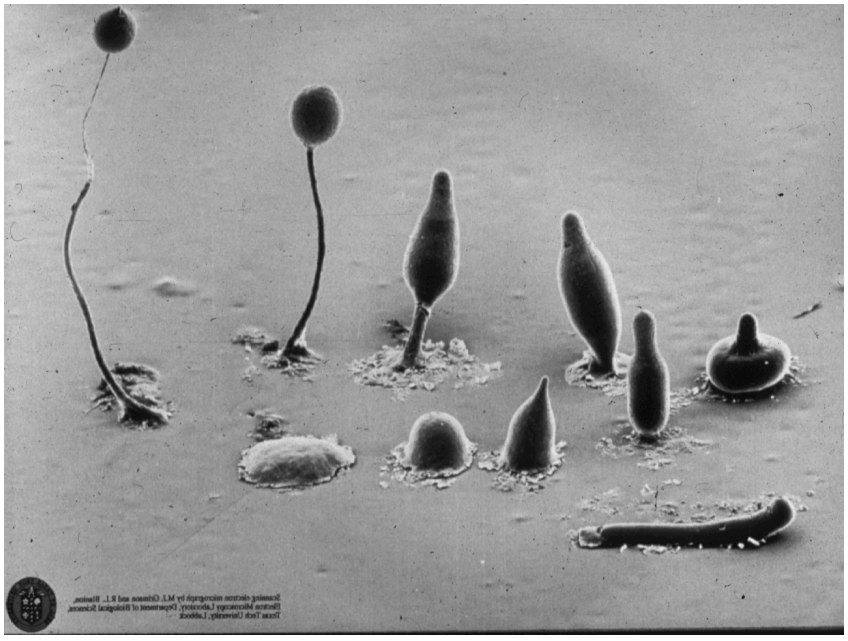
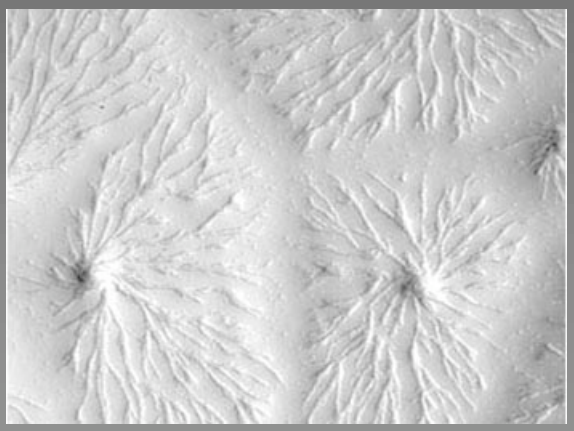
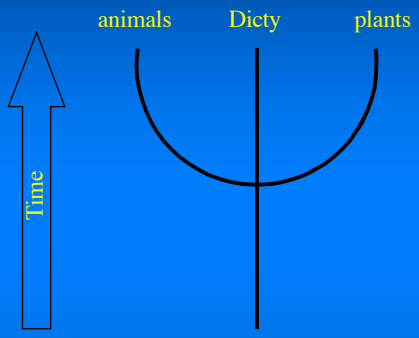
The Dicteostelium Motility Cycle

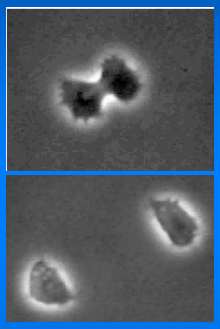


CHEMOTACTIC SIGNALS AND RESPONSES ARE COORDINATED BY AN OSCILLATORY CIRCUIT IN DICTYOSTELIUM



Dictyostelium is a social amoeba that separated from plants and animals about 1 billion years ago. Many genes and pathways are well conserved.

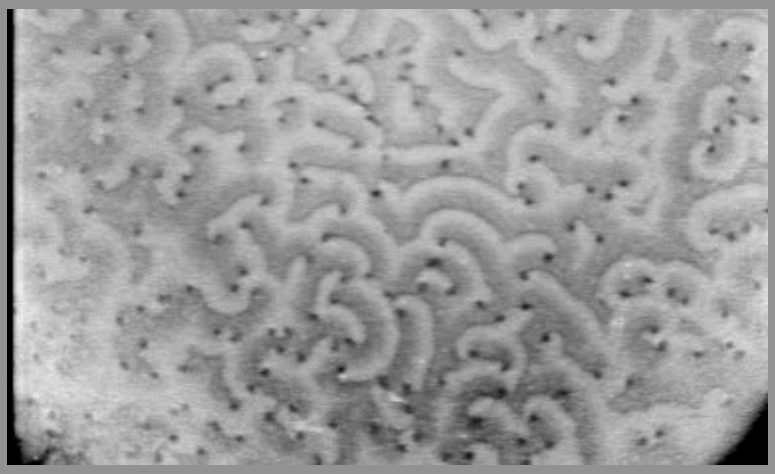




ADVANTAGES

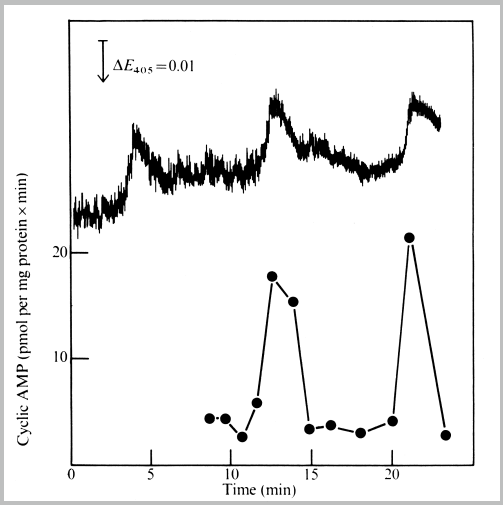
The 34 Mb genome is sequenced. There are many well defined mutant strains.
It grows well and billions of cells can be induced to develop synchronously.
After 4 hours of development cells signal each other with cAMP and respond.

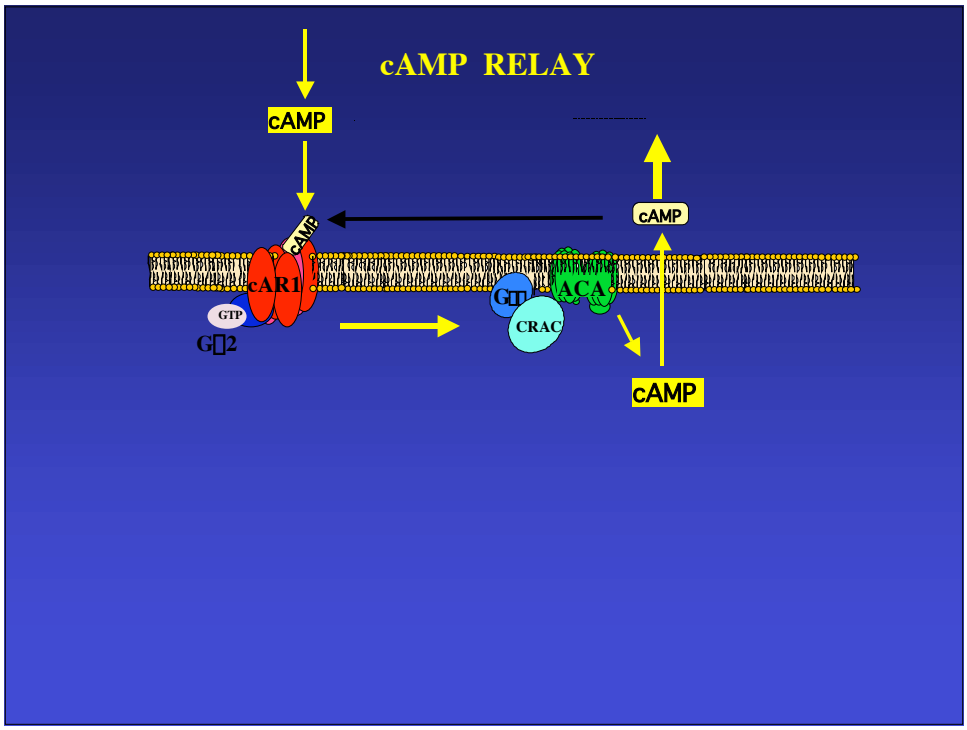
Dynamics of spiral waves seen by dark-field microscopy; the cells contract when a cAMP wave passes over them but there is no net cellular movement

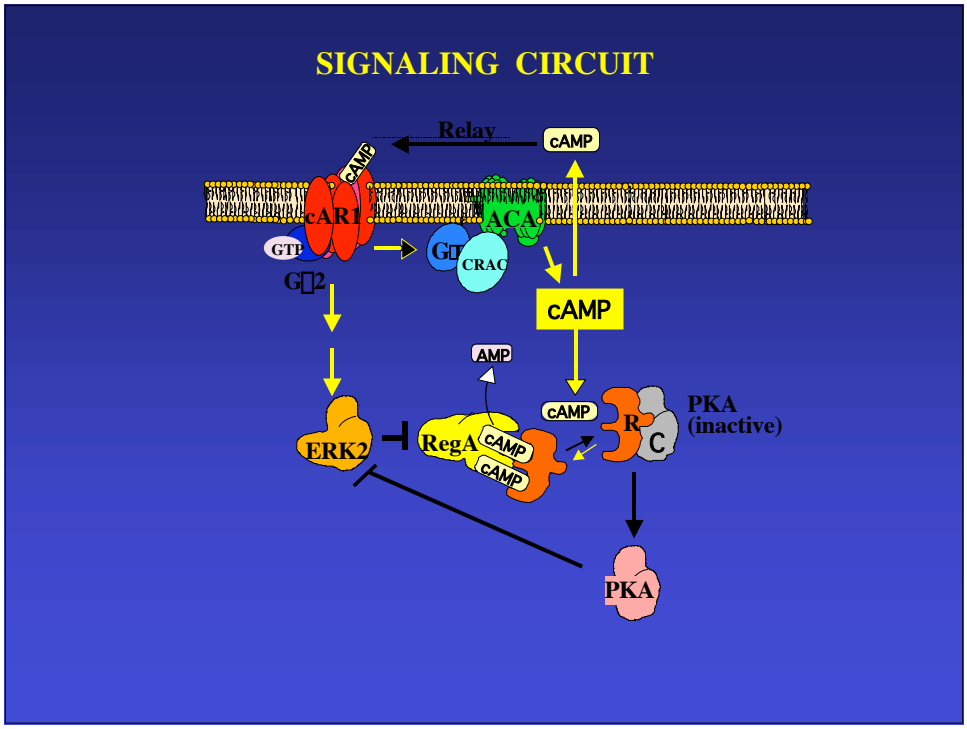


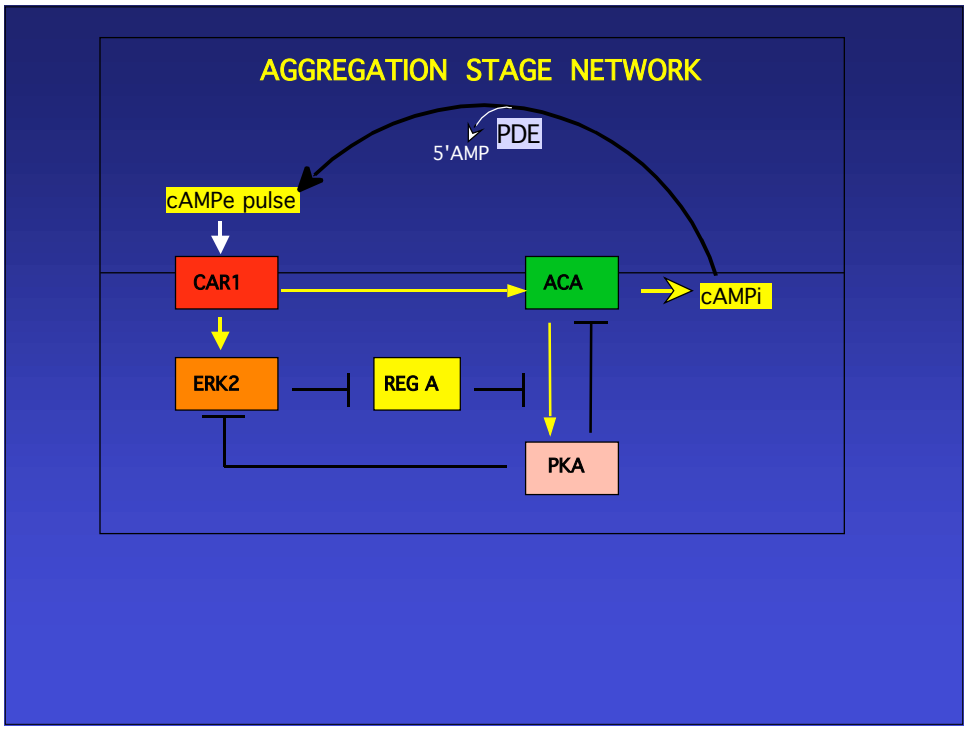
OSCILLATIONS IN LIGHT SCATTERING AND ADENYLYL CYCLASE

Roos, W., Scheidegger, C., and Gerisch, G. (1977). Nature *266*, 259-261.






SIGNALING CIRCUIT
Relay
cAMP
cAMP
cAR1
ACA
GTP
G
CRAC
G2
cAMP
AMP
cAMP
R
C
PKA
(inactive)
ERK2
RegA
cAMP
cAMP
PKA


AGGREGATION STAGE NETWORK
PDE
5'AMP
cAMPe pulse
CAR1
ACA
cAMPi
ERK2
REG A
PKA

INTERACTIVE NONLINEAR DIFFERENTIAL EQUATIONS WITH ACTIVATING AND DEACTIVATING TERMS

$$[ACA]' = k1[CAR1]-k2[ACA][PKA]$$

$$[PKA]' = k3[cAMPi]-k4[PKA]$$

$$[ERK2]' = k5[CAR1]-k6[PKA][ERK2]$$

$$[RegA]' = k7-k8[ERK2][RegA]$$

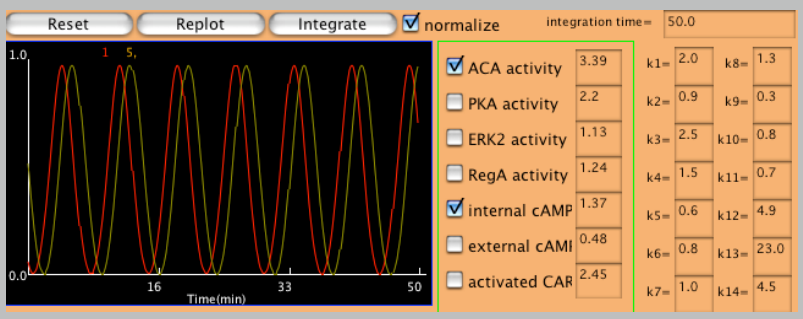
$$[cAMPi]' = k9[ACA]-k10[RegA][cAMPi]$$

$$[cAMPe]' = k11[ACA]-k12[cAMPe]$$

$$[CAR1]' = k13[cAMPe]-k14[CAR1]$$

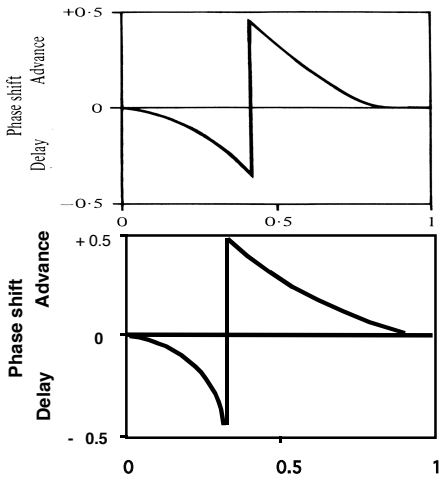
' = differentiation with respect to time

CIRCUIT OSCILLATES WITH A ROBUST 7 MINUTE PERIOD



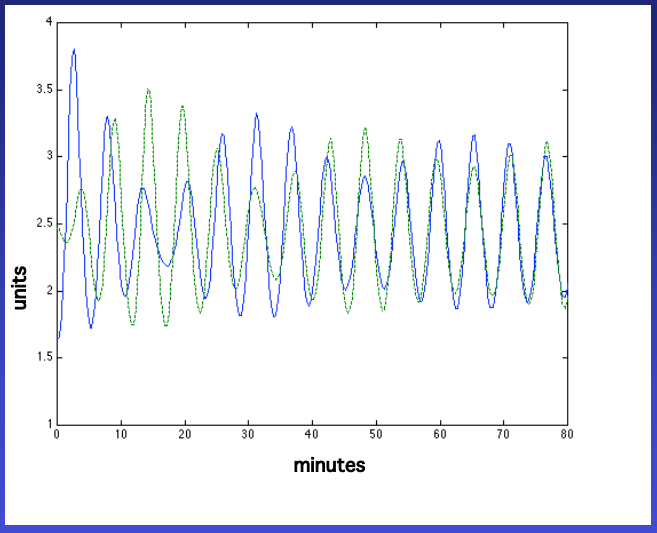
PHASE SHIFT

G. GERISCH AND OTHERS



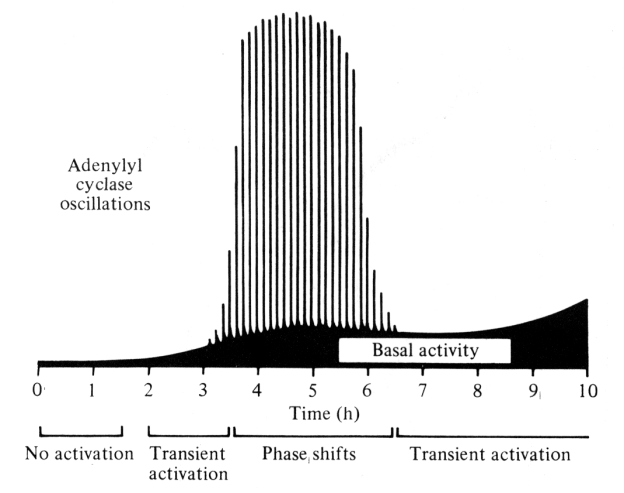
Time of addition of cAMP pulse during 7 minute period

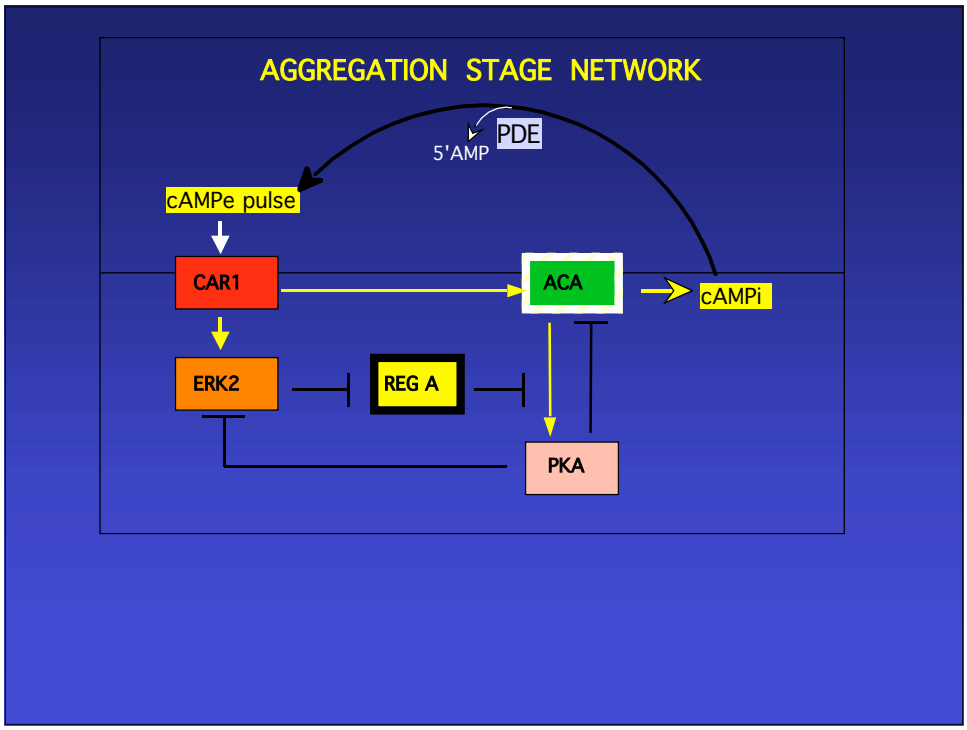
ENTRAINMENT

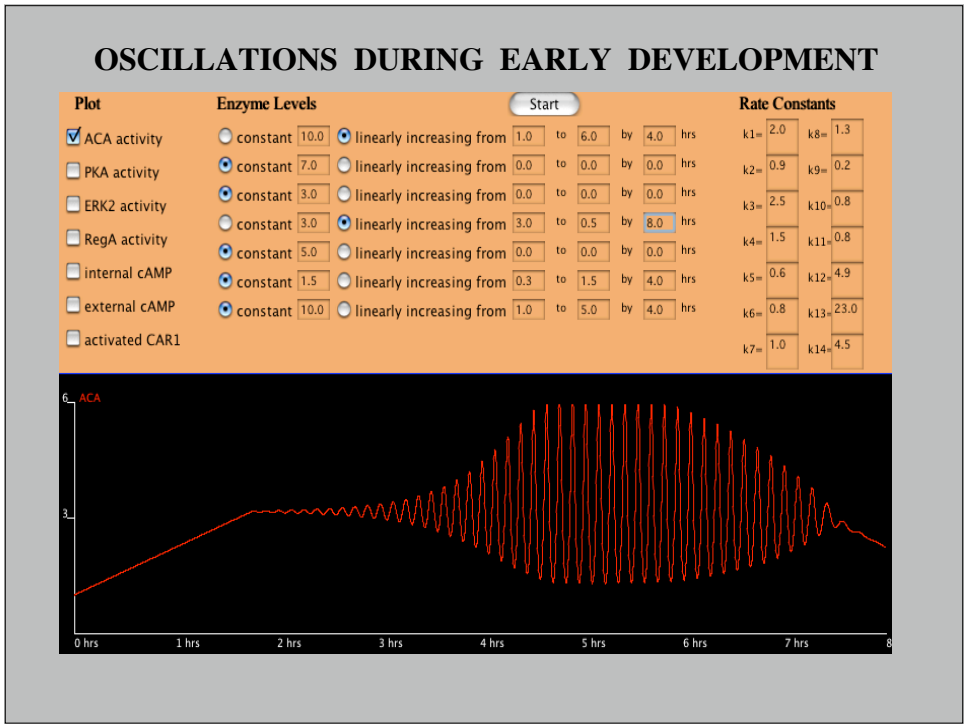


APPEARANCE OF OSCILLATIONS DURING DEVELOPMENT

Gerisch, G., Malchow, D., Roos, W., and Wick, U. (1979). J Exp Biol *81*, 33-47.

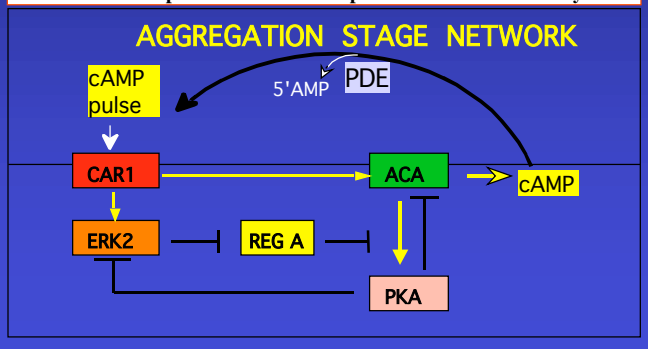




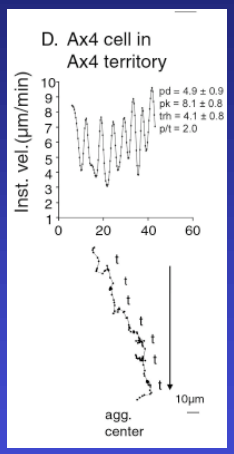


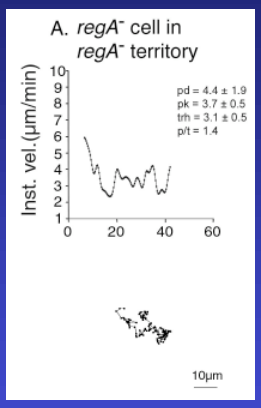
CHEMOTACTIC PROPERTIES OF VARIOUS STRAINS

Mutant	cAMP Signaling	Directional Sensing	Lateral pseudopods
AX4 (none)	periodic	excellent	few
CAR1	none	none	---
ACA	none	poor	---
ERK2	none	poor	many
REGA	poor	poor	many
PKA-R	poor	poor	many

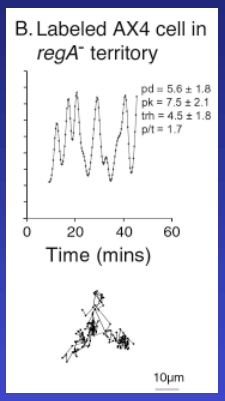


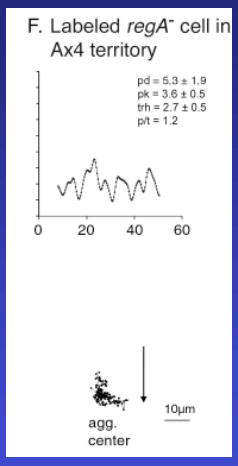
CHEMOTACTIC MIGRATION OF CELLS IN PURE POPULATIONS OF WILD TYPE (AX4) AND MUTANT (regA-) STRAINS



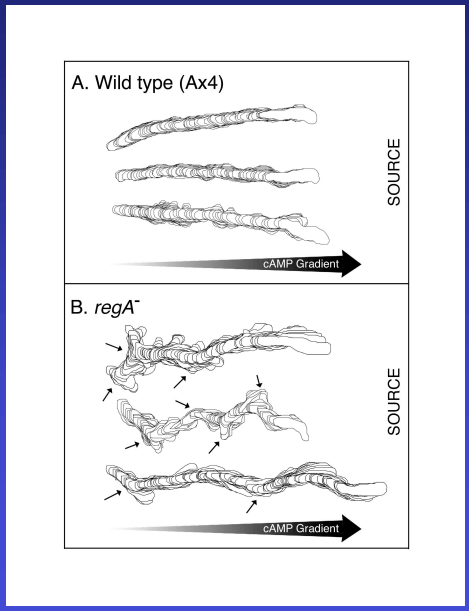


CELLS LACKING RegA NEITHER SIGNAL NOR RESPOND

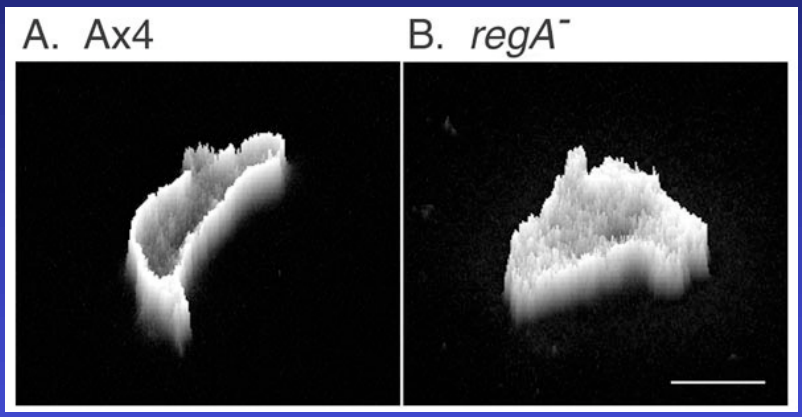




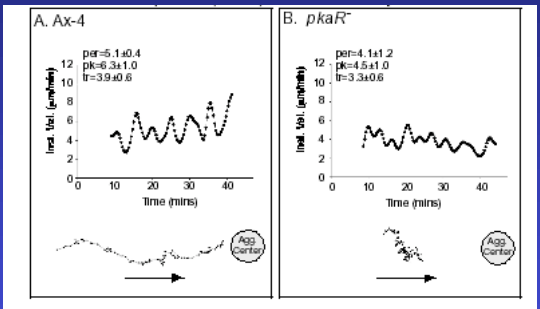
CELLS LACKING RegA MAKE MORE LATERAL PSEUDOPODS



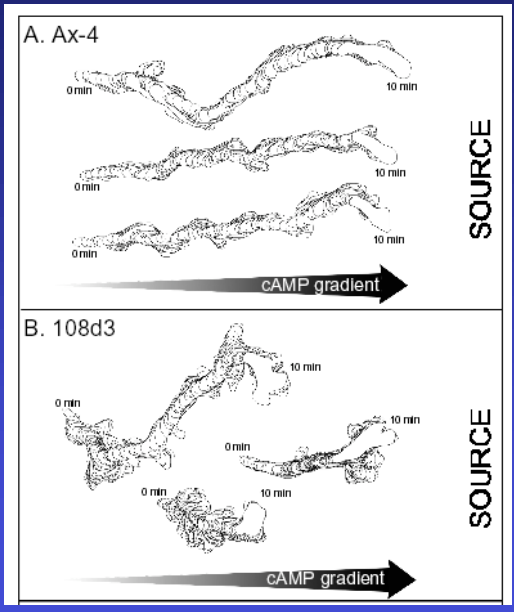
MYOSIN IS NOT RECRUITED TO THE CORTEX OF CELLS LACKING RegA

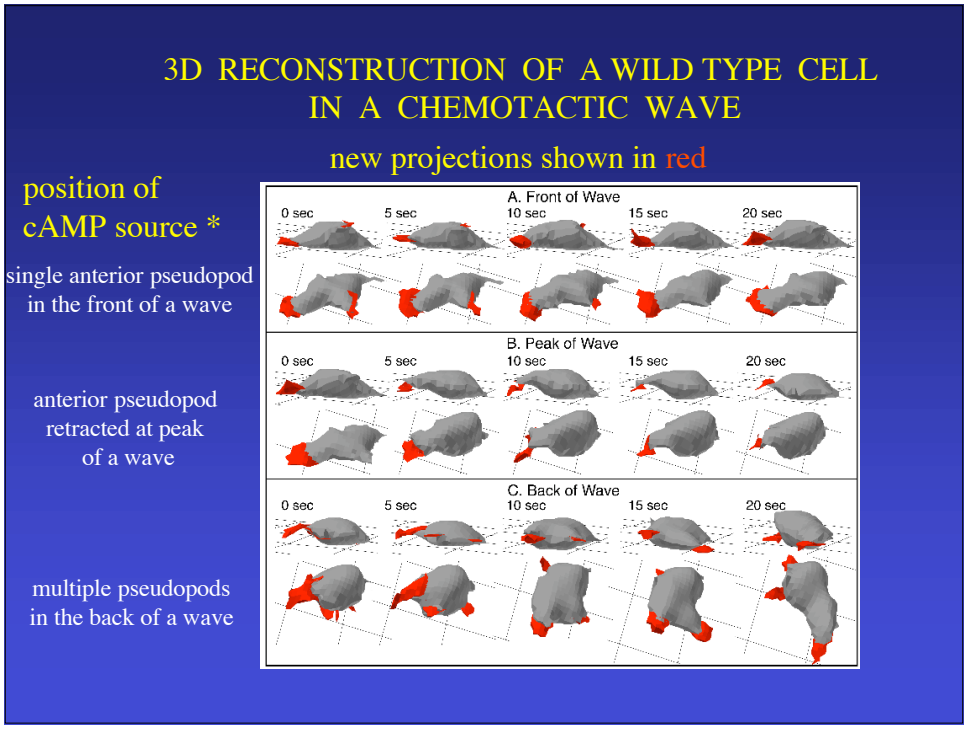


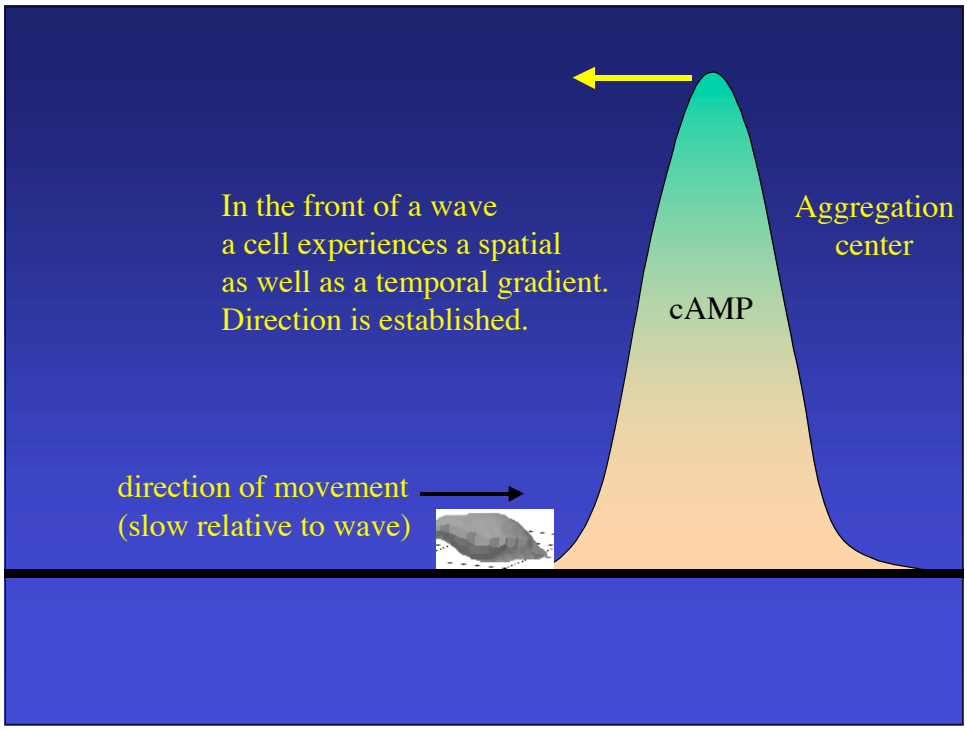
CHEMOTACTIC MIGRATION OF WILD TYPE AND PKA R⁻ CELLS IN A PREDOMINANTLY WILD TYPE POPULATION

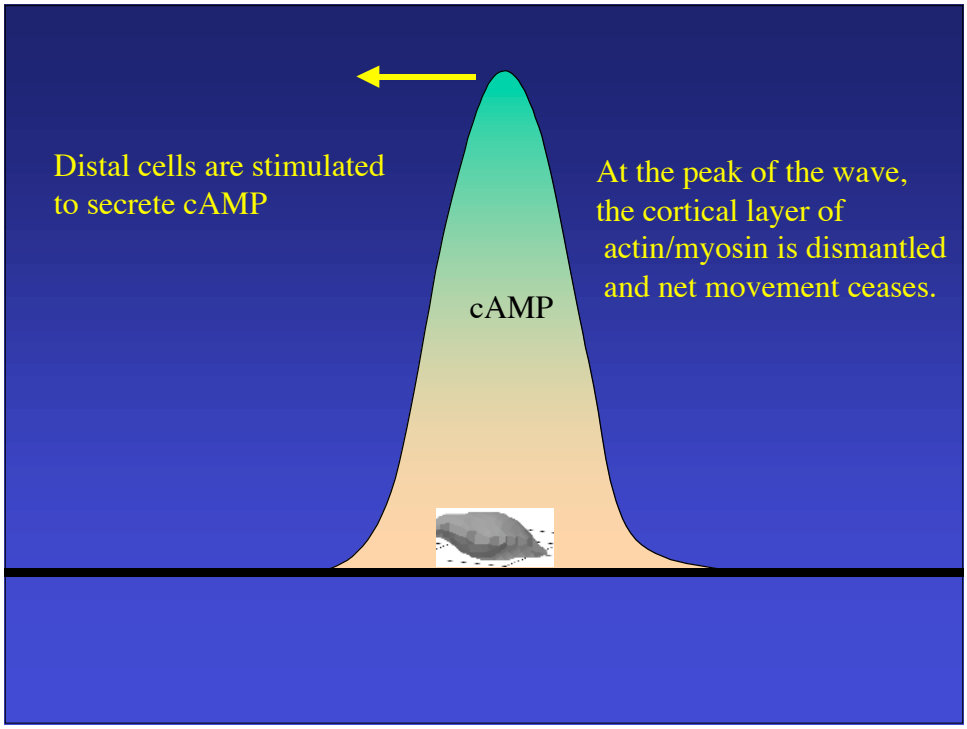


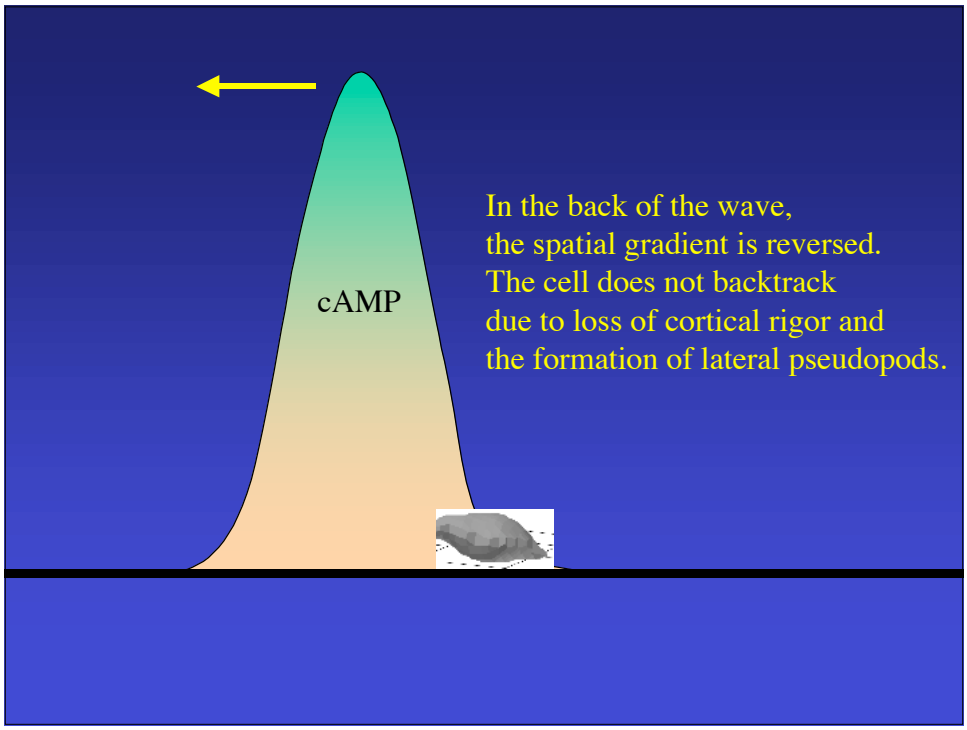
CELLS LACKING PKA MAKE MORE LATERAL PSEUDOPODS

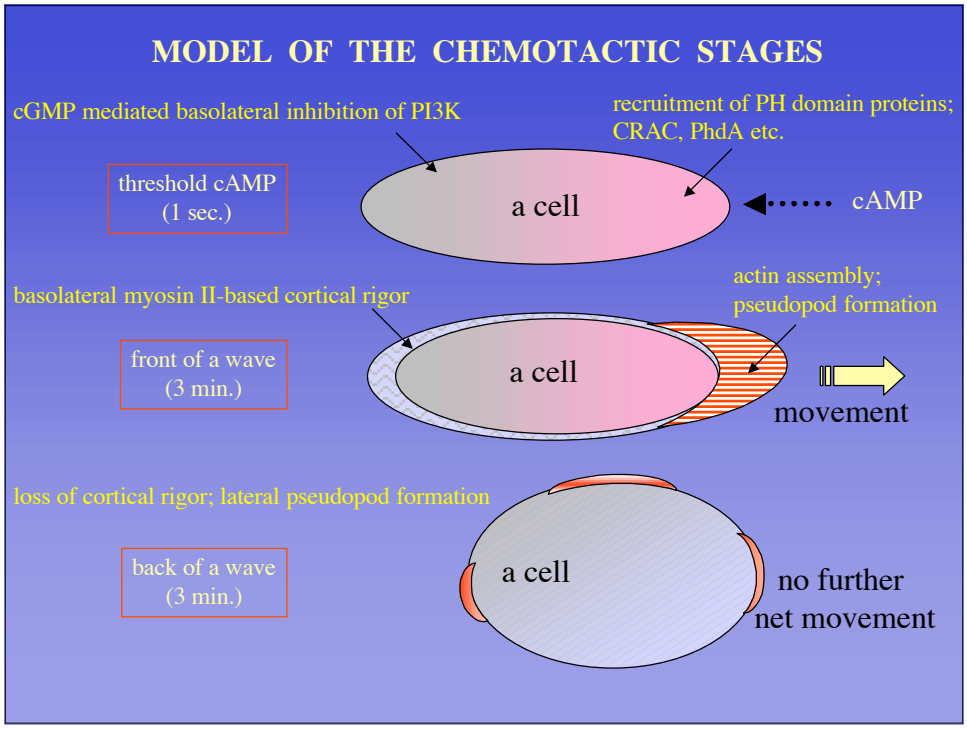


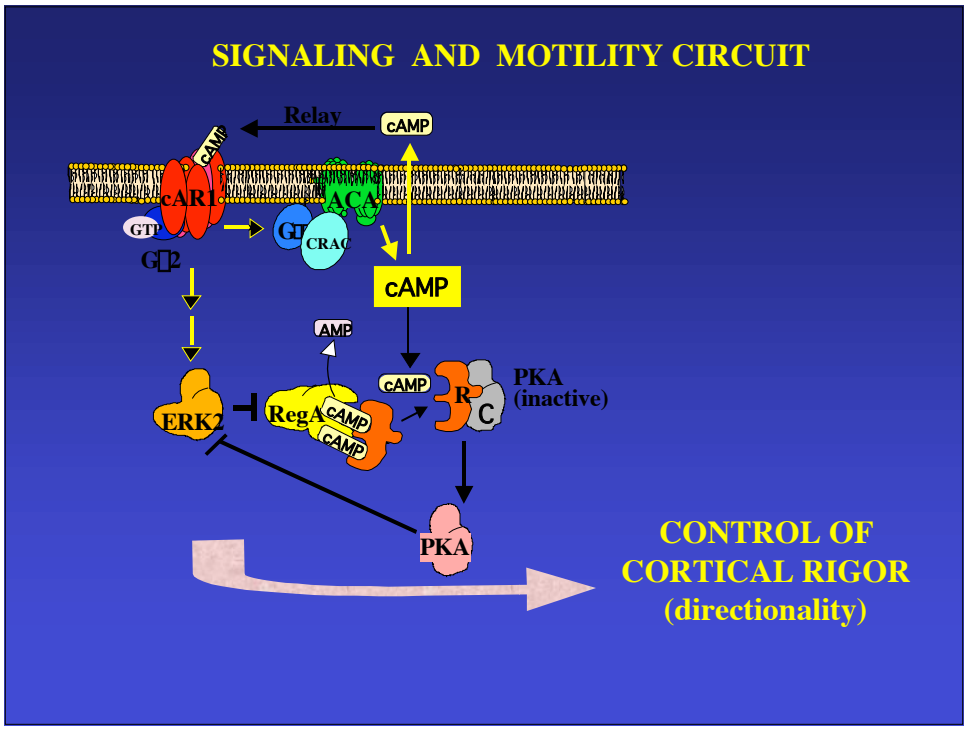

3D RECONSTRUCTION OF A WILD TYPE CELL
IN A CHEMOTACTIC WAVE
new projections shown in red
position of
cAMP source *
single anterior pseudopod
in the front of a wave
anterior pseudopod
retracted at peak
of a wave
multiple pseudopods
in the back of a wave
A. Front of Wave
B. Peak of Wave
C. Back of Wave
0 sec
5 sec
10 sec
15 sec
20 sec


In the front of a wave
a cell experiences a spatial
as well as a temporal gradient.
Direction is established.
Aggregation
center
cAMP
direction of movement
(slow relative to wave)

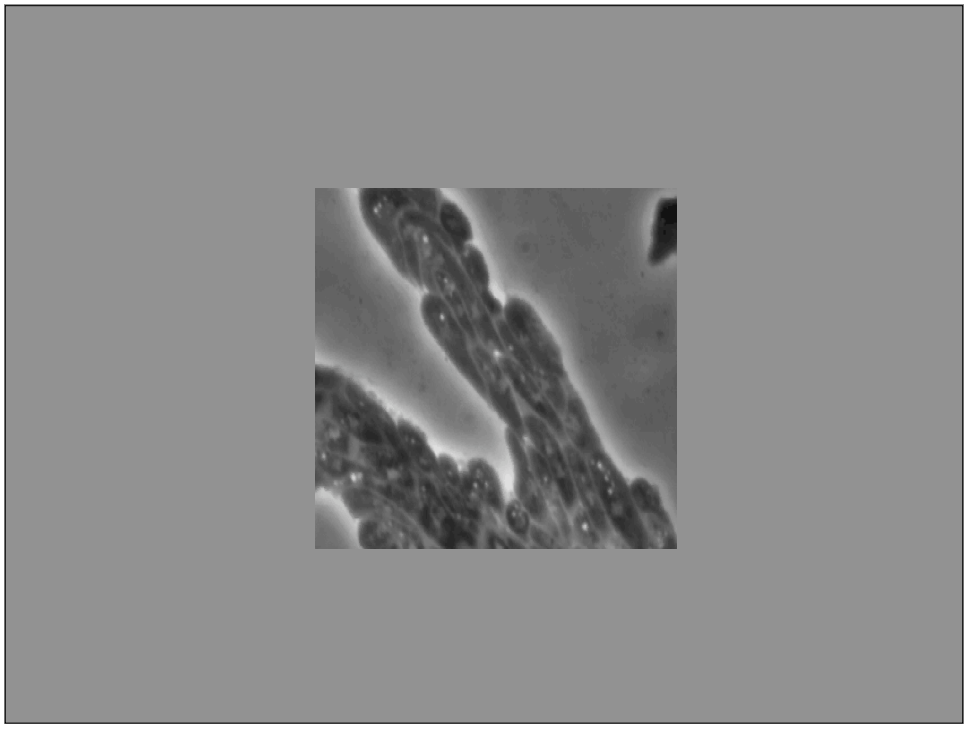

Distal cells are stimulated
to secrete cAMP
cAMP
At the peak of the wave,
the cortical layer of
actin/myosin is dismantled
and net movement ceases.

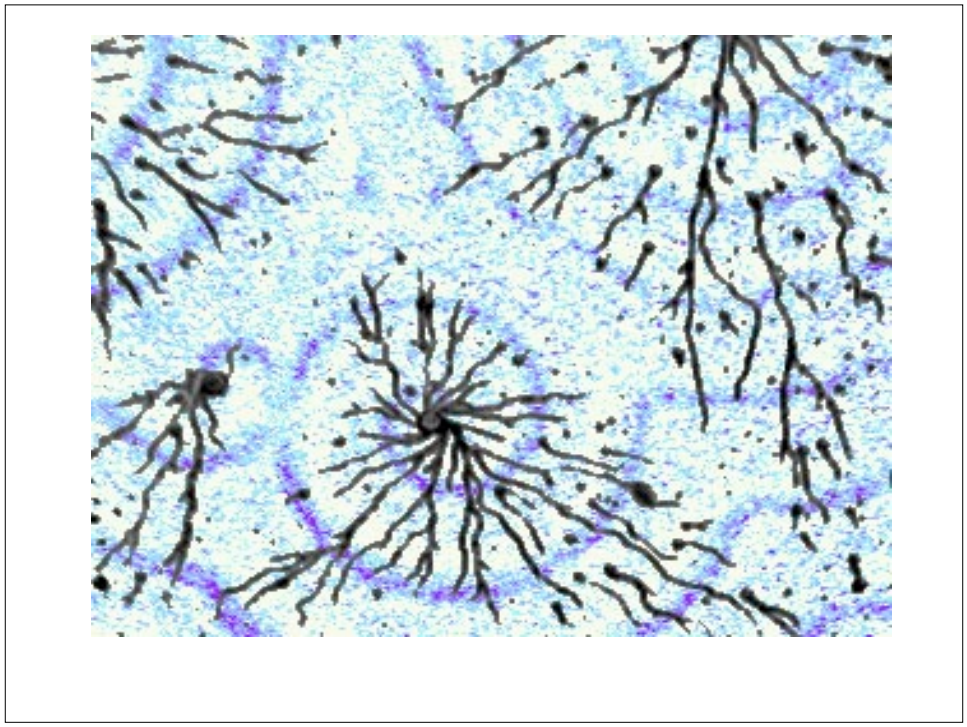

cAMP
In the back of the wave,
the spatial gradient is reversed.
The cell does not backtrack
due to loss of cortical rigor and
the formation of lateral pseudopods.


MODEL OF THE CHEMOTACTIC STAGES
cGMP mediated basolateral inhibition of PI3K
recruitment of PH domain proteins; CRAC, PhdA etc.
threshold cAMP (1 sec.)
a cell
cAMP
basolateral myosin II-based cortical rigor
actin assembly; pseudopod formation
front of a wave (3 min.)
a cell
movement
loss of cortical rigor; lateral pseudopod formation
back of a wave (3 min.)
a cell
no further net movement


SIGNALING AND MOTILITY CIRCUIT
Relay
cAMP
cAR1
ACA
GTP
G2
CRAC
cAMP
AMP
ERK2
RegA
cAMP
cAMP
R
C
PKA (inactive)
PKA
CONTROL OF CORTICAL RIGOR (directionality)

The Dicteostelium Motility Cycle





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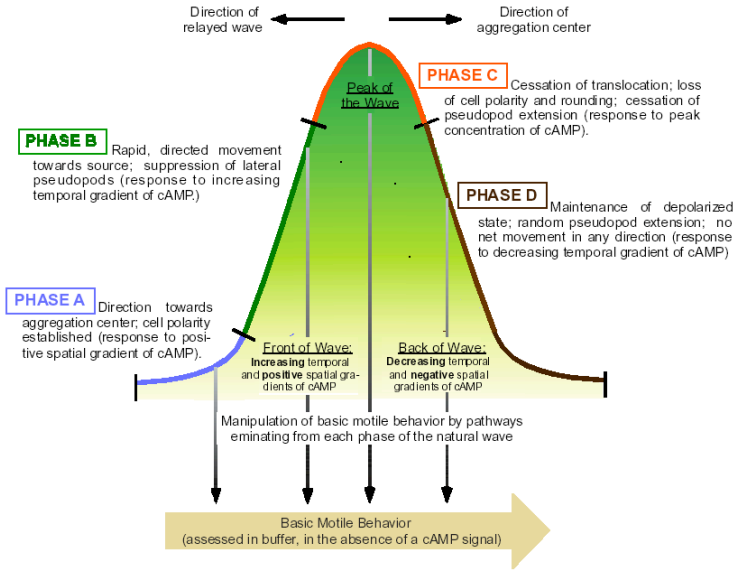
DYNAMICS OF CELLULAR RESPONSES TO A NATURAL WAVE



A human neutrophil chasing a bacterium (S. aureus)

A time-lapse movie made by Dr. David Rogers at Vanderbilt in the 1950's