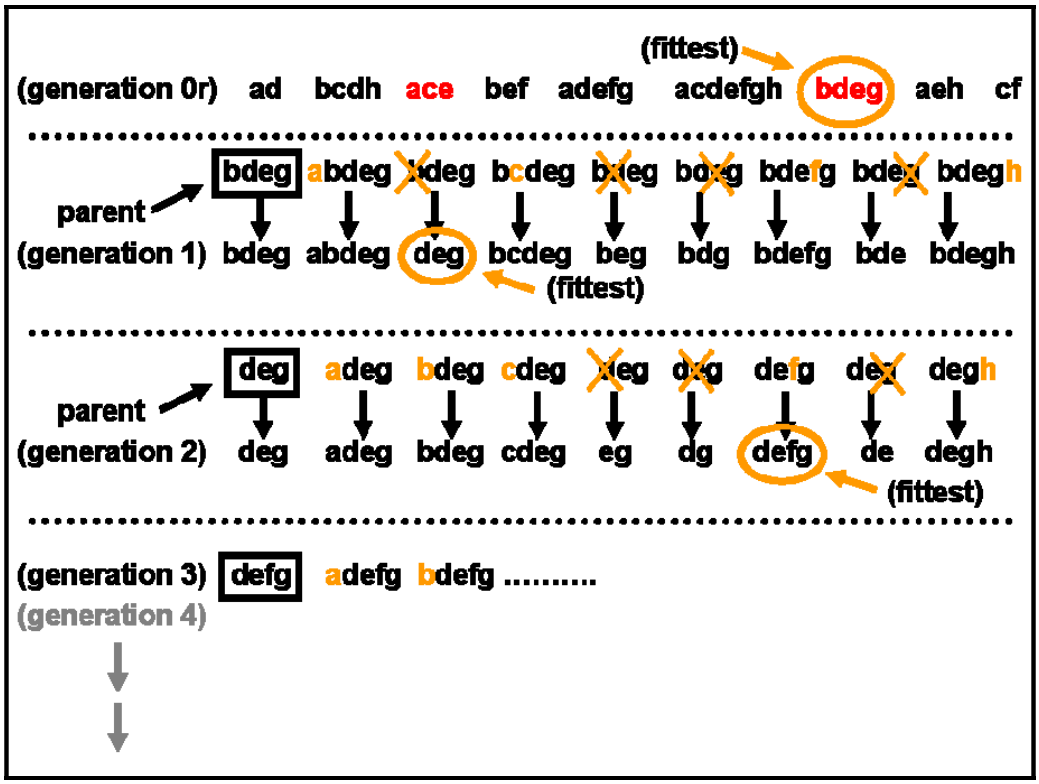
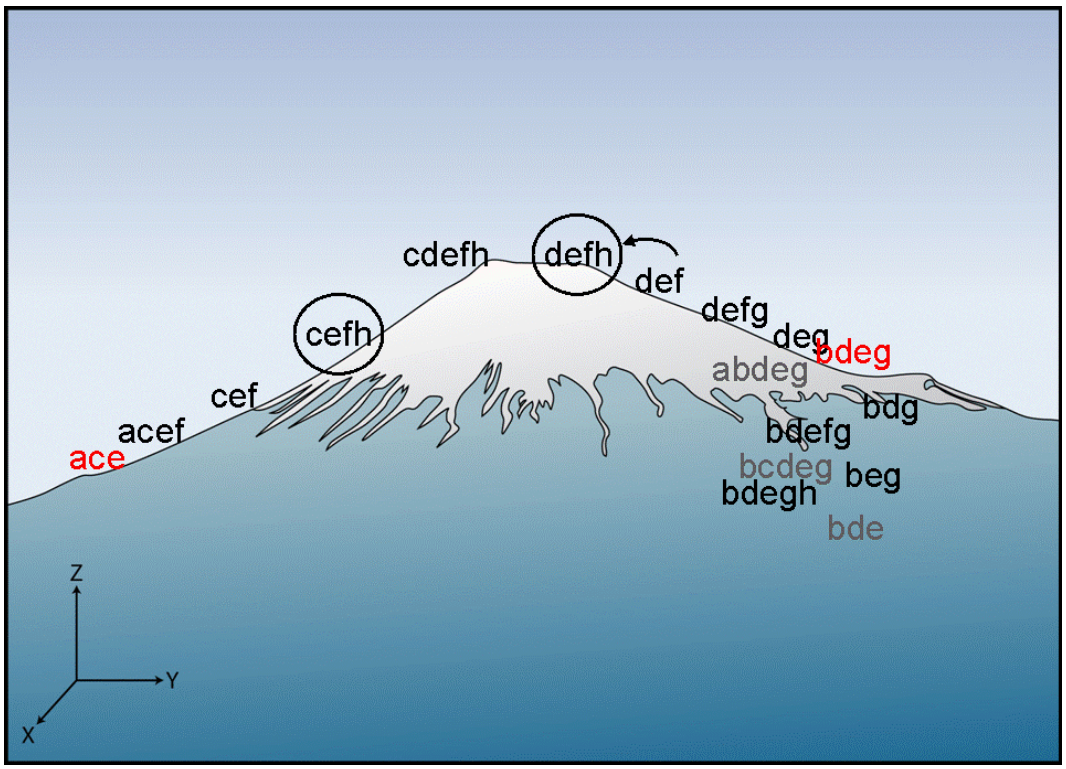
A


(fittest)
(generation 0r) ad bcdh ace bef adefg acdefgh bdeg aeh cf
parent
bdeg abdeg deg bcdeg beg bdg bdefg bde bdegh
(generation 1) bdeg abdeg deg bcdeg beg bdg bdefg bde bdegh
(fittest)
parent
deg adeg bdeg cdeg eg dg defg de degh
(generation 2) deg adeg bdeg cdeg eg dg defg de degh
(fittest)
(generation 3) defg adefg bdefg .....
(generation 4)

B


cdefh
defh
def
cefh
defg
deg
bdeg
abdeg
cef
bdg
acef
bdefg
ace
bcdeg
beg
bdegh
bde
Z
Y
X

C

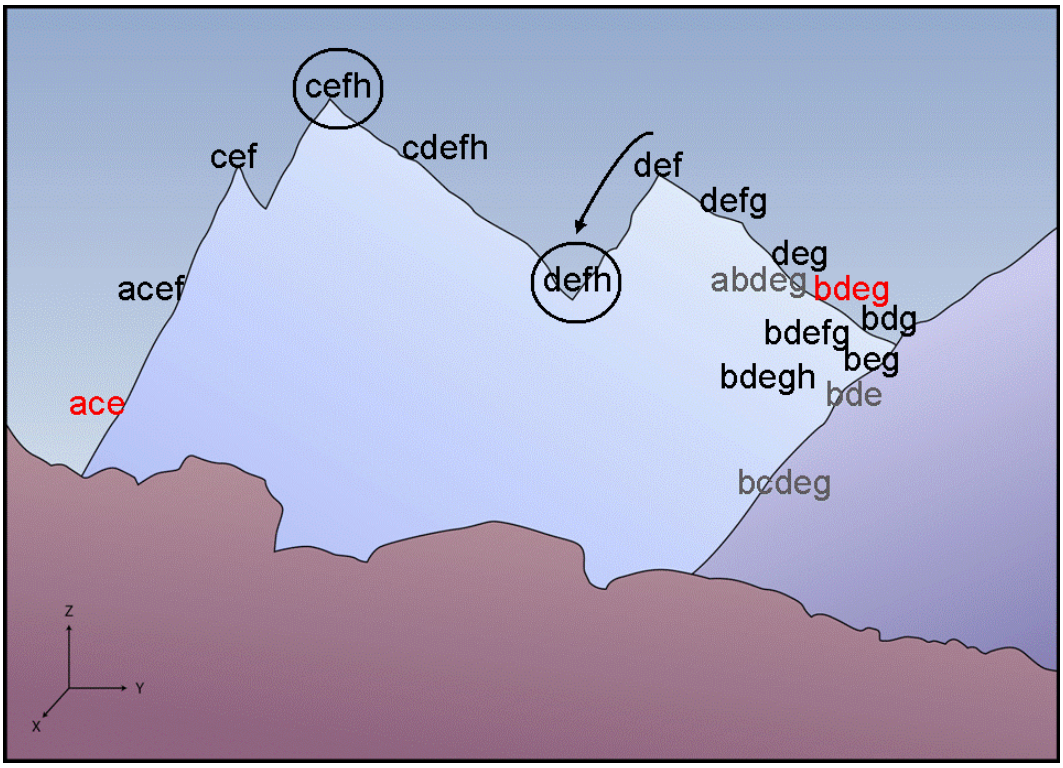


Figure S1. A, is the same hill climb as in Fig. 1A in the main text. **B** and **C**, show two possible fitness landscapes representing the "space" of imaginary cocktails derived from the illustration of a hill climb in **A**. In this way we can demonstrate that different types of landscapes influence the choice of algorithm and also show how highly fit cocktails can be discovered without screening all possible combinations.

The space of cocktails we show here is made up of all 256 possible cocktails that can be formed from 8 drugs. **A**, only a small subset of all possible cocktails are shown, just the ones that are explored through the hill climb in the first few generations. **B** and **C**, display all the cocktails at once as fitness landscapes. The contours of these landscapes are formed by the cocktails and are a function of their positions and their relative fitness.

First, their position is determined by arranging identical cocktails at the same points on the x-y plane. Exactly how this is done is not critical to this discussion. However, it is important to understand that all landscapes that would be compared are assumed to arrange the cocktails in exactly the same positions on the x-y plane. This arrangement is such that cocktails possessing similar compositions of drugs are near to each other.

Second, the relative fitness of each cocktail is indicated by its elevation along the z axis. The fitness value of a given cocktail can vary from landscape to landscape. Thus, the surface of the landscapes are determined by the full set of fitness values of all possible cocktails.

In broad outline, below we will show the following. **B**, we will demonstrate that the hill climb will reach the summit without being stuck at a lower altitude as is the case in panel C. Moreover, we show in panel B that the fittest of all possible 256 cocktails is reached without testing all possible cocktails thereby increasing efficiency. **C**, we will see that one of the hazards of relying on the hill climb can be to miss finding the fittest cocktail.

Here we describe the hill climbs in greater detail. Two of the cocktails in generation 0r, are shown in red on the fitness landscapes, **A** – **C**, and they lie far apart on the landscapes given their substantial differences in composition. **A**, "bdeg" is indicated to be the fittest in its generation. Therefore it is selected to be the parent of the next generation as per the rules of the hill climb. **B** and **C**, "bdeg's" 8 progeny are shown and they are near their parent. The combinations on the far slope are in grey. However, though the respective cocktails are in the same positions on the x-y plane, they have varied altitudes

For the purposes of illustration, "deg" is shown to be fittest among the 8 progeny, **B** and **C,** though this did not have to be the case. As such, "deg" will form the parent of the next generation and so on (only the fittest of the 8 progeny of each generation are shown subsequently). Indeed, in both landscapes, the immediate subsequent generations happen to share the same fittest cocktails. However, the progeny of "def" form a different set of elevations between these two panels as can be seen by the change in the shape of the fitness landscapes between the two panels. **B**, one will ultimately reach the only peak present as the hill climb continues. **C**, however, it can be seen that once "def" is reached, the algorithm stops at a lower peak, or a local maximum since the rule of the hill climb is to choose the best combination, and the parent will be superior to all its progeny. Thus, the hill climb would stop at "def" **C**. Therefore, the global maximum, "cefh", cannot be reached using the hill climb algorithm. Note, that in **B**, there is a different global maximum. Other algorithms referred to in the main text that allow for sampling of

more dissimilar cocktails across the landscape with each generation may be more effective when exploring fitness landscapes with more complicated contours such as in **C**.