

What does it mean?

- Does it mean anything at all?
 - What do you want to know?
 - Do you know what you have measured?
 - Data: enough, good quality, reproducible?

What do you want to know?

- When is my reaction finished?
- What are the optimum conditions for my reaction?
- What is the mechanism of my reaction?

What have you measured?

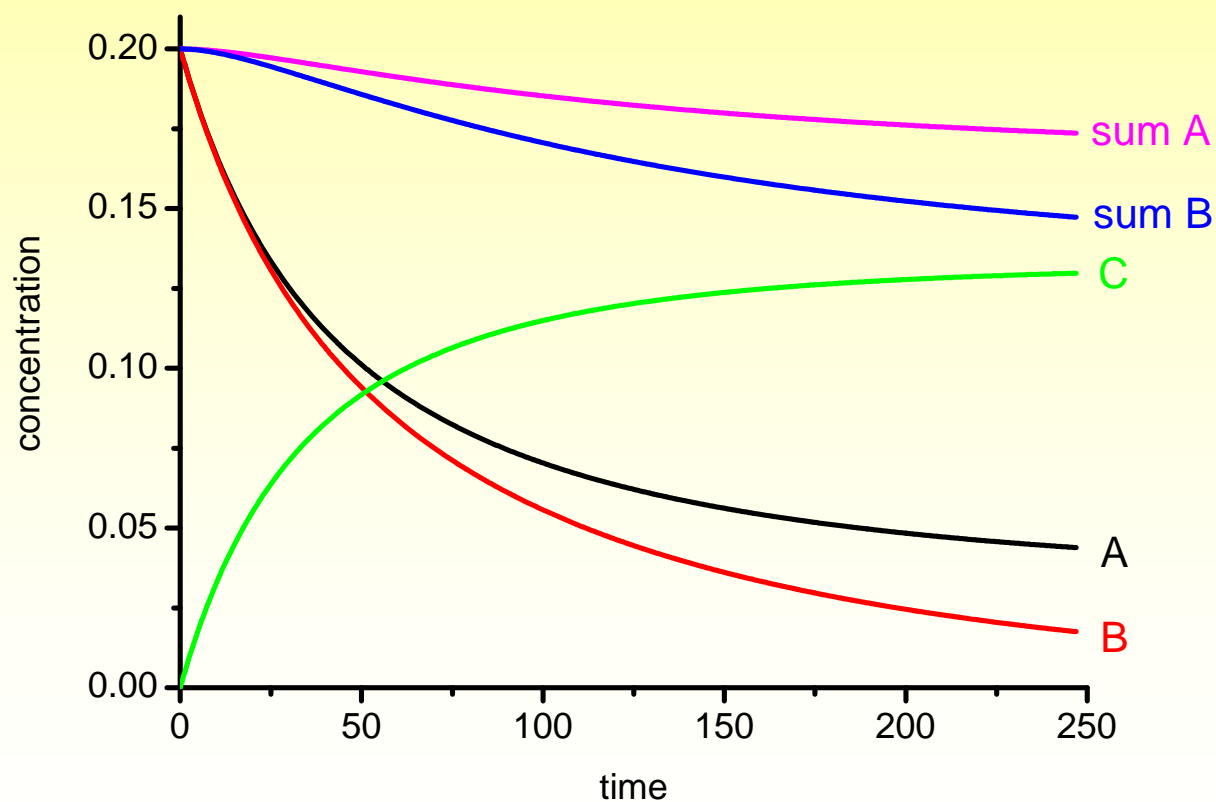
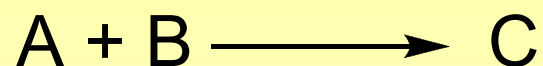
- “Raw” signals
 - NMR integrals, HPLC peak areas, UV-visible absorptions
- Concentrations
 - Calculated using response factors, e.g.: extinction coefficient, HPLC calibration graph
- Reactant, product or intermediate? Sure?

Enough, quality, reproducible?

- How long did you follow the reaction for?
- How sure are you of the numbers you have ($\pm 5\%$ $\pm 10\%$, right ballpark?)
- When you tried it again, was the data essentially the same?

Sum check

Measured concentrations? Is everything there?

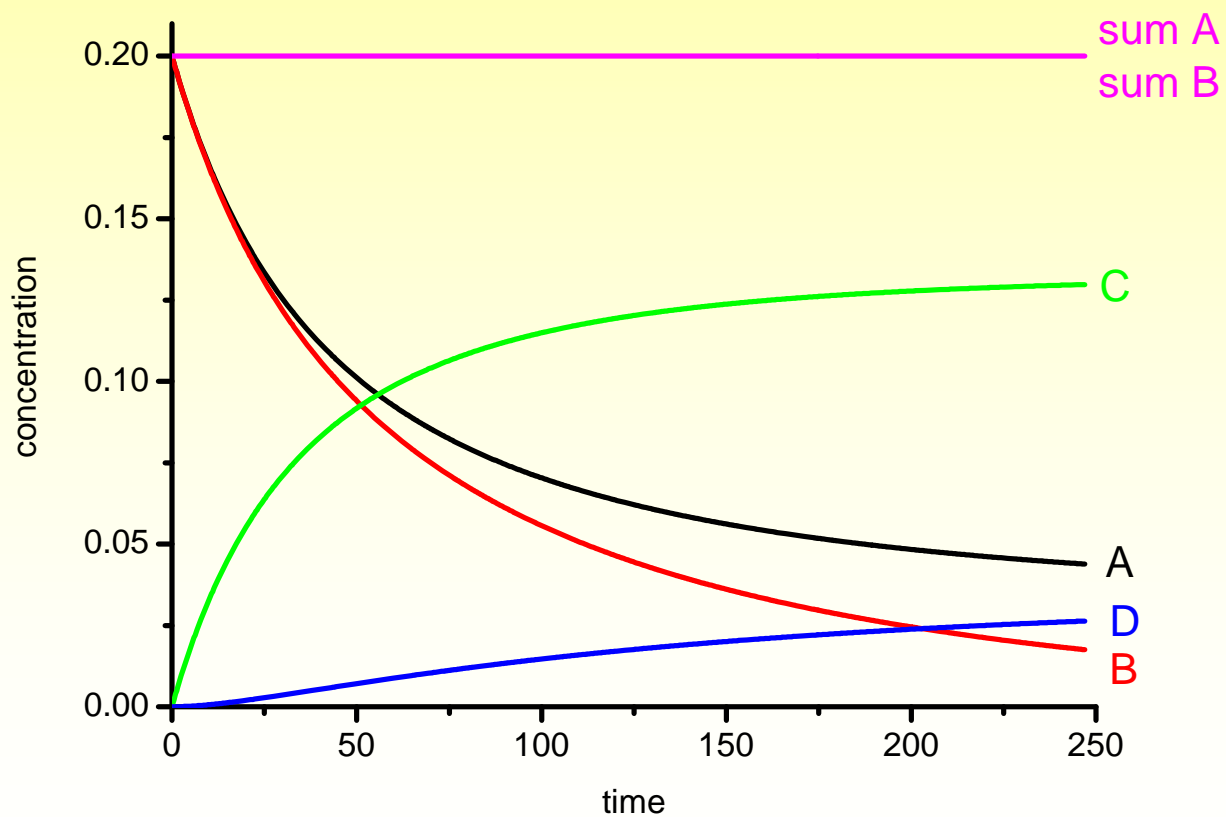
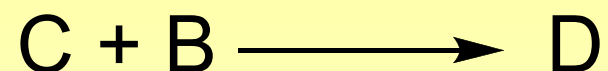
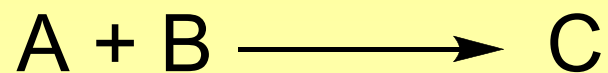


$$\begin{aligned} [A]_0 &= 0.2\text{ M} \\ [B]_0 &= 0.2\text{ M} \\ [C]_0 &= 0.2\text{ M} \end{aligned}$$

NJB

note: simulated data

Sum check



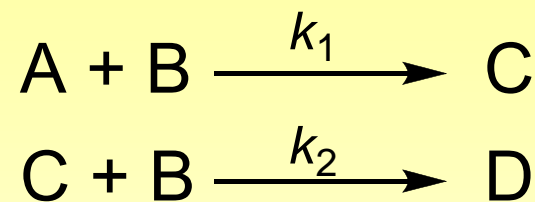
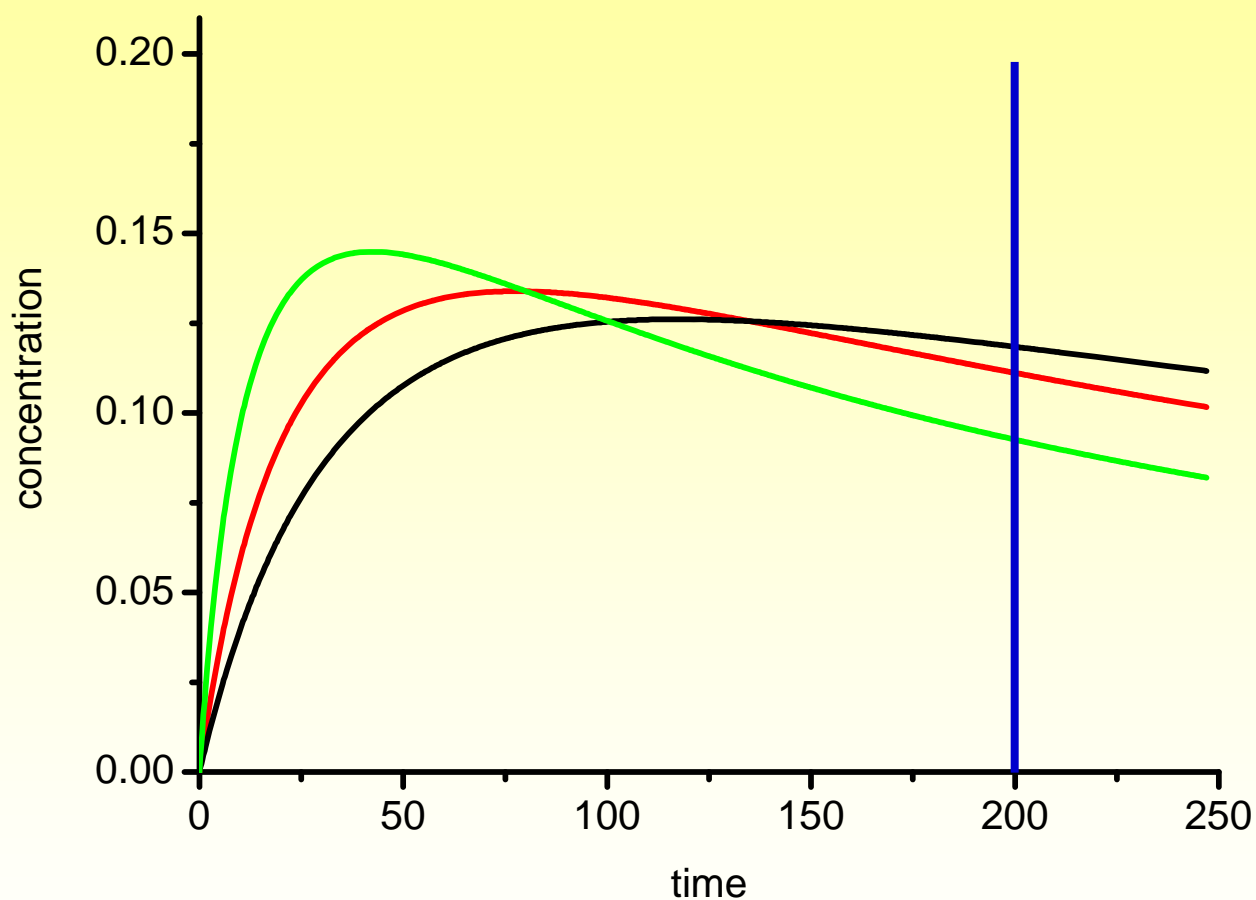
$$[A]_0 = 0.2 \text{ M}$$

$$[B]_0 = 0.2 \text{ M}$$

$$[C]_0 = 0.2 \text{ M}$$

Book keeping has
already taught us
something!

Intermezzo 1



$$[A]_o = 0.2 \text{ M}$$

$$[B]_o = 0.4 \text{ M}$$

$$[C]_o = 0.2 \text{ M}$$

These curves
(even without rate
constants) tell us
far more than
yields after 200
minutes

$$k_1=0.21 \text{ M s}^{-1}; k_2=0.03 \text{ M s}^{-1}$$

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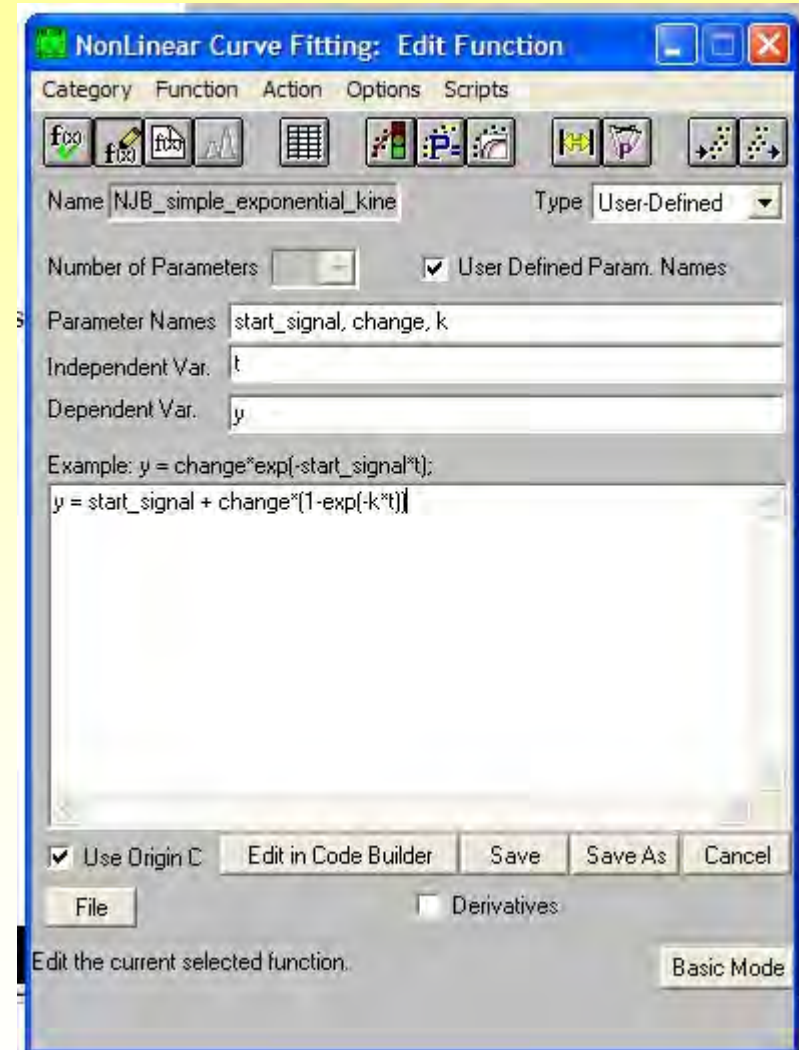
Curve fitting

data can be linearised

typical curve fitting software can fit directly to integrated rate law

convenient form:

$$\text{signal} = \text{signal}_0 + \Delta\text{signal} \cdot (1 - e^{-k \cdot t})$$



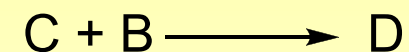
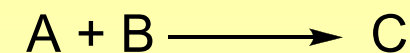
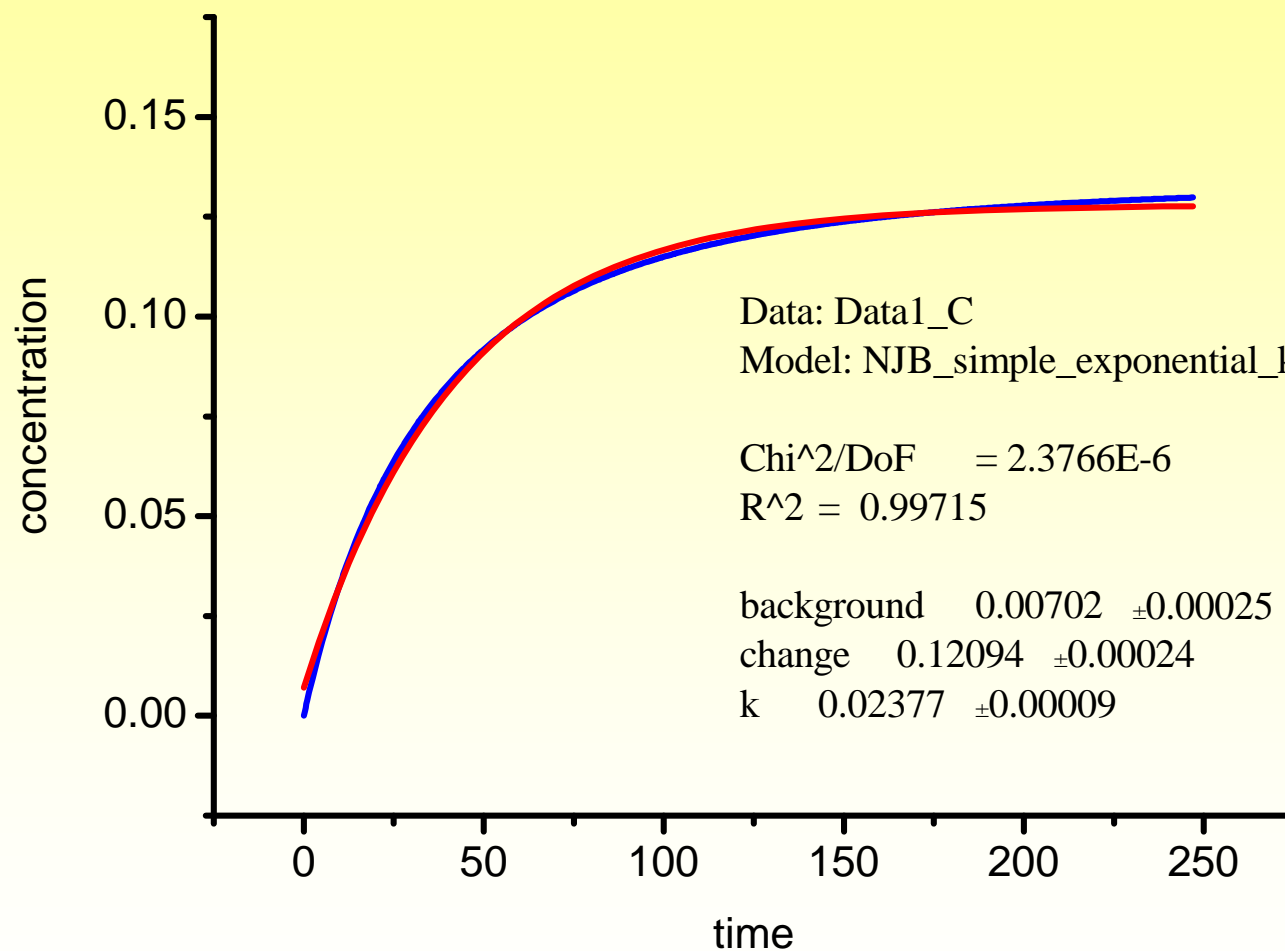
Curve fitting

$$signal = signal_0 + \Delta signal \cdot (1 - e^{-k \cdot t})$$

The *only* reason why this form of the equation describing simple exponential kinetics is convenient is because it allows users to estimate good initial guesses for the parameter values by looking at the graph.

Note that the “business end” of the equation has a term $\Delta signal$. This can be *any* type of signal (including actual concentrations) as long as it is linear with the concentration of the species of interest.

Is my reaction first order?

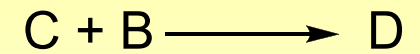
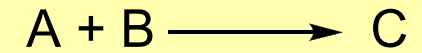
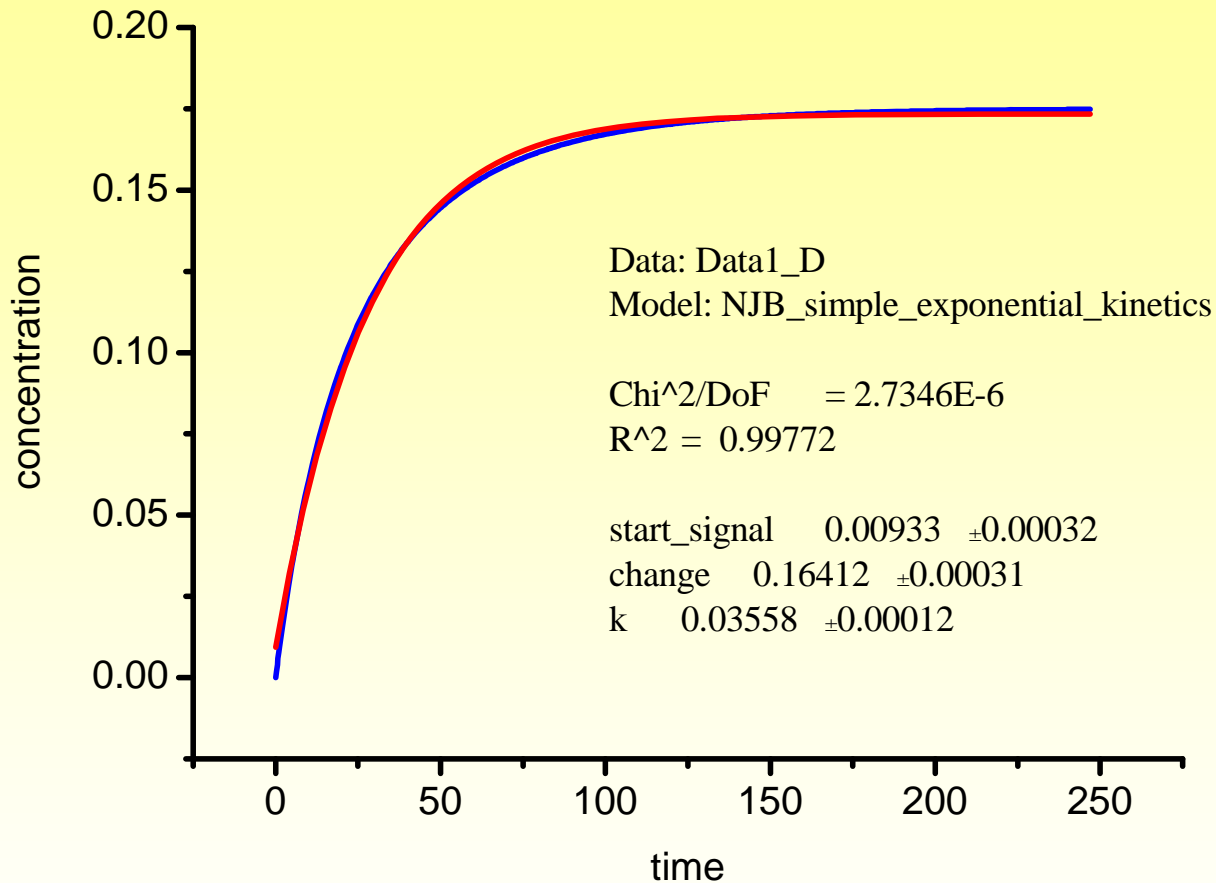


$$[A]_o = 0.2 \text{ M}$$

$$([B]_o = 0.2 \text{ M})$$

measure [C]

Is my reaction first order?



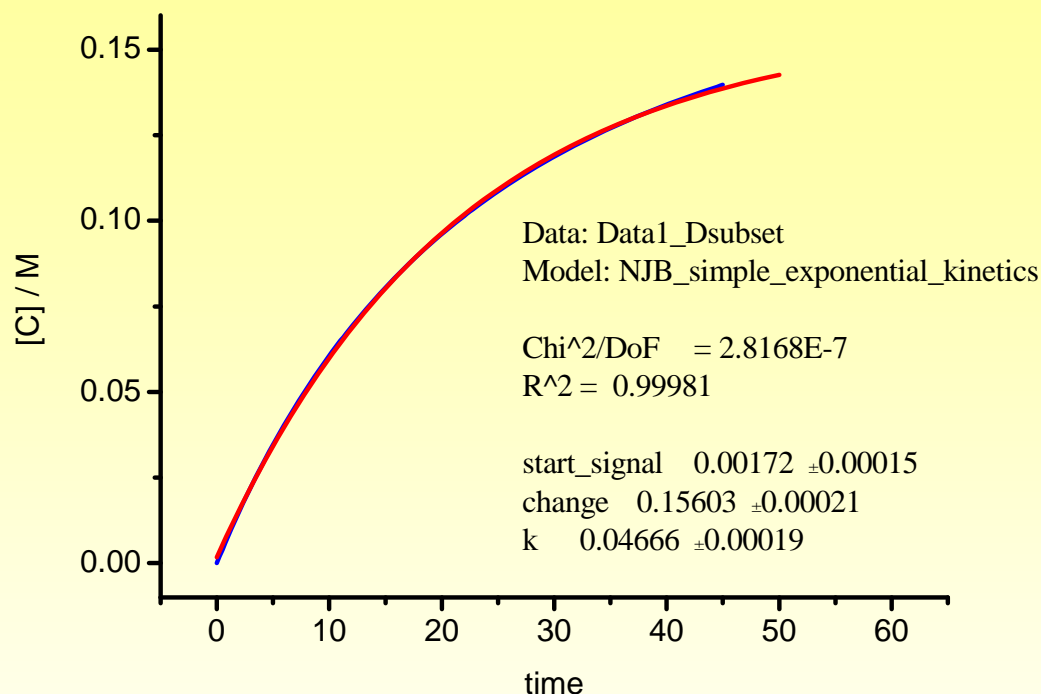
$$[A]_0 = 0.4 \text{ M}$$

$$([B]_0 = 0.2 \text{ M})$$

measure [C]

Three warnings: Fit is shows systematic deviations,
Signal increase didn't double & Rate constant is not constant

Is my reaction first order



When recording data for ~ 3 half lives, a simple exponential fit looks extremely good!

If recording more data is not feasible, record a few data points when the reaction has finished

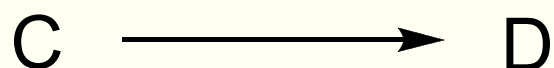
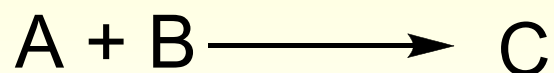
NJB

First order, second order

- Individual fits can give you an indication, but “challenging” your system is important!
- Record enough data for differences between 1st and 2nd order kinetics to become apparent: typically at least 5-6 half-lives (>95% conversion)
- Final data points can be useful if collecting 5-6 half lives worth of data is impractical

Kinetic studies

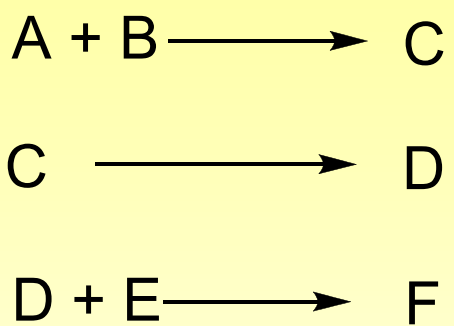
- Given a reaction, one can come up with a hypothesis for the mechanism. The proposed reaction mechanism in itself contains several predictions which can be tested. Additional questions include “What is the rate determining step (for given conditions)?” and “How can we optimise conditions?”



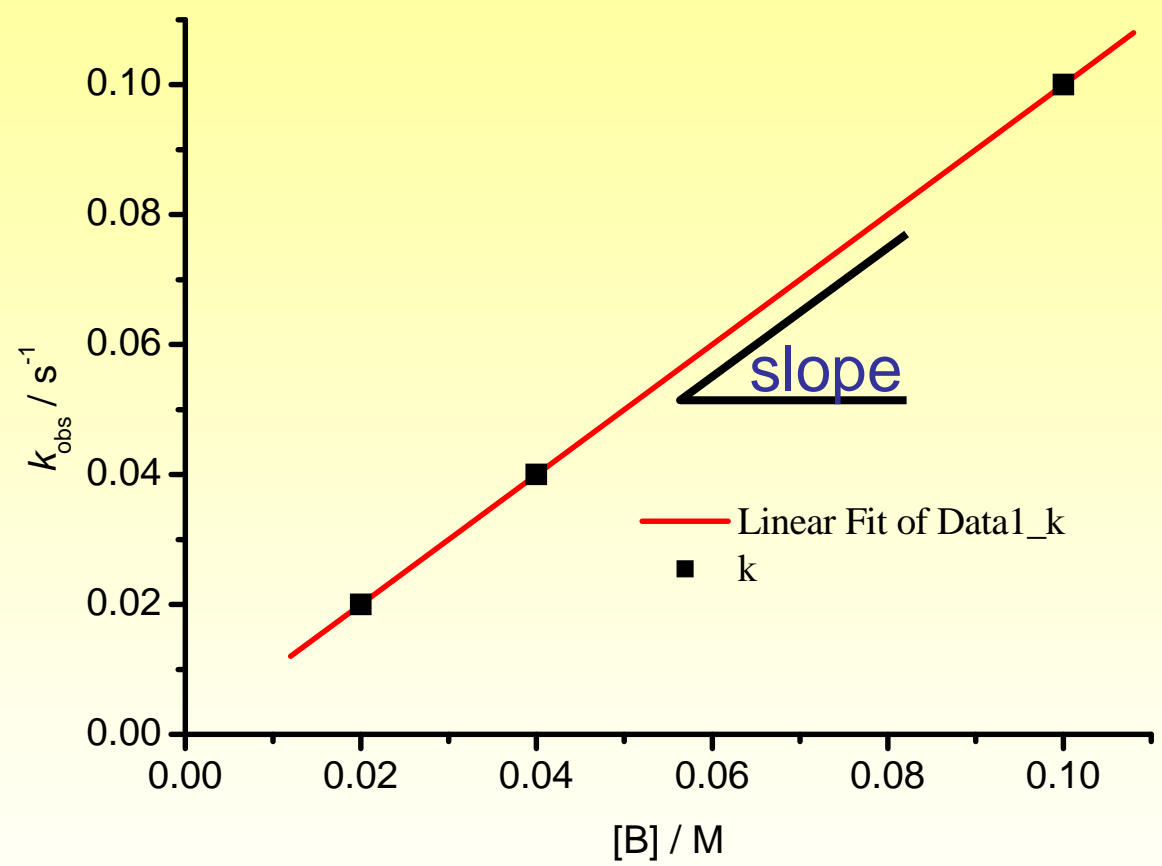
Pseudo first order conditions

- Make one of the reactants limiting
- All other concentrations >20-fold higher
- High concentrations vary by <5% => constant
- Vary one of the high concentrations and see what happens
- Reactions are now pseudo first order in the limiting reactant and data can be analysed using the simple exponential equation

Effect of [B]

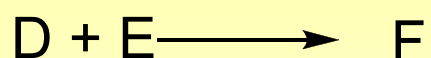
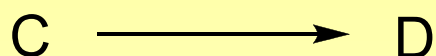
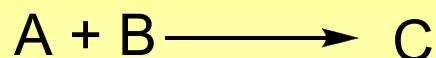


1 mM A
 20, 40 & 100 mM B
 20 mM E



Reaction is first order in B (a similar analysis can be used on A)
 Fit goes through origin: no reaction without B

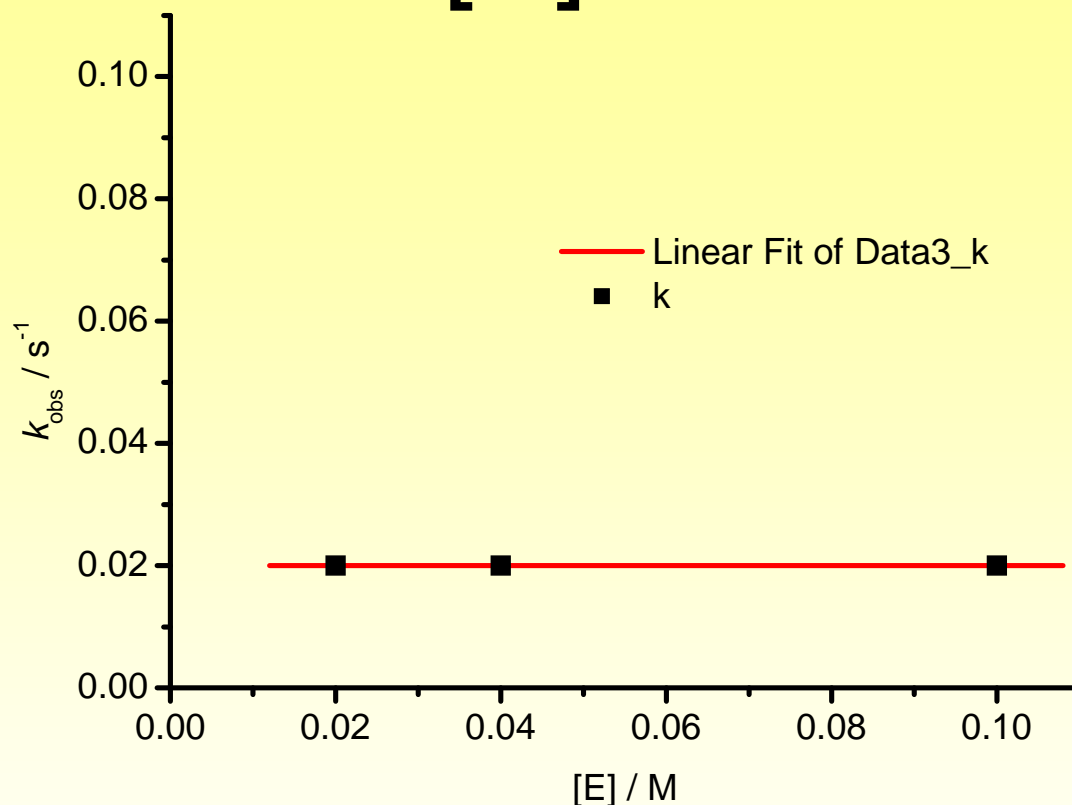
Effect of [E]



1 mM A

20 mM B

20, 40 & 100 mM E

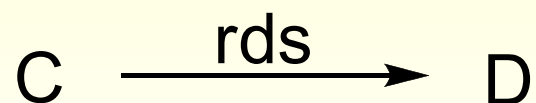
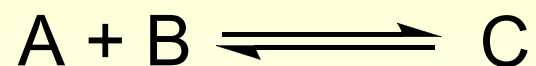


Observed rate constants are independent of $[E]$: step involving E probably occurs after rate determining step.

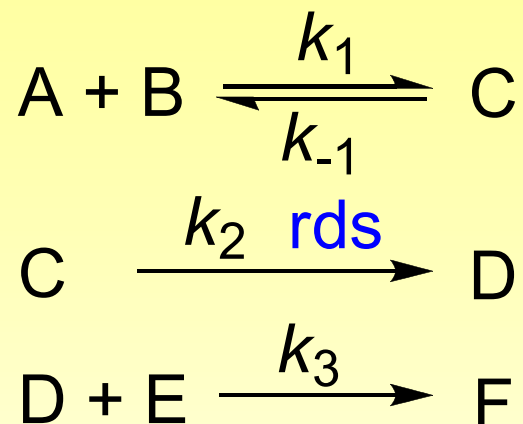
Alternative explanation: proposed mechanism is incorrect: check what happens at $[E] = 0$ M

Rate determining step

- Can we detect (reasonable) concentrations of C?
- Chemical logic/intuition



Overall rate equation

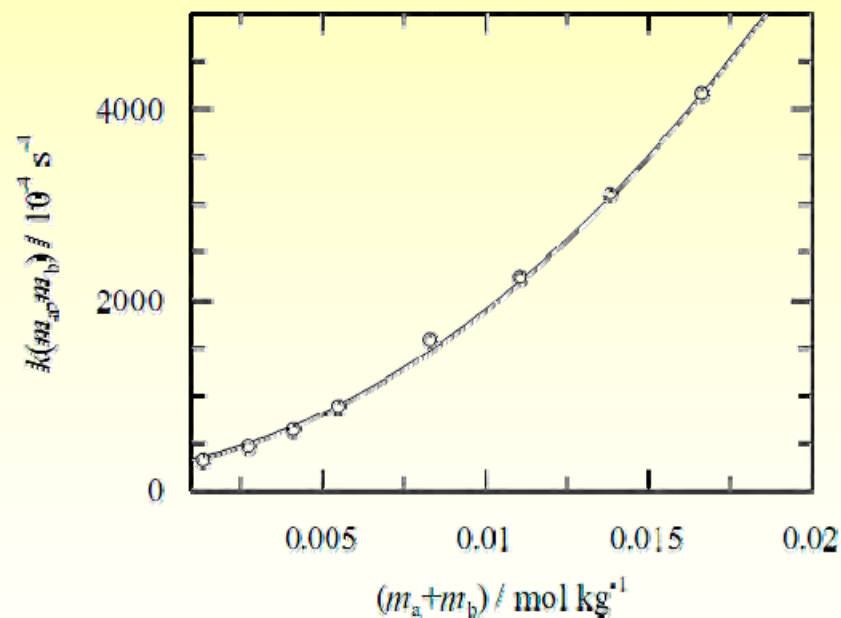
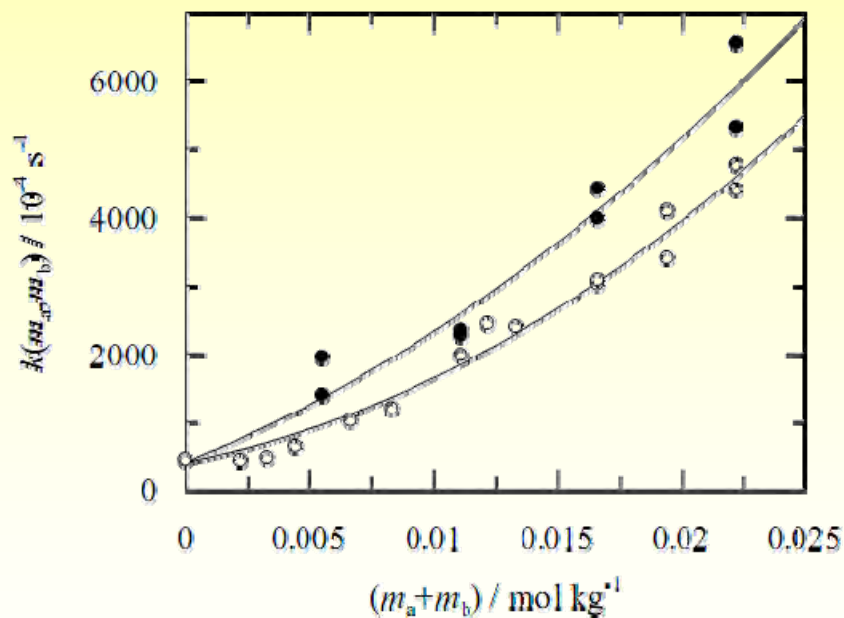
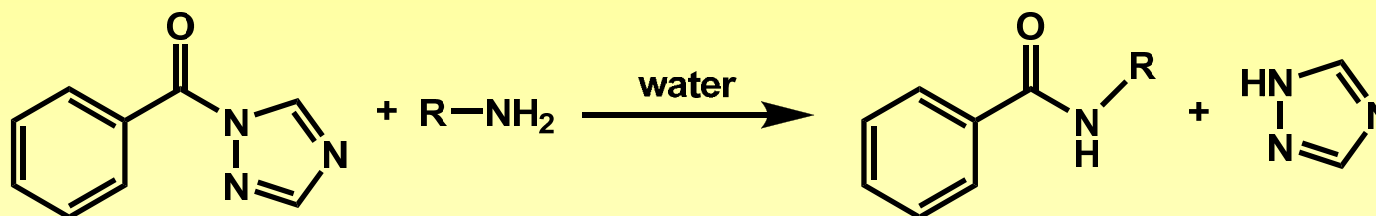


Application of the steady state approximation results in an overall rate law:

$$\frac{d[\text{F}]}{dt} = \frac{d[\text{D}]}{dt} = k_2 \cdot [\text{C}] = k_2 \cdot \frac{k_1 \cdot [\text{A}][\text{B}]}{k_{-1} + k_2} \approx k_2 \cdot K \cdot [\text{A}][\text{B}] \quad \text{if } k_{-1} \gg k_2$$

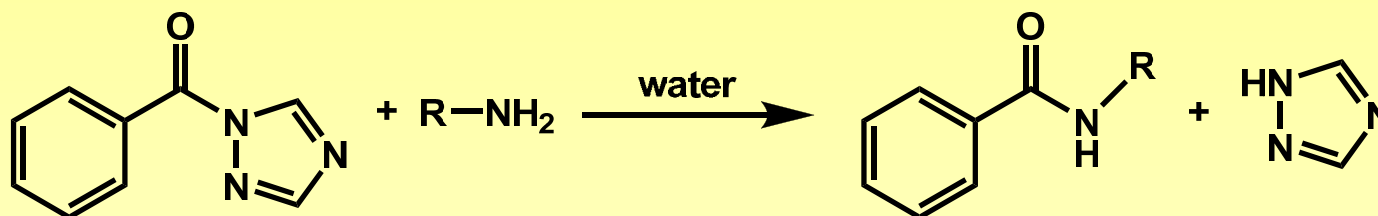
showing exactly what we found: the rate of product formation is linear with ([A] and) [B] and does not depend on [E]. The slope of the graph showing the effect of [B] equals $K \times k_2$.

Simultaneous reaction pathways



analysis using a polynomial: $k_{\text{obs}} = k_0 + k_1 [\text{amine}] + k_2 [\text{amine}]^2$

Interpreting rate data



$$k_{\text{obs}} = k_0 + k_1 [\text{amine}] + k_2 [\text{amine}]^2$$

Contribution not involving amine: hydrolysis as a side reaction?

Contribution which is first order in amine as expected...

Contribution which is second order in amine: nucleophilic attack catalysed by second molecule of amine?

Individual rate constants

- Separating individual steps allows further mechanistic work:
 - Activation enthalpies and entropies
 - Isotope effects
- Predict the rate determining step under different conditions; predict optimum reaction conditions

Notes and warnings

- Concentrations for NMR experiments under pseudo first order conditions can be very high: is your reactant also the solvent? Does this cause solvent effects?
- Are concentrations as used in, e.g., UV-visible experiments relevant for synthetic conditions?
- If you are very successful in optimising your rate determining step, another step may become rate limiting

Recommendations

- Make sure you know what you're measuring, but don't worry if you get this wrong first time around
- Try to simplify your system as much as possible: simple questions give (a better chance of getting) simple answers
- Don't worry about the mistakes you *might* make; basic but thorough analysis will get you a long way!