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How one cell eats another: Experiments and modelling investigate biophysical requirements for uptake

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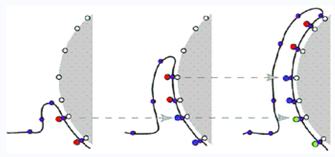
Biophysics of phagocytosis

- Fundamental process of the immune response
- Complex biochemical pathways involved
- Completion depends on biophysical parameters (BP: particle ligand density, shape, size and cell membrane stiffness and tension etc)

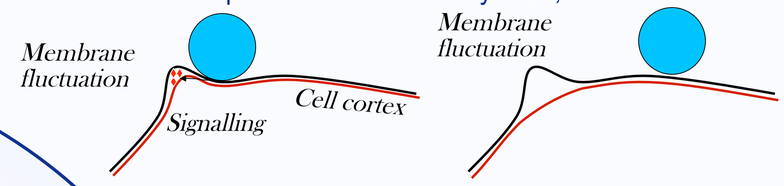
The zipper mechanism (Griffin *et al.* 1975)

- Ligand/receptor (L/R) binding triggers signalling locally
- Signalling triggers actin polymerization
- Actin pushes the membrane outward
- New L/R bonds can be created...



Our main assumptions

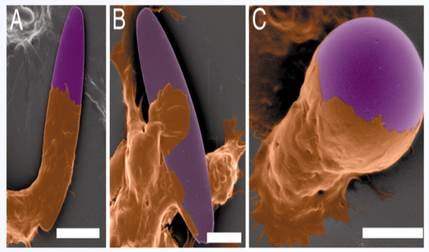
- To polymerize actin, need gap between actin cortex and membrane: use thermal membrane fluctuations
- Gaps near particle are filled by signalling-induced actin polymerization, reinforcing L/R bonds (for engulfment irreversibility)
- Membrane fluctuations far from particle are not filled by actin, and can move backwards



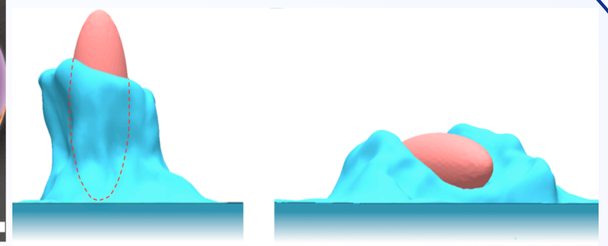
Our model

- Membrane is moved randomly
- Finite element calculation of energy
- Monte Carlo metropolis algorithm
- Stabilization of membrane near the particle

First results in explaining particle-shape dependence



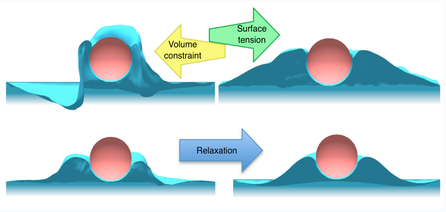
Phagocytosis of polystyrene beads from scanning electron microscopy, by Champion *et al.* PNAS 103:4930 (2006)



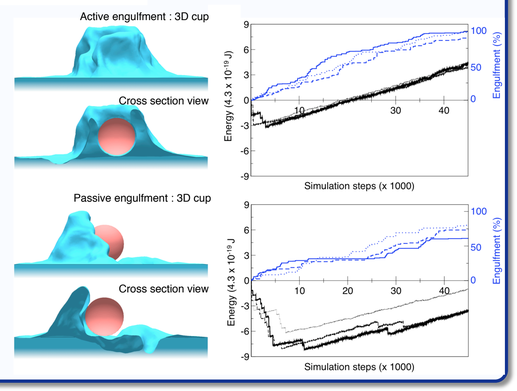
Phagocytosis simulation, demonstrating that the zipper mechanism leads to progressive engulfment. Cup shape depends on BP. Spheroid particles are engulfed more easily if taken with the tip first

Model predictions

- BP & out of equilibrium engulfment regulate cup shape

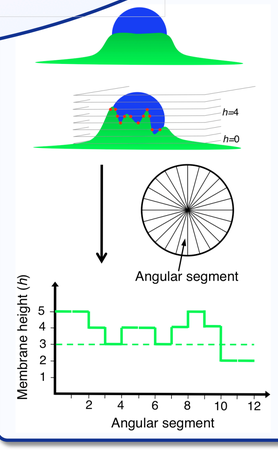


- Active engulfment allows for large increase in energy. Engulfment is faster and more regular →
- Passive engulfment is produced by membrane ruffles, leading to irregular cups →



Can we apply the model successfully to bacteria uptake ?

Campylobacter bacteria. Source: wikipedia

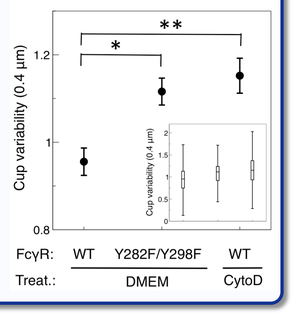


Comparison with experiments: analysis of fluorescence data

- Confocal microscopy imaging of IgG-coated polystyrene particles taken up by COS-7 cells expressing either WT-FcγR or signalling-dead mutant Y282F/Y298F-FcγR. For control, we used WT-FcγR and treatment with CytoD

Computer image analysis: the 3D cup shape variability is characterized by spatial cell-membrane receptors distribution around the particle

- Predictions confirmed: engulfment proceeds even without actin polymerization, but slower and in a less regular fashion
- Biochemical pathways added through evolution for extra-robustness ?



This work is dedicated to the memory of Emmanuelle Caron, and was funded by the Centre for Integrative Systems Biology at Imperial College