Numerical Simulation of the Effects of Repulsive Forces on 2D Membrane Protein Organization and Dynamics

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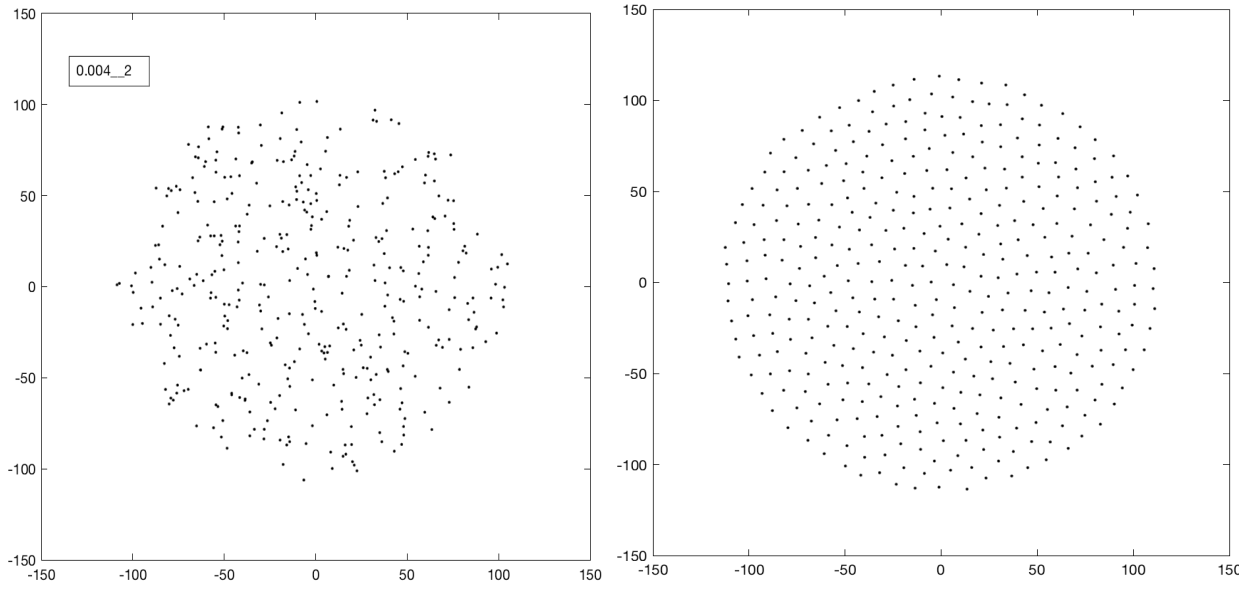
Cell membrane receptors play important roles in transmembrane signaling. Both the distribution and the lateral mobility of the receptors is important, as many ligands act via receptor aggregation. Receptor aggregation can be achieved while retaining receptor mobility through the use of fluid supported lipid bilayers containing ligands. Large receptor patches are thus formed; such patches do still signal.

The mobility of receptors in such patches has been ascertained by single-molecule tracking; the receptors were found to have mobilities comparable to non-liganded receptors on control cells. The concentration of receptors in patches was found to be remarkably uniform, however. A careful quantitative analysis, accounting for CCD camera noise and shot noise, strongly suggested that the pixel-to-pixel variation in receptor number was less than Poissonian, i.e. that the receptors in these large patches do *not* form a 2D ideal gas, but are rather more ordered. The ordering could not be explained by the finite receptor size, as < ca. 10% of the membrane area could be occupied by liganded receptors.

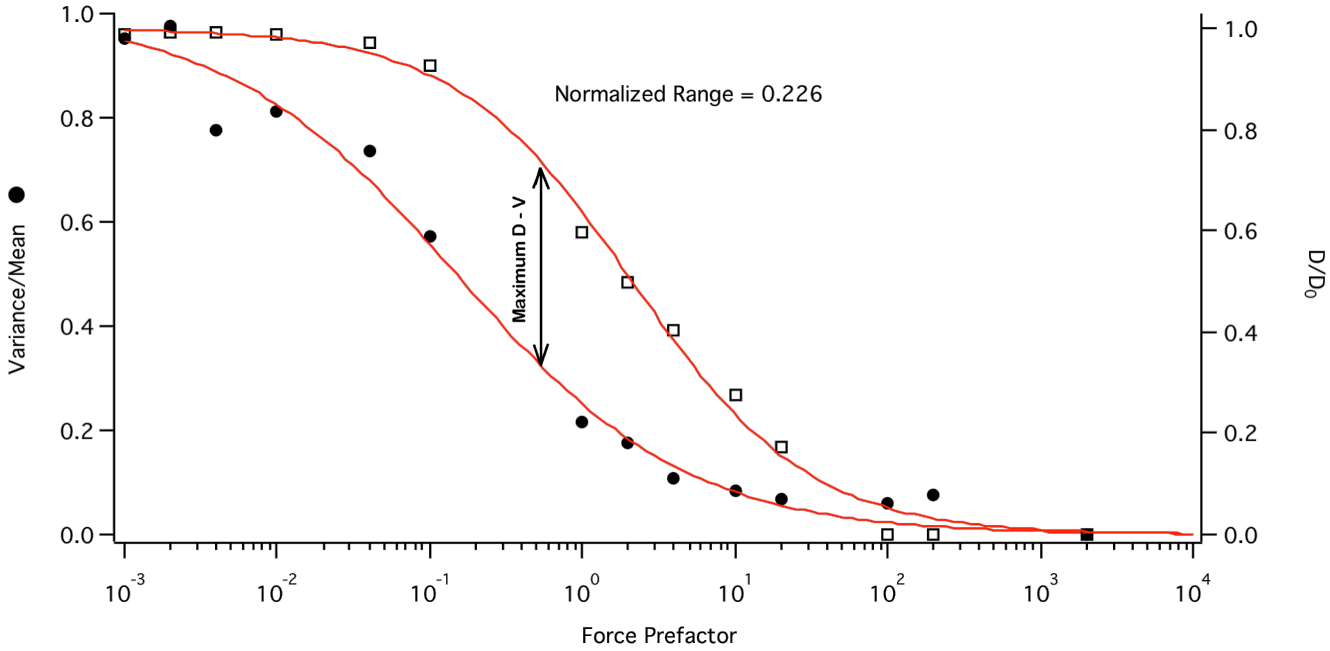
We hypothesized that a long-range repulsive interaction among receptors might cause ordering without immobilization. To further explore this hypothesis, computer simulations of protein diffusion and ordering in a 2D space were undertaken. Periodic boundary conditions proved to be problematic, as long-range forces could cause clearly non-physical (periodic) ordering. Instead, the proteins were confined to a disk by an exponential potential at the perimeter.

With very weak repulsive forces, membrane proteins behave like a 2D ideal gas. Diffusion is rapid, and the concentration variance is Poissonian. With very strong forces, the membrane proteins form a 2D lattice, with near-perfect ordering (zero concentration fluctuations) and negligible diffusion.



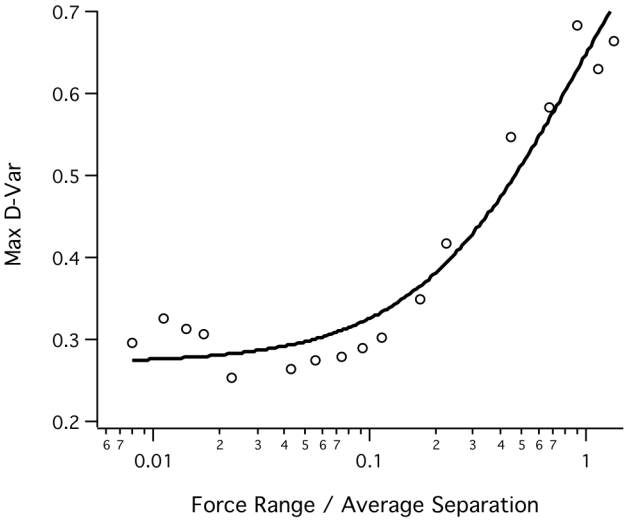
A simulated membrane protein distribution with an exponential (normalized range = 0.226) repulsive force, entrapped in a disk of radius ca. 100 units. With a weak force (left), the proteins are mobile and Poissonian distributed. With a strong force (right), the proteins are ordered and immobile.

In the transition, as the magnitude of an exponential repulsive force is increased, the concentration fluctuations decrease *before* diffusion begins to slow. This was observed for both long range and short range exponential forces.



As the repulsion between membrane proteins is increased, spatial ordering increases (the concentration variance decreases) and, with somewhat stronger forces, the diffusion slows. The curves are "phenomenological" fits to a Hill equation, which was used to further characterize how the range of the force affects variance and diffusion.

However, the differential effect on variance vs diffusion is more pronounced for longer range forces. To quantify the changes, simulation data was fit with the Hill equation and the largest difference between diffusion D/D_0 and Variance/Mean was computed ("Maximum D-V").



When the exponential length scale is comparable to the mean interprotein separation, the concentration variance can be suppressed to 20% of the Poissonian value, while the diffusion coefficient remains at 90% of the dilute limit.