The 8th European Congress on Computational Methods in Applied Sciences and Engineering
ECCOMAS Congress 2022
5 – 9 June 2022, Oslo, Norway

HOW MECHANOBIOLOGY CAPTURES RECEPTOR CLUSTERING ON LIPID RAFTS DURING LIGAND BINDING

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Key Words: *: Cell Mechanobiology, Lipid Membranes, Ligand-Receptor Binding.*

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Clustering of ligand-binding receptors on lipids rafts across the cell membrane is an experimentally noted phenomenon. Various explanations of such phenomenon and its influence on the cell's response have been proposed in the literature, although the role of the coupling between mechanical processes and multi-physics involving the active receptors and the surrounding lipid membrane during ligand binding has not yet been understood. In particular, the morphology of the particular kind of receptor involved in such processes and its conformational changes play a key role to determine cell's response.

The focus of this work is on G-protein-coupled receptors (GPCRs), the widest group of transmembrane proteins regulating specific cell processes through chemical signalling pathways. Those turn out to involve a synergistic balance between the cyclic Adenosine Monophosphate (cAMP) produced in the intracellular environment and its efflux, mediated by Multidrug Resistance Proteins (MRPs). It is worth noting that GPCRs may be relevant for clinical targeting in several diseases, including cancer. Predicting receptors activity associated with the remodelling of the cell membrane may helpfully support quantitative diagnostics, by potentially conceiving new cAMP-based markers for discriminating cells from their membrane activity. A multiphysics approach is developed in this paper featuring the chemo-mechanical principles leading active receptors, such as GPCRs, to likely cluster on lipid rafts across the cell membrane.

The proposed model is based on the interplay among entropic, conformational and membrane strain energy, diffusion and kinetics of binding and unbinding. The latter is regulated by the

chemical potential associated to conformations and transport of transmembrane domains inhabited by active GPCRs and MRPs, which exchange lateral pressure while interacting with the surrounding lipids. In particular it is shown how the mechanobiology involved in the remodelling of the cell membrane allows for motivating from a strong mechanical perspective the actual correspondence found between lipid rafts formation and the activity of ligand-binding receptors, in agreement with the experimentally observed cAMP levels.

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