

INTRODUCTION TO SYSTEMS BIOLOGY AND MATHEMATICAL MODELLING

Karen van Eunen

SYSTEMS BIOLOGY AND MODELLING

- Introduction to modelling of biological processes using computer simulations (by means of R)
- Describe biological processes as mathematical models
- Relations between reality, experiments and models
- Run simulations and interpret the results
- Make use of deSolve package in R and practice plotting results

“All models are wrong, but some are useful”

George E.P. Box

WHY DO WE NEED MODELLING?

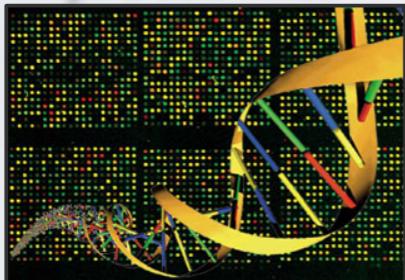
Cellular life combines various different biochemical processes, which have been considered separately in experimental research and in theoretical model building. These processes include metabolism, signalling, gene expression and the cell cycle. We model all these processes because:

- To better understand the system
- To get insights into how various forces act to change a cell/organism/population/ecosystem
- Make predictions of new scenarios
- Models can describe any (biological) phenomenon

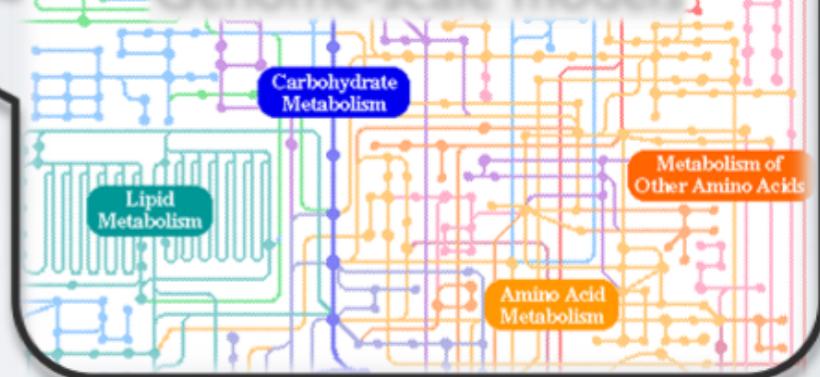
MODELLING APPROACHES (I)

Top-down

Transcriptomics/
proteomics



Genome-scale models

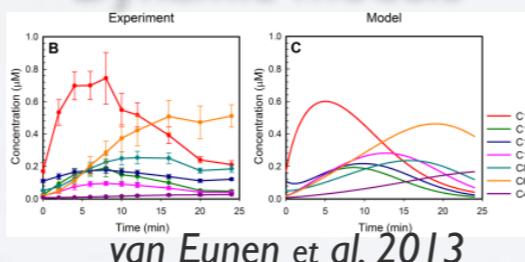


Better understanding of a biological process

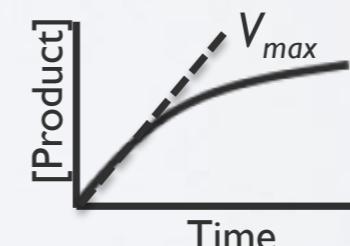
Targeted proteomics



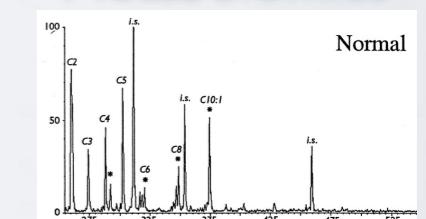
Dynamic models



Enzyme activity



Targeted
Metabolomics



Bottom-down

MODELLING APPROACHES (2)

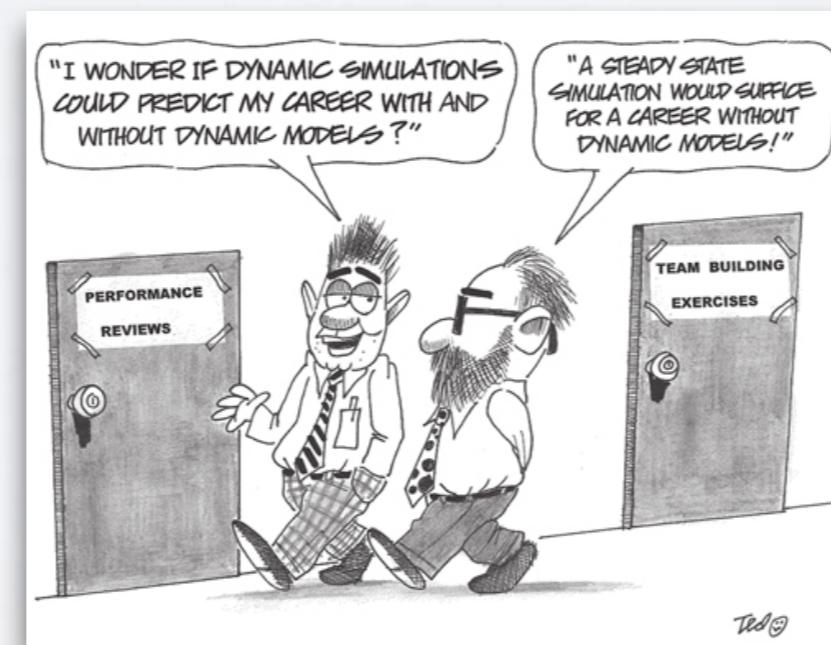
- Top-down
- Based on ‘omics’ data
- Steady-state flux distributions
- Qualitative
- Bottum-up
- Based on kinetic data
- Dynamics of fluxes and metabolites
- Quantitative

MODELLING APPROACHES (2)

- Top-down
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KINETIC MODELS

- Describe the dynamics of a biological network
- You need a realistic description of the kinetics of each step in the network
- Simulate how concentrations and rates in a network behave over time



WHAT DO WE NEED FOR MODEL SIMULATIONS?

- Variables and parameters
- Equations that describe the change / effect
- Initial state
- Time frame for the simulation

EQUATIONS

Differential Equations

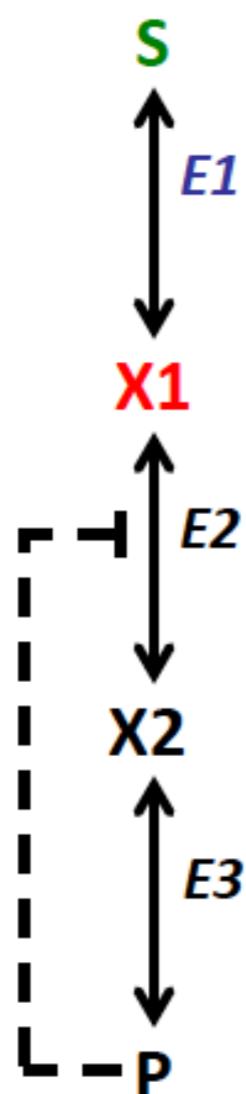
- Describe the change in concentration over time
- Ordinary Differential Equations (ODE) - only one independent variable (e.g. time)
- Partial Differential Equations (PDE) - more than one independent variable (e.g. time and space)

Rate Equations

- Linear - a change per unit time of a variable
- Non-Linear - more complicated function of the variable

CONSTRUCTION OF A KINETIC MODEL

Scheme



Ordinary Differential Equation of X1

$$\frac{dX_1}{dt} = v_{E1} - v_{E2}$$

Rate equation of E1 (Reversible Michaelis-Menten)

$$v_{E1} = \frac{V_{+max} \cdot \frac{S}{K_{MS}} - V_{-max} \cdot \frac{X_1}{K_{MX1}}}{1 + \frac{S}{K_{MS}} + \frac{X_1}{K_{MX1}}}$$

PARAMETERS

- Can be derived from the rate equations
- Can be derived from literature or from experiments

```
MyParms <- c(  
  V+max = 3.6  
  Kms = 0.01  
  V-max = 0.3  
  KmxI = 100)
```



INITIAL STATE AND TIME FRAME

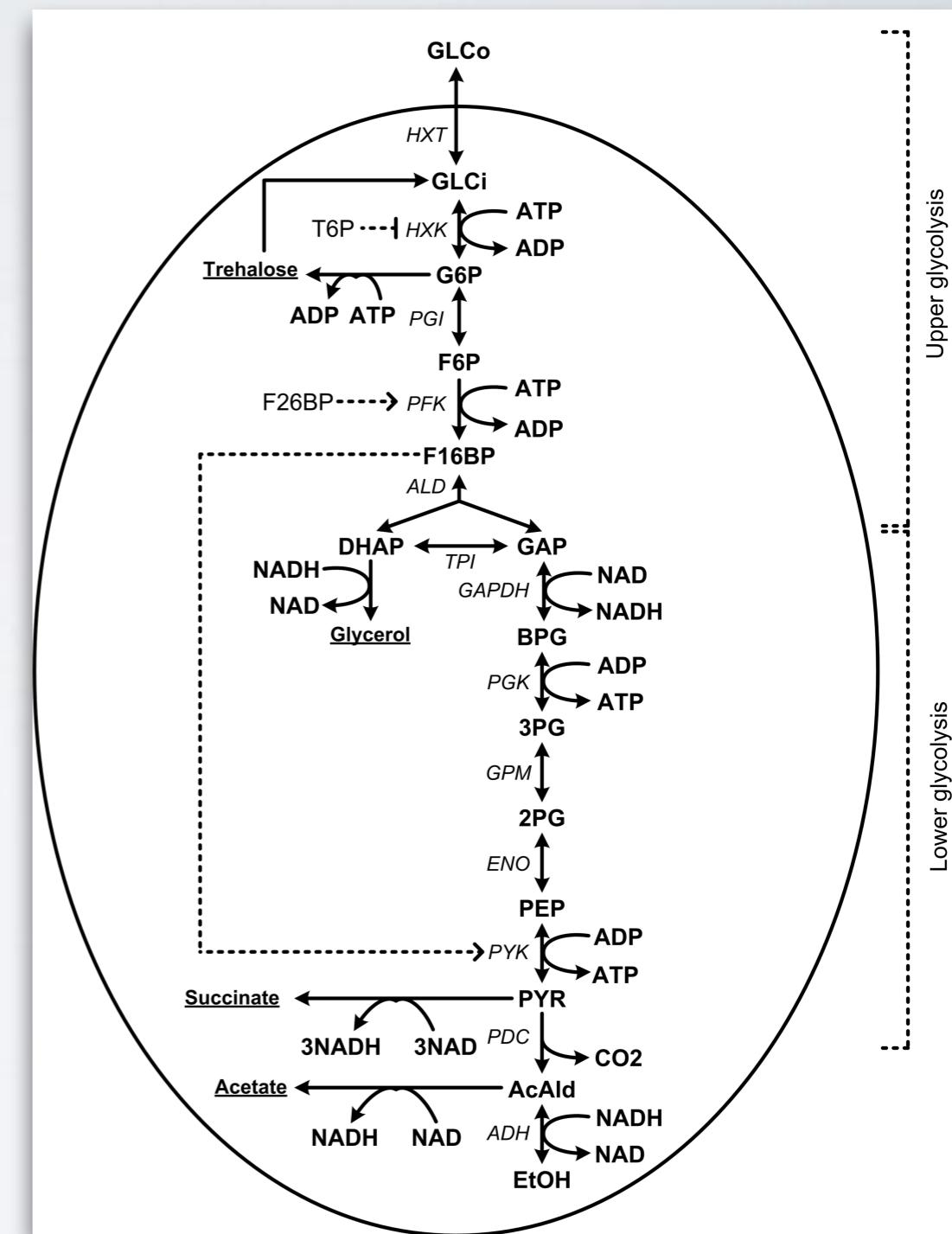
- Start values and simulation time determine the simulation range

```
xstart <- c(S = 5, P = 1)  
times <- seq(0, 24, by = 1)
```

- With the initial state, the time frame, the parameters and the equations we can now run the simulations

EXAMPLE

FULL-SCALE KINETIC MODEL OF YEAST GLYCOLYSIS (I)



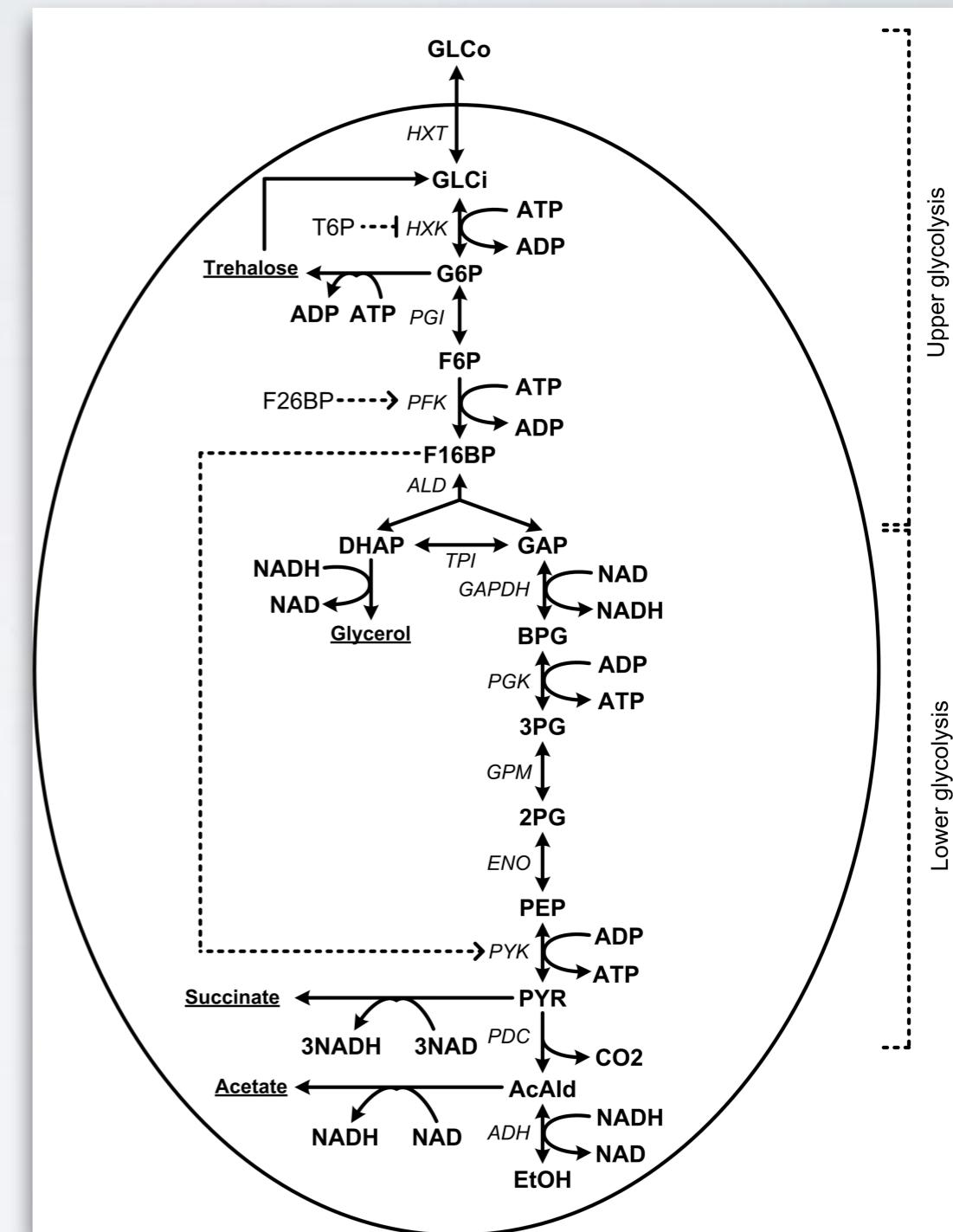
FULL-SCALE KINETIC MODEL OF YEAST GLYCOLYSIS (2)

ODEs

$$\frac{dGLCi}{dt} = v_{HXT} - v_{HXK}$$

$$\frac{dG6P}{dt} = v_{HXK} - v_{PGI} - v_{\text{to trehalose}}$$

.....



FULL-SCALE KINETIC MODEL OF YEAST GLYCOLYSIS (3)

ODEs

$$\frac{dGLCi}{dt} = v_{HXT} - v_{HXK}$$

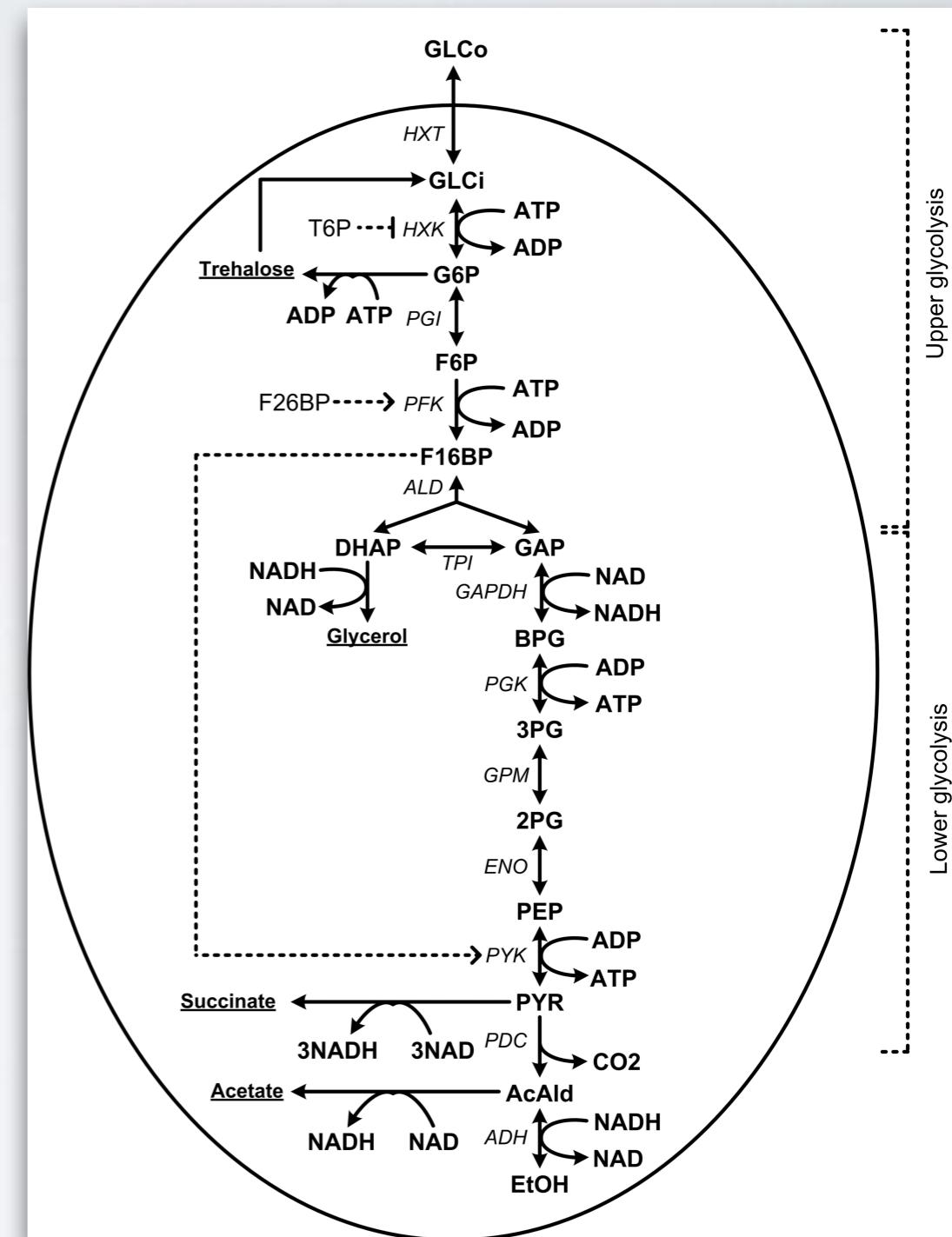
$$\frac{dG6P}{dt} = v_{HXK} - v_{PGI} - v_{\text{to trehalose}}$$

.....

Rate equations

$$v_{HXK} = \frac{V_{max} \cdot \left(\frac{GLCi}{K_{mGLCi}} \cdot \frac{ATP}{K_{mATP}} - \frac{G6P \cdot ADP}{K_{mGLCi} \cdot K_{mATP} \cdot K_{eq}} \right)}{\left(1 + \frac{GLCi}{K_{mGLCi}} + \frac{G6P}{K_{mG6P}} + \frac{T6P}{K_{mT6P}} \right) \cdot \left(1 + \frac{ATP}{K_{mATP}} + \frac{ADP}{K_{mADP}} \right)}$$

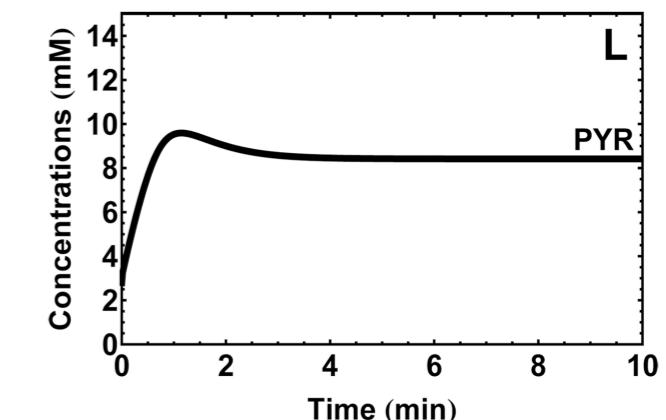
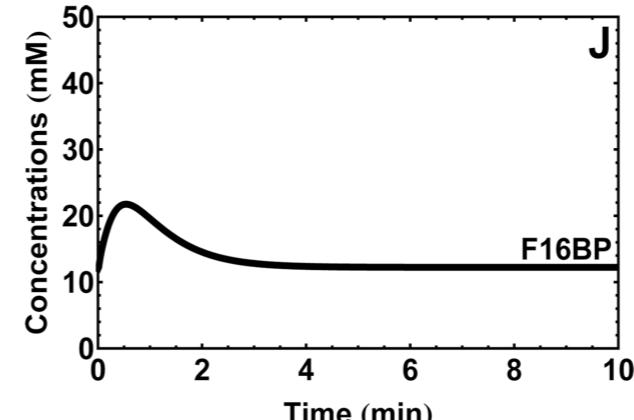
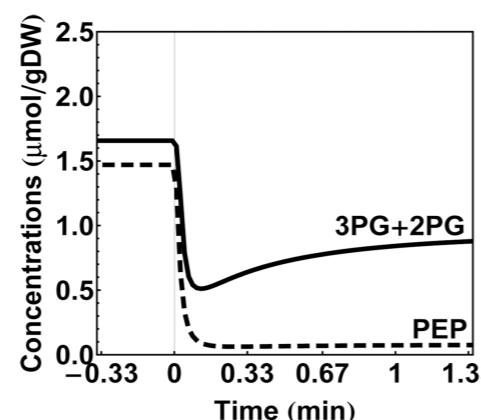
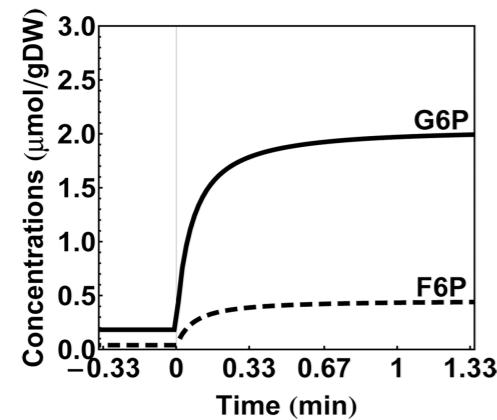
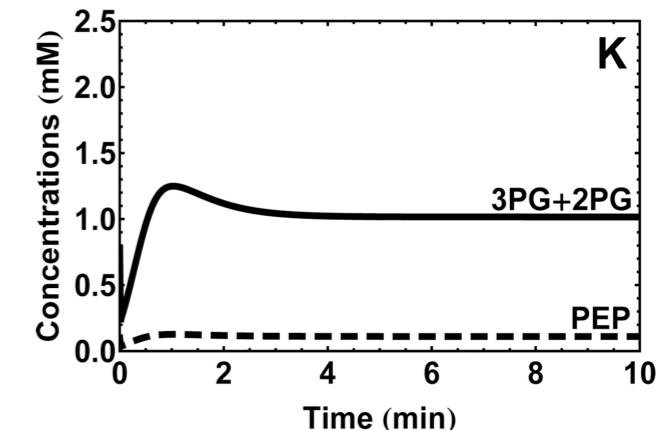
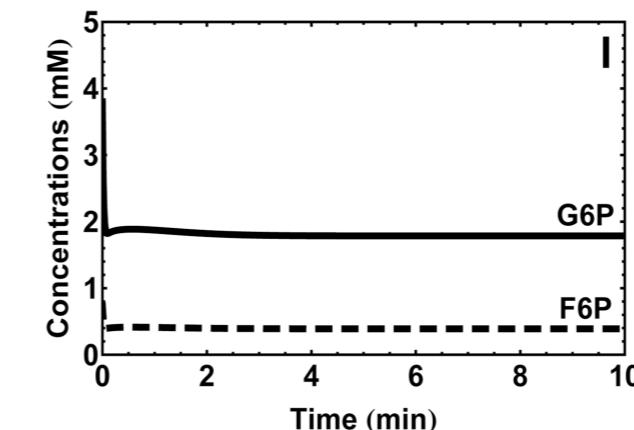
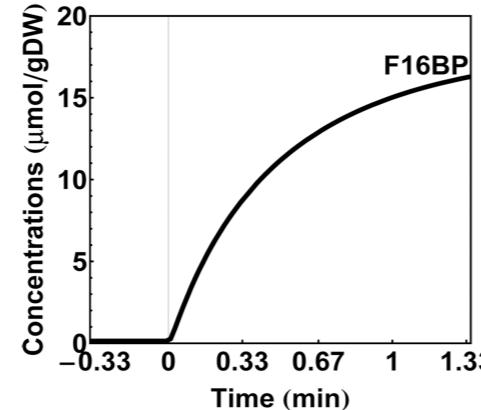
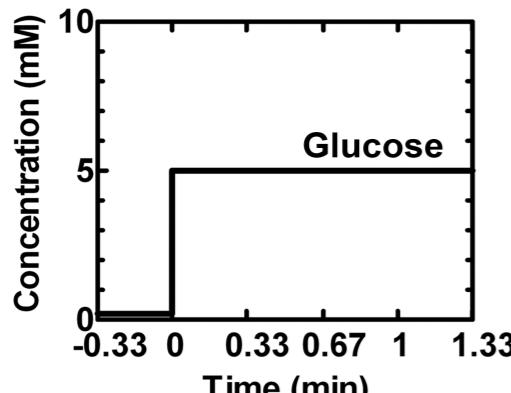
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PATHWAY BEHAVIOUR

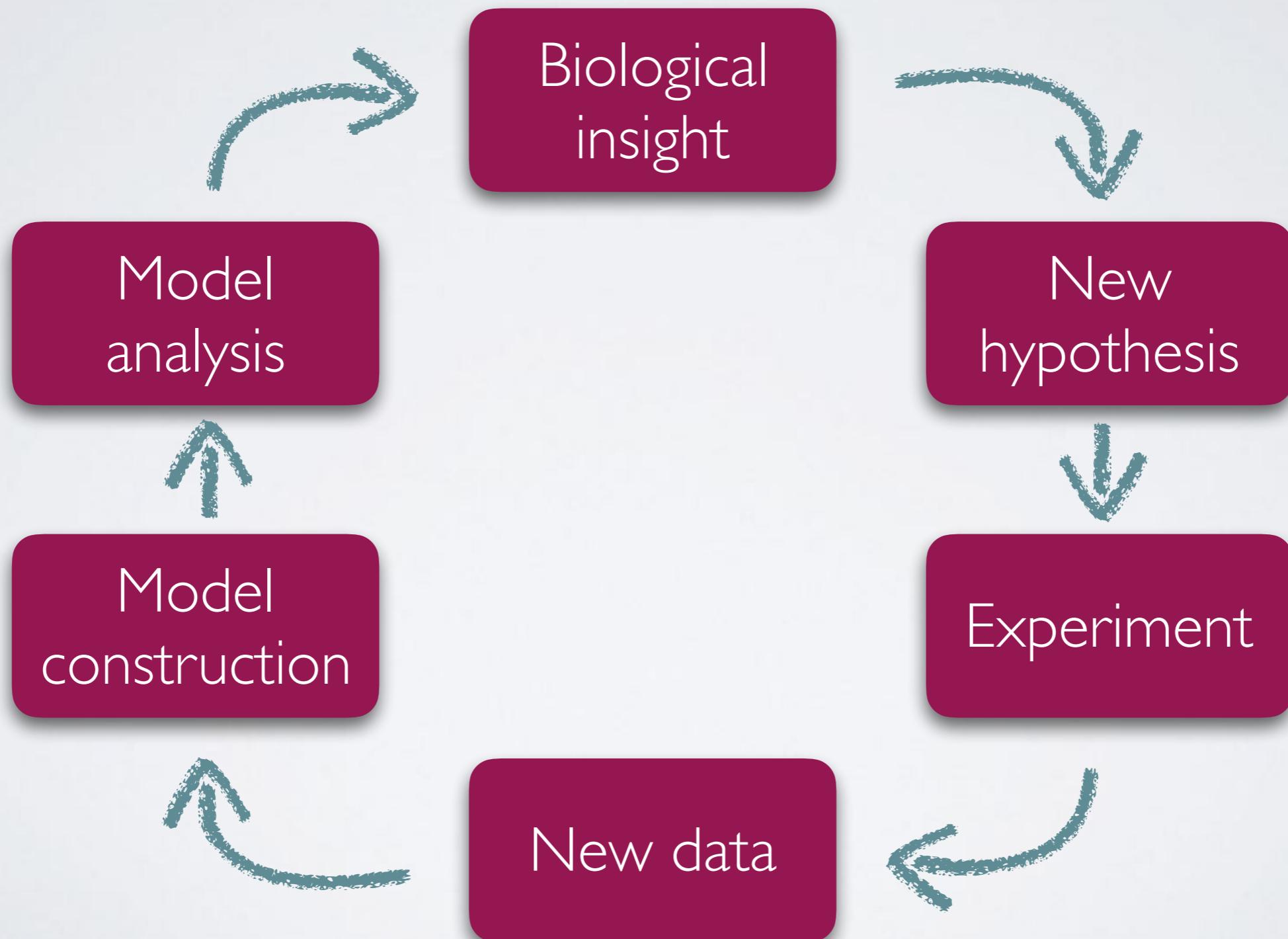
Dynamic...

...and steady state



$$\frac{dF6P}{dt} = v_{PGI} - v_{PFK} = 0$$

SYSTEMS BIOLOGY CYCLE



DETERMINE THE MODEL COMPONENTS

It is fundamental to understand:

- Units
- Equilibrium or steady-state conditions
- Assumptions
- Mass-action interaction
- Constraints on variables and parameters
- Meaning of parameters
- Initial conditions

ANALYSING THE MODEL

- Simulations - need to know initial conditions and parameter values
- Graphical analysis
- Verbal interpretation of the results
- Sensitivity analysis - effect of changes in parameter values
- Long-term or asymptotic behaviour
- Does the model match the experimental data?
- Prediction of new scenarios; perturbations of the system
- Testing predictions

ABOUT THIS THEME

- First we will experiment with change and stability models
- Then we will experiment with deSolve in R
- You will construct assignments with deSolve in R
- Finally you will reproduce a paper with deSolve