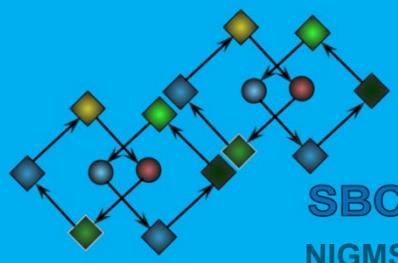


NIGMS funded Center

Experimental Methods in Systems Biology

Part of the Coursera Certificate in Systems Biology

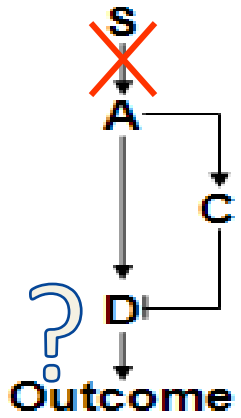
Marc Birtwistle, PhD
Department of Pharmacology & Systems Therapeutics
Fall 2014, Week 7b, Interpreting Dynamic and Single Cell Experiments

Icahn School of Medicine at Mount Sinai

Outline

- Where gene lists and networks are limited
- Dynamical models
  - Differential equations
  - Stochastic processes
- Important relationship between dynamic processes and single cell data—a variety of studies
- Case Study—Interpreting Flow Cytometry Data with Stochastic Dynamical Models

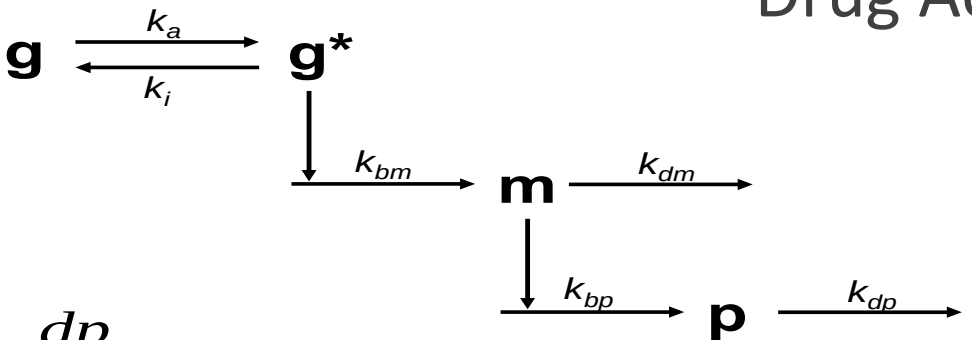
Where gene lists and networks are limited



- **Need to know:**
  - **Magnitude of Effects on D**
    - A strong; C weak → D up
    - A weak; C strong → D down
  - **Dynamics of Interactions with D**
    - A slow; C fast → D down then up
    - A fast; C slow → D up then down
  - **Localization with D**
    - A local; C distant → D up
    - A distant; C local → D down

Dynamical Models Allow Us To Keep Track of These Kinds of Properties in Complex Systems

Example of Chemical Kinetics to Describe Gene Expression or Drug Action

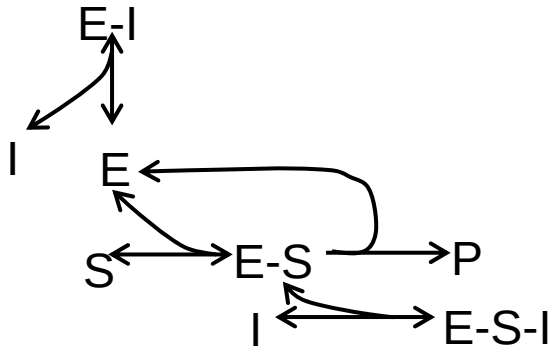


$$\frac{dp}{dt} = k_{bp}m - k_{dp}p$$

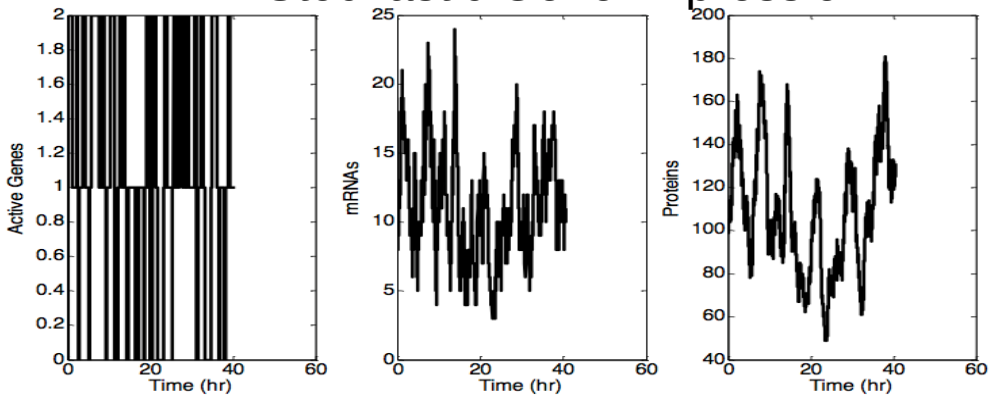
$$\frac{dm}{dt} = k_{bm}g^* - k_{dm}m$$

$$\frac{dg^*}{dt} = k_a g - k_i g^*$$

$$\frac{dg}{dt} = k_i g^* - k_a g$$

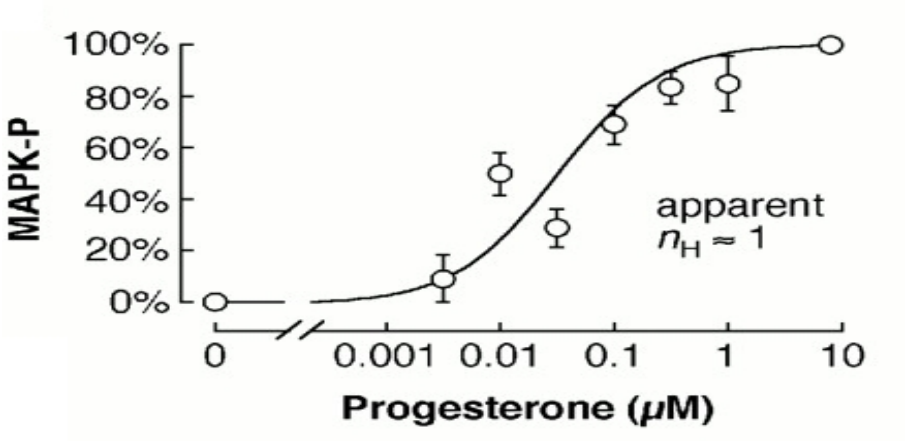


Stochastic Gene Expression



Problems with Population Average Measurements in Dynamic or Noisy Systems

Classic experiment: add progesterone to Xenopus oocytes, measure MAPK

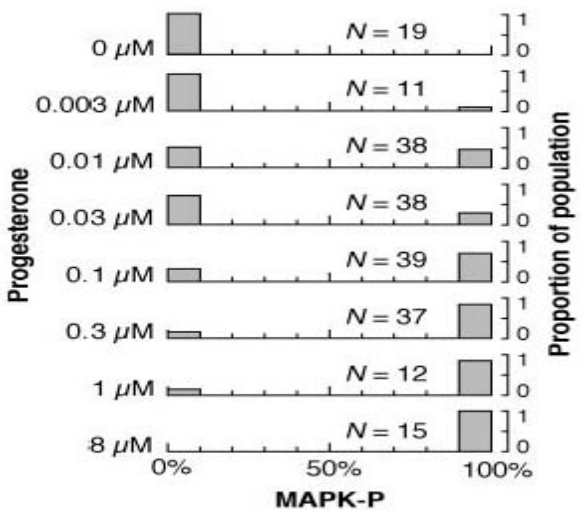


Ferrell & Machleder (1998)
Science 280:895-898.

Population response: gradual increase in MAPK with progesterone

Bistability in Xenopus oocytes?

What happens when MAPK 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

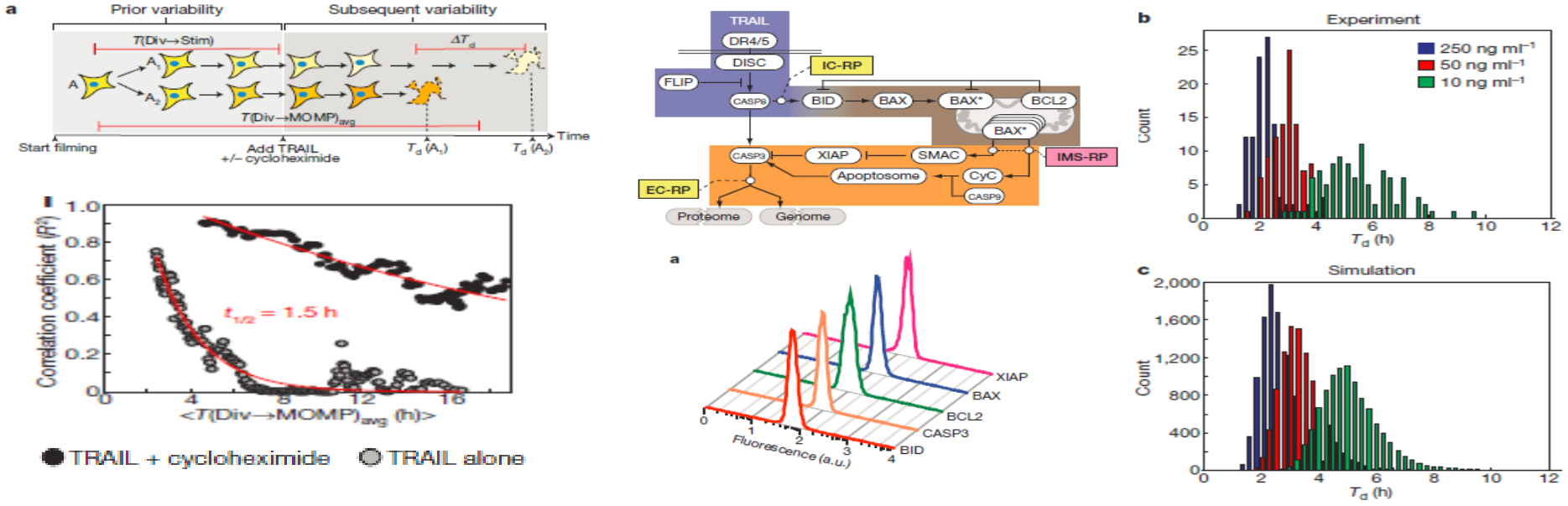
This kind of issue comes up even without considering dynamics

Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis

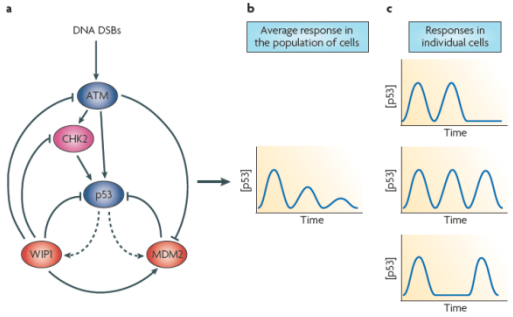
Sabrina L. Spencer[1,2]*, Suzanne Gaudet[1]†*, John G. Albeck[1], John M. Burke[1] & Peter K. Sorger[1]

nature Vol 459|21 May 2009|doi:10.1038/nature08012

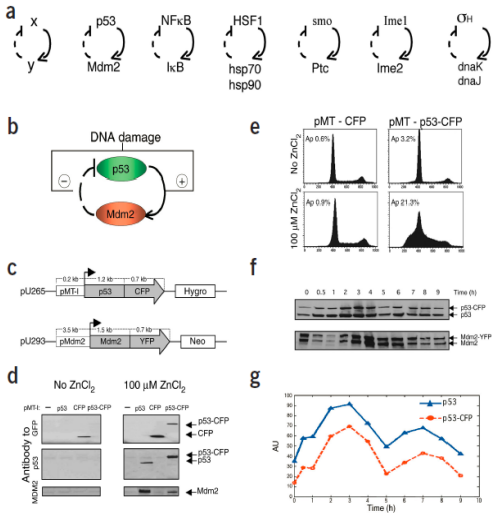
"We show that naturally occurring differences in the levels or states of proteins regulating receptor-mediated apoptosis are the primary causes of cell-to-cell variability in the timing and probability of death in human cell lines."



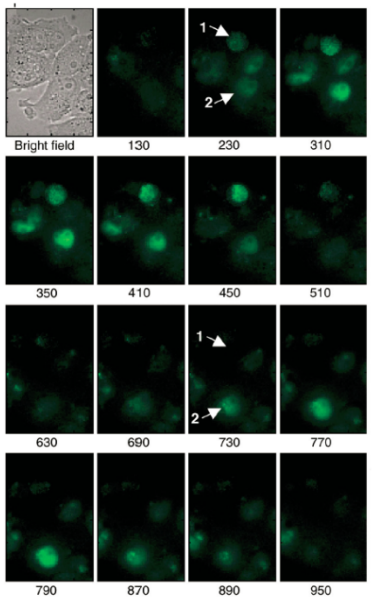
Oscillatory responses of p53

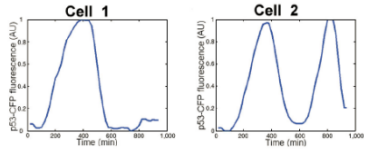


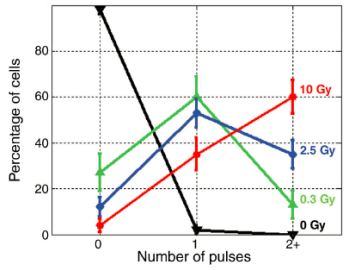
Batchelor et al., Nat Reviews Cancer, 2009



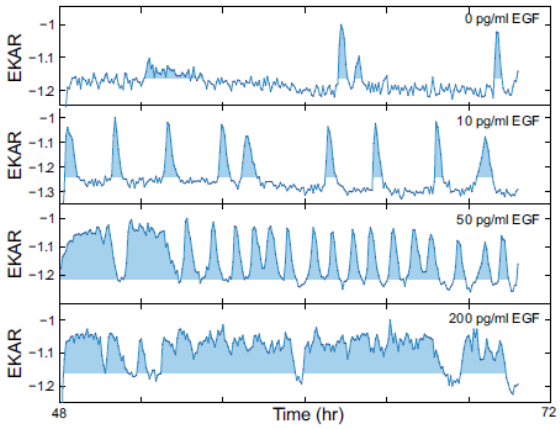
Lahav et al., Nat Genetics, 2004







Stochastic Growth Factor Signaling and Cell Cycle Entry



Albeck et al., Mol Cell, 2013