Errors in Model Building

Models need to obey thermodynamic constraints!

Ensure that there is mass conservation:

Unless you are modeling the synthesis or degradation processes, total mass of each component should be constant during the simulations

For enzymatic reactions total amount (concentration) of product cannot be greater than substrate level (concentration)

Ensure microscopic reversibility:

For systems of coupled ODEs

Product of forward rate constants = product of reverse rate constants

Errors in Simulations

Size of time-steps in ODE models

If time steps are large, and there is likely to be unacceptably large errors in the simulation, due to

1) error in integration and 2) error due to coupling in systems of coupled ODEs

 Final results are unlikely to be correct or meaningful

Solution: *Use smaller time steps to limit computing errors to 1% or less*

Less than the 2-5% error in many biochemical / cell biological experiments

Of course this will increase the amount of computational power needed & time required for the simulations

Size of elements in PDE models

Similarly, if elements are large when solving PDE models, there will be greater error in each step of computation and final result will not be correct

Solution: Use smaller mesh size, which will increase amount of computation required

Trade-off between accuracy of results and speed of computations

Stiffness

When a model contains reactions in very different time scales then it requires unrealistically small time steps to get acceptable level of errors

Such systems are called stiff as they contain stiff equations

e.g. Calcium channels open and close in the msec timescale while calcium driven biochemical reactions (such as activation of protein kinases or phosphatases) occur in the min timescale.

Reactions representing calcium channel opening can be considered to be stiff

There are special solvers in Matlab to solve stiff system

***We should be aware of the relative timescales of the various reactions in our model*!**

Constraining Models with experimental details
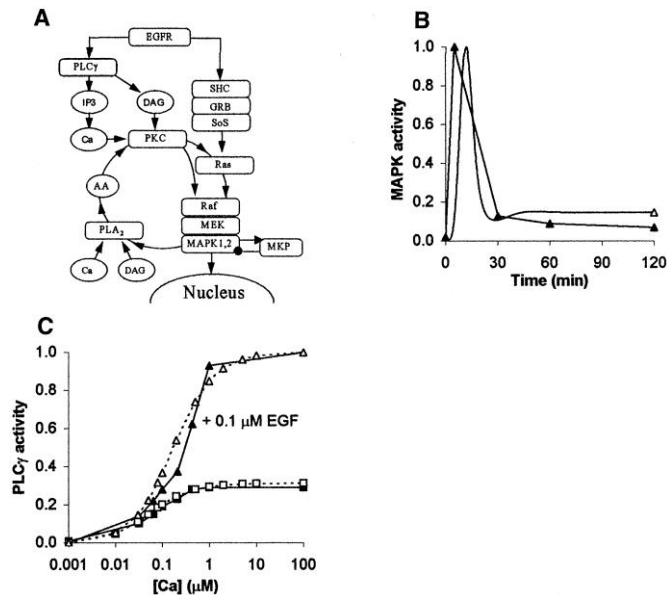
This is very important so that models (and hence the simulations) are as realistic as possible

Model on the left was constrained in parts based on available experimental data

EGFR dose response curve for PLCγ and EGR stimulated time course for MAPK pathway

Bhalla and Iyengar. *Science* 283(5400):381-7 (1999)

Obtaining Predictions from Simulations

Should be non-obvious and need computation: when does a positive feedback loop function as a switch?

Should be experimentally verifiable

Alternatively the computational model can be used as an "accounting tool"
Quite useful for the organization of large quantitative datasets such as those from metabolic network

One type of use DOES NOT preclude the other!

Lecture 6 – Take Home Points

➢ Most biological models are solved by numerical
  simulations, so it is very important that models use
  realistic and reasonable parameters

➢ Models should be well constrained with
   experimental data, and sources of errors minimized

➢ Predictions should be non-obvious and requiring
  computation and be experimentally testable