Data Based Modelling and Model Based Experimentation

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Outline

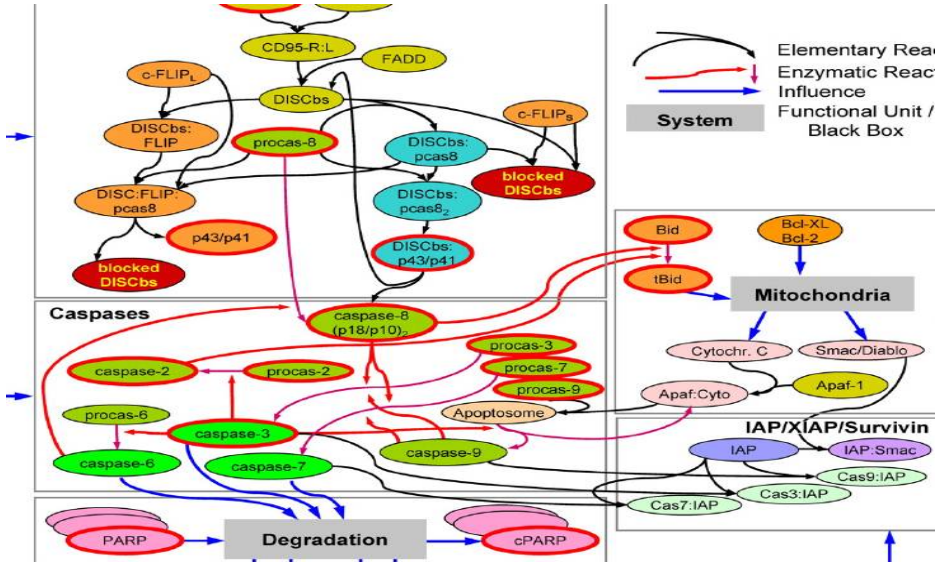
- Part I: Conceptual (this talk)
- Part II: Biological examples (Ursula)
- Part III: Tutorial (Thomas & Marcel)

Outline

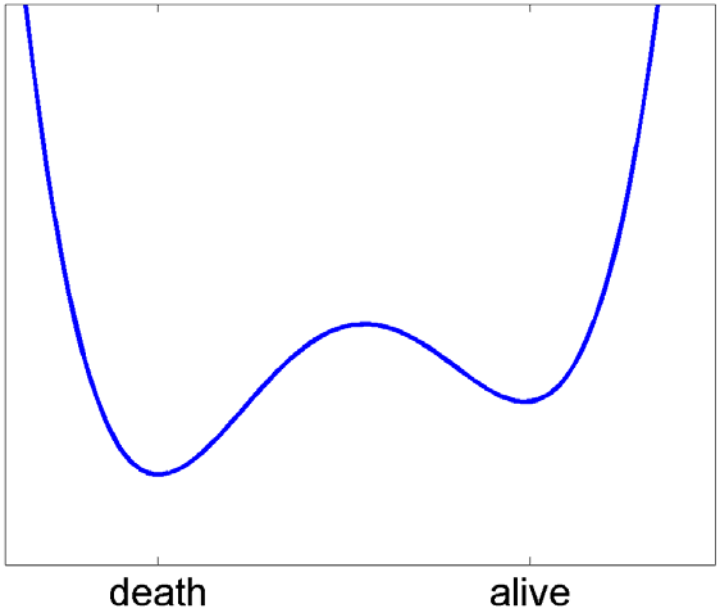
- System’s Behavior
- Looking back to 1952
- Data based modelling ...
- ... Model based experimentation

Examples of Networks I: Apoptosis

Pathway cartoon



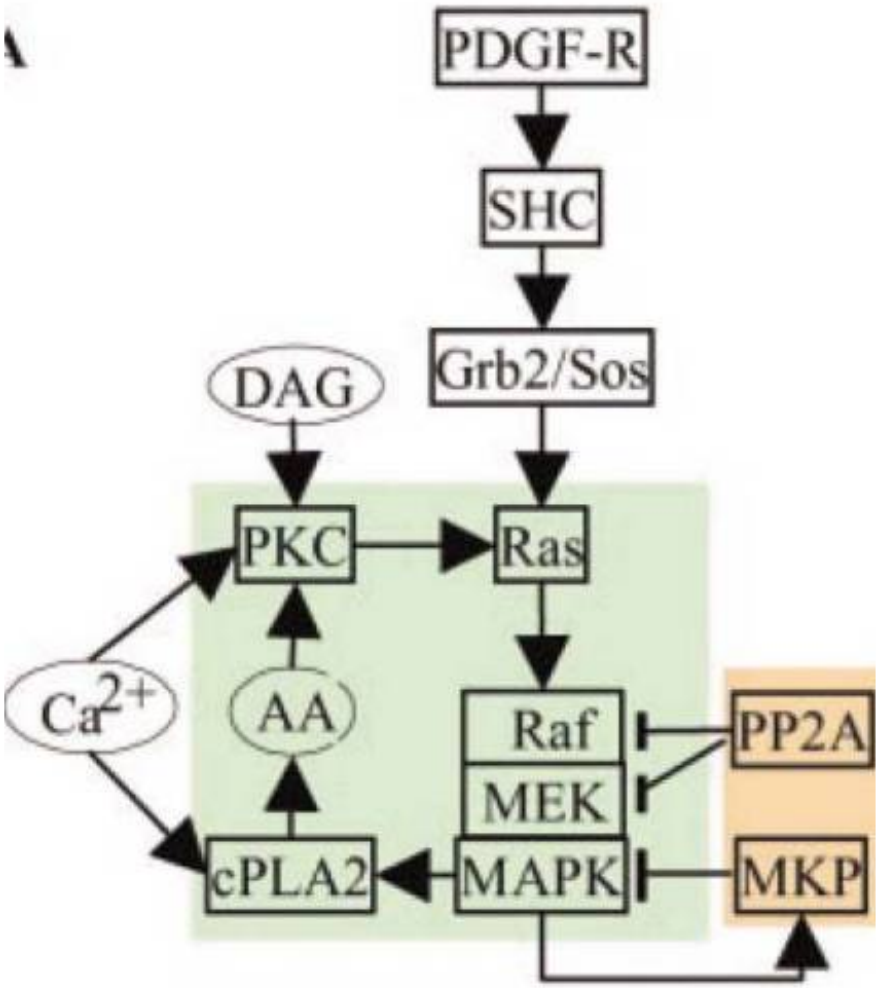
Systems' behavior



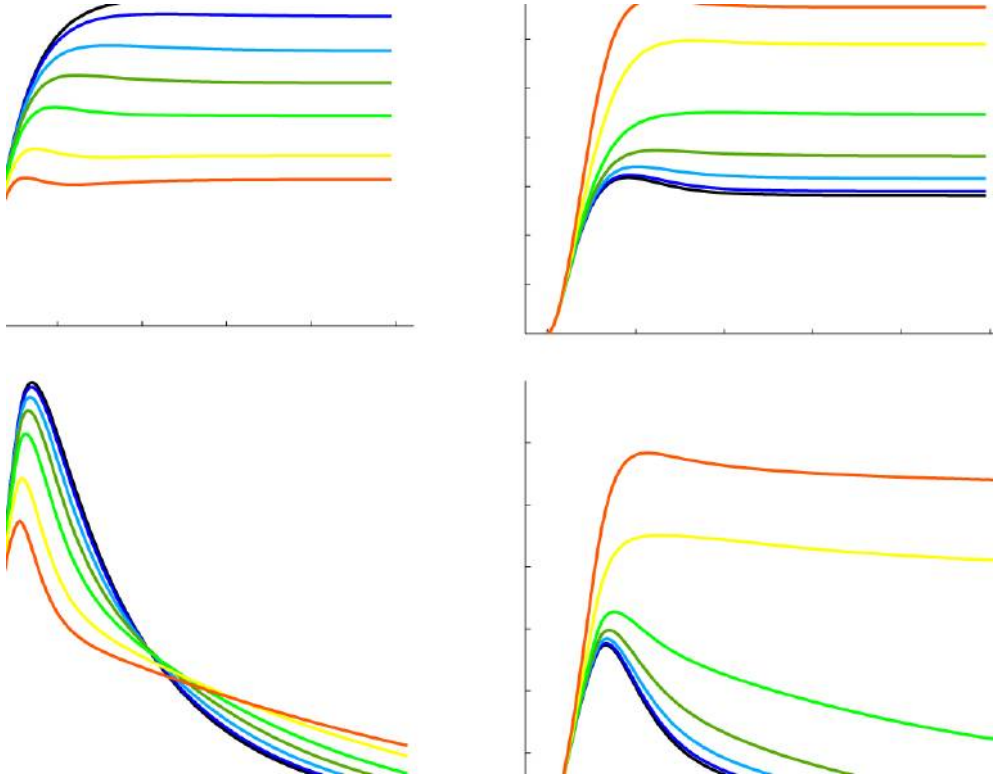
Threshold behavior, bistable

Example of Networks II: MAP Kinase

Pathway cartoon



System's behavior



Time scales/ parameters important

The Promises of Mathematics

- Make assumptions explicit
- Understand essential properties, failing models
- Condense information, handle complexity
- Understand role of dynamical processes, e.g. feed-back
- Impossible experiments become possible
- Prediction and control
- Understand what is known
- Discover general principles
- “You don’t understand it until you can model it”

Looking back to 1952

Two cornerstones:

- A. Turing. The chemical basis of morphogenesis.
  Phil. Trans. Roy. 237, 37-72, 1952

  Pure mathematical derivation of the conditions for pattern generation

  More biologically: A. Gierer & H. Meinhardt. A theory of biological pattern formation. Kybernetik 12, 30-39, 1972

- A.L. Hodgkin, A.F. Huxley.
  A quantitative description of ion currents and its application to conduction and excitation in nerve membranes. J. Physiol. 117, 500-544, 1952

Closest to data development of a mathematical model for nerve excitation

Data based modelling

- Translate cartoon to (differential) equations
- Measure protein dynamics
- Estimate parameters in equations
- Test the mathematical model
- Validation: Predict outcome of new experiment
- Use the model: Identify potential drug targets

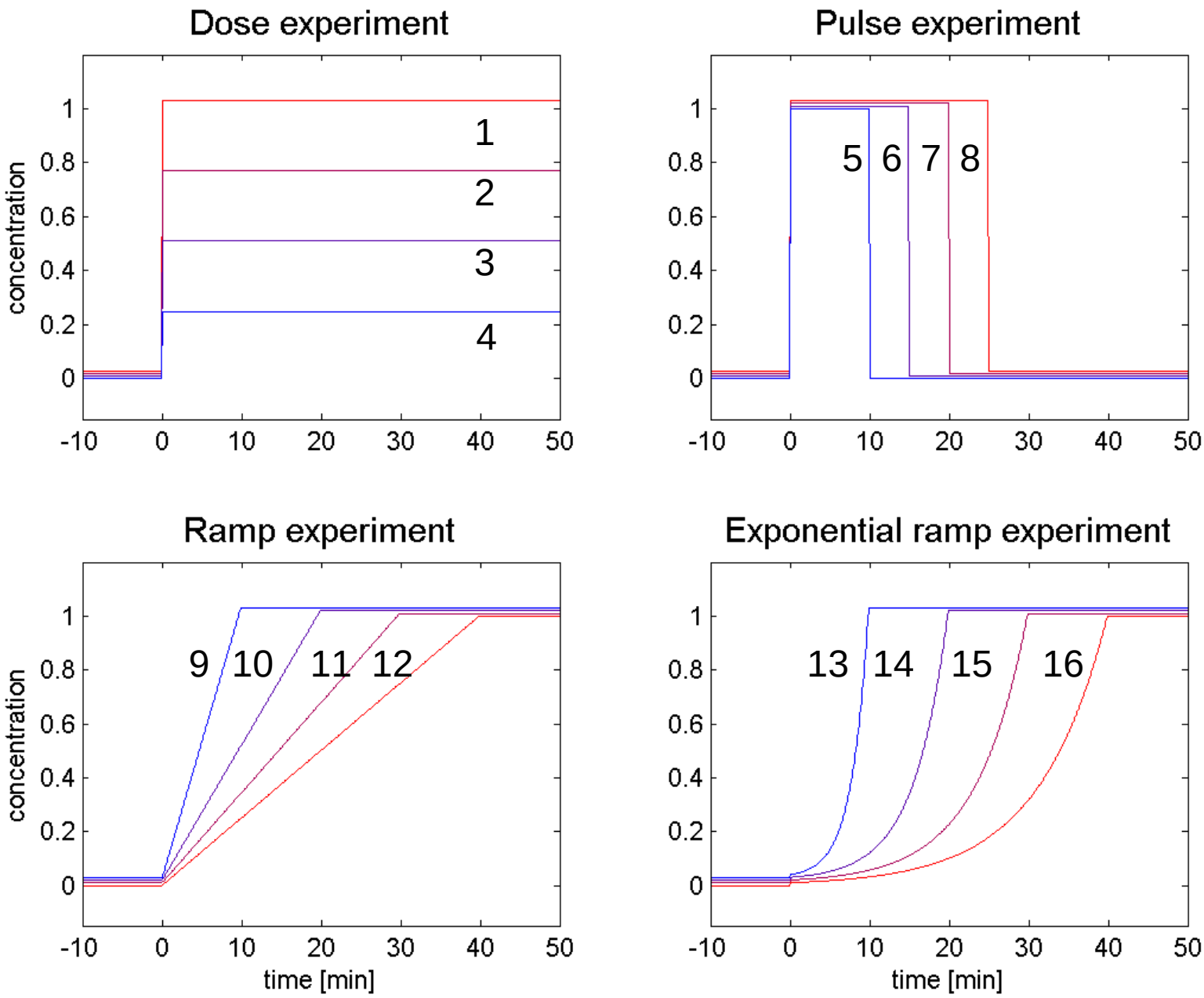
Model based experimentation

- Goal:

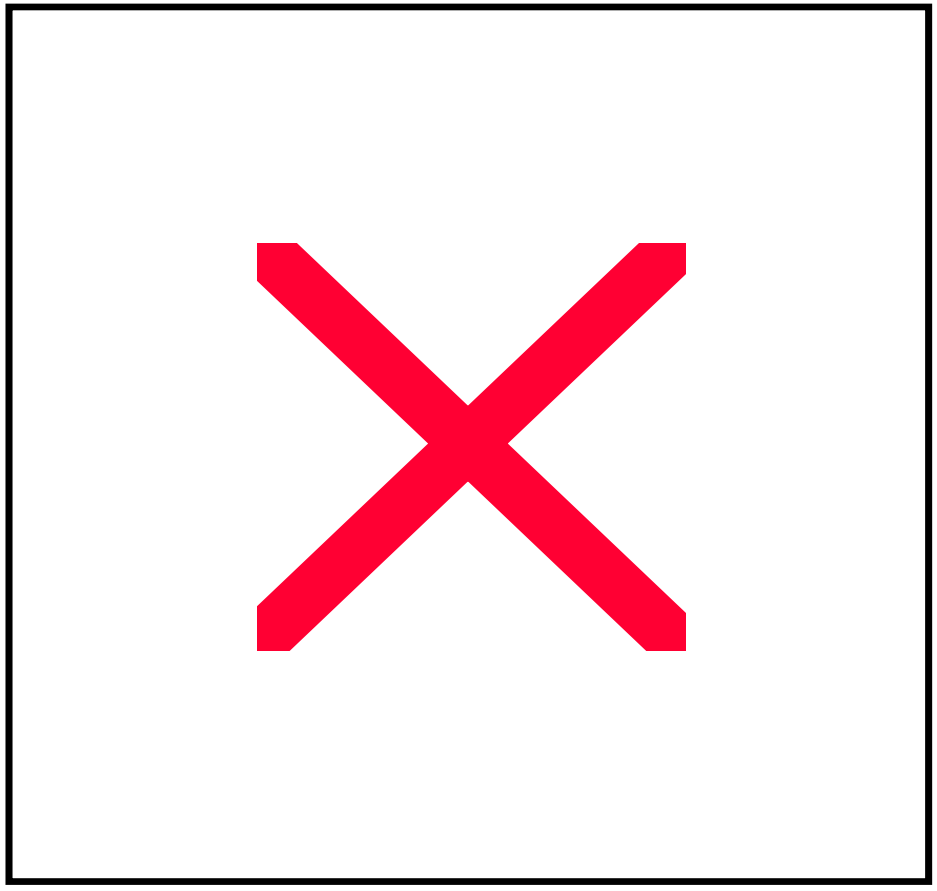
  Obtain maximum information with minimum effort

- Two directions:
  - Parameter estimation
  - Competing biological hypotheses: Model selection
- What to measure ?
- When to measure ?
- Type of stimulation ?

Possible stimuli

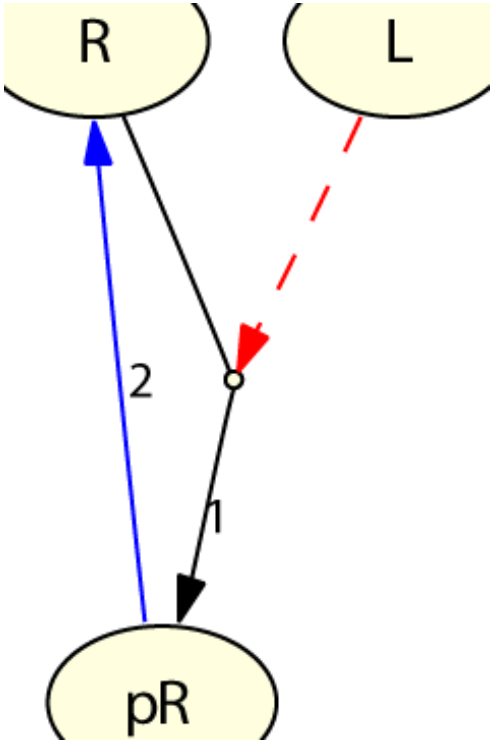


Receptor Deactivation

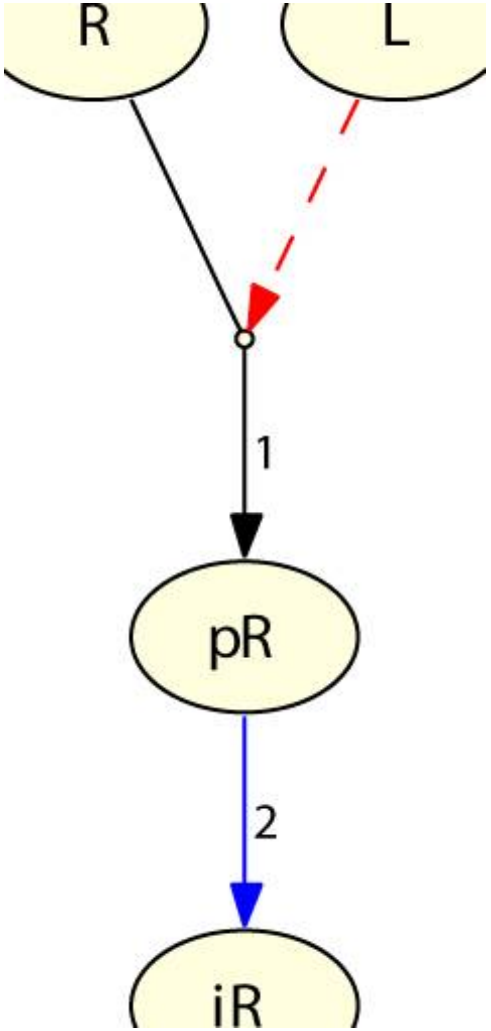


Receptor kinetics: 3 alternatives

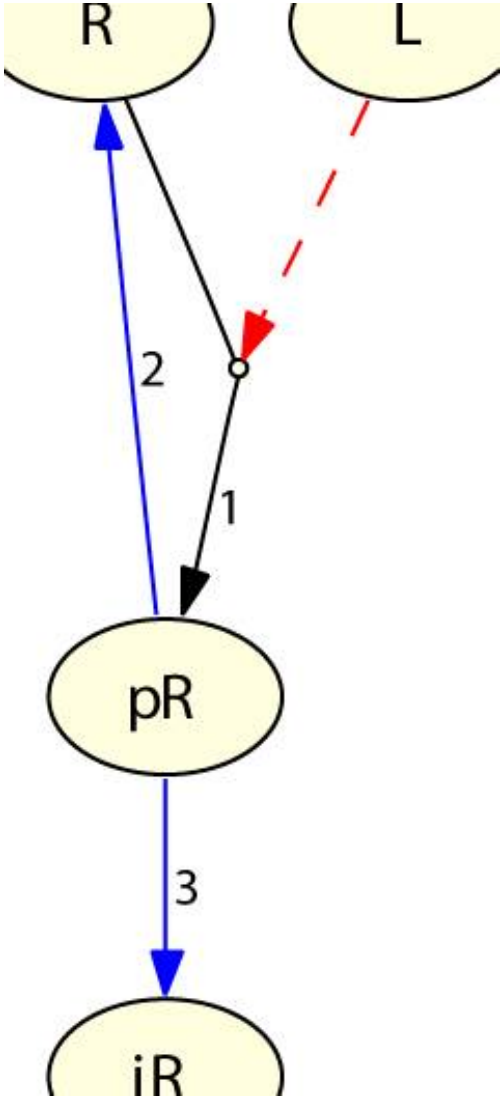
M1



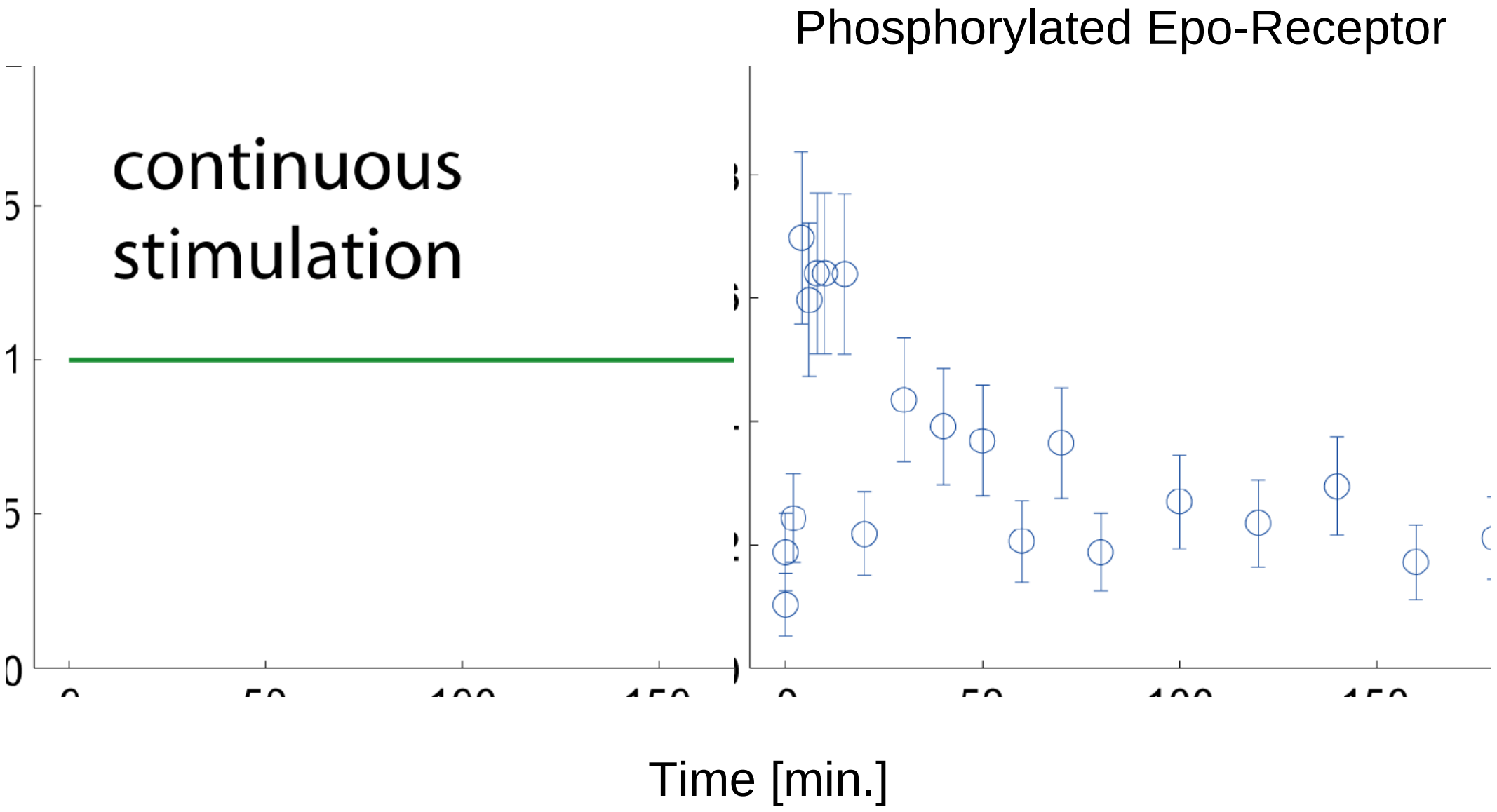
M2



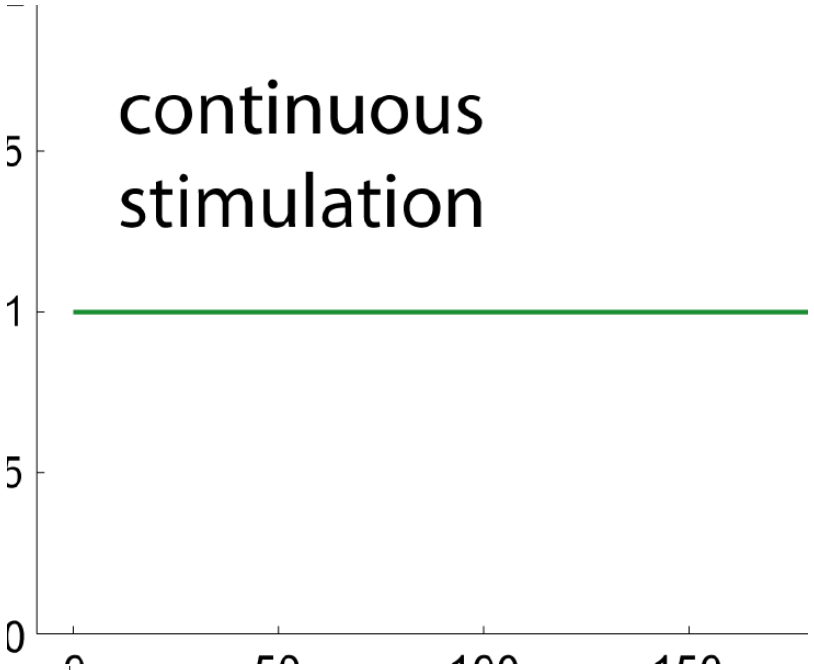
M3

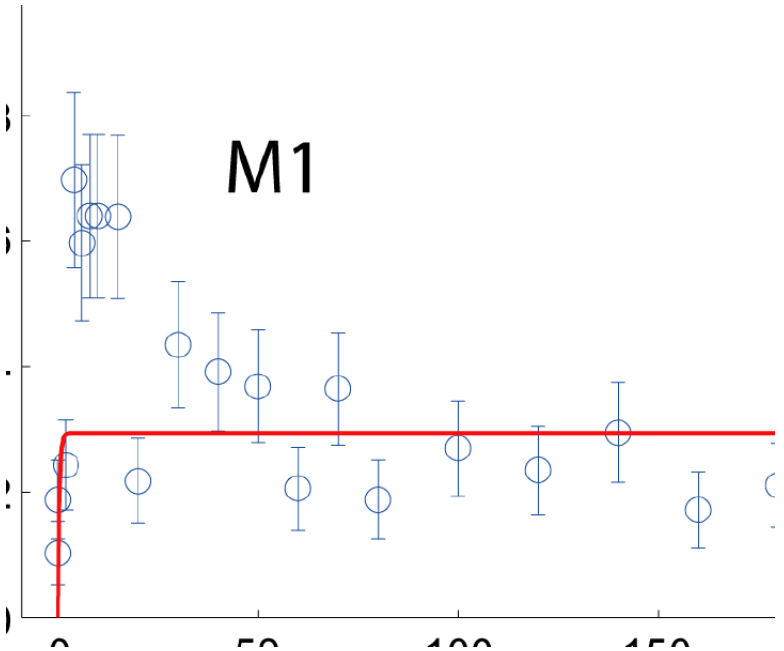


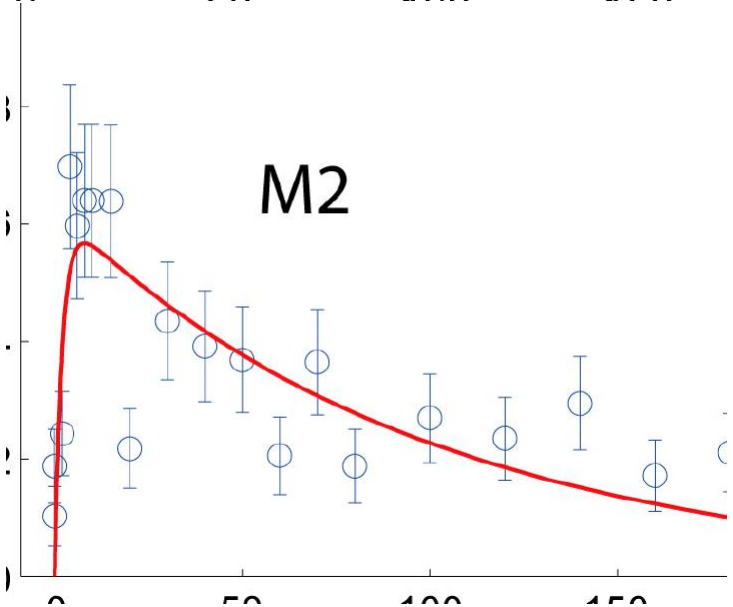
Experiment 1

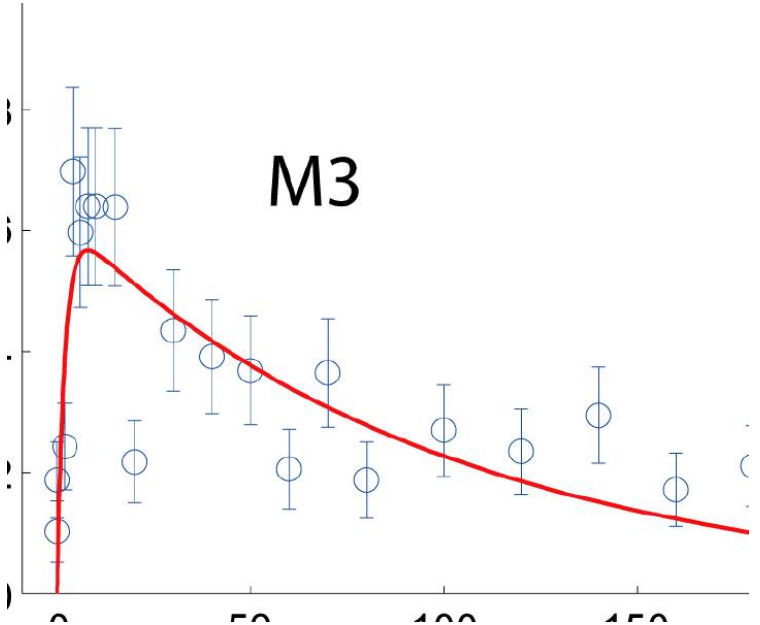


Fits

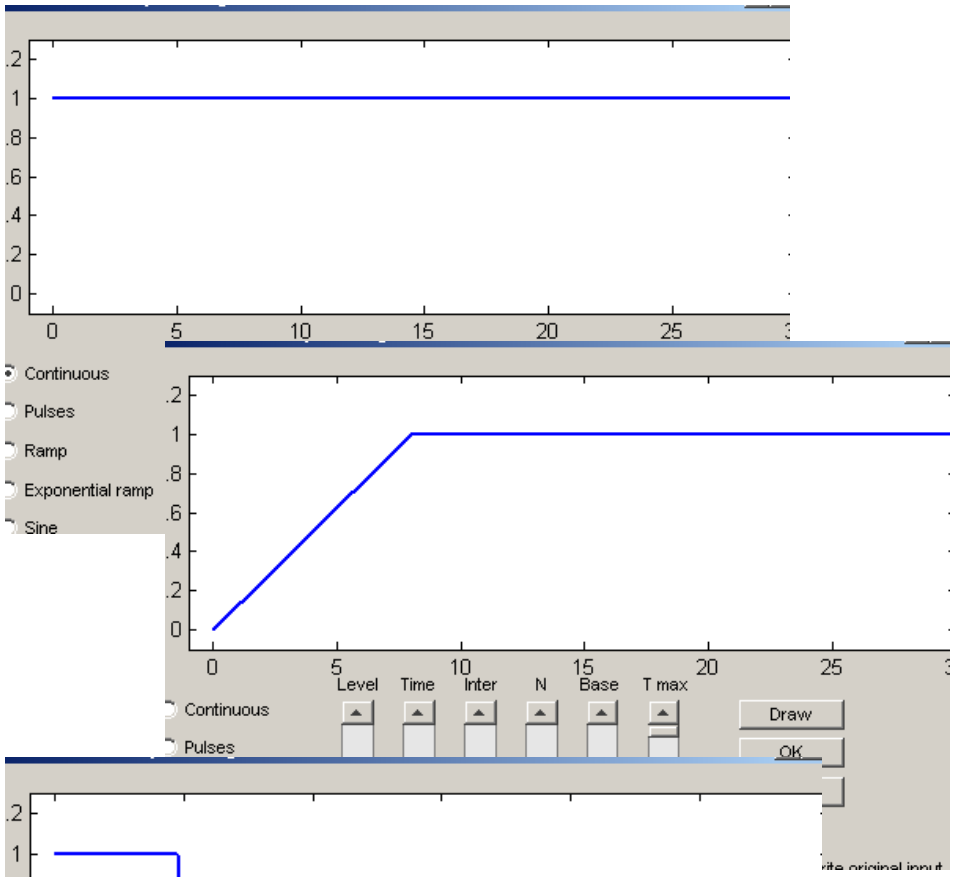


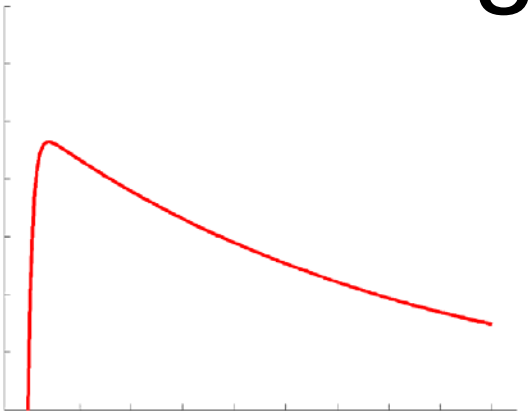


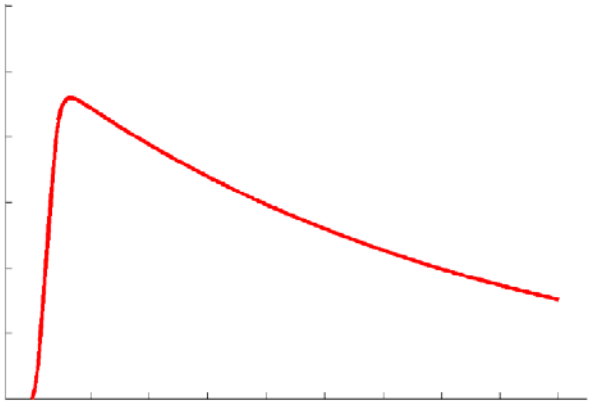


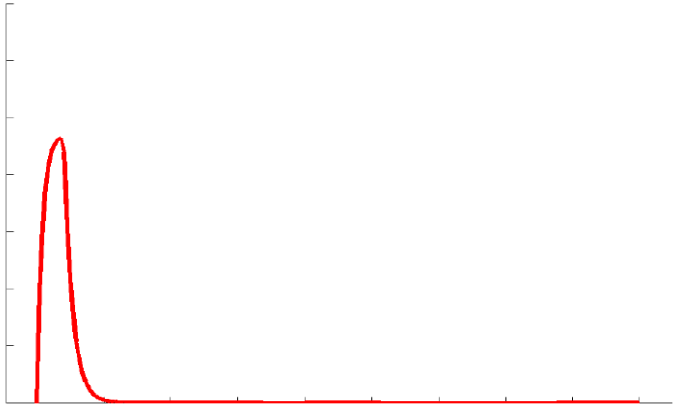


Experimental Design

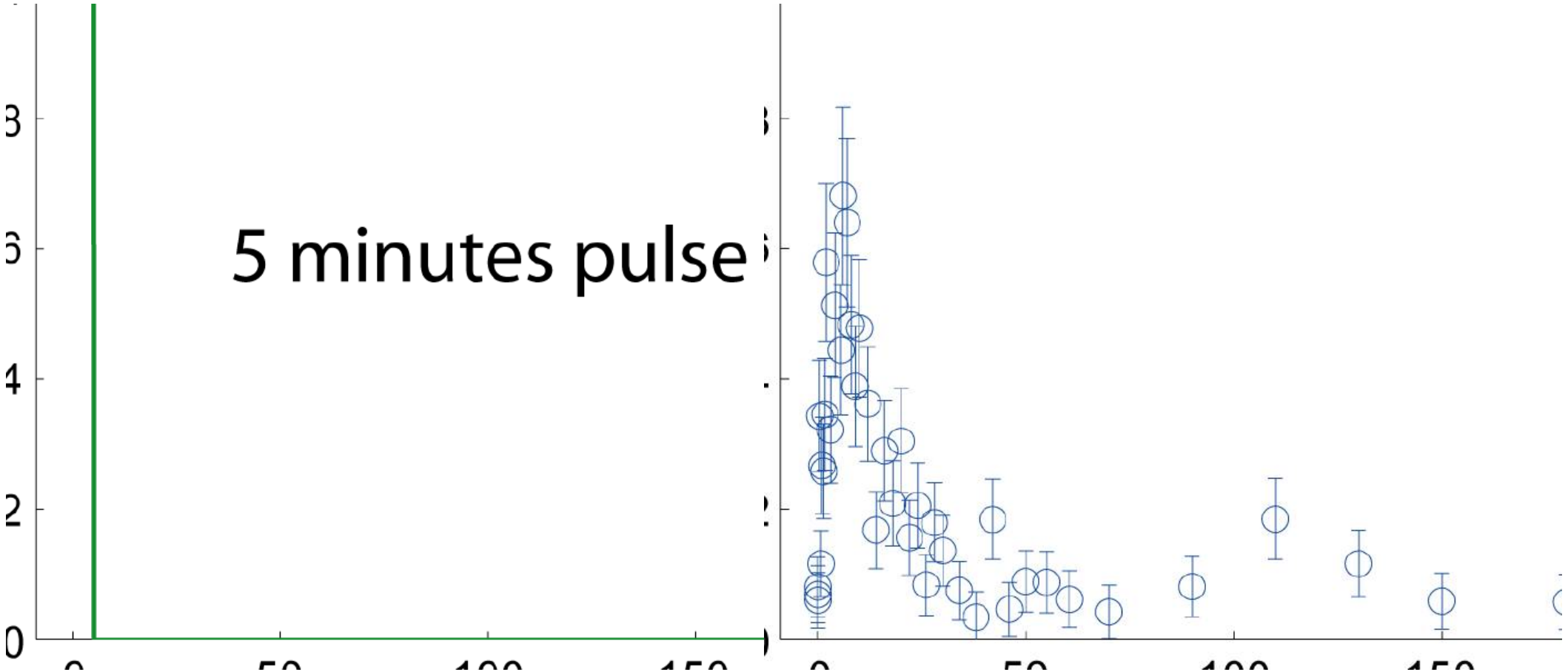




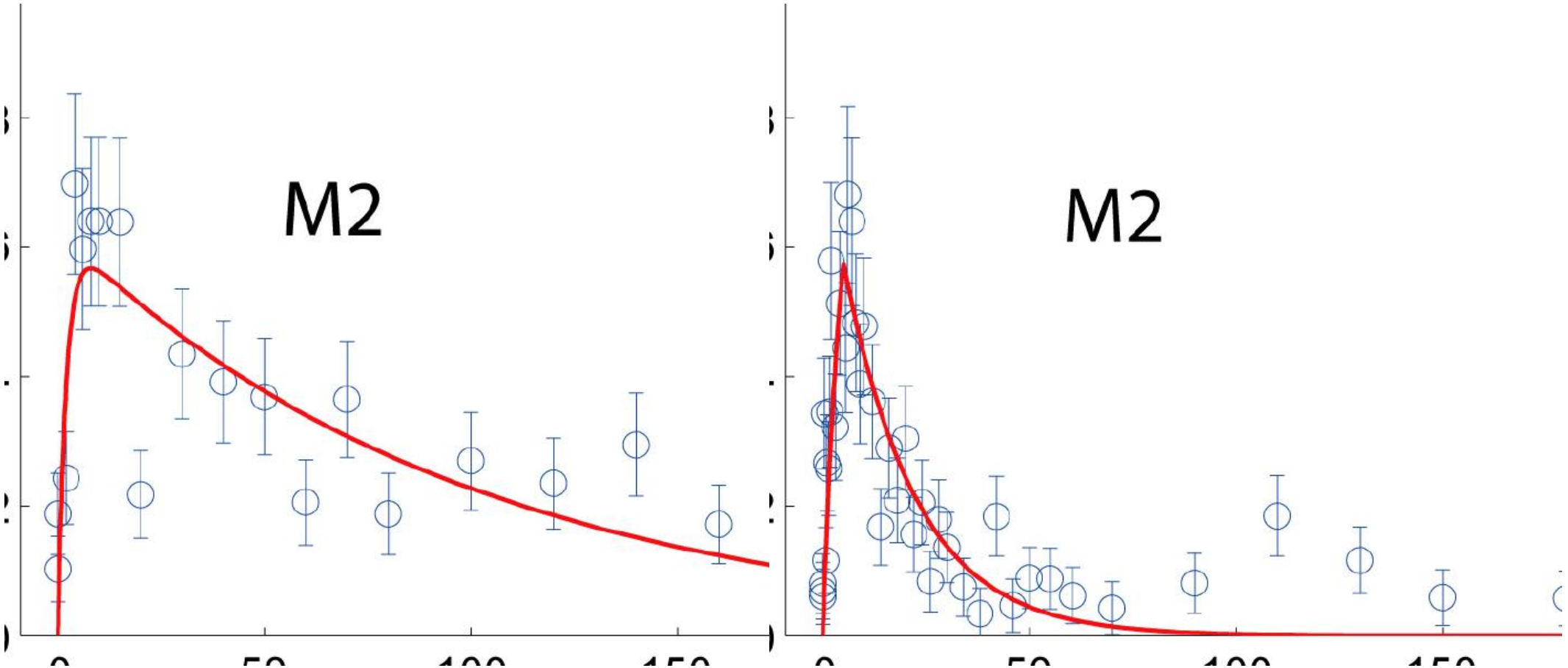




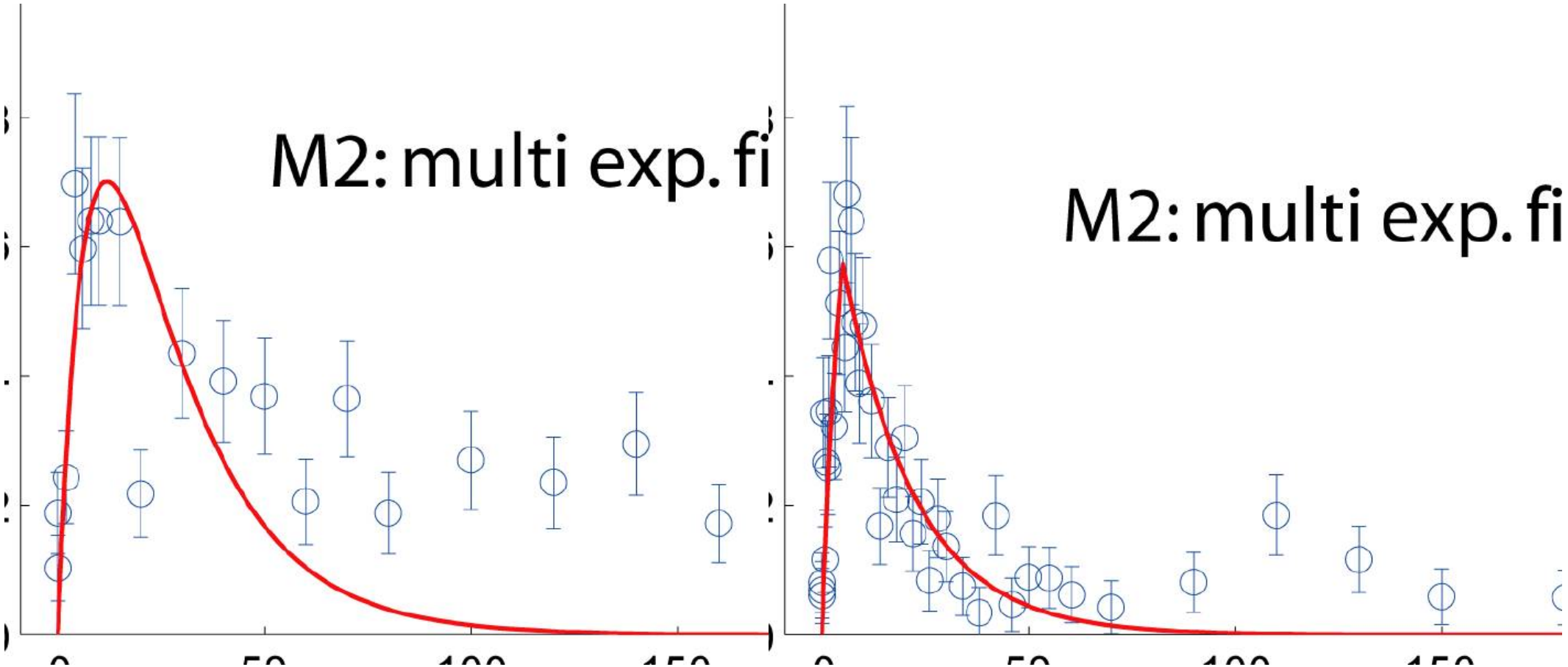
Experiment 2



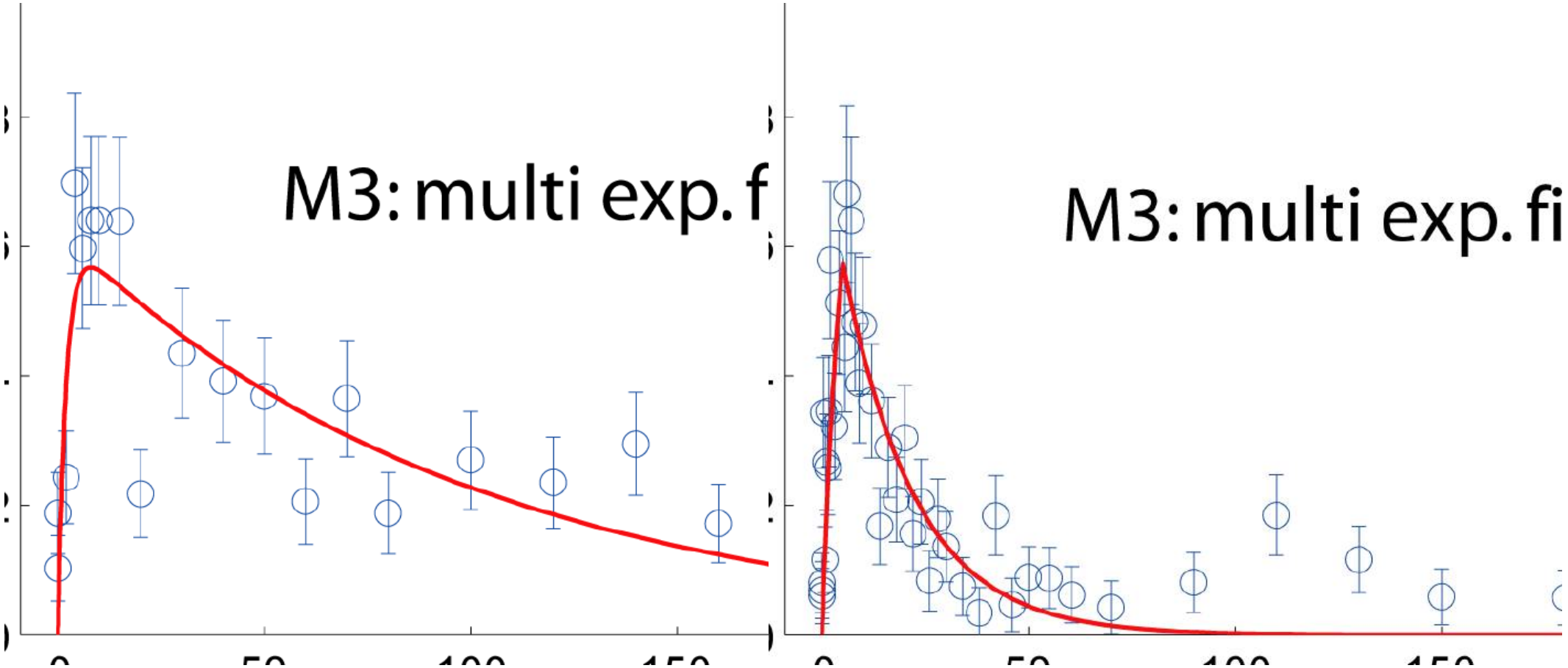
Separate fits



Multi-experiment fit



Multi-experiment fit



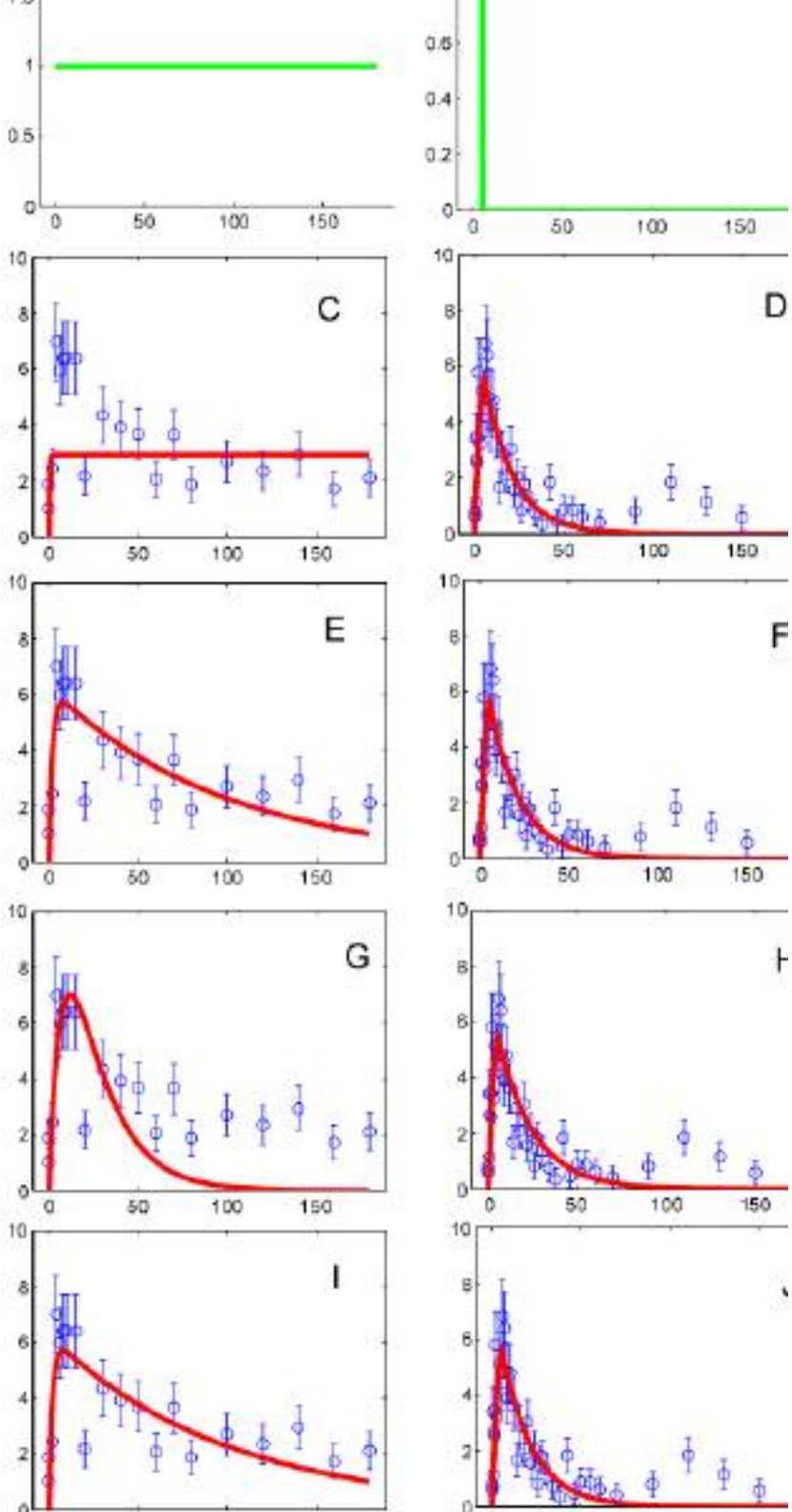
Stimuli: Continuous and pulsed

M1 fitted separately
to both data sets

M2 fitted separately

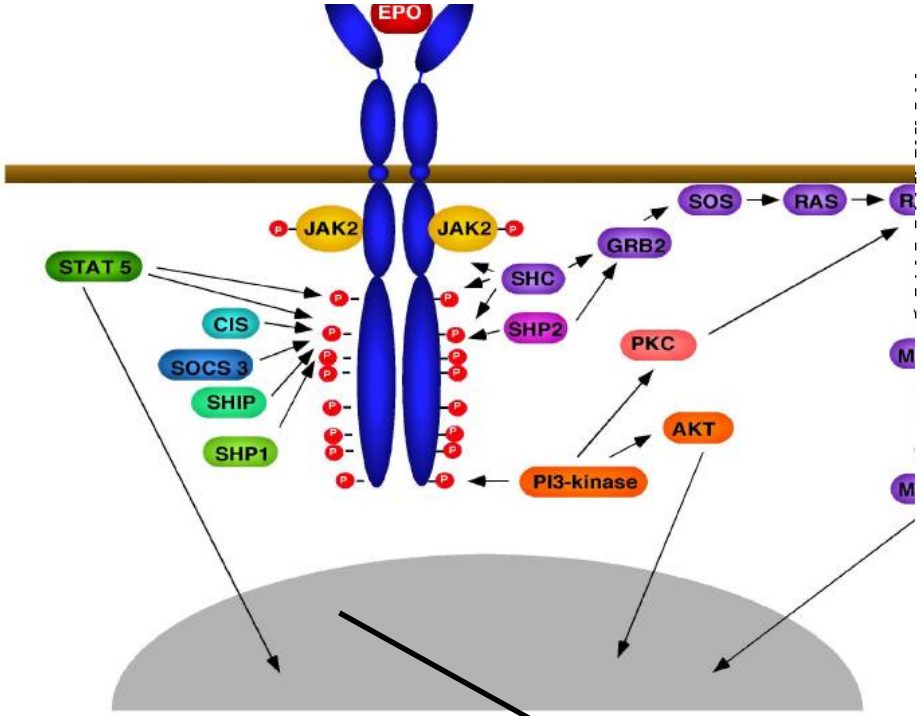
M2 fitted simultaneously

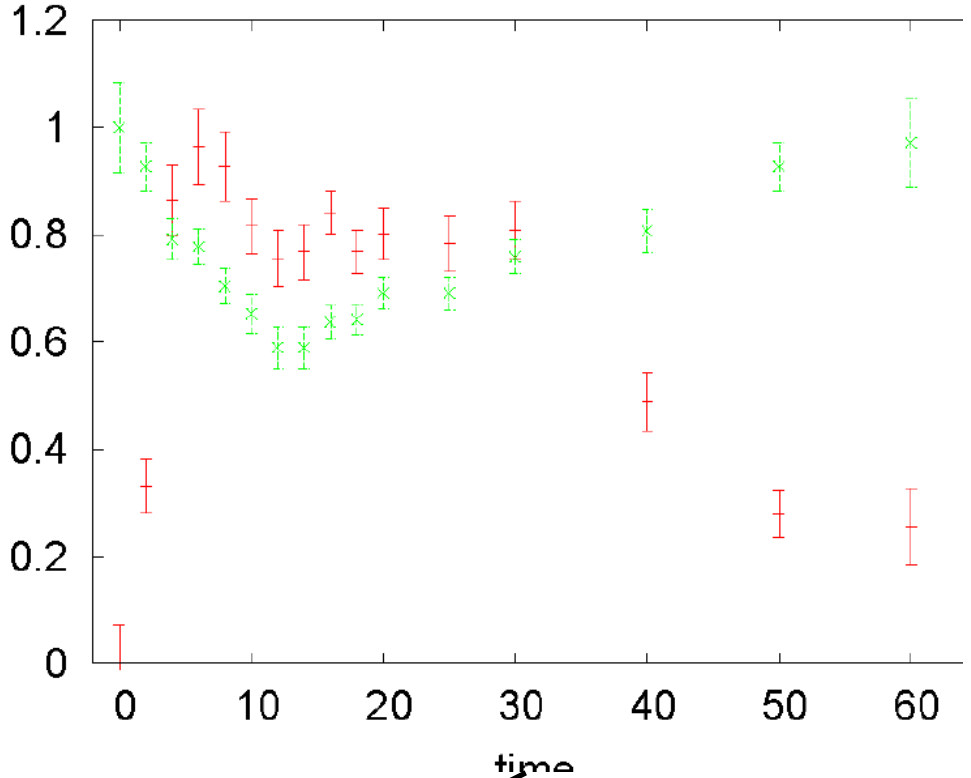
M3 fitted simultaneously

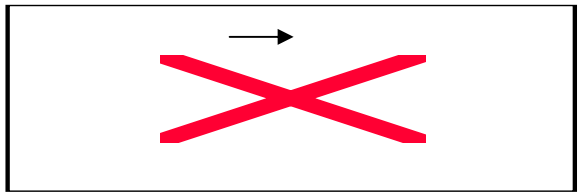


Now: The wet-lab side

10:20 Tutorial PottersWheel







In silico biology

Test the prior knowledge

Understanding systems' properties

Identification of potential drug targets

Experimental design

- Given: laboratory constraints
  - Set of observable players
  - Noise level
- Goal: Optimal experimental setup
  - Sampling time points
  - Combination of stimuli