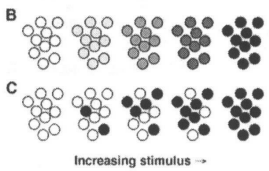
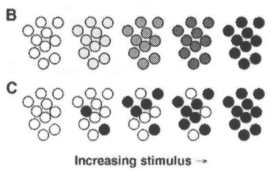
MAPK signaling in Population versus Individual oocytes



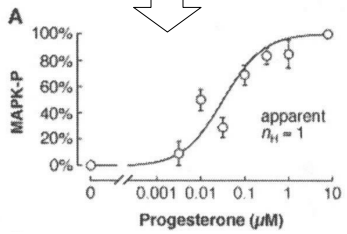
Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

28-1

MAPK signaling in Population versus Individual oocytes



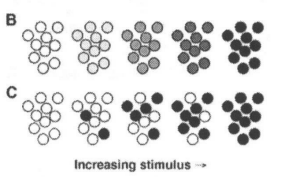
Population response is not switch-like

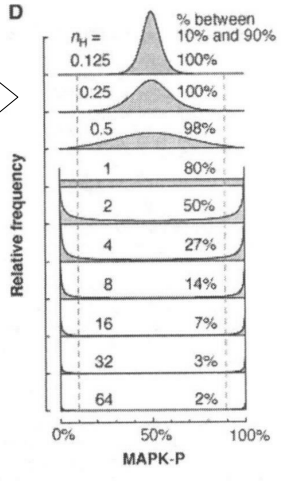


Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

28-2

MAPK signaling in Population versus Individual oocytes



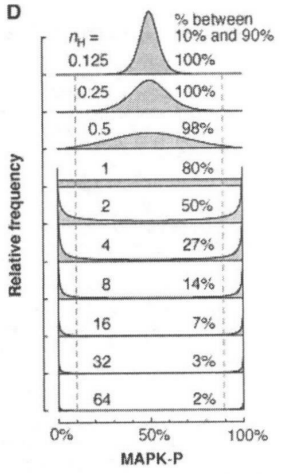


Model of individual oocyte response…
Oocytes are incubated with half-maximal stimulus
Individual cells are assumed to have same nH, but members of the population have different EC_{50}

Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

28-3

Experiments: Individual oocytes



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29-1

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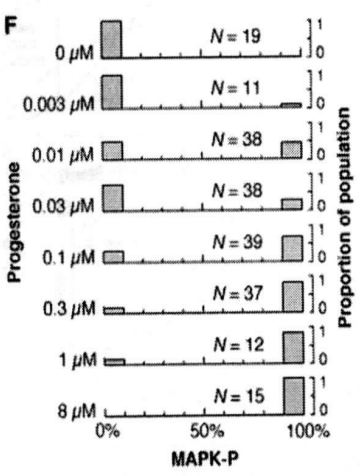
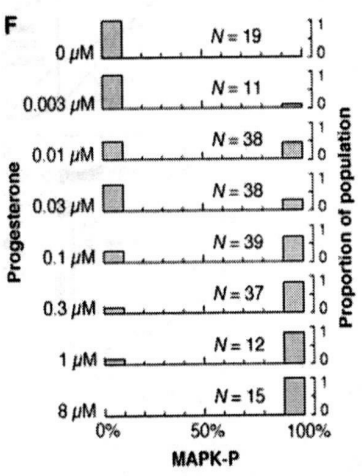


Cumulative MAPK phophorylation data from N = 209 individual oocytes
Immunoblots measured both MAPK and MAPK-P and were binned accordingly
Lower bound on nH was calculated to be 42!! (Up from 4.9 for *in vitro*)

Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

29-2

Experiments: Individual oocytes



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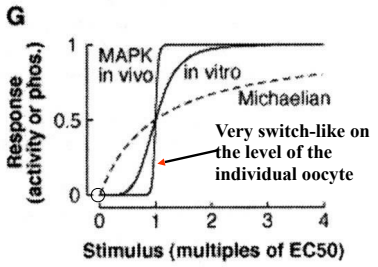

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29-3

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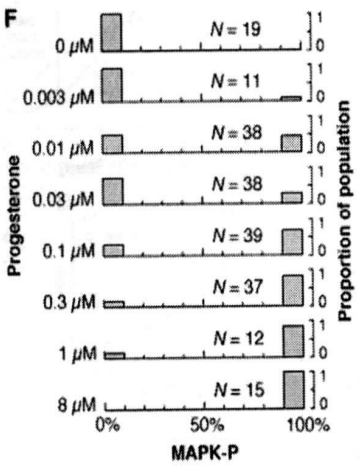

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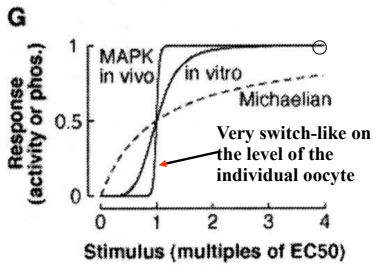
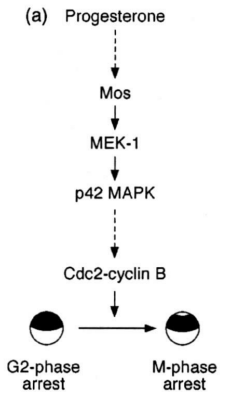


Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

29-4

Positive feedback: another source of ultrasensitivity?

Something makes intact oocytes much more switch-like than extracts…



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30-1

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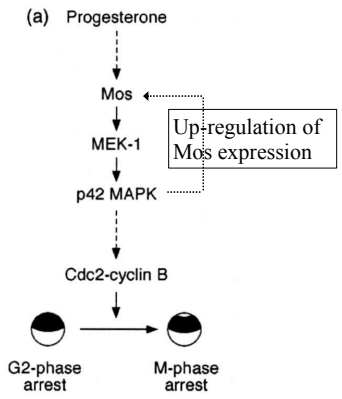

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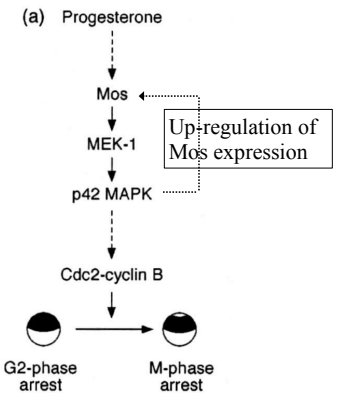
Break positive feedback and recover behavior of extracts in intact oocytes



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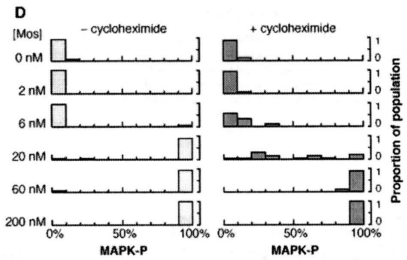

Break positive feedback with cyclohexamide
Results imply a nH = 3, which is similar to that seen in extracts

Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

Positive feedback: another source of ultrasensitivity?

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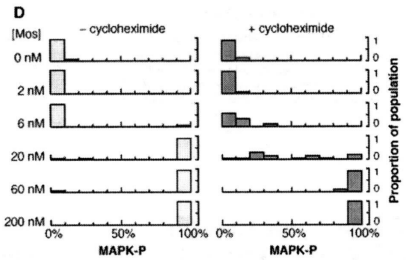
Positive feedback is another source of ultrasensitivity



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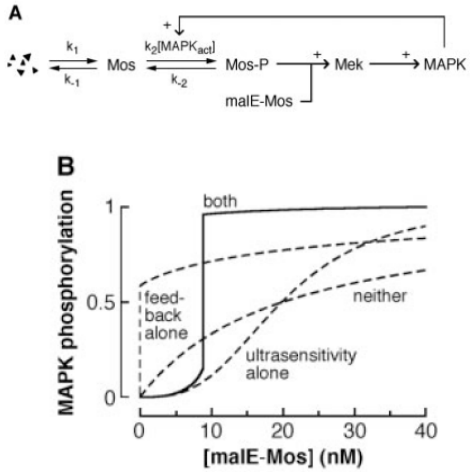
Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

positive feedback & a switch-like response



Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

Switches & more: bistability and irreversibility

switches – but, note that they are reversible…
Recall, oocyte maturation is irreversible

Monostable:
Switch-like instead of graded

Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

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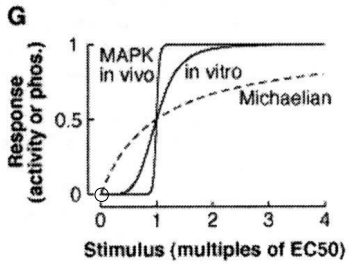

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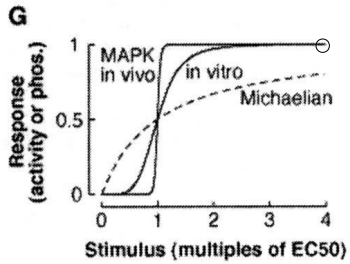

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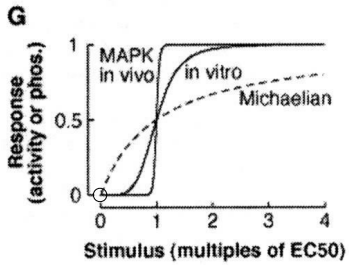


Monostable:
Switch-like instead of graded

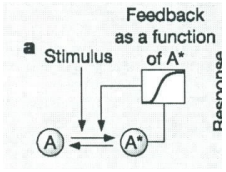
Ferrell, J. and Machleder, E. (1998) *Science* 280, 895-898.

Question

Can positive feedback driven by an ultrasensitive cascade confer more properties?

- Bistability?
- Hysteresis?
- Irreversibility?

Model of positive feedback + ultrasensitivity



Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

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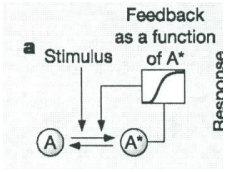

$$\frac{d[A^*]}{dt} = \{\text{stimulus} \times ([A_{tot}] - [A^*])\} + f\frac{[A^*]^n}{K^n + [A^*]^n} - k_{inact}[A^*]$$

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

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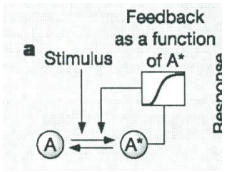

also

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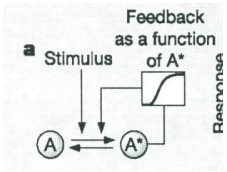
Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

34-3

Model of positive feedback + ultrasensitivity



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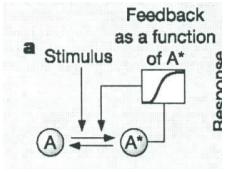
Forward reaction due to direct interaction with stimulus

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

34-4

Model of positive feedback + ultrasensitivity



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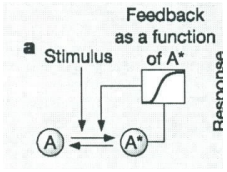
Forward reaction due to direct interaction with stimulus

Positive feedback reaction, nonlinear

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

34-5

Model of positive feedback + ultrasensitivity



Reverse reaction

also

$$\frac{d[A^*]}{dt} = \{\text{stimulus} \times ([A_{tot}] - [A^*])\} + f\frac{[A^*]^n}{K^n + [A^*]^n} - k_{inact}[A^*]$$

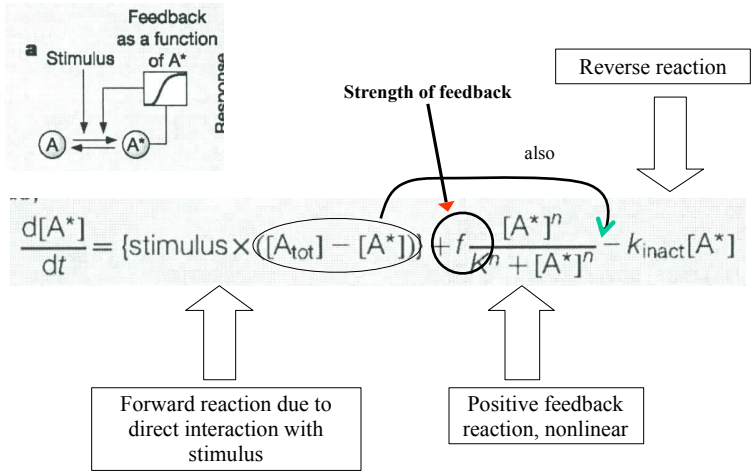
Forward reaction due to direct interaction with stimulus

Positive feedback reaction, nonlinear

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

34-6

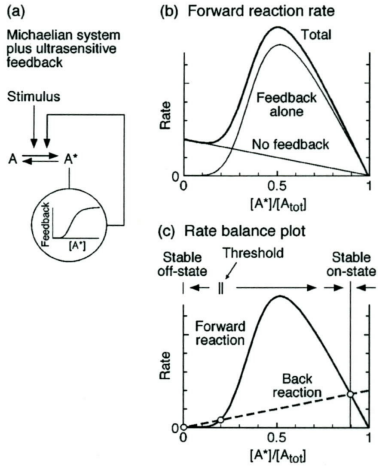
Model of positive feedback + ultrasensitivity



Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

34-7

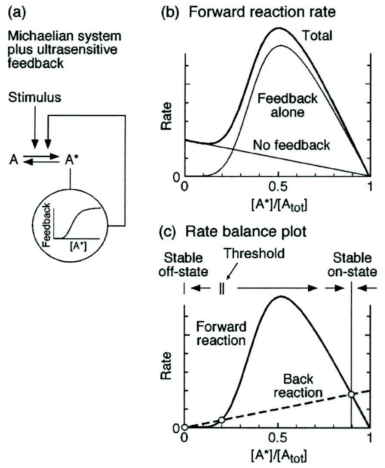
Rate balance plots



Ferrell, J. and Xiong, W. (2001) *Chaos*. 11(1), 227-236.

35-1

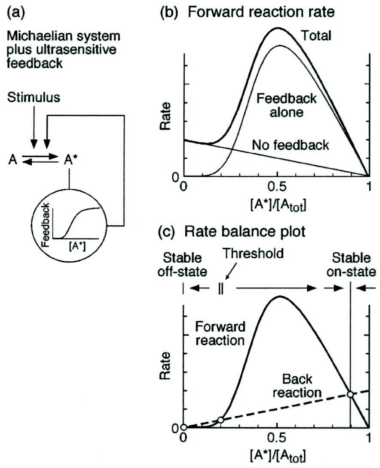
Rate balance plots



Ferrell, J. and Xiong, W. (2001) *Chaos*. 11(1), 227-236.

35-2

Rate balance plots



Two components of forward rate:

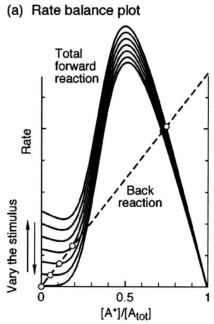
- Direct stimulus activation
- Nonlinear feedback

Rate balance plot shows three steady states for a given stimulus (here, the direct activation contribution is small)

Ferrell, J. and Xiong, W. (2001) *Chaos*. 11(1), 227-236.

35-3

Rate balance plot for different stimulus doses



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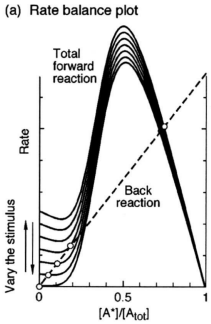

Note that the stable off-state moves with the stimulus
Once the stable on-state has been attained, original stimulus is not necessary to maintain the activation

Ferrell, J. and Xiong, W. (2001) *Chaos*. 11(1), 227-236.

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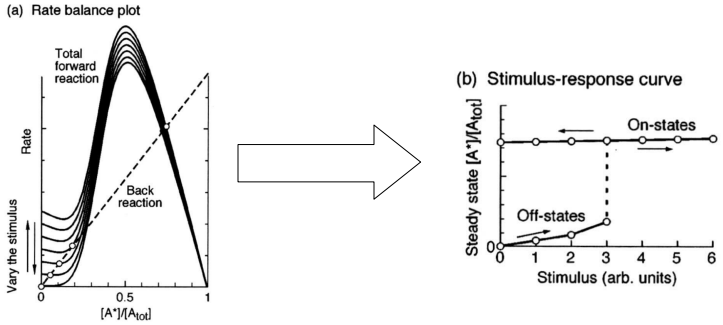

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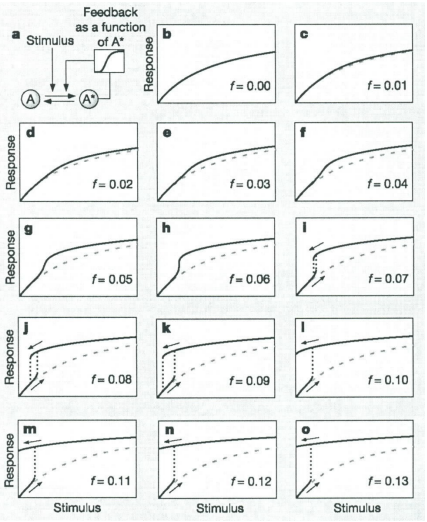
Feedback strength (f)



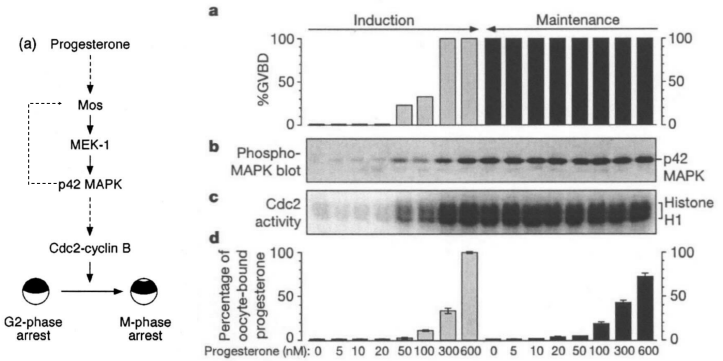
As f increases…

- b-h, monostable system becomes more switch-like
- i-k, bistable system exhibits hysteresis
- l-o, hysteresis loop expands beyond zero stimulus point… system is irreversible

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465

Memory module governs cell-fate decision

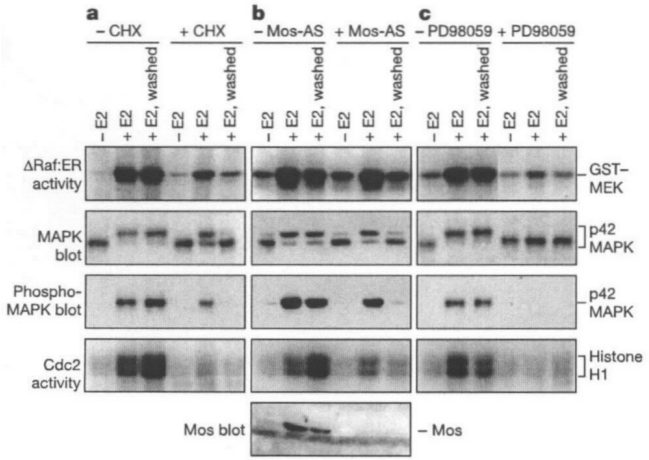
Induction of oocytes with progesterone leads to irreversible cell fate induction



Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

38

Memory module governs cell-fate decision



Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

39-1

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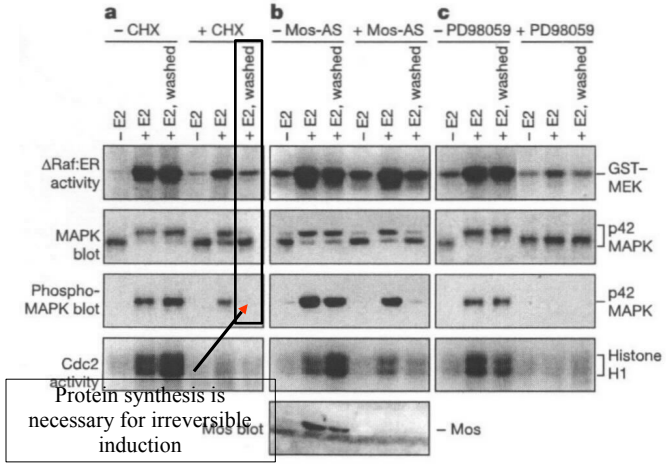

Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

39-2

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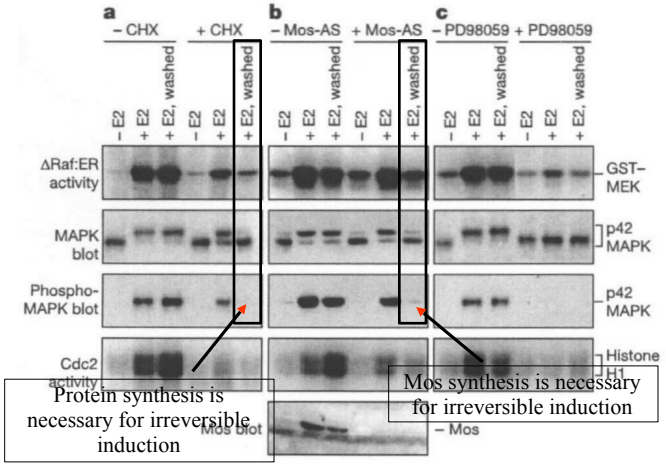
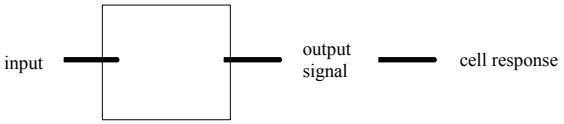


Xiong, W. and Ferrell, J. (2003) *Nature*. 426, 460-465.

39-3

Quick synopsis



Need for switches and hysteresis

A common signal transduction protocol

- Ultrasensitivity (graded input into switch output)
- Bistability (2 possible steady states for some inputs)
- Hysteresis (turn ON, but cannot turn back OFF)

Switches ubiquitous? What about dynamics?

MAP kinase cascades are not always switches

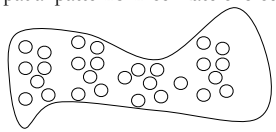
Mammalian cells (ERK) -- Blenis et. al. MCB 2005.

Yeast (Fus3, Kss1) -- Brent et. al. Nature 2005.

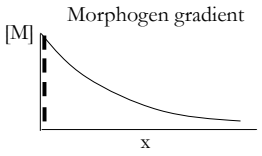
Why isn't it always a switch? Some responses are analog (migration) others are switches (death).

The need for "lockable switches": multicellular patterning

Spatial patterns in cell fate choices

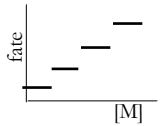


Morphogen gradient



* *development,*
* *tissue engineering.*

* Discrete fate choices



* M is present for finite time, but fates "locked"