Supplementary Information

Claim 1. *$\Gamma_k^\dagger$ in Algorithm 1 are contiguous.*

Justification. We proceed by induction. $\Gamma_0^\dagger = \{y\}$ is trivially contiguous. Assume $\Gamma_k^\dagger$ is contiguous but $\Gamma_{k+1}^\dagger = \Gamma_k^\dagger \cup \delta\Gamma_k$ is not. Then there exist disjoint, non-empty subsets G and H of $\Gamma_{k+1}^\dagger$ such that $\Gamma_{k+1}^\dagger = G \cup H$ and all points in G have Manhattan distance of at least 2 from all points in H. Since $\Gamma_k^\dagger$ is contiguous, $\Gamma_k^\dagger \subseteq G$ or $\Gamma_k^\dagger \subseteq H$, otherwise there would exist points with minimal distance 1 between each other in G and H. Without loss of generality, let $\Gamma_k^\dagger \subseteq H$. It follows that $G \subseteq \delta\Gamma_k$ by definition of $\Gamma_{k+1}^\dagger$. But by construction, all points of $\delta\Gamma_k$ have exactly distance 1 from $\Gamma_k^\dagger \subseteq H$. Hence, G must be empty violating the assumption. Therefore, $\Gamma_{k+1}^\dagger$ is contiguous. □

Claim 2. *In Algorithm 1, $N(\delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger = N(\Gamma_{k+1}^\dagger)\backslash\Gamma_{k+1}^\dagger$*

Justification. We use $\delta\Gamma_k = N(\Gamma_k^\dagger)\backslash\Gamma_k^\dagger$ and $\Gamma_{k+1}^\dagger = \Gamma_k^\dagger \cup \delta\Gamma_k$. By definition of N,

$$
\begin{aligned}
N(\Gamma_k^\dagger \cup \delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger =& (N(\Gamma_k^\dagger) \cup N(\delta\Gamma_k))\backslash\Gamma_{k+1}^\dagger && (1)\\
=& N(\Gamma_k^\dagger)\backslash(\Gamma_k \cup \delta\Gamma_k)^\dagger \cup N(\delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger && (2)\\
=& \delta\Gamma_k\backslash\delta\Gamma_k \cup N(\delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger && (3)\\
=& N(\delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger && (4)
\end{aligned}
$$

Therefore, $\delta\Gamma_{k+1} = N(\delta\Gamma_k)\backslash\Gamma_{k+1}^\dagger = N(\Gamma_{k+1}^\dagger)\backslash\Gamma_{k+1}^\dagger$. □

Corollary 1. *$\delta\Gamma_k$ are non-empty unless $\Gamma_k^\dagger = \Gamma$.*

Justification. If $\Gamma_k^\dagger \neq \Gamma$, then there exists $x \in \Gamma\backslash\Gamma_k^\dagger$ with distance 1 to $\Gamma_k^\dagger$ because Γ is contiguous. By definition $x \in N(\Gamma_k^\dagger)\backslash\Gamma_k^\dagger = \delta\Gamma_k^\dagger$. □

Claim 3. *To first order, the order of the average performance of substituents puts high performers adjacent.*

Justification. To first order the performance of a compound $x = (X_1, \ldots, X_N)$ is

$$C + \sum_d \sum_{a=1}^{N_d} H_d^a \delta_{X_d,a}, \tag{5}$$

where C is a constant, H_d^a is the linear contribution of substituent a at position d, and δ_{ij} is the Kronecker delta. The average performance of a substituent a at position d in a sample of the search space is

$$C + H_d^a + \frac{\sum_{e\neq d}\sum_{b=1}^{N_e} H_e^b \rho_{da,eb}}{\rho_{da}}, \tag{6}$$

where $\rho_{da,eb}$ is the joint frequency of substituent a at position d and substituent b at position e, and ρ_{ia} is the frequency of substituent a at position d in the search space. Given representative sampling, the fraction and the constant C are approximately the same for all substituent options at position d. Hence, the substituent options are ordered according to H_a^d. By construction of the ordering high performing substituents in each direction are adjacent. Due to linearity, overall high performers have high performance substituents at all sites and therefore are close at each position implying overall proximity. $\square$