Receptor uniformity affects superselectivity in multivalent nano-particle binding

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Multivalency is omnipresent in various biological systems and biorelevant applications, owing to the superselectivity that emerges from the cooperativity of multivalent binding. As a consensus, weak individual binding enhances the selectivity in the multivalent targeting. Here, using analytical mean field theory combined with Monte Carlo simulations, we find that for highly uniform receptor distributions, the maximum selectivity occurs at intermediate binding energy and can be significantly larger than the weak binding limit. This originates from an exponential dependence of the bound fraction on the receptor concentration, which is driven by both the strength and combinatorial entropy of binding. We provide the range of parameters where the exponential dependence occurs in the single-site scenario. Our finding offers new guidelines for the rational design of new-generation drug delivery systems and suggests an extra axis in understanding biological processes involving multivalency.

INTRODUCTION

Multivalent interactions play a key role in various biological-related processes, such as cell–cell adhesion and signal transduction, etc.1–6. They provide an “on-off” binding around a threshold receptor concentration for a biological barcode, i.e., target surfaces that receptors over-express above the threshold while leaves others unaffected. The multivalent binding strategy has been widely used in many biorelated applications, especially the drug delivery7–11 and bio-sensing12–14.

The Martinez-Veracoecha and Frenkel (MF) model provides a selectivity parameter α=dlnθ/dlnnR quantifying the dependence of targeted adsorption θ on the receptor concentration nR.15. Generally, the maximum selectivity αmax, where the targeted adsorption grows fastest, is employed to characterize the overall selectivity, which indicates the onset of guests binding and clustering 15,17. To approach the “on-off” binding behavior, αmax should be optimized by precisely tuning various parameters, especially the guest-host binding affinity. The MF model predicts that αmax increases as the binding strength becomes weaker when neglecting nonspecific interactions 15,18. In other words, weaker binding enhances selectivity in the multivalent targeting. Recent experimental studies have proven the prediction from the perspective of thermodynamics and kinetics for various systems, such as DNA coated colloids 19,21, multivalent guest-host polymers 16,22–24 and influenza virus particles 25.

All studies mentioned above assume that the receptors follow the Poisson distribution considering they are spatially uncorrelated, or only consider the single-site closed form at the weak binding limit. However, due to the complex environment on cell membranes, the receptors are heterogeneously distributed and correlated 26, of which the effect remains unknown. To this end, here we investigate how the uniformity of receptor distribution affects the selectivity in multivalent nano-particle binding by focusing on the hyperuniform distributions. Poisson distribution and anti-hyperuniform distributions. We find that the more uniformly distributed receptors lead to larger αmax, and intriguingly, αmax peaks at certain intermediate binding energy for hyperuniform distributions, which is qualitatively different from the Poisson distribution and anti-hyperuniform distributions with αmax at infinitely weak binding energy. Moreover, the maximum αmax obtained for receptors of hyperuniform distributions can be significantly larger than the upper bound in the Poisson and anti-hyperuniform distributions, where the relatively large number fluctuation of receptors masks the effect and causes the selectivity to increase monotonically with decreasing the binding strength.

RESULTS

Model and numerical methods

We consider the same prototypical adsorption model as in Ref. 15. As shown in Fig. 1a, immobile receptors are grafted on a host substrate. The nano-particles are controlled by an activity z=v0exp(βµ) with µ the chemical potential of nano-particles and β=1/kBT, where v0 is the volume that each particle can explore when bound to the chem-
tional entropic contributions. In the mean field scenario, assuming that the adsorption of each guest particle is independent, we divide the substrate into \( N_{\text{max}} \) sites, each of which can bind with one guest particle at most. Briefly, the MF model provides an analytical solution to the bound fraction, i.e., the fraction of sites that are occupied by particles with at least one bond formed:

\[
\theta(z,n_R) = \frac{zq(n_R)}{1+zq(n_R)}. \tag{1}
\]

Using the unbound site as the reference state, the single-site bound state partition function \( q(n_R) \) with \( n_R \) receptors, can be written as

\[
q(n_R) = \sum_{\lambda=1}^{\min(n,n_R)} Q(\lambda,n_R), \tag{2}
\]

where \( \lambda \) is the number of bonds and

\[
Q(\lambda,n_R) = e^{-\lambda\beta\mu} \frac{\kappa!n_R!}{(\kappa-\lambda)!\lambda!(n_R-\lambda)!}. \tag{3}
\]

Then the fraction of bound sites or adsorption is

\[
\langle \theta \rangle = \left\langle \frac{zq}{1+zq} \right\rangle (n_R), \tag{4}
\]

where \( \left\langle \cdot \right\rangle (n_R) \) calculates the average over the receptor number distribution with the mathematical estimate \( \langle n_R \rangle \). The selectivity parameter is defined as

\[
\alpha = \frac{d\ln(\theta)}{d\ln(\langle n_R \rangle)}. \tag{5}
\]

Since \( \alpha_{\text{max}} \) usually appears at small activity \cite{15, 27}, the time for the substrate to exchange nano-particles with the reservoir to reach equilibrium is very long, which makes the direct Monte Carlo (MC) simulations in 3D systems expensive and inefficient. Here we propose a \( \kappa \)-\( \mu \)VT MC simulation method with implicit ligands and bonds in 2D (see Methods), which enables us to efficiently sample in an additional bond number dimension. As shown in Fig. 1b, we model the particles as hard disks of diameter \( \sigma \) and volume \( s_{\text{hd}} = \pi \sigma^2/4 \) controlled by the chemical potential \( \mu \). We assume one receptor can only bind with the particle covering it, i.e., the center-to-center distance between the receptor and ligand is less than \( \sigma/2 \). The total number of sites \( N_{\text{max}} = L^2/s_{\text{hd}} \), and the average number of receptors per site \( \langle n_R \rangle = N_R s_{\text{hd}}/L^2 \). The activity \( z = s_{\text{hd}} \exp(\beta\mu)/\Lambda \) with \( \Lambda \) the de Broglie wavelength. The distribution \( p(n_R) \) is numerically sampled by the number of receptors within a 2D spherical window of radius \( \sigma/2 \).

We consider four different types of receptor distributions: anti-hyperuniform (Anti-HU) distributions \cite{28}, the Poisson distribution, stealthy hyperuniform (SHU) distributions \cite{29, 30} and a square lattice (See Methods).

FIG. 1. **Multivalent nano-particle binding.** (a) Schematic representation of the prototypical multivalent adsorption model, in which the ligands (blue) on the particles (white) can bind with the immobile receptors (pink) on the substrate (grey) reversibly. (b) Illustration of the 2D numerical simulations, in which some receptors (red) are bound with implicit ligands on the nano-particles (blue) while the others (black) are unbound. In the simulation, the bonds are implicit. (c) Relative local number variance of the distribution \( \sigma^2(n_R)/\langle n_R \rangle \) as a function of \( \langle n_R \rangle \) for various receptors distributions. (d) Part of typical snapshots of receptors obeying various distributions.
In equilibrium, Anti-HU can describe systems close to a critical point, and SHU describes the disordered systems with long range correlations \[28\]. All those distributions are statistically homogeneous point processes and follow the central limit theorem, i.e., they can be approximated by Gaussian distributions at the large \(\langle n_R \rangle\) limit \[31\]. As shown in Fig. 1 and d, the spatial uniformity of a receptor distribution at given \(\langle n_R \rangle\) can be characterized by the relative local number variance \(\sigma_{nR}^2/\langle n_R \rangle\). For the Poisson distribution in 2D, \(\sigma_{nR}^2/\langle n_R \rangle = 1\), while for a perfect square lattice, \(\sigma_{nR}^2/\langle n_R \rangle \sim \langle n_R \rangle^{-1/2}\), which essentially implies that the square lattice is more uniform than the Poisson distribution. Similarly, for SHU distributions, \(\sigma_{nR}^2/\langle n_R \rangle\) increases faster than \(\langle n_R \rangle\), and here we choose configurations that exhibit \(\sigma_{nR}^2/\langle n_R \rangle \sim \langle n_R \rangle^{1/2}\), in which the prefactor depends on the parameter \(a\) with the larger \(a\) being less uniform or with the larger density fluctuations (see Methods).

In Fig. 2, we plot the average bound fraction \(\langle \theta \rangle\) as a function of \(\langle n_R \rangle\) for various receptor distributions, in which the symbols and solid curve are from \(\kappa-\mu VT\) MC simulations and theoretical predictions (Eqs. 4 and 5), respectively. One can see that Eqs. 4 and 5 agree quantitatively with computer simulations when \(\langle \theta \rangle < 0.5\) (indicated by the dotted horizontal line), and at very large \(\langle n_R \rangle\), the theoretically predicted \(\langle \theta \rangle\) is larger. This discrepancy is due to the fact that the excluded volume effect between nano-particles is not considered in the mean field theory, which overestimates the adsorption at high density. When \(\langle n_R \rangle \to 0\), all curves collapse with \(\alpha = 1\). This is due to the fact that at \(\langle n_R \rangle \to 0\), most of the sites have either 0 or 1 receptors, in which about \(\langle n_R \rangle\) sites have one receptor each. In this case, the binding of nano-particles becomes essentially monovalent, in which the receptor distribution is not important, and \(\langle \theta \rangle \approx \langle n_R \rangle \beta_f (\langle n_R = 1 \rangle \sim \langle n_R \rangle\) and \(\alpha \to 1\) for all receptor distributions. With increasing \(\langle n_R \rangle\), less uniform distributions lead to larger value of \(\langle \theta \rangle\). To understand this, we refer to Eq. 4 which implies \(\langle \theta \rangle \approx z(q)\), where \(z(q)\) is small, where \(z(q)\) is the average bond state partition function over the receptor distribution. We prove that \(q(n_R)\) is a convex function (see Supplementary Materials), hence \(z(q)\) increases with increasing the variance of the distribution \(\sigma_{nR}^2\). As shown in Fig. 2e with increasing the uniformity, i.e., from Anti-HU to the Poisson, SHU structures and square lattice, \(\alpha_{\text{max}}\) increases monotonically, and for SHU structures and square lattice, \(\alpha_{\text{max}}\) is even larger than \(\kappa = 4\). This is intriguing as it is known that weaker binding energy enhances selectivity, of which the upper bound of \(\alpha_{\text{max}}\) is \(\kappa\) \[15\].

**Achieve maximum selectivity by tuning binding energy**

To understand the effect of receptor uniformity on selectivity, in Fig. 3 and Fig. 5, we plot \(\langle \theta \rangle\) and \(\alpha\) as functions of \(\langle n_R \rangle\) for binding energy from strong \((\beta f_B = -8)\) to weak \((\beta f_B = 4)\) of various receptor distributions. For the receptor structures of the Poisson and Anti-HU distributions, \(\alpha_{\text{max}}\) increases monotonically with increasing \(\beta f_B\), namely weaker binding enhances selectivity, while for the hyperuniform distributions, e.g., SHU with \(\chi = 0.48\) and square lattice, \(\alpha_{\text{max}}\) reaches the maximum at about \(\beta f_B = -4\).

To understand the physics behind, we start with the selectivity in the single-site scenario \(\alpha_{\text{ss}} = d \ln \theta(n_R)/d \ln n_R\). At the low activity limit, according to Eq. 1 \(zq \to 0\), \(\theta(n_R) \approx z_q(n_R)\) and \(\alpha_{\text{ss}} \approx d \ln q/d \ln n_R\). We define the selectivity in zero activity as \(\alpha_{\text{ss,0}} = d \ln q/d \ln n_R\) \[32\]. We plot the probability of forming \(\lambda\) bonds on the guest nano-particle in the bound state in Fig. 4a. For weak binding \(\beta f_B = 4\) and small \(n_R\), one can see \(q(n_R) \approx Q(\langle \lambda \rangle_{\text{bound}}, n_R)\) with the most probable bond number \(\langle \lambda \rangle_{\text{bound}}\approx 1\), which implies that there is only one bond formed for the particle bound on the substrate, and the ligands on each particle

**Receptor uniformity enhances selectivity**

In Fig. 2, we plot the average bound fraction \(\langle \theta \rangle\) (top panel) and the selectivity parameter \(\alpha\) (bottom panel) as functions of \(\langle n_R \rangle\) for various receptor distributions, in which the symbols and solid curve are from \(\kappa-\mu VT\)
cannot bind cooperatively. As shown in Fig. 4b, this leads to a linear dependence $q \approx n_R e^{-\beta f_B}$ and $\alpha_{ss,0} \approx 1$ with no superselectivity. With increasing $n_R$, $\langle \lambda \rangle_{bound}$ approaches $\kappa$ at the large $n_R$ limit due to the restriction from the number of ligands, which leads to a power-law dependence of $q$ on $n_R$:

$$q \approx Q(\lambda = \kappa, n_R) = e^{-\kappa \beta f_B} \frac{n_R!}{(n_R - \kappa)!} \approx (n_RE^{-\beta f_B})^\kappa, \quad (6)$$

and $\alpha_{ss,0} \approx \kappa$. Here, $\kappa$ ligands on each particle bind with crowded receptors together, and the emergent combinatorial entropy induces the power-law dependence. At the strong binding $\beta f_B = -4$, the power-law dependence also appears at the large $n_R$ limit, whereas, in the small $n_R$ regime, i.e., $1 < n_R < \kappa$, the most probable bond number is restricted by the available receptors instead of the ligands available, i.e., $\langle \lambda \rangle_{bound} \approx n_R$ (shown in Fig. 4a). This implies an exponential dependence of $q$ on $n_R$:

$$q \approx Q(\lambda = n_R, n_R) = e^{-n_R \beta f_B} \frac{\kappa!}{(\kappa - n_R)!} \approx (n_RE^{-\beta f_B})^n, \quad (7)$$

and $\alpha_{ss,0} \approx n_R (\ln \kappa - \beta f_B) \sim n_R$. The derivation of Eqs. 6 and 7 based on the saddle-point approximation method can be found in Supplementary Materials. As shown in Fig. 4a, $\alpha_{ss,0}$ peaks around $n_R = \kappa$, which is independent of the binding energy, and $\alpha_{max} \approx \kappa (\ln \kappa - \beta f_B)$ can be larger than $\kappa$ when $\beta f_B < \ln \kappa - 1$. In the single-site binding scenario, $\ln \kappa - 1$ is a threshold of binding energy, lower than which $\alpha_{max} > \kappa$ occurs at $n_R \approx \kappa$, and if $\beta f_B > \ln \kappa - 1$, $\alpha_{max}$ has an upper bound $\kappa$ with $n_R \rightarrow +\infty$.

As shown in Fig. 4c and Fig. S3, the rescaled (average) bound fractions $\theta/\kappa$ (single-site scenario) and $\langle \theta \rangle/\kappa$ (structures of the Poisson and SHU distributions) at various activity $z$ collapse at small $n_R$, while reach the plateaus of different height with increasing $n_R$. This indicates that the bound fraction saturates at the threshold $n_R^\theta$, where $\theta(q(n_R)) \approx 1$, and the activity does not affect the selectivity when $n_R < n_R^\theta$. As the result, the single-site activity $\alpha_{ss} \approx \alpha_{ss,0}$ at $n_R$ lower than the threshold, and drops to 0 with further increasing $n_R$. Moreover, when $\theta(q(n_R = 1) > 1$, i.e., $\beta f_B < \ln (\kappa z)$, the bound fraction saturates even if one nano-particle only binds to one receptor, and no superselectivity occurs. To sum up, an exponential dependence occurs at $\ln (\kappa z) < \beta f_B < \ln \kappa - 1$ and $1 < n_R < \kappa$ in the single-site scenario.

For the highly uniformly distributed receptors, e.g., SHU $\chi = 0.48$ and the square lattice in Fig. 3, the situation is qualitatively similar to the single-site scenario since the variance of the receptor distribution is small. The maximum $\alpha_{max}$ occurs at an intermediate binding energy with a larger value than $\kappa$. Moreover, the critical $\langle n_R \rangle$ with $\alpha_{max}$ appears independent of the binding energy from $\beta f_B = -8$ to $-4$ for SHU $\chi = 0.48$ and the square lattice, which is a distinct feature of the exponential dependence. Moreover, for the Poisson and less uniform receptor distributions, e.g., Anti-HU, our numerical evidence shows that $\alpha_{max}$ increases monotonically with increasing $\beta f_B$ and approaches $\kappa$ at $\beta f_B \rightarrow +\infty$ (Fig. 3). We believe that this is due to the relatively large receptor number fluctuations masking the exponential dependence in the intermediate binding energy. As shown in Fig. S4, in the weak binding limit, receptor uniformity has little

![FIG. 3. Achieving maximum selectivity by tuning binding free energy $\beta f_B$. $\langle \theta \rangle$ and $\alpha$ as a function of $\langle n_R \rangle$ for various binding free energy $\beta f_B$ for typical receptor structures: Anti-HU $a = 10$, Poisson, SHU $\chi = 0.48$ and square lattice. The solid curves are the theoretical predictions of Eqs. 4 and 5, and the symbols are obtained from simulations. In all simulations, $\kappa = 4$ and $\beta \mu = -10$.](image)
FIG. 4. **Multivalent binding of nano-particles in the single-site scenario.** (a) The probability for λ bonds formed on bound guest nano-particles $Q(\lambda)/q$ as a function of $n_R$ for (upper) $\beta f_B = 4$ and (lower) $-4$. (b,c) The single-site bound state partition function $q$ and single-site selectivity at zero activity $\alpha_{ss,0}$ as a function of $n_R$. Empty symbols are the analytical results from Eq. 2. Colored dotted lines are from Eq. 6. Colored dashed lines are from (a) $q=n_R$ and (b) Eq. 7 respectively. Black dashed and dotted lines indicate $\alpha_{ss,0}=1$ and $\kappa$, respectively. (d) $\theta/z$, $q$ (upper) and $\alpha_{ss}$, $\alpha_{ss,0}$ (lower) as a function of $n_R$ with $\beta f_B = 4$ for various activity $z$. In all calculations, $\kappa=10$.

**DISCUSSION**

In conclusion, we have investigated the effect of receptor uniformity on the superselective binding of multivalent nano-particles, for which we devised a $\kappa$-$\mu VT$ MC simulation method to compare with analytical theory without any fitting parameter. Our results show that more uniformly distributed receptors lead to higher superselective binding of multivalent particles. For receptors of SHU structures and square lattice, the maximum selectivity $\alpha_{max}$ can be significantly larger than $\kappa$ the valence of the nano-particle, which is the maximum superselectivity that receptors of the Poisson and Anti-HU distributions can reach. More intriguingly, the maximum $\alpha_{max}$ exists at some intermediate strength of binding energy for receptors of SHU distributions and square lattice, which is due to an exponential dependence of bound fraction on the receptor concentration originating from the restriction of available receptors because of both the energy and combinatorial entropy. This is qualitatively different from the binding on receptors of the Poisson or Anti-HU distributions, in which weaker binding always enhances the superselectivity. This suggests that for highly uniformly distributed receptors, one does not need to use nano-particles with very high valence to realize the ultra-selective nano-particle binding. Although in principle, many receptors on cell membranes are mobile, the diffusion time scale of the receptor on cell membranes $t_{diff}$ could be much larger than that of forming/breaking a bond with ligands on nano-particles $t_{on/off}$, and they can be seen as effectively immobile receptors. Moreover, there are also many immobile receptors on cell mem-

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Effect on $(\theta)$, and $\alpha_{max} \rightarrow \kappa$ holds as long as the receptor distribution obeys the central limit theorem and satisfies $\sigma^2_{n_R}/\langle n_R \rangle^2 < 1$ at large $\langle n_R \rangle$ (see Supplementary Materials). Therefore, weaker binding enhances the maximum selectivity with an upper bound limit $\kappa$ for those less uniform distributions [15].

Next, we investigate the binding of multivalent nanoparticles on the surface coated with receptors of tunable uniformity. Here we use the configurations of receptors obtained from equilibrium fluids of hard disks (HD) of various packing fraction $\phi$. When $\phi \rightarrow 0$, the HD system recovers an ideal gas of the Poisson distribution, i.e., $\sigma^2_{n_R}/\langle n_R \rangle = 1$, and with increasing $\phi$, at certain length scale, $\sigma^2_{n_R}/\langle n_R \rangle \sim \langle n_R \rangle^x$ with $x < 0$, which is the local uniformity induced by the increased short range correlation because of the excluded volume effect (Fig. S5).

The local uniformity of the configuration increases with increasing $\phi$ of HD systems, while at large enough length scale $\sigma^2_{n_R}/\langle n_R \rangle \sim \langle n_R \rangle^0$ (Fig. S5). In Fig. 5, we plot $(\theta)$ and $\sigma$ for receptor structures of various local uniformity, i.e., obtained from equilibrium HD systems of different $\phi$. One can see that with small local uniformity, e.g., $\phi = 0.01$, $\alpha_{max}$ increases monotonically with increasing $\beta f_B$, which is the same as receptors of the Poisson distribution. However, with increasing $\phi$, the non-monotonic dependence of $\alpha_{max}$ on $\beta f_B$ appears when $\phi > 0.15$. This implies that the local uniformity induced by the excluded volume effect can trigger the non-monotonic dependence of selectivity on the binding free energy.
branes restricted and compartmentalized because of the interaction with the cytoskeleton [35]. Therefore, our results highlight the importance of receptor distribution in biological systems. We also show that the local uniformity induced by excluded volume effects can trigger the non-monotonic dependence of selectivity on the binding free energy, which suggests that our finding can be expected in systems of relatively densely packed receptors, like the situation in many biological membranes. Although the purpose of our simulations is to capture the essential physics rather than seeking quantitative predictions for realistic multivalent nano-particle binding, it is possible to incorporate other effects, e.g., the geometrical constraints of substrates and nano-particles, the interactions among ligands and receptors, by changing the form of Q in Eq. 3 and local activity [36] for more quantitative modelling of multivalent nano-particle binding.

**METHODS**

**Monte Carlo simulations in \( \kappa-\mu VT \) ensemble**

To sample the equilibrium properties of the coarse-grained multivalent nano-particle binding systems, we propose a grand canonical \( \kappa-\mu VT \) MC simulation method with a fixed number of ligands per particle. Simulations are performed with \( 10^4 \) explicit immobile receptors located at given position \( \mathbf{r}_{NR} \) on a substrate, and periodical boundary conditions are applied in both directions with the box length \( L \). The ligands on particles and bonds formed between ligands and receptors are implicit. The
partition function is
\[
\Xi(\kappa, \mu, V, T) = \sum_{N=0}^{\infty} \frac{\exp(\beta \mu N) [(\kappa+1)V]^N}{\Lambda^2 N!} \int [-\beta U(s^N)] \sum_{\Lambda^N} \prod_{i=1}^{N} Q'[\lambda_i, n_R(s_i, r_i^{NR})] \, ds^N,
\]
where \(s^N\) and \(\Lambda^N\) are the coordinates and bonds formed for all \(N\) particles, respectively, and \(U\) is the interaction potential between nano-particles. The summation \(\sum_{\Lambda^N}\) accounts for all possible combination of bonds, i.e., \(\sum_{\Lambda^N} = \sum_{\lambda_1=0}^{N} \sum_{\lambda_2=0}^{N} \cdots \sum_{\lambda_N=0}^{N} \cdot Q'\) is the bound partition function with \(\lambda_i\) the number of bonds, \(n_R\) the number of receptors able to form bonds with particle \(i\) at \(s_i\), and \(r_i^{NR}\) the receptor coordinates:
\[
Q'(\lambda, n_R) = \begin{cases} 
1, & \lambda = 1; \\
Q(\lambda, n_R), & 1 < \lambda \leq n_R; \\
0, & \lambda > n_R.
\end{cases}
\]

**Insertion and removal of nano-particles.** A particle is inserted at a random position with forming \(\lambda'\) bonds where \(\lambda'\) is an integer uniformly distributed in \([0, \kappa]\). The trial move of insertion is accepted with the probability [37]
\[
\text{acc}(N \rightarrow N + 1) = \min \left[ 1, \frac{(\kappa + 1) V Q'(\lambda', n_R')}{\Lambda^2 (N + 1)} e^{\beta \mu [U(N + 1) - U(N)]} \right] ,
\]
and the removal of a particle with \(\lambda\) bonds is accepted with a probability
\[
\text{acc}(N \rightarrow N - 1) = \min \left[ 1, \frac{\Lambda^2 N}{(\kappa + 1) V Q'(\lambda, n_R)} e^{\beta \mu [U(N - 1) - U(N)]} \right] .
\]

**Translational move for particles.** We randomly select a particle and perform random walks in the \((\lambda, s)\) space. The move is accepted by a probability
\[
\text{acc}(\lambda, s) \rightarrow (\lambda', s')) = \min \left[ 1, \frac{Q'(\lambda', n_R')}{Q'(\lambda, n_R)} e^{-\beta \Delta U} \right] .
\]
The ratio between the three types of trial moves is 1:1:1. In each simulation with a given set of receptor coordinates, we perform \(10^8\) MC moves for equilibration and \(10^8\) MC moves for sampling.

**Generation of receptor configurations**

The anti-hyperuniform configurations are generated using the algorithm detailed in Ref. [38]. Specifically, we use the limited-memory BFGS algorithm to minimize \(\sum_{|k|<K} [(S(k) - S_0(k))^2\), in which \(K = 10\), \(S(k)\) is the average structure factor
\[
S(k) = \frac{1}{N \epsilon} \sum_{i=1}^{N \epsilon} \exp(-i \mathbf{k} \cdot \mathbf{r}_i) / N
\]
over \(N \epsilon = 100\) configurations, and the targeted structure factor for various \(a\) is \(S_0(k) = 1 + a \exp(-|k|)/|k|\).

The stealthy hyperuniform configurations are generated by minimizing \(\Phi(r^N) = \sum_{|k|<R} S(k)\) using the limited-memory BFGS algorithm [39], starting from a Poisson configuration with number density \(\rho = 1\). Here \(K = 4\sqrt{\pi} N\) [30] and \(\chi = M(K)/[D(N \epsilon - 1)]\) denotes the relative fraction of constrained degrees of freedom compared to the total degrees of freedom \(D(N \epsilon - 1)\) with \(M(K)\) the number of independently constrained wave vectors [28].

For each structure, we individually generate 10 snapshots of \(10^4\) receptors to sample the spatial distribution and to be used in MC simulations.

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at XXXXXX-XXXXXX

**Acknowledgments:** This work is supported by the Academic Research Fund from Singapore Ministry of Education Tier 1 Grant (RG59/21) and Tier 2 Grant (MOE2019-T2-2-010). **Author contributions:** R.N. and X.X. conceived the research; X.X. performed the computer simulations and formulated the analytical theory; G.Z. and Y.J. generated the stealthy hyperuniform and anti-hyperuniform structures for computer simulations; R.N. directed the research; all authors discussed the results and wrote the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are presented in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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