Analysis of the Anthrax Vaccine Studies

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Plan of Campaign

- Modulate NHP immune response to AVA by dose variation (2003 committee)
  - Hu-AVA, 1/5, 1/10, 1/20, 1/40, saline controls
  - 0-wk, 4-wk, 26-wk IM
- Build comprehensive immunologic profile
- Challenge at 12, 32, & 42 months after first vaccination
- Build a model for predicting a defined outcome (i.e. survival)
- Apply this relationship to the human clinical study to predict protection of vaccinees

Review of the CDC Macaque Study Analysis

Table 1. Basic Statistics for Primate Groups

Group Number	Count		Approx. Week Challenged	Vaccine Dilution
	Treated	Control		
1	10	2	228	1:1
2	9	1	228	1:5
3	10	2	228	1:10
4	10	2	52	1:20
5	10	2	52	1:40
6	10	2	52	1:10
7	10	2	52	1:20
8	10	2	52	1:40
9	9	2	124	1:10
10	10	2	124	1:1
11	8	2	124	1:5
12	8	2	124	1:20
Total	114	23		

Table 2. Death Rate by Dose

Vaccine Dilution	Count	Outcome	
		Died	Death Rate
1:1	20	2	10%
1:5	17	0	0%
1:10	29	9	31%
1:20	28	10	36%
1:40	20	7	35%
control	23	16	70%
Total	137	44	32%

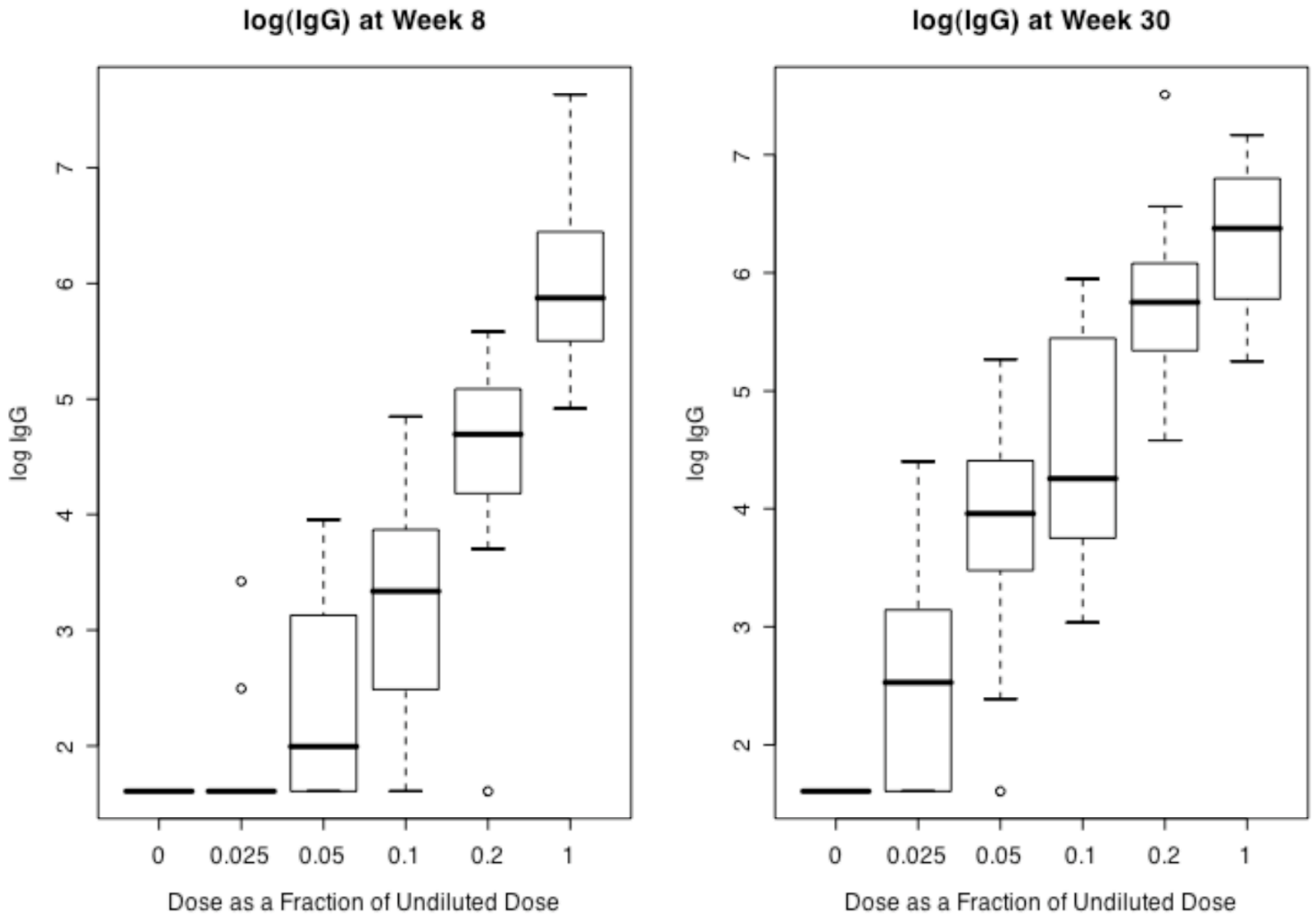


Figure 1. Log IgG at weeks 8 and 30 as a function of vaccine dose.

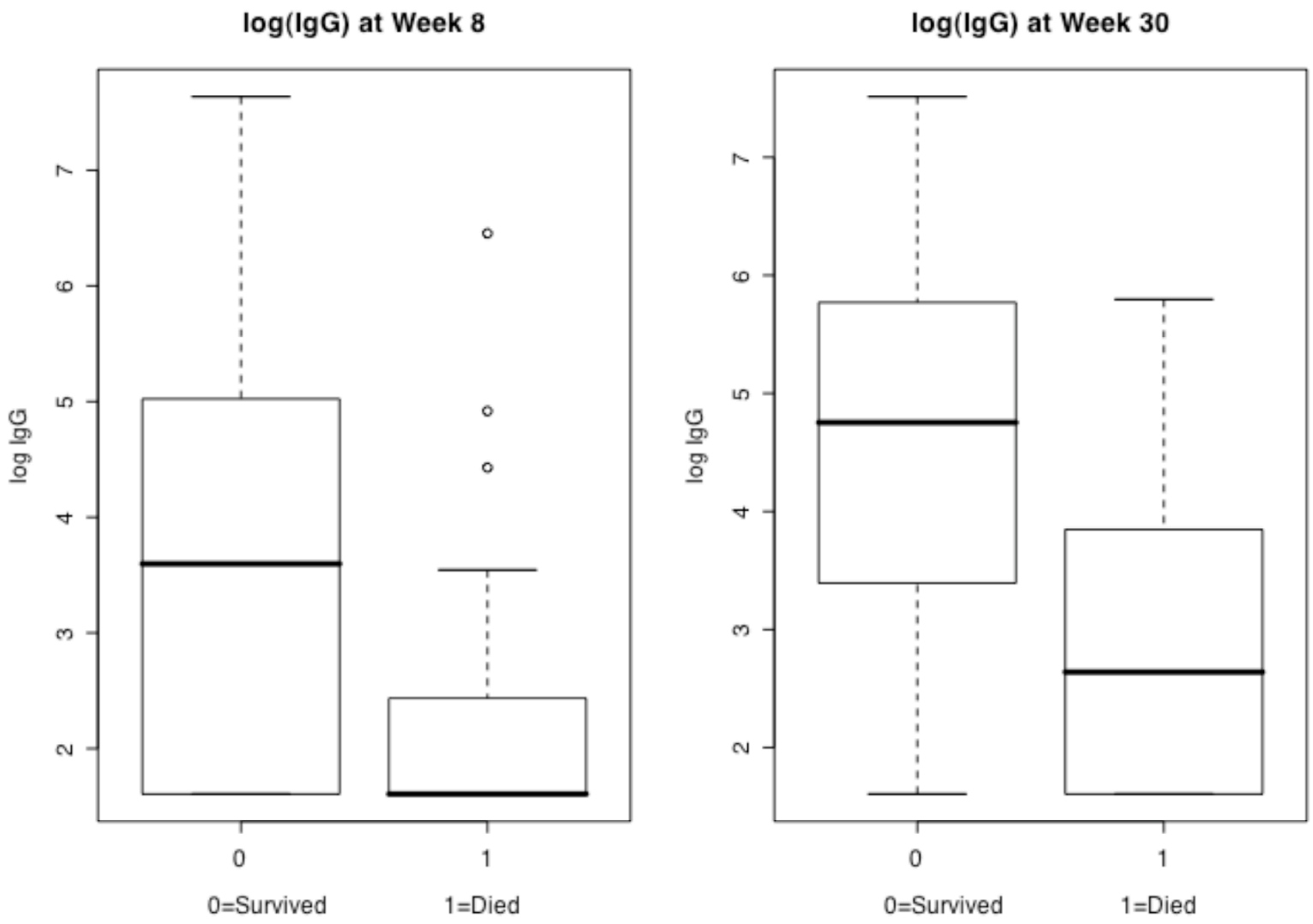
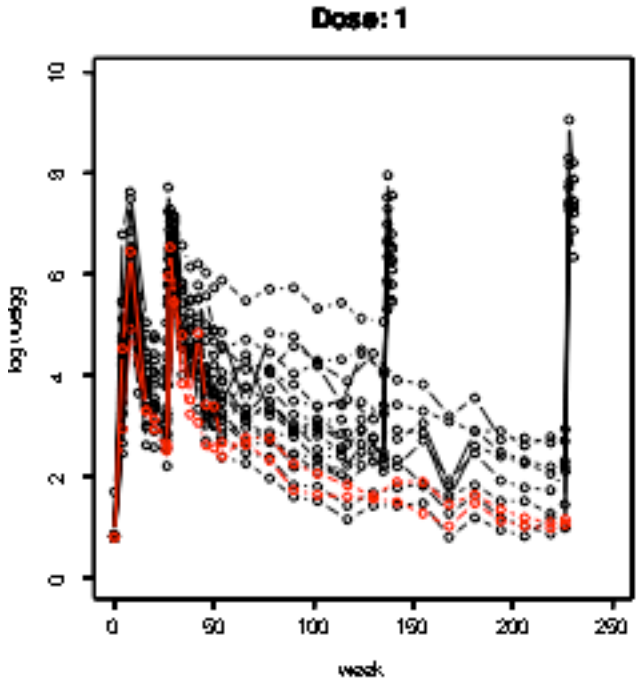
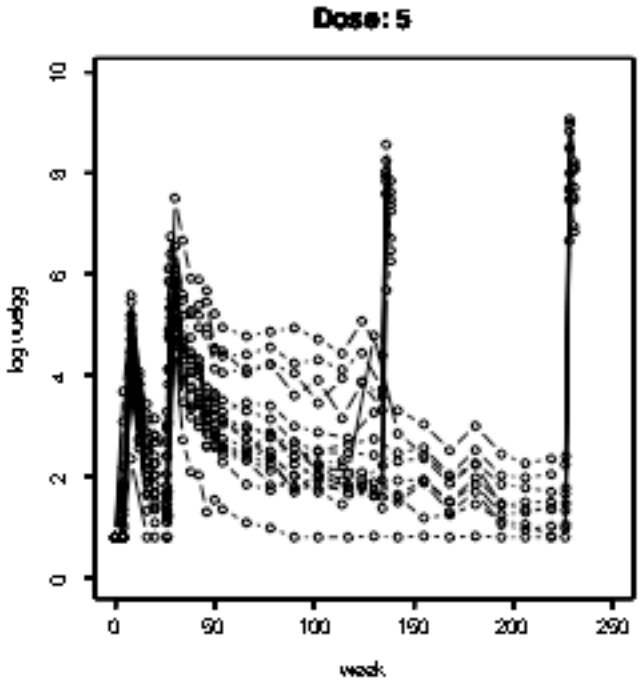
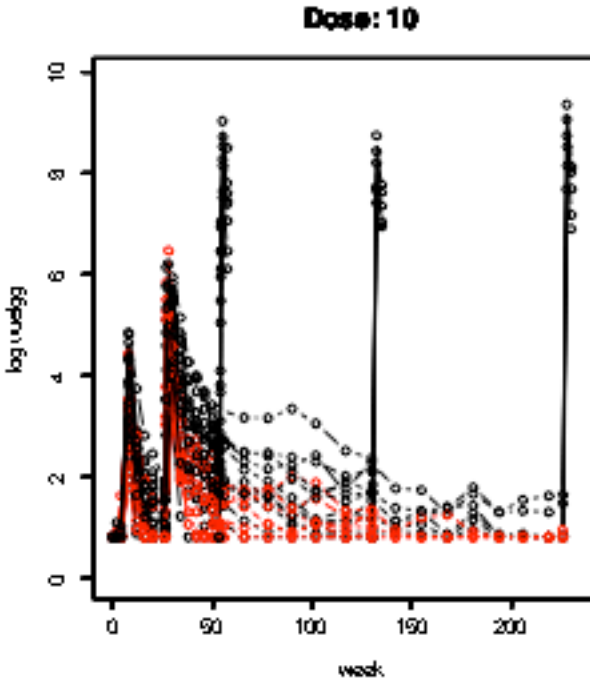
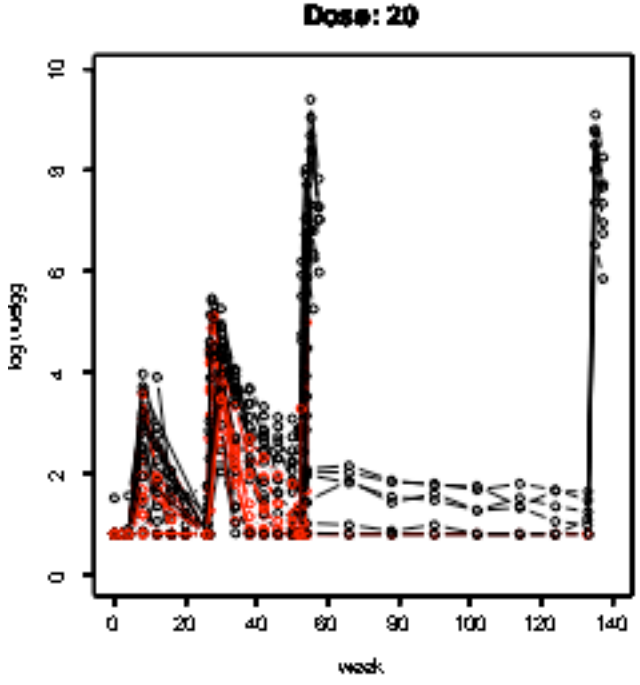


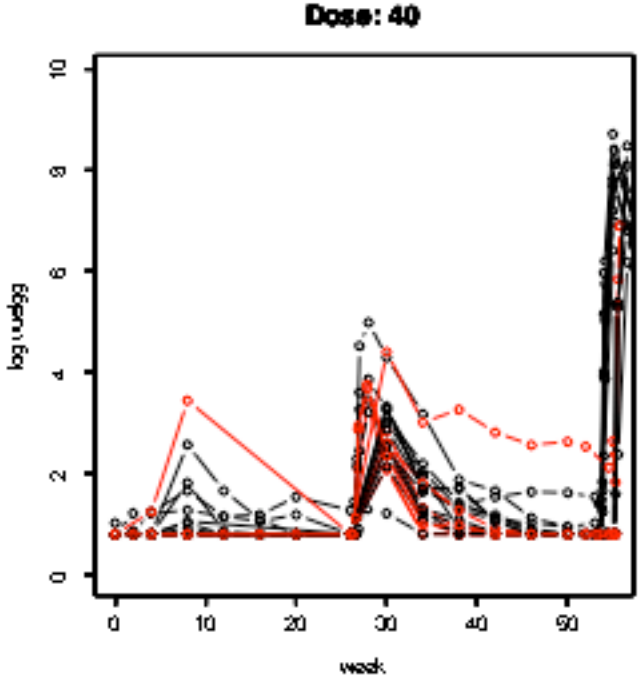
Figure 2. Log IgG at weeks 8 and 30 as a function of survival status.


Dose: 1
log titer
week

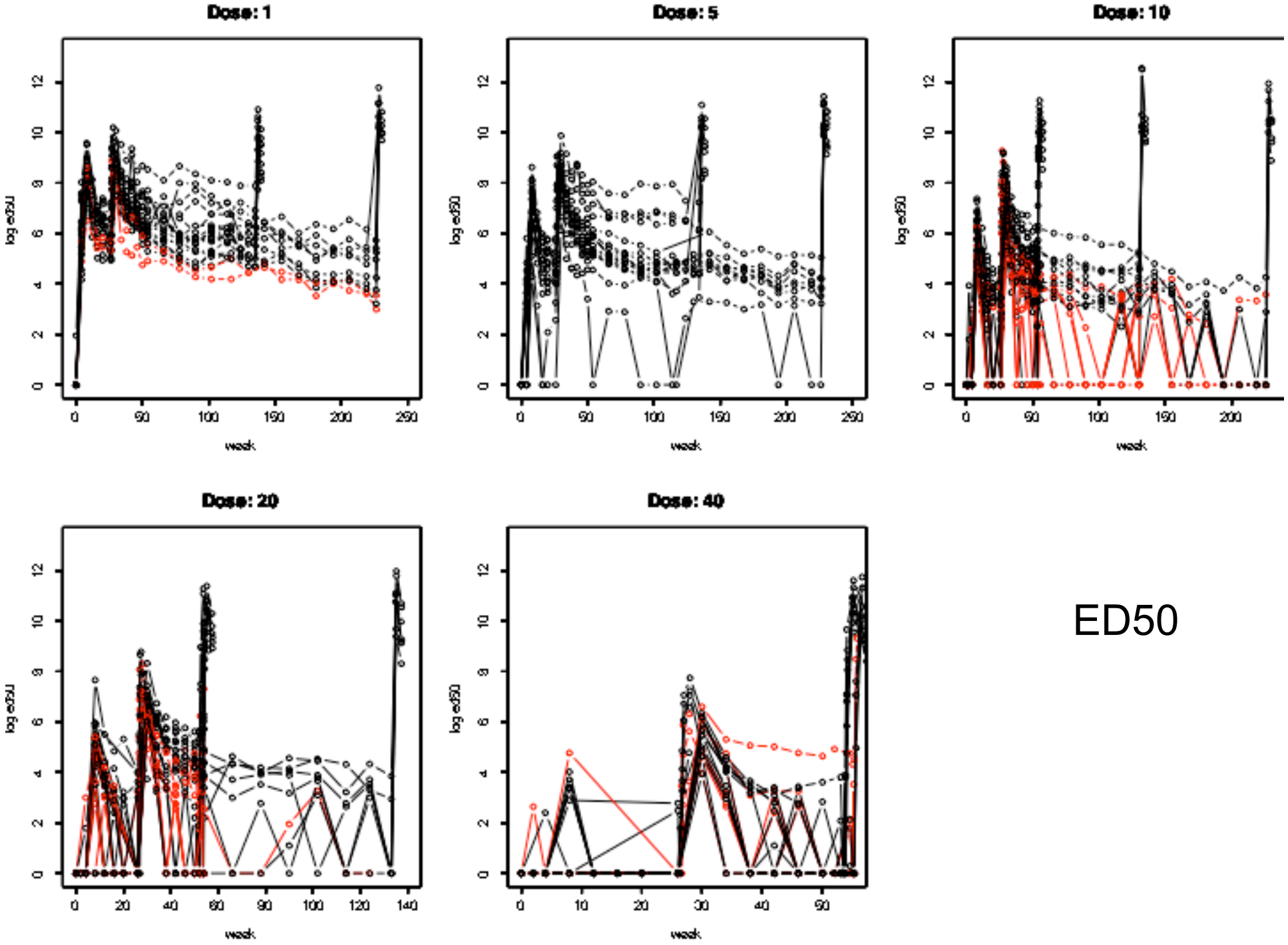

Dose: 5
log titer
week


Dose: 10
log titer
week


Dose: 20
log titer
week


Dose: 40
log titer
week

IgG



ED50

Logistic Regression Model

- Linear model for log odds of category membership:

$$\log \frac{p(y=1 \mid \boldsymbol{x}_i)}{p(y=-1 \mid \boldsymbol{x}_i)} = \sum \beta_j x_{ij} = \boldsymbol{\beta} \boldsymbol{x}_i$$

- Conditional probability model

"Stage 2" Analysis

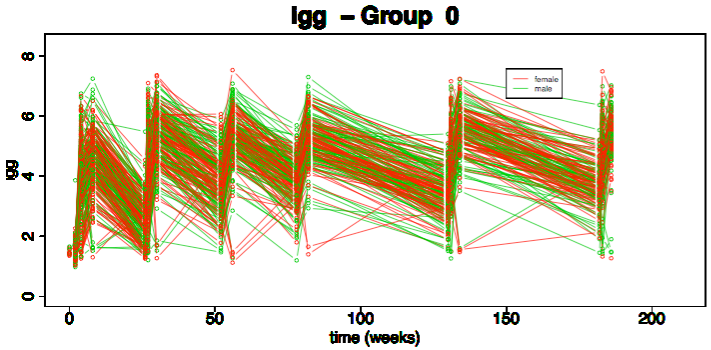
Predictor	All Groups	
	Estimate	p-value
log IgG week 8	-0.34	0.37
log IgG week 30	-0.65	*0.02*
Sex=F	-0.21	0.36
Dose	1.39	0.32

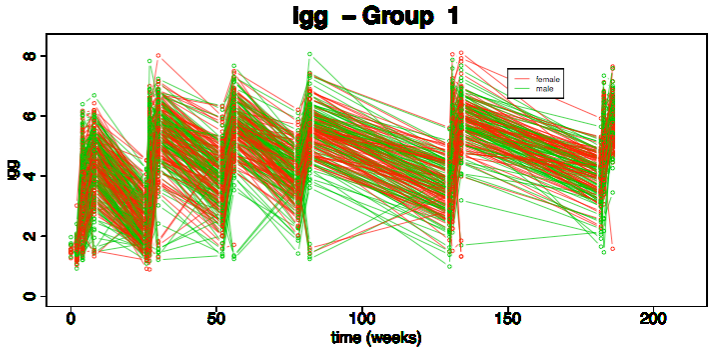
"Stage 3" Analysis

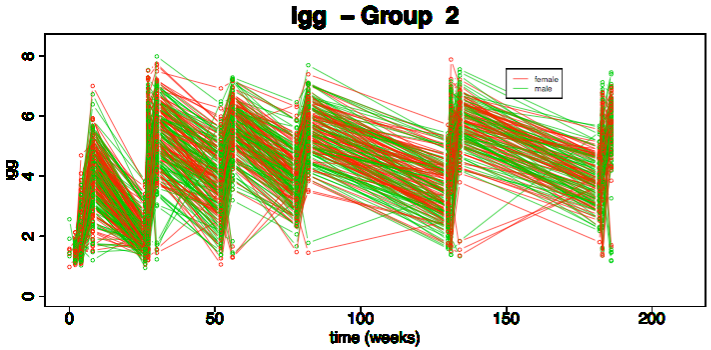
Predictor	All Groups	
	Estimate	p-value
log IgG peak	-0.29	0.09
Last ED50	-0.97	***0.01***
Last IFNeli	-0.05	0.71
Last SI	0.06	0.76

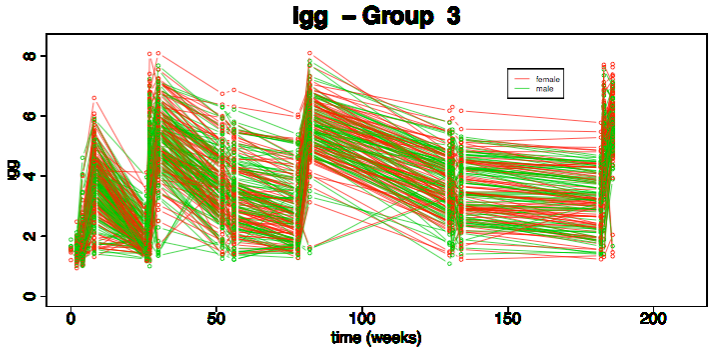
Out-of-Sample Predictive Performance

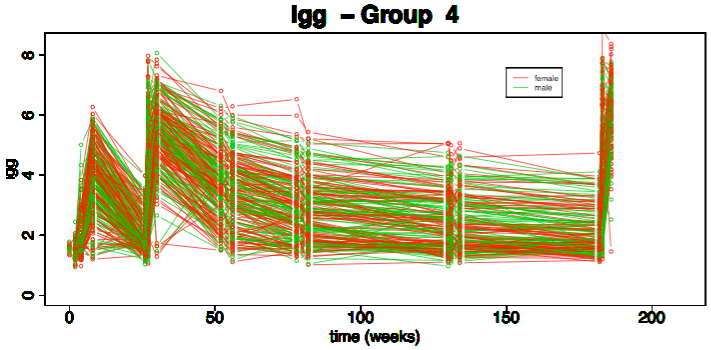
Model	CV Performance	
	Accuracy	ROC Area
Stage 2, Four Predictor	*0.73*	*0.77*
Stage 2, IgG Week 30	*0.73*	*0.78*
Stage 3, Four Predictor	*0.70*	*0.76*
Stage 3, peakIgG + last ED50	*0.70*	*0.79*
Stage 4, Eight Predictor, Complete	*0.76*	*0.80*
Stage 4, IgG38+IL4/IFNeli, Complete	*0.75*	*0.79*
Stage 4, Three Predictor, Limited	*0.73*	*0.78*
Stage 4, IgG34+SI8, Limited	*0.71*	*0.79*

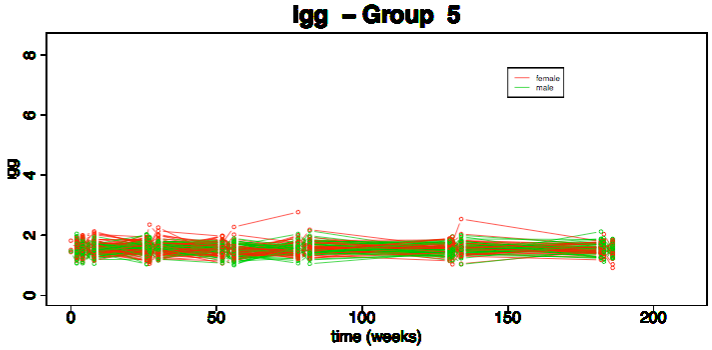

Igg – Group 0
Igg
time (weeks)
female
male

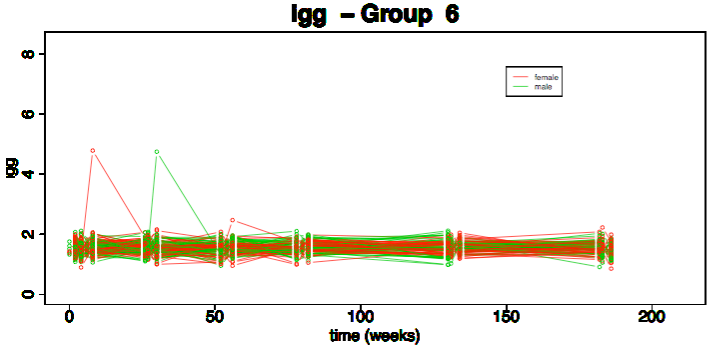

Igg – Group 1
Igg
time (weeks)
female
male


Igg – Group 2
Igg
time (weeks)
female
male


Igg – Group 3
Igg
time (weeks)
female
male


Igg – Group 4
Igg
time (weeks)
female
male


Igg – Group 5
Igg
time (weeks)
female
male


Igg – Group 6
Igg
time (weeks)
female
male

A Model for IgG response in humans

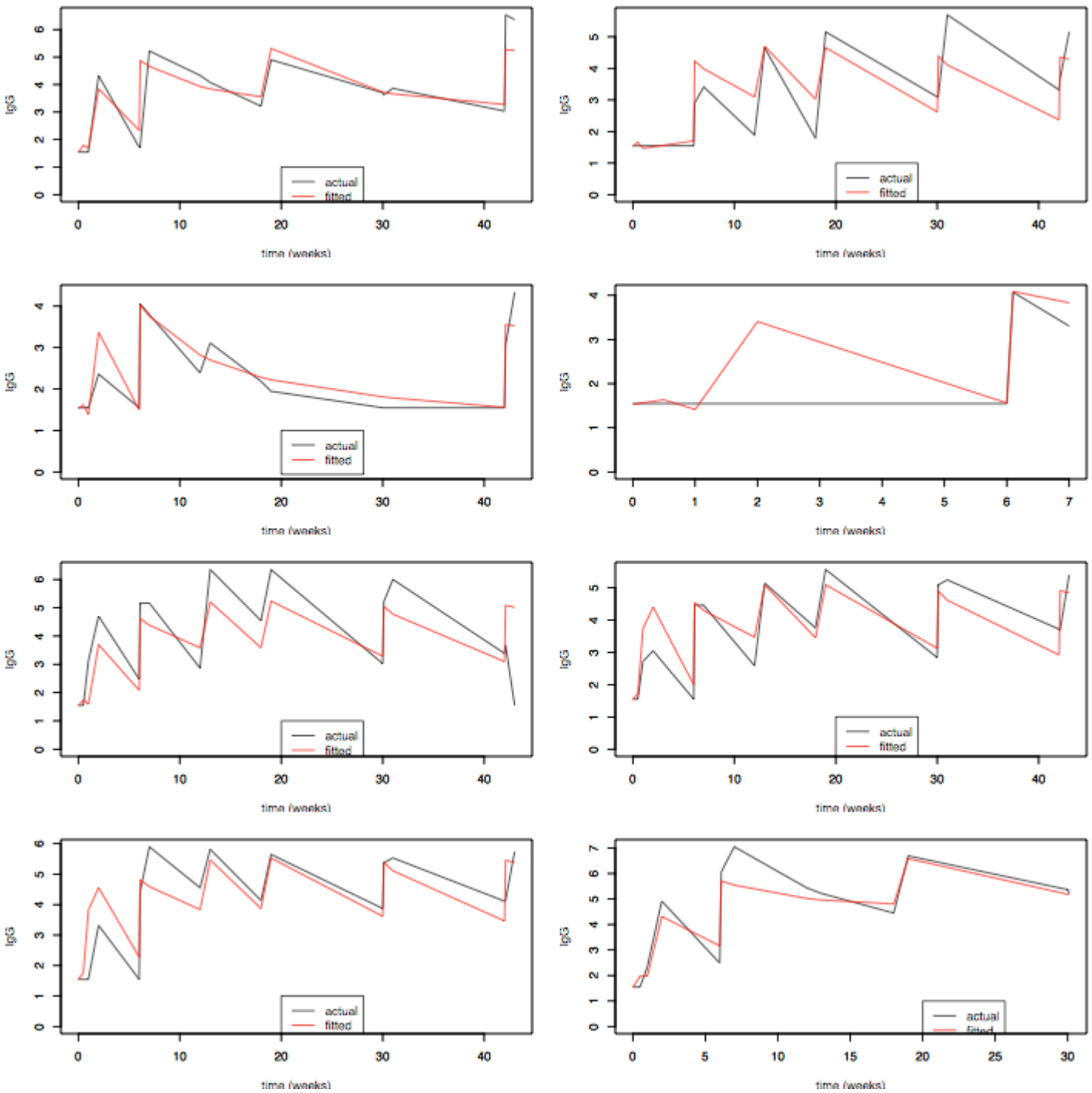
$$IgG(i,t) = b_0 + (b_1(i) \times \log(t)) + \sum_{d \in doses} b_3(d) \times \exp(b_4(d) \times \text{timesincedose}(d))$$

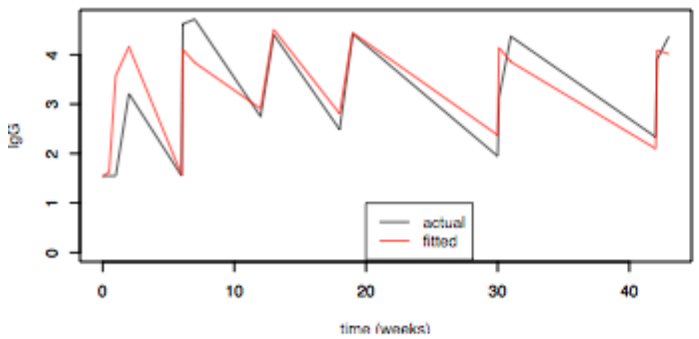
intercept

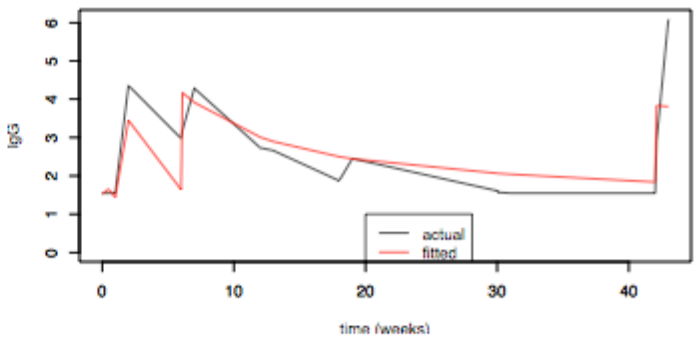
subject specific random slope

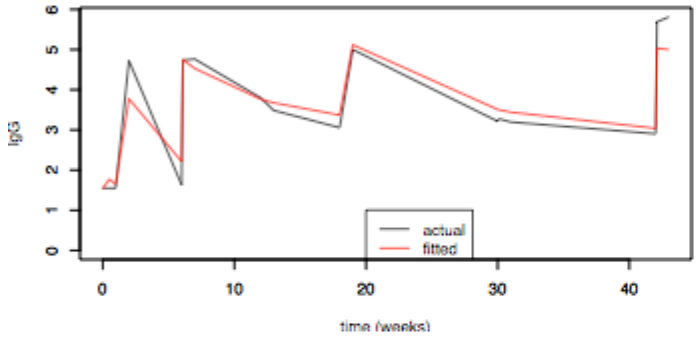
height of the dose *d* shock

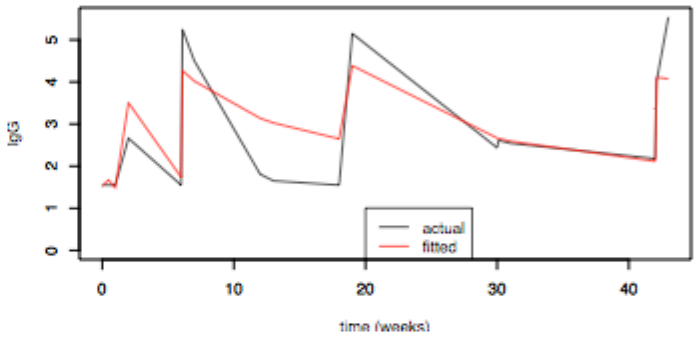
exponential rate of decay for dose *d*

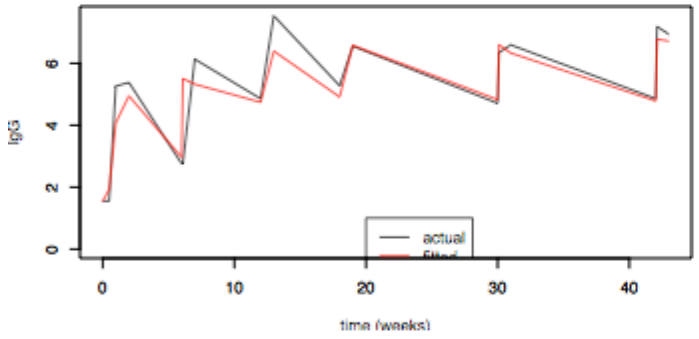

IgG
time (weeks)
actual
fitted

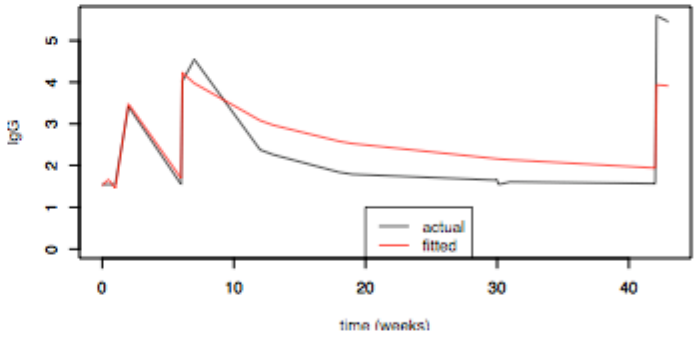

IgG
time (weeks)
actual
fitted

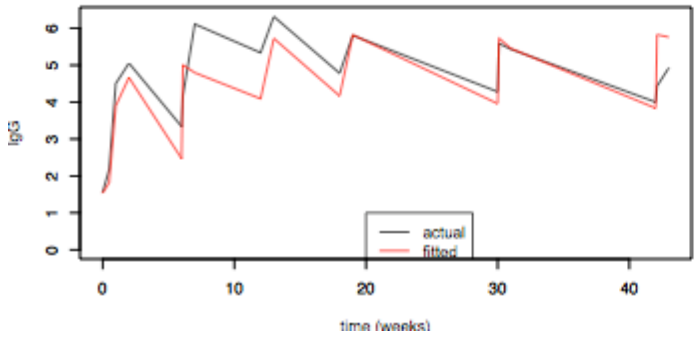

IgG
time (weeks)
actual
fitted

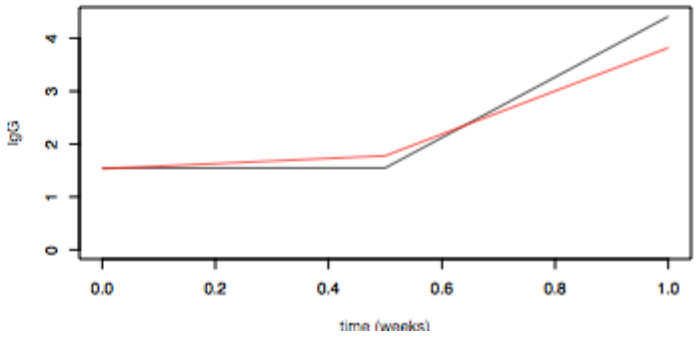

IgG
time (weeks)
actual
fitted

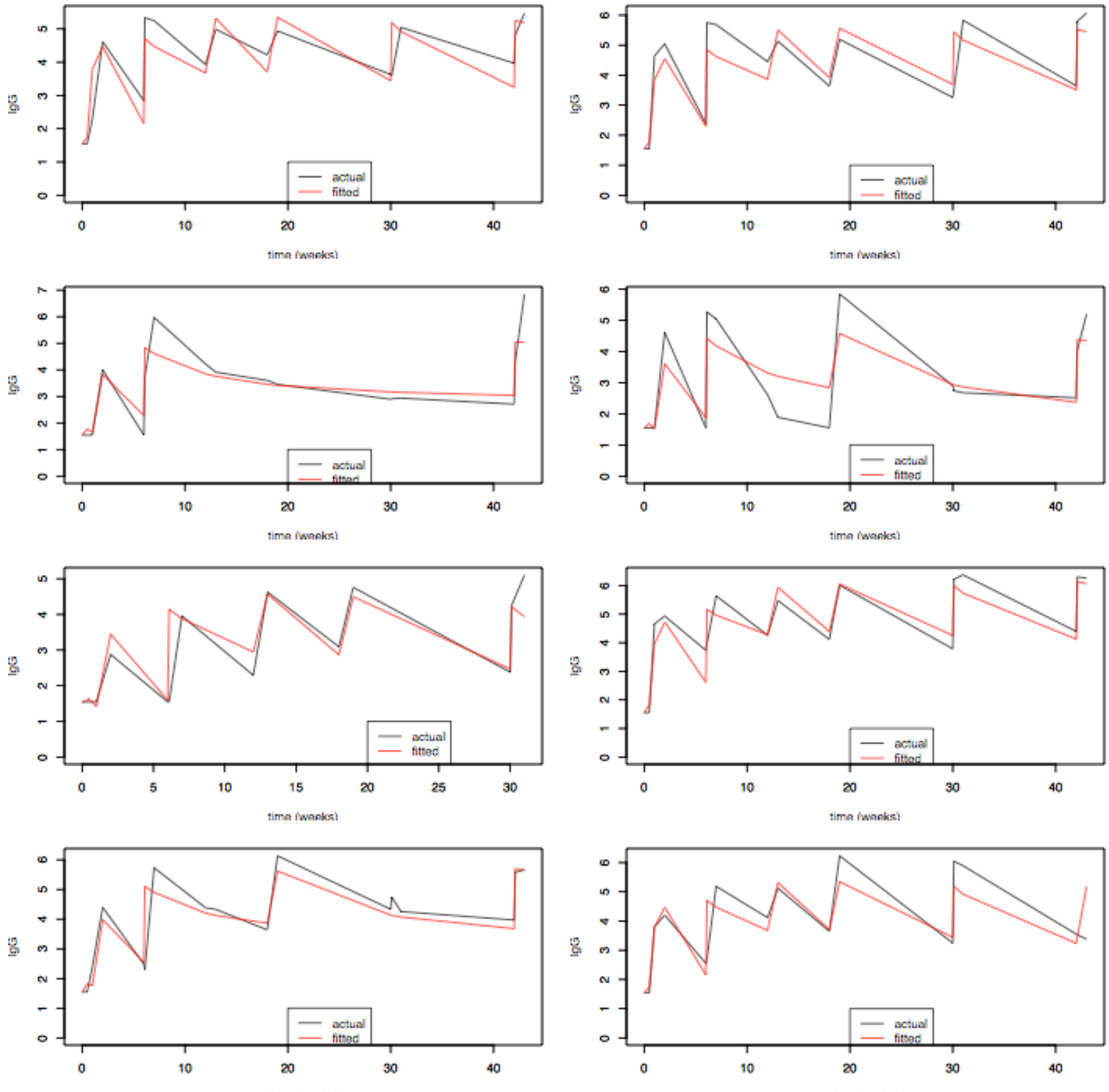

IgG
time (weeks)
actual
fitted


IgG
time (weeks)
actual


IgG
time (weeks)
actual
fitted


IgG
time (weeks)
actual
fitted


IgG
time (weeks)



IgG
actual
fitted
time (weeks)
IgG
actual
fitted
time (weeks)
IgG
actual
fitted
time (weeks)
IgG
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time (weeks)
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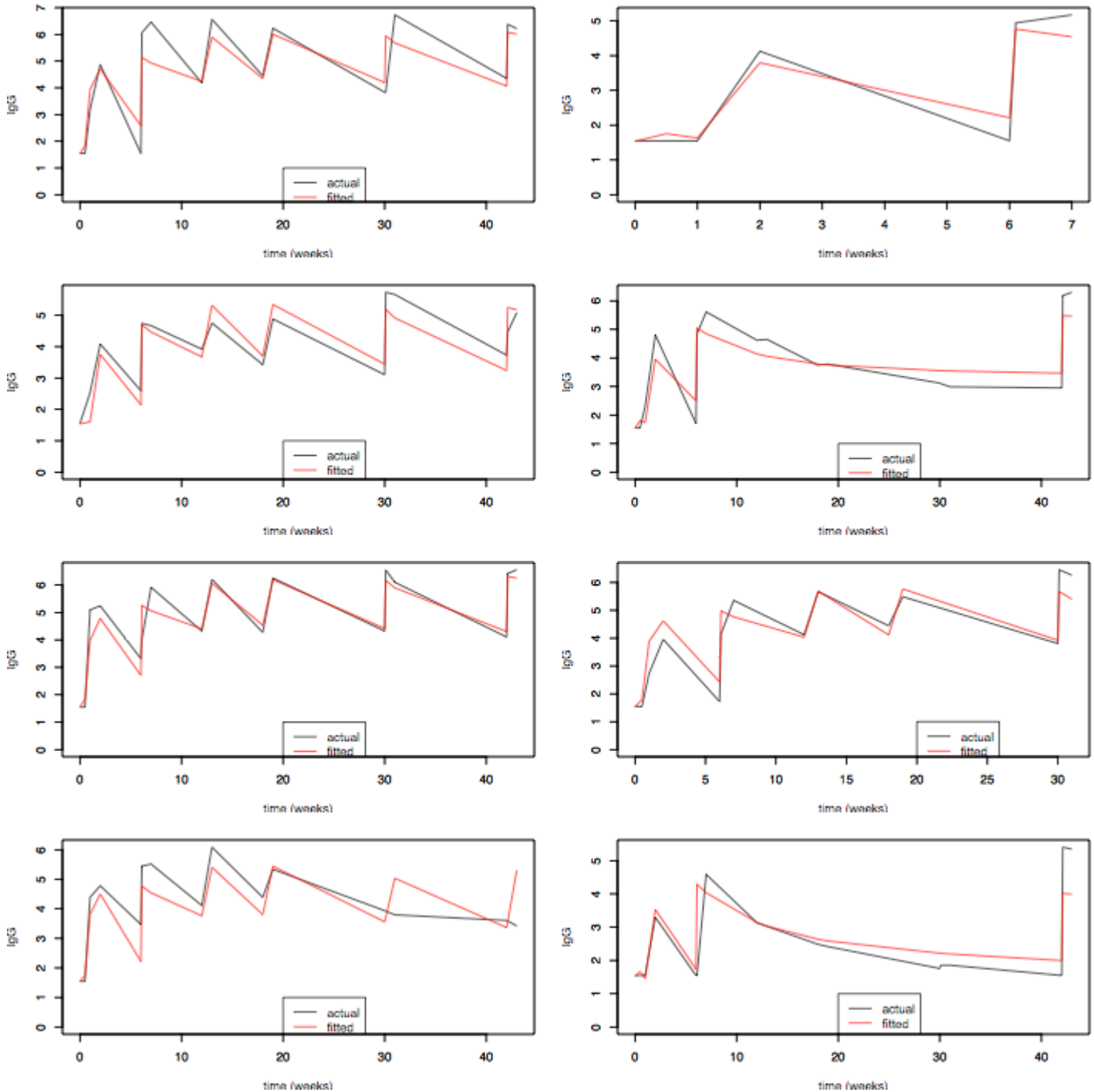
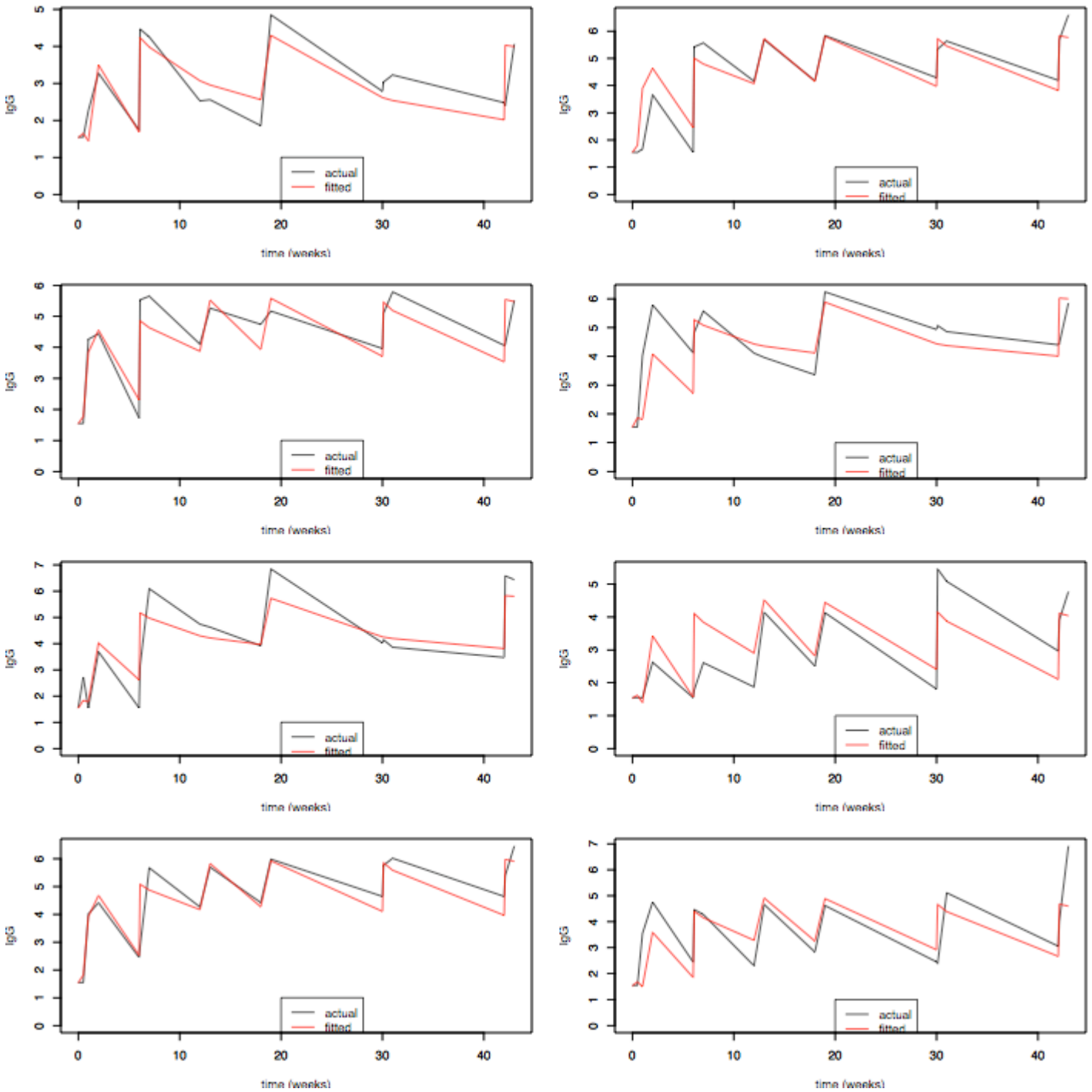
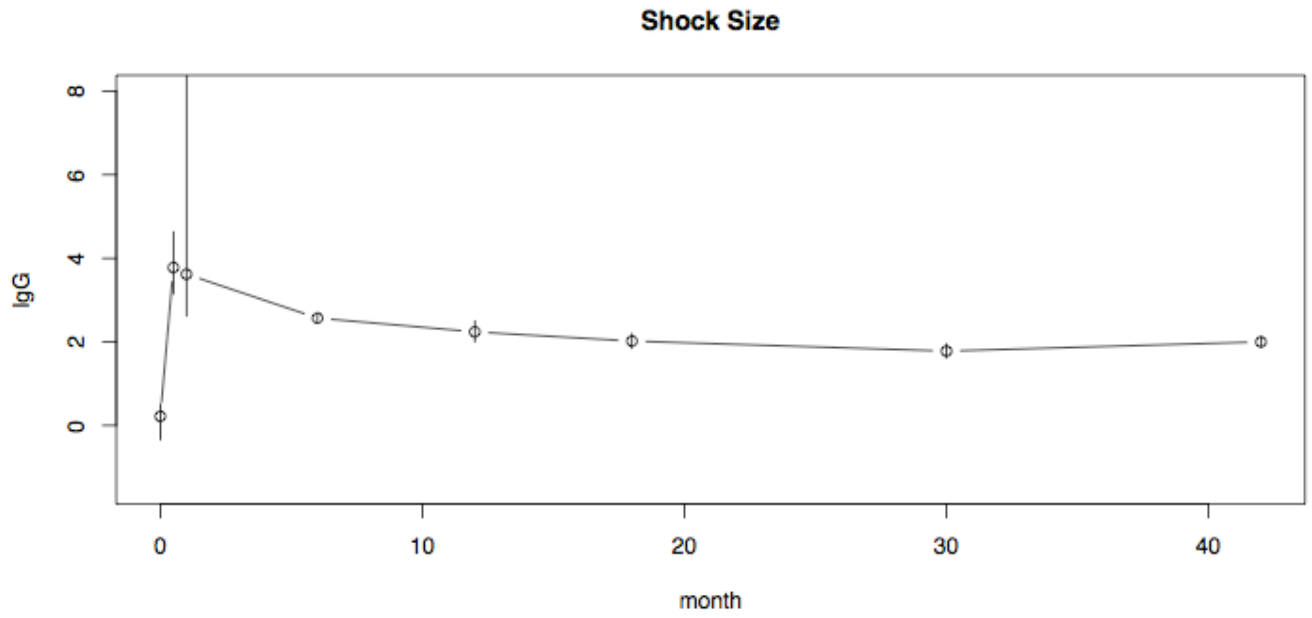
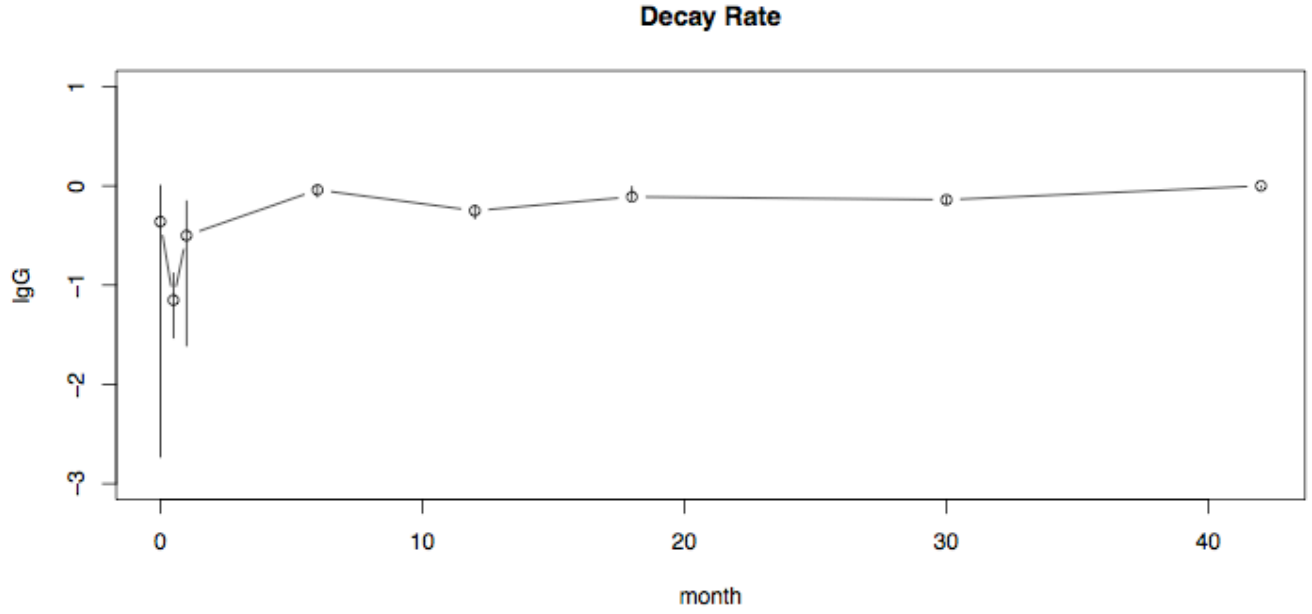
time (weeks)

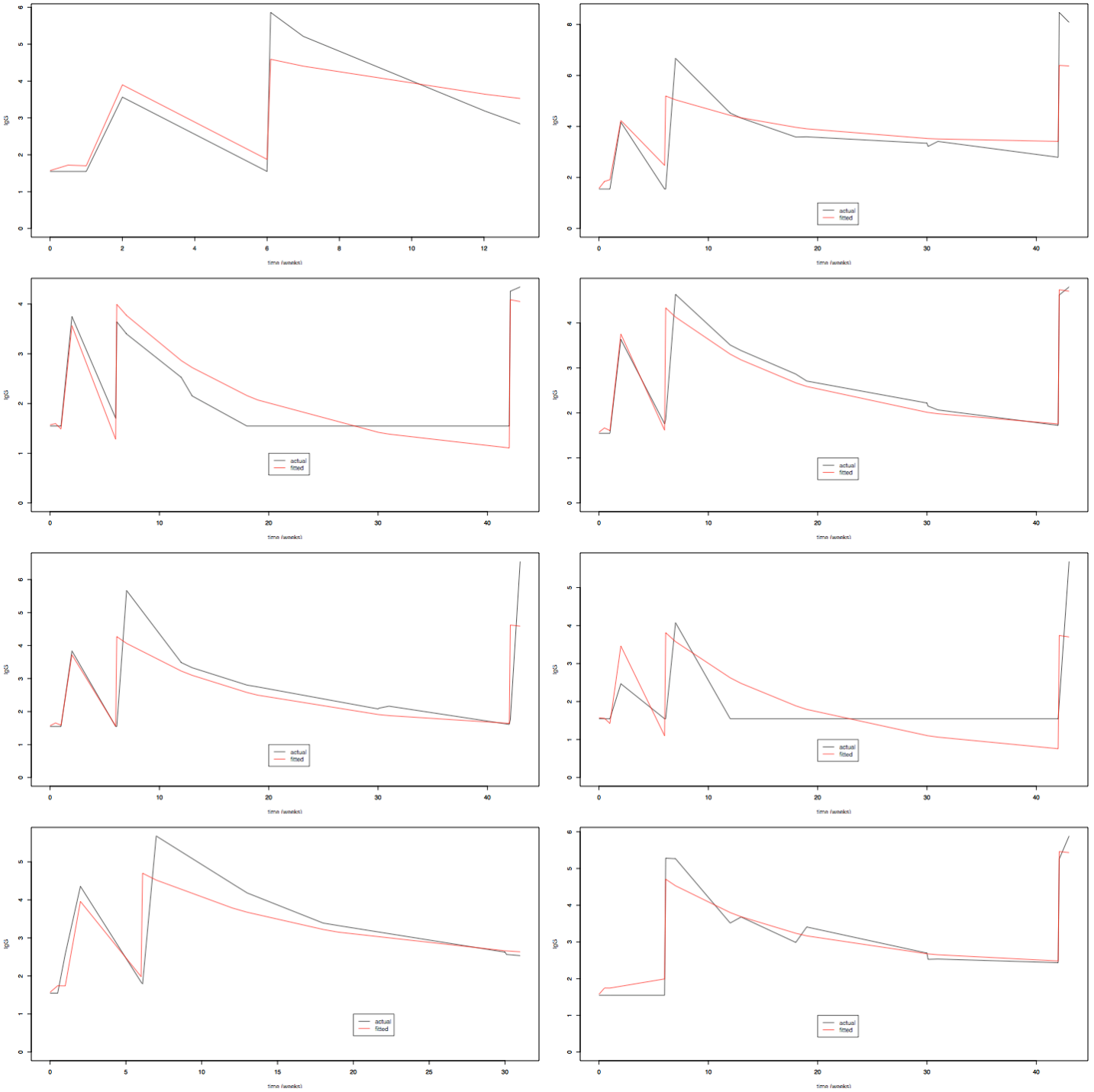

IgG
time (weeks)
actual
fitted


IgG
time (weeks)
actual
fitted

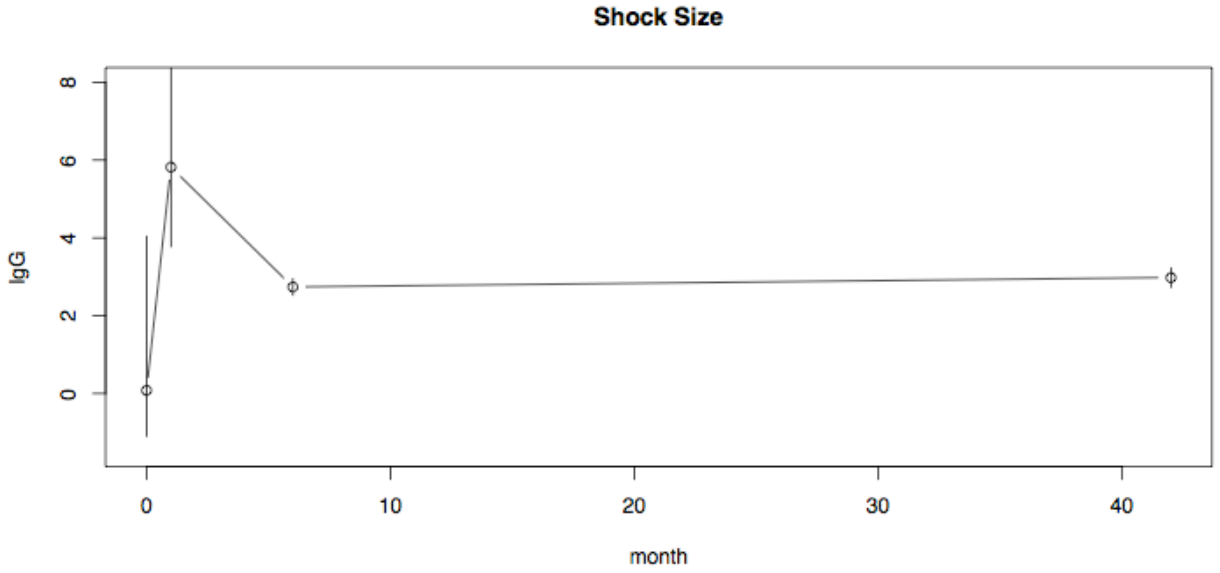

Shock Size
IgG
0
2
4
6
8
0
10
20
30
40
month

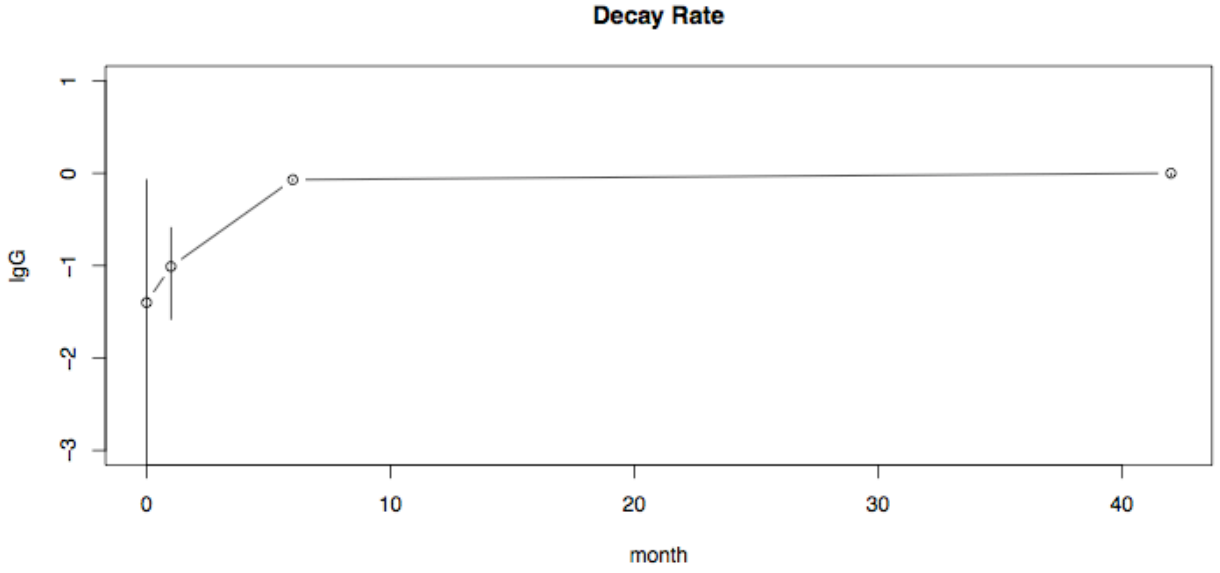

Decay Rate
IgG
−3
−2
−1
0
1
0
10
20
30
40
month

4IM



4IM Group


Shock Size
IgG
0
2
4
6
8
0
10
20
30
40
month


Decay Rate
IgG
−3
−2
−1
0
1
0
10
20
30
40
month

Why a model?

- Provides a simplified characterization of immune response to dosing schedules
- Quantifies the relationship between immune response and age, sex, etc.
- Can be used to predict immune response to future doses or challenges