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Modelling Endocytosis - from the Molecules to the Liver Cell

Endocytosis is a conserved cellular process in eukaryotes by which nutrients are assimilated by the cell. Internalized material is transported by endosomes and sorted by means of endosome transitions. Endosome transitions result from dynamic interactions among Rab GTPases. We focus on Rab5-Rab7 and Rab5-Rab4/11 interactions underlying respectively early-to-late and early-to-recycling endosome transitions that select among the degradative, recycling and transcytotic routes in liver cells. As a model of endosome transitions, we consider the spatial concentration profiles of competing GTPases and the shift of the resulting concentration front in a one-dimensional system across the endosomal membrane. Locally, interacting GTPases can be modelled as a bistable system of either the cut-out switch or the toggle switch type [1]. For the toggle switch, all stable steady state solutions depend monotonically on parameters whereas the cut-out switch yields an increasing solution which then switches off. We extend those two models by diffusive spatial coupling. Heterogeneous initial conditions of the reaction-diffusion system lead to spatially alternating GTPase concentration domains and interjacent concentration fronts. In general, the front is invading that domain which has the smaller concentration difference from the unstable saddle solution. Hence, an intermediate parameter value exists at which the front remains stationary. The toggle switch kinetics yields this expected behaviour whereas the cut-out switch system shows novel behaviour. Corresponding to the toggle switch properties, we propose that this mechanism underlies the observed coexistence of Rab5-Rab4/11 domains during the early-to-recycling endosome transition. On the other hand, the behaviour of the spatially extended cut-out switch system reinforces the role of the cut-out switch for early-to-late endosome transitions. Moreover, we link this molecular understanding to the cell level by means of an agent-based model representing the population of and biophysical interactions between early endosomes within one cell. Simulation results identify critical regulatory steps that control efficient cargo flux which is essential for liver cells.

References

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