This talk is based on joint work with Chenette, Philipps, Pudwell

Occurrences of a specific pattern in hypercube orientations

Manda Riehl

Math, then bio?

Bio, then math

Fitness Landscapes (Crona and Wiesner)

The typical allele (unmutated type) will be called the *wild type*. Populations have members with mutations, and those mutants can have better or worse fitness for their environment.

Over generations, we expect the population fitness to increase from the pressures of natural selection.

We can imagine these mutations occurring on some axes (2 in the following figure) and the fitness changes by height. This is a *landscape*.

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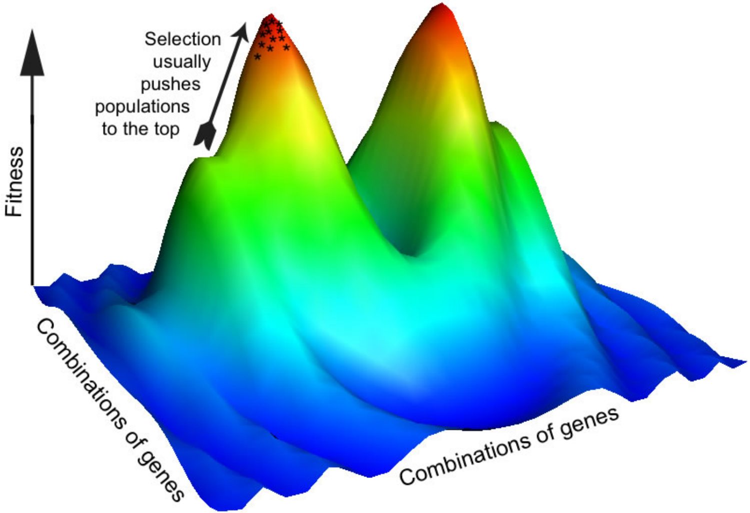
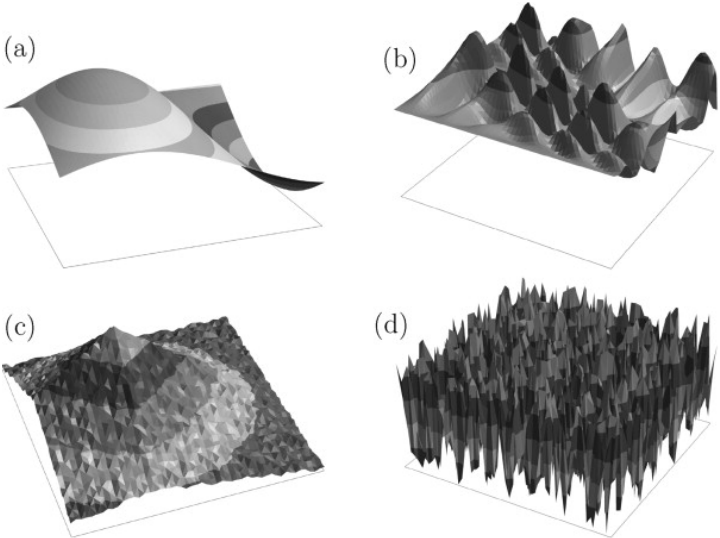
Fitness Landscapes



Which landscape is most likely?



Why do we care?

We can predict evolution under specific pressures.

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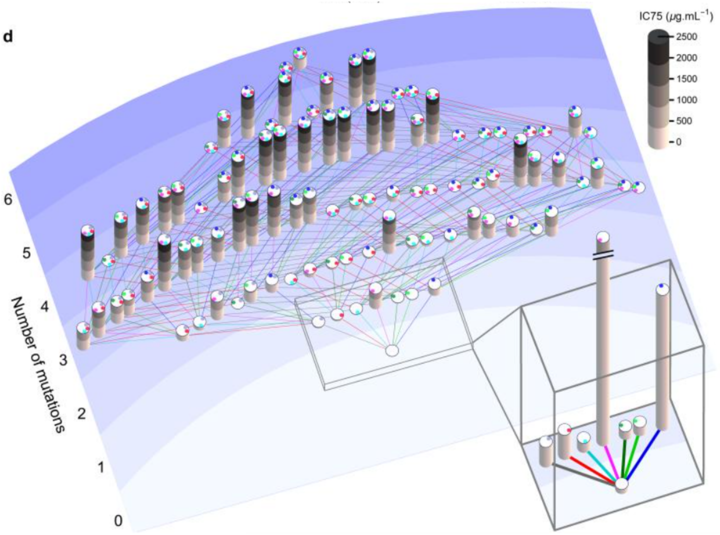
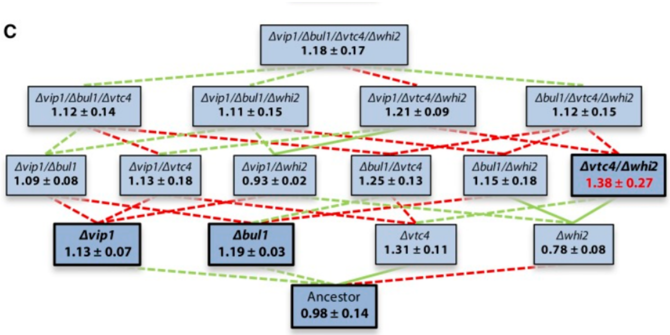
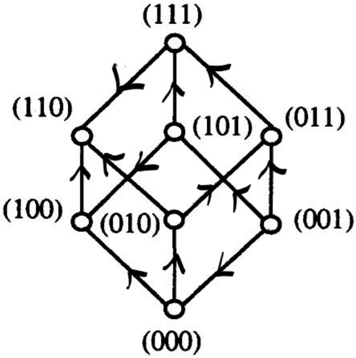

d
IC75 (μg.mL^{-1})
2500
2000
1500
1000
500
0
6
5
4
3
2
1
0
Number of mutations


C
Δvip1/Δbul1/Δvtc4/Δwhi2
1.18 ± 0.17
Δvip1/Δbul1/Δvtc4
1.12 ± 0.14
Δvip1/Δbul1/Δwhi2
1.11 ± 0.15
Δvip1/Δvtc4/Δwhi2
1.21 ± 0.09
Δbul1/Δvtc4/Δwhi2
1.12 ± 0.15
Δvip1/Δbul1
1.09 ± 0.08
Δvip1/Δvtc4
1.13 ± 0.18
Δvip1/Δwhi2
0.93 ± 0.02
Δbul1/Δvtc4
1.25 ± 0.13
Δbul1/Δwhi2
1.15 ± 0.18
Δvtc4/Δwhi2
1.38 ± 0.27
Δvip1
1.13 ± 0.07
Δbul1
1.19 ± 0.03
Δvtc4
1.31 ± 0.11
Δwhi2
0.78 ± 0.08
Ancestor
0.98 ± 0.14

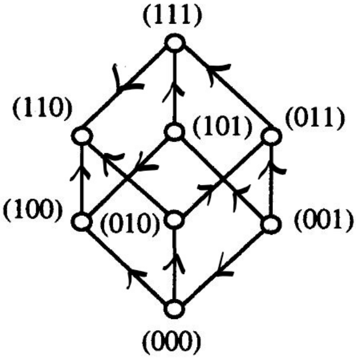
Discrete Landscapes



Here we have 3 genes, with increasing fitness marked with arrows.

It's acyclic!

Discrete Landscapes



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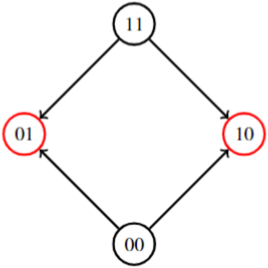
Which animal is this?

Reciprocal Sign Epistasis (RSE)

Two mutations, each beneficial, but both is worse than either individually



Or two mutations, each deleterious, but together beneficial.

Both are square faces of a hypercube with no maximal path of nontrivial length.

Or two mutations, each deleterious, but together beneficial.
Both are square faces of a hypercube with no maximal path of nontrivial length.

One early theorem in this area by Poelwijk et.al. states:

Theorem

A fitness landscape cannot have more than one peak without an occurrence of RSE.

Extension of Poelwijk

Theorem (CPPR '21)

In any dimension, a lattice with k peaks contains at least $k-1$ RSEs.

Sketch of proof:

By induction: Take an n-dimensional acyclic hypercube Q_n with $k > 2$ peaks. Pick two of them, identify the sub-lattice between them, call it $Q*$, with one peak at the bottom and the other at the top. $Q*$ has at least 1 RSE, and in that RSE some label has a bit 0 change to 1 in position i.

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Define Q_{n-1}^0 to be the hypercube with 0 in position i and Q_{n-1}^1 with 1.

Q_{n-1}^0 has $j > 0$ peaks (therefore at least $j-1$ RSE), and Q_{n-1}^1 has $k-j > 0$ peaks (therefore at least $k-j-1$ RSE.

So total we have at least $(j-1)+(k-j-1)+1 = k-1$ RSEs.

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Define Q^0_{n-1} to be the hypercube with 0 in position i and Q^1_{n-1} with 1.
Q^0_{n-1} has $j > 0$ peaks (therefore at least $j - 1$ RSE), and Q^1_{n-1} has $k - j > 0$ peaks (therefore at least $k - j - 1$ RSE.
So total we have at least $(j - 1) + (k - j - 1) + 1 = k - 1$ RSEs.

Visual Example

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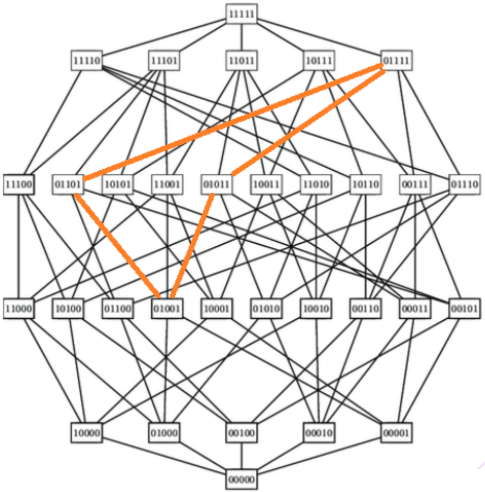

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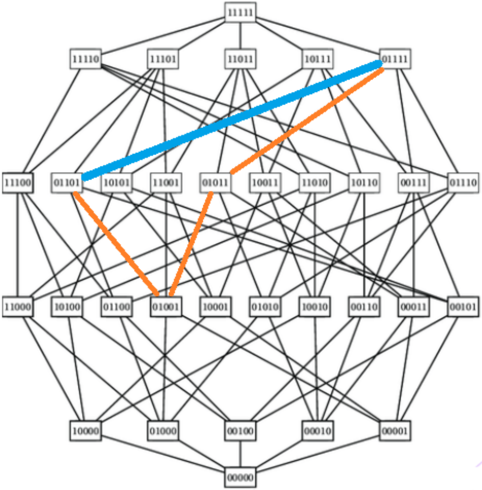

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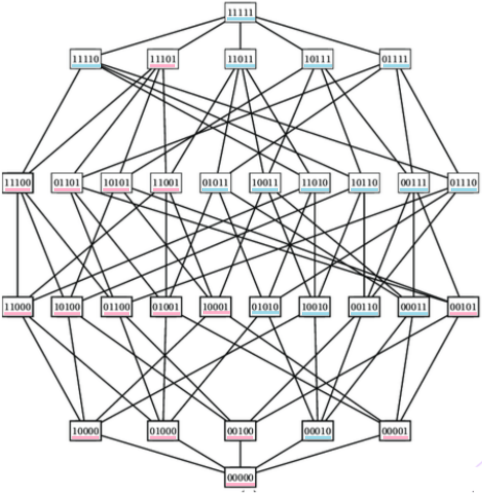

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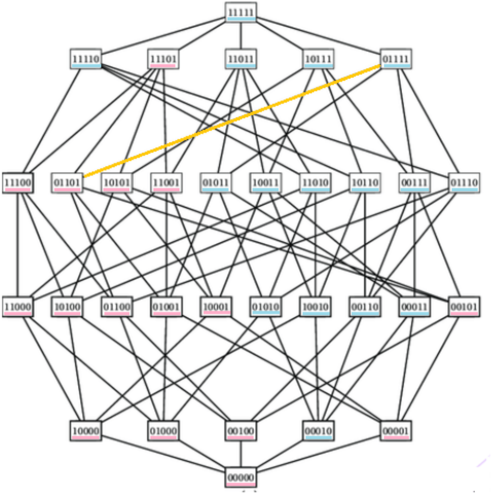

We computationally study which combinations of peaks and RSEs are possible. Our results can therefore be described as theorems on the joint distribution of two patterns (peaks and RSEs) in acyclic Boolean lattices, and likewise finding the maximum number of RSEs can be considered a form of pattern packing.

Our primary focus is on which combinations of peak counts and RSE counts are possible, in other words the nonzero entries in the joint distribution of the two patterns peak and RSE.

		Peaks				
		0	1	2	3	4
	0	0	91	0	0	0
	1	0	84	42	0	0
	2	0	0	93	0	0
RSEs	3	0	0	12	8	0
	4	0	0	0	9	0
	5	0	0	0	0	0
	6	0	0	0	0	1

Table: For dimension 3, number of acyclic orientations with each (number of RSEs, number of peaks).

		Peaks								
		0	1	2	3	4	5	6	7	8
	0	0	299511	0	0	0	0	0	0	0
	1	0	913656	227580	0	0	0	0	0	0
	2	0	1590669	1042032	11211	0	0	0	0	0
	3	0	1482852	2474108	153132	0	0	0	0	0
	4	0	974148	3355704	614796	0	0	0	0	0
	5	0	376440	2623086	1367388	12876	0	0	0	0
	6	0	127548	1459384	1523046	75708	0	0	0	0
	7	0	27936	524706	1211520	196788	0	0	0	0
	8	0	1485	192600	614094	248253	297	0	0	0
	9	0	0	22470	287724	231820	4828	0	0	0
	10	0	0	6180	72684	133764	12012	0	0	0
	11	0	0	0	19980	72144	15444	0	0	0
RSEs	12	0	0	75	2430	21488	14361	25	0	0
	13	0	0	0	612	8670	9276	306	0	0
	14	0	0	0	0	1116	5220	744	0	0
	15	0	0	0	0	480	1696	650	0	0
	16	0	0	0	0	0	936	798	0	0
	17	0	0	0	0	0	0	216	0	0
	18	0	0	0	0	0	35	264	25	0
	19	0	0	0	0	0	0	42	36	0
	20	0	0	0	0	0	0	0	0	0
	21	0	0	0	0	0	0	0	28	0
	22	0	0	0	0	0	0	0	0	0
	23	0	0	0	0	0	0	0	0	0
	24	0	0	0	0	0	0	0	0	1

Theorem (CPPR '21)

Single-peaked n-dimensional lattices exist with r_n RSEs, where

$$r_n = 2^{n-3}(n^2 - 5n + 8) - 1. \tag{1}$$

Notably, the most significant term in this expression is $2^{n-3}n^2$. The total number of faces is $2^{n-3}(n^2 - n)$, which has the same most significant term. This means that, in high enough dimensions, an arbitrarily large proportion of the faces in a lattice can be RSEs while still having only one peak.

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Theorem (CPPR '21)

A single-peaked n-dimensional lattice cannot have more than

$$2^{n-3}(n^2 - n - 2\lfloor n/2 \rfloor) \tag{2}$$

RSE faces.

Conjecture (CPPR '21)

The maximum number of RSEs in a single-peaked n-dimensional lattice is $2^{n-3}(n^2 - 4n + 4)$.

n	2	3	4	5	6	7	8
Lower bound (known to be possible)	0	1	7	31	111	351	1023
Conjectured maximum	0	1	8	36	128	400	1152
Upper bound (more is impossible)	0	4	16	64	192	576	1536

Theorem (CPPR '21)

For $n \geq 4$, an n-dimensional lattice with $2^{n-1} - (n-1)$ peaks can have $2^{n-2}\binom{n}{2} - \binom{n}{2}$ RSEs but not $2^{n-2}\binom{n}{2} - \binom{n}{2} - 1$ RSEs.

Theorem

For $n \geq 4$, if an n-dimensional lattice has at least $2^{n-2}\binom{n}{2} - (n-1) - (n-2)$ RSEs, then it must have exactly:

$2^{n-2}\binom{n}{2}$ *(every face),*

$2^{n-2}\binom{n}{2} - (n-1)$, *or*

$2^{n-2}\binom{n}{2} - (n-1) - (n-2)$

RSEs.

We also came up with a variety of explicit construction algorithms, mostly involving adding connecting edges between two smaller lattices, to give an explicit examples of a wide variety of RSE/peak combinations.

RSEs \ Peaks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
0	g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1	g	G	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2	g	G	G	X	X	X	X	X	X	X	X	X	X	X	X	X
3	g	G	G		X	X	X	X	X	X	X	X	X	X	X	X
4	g	G	G	P		X	X	X	X	X	X	X	X	X	X	X
5	g	G	G	G			X	X	X	X	X	X	X	X	X	X
6	g	G	G	G				X	X	X	X	X	X	X	X	X
7	g	G	G	G	P				X	X	X	X	X	X	X	X
8	g	G	G	G	G					X	X	X	X	X	X	X
9	g	G	G	G	G						X	X	X	X	X	X
10	g	G	G	G	G	P						X	X	X	X	X
11	g	G	G	G	G	P							X	X	X	X
12	g	G	G	G	G	G								X	X	X
13	g	G	G	G	G	G									X	X
14	g	G	G	G	G	G	P									X
15	g	G	G	G	G	G	P									X
16	g	G	G	G	G	G	P									X
17	B	G	G	G	G	G	P									X
18	B	G	G	G	G	G	G	P								X
19	B	G	G	G	G	G	G	P								X
20	B	G	G	G	G	G	G	P								X
21	B	g	G	G	G	G	G	P								X
22	B	g	G	G	G	G	G	P								X
23	B	g	G	G	G	G	G	P	P							X
24	B	g	G	G	G	G	G	G	P							X
25	B	B	G	G	G	G	G	G	P							X
26	B	B	G	G	G	G	G	G	P							X
27	B	B	G	G	G	G	G	G	P							X
28	B	B	g	G	G	G	G	G	P							X
29	B	B	g	G	G	G	G	G	P	P						X
30	B	B	B	G	G	G	G	G	P	P						X
31	B	B	B	G	G	G	G	G	P	P						X
32	B	B	B	G	G	G	G	G	P	P						X
33	F	B	B	G	G	G	G	G	P	P						X
34		B	B	g	G	G	G	G	P	P						X
35		F	B	g	G	G	G	G	P	P	P					X
36		B	B	B	G	G	G	G	P	P	P					X
37		F	B	B	G	G	G	G	P	P	P					X
38		F	F	B	G	G	G	G	P	P	P					X
39		F	F	B	g	G	G	G	P	P	P					X
40		F	F	F	g	G	G	G	P	P	P					X
41			F	F	F	G	P	G	P	P	P					X
42		F	F	F	g	G	G	G	P	P	P	P				X
43			F	F	F	G	G	G	P	P	P	P				X
44			F	F	F	P	P	P	P	P	P	P				X
45				F	F	O	G	G	P	P	P	P				X
46				F	F	O	P	P	P	P	P	P				X
47				F	F	O	P	P	P	P	P	P				X
48					F	F	P	G	P	P	P	P				X
49					F	F	O	P	P	P	P	P				X
50						F	O	P	P	P	P	P				X
51					F		O	P	P	P	P	P	P			X
52						F	F	P	P	P	P	P	P			X
53						F	O	P	P	P	P	P	P			X
54							F	P	P	P	P	P	P			X
55								O	P	P	P	P	P			X
56							F	F	P	P	P	P	P			X
57								O	O	P	P	P	P			X
58									P	P	P	P	P			X
59									O	P	P	P	P			X
60								O		P	P	P	P	P		X
61									O		P	P	P	P		X
62										P	P	P	P	P		X
63										O	P	P	P	P		X
64											P	P	P	P		X
65	X											P	P	P		X
66	X										O	P	P	P		X
67	X											P	P	P		X
68	X												P	P		X
69	X											X	P	P		X
70	X											O		P	P	X
71	X												P		P	X
72	X													P		X
73	X													P	P	X
74	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
75	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
76	X														P	X
77	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
78	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
79	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
80	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	P

Thank you all! Thank you Lara!

A 3 drug cycle alternating the antibiotics cefepime, ceftazidime, and cefprozil