# Effects of confinement on reaction kinetics in the plasma membrane

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***Short Abstract* — We study the effects of cytoskeleton induced confining domains on the interactions between plasma membrane molecules. Our findings show that although the average rate of molecular interaction is unchanged (in the absence of crowding and strong particle-boundary interactions); its variance significantly increases due to temporary confinement. Therefore, molecules encounter less frequently in the presence of confining domains, but following each encounter they sustain many collisions. As a result: 1) reactions between molecules with low affinity are enhanced, 2) the strategy of temporal regulation of molecular interaction is modified, such that the molecules undergo bursts of strong interactions rather than continuously interacting at low rates.**

***Keywords* — Confinement effects, reaction kinetics, membrane skeleton, plasma membrane domains, spatial organization, mesoscopic phenomena**

## I. BACKGROUND

FOR many decades, the environment inside/on the surface of a cell where a multitude of biochemical reactions take place has been treated like a featureless and well-mixed solution. However, recent observations imply that the inhomogeneous structure of the cytoplasm and the cell membrane play a critical role in organizing biomolecules and performing cellular functions [1]. Cell membrane hosts many receptor proteins that enable the cell to communicate with the outside world. These receptors are critical for healthy cell existence, and are also in the focus of drug development research as shown by the fact that around %60 percent of the drugs target a broad family of receptor proteins called G-protein coupled receptors [2]. In many cases, these receptors need to react with each other to become active and take part in signaling. Therefore, understanding the details of how they interact is critical in understanding how cells work.

With the help of single molecule observation techniques, molecules have been found to be temporarily confined in mesoscopic domains in the plasma membrane of many different mammalian cells [3], which is a highly heterogeneous medium that contains many different types of lipids, proteins, and complex structures made of proteins [4]. One of the prevailing ideas that aim to account for the general aspects of organization in the plasma membrane by referring to confinement effects is that molecules such as transmembrane proteins, and even phospholids, are temporarily trapped inside domains delimited by actin filaments positioned closely to the cell surface [3]. The interaction between the actin cytoskeleton and the plasma membrane can lead to temporary confinement of membrane molecules in mesoscopic domains of size 30~250 nm, with a typical duration of 1~100 ms, which is observed in many cell types [3]. Temporary confinement in membrane domains can be functional in many cellular processes as we previously discussed in ref. [5].

## II. OUR STUDY AND FINDINGS

We theoretically and experimentally study the effects of cytoskeleton induced confining domains on the interactions between molecules in the cell membrane [6]. In the theoretical part, we are interested in determining how the statistics of random collisions between molecules is altered due to the presence of confinement effects, with exact calculations and Brownian dynamics simulations. In the experimental part, the distribution of trapping times for proteins and lipids are observed with single molecule tracking techniques [7]. Our theoretical results indicate that confinement does not modify the mean time between collisions (in the absence of crowding and strong particle-boundary interactions); however, it significantly changes its variance. By considering multiple diffusing and interacting particles, we theoretically show that this effect critically depends on the density of molecules, and is stronger at low densities (at densities comparable to those in real cells [8]). Based on these, we argue that confinement has two important implications on the interaction dynamics of membrane molecules: 1) reactions between molecules with low affinity can be enhanced, as confinement leads to temporary increase in local concentration, 2) confinement causes the molecules to undergo bursts of interactions rather than continuously interacting at low rates. The second effect is particularly interesting as it suggests that confinement may regulate signaling by adjusting the frequency at which strong interactions between signaling molecules occur.

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