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How diffusion might lead to non-linear response

Freek van Hemert[1], **B. Ewa Snaar Jagalska**[2], **Thomas Schmidt**[1*]

[1]Leiden Institute of Physics, Leiden University, Leiden, The Netherlands
[2]Leiden Institute of Biology, Leiden University, Leiden, The Netherlands
schmidt@physics.leidenuniv.nl

Chemotaxis is a complex interplay between numerous molecular species whose coordinated interactions culminate in highly effective directed motion in concentration gradients. Many proteins that play vital, important and minor roles have been identified and biochemically characterized. Several pathways have been recognized to act in parallel each of which contributes to, but is not essential for chemotaxis. Nevertheless a definitive answer as to how cells like *Dictyostelium disciodeum* perform chemotaxis is still unknown. Qualitative descriptions of molecular interactions have proven to be insufficient when trying to understand complex cellular cascades. New techniques such as single molecule microscopy are able to add temporal, spatial and quantitative information to the network of molecular interactions. Further probing the properties of cytoskeleton meshworks and tightly controlled artificial membranes *in vitro* provides information on cellular components relevant to chemotaxis which cannot be investigated in the complex environment of the living cell. Finally simulations give insight in the effects of noise in the biological systems and lead to new ways of interpreting biochemical data. Here we will look at chemotaxis from a biophysicists' view, combining *in vivo*, *in vitro*, and *in silico* experiments with a particular emphasis on single molecule work.

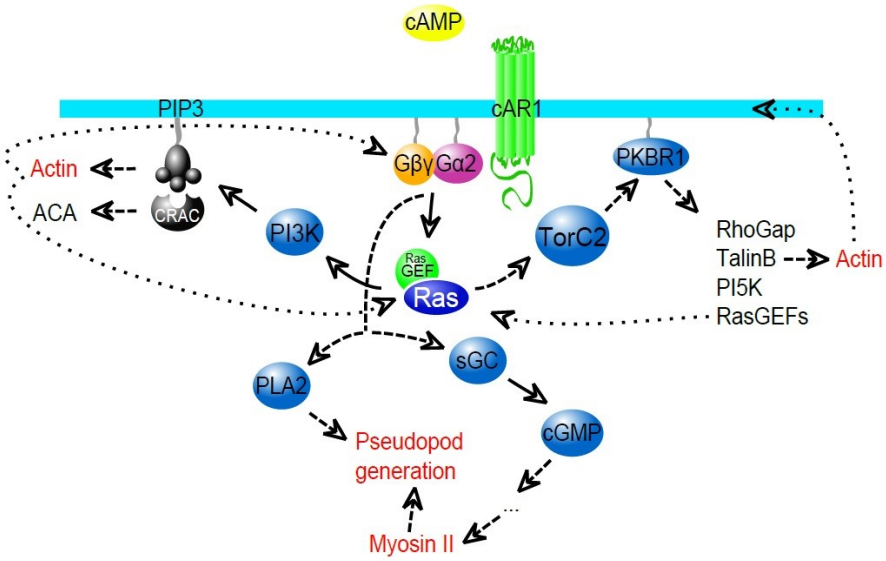

Figure 1: *D. Discoideum* chemotaxis pathway. Upon activation of cAR1 by cAMP, the Ga2β heterotrimer dissociates. Both subunits engage in signaling, Ga2 is more important in pathways that lead to pseudopod extension whereas Gβ is more important for cAMP relay involving cytosolic regulator of ACA (CRAC) and ACA. The PLA2 and soluble guanilyl cyclase (sGC) pathways are activated; these pathways play important roles in the regulation of pseudopod placement. RasGEFs activate Ras proteins. Ras proteins and other small G proteins locally activate TorC2 which via membrane localized PKBR1 subsequently activates a multitude of factors including TalinB. Talin mediates cytoskeleton membrane interactions and plays a role in cell adhesion. Ras proteins futher activate the PI3K pathway. PI3K localizes to the leading edge where it produces PI(3,4,5)P from PI(4,5)P. PI(3,4,5)P functions as a docking site for several chemotaxis-related proteins like the ACA regulator CRAC. A feedback loop involving F-actin that activates Ras proteins leads to the generation of pseudopods without G protein input facilitating random cell motility. We propose a feedback from actin acting on the Gβ subunit specifically at the leading edge. This conceivably leads to a more persistent leading edge or the stabilisation of pseudopods. More generally, actin polymers form fences in the membrane functioning as physical diffusion barriers that influence and maintain localized signaling.