Fusion and fission control the heterogeneity of endosome maturation

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The fate of many intracellular processes relies on the evolution of an intricate network of endosomes that transport cargo after endocytosis to their final destinations. Recent experimental techniques have provided valuable information about organelle maturation and its specific role in, for instance, the ability of a virus to escape the endosome and release its genetic material in the cytoplasm. Endosome dynamics and function depend on different GTPases (called Rabs) that decorate its membrane. While these molecules have been studied experimentally and even modeled mathematically in the past, there are still many open questions related to their individual dynamics and singularity. In Fig. 2 we depict the interrelationship between different activation states of Rab5 and Rab7 in an endosome.

In this work, we present a mathematical framework, based on the classical theory of drop coagulation and fragmentation to model endosomes with certain levels of Rab5 and Rab7 (in their active form). Let us define $c(x_5, x_7, t)$ as the number of endosomes at a given time t with a given concentration of activated Rab5 and Rab7 (technically, [Rab5:GTP] and [Rab7:GTP], respectively), denoted by x_5, x_7, respectively, at the endosome membrane. That number follows an integro-partial differential equation that is intractable analytically.

Our model allows us to derive simple equations for the mean and standard deviations of the concentrations of Rab5/Rab7 as well as the number of endosomes and fit them to experiments of Dengue virus escape.

$$\dot{N} = S_0 + (K^{(0)}_{\rm FIS} - \mu_0 - \tfrac{1}{2}K^{(5)}_{\rm FUS}R_5 + \tfrac{1}{2}K^{(7)}_{\rm FUS}R_7)N - \tfrac{1}{2}K^{(0)}_{\rm FUS}N^2 \quad (1a)$$

$$\dot{R}_5 = v_{50}N - (v_{55} + \mu_0)R_5 - v_{57}R_7 \quad (1b)$$

$$\dot{R}_7 = v_{70}N + v_{75}R_5 - (v_{77} + \mu_0)R_7 \quad (1c)$$

In Fig. 1 we show the comparison of the theory *vs.* the experimental data for Dengue virus in Ref. [1]. We also make a connection between Rab levels and the endosome pH, thus suggesting a mechanism to account for the experimental variability in the escape times of many viruses.

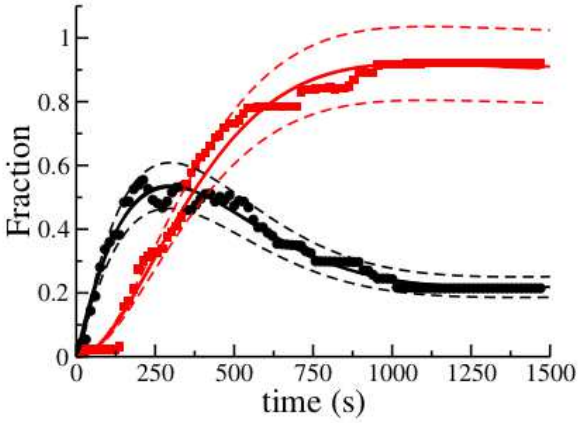

Fig. 1.

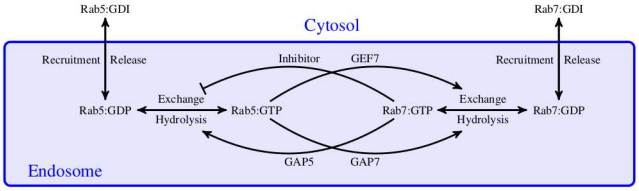

Fig. 2.

Finally, we discuss our approach in the context of other mathematical models that can be derived from our theory and are based on ordinary differential equations for the mean concentrations of Rabs at the cell level.

[1] H. M. van der Schaar, M. J. Rust, C. Chen, H. van der Ende-Metselaar, J. Wilschut, X. Zhuang, J. M. Smit, Dissecting the cell entry pathway of dengue virus by single-particle tracking in living cells, PLoS Pathog. **4**, e1000244 (2008).