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Mathematical model(s) for the dynamics of (TNF-) Receptor Clustering

Responses of the immune system are coordinated by immune hormones, called cytokines. Tumor necrosis factor (TNF) is a cytokine regulating the innate immune system, including cells like dendritic cells, macrophages and neutrophils. Disregulated TNF has been recognized as the main factor in progression of many autoimmune diseases, like Rheumatoid Arthritis and Morbus Crohn. TNF is a homotrimeric protein capable to bind three receptors. But also unligated receptors occur on the cell surface as homomultimers due to a homophilic interaction domain. Based on these two interaction motivs (ligand/receptor and receptor/receptor) we present two different modelling and simulation strategies.

Firstly, we use a mass action kinetics approach to propose an ordinary differential equations model for the dynamics of subsequent formation of signal clusters on the cell membrane. Thereby, we focus our attention on the essential components of the system of elementary ligand/receptor complexes that can initiate intracellular signaling processes eventually leading to caspase mediated cell death. Therefore we develop our model in a way that not only receptor cross-linking by ligand but also homophilic interaction of receptors leading to homodimer formation in the absence of ligand is encompassed.

It turns out that using parameter values for binding affinities consistent with experimentally determined values the analysis of our model suggests that in the case of high ligand and low receptor concentration no substrate inhibition in the receptor cross-linking can be observed. In contrast, our model shows that an increasing ligand concentration leads to a saturation in receptor cross-linking and therewith illustrating the persistence of the downstream signaling events even in the case of ligand excess. These results are underlined by numerical simulations, which are confirmed by experimental data.

Secondly, we apply a population balance model with simultaneous growth and breakage processes in order to describe the forming of the signaling clusters along

with the evolution of the cluster sizes and couple this with a further equation characterising the concentration of free receptors. For the numerical solution of this system in its integro-differential form we use several discretization techniques including finite differences and semi-discrete moment preserving finite volume schemes which can be extended to incorporate further spatial effects on cell surfaces. Thereby we examine the results obtained not only with regard to biological relevance but also with respect to stability and robustness of the discretization.