Optimal multivalent targeting of cell membranes

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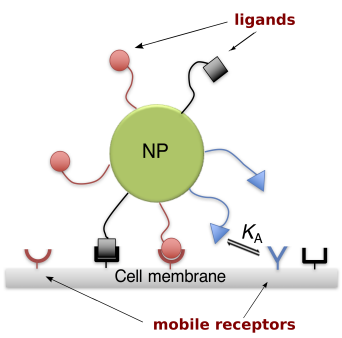
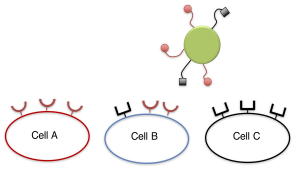
Motivation

A key challenge in biomedical research is the ability to specifically target cells and tissues. Targeting typically relies on identifying a suitable marker, e.g., a highly expressed receptor, and choosing a ligand that strongly and specifically binds to the marker. However, this procedure fails when a suitable marker unique to the targeted cells cannot be identified, notably in many forms of cancer. We show that properly designed multivalent targeting of multiple cognate receptor types results in a specificity toward a chosen receptor density profile, thus demonstrating a general route toward targeting cells without particularly dominant markers.

The challenge



How to target cell B in the presence of cells A and C ?



- Each multivalent particle (NP) characterized by the profile of different ligands: ***p***
- Membrane is characterized by the receptor concentration vector: ***c***
- Ligands and receptors interact via interaction matrix: **K**

configurational (polymeric) term

ratio of ligand bound/ unbound probabilities

$$\frac{P_{ij}^{\text{bound}}}{P_i^{\text{free}}} = c_j K_{ij}^A \frac{e^{-\beta \Delta \tilde{G}_i^{cnf}}}{h_0} \equiv c_j K_{ij}$$

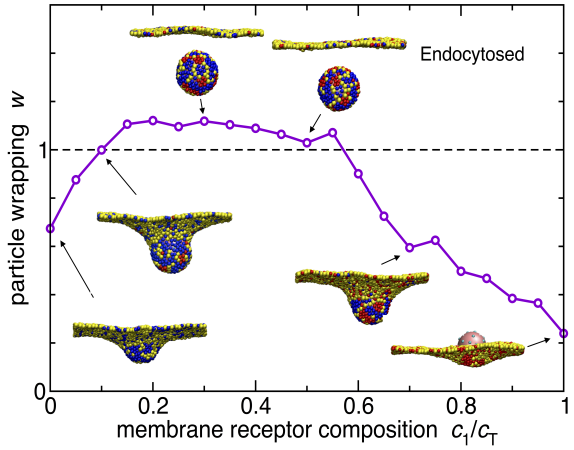
ligand-receptor affinity

mean-field free energy per ligand

$$f_b(\mathbf{c},\mathbf{p},\mathbf{K}) = -\sum_i p_i \ln\left(1+\sum_j c_j K_{ij}\right)$$

Endocytosis

Particle is only endocytosed when the membrane composition of receptors roughly matched the profile of ligands on the nanoparticle.



Selectivity optimisation

How to specifically target a given receptor composition ***c**** ?

$$\left.\frac{\partial f_b(\mathbf{c},\mathbf{p},\mathbf{K})}{\partial \mathbf{c}}\right|_{\mathbf{c}=\mathbf{c}^*} = 0$$

free energy must be a minimum at *c**

$$\mathcal{S} = \det\left(\frac{\mathbf{H}(f_b)}{|f_b|}\right)_{\mathbf{c}=\mathbf{c}^*}$$

maximize the relative curvature (determinant of the Hessian matrix)

Optimise using Lagrange multipliers

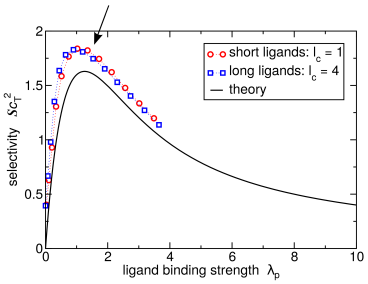
$$\left.\frac{\partial f_b(\mathbf{c},\mathbf{p},\mathbf{K})}{\partial \mathbf{p}}\right|_{\mathbf{c}=\mathbf{c}^*} = 0.$$

robustness condition

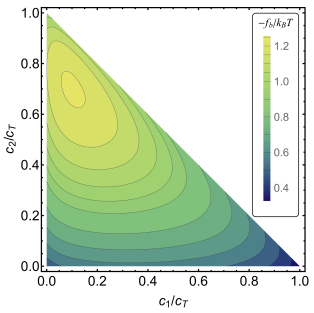
SIMPLE ANALYTICAL RESULT: $\lambda_p \approx 1.256\cdots$

Interaction free energy between each Individual ligand and a targeted membrane should be ~1.3k_BT, regardless of the details of the system.

MC Wang-Landau Free energy calculations



Targeting 3 receptor types

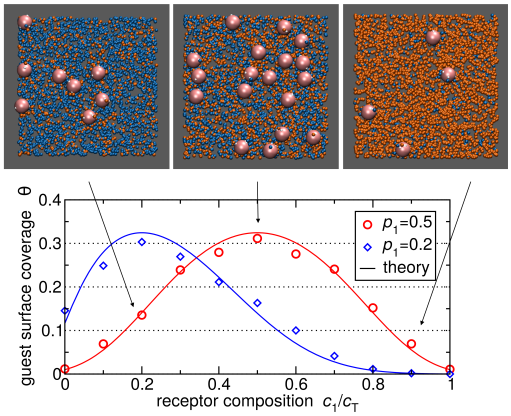


Design Rules

For optimal multivalent targeting of specific receptor composition the following rules apply:

- Individual ligand binding should be weak, each ligand having the probability of being unbound (free): $P_i^{\text{free}} = e^{-\lambda_p} \approx 0.3$
- Interaction matrix **K** should be diagonal and inversely proportional to the targeted membrane composition: $K_{ii} \sim 1/c_i$
- Density matching of (cognate) ligands to the targeted receptor composition: ***p*** **~** ***c****

Monte Carlo simulations confirm theoretcal predictions



References

T. Curk, J. Dobnikar and D. Frenkel, *Optimal multivalent targeting of membranes with many distinct receptors*, PNAS, **114**, 28 (2017)

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