022 | 0.007 | 3.155     | 0.869 | 0.717 | 1.212     |
| 18  | {10110}+{10000,10010,00111,10111}+{10011}                              | red/red   | 0.031 | 0.012 | 2.513     | 0.693 | 0.277 | 2.502     |
| 17  | {00100}+{10000,00110,10101,00111}+{10110}                              | red/red   | 0.040 | 0.018 | 2.266     | 0.915 | 0.290 | 3.155     |
| 16  | {00100}+{10000,00110,10110,10101}+{00111}                              | red/red   | 0.049 | 0.022 | 2.266     | 0.915 | 0.290 | 3.155     |
| 15  | {00001}+{10000,00100,00010,00111}+{10010}                              | red/blue  | 0.079 | 0.026 | 3.047     | 0.688 | 0.023 | 30.749    |
| 14  | {00010}+{10000,10010,00110,00111}+{10110}                              | red/red   | 0.113 | 0.008 | 13.352    | 0.295 | 0.461 | 0.640     |
| 13  | {00000}+{10000,00100,00010,00001}+{00111}                              | red/blue  | 0.133 | 0.048 | 2.775     | 0.476 | 0.001 | 707.281   |
| 12  | {10010}+{10000,10011,00111,10111}+{10101}                              | red/red   | 0.133 | 0.023 | 5.788     | 0.776 | 0.075 | 10.402    |
| 11  | {10101}+{10000,10110,00111,10111}+{10101}                              | red/red   | 0.133 | 0.023 | 5.788     | 0.776 | 0.075 | 10.402    |
| 10  | {00011}+{10000,00001,10011,00111}+{10101}                              | red/red   | 0.208 | 0.001 | 275.689   | 0.413 | 0.949 | 0.435     |
| 9   | {00010}+{10000,00100,00001,00111}+{00101}                              | red/red   | 0.227 | 0.017 | 13.654    | 0.262 | 0.211 | 1.242     |
| 8   | {00100}+{10000,00001,00101,00111}+{10101}                              | red/red   | 0.269 | 0.033 | 8.193     | 0.579 | 0.101 | 5.733     |
| 7   | {00001}+{10000,00100,00010,00111}+{10101}                              | red/red   | 0.269 | 0.033 | 8.193     | 0.579 | 0.101 | 5.733     |
| 6   | {00010}+{10000,00010,00011,00111}+{10010}                              | red/red   | 0.275 | 0.004 | 67.167    | 0.493 | 0.755 | 0.653     |
| 5   | {00001}+{10000,00001,00111,00111}+{10010}                              | red/red   | 0.275 | 0.004 | 67.167    | 0.493 | 0.755 | 0.653     |
| 4   | {00110}+{10000,00100,10011,00111}+{00101}                              | red/red   | 0.306 | 0.009 | 32.813    | 0.413 | 0.610 | 0.677     |
| 3   | {00110}+{10000,10010,10110,00111}+{10111}                              | red/blue  | 0.344 | 0.024 | 14.403    | 0.186 | 0.035 | 5.345     |
| 2   | {00100}+{10000,00010,10010,00111}+{00011}                              | red/blue  | 0.354 | 0.024 | 14.760    | 0.175 | 0.030 | 5.853     |
| 1   | {00100}+{10000,00010,00001,00111}+{00011}                              | blue/red  | 0.421 | 0.008 | 53.234    | 0.026 | 0.526 | 0.049     |
|     | {00110}+{10000,10110,10010,00111}+{10111}                              | red/blue  | 0.486 | 0.034 | 14.403    | 0.186 | 0.035 | 5.345     |
**Table 17.** Parallel analysis GouldCFU \(*1^{***} \rightarrow \) Gould \(*1^{***} ,\) non-critical red/red-case omitted.

| No. | bipyramid | type      | \(e_o\) | \(e_p\) | \(e_o/e_p\) | \(p_o\) | \(p_p\) | \(p_o/p_p\) |
|-----|-----------|-----------|--------|--------|-------------|--------|--------|-------------|
| 23  | \{01100\}+\{11000,01110,01101,11110\}+\{11101\} | red/red   | 0.001 | 0.018 | 0.054       | 0.998 | 0.292 | 3.418       |
| 22  | \{01010\}+\{11000,01010,01001,01110\}+\{11101\} | red/red   | 0.001 | 0.018 | 0.054       | 0.998 | 0.292 | 3.418       |
| 21  | \{01000\}+\{11000,01001,01110,01101\}+\{11101\} | red/red   | 0.001 | 0.018 | 0.054       | 0.998 | 0.292 | 3.418       |
| 20  | \{11001\}+\{11000,01001,11101,11011\}+\{11111\} | red/blue  | 0.002 | 0.059 | 0.033       | 0.962 | 0.001 | 1286.096    |
| 19  | \{11110\}+\{11010,01110,01101,11111\}+\{01111\} | red/red   | 0.005 | 0.009 | 0.488       | 0.945 | 0.576 | 1.641       |
| 18  | \{11100\}+\{11000,01100,11110,11101\}+\{01101\} | red/red   | 0.005 | 0.023 | 0.218       | 0.952 | 0.193 | 4.933       |
| 17  | \{11000\}+\{11010,11011,01101,11110\}+\{11111\} | red/red   | 0.010 | 0.026 | 0.369       | 0.981 | 0.106 | 9.255       |
| 16  | \{01110\}+\{11000,11010,01101,11110\}+\{11111\} | red/red   | 0.010 | 0.026 | 0.369       | 0.981 | 0.106 | 9.255       |
| 15  | \{01010\}+\{11000,11010,11111,11111\}+\{11111\} | red/red   | 0.013 | 0.014 | 0.905       | 0.866 | 0.346 | 2.503       |
| 14  | \{11000\}+\{01001,11010,01110,01101\}+\{01111\} | red/red   | 0.013 | 0.020 | 0.656       | 0.974 | 0.160 | 6.087       |
| 13  | \{11000\}+\{01001,11010,01110,11111\}+\{01111\} | red/red   | 0.013 | 0.020 | 0.656       | 0.974 | 0.160 | 6.087       |
| 12  | \{01000\}+\{11000,01001,01010,01001\}+\{01110\} | red/red   | 0.024 | 0.015 | 1.584       | 0.783 | 0.433 | 1.808       |
| 11  | \{11010\}+\{11000,01001,01101,11111\}+\{11101\} | red/red   | 0.059 | 0.017 | 3.428       | 0.905 | 0.318 | 2.846       |
| 10  | \{11010\}+\{11000,11010,11110,11101\}+\{11101\} | red/red   | 0.059 | 0.017 | 3.428       | 0.905 | 0.318 | 2.846       |
| 9   | \{11110\}+\{11000,01110,11111,11111\}+\{11111\} | red/red   | 0.059 | 0.017 | 3.428       | 0.905 | 0.318 | 2.846       |
| 8   | \{01010\}+\{01001,11010,01110,01011\}+\{01111\} | red/red   | 0.067 | 0.018 | 3.722       | 0.323 | 0.186 | 1.737       |
| 7   | \{01110\}+\{01001,11010,01101,01111\}+\{11111\} | red/red   | 0.075 | 0.022 | 3.483       | 0.841 | 0.136 | 6.184       |
| 6   | \{01001\}+\{11010,01110,01101,01111\}+\{11111\} | red/red   | 0.075 | 0.022 | 3.483       | 0.841 | 0.136 | 6.184       |
| 5   | \{11011\}+\{01101,11010,01011,11111\}+\{01111\} | red/red   | 0.081 | 0.000 | 1235.241    | 0.126 | 0.996 | 0.127       |
| 4   | \{11000\}+\{01010,01001,11001,11011\}+\{01011\} | red/blue  | 0.170 | 0.030 | 5.666       | 0.718 | 0.026 | 27.722      |
| 3   | \{11000\}+\{11000,01101,11101,11111\}+\{01011\} | red/blue  | 0.170 | 0.030 | 5.666       | 0.718 | 0.026 | 27.722      |
| 2   | \{01101\}+\{01001,11010,11110,11111\}+\{01111\} | red/red   | 0.192 | 0.013 | 15.097      | 0.533 | 0.362 | 1.472       |
| 1   | \{01101\}+\{01001,11010,01111,11111\}+\{01111\} | red/red   | 0.192 | 0.013 | 15.097      | 0.533 | 0.362 | 1.472       |
Table 18. Parallel analysis GouldCFU_log10 0**** → Gould 0****, non-critical red/red-case omitted.

| No. | bipyramid                                                                 | type       | $e_o$ | $e_p$ | $e_o/e_p$ | $p_o$ | $p_p$ | $p_o/p_p$ |
|-----|---------------------------------------------------------------------------|------------|-------|-------|-----------|-------|-------|-----------|
| 23  | {01110}+(00000,01000,01111,01111)+{01010}                                | red/red    | 0.001 | 0.001 | 0.662     | 0.968 | 0.956 | 1.013     |
| 22  | {01110}+(00000,01000,01111,01111)+{01011}                                | red/red    | 0.001 | 0.001 | 0.662     | 0.968 | 0.956 | 1.013     |
| 21  | {00010}+(00000,01110,01111,01111)+{01111}                                | red/blue   | 0.001 | 0.029 | 0.032     | 0.971 | 0.029 | 32.915    |
| 20  | {00010}+(00000,01110,01111,01111)+{01111}                                | red/blue   | 0.001 | 0.029 | 0.032     | 0.971 | 0.029 | 32.915    |
| 19  | {01001}+(00000,01000,01101,01111)+{01111}                                | red/red    | 0.002 | 0.013 | 0.123     | 0.917 | 0.362 | 2.533     |
| 18  | {01001}+(00000,01111,01111,01111)+{01111}                                | red/red    | 0.002 | 0.019 | 0.123     | 0.917 | 0.362 | 2.533     |
| 17  | {01110}+(00000,01000,01111,01111)+{01111}                                | red/blue   | 0.005 | 0.049 | 0.097     | 0.794 | 0.003 | 316.335   |
| 16  | {00010}+(00000,01100,01110,01111)+{01010}                                | red/blue   | 0.006 | 0.059 | 0.097     | 0.794 | 0.003 | 316.335   |
| 15  | {01001}+(00000,01011,01111,01111)+{01011}                                | red/blue   | 0.006 | 0.053 | 0.111     | 0.702 | 0.001 | 1355.212  |
| 14  | {01001}+(00000,01011,01111,01111)+{00011}                                | red/red    | 0.012 | 0.014 | 0.821     | 0.398 | 0.312 | 1.276     |
| 13  | {01100}+(00000,01000,01110,01111)+{01111}                                | red/red    | 0.012 | 0.006 | 2.033     | 0.475 | 0.677 | 0.702     |
| 12  | {01100}+(00000,01000,01110,01111)+{01111}                                | red/red    | 0.012 | 0.006 | 2.033     | 0.475 | 0.677 | 0.702     |
| 11  | {00101}+(00000,01010,01111,01111)+{01111}                                | red/red    | 0.013 | 0.019 | 0.678     | 0.372 | 0.195 | 1.908     |
| 10  | {00101}+(00000,01010,01111,01111)+{00011}                                | red/blue   | 0.018 | 0.029 | 0.617     | 0.464 | 0.030 | 15.518    |
| 9   | {01110}+(00000,01100,01110,01111)+{00111}                                | red/red    | 0.020 | 0.016 | 1.237     | 0.289 | 0.147 | 1.966     |
| 8   | {01110}+(00000,01100,01110,01111)+{00111}                                | red/red    | 0.020 | 0.016 | 1.237     | 0.289 | 0.147 | 1.966     |
| 7   | {01010}+(00000,01110,01111,01111)+{00110}                                | red/red    | 0.020 | 0.011 | 1.912     | 0.454 | 0.425 | 1.068     |
| 6   | {01010}+(00000,01110,01111,01111)+{00110}                                | red/red    | 0.021 | 0.018 | 1.174     | 0.216 | 0.186 | 1.161     |
| 5   | {00101}+(00000,01010,01111,01111)+{01101}                                | blue/red   | 0.065 | 0.009 | 7.056     | 0.005 | 0.465 | 0.010     |
| 4   | {00101}+(00000,01100,01111,01111)+{01101}                                | blue/red   | 0.065 | 0.009 | 7.056     | 0.005 | 0.465 | 0.010     |
| 3   | {01000}+(00000,01110,01111,01111)+{00100}                                | blue/red   | 0.085 | 0.025 | 3.382     | 0.000 | 0.147 | 0.001     |
| 2   | {01000}+(00000,01110,01111,01111)+{00010}                                | blue/blue  | 0.132 | 0.004 | 34.628    | 0.000 | 0.809 | 0.000     |
| 1   | {00100}+(00000,01110,01111,01111)+{00010}                                | blue/blue  | 0.142 | 0.009 | 16.200    | 0.000 | 0.619 | 0.000     |
|     | {00100}+(00000,01110,01111,01111)+{01010}                                | blue/red   | 0.143 | 0.008 | 18.337    | 0.000 | 0.567 | 0.000     |
|     | {00100}+(00000,01110,01111,01111)+{01100}                                | blue/red   | 0.143 | 0.008 | 18.337    | 0.000 | 0.567 | 0.000     |
|     | {00010}+(00000,01110,01111,01111)+{00010}                                | blue/blue  | 0.200 | 0.028 | 7.074     | 0.000 | 0.026 | 0.000     |
Higher-Order Interactions in Fitness Landscapes Are Sparse

Table 19. Parallel analysis GouldCFU_log10 1**** → Gould 1****, non-critical red/red-case omitted.

| No. | bipyr.a | type    | $e_a$ | $e_p$ | $e_a/e_p$ | $p_a$ | $p_p$ | $p_a/p_p$ |
|-----|---------|---------|-------|-------|-----------|-------|-------|-----------|
| 22  | {11010}+{11000,11001,10101,11111}+{11011} | red/blue | 0.000 | 0.051 | 0.002     | 0.995 | 0.001 | 1330.214  |
| 21  | {10110}+{11000,10010,11010,10101}+{11011} | red/blue | 0.001 | 0.063 | 0.011     | 0.972 | 0.001 | 943.689   |
| 20  | {11000}+{10010,11010,10101,11011}+{11011} | red/blue | 0.001 | 0.063 | 0.011     | 0.972 | 0.001 | 943.689   |
| 19  | {10010}+{11010,10101,11111}+{10110} | red/blue | 0.001 | 0.063 | 0.011     | 0.972 | 0.001 | 943.689   |
| 18  | {10110}+{11000,11100,10101,11111}+{10111} | red/blue | 0.001 | 0.063 | 0.011     | 0.972 | 0.001 | 943.689   |
| 17  | {11000}+{10010,10101,10011,11011}+{10111} | red/red | 0.001 | 0.002 | 0.661     | 0.902 | 0.838 | 1.076     |
| 16  | {11010}+{10100,10101,10101,11011}+{11111} | red/blue | 0.002 | 0.049 | 0.043     | 0.892 | 0.001 | 961.207   |
| 15  | {11010}+{10110,10101,11011,11111}+{11111} | red/blue | 0.002 | 0.049 | 0.043     | 0.892 | 0.001 | 961.207   |
| 14  | {11000}+{10010,10001,10101,11011}+{10011} | red/red | 0.003 | 0.017 | 0.197     | 0.753 | 0.090 | 8.357     |
| 13  | {10001}+{11000,10010,10101,11011}+{11010} | red/blue | 0.003 | 0.072 | 0.047     | 0.827 | 0.000 | $\infty$ |
| 12  | {11010}+{11000,11100,11110,11111}+{10101} | red/blue | 0.004 | 0.037 | 0.099     | 0.834 | 0.026 | 32.201    |
| 11  | {10001}+{11000,10000,10101,10101}+{11110} | red/red | 0.004 | 0.015 | 0.296     | 0.763 | 0.225 | 3.391     |
| 10  | {11010}+{11000,11100,11011,11110}+{11110} | red/red | 0.004 | 0.023 | 0.189     | 0.761 | 0.065 | 11.744    |
| 9   | {10010}+{11100,10101,10101,11111}+{11111} | red/red | 0.004 | 0.015 | 0.296     | 0.746 | 0.215 | 3.470     |
| 8   | {10101}+{11000,11001,10101,11111}+{11110} | red/blue | 0.004 | 0.046 | 0.099     | 0.834 | 0.026 | 32.201    |
| 7   | {10010}+{11000,11010,10101,11111}+{11101} | red/blue | 0.005 | 0.048 | 0.106     | 0.782 | 0.012 | 66.271    |
| 6   | {10001}+{11000,10101,10101,11111}+{11101} | red/blue | 0.005 | 0.048 | 0.106     | 0.782 | 0.012 | 66.271    |
| 5   | {10000}+{11000,10010,10101,11001}+{11111} | red/red | 0.008 | 0.006 | 1.228     | 0.595 | 0.689 | 0.864     |
| 4   | {10000}+{11000,10010,10101,11001}+{11100} | red/red | 0.009 | 0.020 | 0.431     | 0.491 | 0.199 | 2.467     |
| 3   | {10000}+{11000,10010,10101,11010}+{11111} | red/blue | 0.009 | 0.030 | 0.296     | 0.479 | 0.011 | 44.352    |
| 2   | {10000}+{11000,10010,10101,11010}+{11101} | red/red | 0.010 | 0.009 | 1.111     | 0.353 | 0.498 | 0.709     |
| 1   | {10000}+{11000,10101,10101,11010}+{11100} | red/blue | 0.010 | 0.068 | 0.143     | 0.505 | 0.000 | $\infty$  |
|     | {10000}+{11000,10101,10101,11101}+{11101} | red/blue | 0.012 | 0.056 | 0.210     | 0.458 | 0.002 | 221.256   |
|     | {11001}+{11000,10101,11101,11111}+{11110} | red/blue | 0.012 | 0.030 | 0.406     | 0.316 | 0.033 | 9.518     |
Table 20. Parallel analysis GouldCFU_log10 *0*** → Gould *0***, non-critical red/red-case omitted.

| No. | bipyrramid                              | type           | e_o  | e_p  | e_o/e_p | p_o  | p_p  | p_o/p_p |
|-----|----------------------------------------|----------------|------|------|---------|------|------|---------|
| 23  | {10001}+{00000,10010,10101,10011}+{10111} | red/red        | 0.002| 0.003| 0.661   | 0.902| 0.838| 1.076   |
| 22  | {10001}+{00000,10101,10011,00111}+{10111} | red/red        | 0.003| 0.004| 0.661   | 0.902| 0.838| 1.076   |
| 21  | {10110}+{00000,10010,10101,10111}+{10011} | red/red        | 0.003| 0.012| 0.230   | 0.830| 0.277| 2.996   |
| 20  | {00010}+{00000,10010,00110,10011}+{10111} | red/red        | 0.003| 0.005| 0.670   | 0.898| 0.703| 1.277   |
| 19  | {00010}+{00000,00110,10011,00111}+{10111} | red/red        | 0.003| 0.005| 0.670   | 0.898| 0.703| 1.277   |
| 18  | {10001}+{00000,00010,10101,00111}+{00101} | red/red        | 0.004| 0.029| 0.130   | 0.809| 0.053| 15.293  |
| 17  | {10110}+{00000,10010,00110,10111}+{10011} | red/red        | 0.004| 0.018| 0.230   | 0.830| 0.277| 2.996   |
| 16  | {10001}+{00000,10000,10101,10011}+{10110} | red/red        | 0.004| 0.015| 0.296   | 0.763| 0.225| 3.391   |
| 15  | {10001}+{00000,00001,10111,00111}+{00011} | red/red        | 0.005| 0.020| 0.234   | 0.681| 0.136| 5.007   |
| 14  | {10101}+{00000,00001,10001,00111}+{00101} | red/blue       | 0.012| 0.035| 0.349   | 0.437| 0.026| 16.679  |
| 13  | {10000}+{00000,10010,10000,10101}+{10011} | red/red        | 0.013| 0.025| 0.505   | 0.361| 0.088| 4.107   |
| 12  | {00000}+{00000,10001,10110,00111}+{10101} | red/blue       | 0.015| 0.042| 0.349   | 0.437| 0.026| 16.679  |
| 11  | {10100}+{00000,10000,10110,10110}+{10010} | red/red        | 0.017| 0.015| 1.199   | 0.302| 0.400| 0.755   |
| 10  | {00101}+{00000,00110,10110,11001}+{00011} | red/blue       | 0.018| 0.029| 0.617   | 0.464| 0.030| 15.518  |
| 9   | {00101}+{00000,00100,10101,00111}+{11011} | red/red        | 0.020| 0.016| 1.301   | 0.210| 0.293| 0.717   |
| 8   | {10010}+{00000,00010,00110,10011}+{00111} | red/blue       | 0.021| 0.036| 0.585   | 0.234| 0.001| 372.019 |
| 7   | {10110}+{00000,00010,10011,10011}+{00111} | red/blue       | 0.021| 0.036| 0.585   | 0.234| 0.001| 372.019 |
| 6   | {10100}+{00000,00010,00110,01011}+{11011} | red/red        | 0.024| 0.024| 1.008   | 0.187| 0.035| 5.374   |
| 5   | {00110}+{00000,00100,10111,11011}+{10101} | blue/red       | 0.060| 0.006| 9.634   | 0.012| 0.624| 0.020   |
| 4   | {00101}+{00000,00100,10110,11011}+{10110} | blue/red       | 0.060| 0.006| 9.634   | 0.012| 0.624| 0.020   |
| 3   | {10000}+{00000,00110,10110,11011}+{01000} | blue/red       | 0.084| 0.030| 2.783   | 0.000| 0.080| 0.004   |
| 2   | {00100}+{00000,10011,10101,11111}+{10000} | blue/red       | 0.138| 0.007| 19.460  | 0.000| 0.618| 0.000   |
| 1   | {00010}+{00000,10011,10101,11111}+{10010} | blue/red       | 0.138| 0.007| 19.460  | 0.000| 0.618| 0.000   |
|     |                                        | blue/blue      | 0.139| 0.046| 3.043   | 0.000| 0.002| 0.000   |
|     |                                        | blue/blue      | 0.141| 0.019| 7.218   | 0.000| 0.142| 0.000   |
|     |                                        | blue/blue      | 0.141| 0.019| 7.218   | 0.000| 0.142| 0.000   |
|     |                                        | blue/red       | 0.197| 0.001| 217.990 | 0.000| 0.953| 0.000   |
|     |                                        | red/red        | 0.200| 0.013| 15.038  | 0.000| 0.413| 0.000   |
|     |                                        | red/red        | 0.200| 0.013| 15.038  | 0.000| 0.413| 0.000   |
|     |                                        | blue/blue      | 0.200| 0.028| 7.074   | 0.000| 0.026| 0.000   |
|     |                                        | red/red        | 0.221| 0.023| 9.646   | 0.000| 0.170| 0.000   |
|     |                                        | red/red        | 0.224| 0.018| 12.142  | 0.000| 0.335| 0.000   |

Gould

*Gould*/
Table 21. Parallel analysis GouldCFU_log10 *1*** → Gould *1***, non-critical red/red-case omitted.

| No. | bipyramid                                                                 | type     | $c_0$ | $c_p$ | $c_0/c_p$ | $p_0$ | $p_p$ | $p_0/p_p$ |
|-----|----------------------------------------------------------------------------|----------|-------|-------|-----------|-------|-------|-----------|
| 21  | $\{1100\}+\{1100,01101,01101,11111\}+\{11011\}$                         | red/blue | 0.000 | 0.051 | 0.002     | 0.995 | 0.001 | 1.330     |
| 20  | $\{11000\}+\{01000,11001,01101,11011\}+\{01010\}$                      | red/red  | 0.000 | 0.015 | 0.007     | 0.994 | 0.431 | 2.306     |
| 19  | $\{01110\}+\{01000,01011,11011,01111\}+\{01101\}$                      | red/red  | 0.001 | 0.001 | 0.662     | 0.968 | 0.956 | 1.013     |
| 18  | $\{01101\}+\{01000,01101,11011,01111\}+\{01011\}$                      | red/red  | 0.001 | 0.001 | 0.662     | 0.968 | 0.956 | 1.013     |
| 17  | $\{11100\}+\{11000,01100,11110,11101\}+\{01110\}$                      | red/red  | 0.001 | 0.006 | 0.147     | 0.964 | 0.725 | 1.330     |
| 16  | $\{01001\}+\{01000,01101,01111,11101\}+\{01111\}$                      | red/red  | 0.002 | 0.013 | 0.123     | 0.917 | 0.362 | 2.533     |
| 15  | $\{11000\}+\{01110,01101,11011,11111\}+\{01111\}$                      | red/red  | 0.002 | 0.008 | 0.211     | 0.880 | 0.480 | 1.833     |
| 14  | $\{11000\}+\{01000,01110,01101,11101\}+\{01111\}$                      | red/red  | 0.002 | 0.012 | 0.211     | 0.880 | 0.480 | 1.833     |
| 13  | $\{11001\}+\{01000,01001,01101,11101\}+\{01011\}$                      | red/blue | 0.003 | 0.026 | 0.124     | 0.790 | 0.028 | 27.817    |
| 12  | $\{11001\}+\{11000,01100,11101,11111\}+\{01110\}$                      | red/blue | 0.004 | 0.037 | 0.105     | 0.709 | 0.002 | 347.549   |
| 11  | $\{11000\}+\{01000,11010,01110,11111\}+\{01011\}$                      | red/red  | 0.004 | 0.017 | 0.243     | 0.783 | 0.362 | 2.163     |
| 10  | $\{11110\}+\{11000,01101,01110,11111\}+\{11011\}$                      | red/blue | 0.005 | 0.031 | 0.169     | 0.707 | 0.035 | 20.493    |
| 9   | $\{11010\}+\{01000,11000,01110,11101\}+\{01101\}$                      | red/blue | 0.006 | 0.032 | 0.186     | 0.596 | 0.006 | 106.239   |
| 8   | $\{11010\}+\{11000,01101,11011,11111\}+\{01101\}$                      | red/blue | 0.006 | 0.032 | 0.186     | 0.596 | 0.006 | 106.239   |
| 7   | $\{11101\}+\{11000,01110,01101,11111\}+\{11011\}$                      | red/red  | 0.006 | 0.022 | 0.273     | 0.767 | 0.272 | 2.820     |
| 6   | $\{01100\}+\{11000,01110,01101,11101\}+\{11111\}$                      | red/red  | 0.007 | 0.001 | 8.612     | 0.705 | 0.957 | 0.737     |
| 5   | $\{01100\}+\{11000,01110,11101,11111\}+\{11111\}$                      | red/red  | 0.007 | 0.001 | 8.612     | 0.705 | 0.957 | 0.737     |
| 4   | $\{01000\}+\{11000,01110,01101,11111\}+\{11111\}$                      | red/red  | 0.007 | 0.007 | 0.995     | 0.460 | 0.573 | 0.803     |
| 3   | $\{01010\}+\{11000,01100,01110,11101\}+\{11110\}$                      | red/red  | 0.007 | 0.015 | 0.486     | 0.656 | 0.305 | 2.151     |
| 2   | $\{01000\}+\{11000,01100,01110,01101\}+\{11110\}$                      | red/red  | 0.008 | 0.039 | 0.191     | 0.637 | 0.006 | 100.157   |
| 1   | $\{01010\}+\{01000,11010,01110,01101\}+\{11111\}$                      | red/red  | 0.016 | 0.025 | 0.638     | 0.364 | 0.131 | 2.779     |