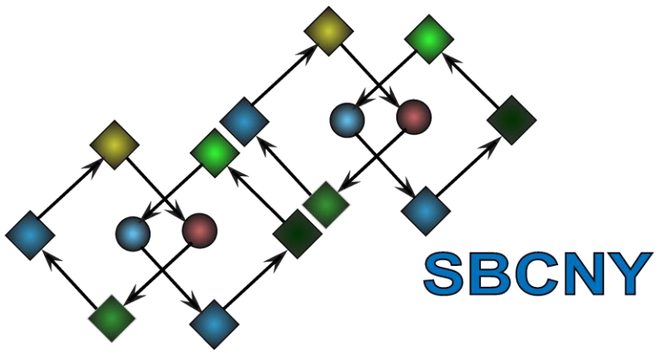
Bistability in biochemical signaling models

Part 1

Icahn School of Medicine at Mount Sinai



Outline

Some biological background

Biological importance of bistability

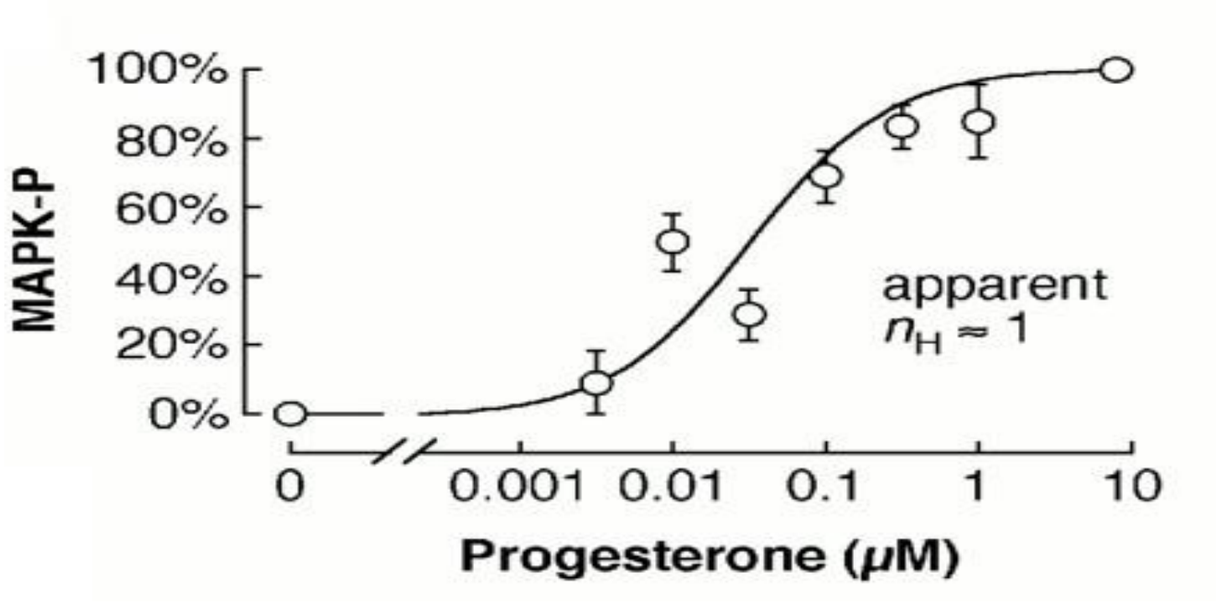
Qualitative requirements of bistability

What is bistability?

A situation in which two possible steady-states are both stable.

In general, these correspond to a "low activity" state and a "high activity" state.

Classic experiment: add progesterone to Xenopus (frog) oocytes, measure MAPK activity



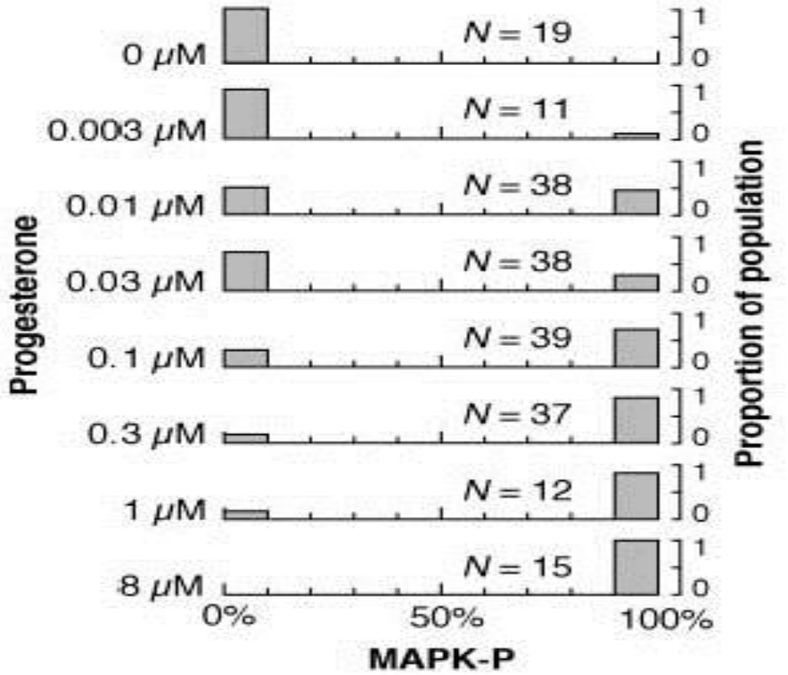
MAPK = Mitogen Activated Protein Kinase

Ferrell & Machleder (1998)
***Science* 280:895-898.**

Population response: gradual increase in MAPK with progesterone

Bistability in Xenopus oocytes?

What happens when MAPK activity is measured in each cell?



Ferrell & Machleder (1998)
***Science* 280:895-898.**

With ↑ progesterone, oocytes switch from low state to high state

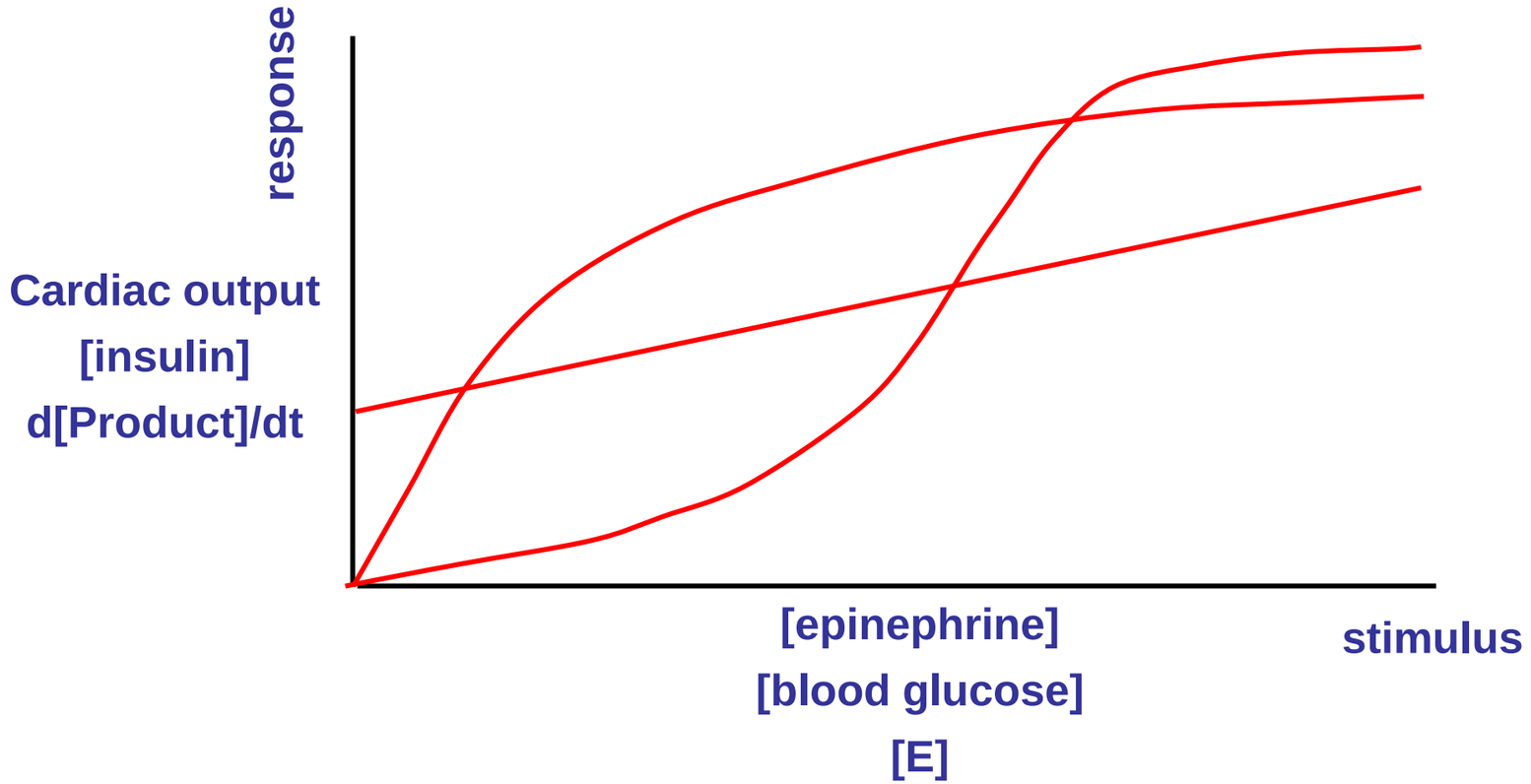
At intermediate [progesterone] both high and low states are present

Biology: generally monostable and analog

Epinephrine → increased cardiac output

Increased blood glucose → insulin production

Enzyme → conversion of substrate to product



Response depends directly on level of stimulus

When stimulus removed, response returns to prior level

When is analog not good enough?

Fertilization

Cell division

Differentiation

Action potentials

Apoptosis

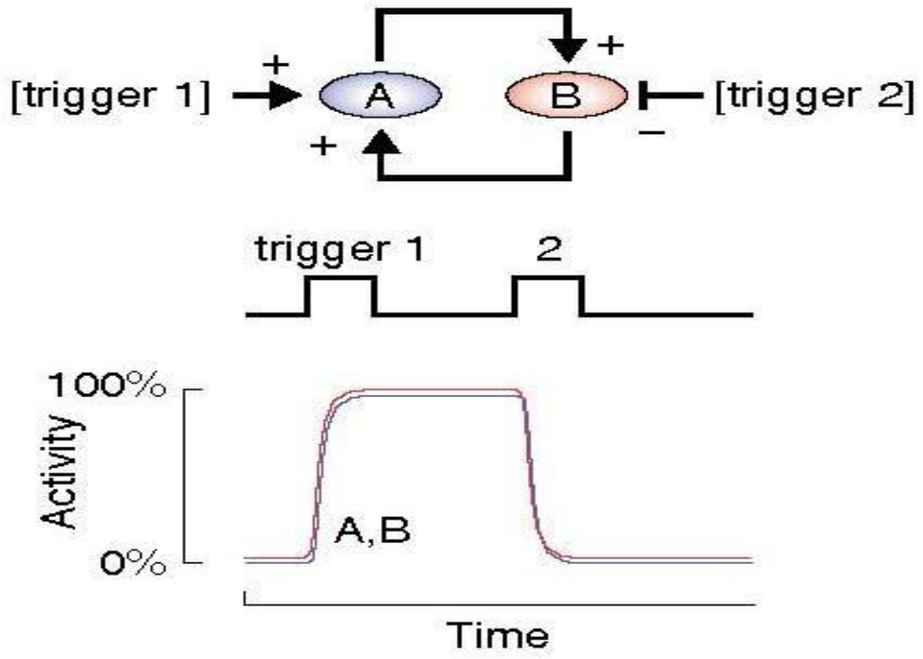
Learning

For these processes, a graded response is inadequate

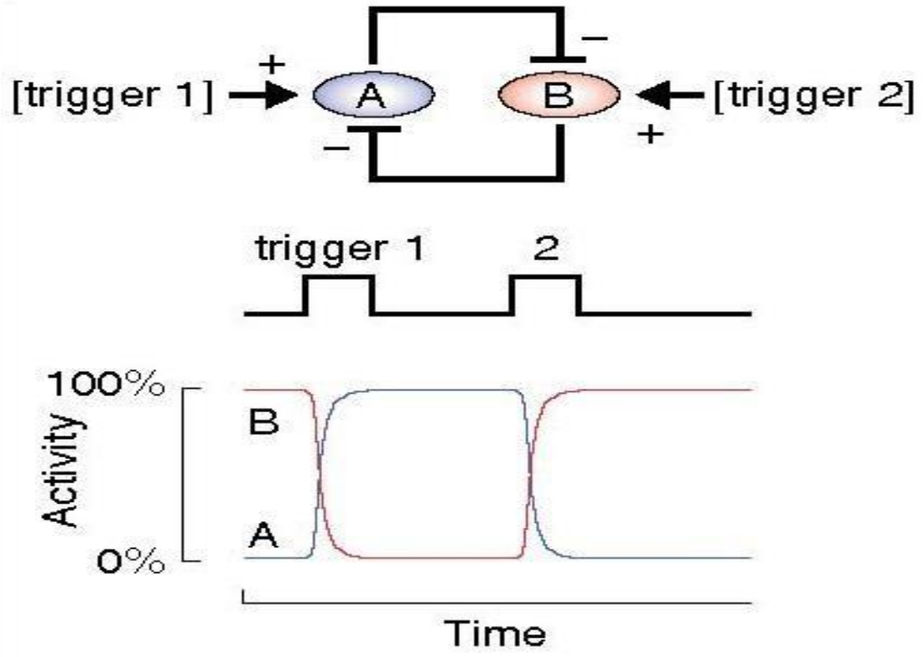
These phenomena also require persistence

At the biochemical level, how does bistability arise?

Mutual activation



Mutual inhibition



Ferrell (2002) *Curr. Op. Cell Biol.* 14:140–148.

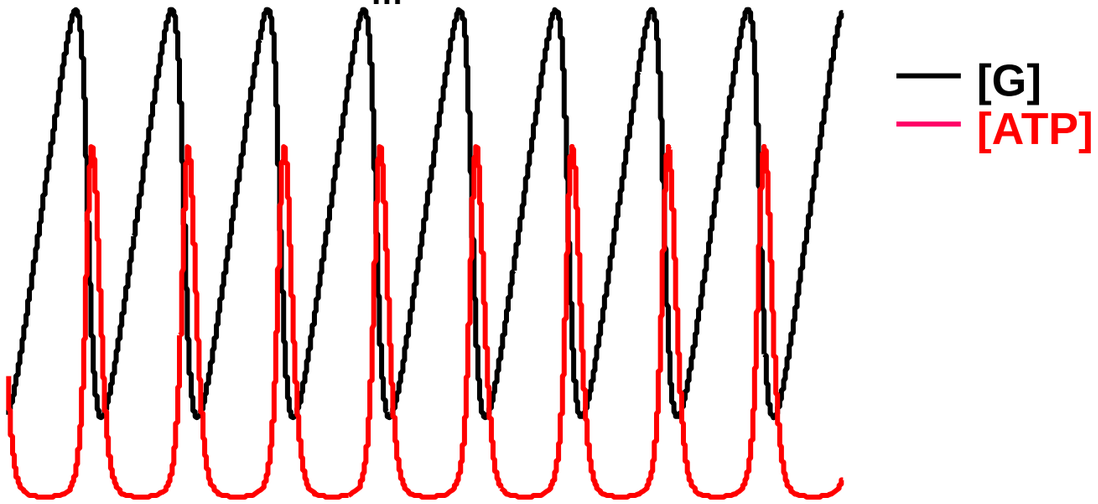
These types of circuits CAN produce bistability, but they do NOT guarantee bistability

This is why we need quantitative analyses

Bistability in terms of dynamical behavior

Previously we encountered stable and unstable fixed points and limit cycles

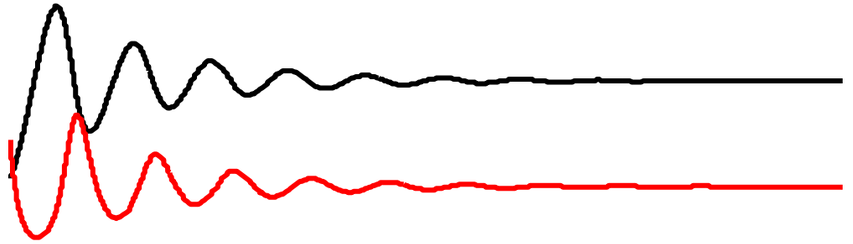
$K_m = 13$



The fixed point is “unstable.”

The oscillation is a “stable limit cycle.”

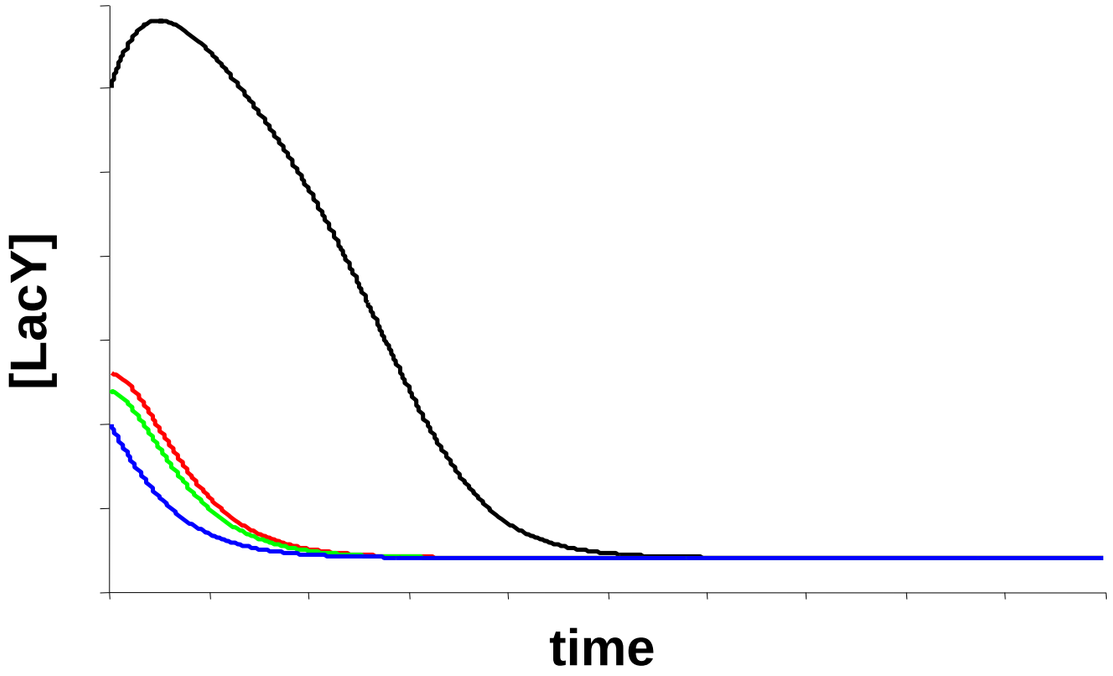
$K_m = 20$



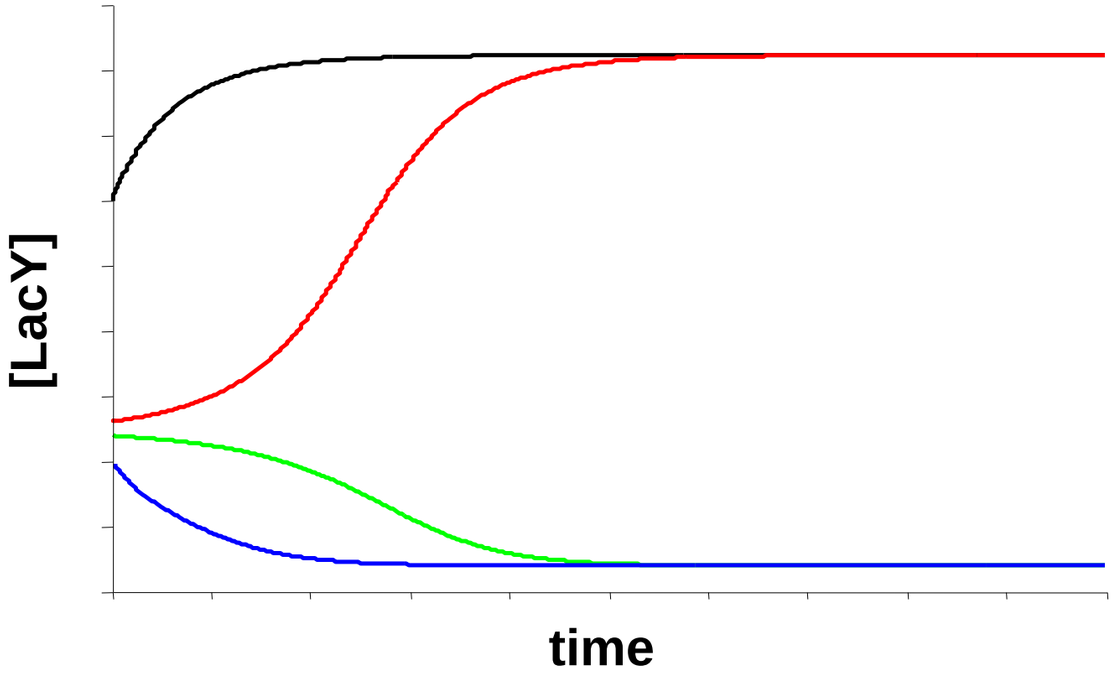
The fixed point is “stable.”

Bistability in terms of dynamical behavior

A monostable system



A bistable system



Multiple steady-states are possible
Initial conditions determine which steady-state is reached

Summary

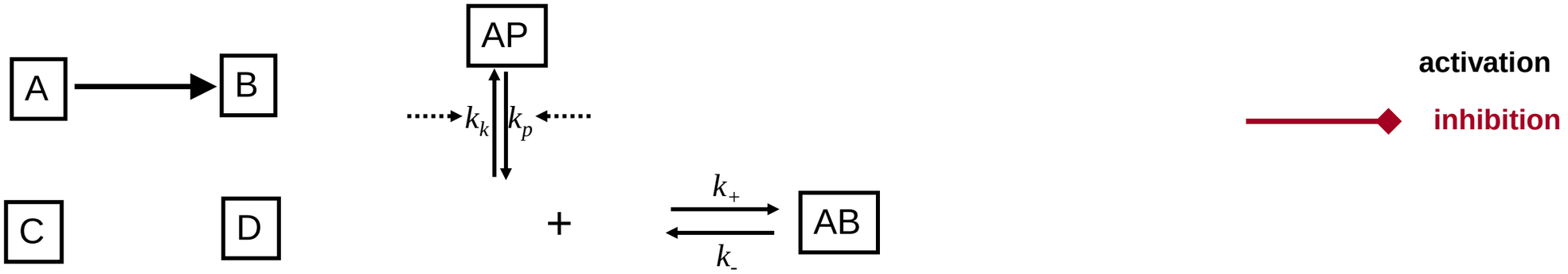
Bistability can be a useful property for biological processes that require persistence.

Bistability means that a biological response will be essentially digital, or all-or-none, rather than graded.

In the language of dynamical systems, bistability means that two fixed points are possible, with initial conditions determining which fixed point is reached.

Self-assessment question

As discussed, mutual activation or mutual inhibition can produce bistability. This is true when two species A and B are present, and is also true when multiple species are present, as long as the overall regulation is mutual activation or inhibition. Given this, which of the following schemes might produce bistability? Multiple correct answers are possible.



<u>Answers</u>: (1) You do not tell MATLAB to plot each column of `A`, instead it is only instructed to plot a single element of `A` each time through the loop.

(2) MATLAB has not been instructed to plot in a different color each time through the `for` loop.

(3) MATLAB has not been instructed to plot the time courses together.