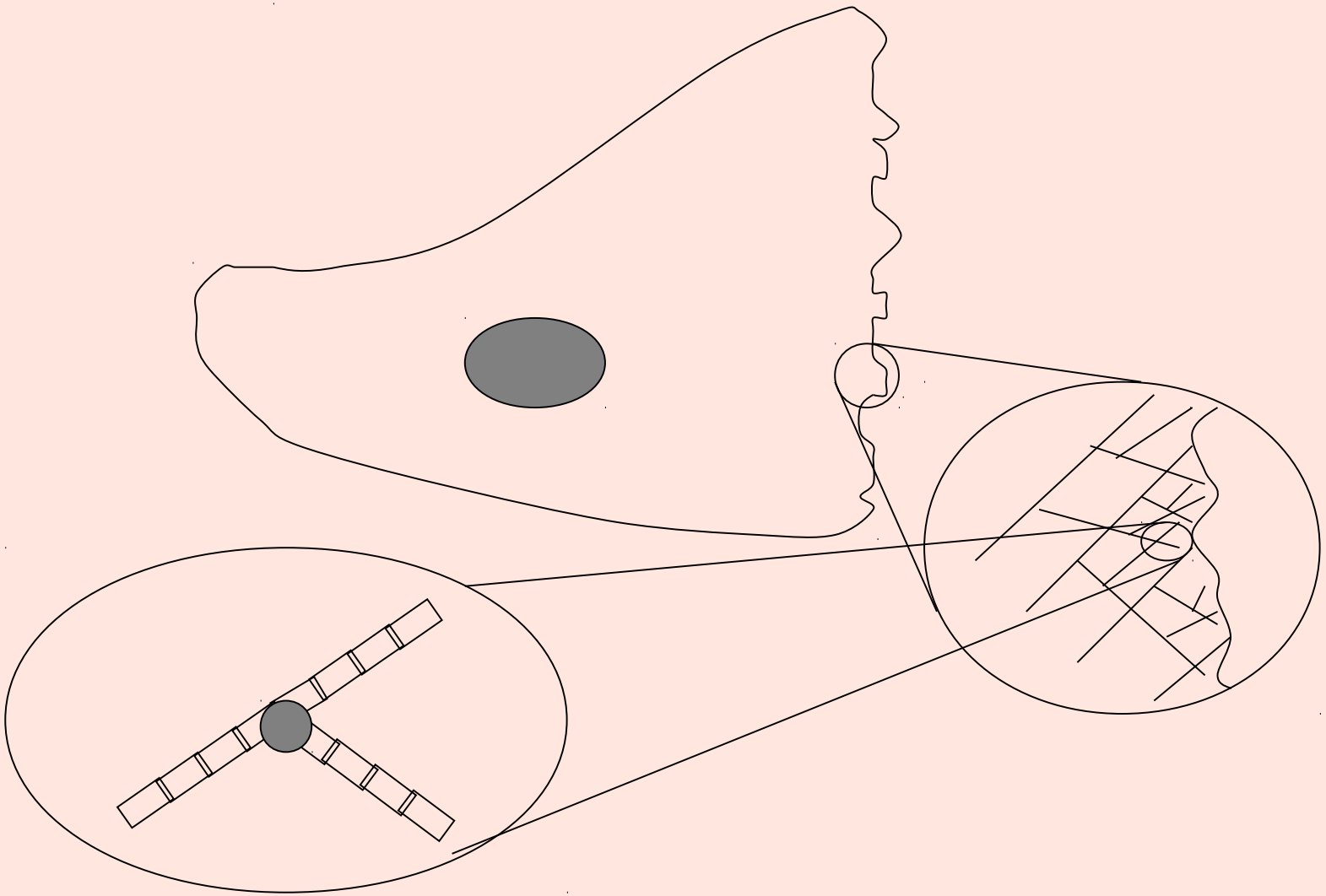
Mechanisms of movement

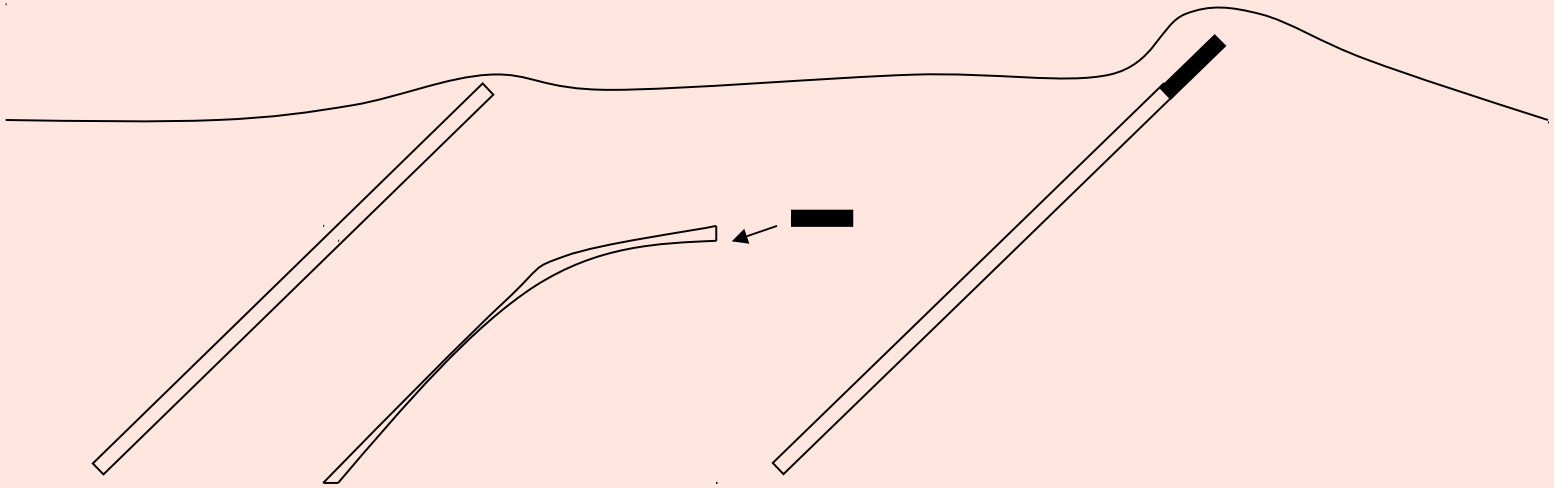
- Flagellar beat
- Ciliary beat
- Crawling
- Passively (blood)

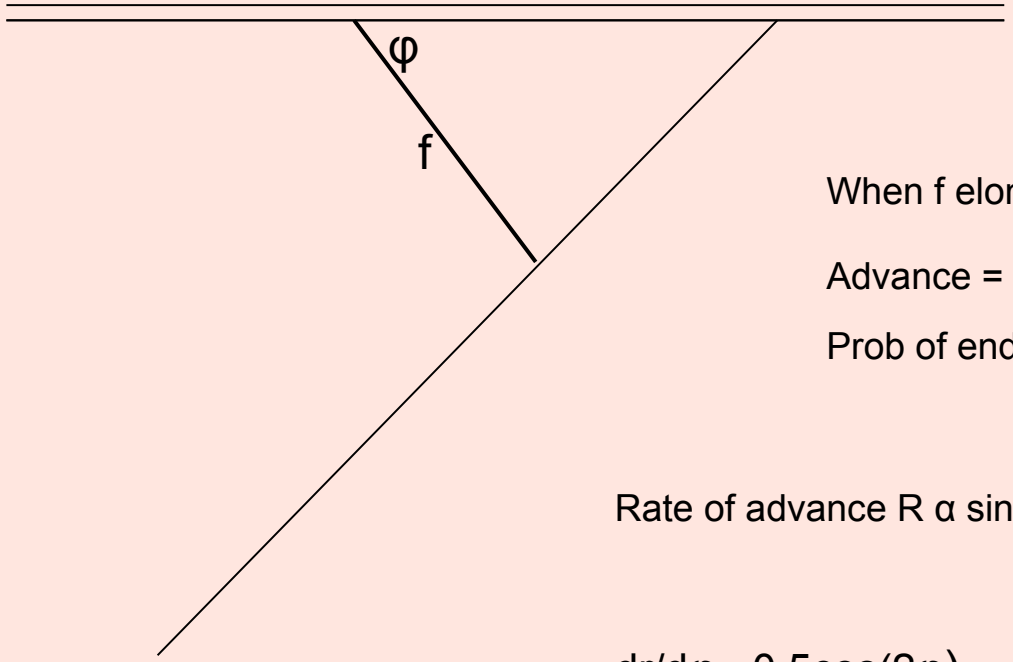
The leading edge:



The elastic Brownian ratchet:

Young's Modulus of actin = 2.6 GPa (=plastic ruler)





When f elongates by δf,

Advance = $\delta f \sin(\varphi)$

Prob of end being free α $\cos(\varphi)$

Rate of advance R α $\sin(\varphi)\cos(\varphi)$

$=0.5\sin(2\varphi)$

$dr/d\varphi = 0.5\cos(2\varphi)$

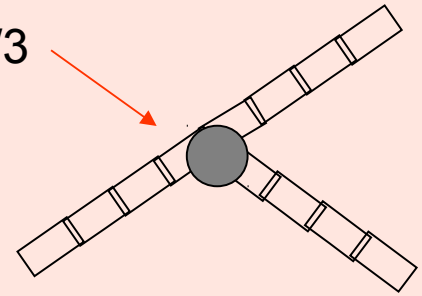
Peaks at $dr/d\varphi = 0$ so $0.5\cos(2\varphi)=0$

Cos peaks at 90 deg so $2\varphi=90$ so $\varphi=45^{o}$

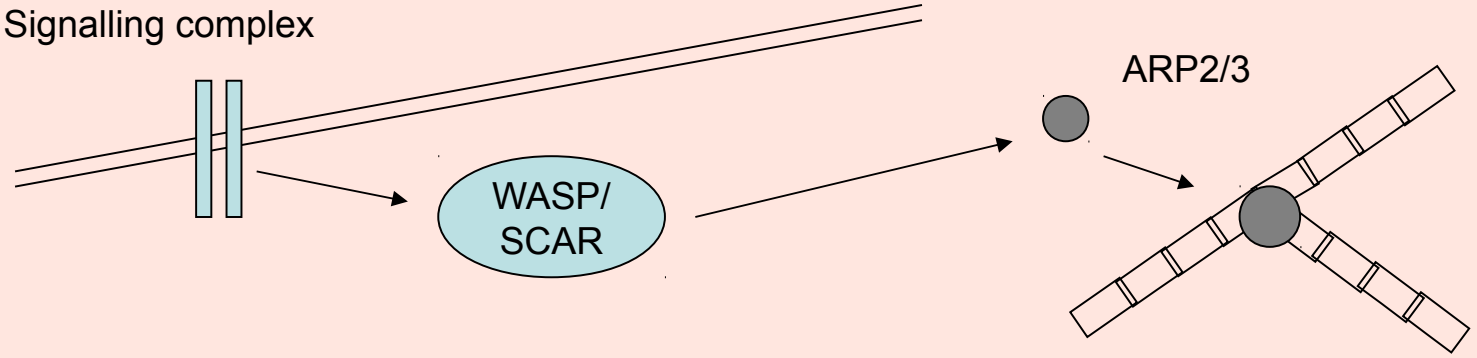
Problem: filaments are bendy (have to be for the elastic Brownian ratchet).

Max unsupported length about 150nm

New filaments are nucleated by Arp2/3

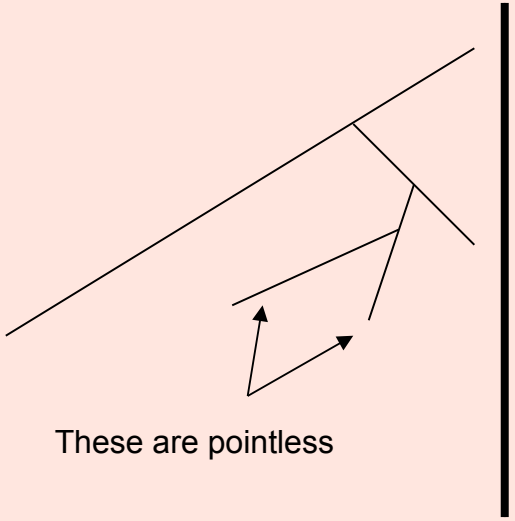


Arp2/3 needs to be activated:



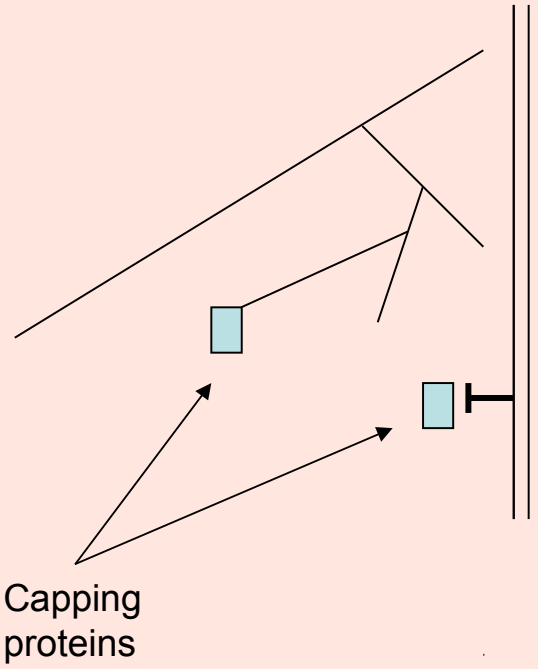
So Arp2/3 activated only near membrane

Potential problem:



Growth is blocked by capping proteins

Capping proteins are blocked by PIP & PIP2 (ie at the membrane)



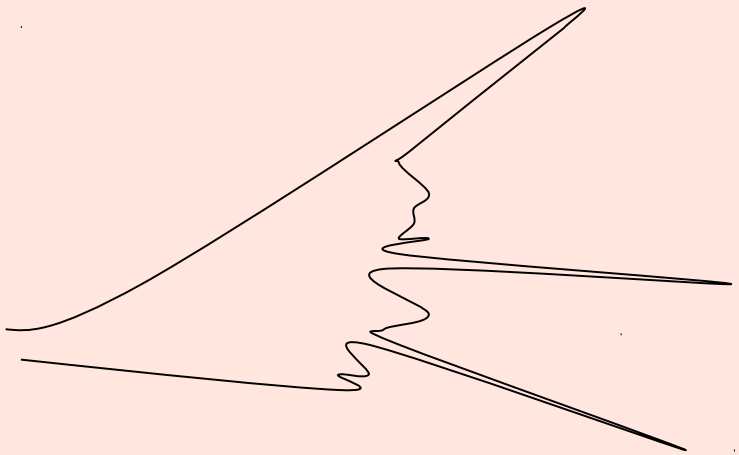
Self-organization

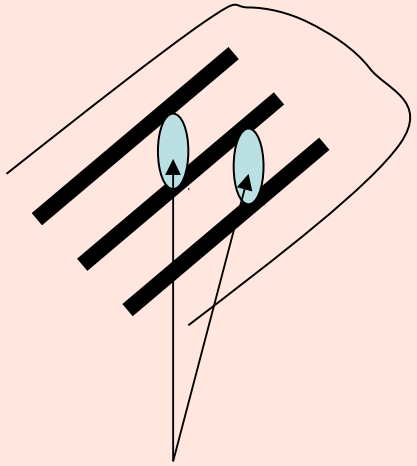
Filaments are unstable: $T_{1/2}$ about 500sec

Breakdown accelerated by ADF / cofilin

These are active behind the leading edge

Filopodia





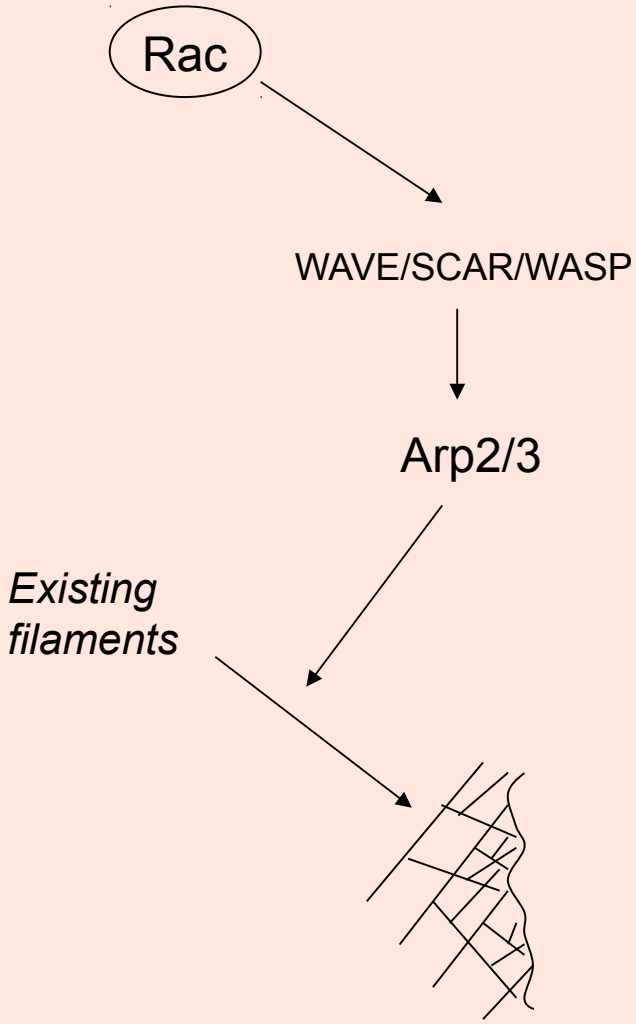
fascin

Also grow from barbed ends (distal)

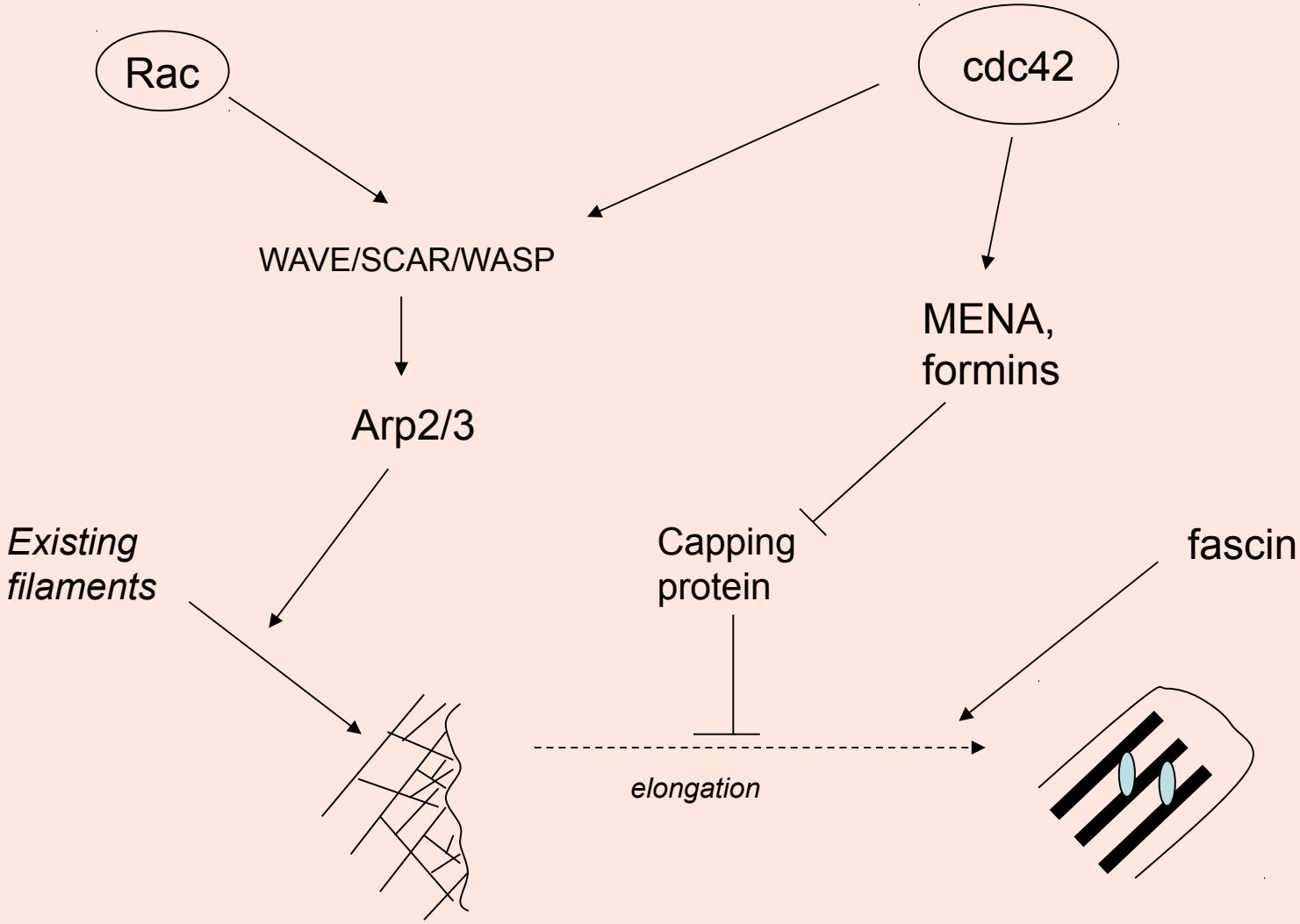
Begin as areas of lamellipodium in which fascin displaces ARP2/3 and makes a Λ precursor

Self-spacing: takes away local reserves of formin.

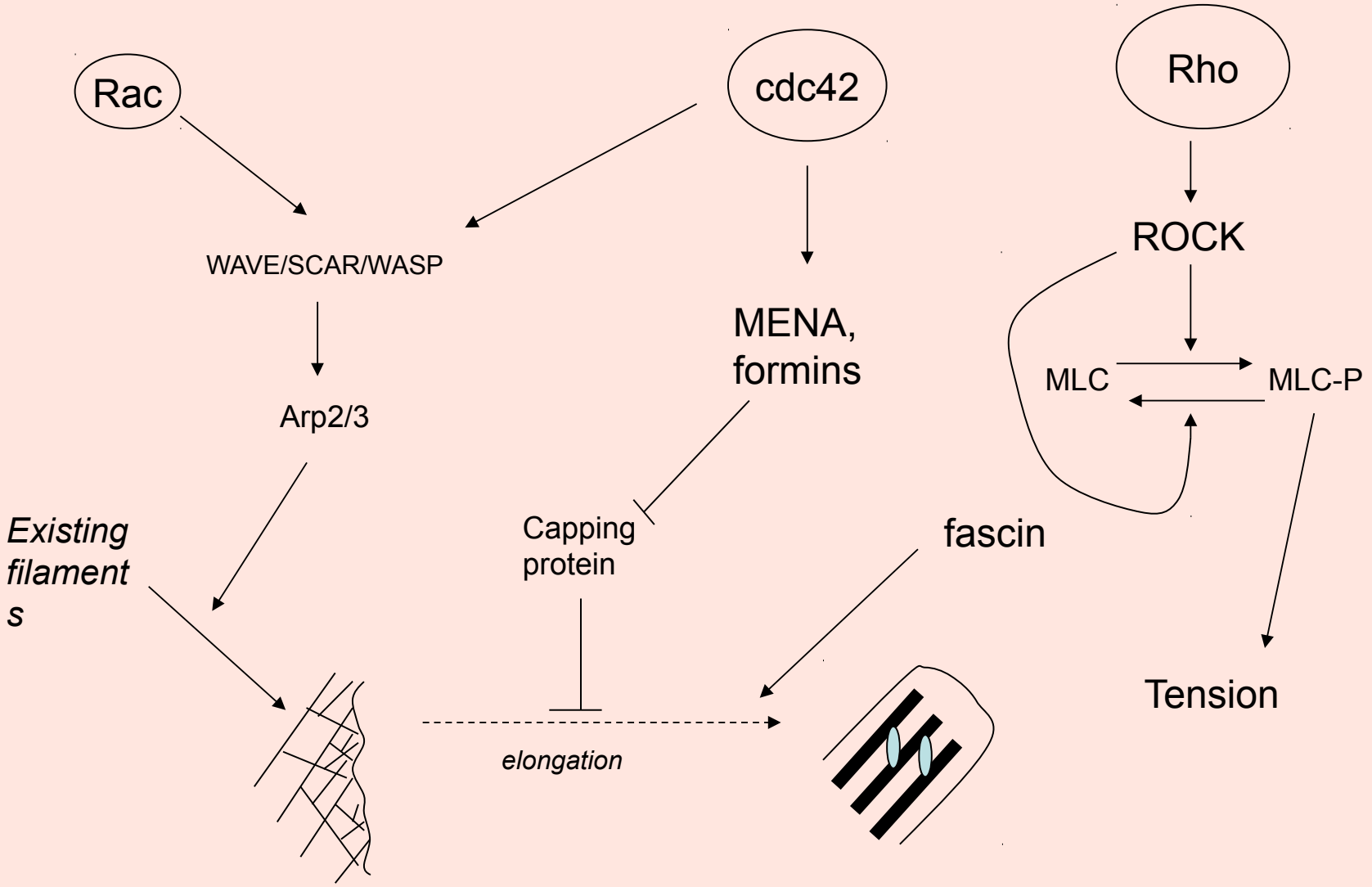
Choosing how to arrange actin (this diag is detailed more on other slide)



Choosing how to arrange actin (this diag is detailed more on other slide)



Choosing how to arrange actin (this diag is detailed more on other slide)



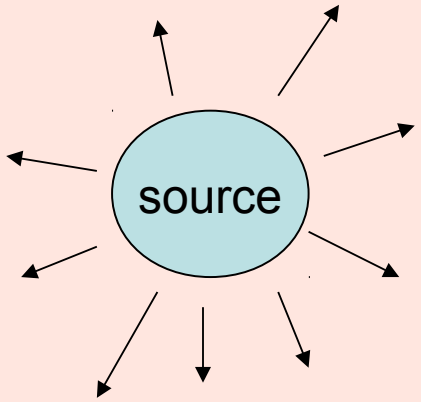
Warn them that they need to remember all of this for next week!!!

Lecture 6 – navigation and the internal compass

CHEMOTAXIS – needs -

1. An external gradient
2. A mechanism to detect it
3. A mechanism for translating a shallow external gradient to a steep internal one.

Gradients:

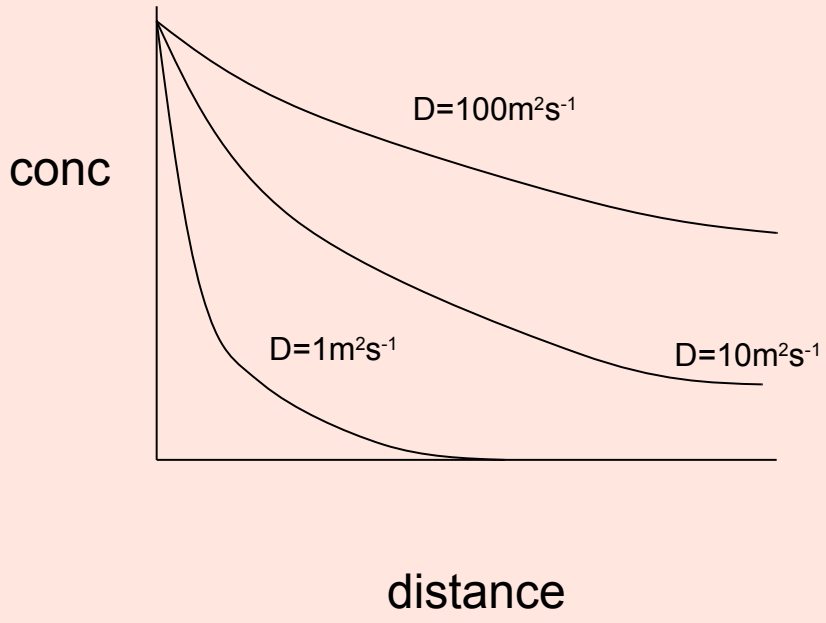


Fick's law: $\frac{dm}{dt} = -D.\frac{d^2m}{dx^2}$

$\frac{dm}{dt} = D \nabla^2 m$

ie $\frac{d^2}{dx^2}, \frac{d^2}{dy^2}, \frac{d^2}{dz^2}$

Steady state:



Real values

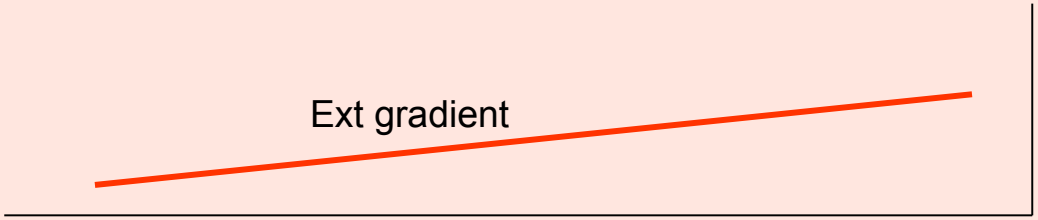
Matrix proteins <1μm²s⁻¹

Soluble proteins 10μm²s⁻¹

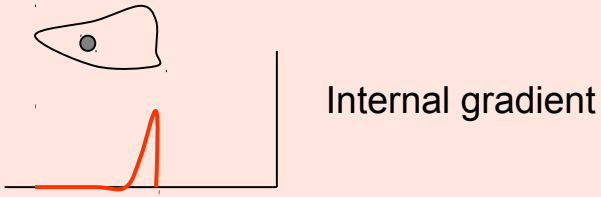
cAMP etc >100μm²s⁻¹

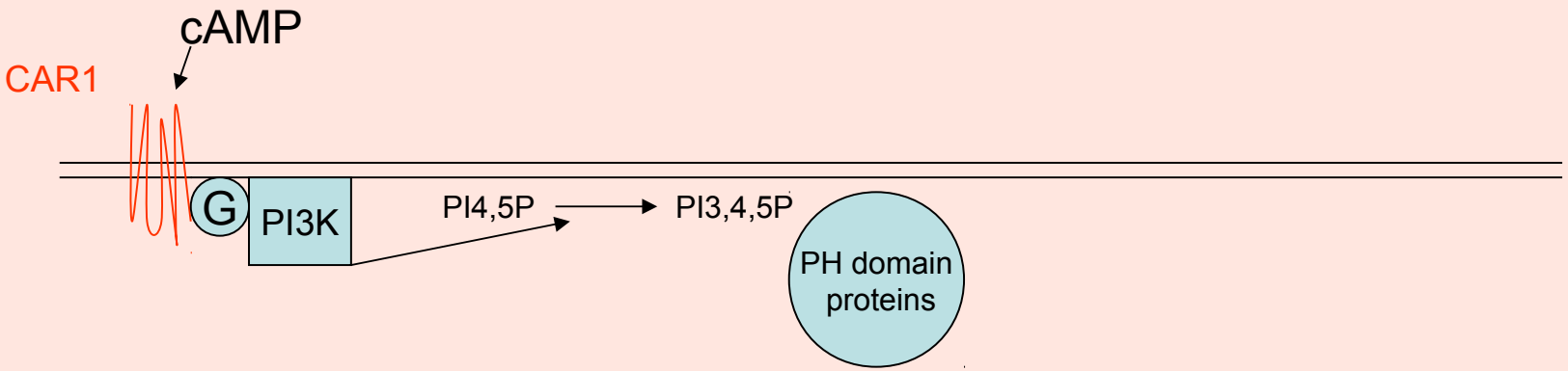
Problem:

Hi D



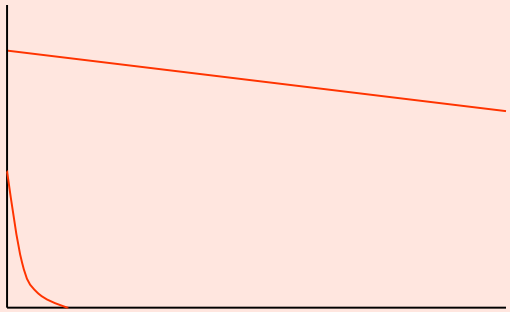
Lo D





cAMP 100um^{2}s^{-1}

PI(3,4,5)P_3 1um^{2}s^{-1}

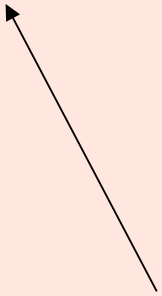


Distribution in membrane:

CAR1 – all over membrane

Gprot – all over membrane

$PI(3,4,5)P_3$ up gradient end only



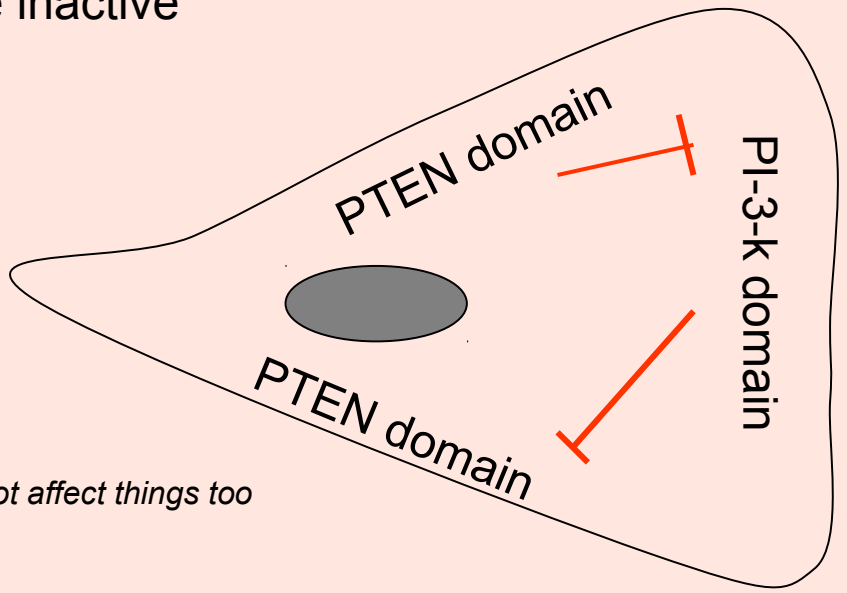
But not if the cell is in homogenous cAMP – then its homog

PI-3-kinase is inhibited by PTEN

PTEN binds $PI(4,5)P_2$ (ie the stuff destroyed by PI-3-K)

-> FEEDBACK

PTEN concentrates where PI3 kinase is inactive, and keeps PI-3-kinase inactive there.



But this is not the whole story – inhibiting PTEN does not affect things too much

Link to motility:

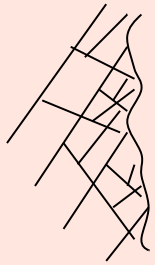
cAR → G → PI-3-K → PI-3-4-5P_3

vav

Hyperactivate Rac – ruffles all round cell.

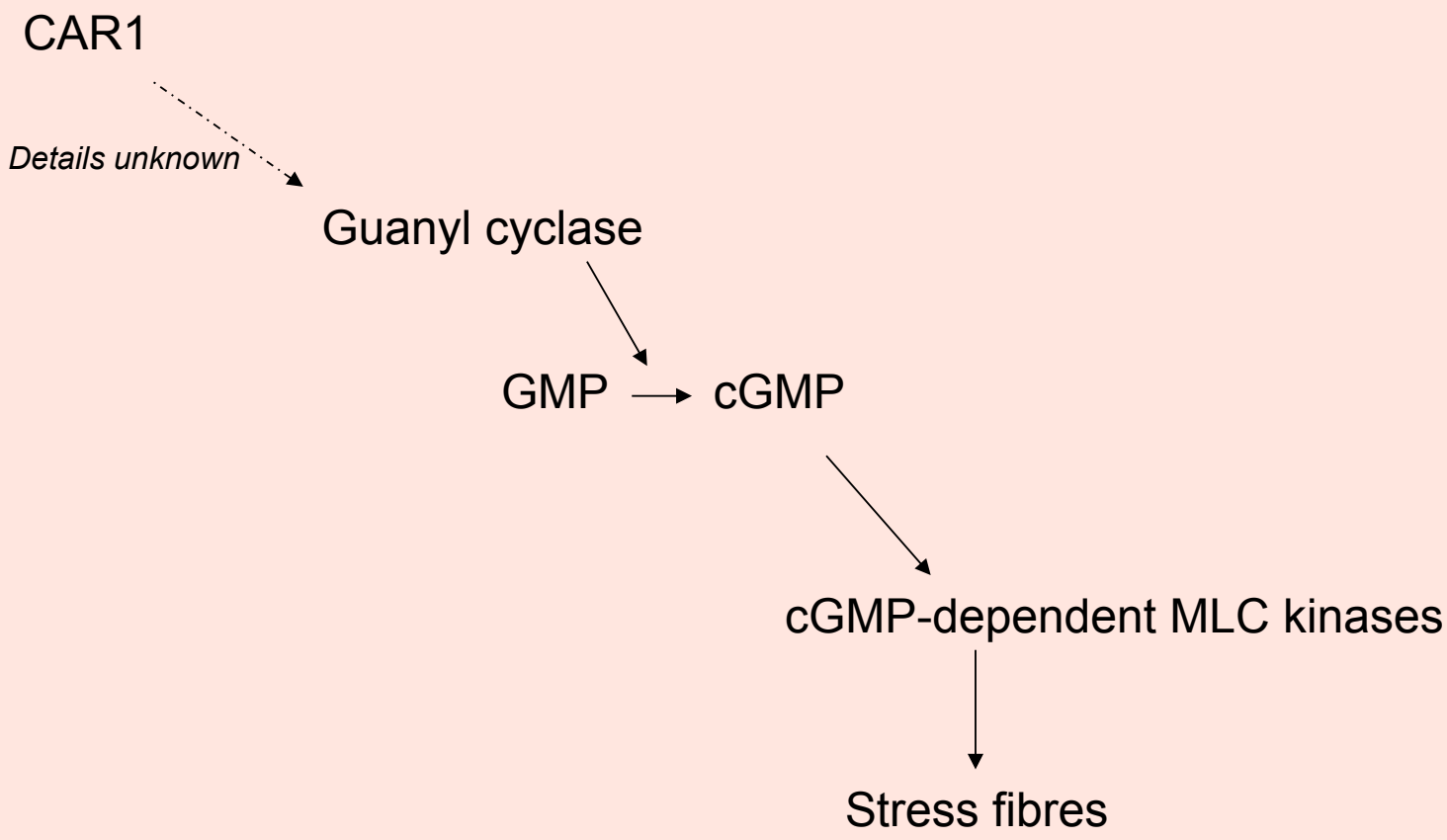
Inactivate Rac – no movement

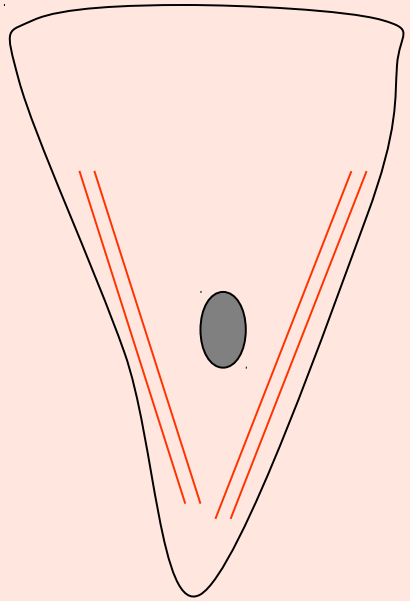
Rac



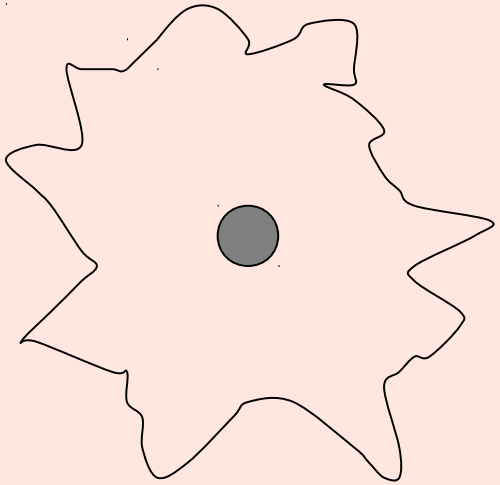
lamellipodium

Suppression of back of cell:





Wild type

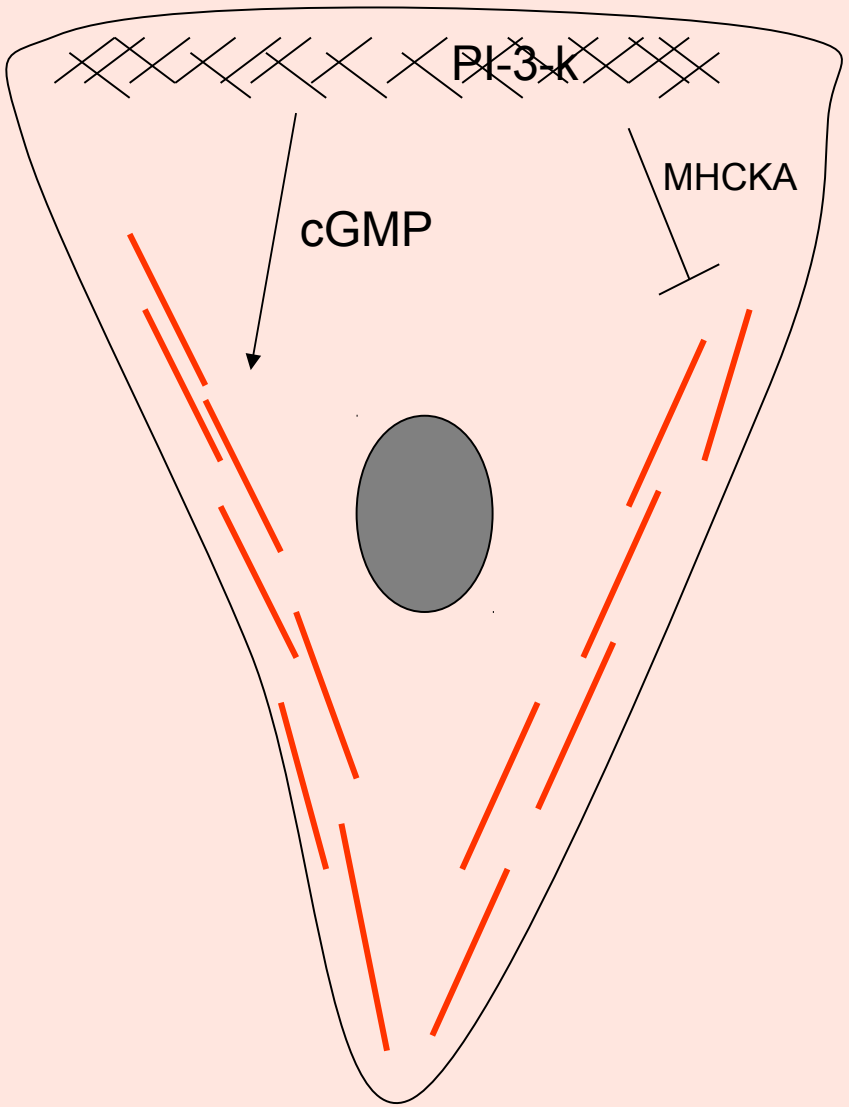


myosin II deficient

Myosin HEAVY chain kinase binds fine lamellipodial actin and inhibits myosin.

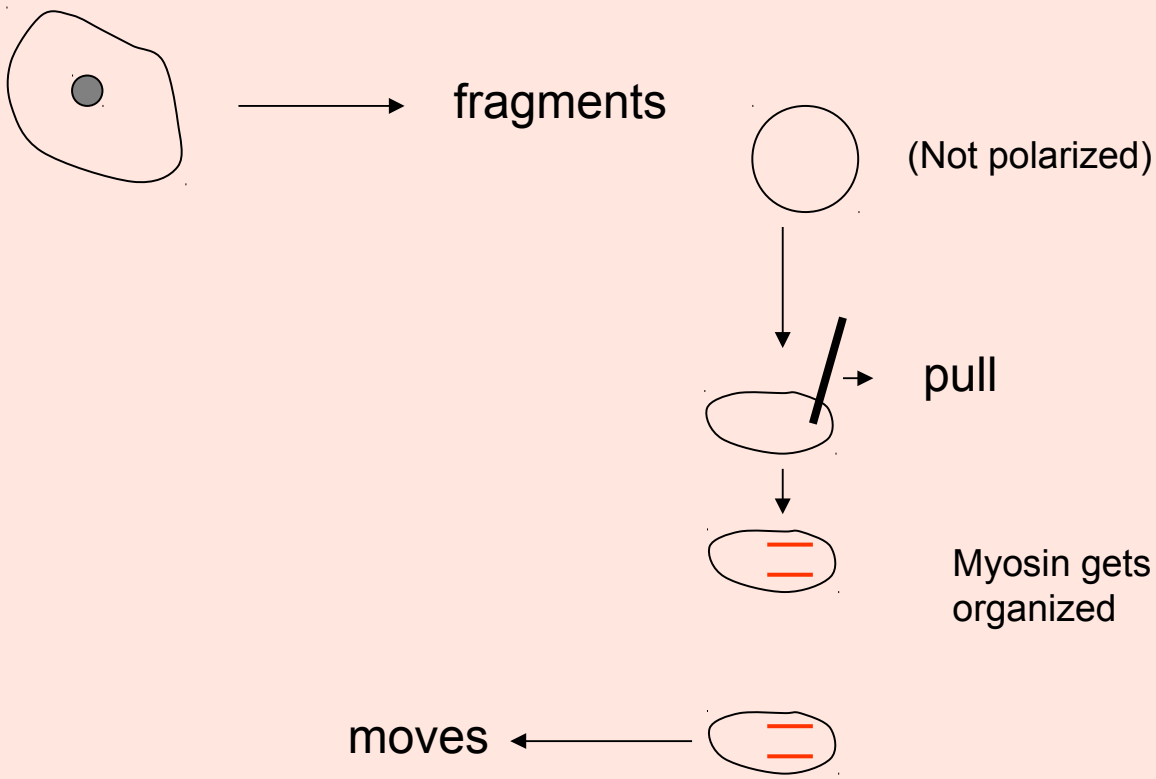
-> protects lamellipodial region from stress fibres.

cAMP



Stress fibres are enough to polarize the cell

Fish keratinocytes



An additional trick in the time domain

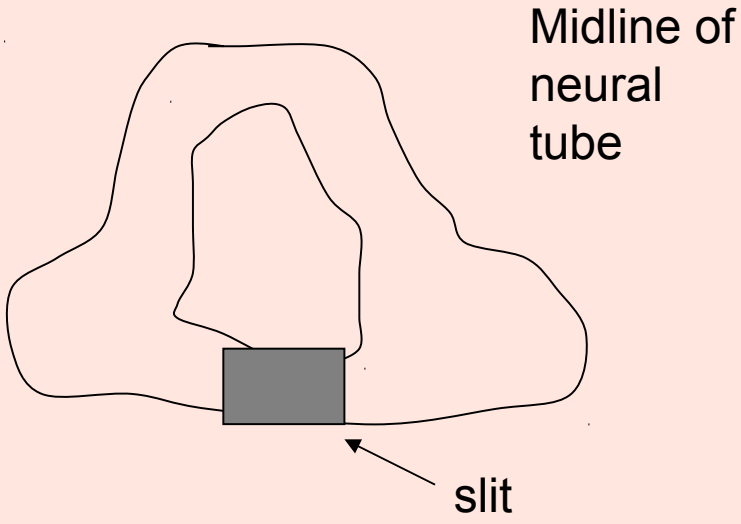
$$[cGMP] \quad \alpha \quad \frac{d}{dt}[cAMP]$$

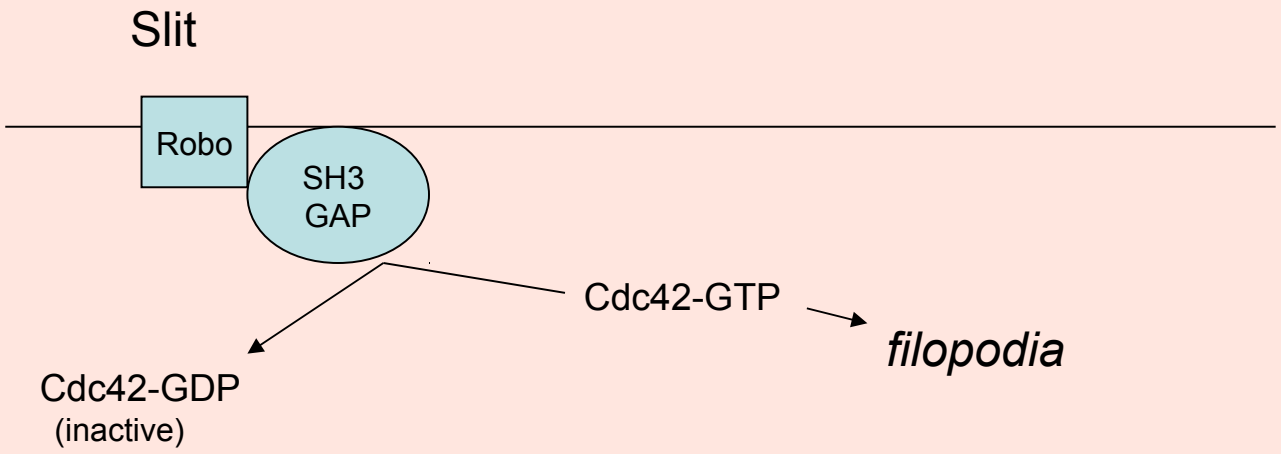
synthesis

So any cell going up-gradient has a clear leading edge

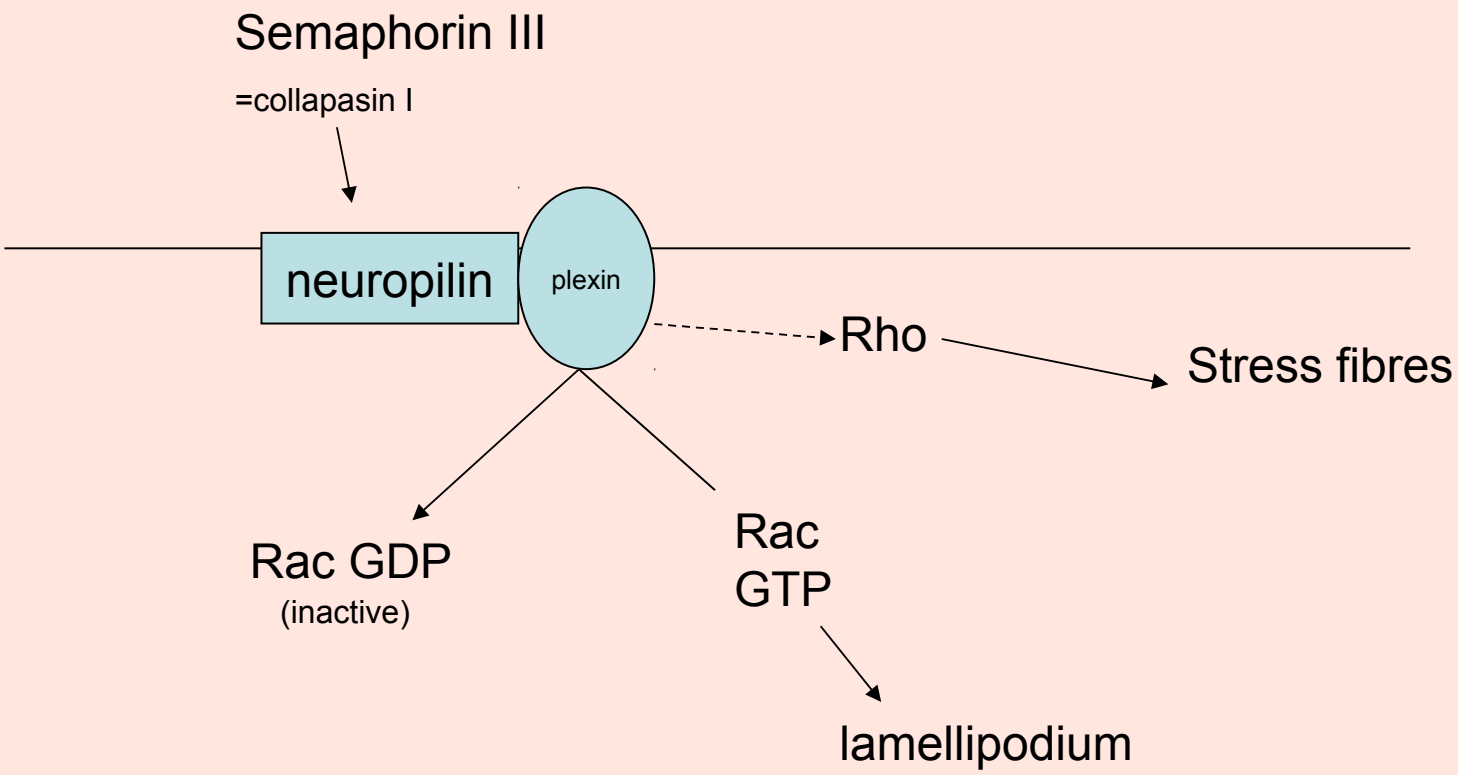
A cell going cross-gradient loses suppression of the sides and back so a new front can form.

Chemorepulsion 1

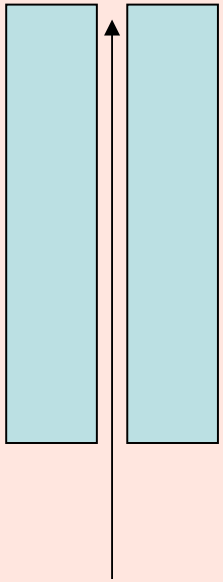




Chemorepulsion 2



Chemorepulsion can define narrow paths

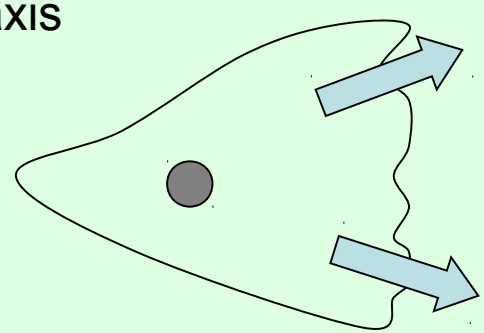


Attractive paths are either wide enough to catch lots of cells and therefore too wide, or narrow and too narrow to catch enough cells.

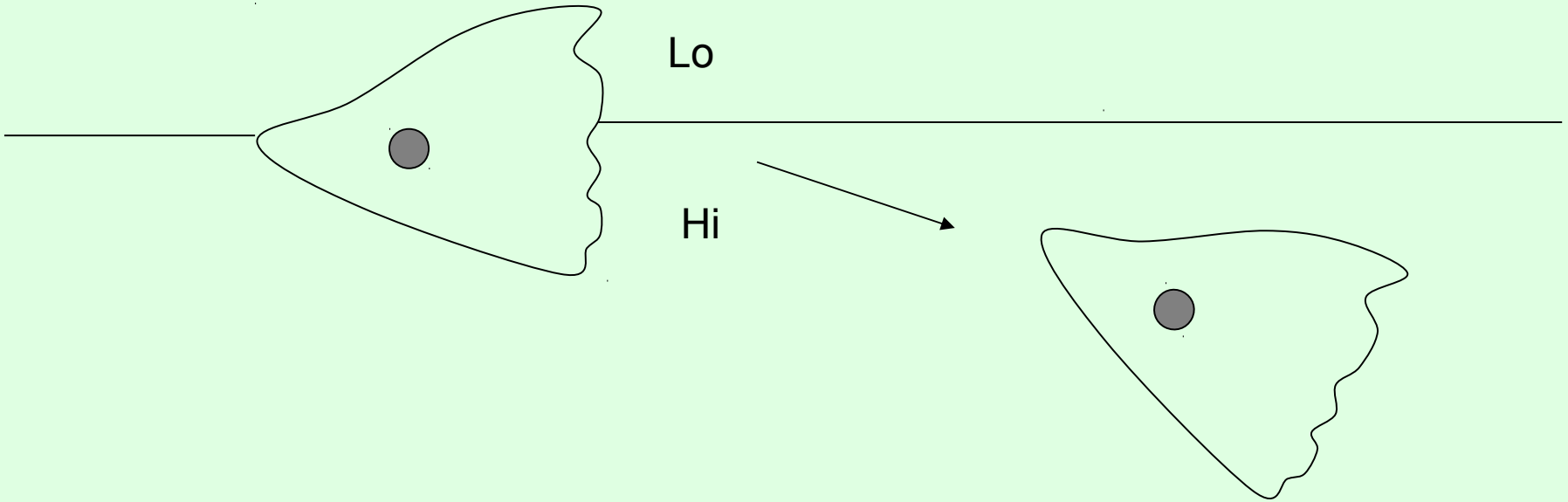
Session 5: more guidance, and epithelial morphogenesis

Lecture 7 – guidance by contact

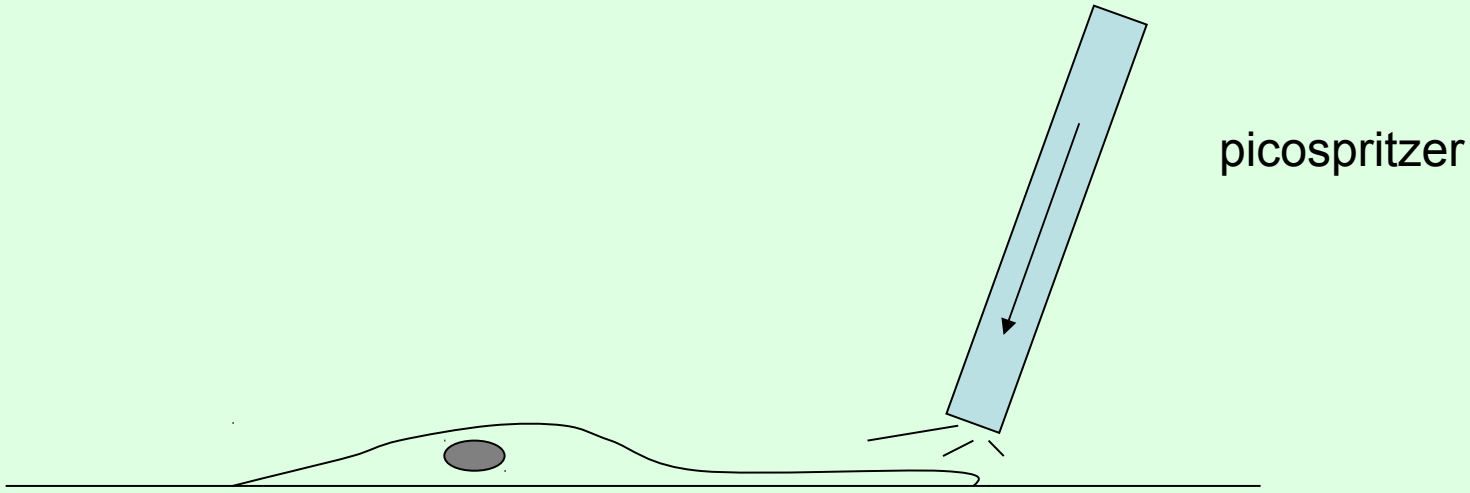
Haptotaxis



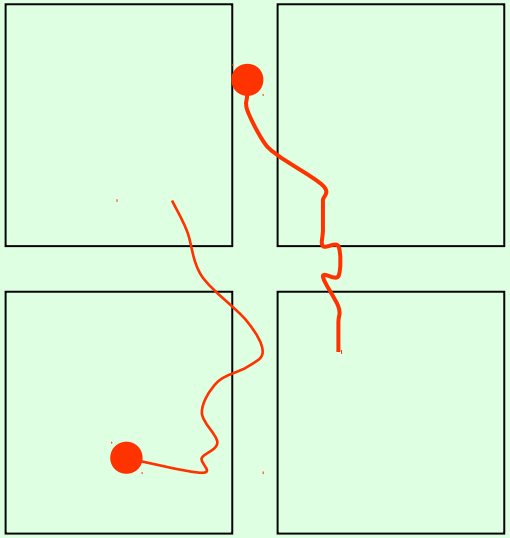
"tug of war"



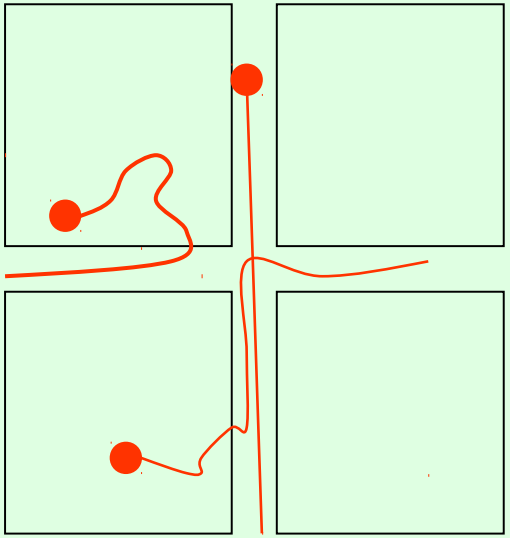
Can measure cell adhesion



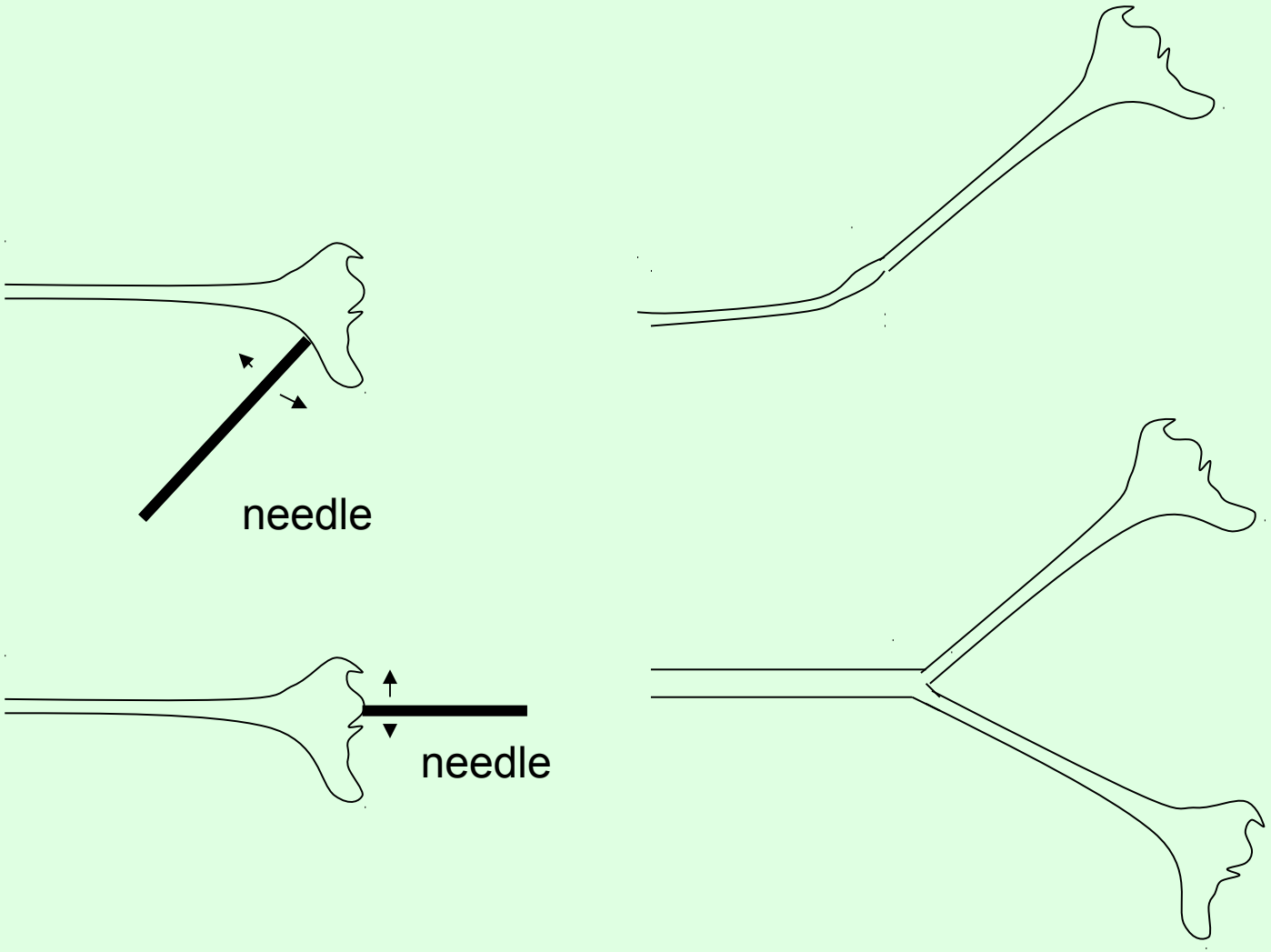
EM grid shadows



Equal



unequal

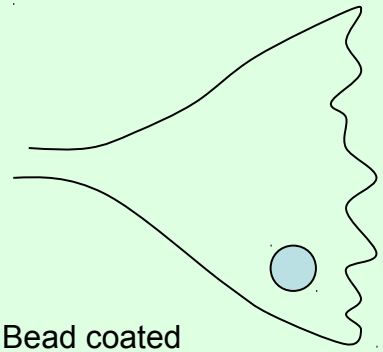

needle
needle

Is it mechanics or signalling?

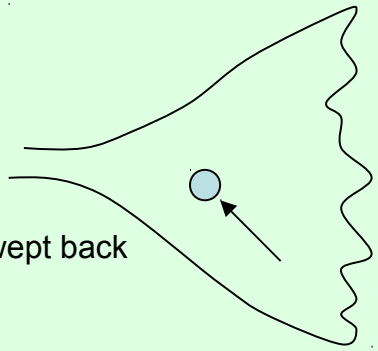
Get them to think of the experiment

Is it mechanics or signalling?

Aplysia – growth cones bear apCAM

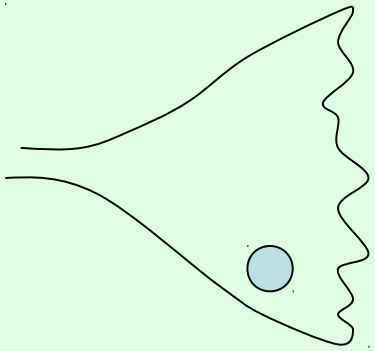


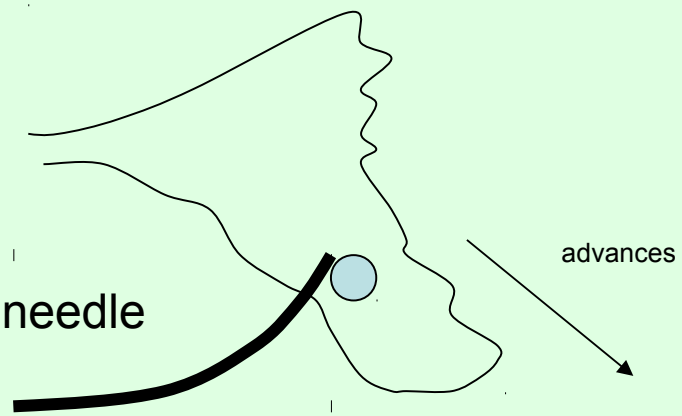
Bead coated
in apCAM

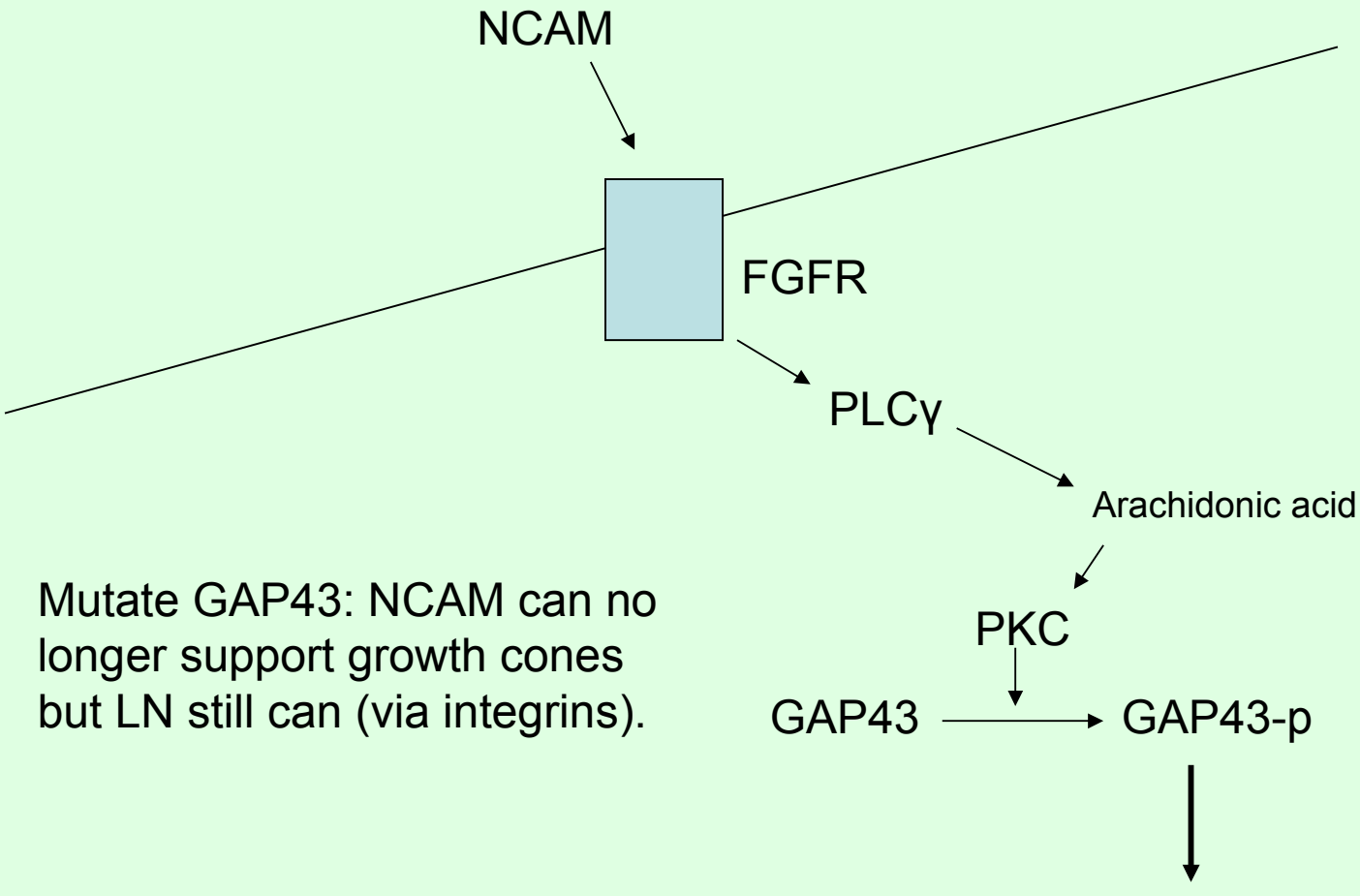


Gets swept back

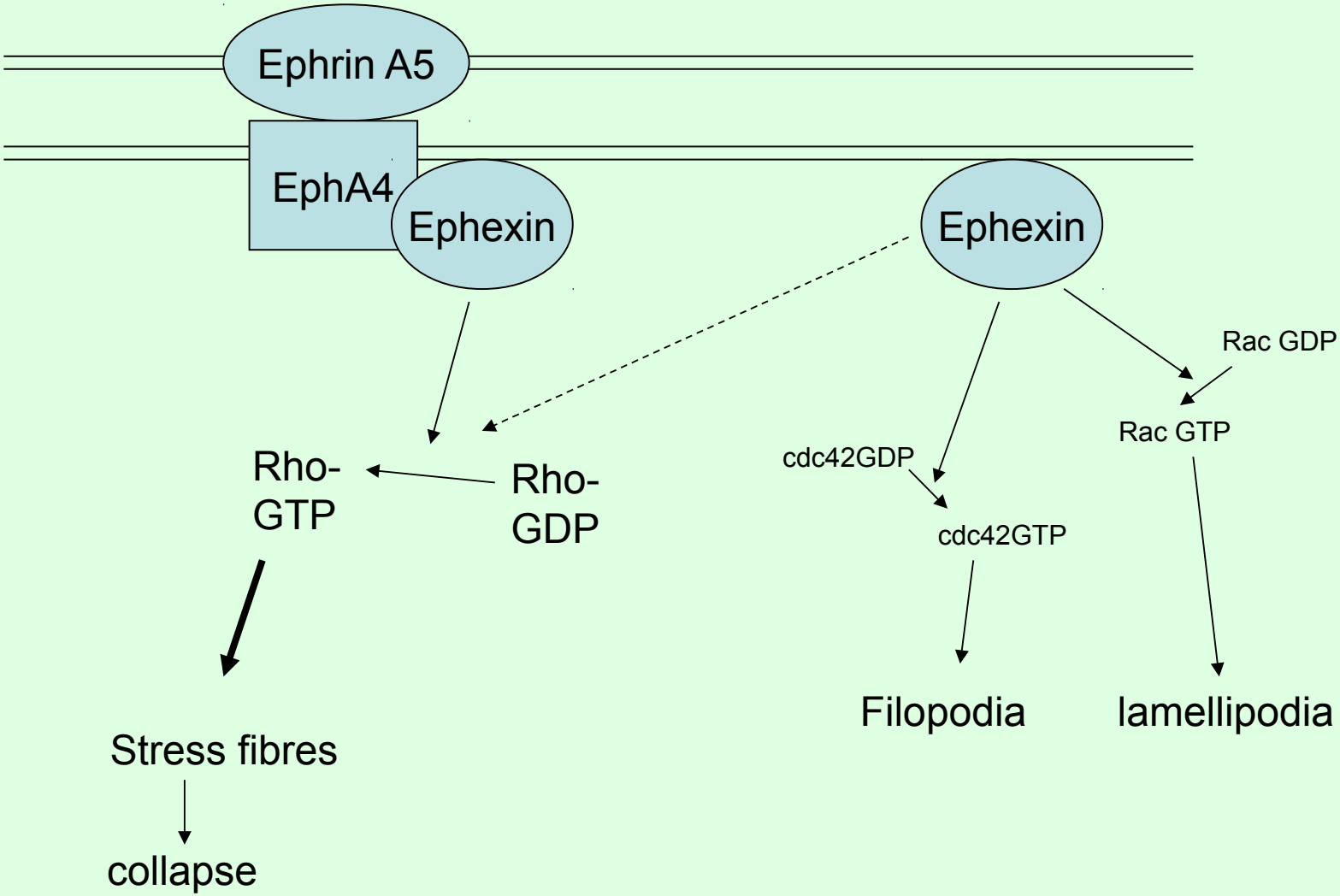
But signalling
the same







Mutate GAP43: NCAM can no longer support growth cones but LN still can (via integrins).


Ephrin A5
EphA4
Ephexin
Ephexin
Rac GDP
Rho-
GTP
Rho-
GDP
cdc42GDP
Rac GTP
cdc42GTP
Stress fibres
Filopodia
lamellipodia
collapse