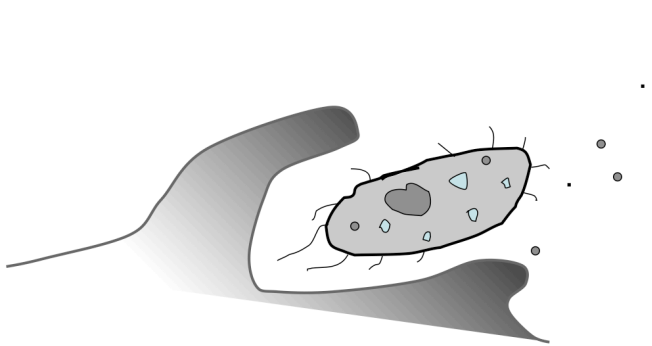
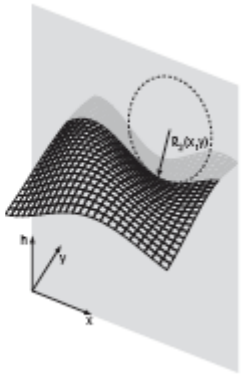
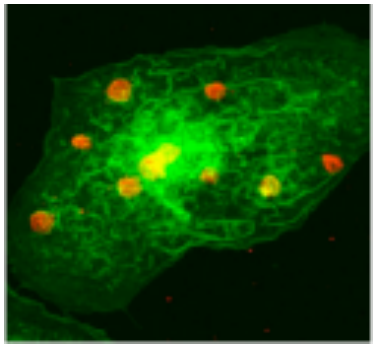
CISBIC Subproject 2: How one cell eats another – Experiments and modelling elucidate early signalling events and biophysical requirements for uptake







Robert Endres, Sylvain Tollis, Anna Dart

CISBIC IAB Oct 8, 2010

Biological Physics Group at Imperial College:
http://www3.imperial.ac.uk/biologicalphysics

bbsrc
biotechnology and biological sciences research council

Publications

Tollis, Dart, Tzircotis, Endres, **The zipper mechanism in phagocytosis: Energetic requirements and variability in phagocytic cup shape**, submitted.

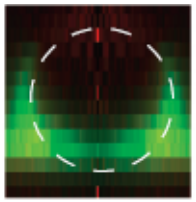
Tzircotis, Braga, Caron, **RNAi screen demonstrates the requirement of RhoG in both FcγR- and CR3-mediated phagocytosis**, submitted.

Molecular Systems Biology 5; Article number 298; doi:10.1038/msb.2009.59
Citation: *Molecular Systems Biology* 5:298

www.molecularsystemsbiology.com

molecular systems biology

A mechanical bottleneck explains the variation in cup growth during FcγR phagocytosis

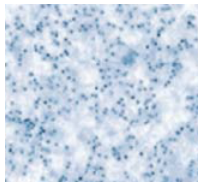


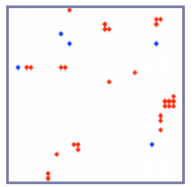
Jeroen S van Zon[1,4], George Tzircotis[1,2,4], Emmanuelle Caron[1,2] and Martin Howard[3,*]

OPEN ACCESS Freely available online

PLoS one

Biophysical Mechanism for Ras-Nanocluster Formation and Signaling in Plasma Membrane

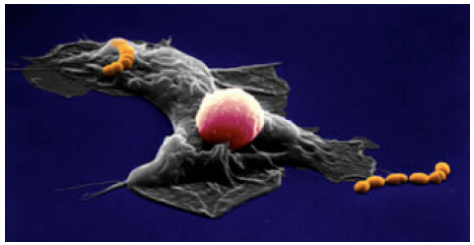


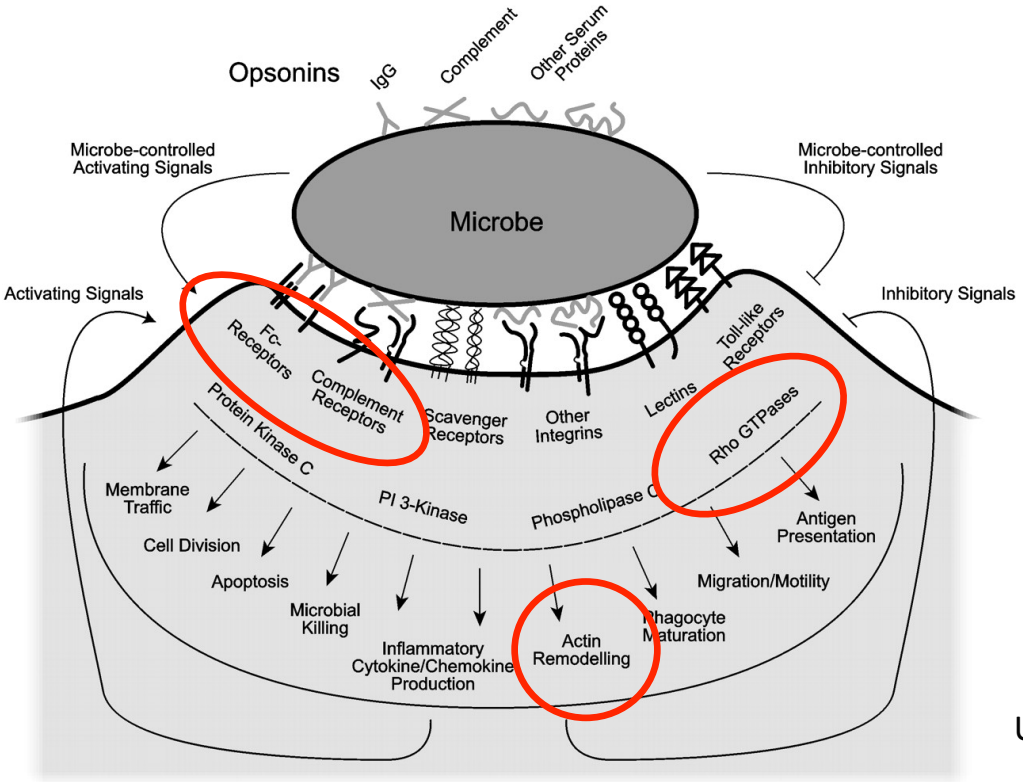


Thomas Gurry[1,2], Ozan Kahramanoğulları[1,3], Robert G. Endres[1,4]*

Clausznitzer, Oleksiuk, Løvdok, Sourjik, Endres, **Chemotactic response and adaptation dynamics in *Escherichia coli***. PLoS Comp Biol (2010)

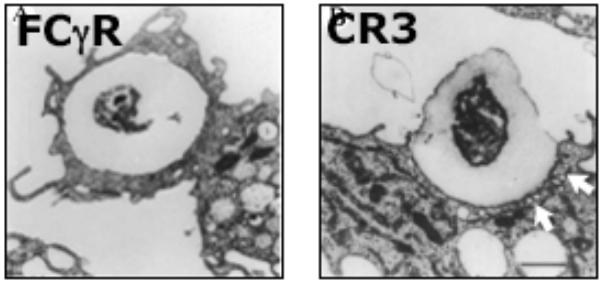
Daunting signalling complexity in phagocytosis





Underhill & Ozinsky (2002)

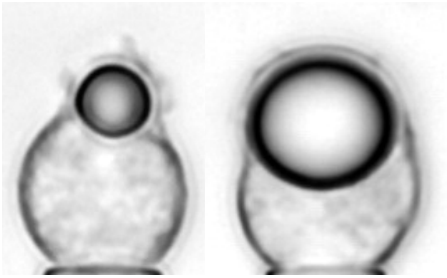
about 140 different molecular species are involved



Allen & Aderem (1996)

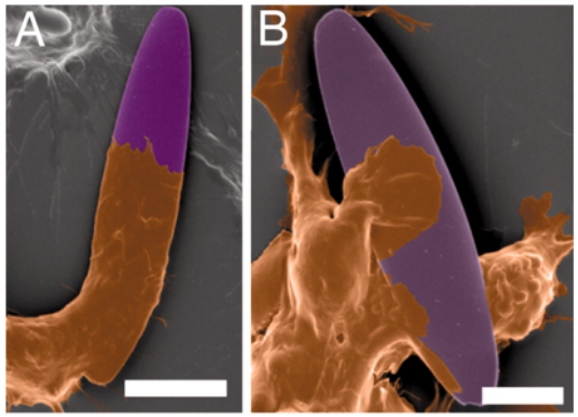
Universal biophysical aspects of phagocytosis

Size independence



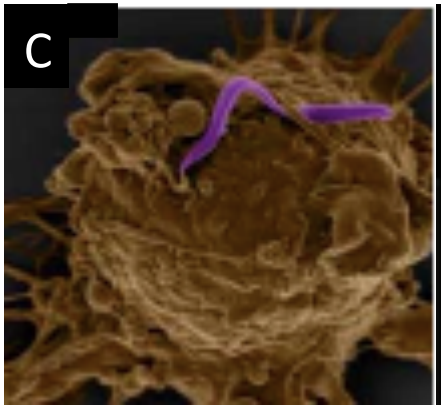
Herant et al. (2006)

Shape and orientation dependence

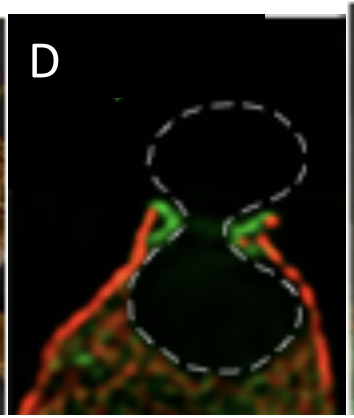


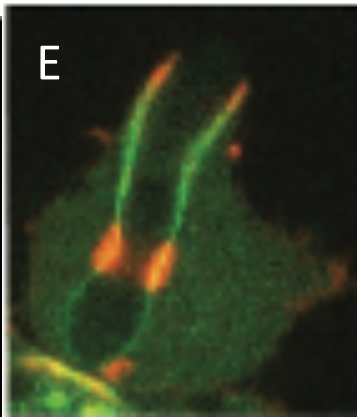
Champion et al. (2006,2009)

Acto-myosin dynamics



Dieckmann R *et al.* (2010)

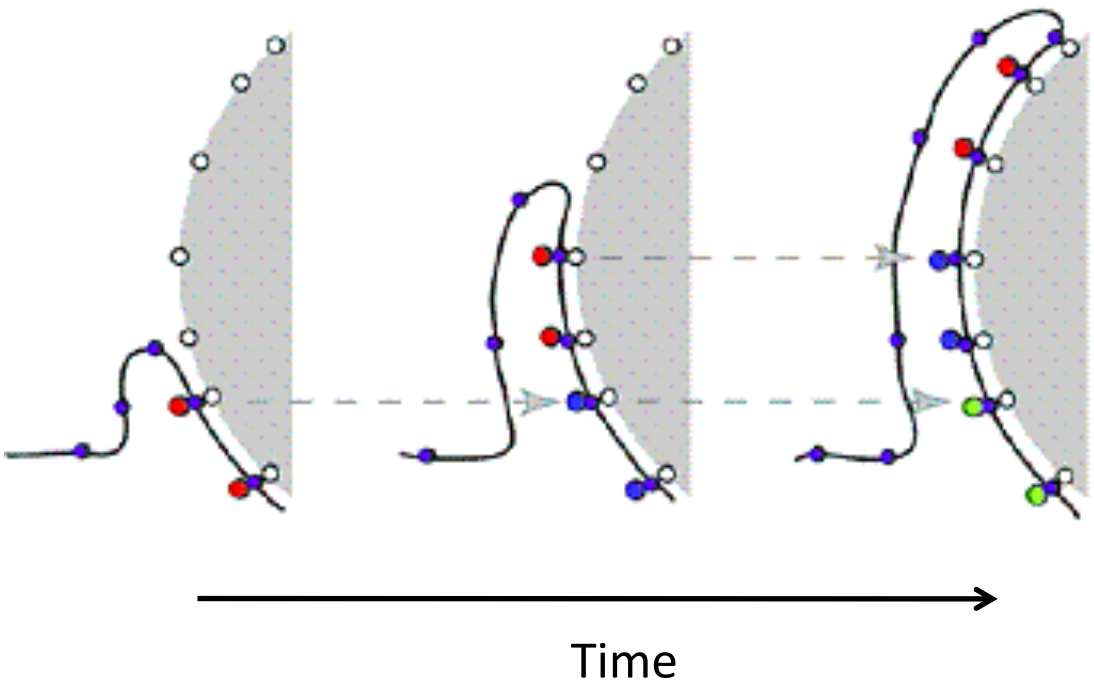




Gerisch G *et al.* (2009)

Conceptual Zipper mechanism

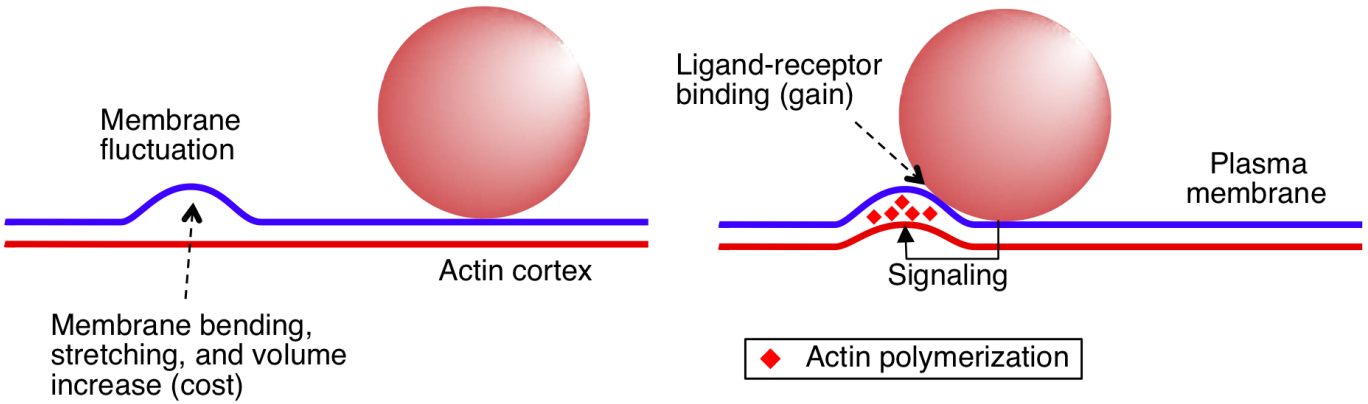
for explaining dependence on ligand density



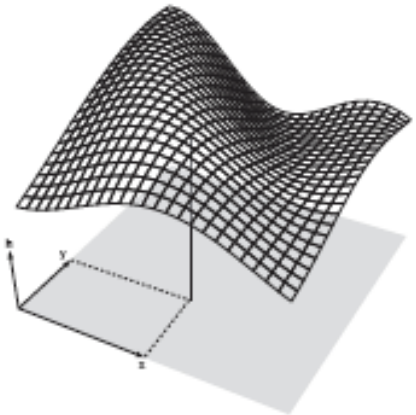
Ratchet

Griffin et al. (1975), Swanson (2008)

Implementation of zipper mechanism



Cell-membrane energy:



$$E = \underbrace{\frac{\kappa_B}{2}\oint (C_1 + C_2 - C_0)^2 dA}_{\text{bending}} + \underbrace{\Sigma A}_{\substack{\text{membrane}\\ \text{stretching}}} + \underbrace{PV}_{\substack{\text{vesicle}\\ \text{swelling}}} + \underbrace{E_{LR}}_{\substack{\text{Ligand-}\\ \text{receptor}\\ \text{binding}}}$$

Ligand-receptor binding induces actin polymerization, making membrane deformation effectively irreversible → **ratchet**.

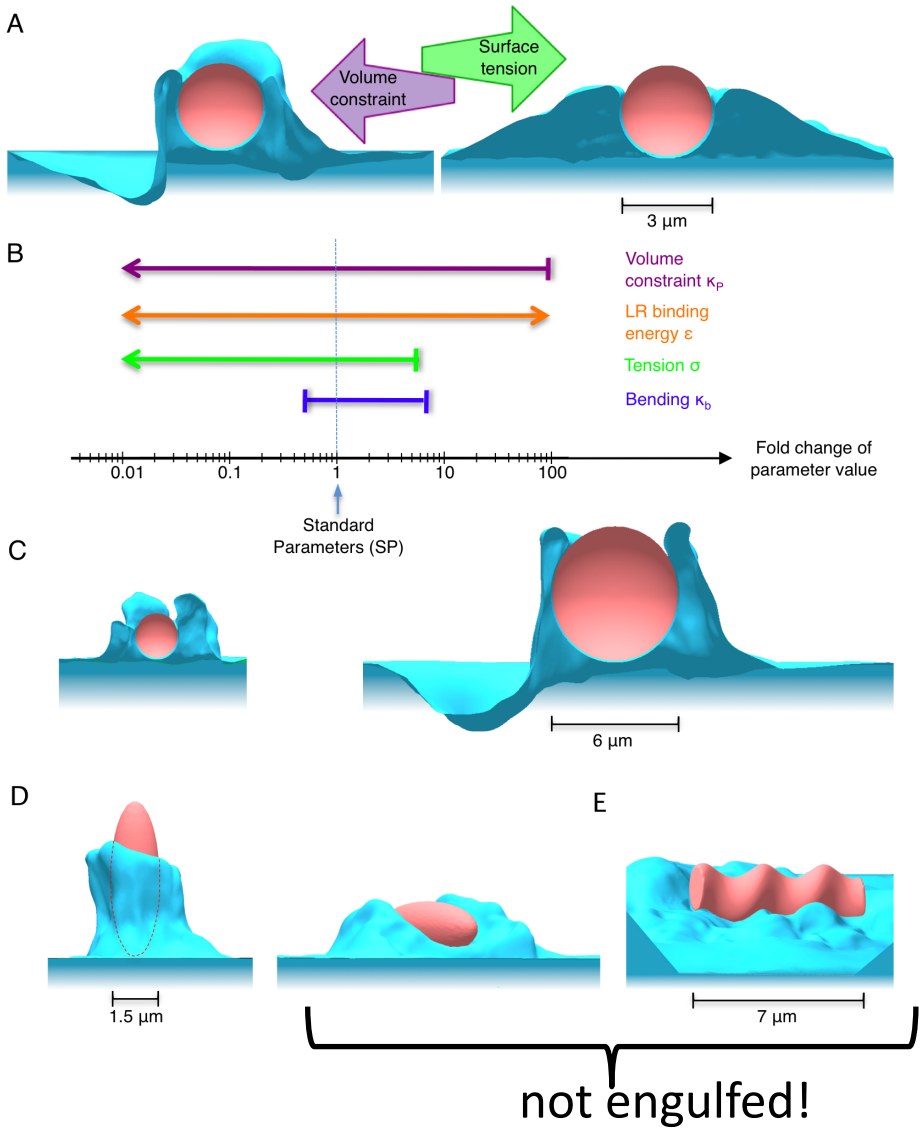
Successful engulfment for wide range of parameters

Cup shape

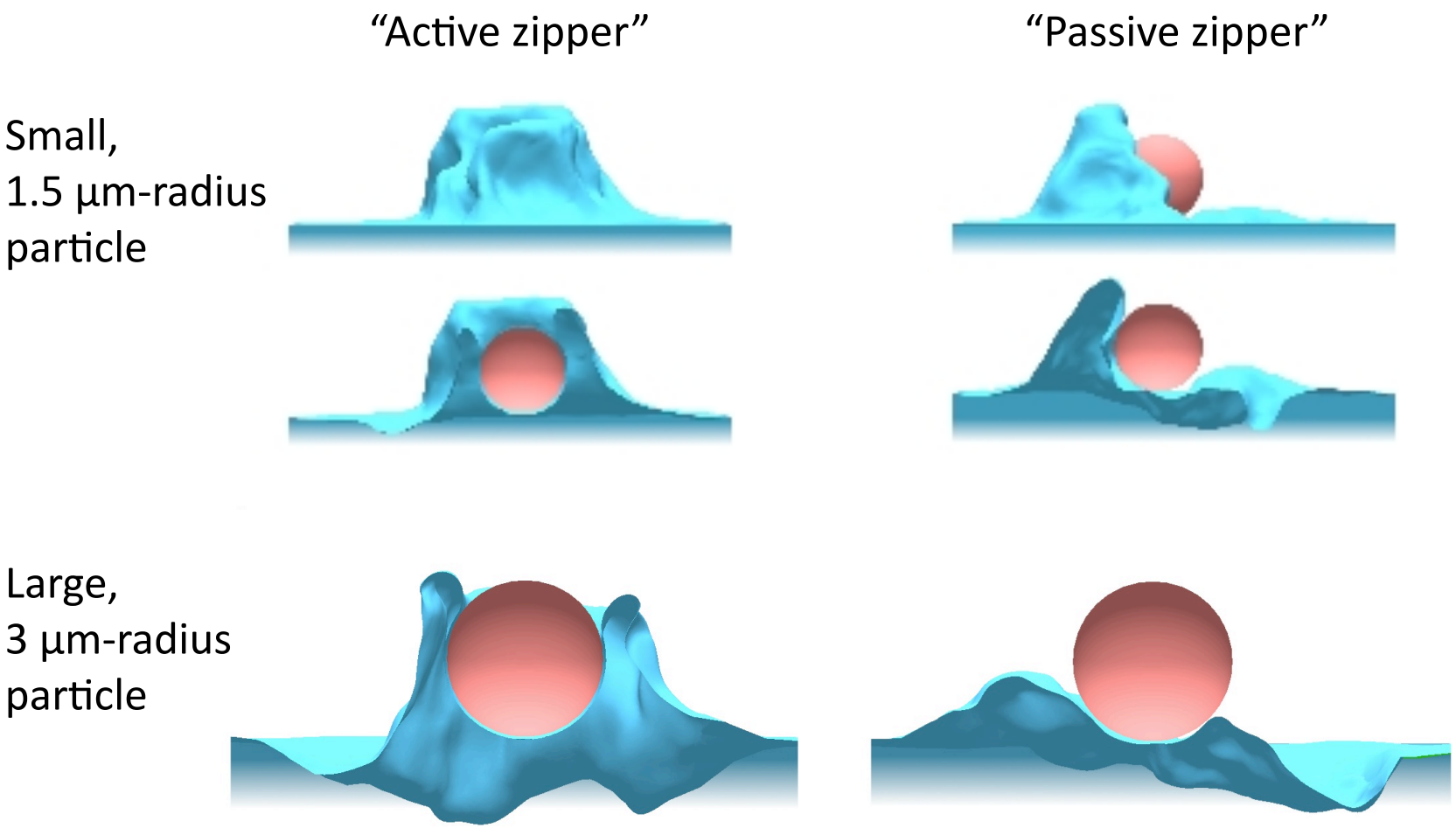
Parameter range

Particle size

Particle shape and orientation



Energetic requirements of engulfment

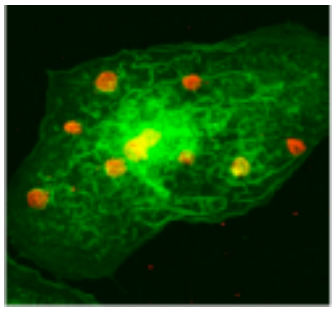


→ Active zipper easily engulfs small and large particles

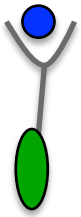
Passive zipper ONLY engulfs small particles - slowly with highly variable cups

Experiments and image analysis

COS-7 cell



Fcγ receptor



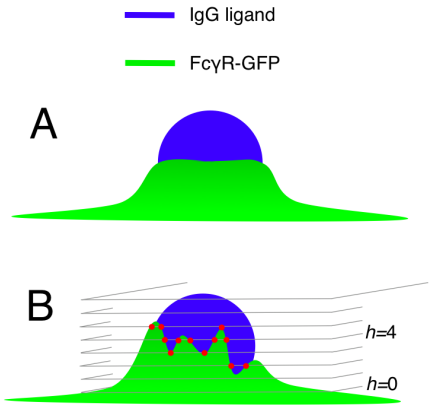
GFP

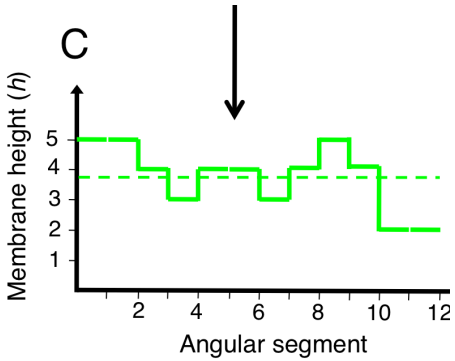
(a) Cells expressing wild-type Fcγ receptor = **active zipper**

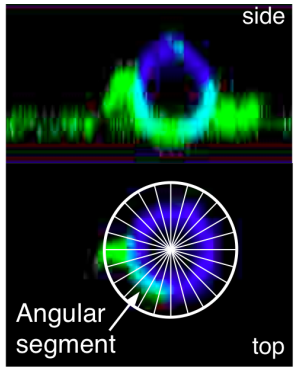
(b) Cells expressing signalling-dead mutant receptor
(c) Cells transfected with cytochalasin D

} **passive zippers**

→ Cup height and variability

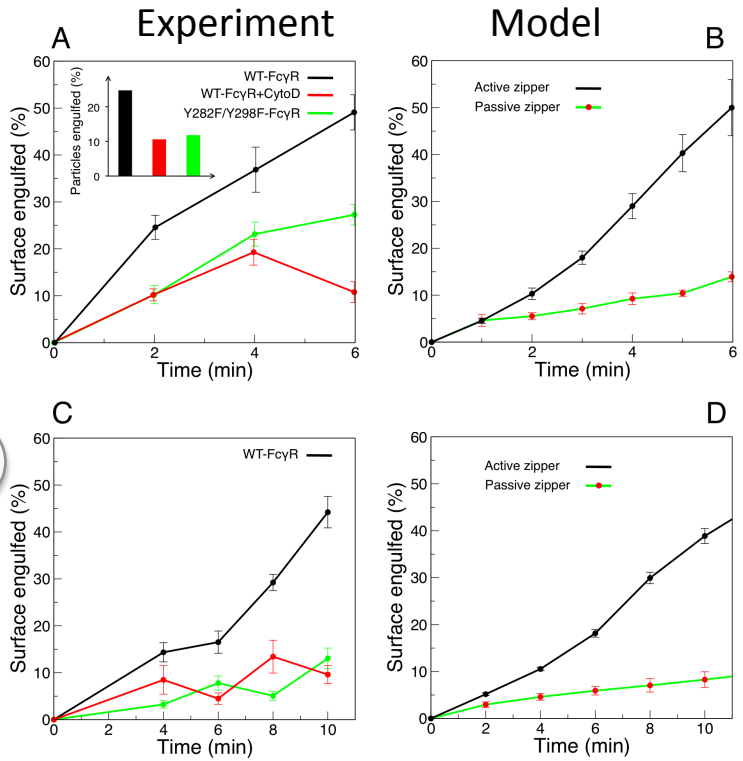






Test of model predictions by experiments

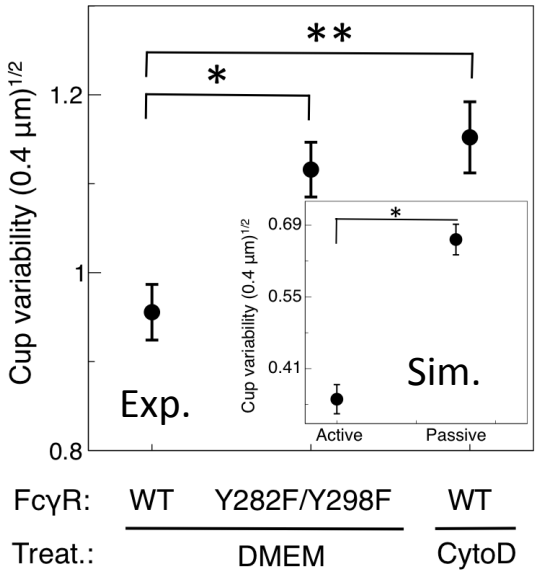
Engulfment time



Active zipper engulfs faster than passive zipper

Variability in cup shape

for 20-40% Engulfment



Passive zipper produces more variable cup shapes than active zipper

Due to difficulties in cup closure in model → new round of model and experiments