Freie Universität Berlin

Parameter estimation:

non-linear least squares and non-linear mixed effects modeling

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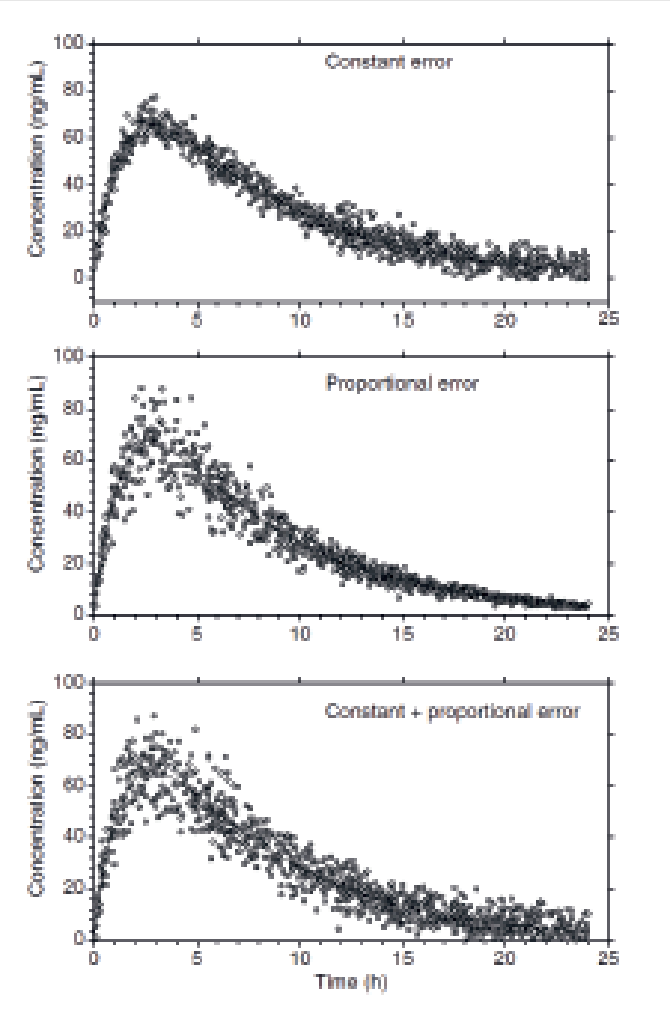
Structure

1. Inverse problems recap
2. Application
3. Population averaging
4. Fits for single patients
5. NLME
6. Summary
7. Sources

1. Inverse problems recap

- **Inverse problem:**
- Infer causal factors from observations that produced them
- estimate θ, M to maximize accordance with data
- Assumptions! i.e. usually $\eta_i \sim N(0, \sigma_i^2)$
- error types:



1. Inverse problems recap

- writing down Likelihood according to error model:

$$y_i = x_{i|M,\theta} + \eta_i, \qquad \eta_i \sim N(0, \sigma_i^2)$$ additive error

$$L_y = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(y_i - x_i)^2}{2\sigma^2}}$$

$$l_y = \log\left(\sqrt{2\pi\sigma^2}\right) + \frac{1}{2\sigma^2}\left(\sum_{i=1}^{N} -(y_i - x_i)^2\right)$$

$$l_y \propto \sum_{i=1}^{N} (y_i - x_i)^2$$ proportional to least squares problem

$$y_i = x_{i|M,\theta}(1 + \eta_i), \qquad \eta_i \sim N(0, \sigma_i^2)$$ proportional error

$$y_i = x_{i|M,\theta} + \epsilon_i, \qquad \epsilon_i \sim N(0, x_i \sigma_i^2)$$

$$l_y \propto \sum_{i=1}^{N} \frac{(y_i - x_i)^2}{x_i}$$ proportional to weighted least squares

2. Application

- pandemia of H1N1 in 2009 (Swineflu)
- children have the highest risk of hospitalization
- used Oseltamivir (Tamiflu) for treatment
- little known about Tamiflu in infants → duration of drug therapy?
- virus quantification at Robert-Koch institute, determined from qtip sample
- data points for 36 children, 2 to 5 data points per patient

  → sparse
- 91 datapoints overall

2. Application

- assume decay of virus load with treatment to be:

$$V_{estimated}(i,t) = x_0(i)\, e^{-t\, CL_v(i)}$$

- which $x_0(i)$ $initial\ viral\ load$, $\frac{copies}{ml}$

$CL_V(i)$ $virus\ clearance$, $\frac{1}{day}$ will minimize the error?

- → infer $t_{\emptyset}(i) = \log\left(\frac{x_0(i)}{10}\right)\frac{1}{CL_V(i)}$ time when virus load is unrecognizable

- → equal to lower limit of quantification, LLQ = 10

2. Application

- error models:

$y_i = x_{i|\theta,M}\, e^{\epsilon_i}$ exponential

$y_i = x_{i|\theta,M}(1+\epsilon_i)$ proportional

$\log(y_i) = \log(x_{i|\theta,M}) + \epsilon_i$

$\log(y_i) = \log(x_{i|\theta,M}) + \log(1+\epsilon_i)$

- → both turn into additive error model when taking logarithm
- fitting:

$$\underset{x_0(i),CL_V(i)}{argmin} \sum_t \frac{\left(V_{estimated}(i,t) - V_{observed}(i,t)\right)^2}{V_{observed}(i,t)}$$ weighted, or

$$\underset{x_0(i),CL_V(i)}{argmin} \sum_t \left(V_{estimated}(i,t) - V_{observed}(i,t)\right)^2$$ not weighted

2. Application

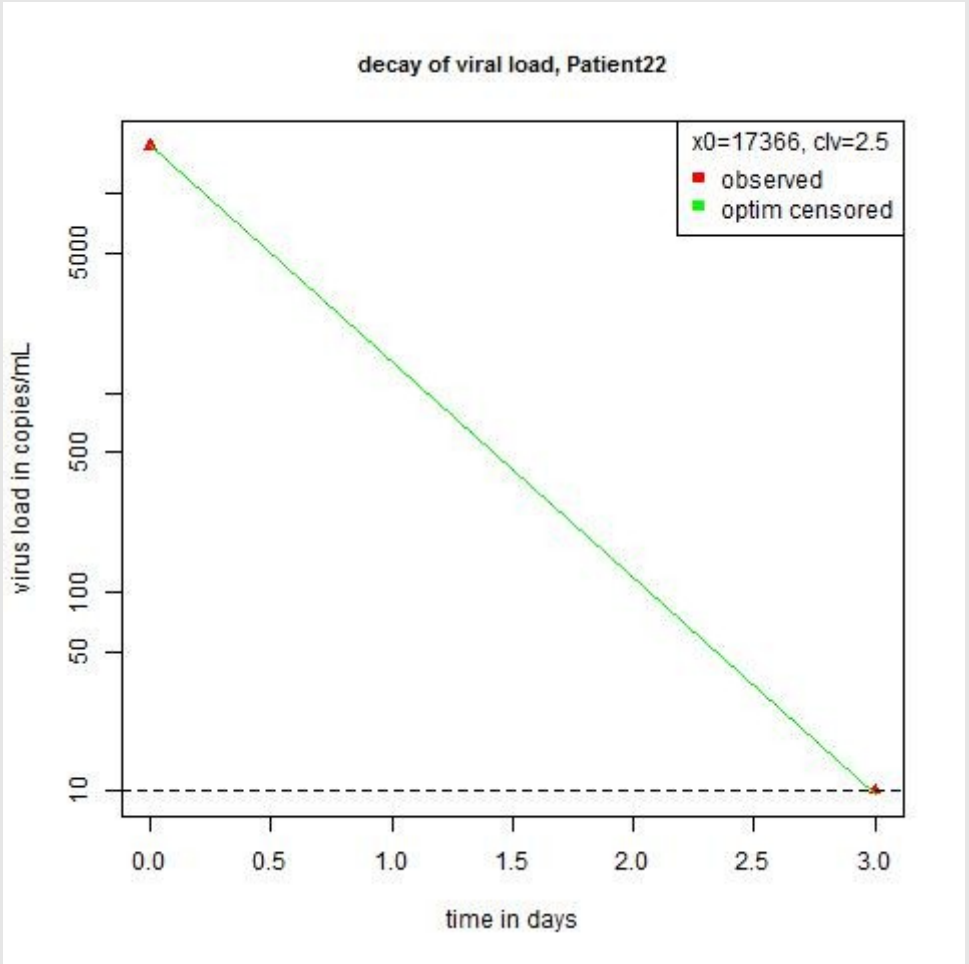
- which means

$$\underset{x_0(i),CL_V(i)}{argmin} \sum_t \frac{\left(\left(x_0(i)\, e^{-t\ CL_V(i)}\right) - V_{observed}(i,t)\right)^2}{weight}$$

$$with\ \left(V_{estimated}(i,t) - V_{observed}(i,t)\right)^2 = 0$$

$$if\ V_{estimated}(i,t) \leqslant 10 \wedge V_{observed}(i,t) \leqslant 10$$

- → **Censoring**
- → $CL_V(22)$ $[\,2.5\,,\infty\,)$



2. Application

- choices in R:

- nlm: Gauss-Newton type algorithm
- optim: Nelder-Mead, quasi-Newton

- convergence issues:
- → use V(i,0) as start value for x0
- multistart for Clv from -10 to 10 in 0.5 sized steps
- choose parameter estimates with minimal objective function value

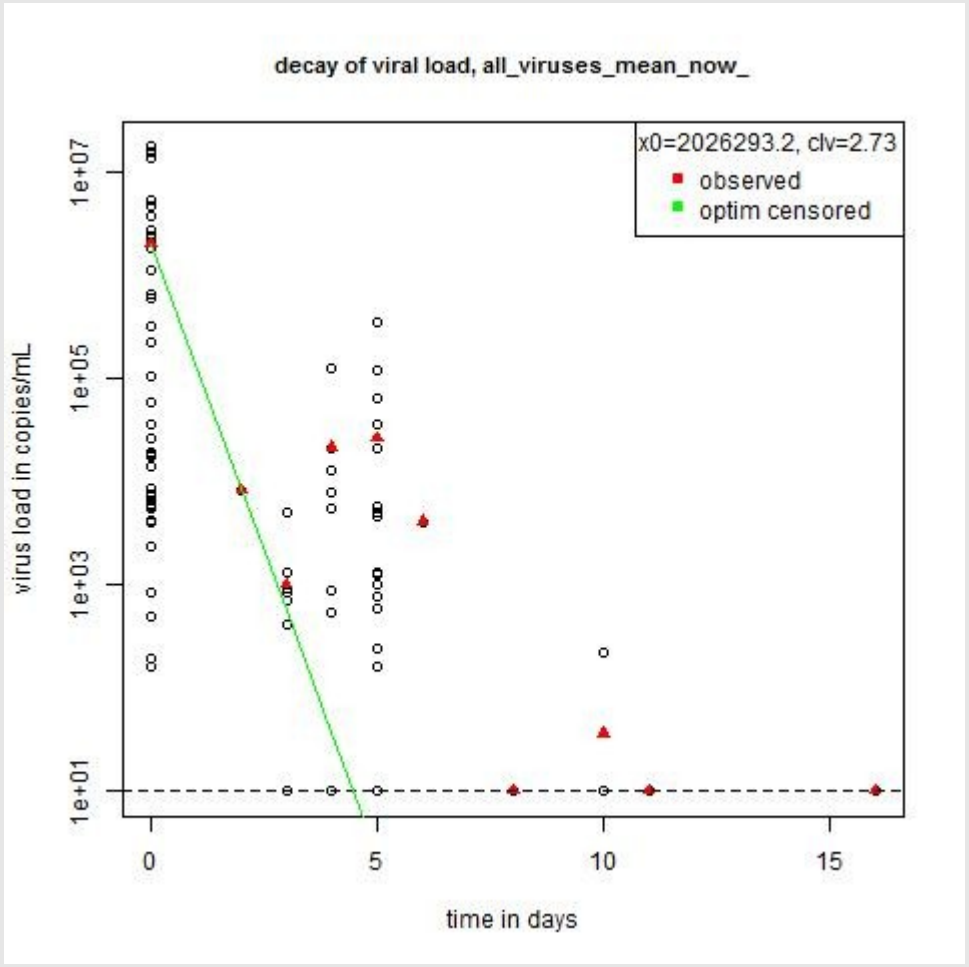
3. Population approaches

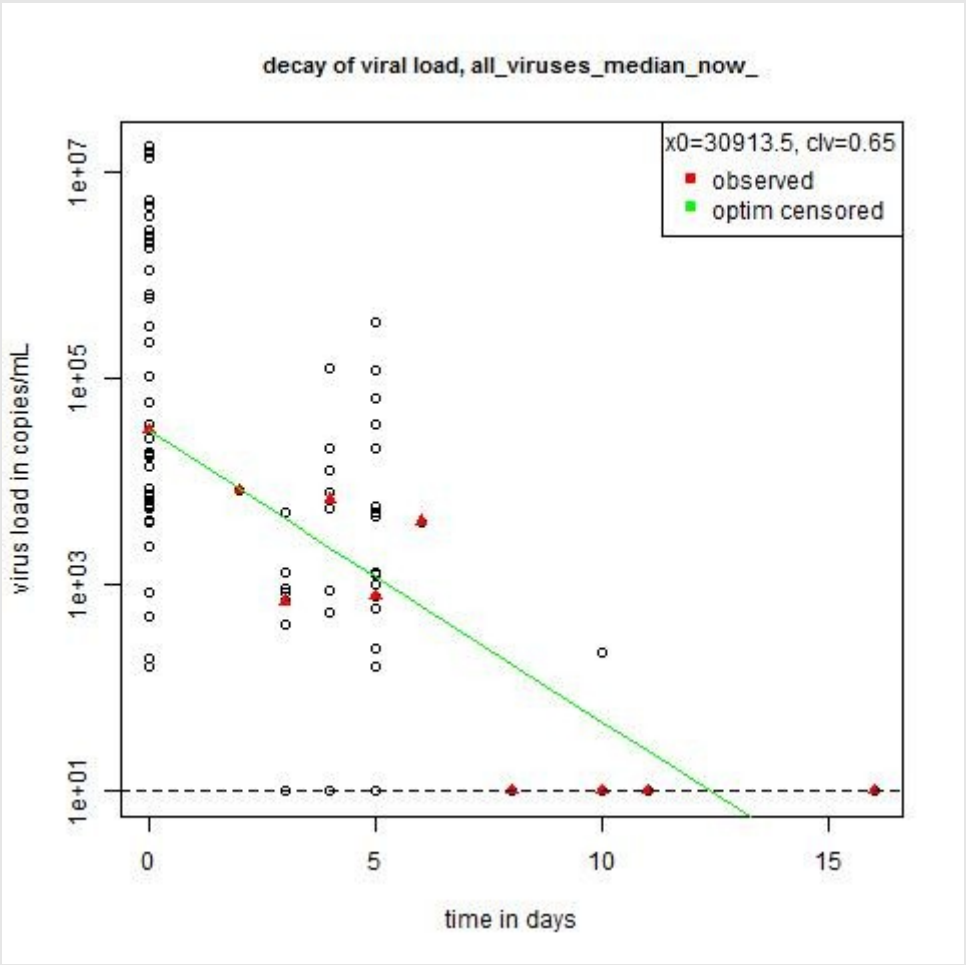
How to model?

- fit individual data for each patient
- averaging, use mean or median of all data points at each time t
- averaging, use mean or median of virus type grouped data
- use NLME (non linear mixed effect modelling)

3. Population approaches

- example for fitted curves:

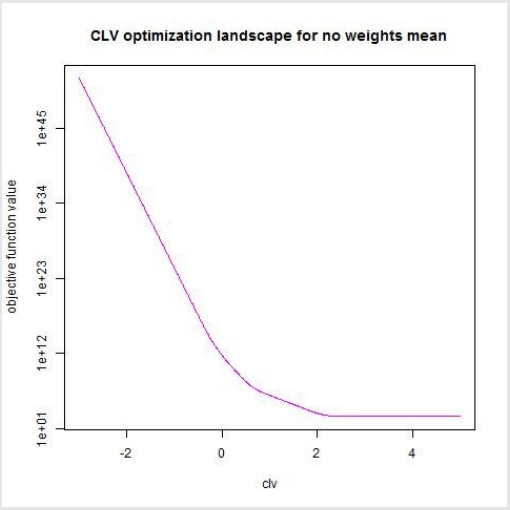


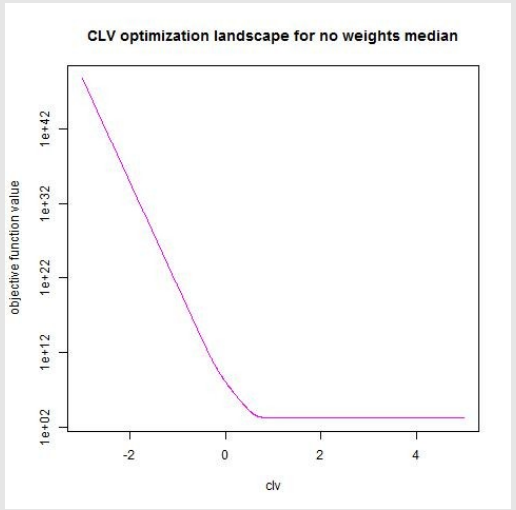


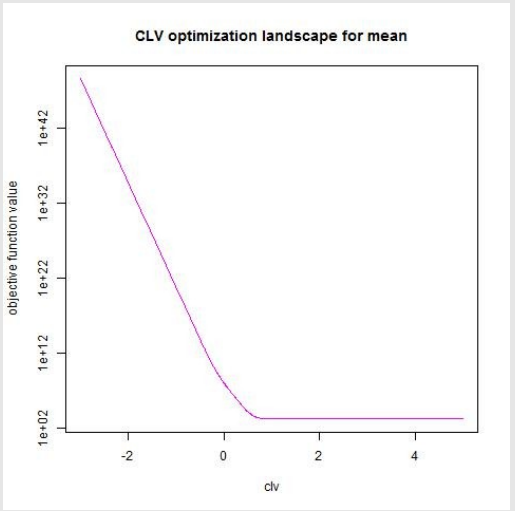
- enough data points available

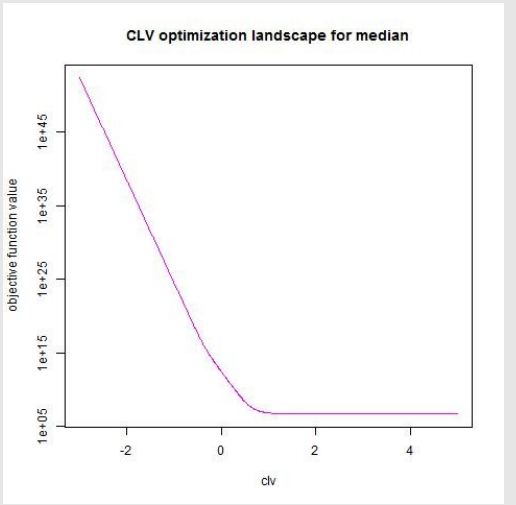
3. Population approaches

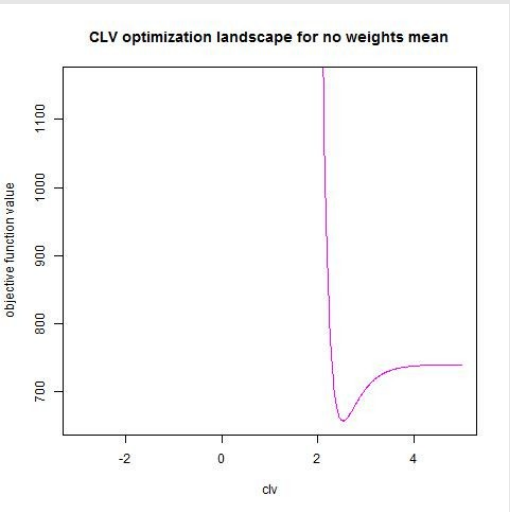
- Optimization landscapes:

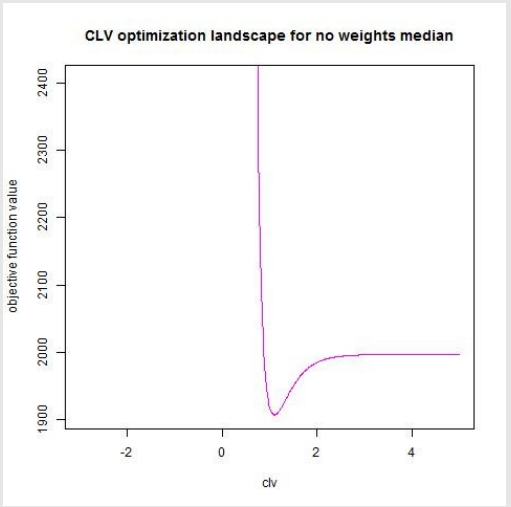


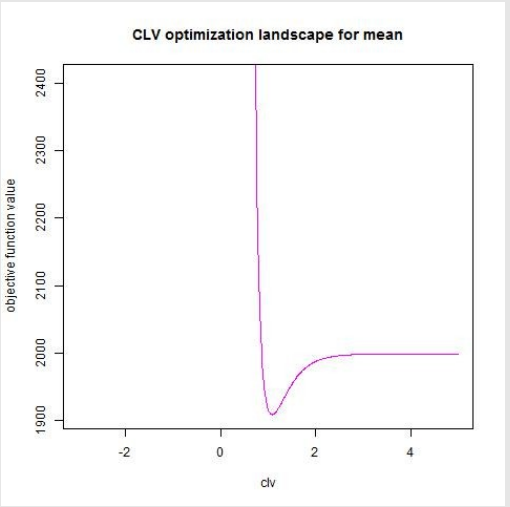


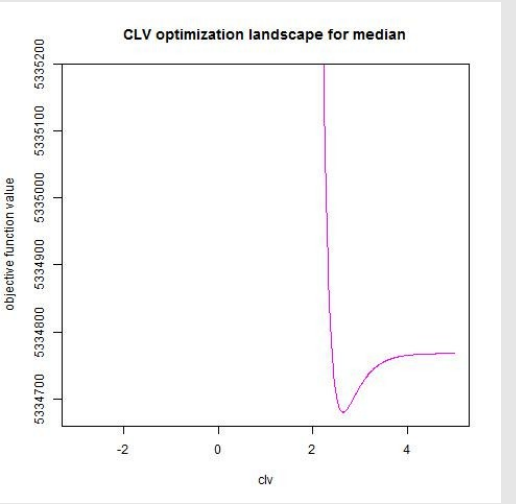






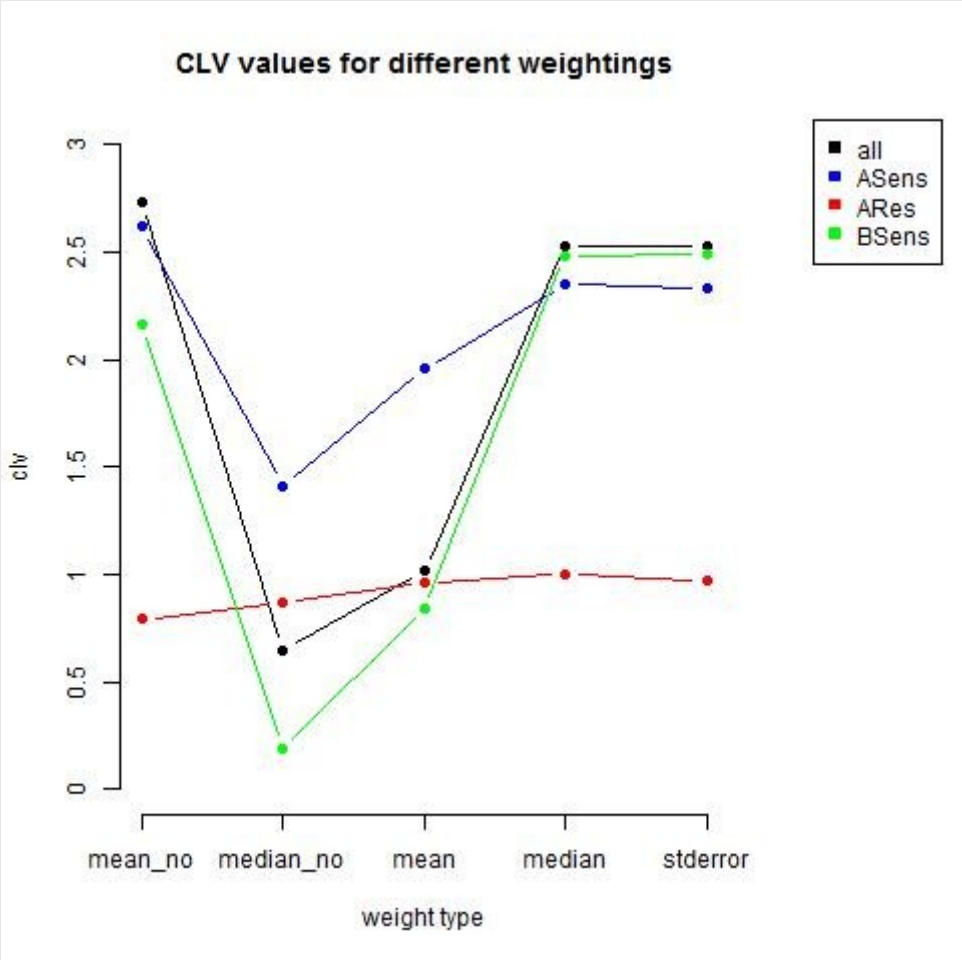






3. Population approaches

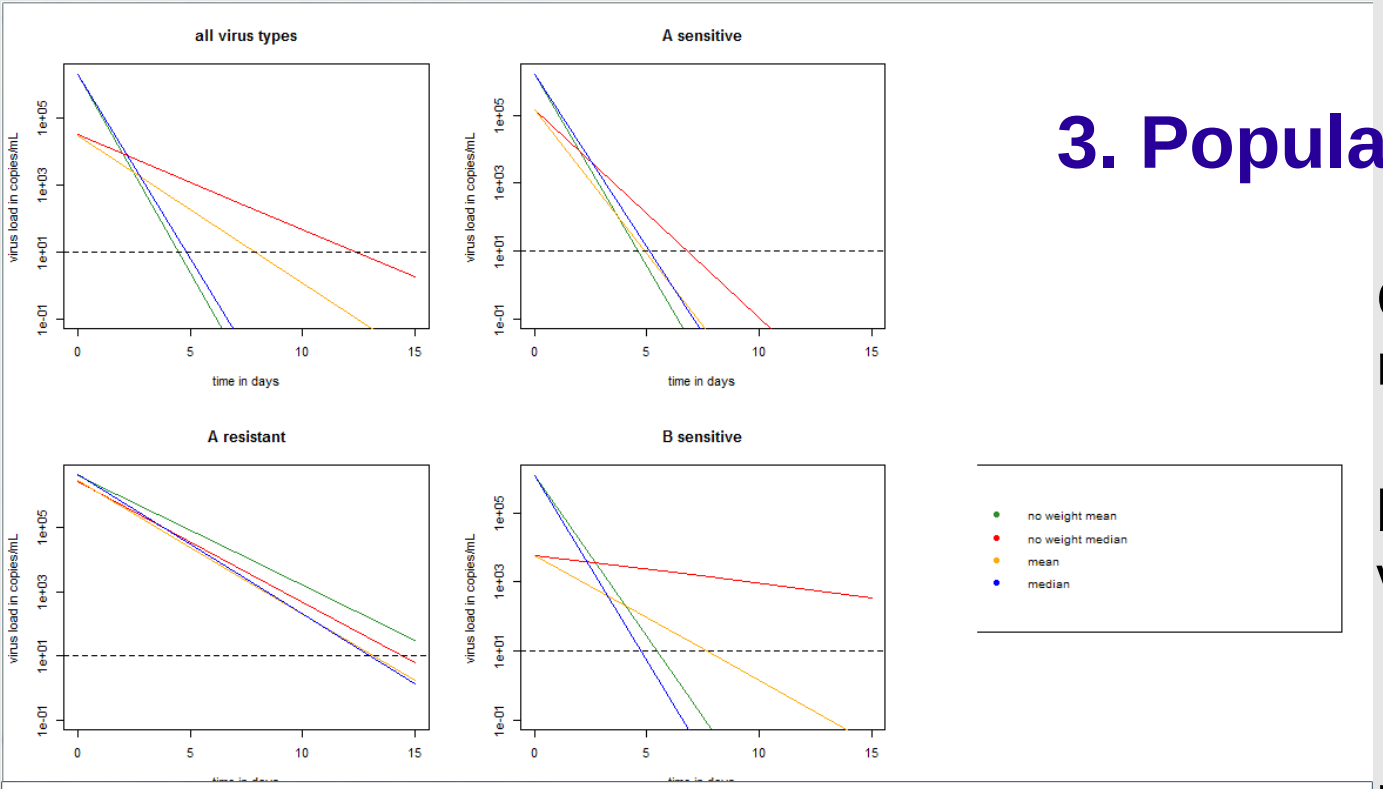
- influence of weight and grouping on Clv



- number of data points at time 0 for

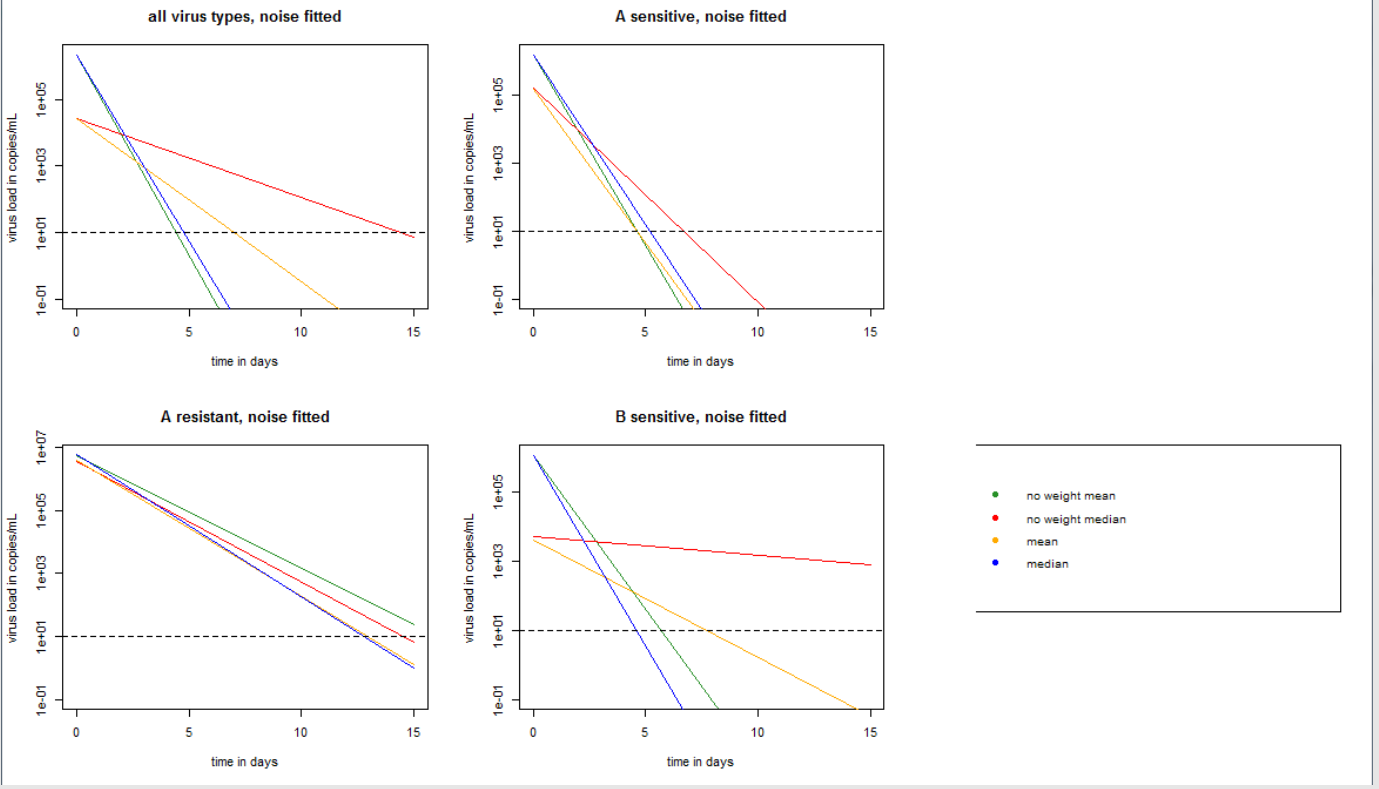
- all viruses: 36
- A sensitive: 18
- A resistant: 7
- B sensitive: 11

3. Population approaches



CLv is very dependent on measure and weights

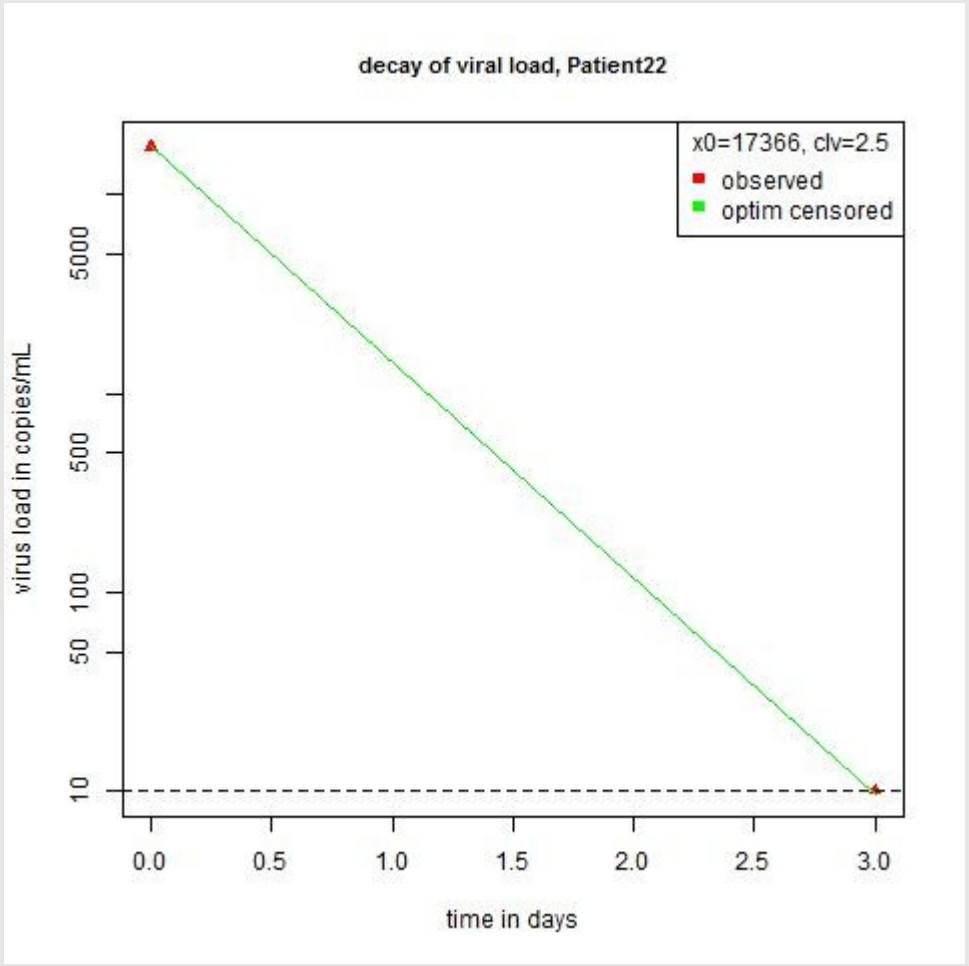
big differences between virus types

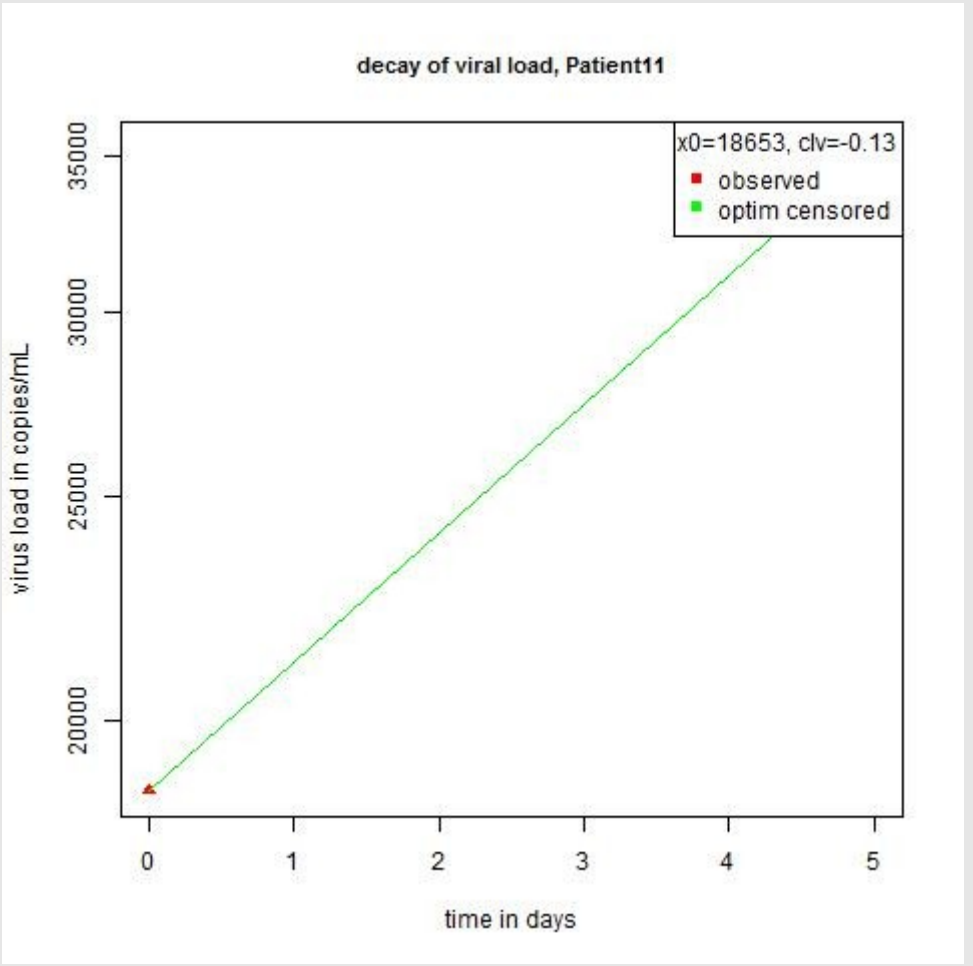


robust to noise

4. Fits for individual patients

- example for fitted curves:

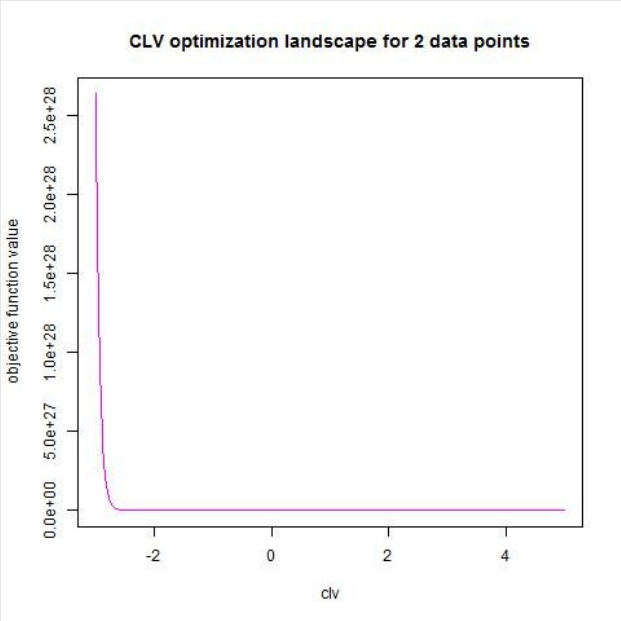


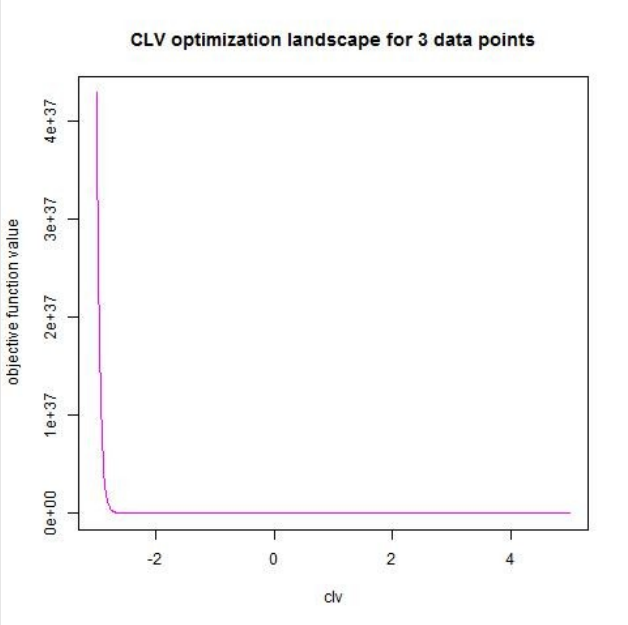


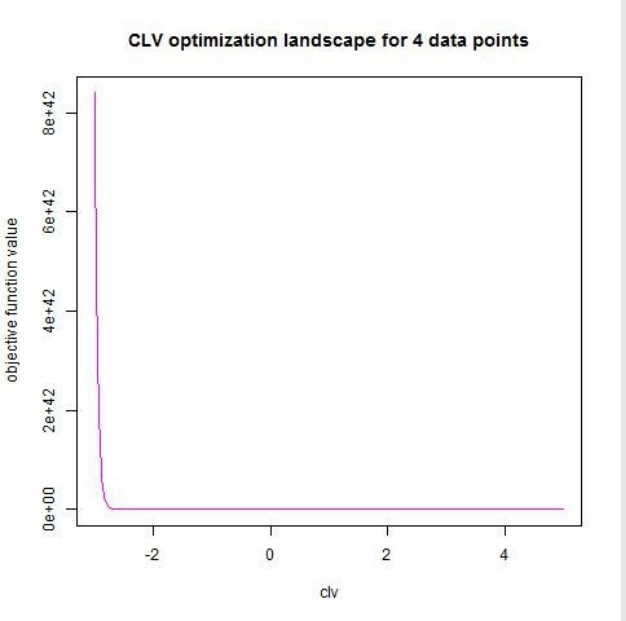
- some patients don‘t behave as expected
- least assumptions made in fitting

4. Fits for individual patients

- Optimization landscapes:



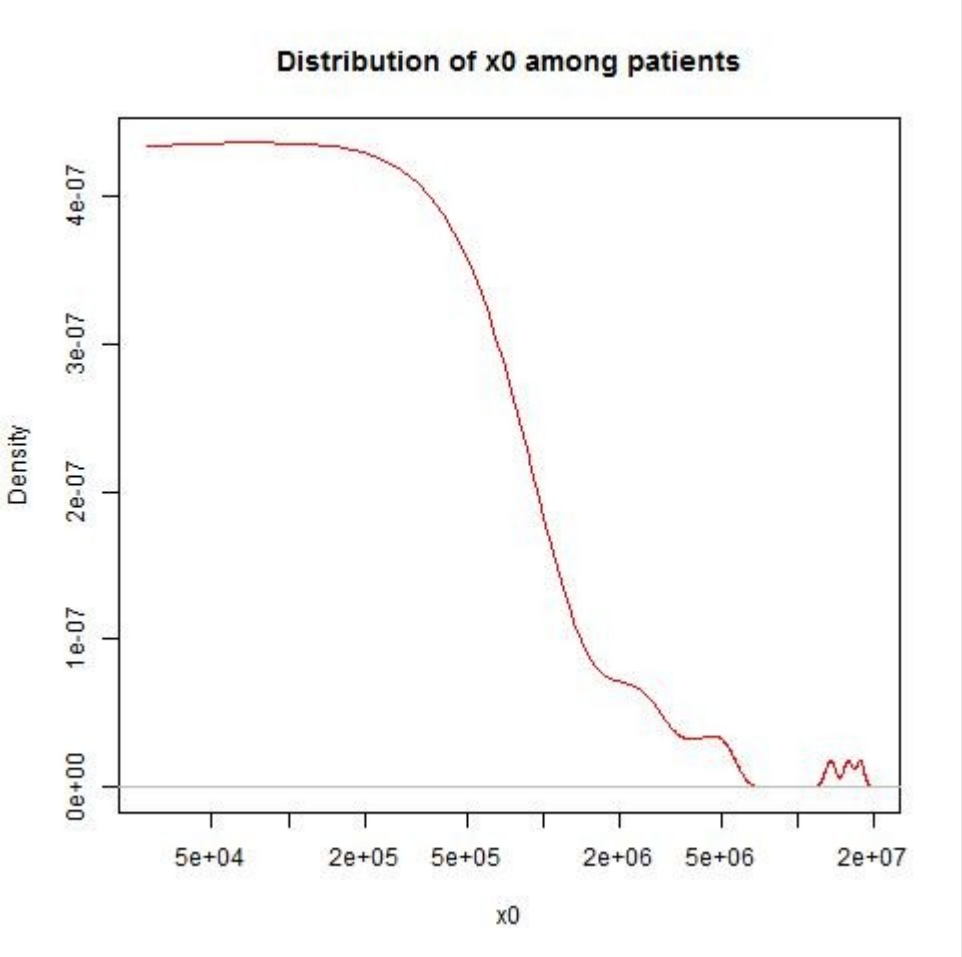


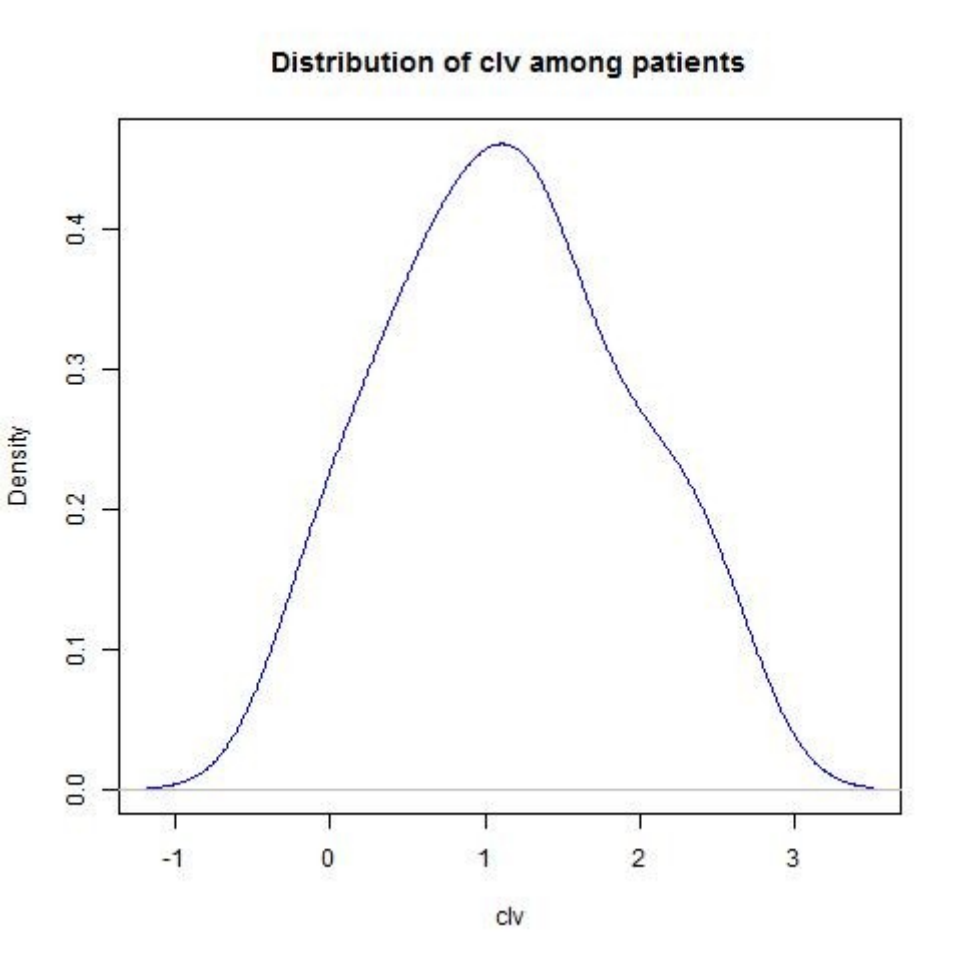


- ugly landscape, big range of CLv legitimately possible because of sparsity
- assume no error if we fit only 2 points

4. Fits for individual patients

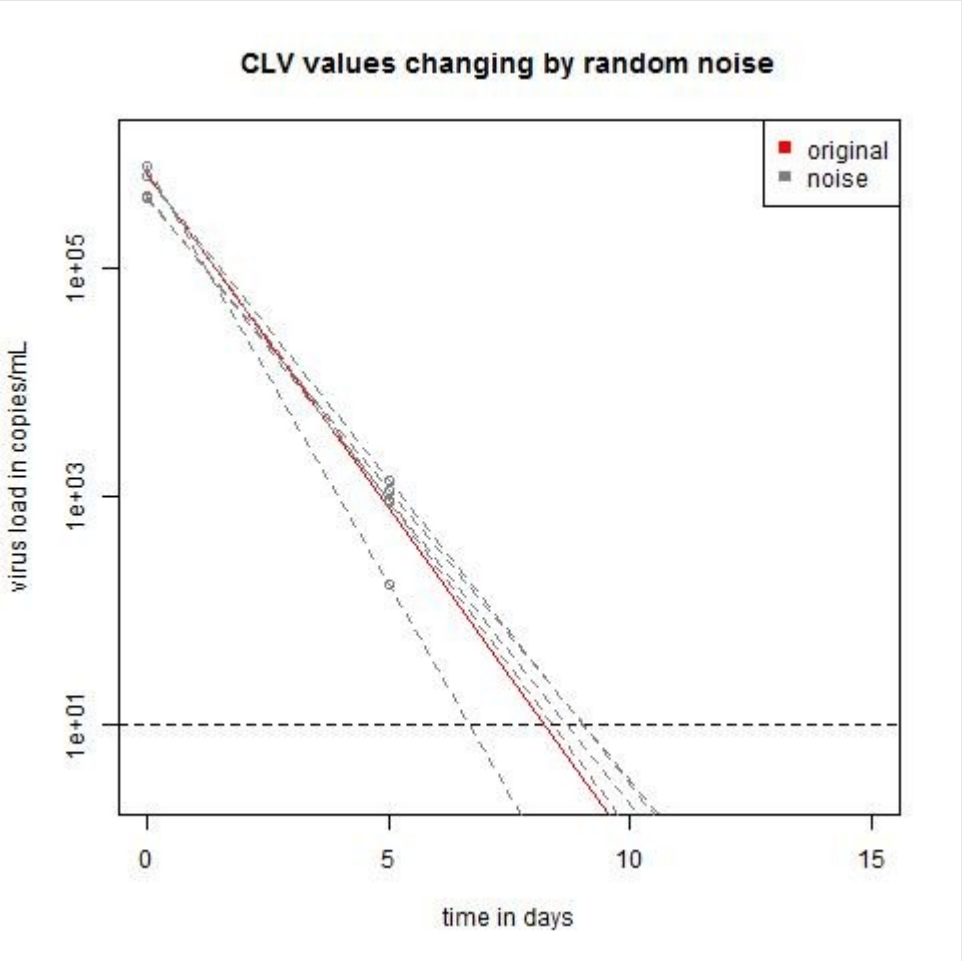
- Distributions over all patients:

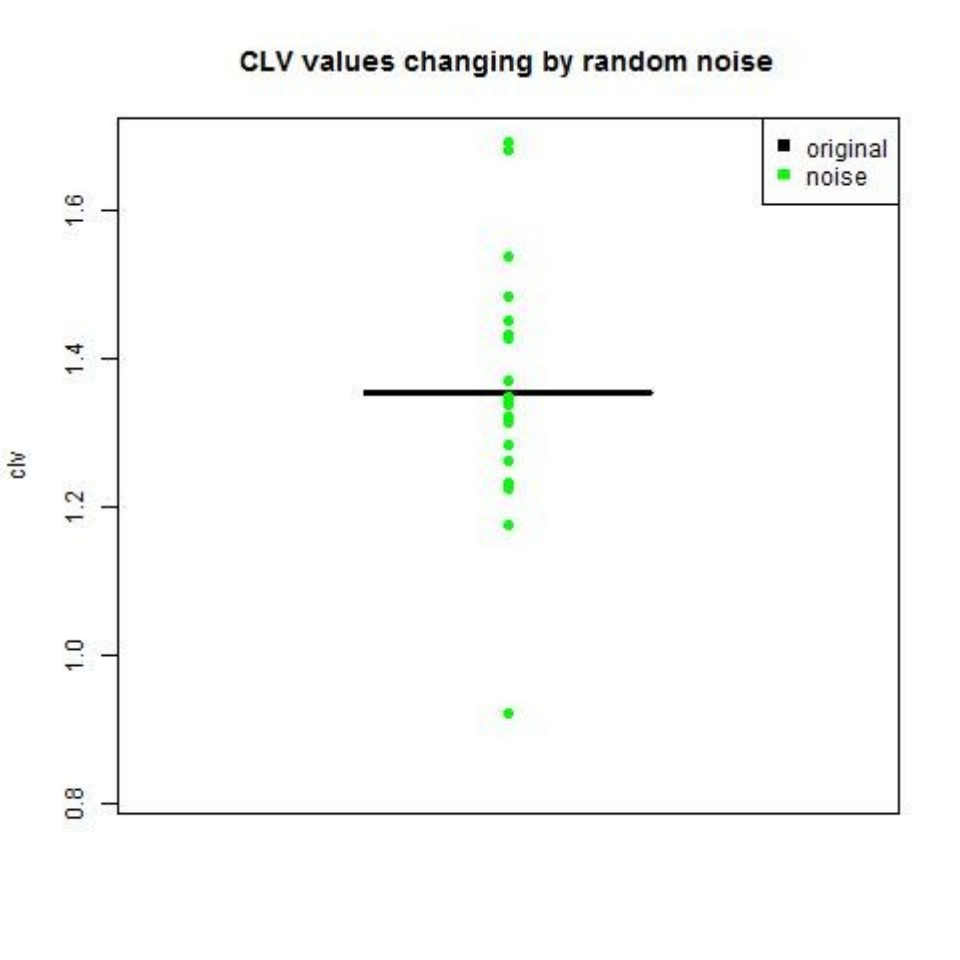




4. Fits for individual patients

- influence of noise





- not robust to noise, CLv [0.9, 1.7] → treatment time influence

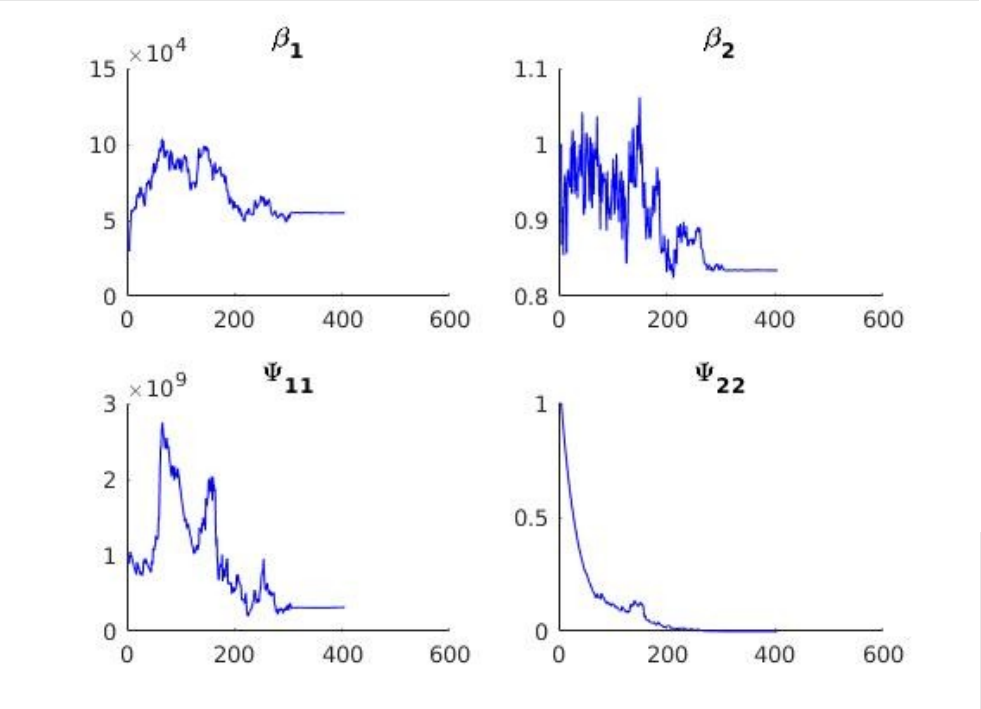
5. NLME

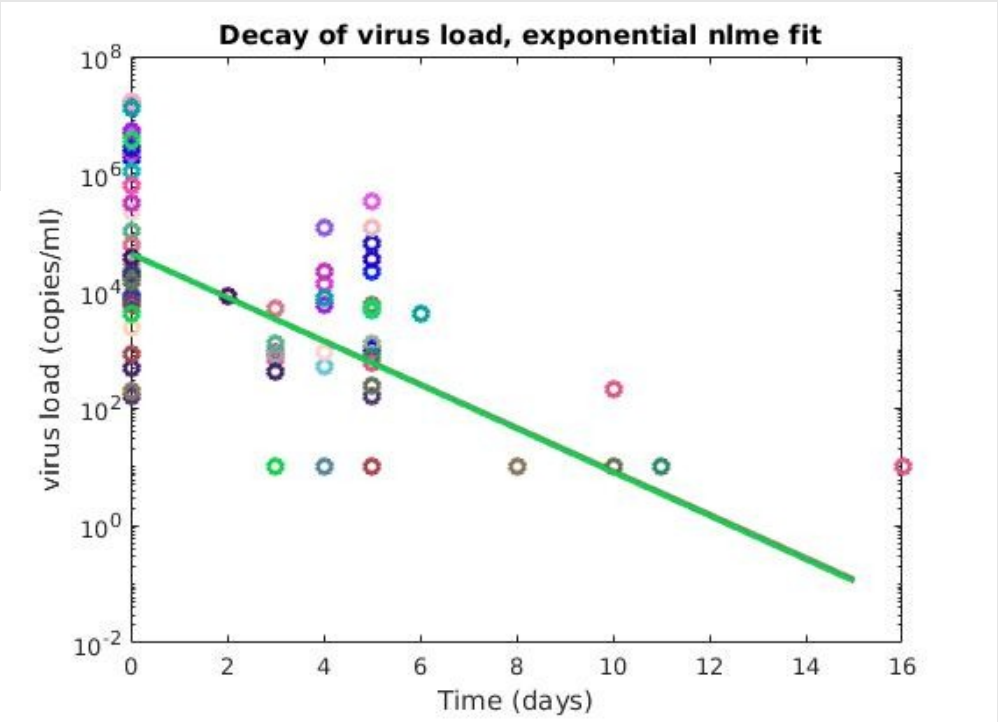
- approach for sparse data
- population model is collection of models of individual observations
- response variability reflects errors and intersubject variability
- N patients, unknown parameters $\theta_{pop}, \Omega, \sigma$
- $Y_i = f(x_i|\theta_i) + \epsilon_i(\sigma) \qquad \theta_i = \theta_{pop} + \eta_i(\Omega)$
- f nonlinear model
- Y_i partial observations
- **Assumptions:**
- $\epsilon_i(\sigma)$ *measurement errors* $i.i.d. \sim N(0, \sigma_i^2) \wedge$ *independent of random effects*
- θ_i *random effects* $\sim N(\theta_{pop}, \Omega) \wedge$ *independent among groups*

5. NLME

- R: nlme(), but was not documented understandably
- Matlab: nlmefit(), convergence issues → had to use nlmefitsa(), expectation maximization stochastic algorithm

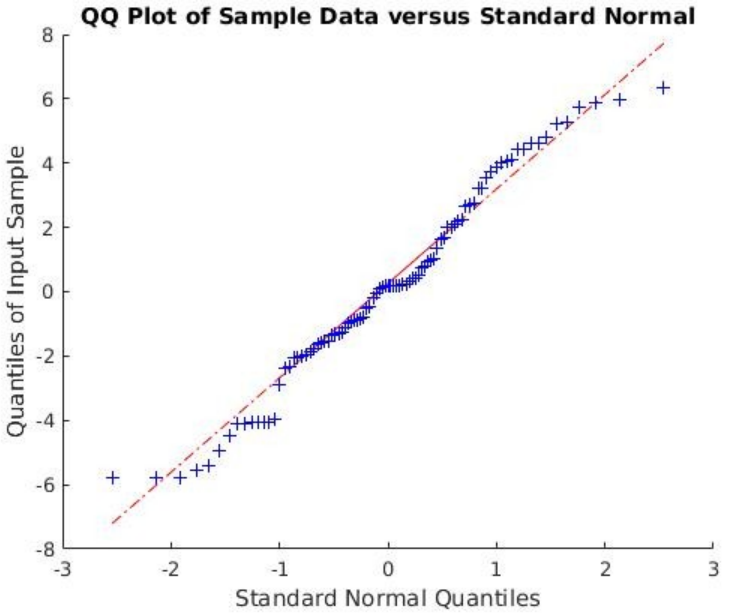
- exponential model:

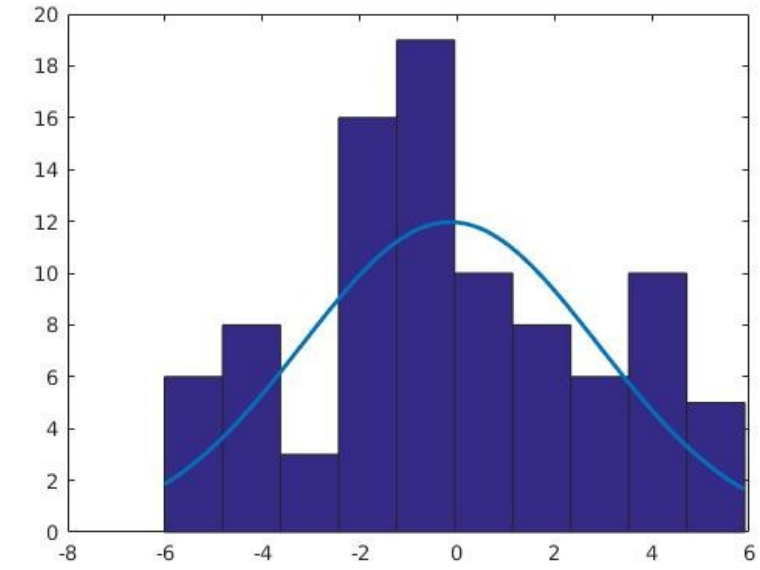


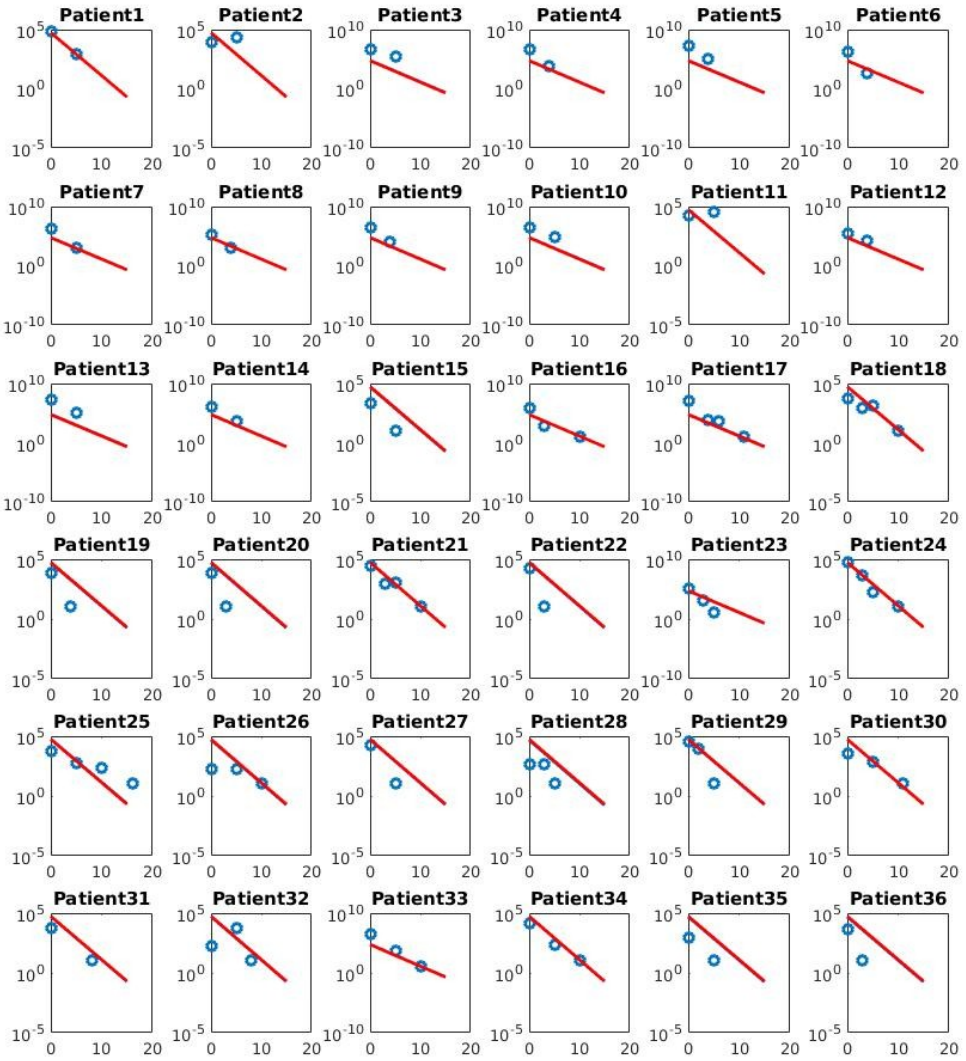


5. NLME

- exponential error model:

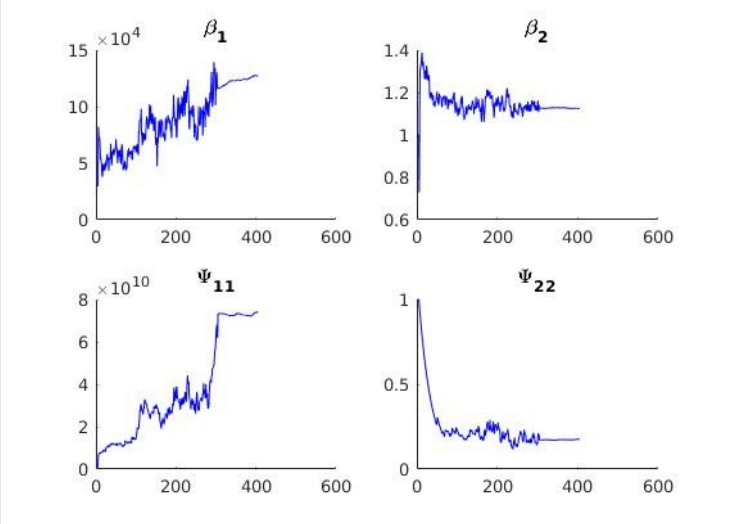


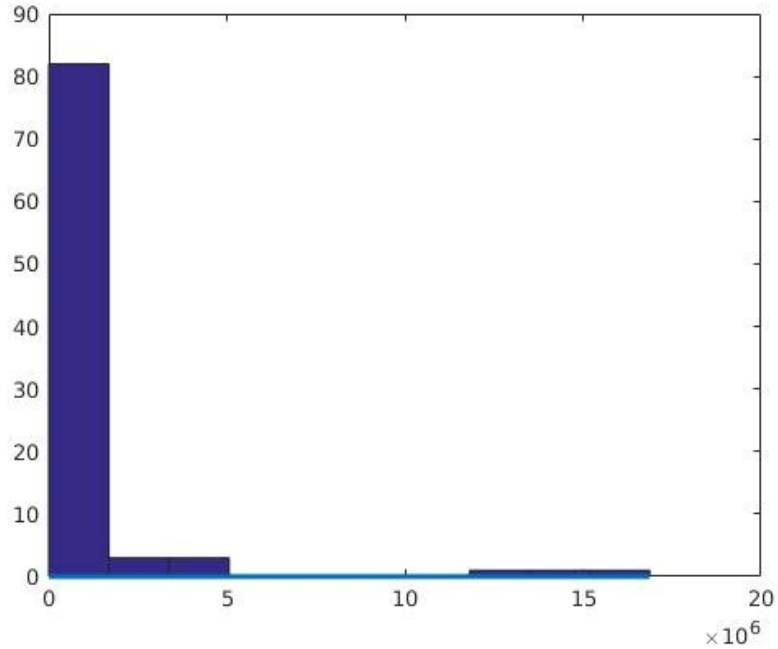


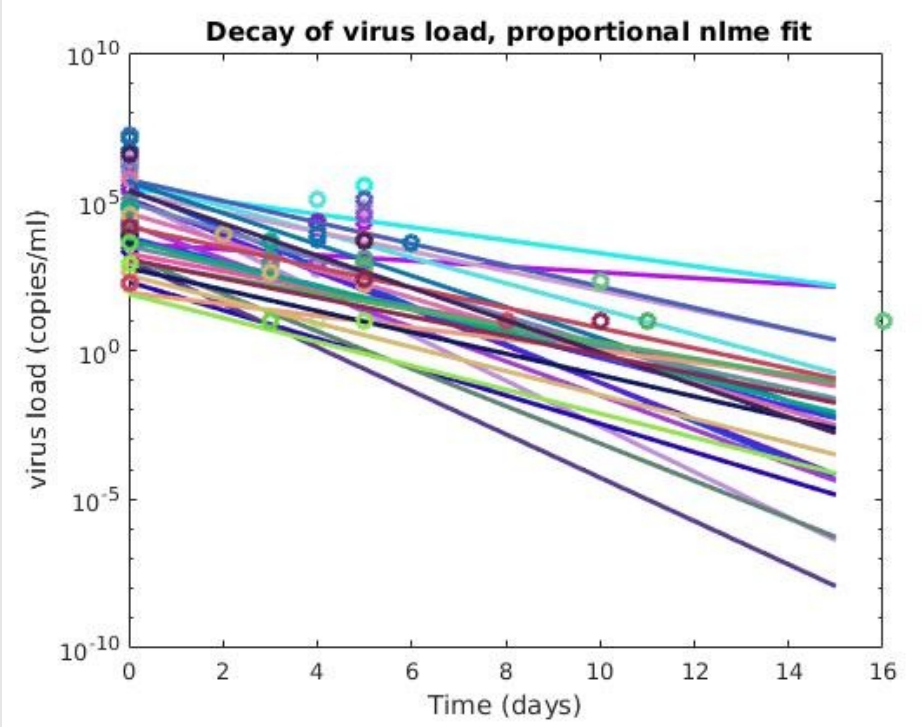


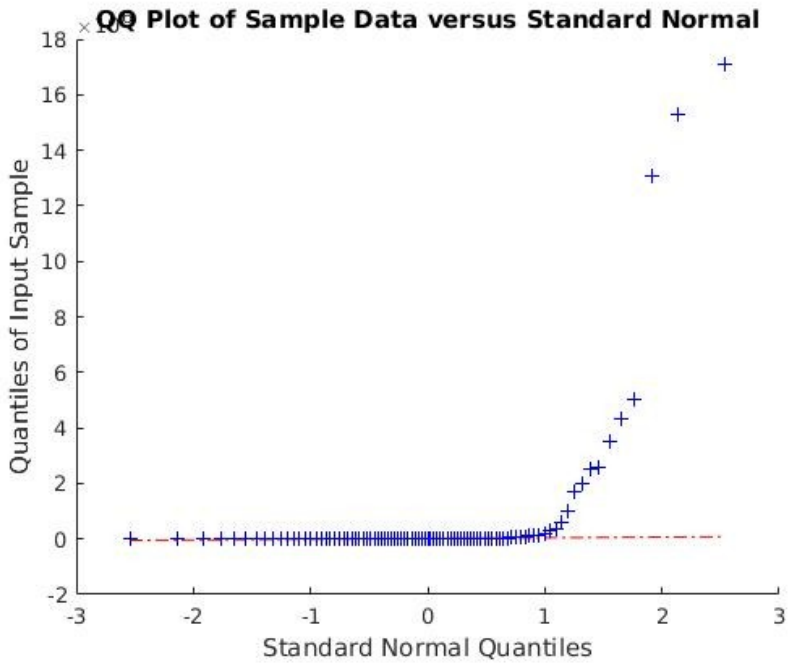
5. NLME

- proportional error model:



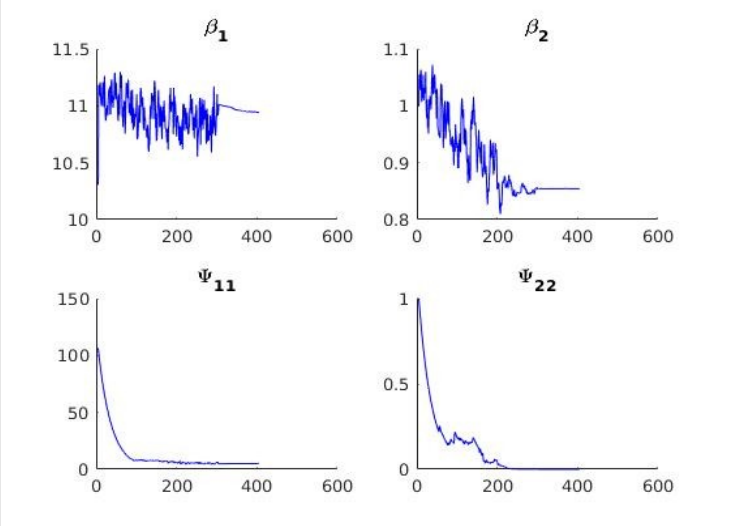


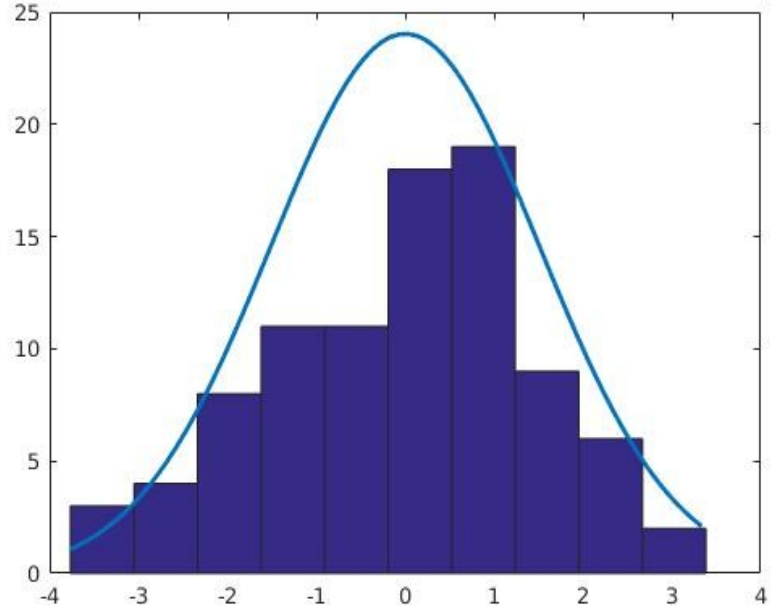


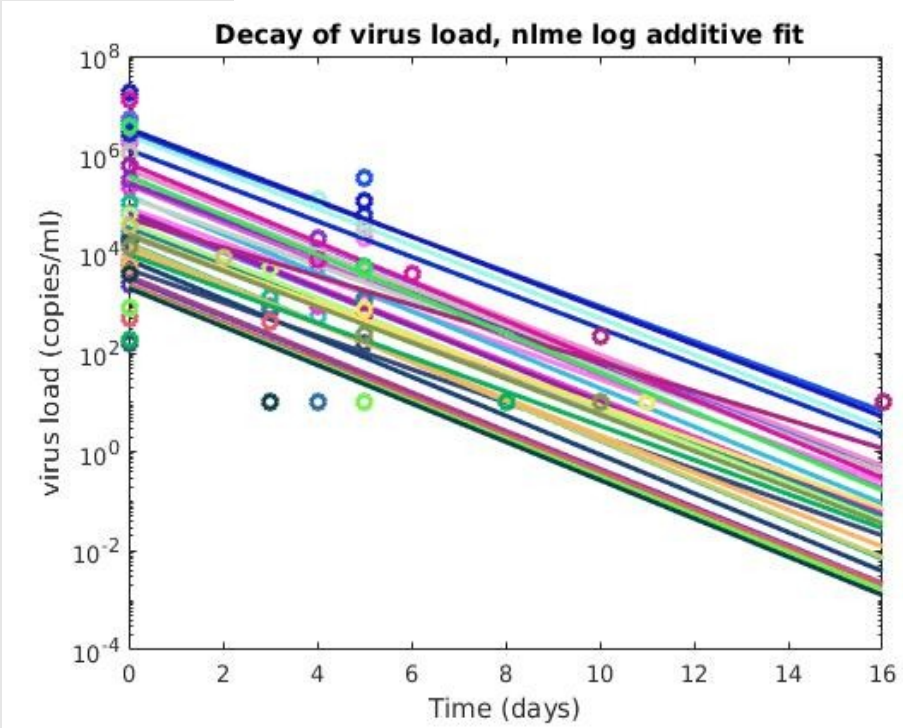


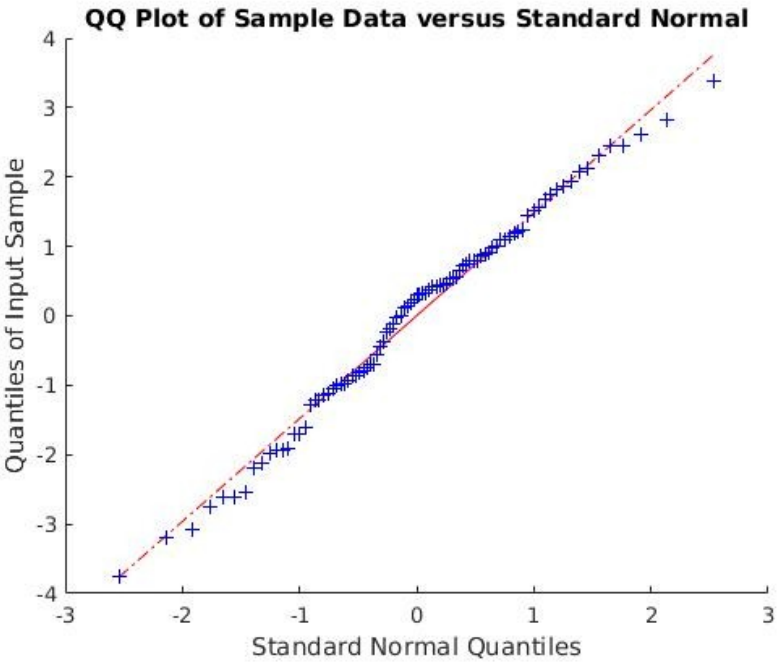
5. NLME

- additive error model + log fit:

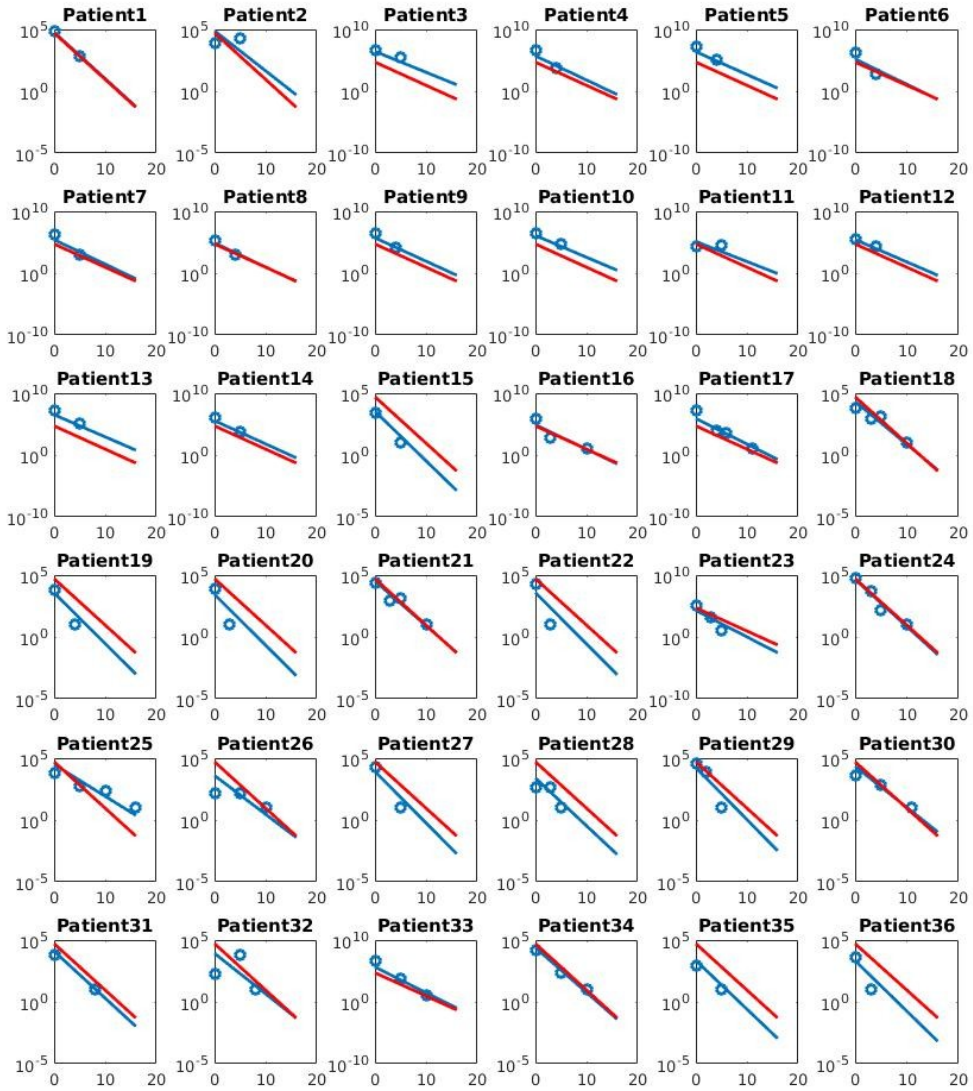




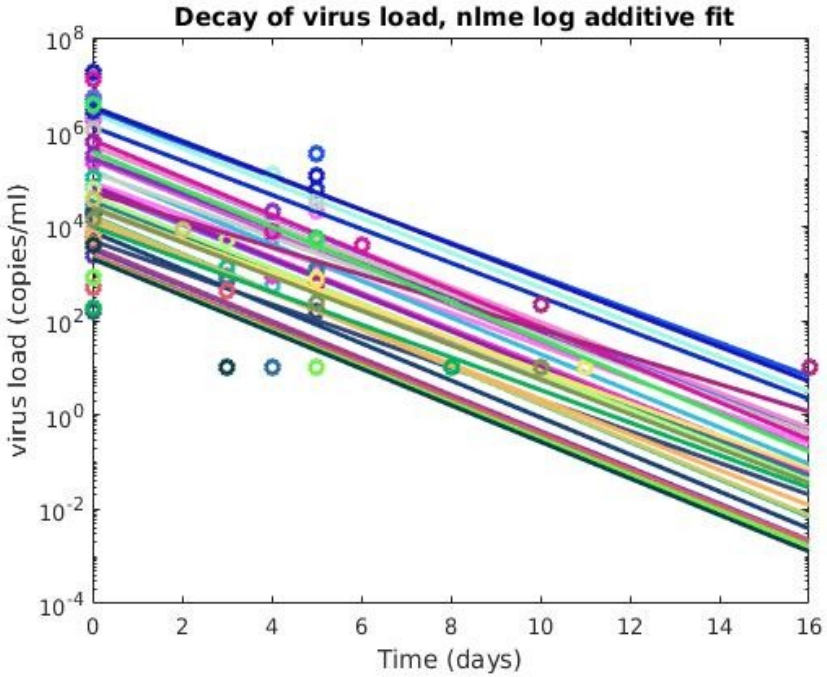




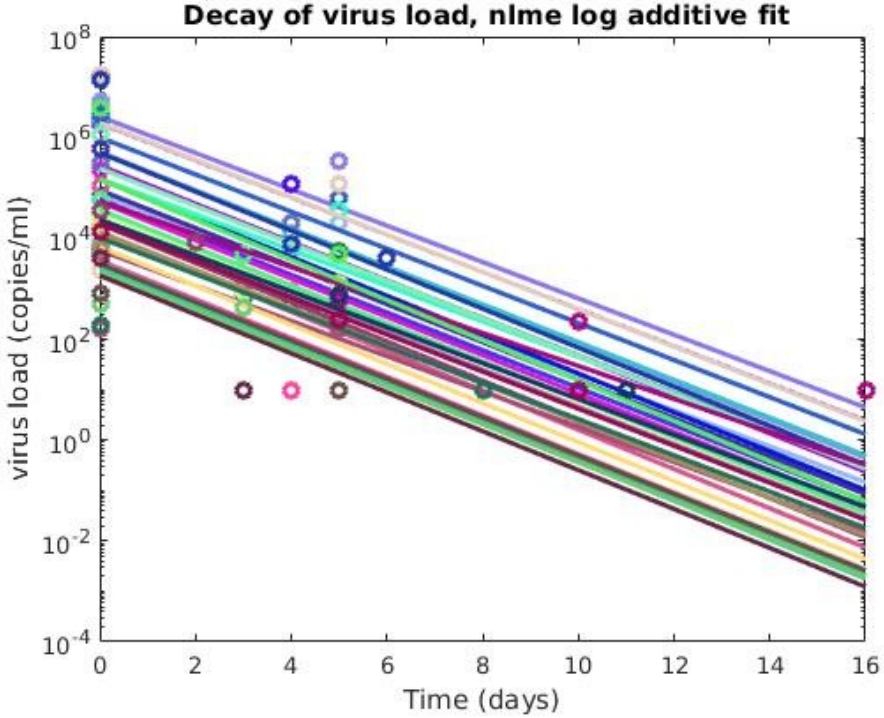
- additive error model + log fit:



original



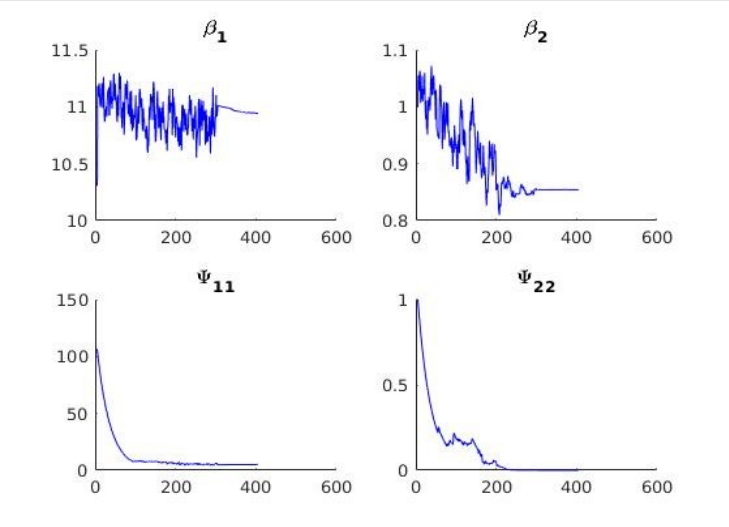
with noise



5. NLME

- additive error model + log fit:
- very robust to noise
- both random effects go to 0 → try model with only one random effect
- random effect on x0 and CLv: BIC = 462.26
- random effect on x0 only: BIC = 460
- random effect on CLv only: BIC = 476.87

- overall parameters:
- exponential 43345 x0 0.8715 CLv
- proportional 88409 x0 1.1723 CLv
- additive log 50784 x0 0.8646 CLv



6. Summary

- sparse data: fitting to individual patient data makes least assumptions → would be best, but not robust to errors
- fitting on pooled data is robust but doesn‘t tell us much about single patients
- pooled fitting is a good approximation if we knew what covariate groups data best (i.e. age, virus type, …)

  BUT

- NLME is the best way to deal with sparse data, robust to errors and keeps characteristics of the groups (patients)
- NLME has easy ways of checking whether it‘s assumptions are met for the input data
- easy to try out different error models

7. Sources

- Rath, von Kleist, Tief et al: Virus load kinetics and resistance development during Oseltamivir treatment in infants and children infected with Influenza A (H1N1) 2009 and Influenza B viruses, The Pediatric Infectious Disease Journal, Volume 31, September 2012, p.899-905
- von Kleist, Sunkara: Numerics for Bioinformaticians, Semester 1 Lecture 15, 2017, http://systems-pharmacology.de/wp-content/uploads/2017/02/Posterior2.pdf , last accessed 15.07.2017
- Huisinga: Nonlinear Mixed Effect Modelling, 2016, PharmetrX module, Universität Potsdam
- The MathWorks, Inc.: nlmefit Documentation, https://de.mathworks.com/help/stats/nlmefit.html, last accessed 17.07.2017
- Ette, Williams: Pharmacometrics. The Science of Quantitative Pharmacology, Wiley 2007


THANK YOU
FOR YOUR ATTENTION