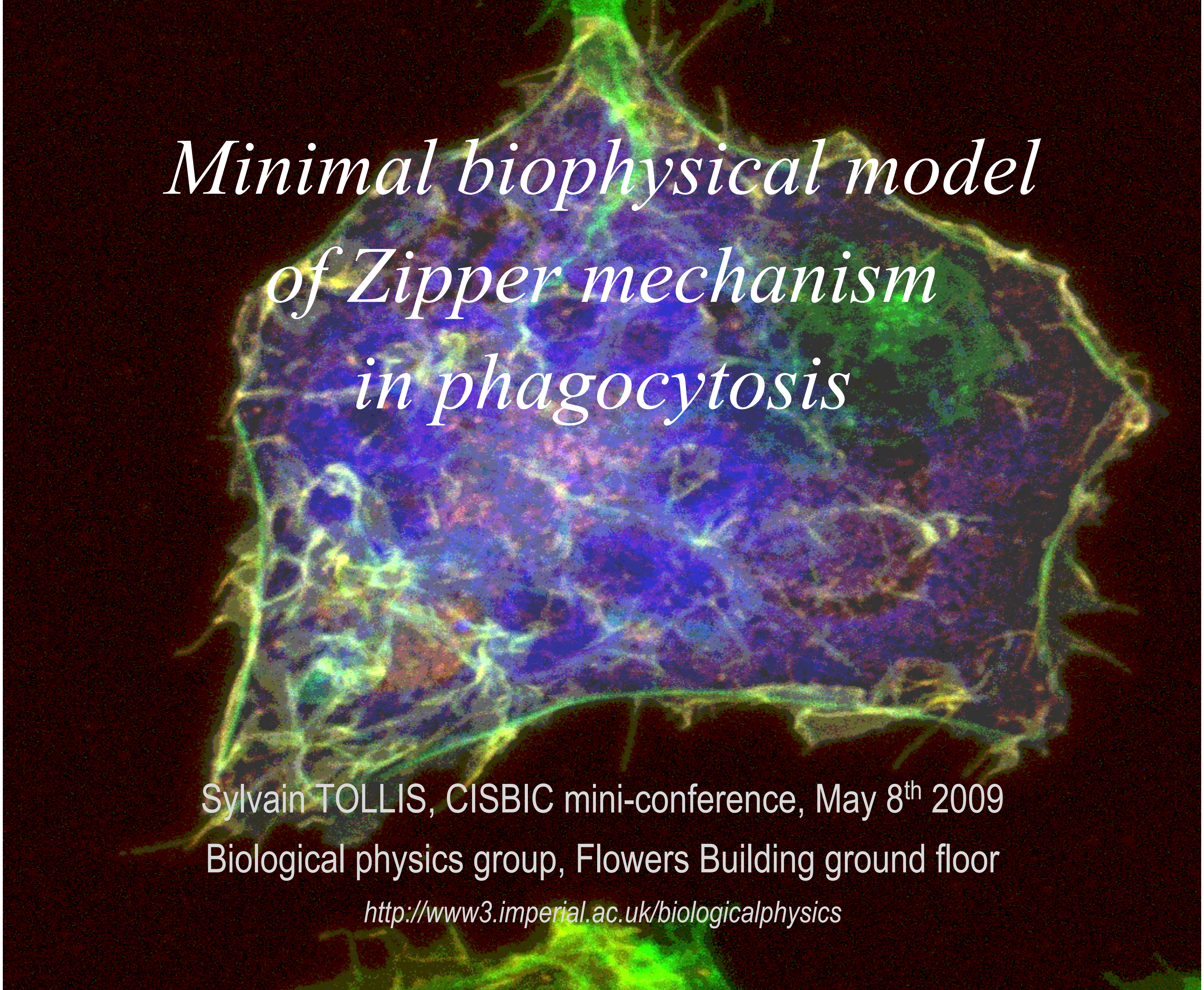


Minimal biophysical model of Zipper mechanism in phagocytosis

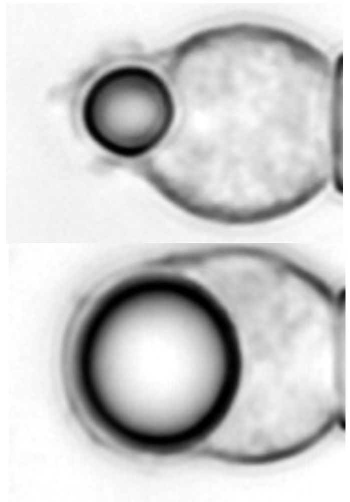
Sylvain TOLLIS, CISBIC mini-conference, May 8th 2009
Biological physics group, Flowers Building ground floor
http://www3.imperial.ac.uk/biologicalphysics

Biophysical aspects of phagocytosis

Phagocytosis requires cell-shape changes

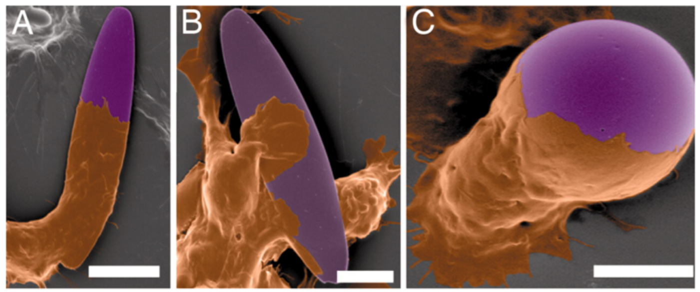
Relevance of cell and particle's physical parameters

Influence of particle's size



Phagocytosis of polystyrene beads by neutrophils. Optical microscopy images, from Herant et. al., Journal of Cell Science)2006(1903 ,119

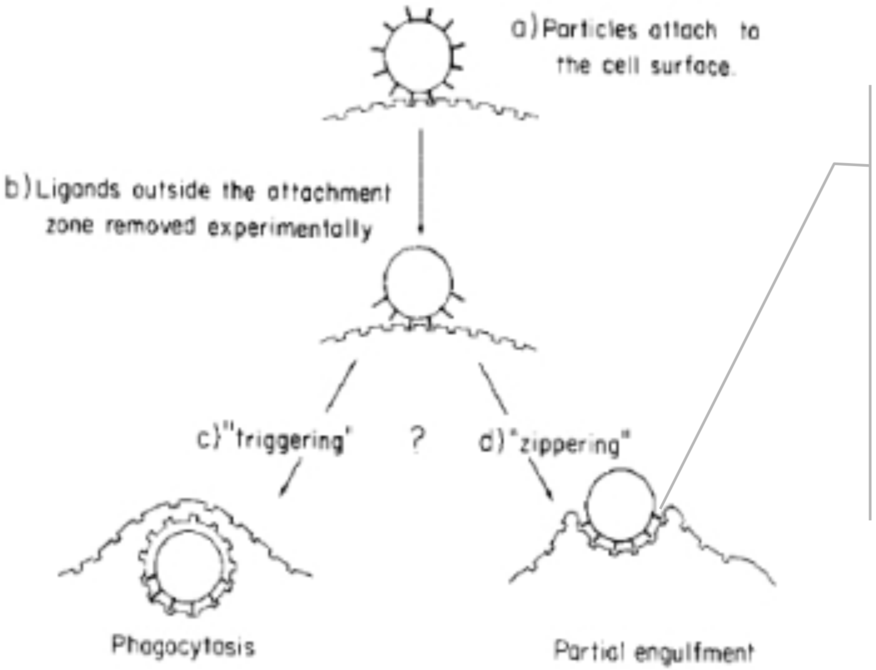
Influence of target's shape

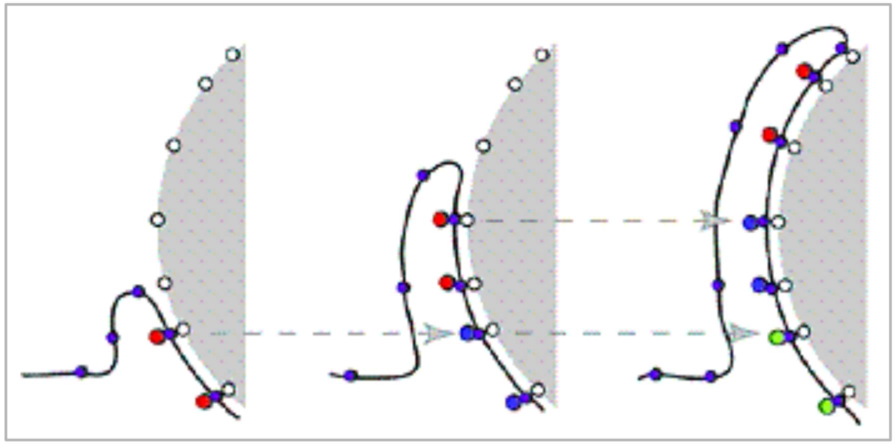


Phagocytosis of polystyrene beads by rat macrophage cells. Scanning electrons micrographs, from Champion et. al., PNAS 2006;103:4930-4934

The Zipper mechanism

Particles partially bleached are partially engulfed



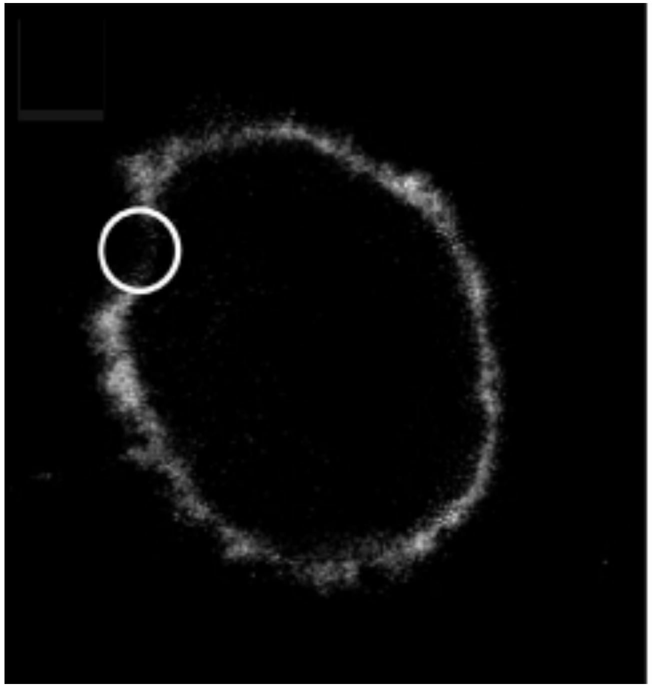


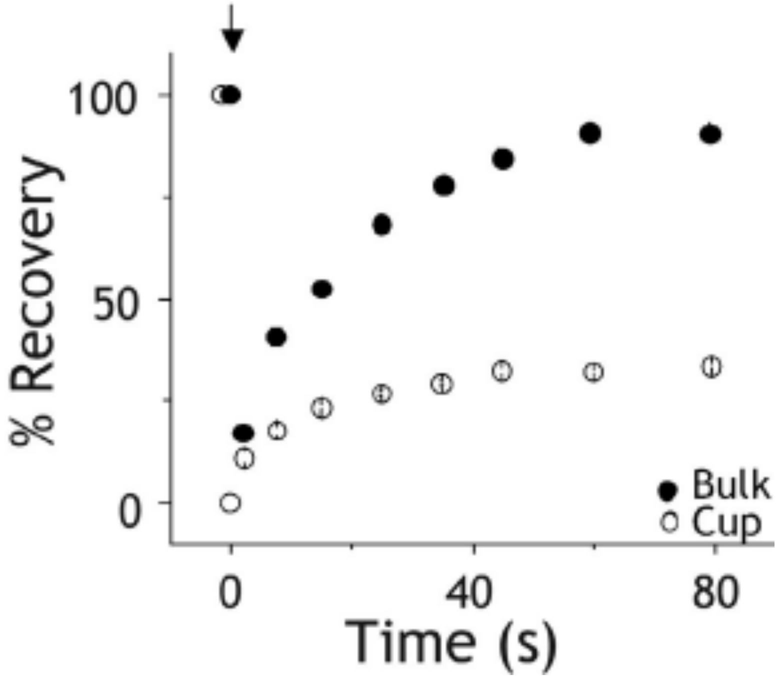
Griffin et. al., Journal of Exp. Med. 142, 1263-1282 (1975)

Threshold in local concentration of receptors and ligands rather than overall concentration ?

The Zipper mechanism

Membrane proteins involved in phagocytosis have a reduced mobility





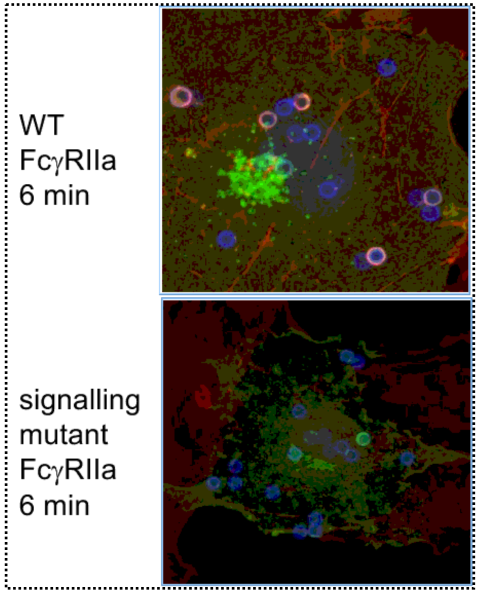
Fluorescence recovery after photobleaching of RAW264.7 macrophages uptaking IgG coated particles.
Plasma membrane GFP's diffusion is strongly reduced at the phagocytic cup.
From Corbett-Nelson et. al., Journal of Cell Biology 174, 255-265 (2006)

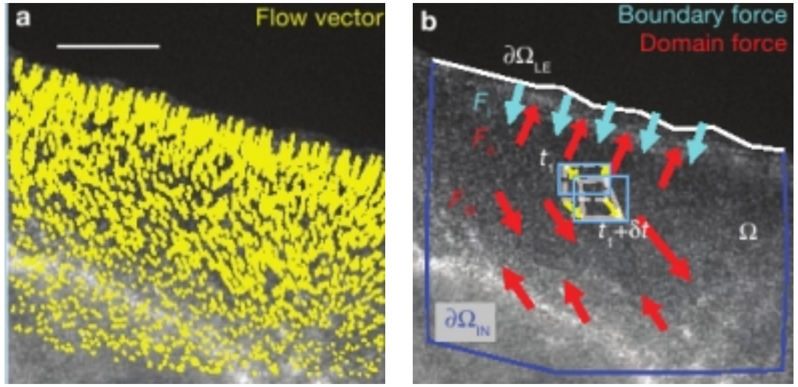
Modelling actin force : irreversible bonds

Phagocytosis is an active out of equilibrium process

Potential sources of energy to drive engulfment

- Chemical (force generated by the actin network, L-R attraction)
- Thermal (no direct force, thermal fluctuations are ordinated by the zipper)





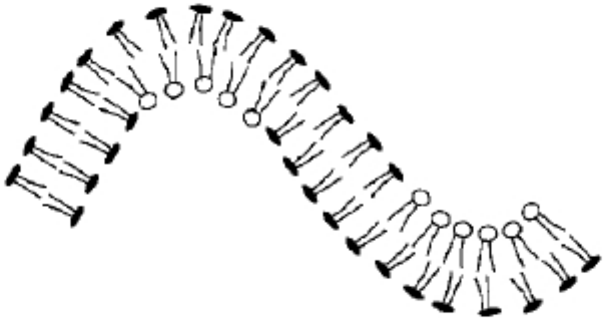
Actin flow and intracellular forces. Polymerization drives membranes protrusions in the "good" direction. Fluorescent speckle microscopy image, from Ji et. al., Nature Cell Biology 10, 12 (2008)

Our assumption : active processes make the L-R bonds irreversible

- Ratchet mechanism

Modelling a cell membrane

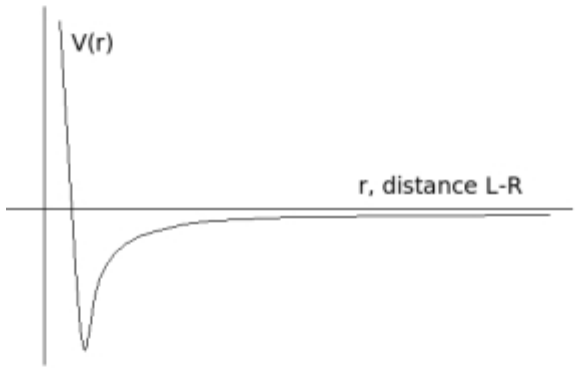
Fluid membrane model : surface tension σ, bending stiffness κ_b



A lipid bilayer : stretching increases the interlipid space of both layers, and bending tends moreover to constrict the inner layer lipids, leading to two distinct energy contributions.
From Kumar et. al., Phys. Rev. E 60, 4610-4618 (1999)

Cell volume constrained : expansion and shrinkage cost energy κ_P

Short range L-R attraction
Lennard-Jones potential V_{LJ}

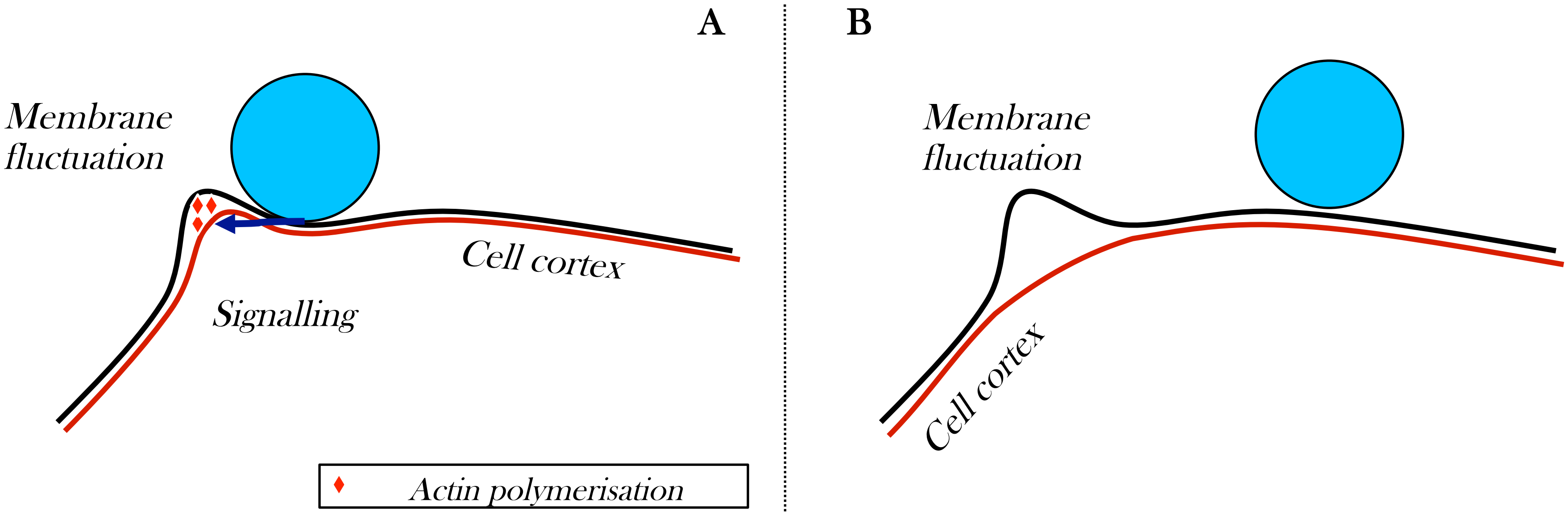


Our model for the Zipper mechanism

No predictive power of the Zipper mechanism

Need for a quantitative model (kinetics of engulfment, cup shape...)

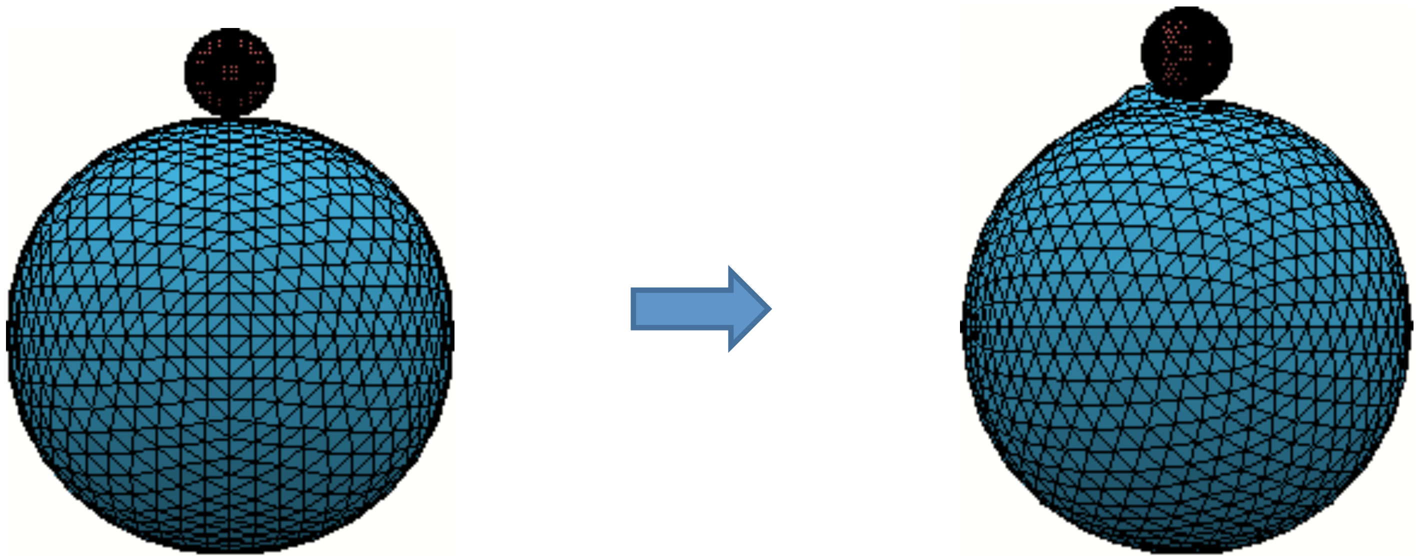
Contribution of the thermal energy : membrane fluctuations support actin polymerization



Our model for the Zipper mechanism

Finite elements calculations and Monte Carlo simulations

- Cell surface sampled
- MC simulations (random membrane moves)
- Move accepted with probability :
  (Metropolis algorithm at finite T)



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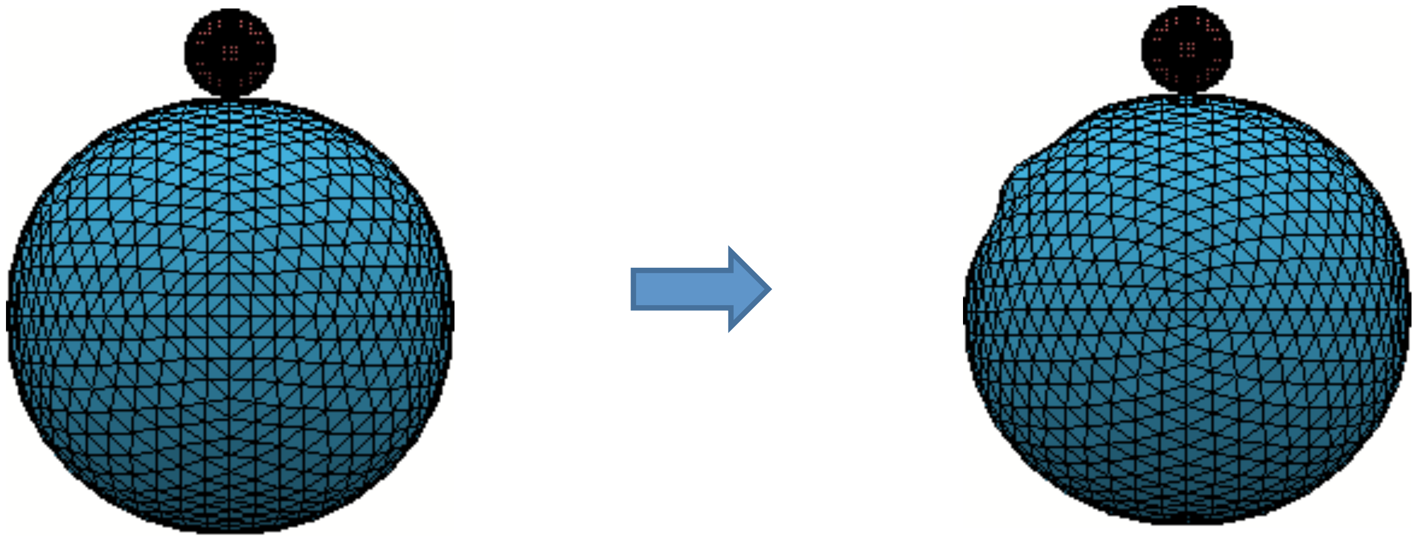
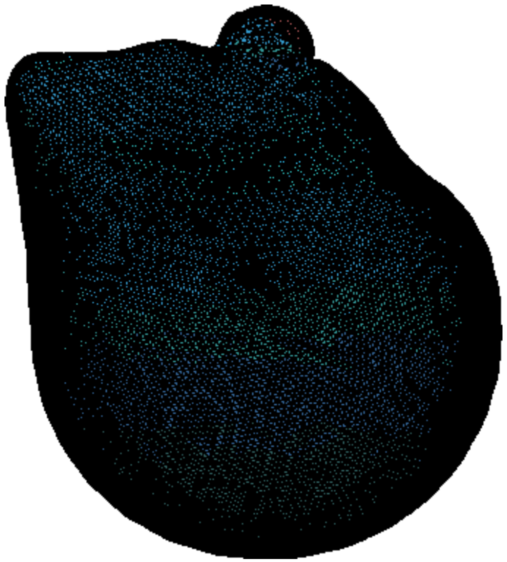
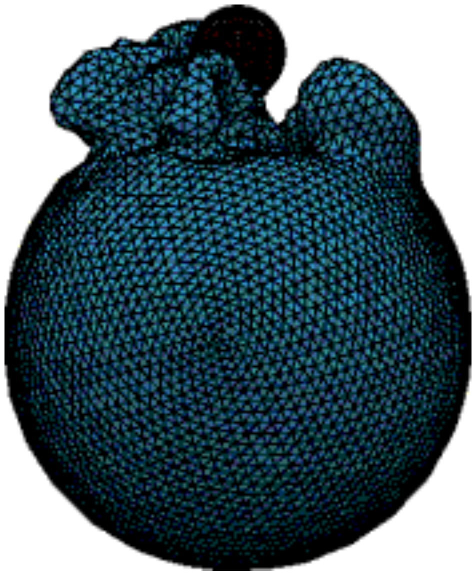


First results

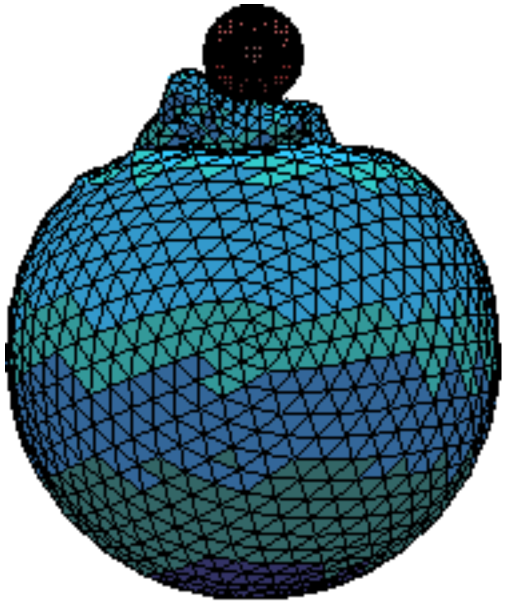
Different shapes for engulfment



No volume constraint



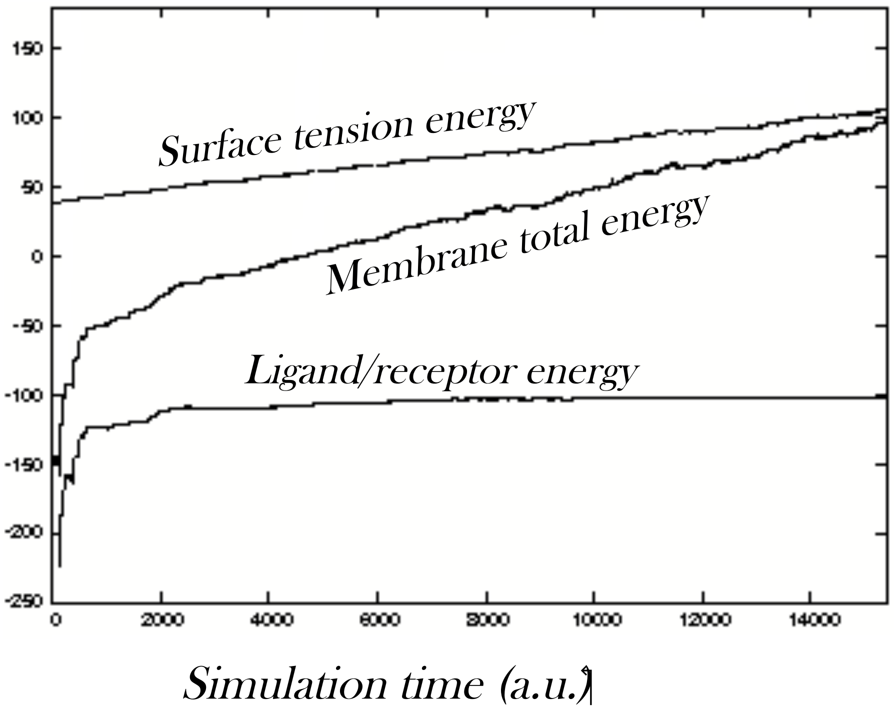
Volume constraint and low surface tension modulus

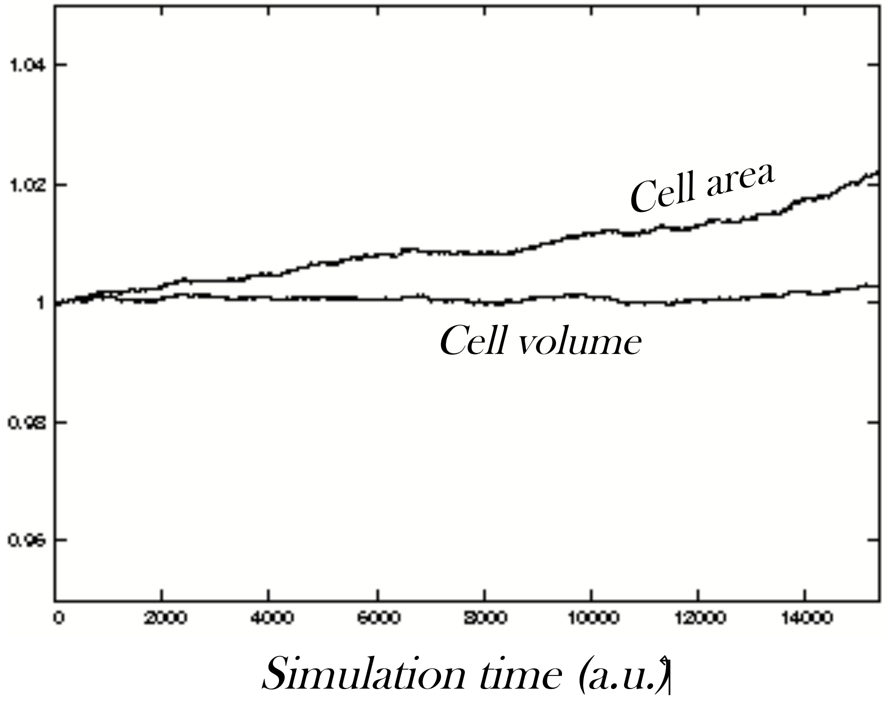


Volume constraint and higher surface tension modulus

First results

Energy and cell geometry vs simulation time : active process





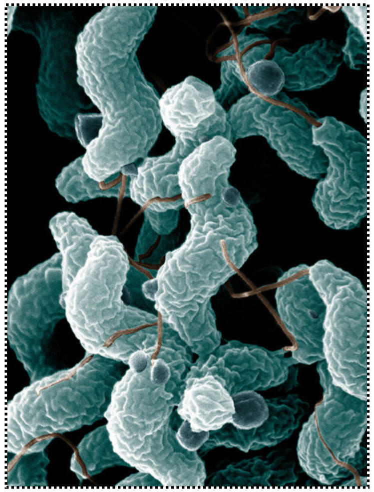
Connection to experiments : future directions

Need to sort out optimal simulation parameters (mesh size...)

Studies will be carried out only by varying biophysical parameters (σ, T,…)

Aim 1 :
passive vs active phagocytosis

Aim 2 :
dependence on particle shape : existing data + phago. of actual bacteria (helicoidal Campylobacter)



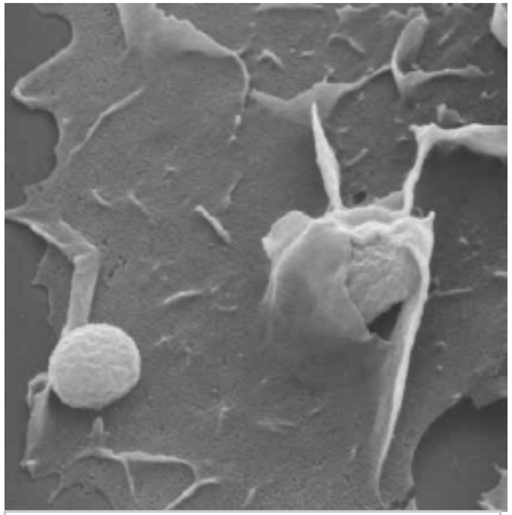
Aim 3 :
can we smoothly go from F_cR to CR3 type zippering varying physical parameters ?

time

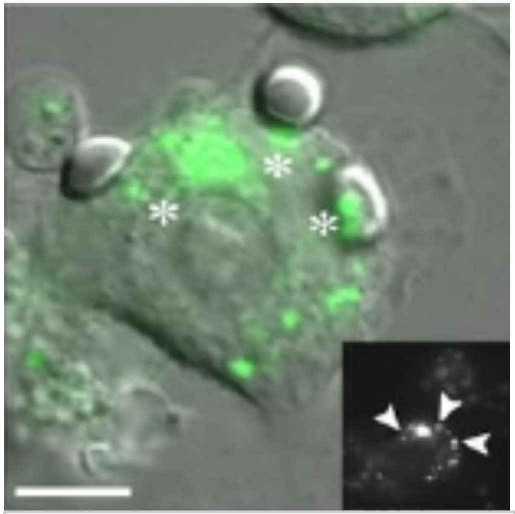
Future directions : FcR vs. CR3 phagocytosis

Both seem to occur via the Zipper mechanism

So why are the cup shapes so different ?



FcR-mediated phagocytosis. The cup forms "outside" the cell body. Electron micrograph image of IgE-opsonised Zimosan particle engulfed by an RBL-2H3 cell. From May et. al., Journal of Cell Science 114, 1061-1077



CR3-mediated phagocytosis. C3bi-opsonised particles seem to "sink" into RAW264.7 macrophages. Scanning electron microscopy image from Patel et. al., Molecular Biology of the Cell 19, 4628-4639 (2008)

Different receptors and signalling pathways :

Different effective physical parameters ?

Acknowledgements

Thanks to :

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