SPIDA 2012 – Part 4

Mixed Models with R:

Non-linear Models: Asymptotic Functions of Time

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Longitudinal models for IQ recovery after coma

Data: IQ tests on 200 post coma patients at QEH

Number of observations per patient:

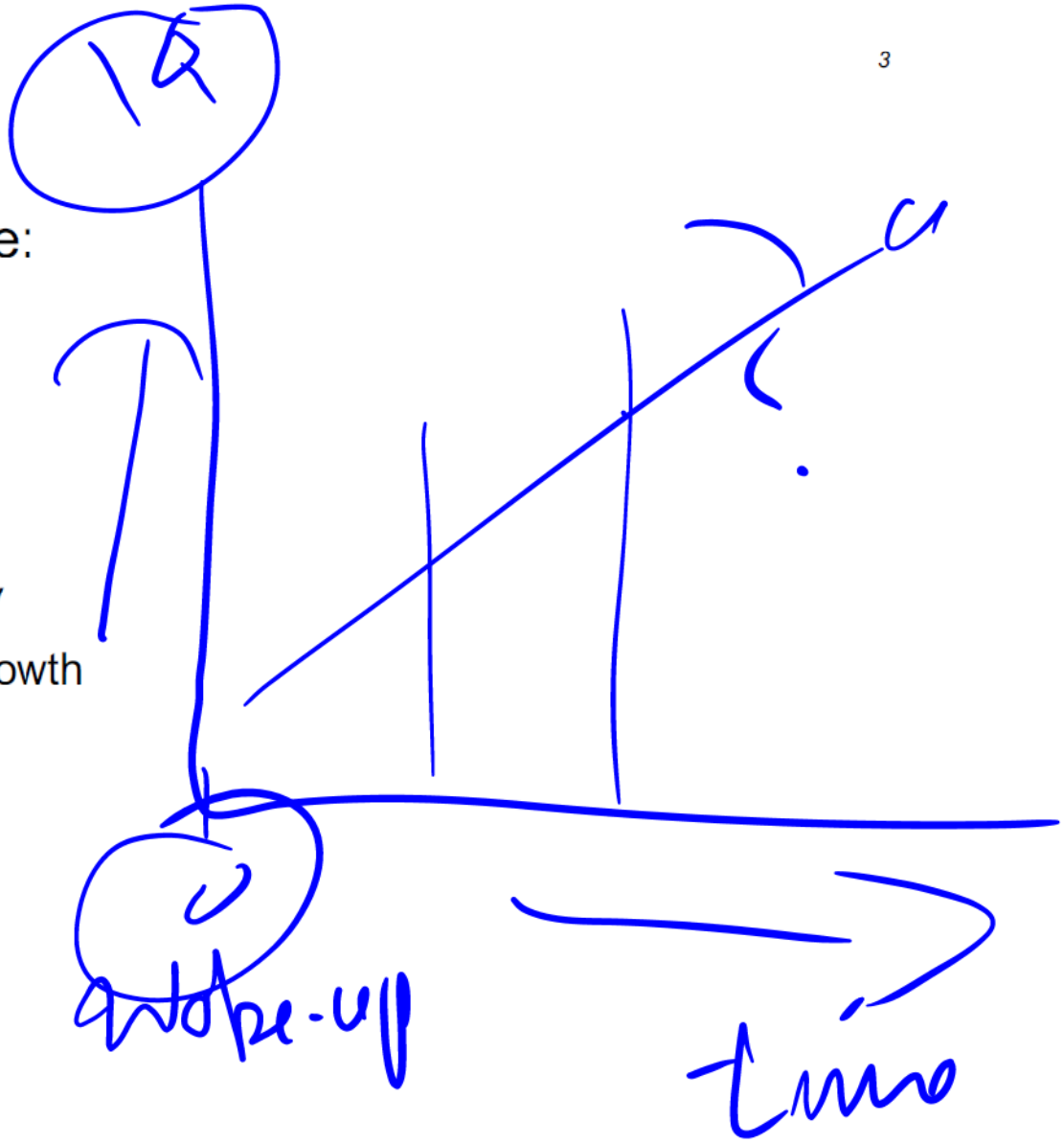
Number of observations	1	2	3	4	5	Total
Number of patients	107	61	27	4	1	200

Method of analysis: Mixed models for longitudinal data
Problem: Representing IQ recovery over time

2

Some functions of time:

- linear
- quadratic
- higher polynomials
- splines
- exponential growth, decay
- exponential asymptotic growth
- periodic functions



Polynomials:

Linear function:

$$E(IQ) = \beta_0 + \beta_1 T$$

Quadratic:

$$E(IQ) = \beta_0 + \beta_1 T + \beta_2 T^2$$

Cubic

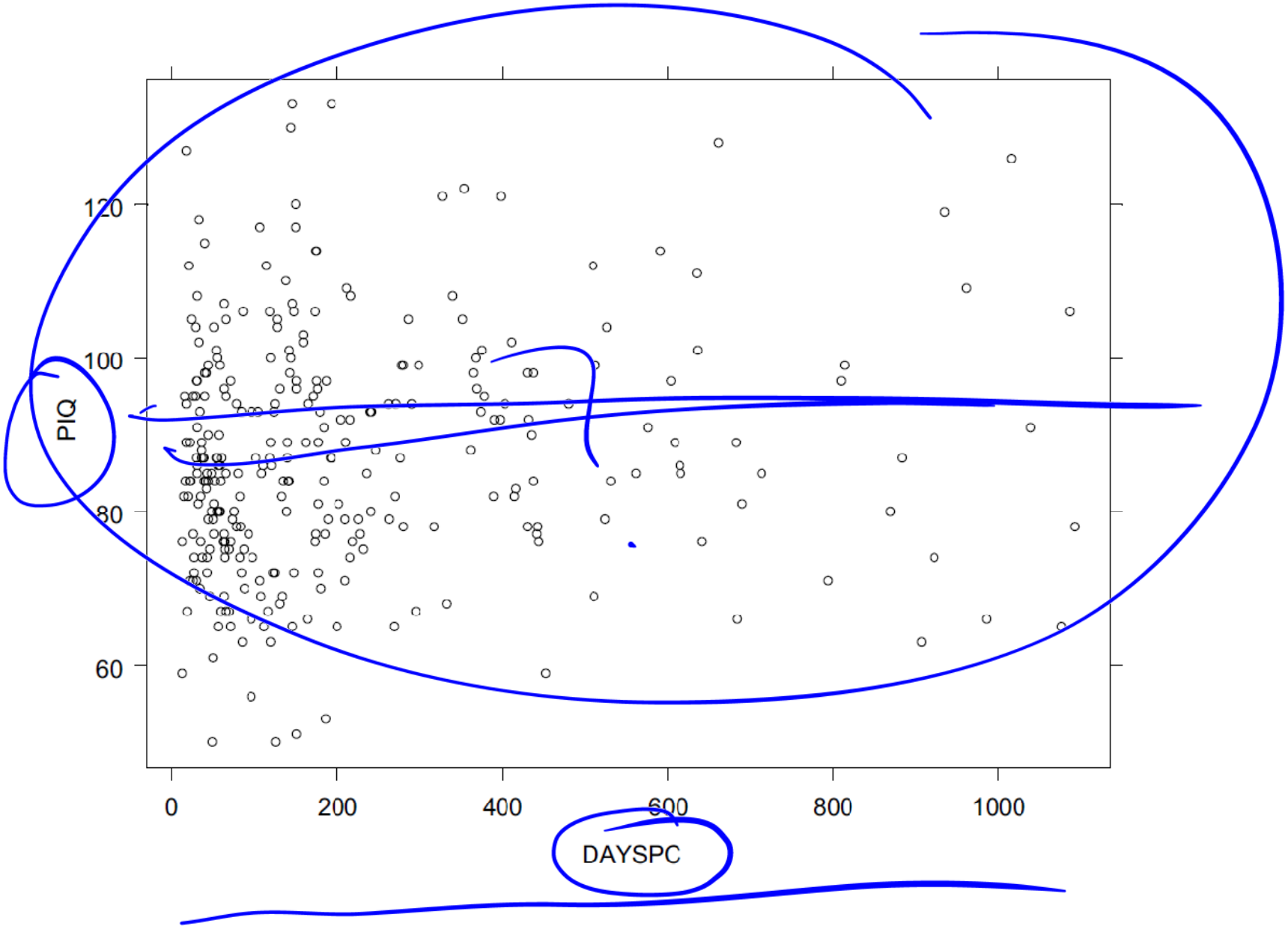
$$E(IQ) = \beta_0 + \beta_1 T + \beta_2 T^2 + \beta_3 T^3$$

Quartic:

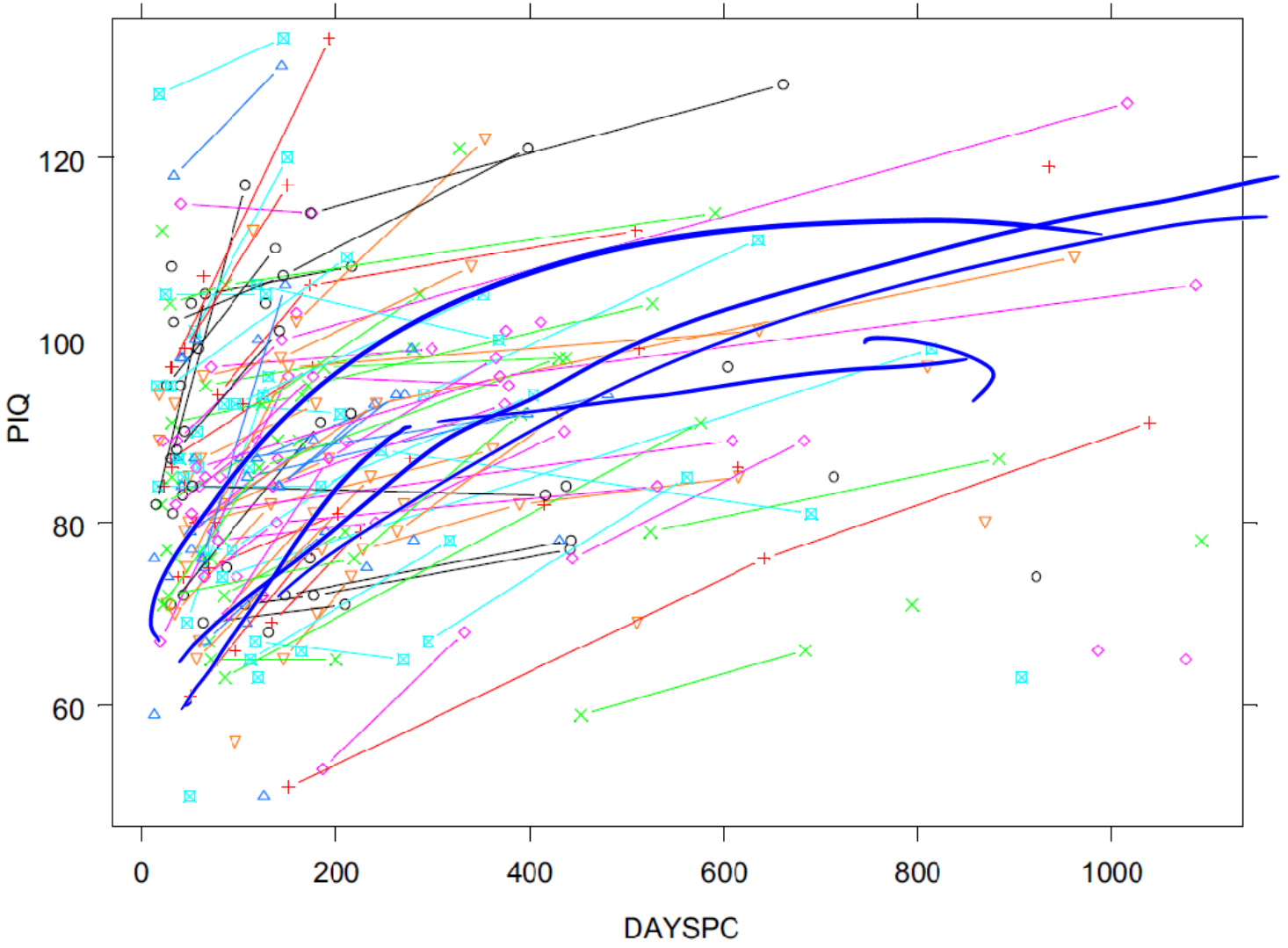
$$E(IQ) = \beta_0 + \beta_1 T + \beta_2 T^2 + \beta_3 T^3 + \beta_4 T^4$$

Note the change in meaning of parameters as we move up: Last parameter has global interpretation, previous parameters at time = 0

4



5



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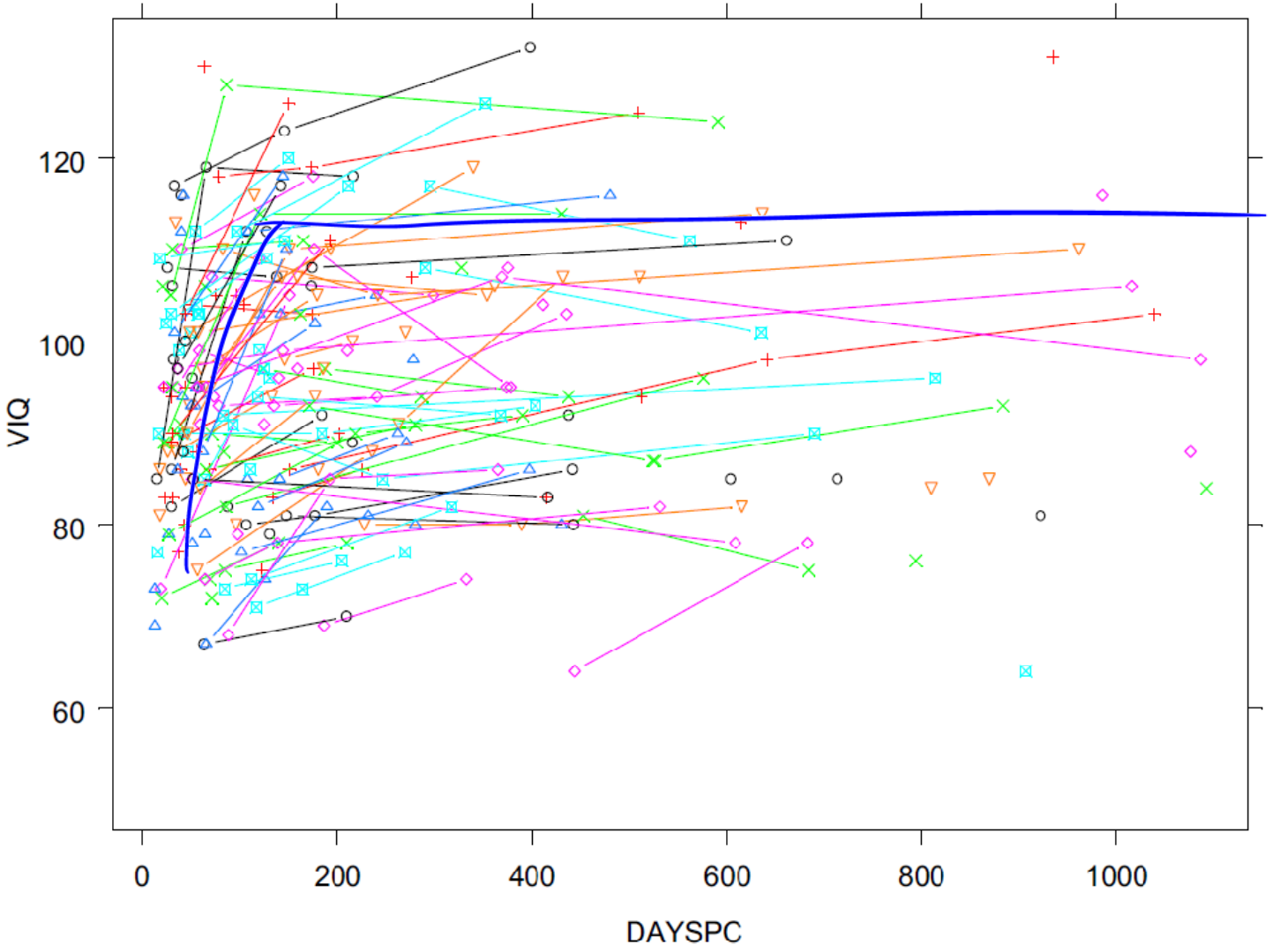


7

Modeling individual trajectories

A good strategy in longitudinal data analysis is to start by building a plausible model for individual trajectories even if there isn't enough data from any one individual to actually fit the model. If the data are unbalanced and you are willing to assume that the between-subject effect is close to the within-subject effect, then the estimation of individual trajectories 'borrows strength' from the between-subject model.

Within the limits imposed by sample size, we try to construct a model that:

1. captures the main theoretical properties of the phenomenon,
2. preferably has interpretable parameters

8

To experiment with your model don't hesitate to simulate. Just create some plausible data with **locator** and play with models.

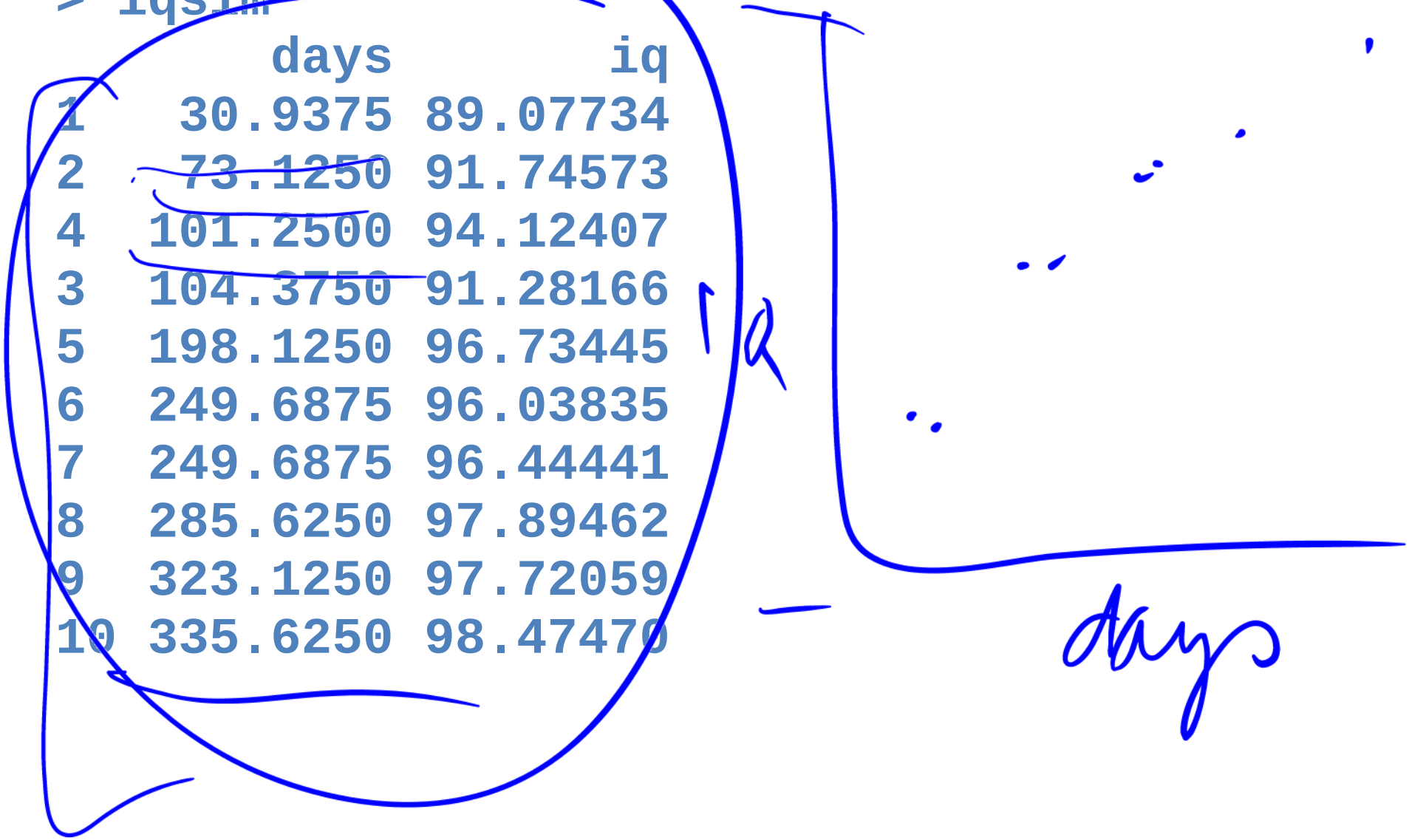
Make an emply plotting surface, click to create some xy data, give the columns the names you want:

```
plot(0,0, xlim = c(0,800),
      ylim = c(85,105), type = 'n')
iqsim.ex <- locator( 10 , type = 'p')
iqsim.ex
iqsim.ex <- as.data.frame( iqsim.ex )
iqsim.ex
names( iqsim.ex ) <- c('days','iq')
iqsim.ex <- iqsim.ex[
            order(iqsim.ex$days),]
```


9

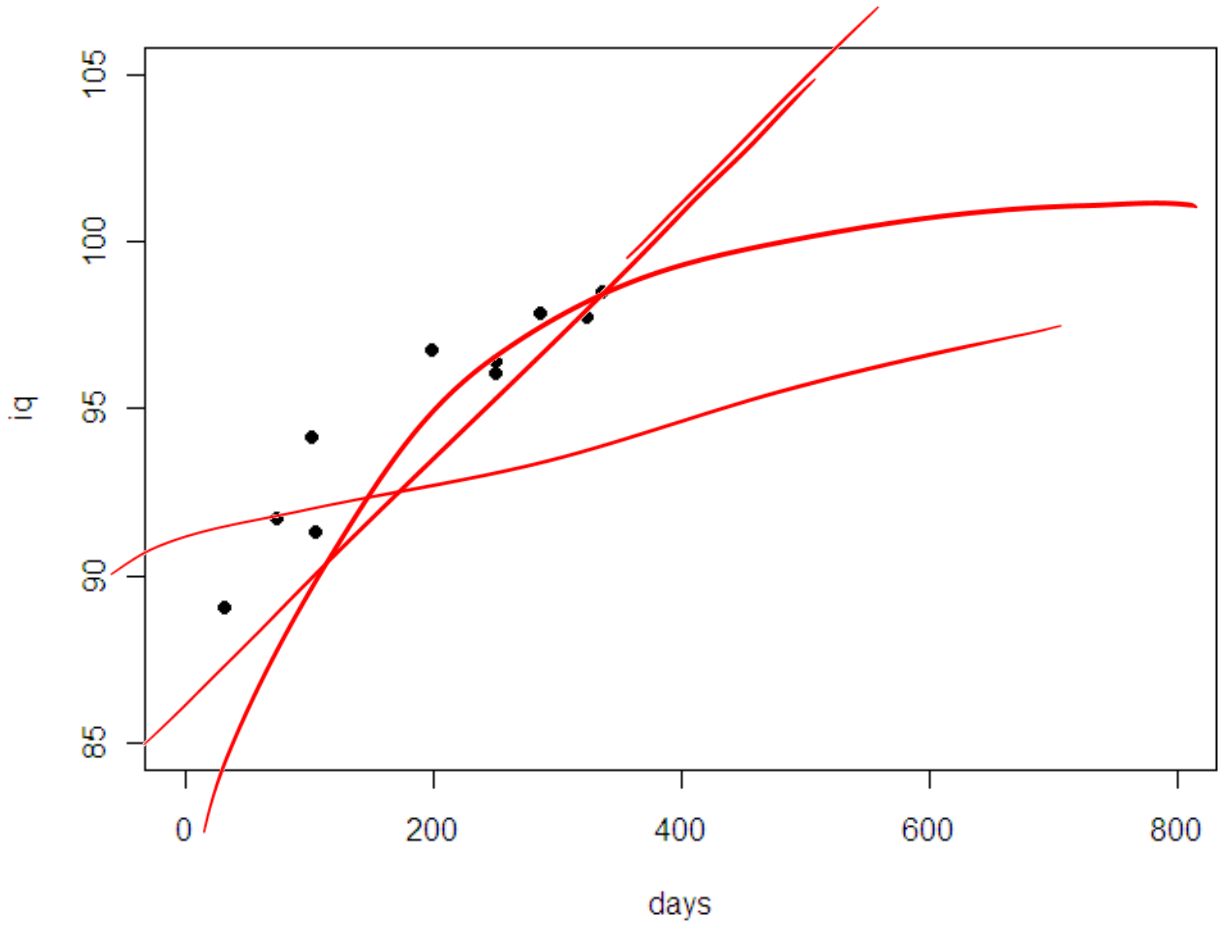
However, we'll use precooked data:

```
> data( iqsim )     # from spida
> iqsim
      days       iq
1  30.9375 89.07734
2  73.1250 91.74573
4 101.2500 94.12407
3 104.3750 91.28166
5 198.1250 96.73445
6 249.6875 96.03835
7 249.6875 96.44441
8 285.6250 97.89462
9 323.1250 97.72059
10 335.6250 98.47470
```



10

```
plot( iq ~ days ,
      iqsim, pch = 16, xlim = c(0,800),
      ylim = c(85,105) )
```



11

Fitting a line:

```
> fit.lin <- lm ( iq ~ days, iqsim )
> summary( fit.lin )
. . . . .

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) 89.540151   0.759021  117.97 2.98e-14 ***
days         0.027739   0.003429    8.09 4.03e-05 ***


Residual standard error: 1.133 on 8 degrees of freedom
Multiple R-squared: 0.8911,     Adjusted R-squared: 0.8775
F-statistic: 65.45 on 1 and 8 DF,  p-value: 4.029e-05
```

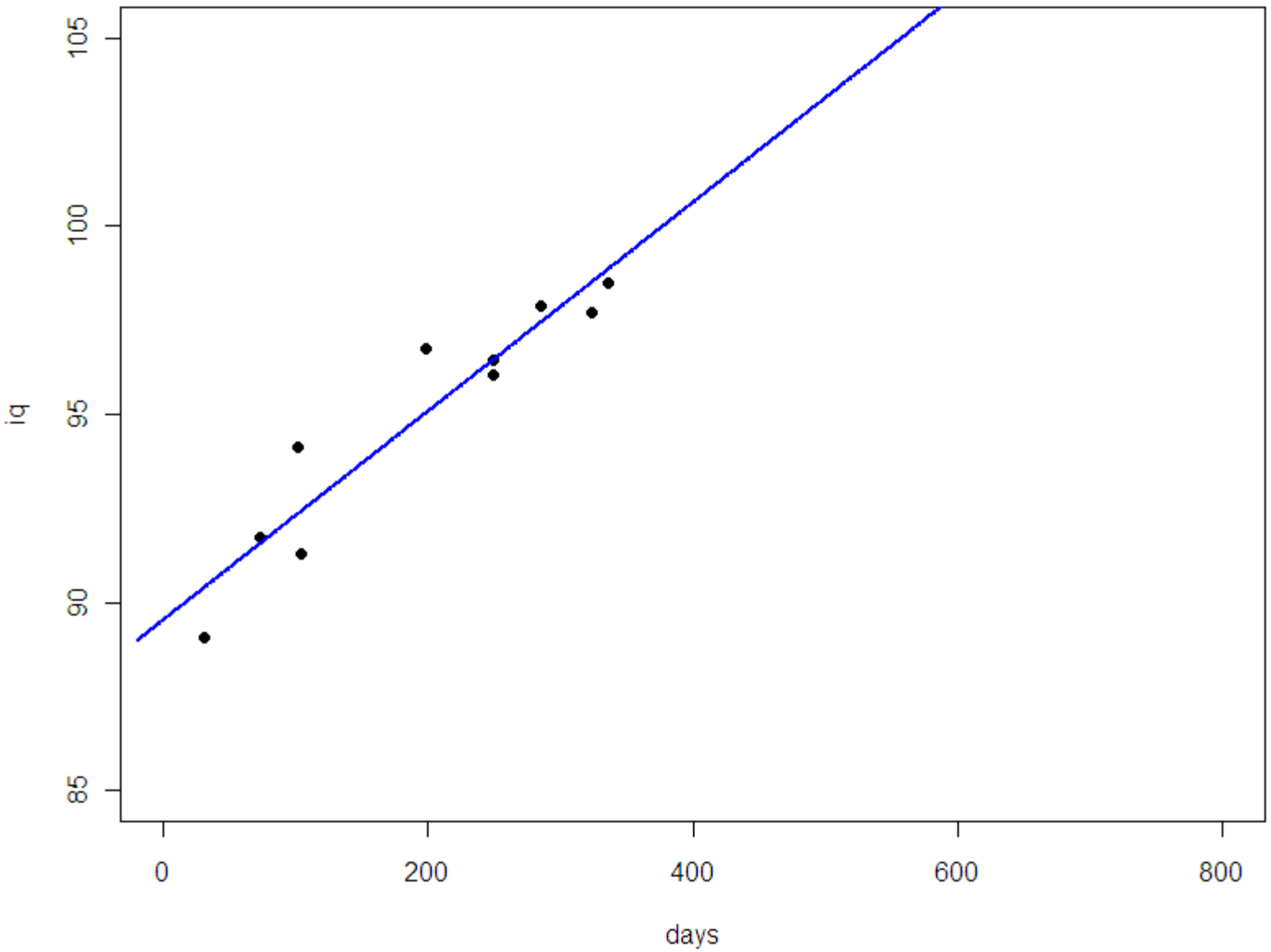

12

Graphing a fitted line

We would like to show the predicted value over the whole range of days in the graph, not just the values that were observed. With a straight line we could just use **abline**. With curved lines we will need a different approach. So we create a prediction data frame, with the one predictor variable.

```
> pred <- expand.grid( days = seq( -20, 850, 1))
> pred$iq.lin <- predict( fit.lin, pred )
> some( pred )
     days    iq.lin
94     73  91.56510
137   116  92.75788
203   182  94.58865
.   .   .   .   .
746   725 109.65094
753   732 109.84511
> lines( iq.lin ~ days, pred,
                col = 'blue', lwd = 2)
```


13



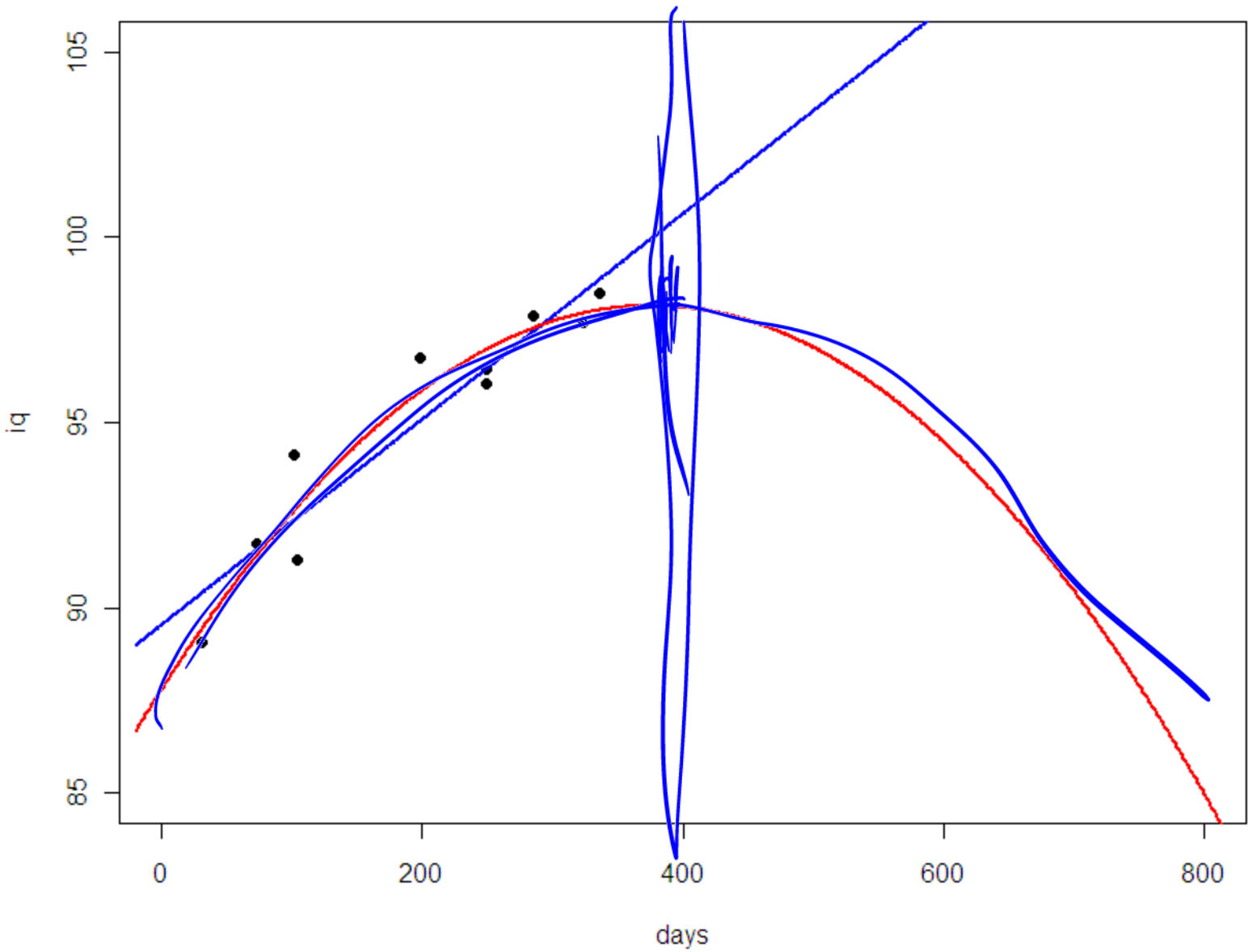
14

Doesn't make much sense!

Let's try a quadratic

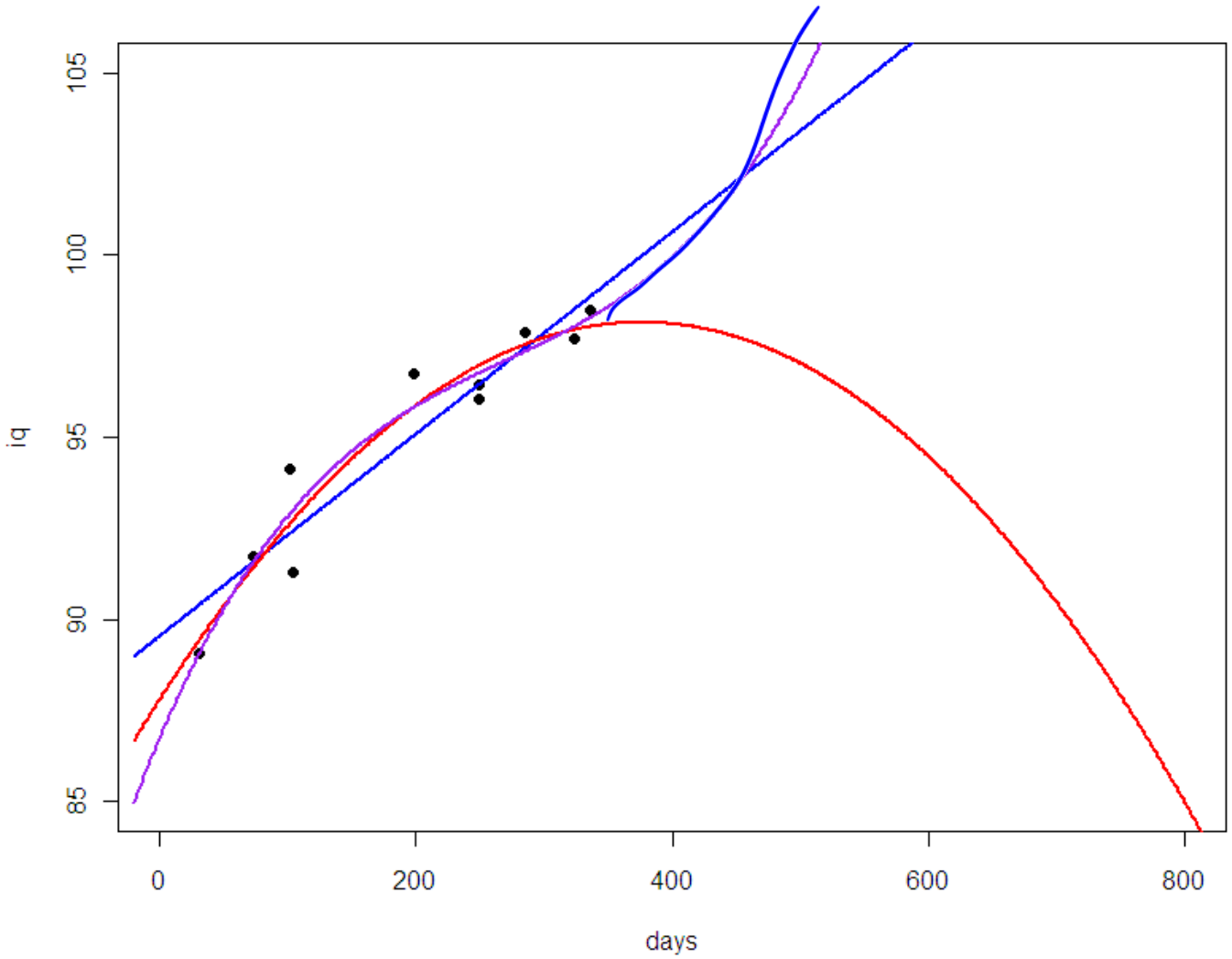
```
>    fit.quad <- lm( iq ~ days + I(days ^2), iqsim)
>    summary( fit.quad )
. . . .
Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)  8.780e+01  1.170e+00  75.020 1.97e-11 ***
days         5.506e-02  1.535e-02   3.586   0.0089 **
I(days^2)   -7.324e-05  4.036e-05  -1.815   0.1124

Residual standard error: 0.9988 on 7 degrees of freedom
Multiple R-squared: 0.9259,     Adjusted R-squared: 0.9048
F-statistic: 43.75 on 2 and 7 DF,  p-value: 0.0001106

>    pred$iq.quad <- predict( fit.quad, pred )
>    lines( iq.quad ~ days , pred, col = 'red', lwd = 2)
>
```


15



16

With a quadratic, what goes up must come down … the same way it went up! Maybe a cubic makes more sense:



17

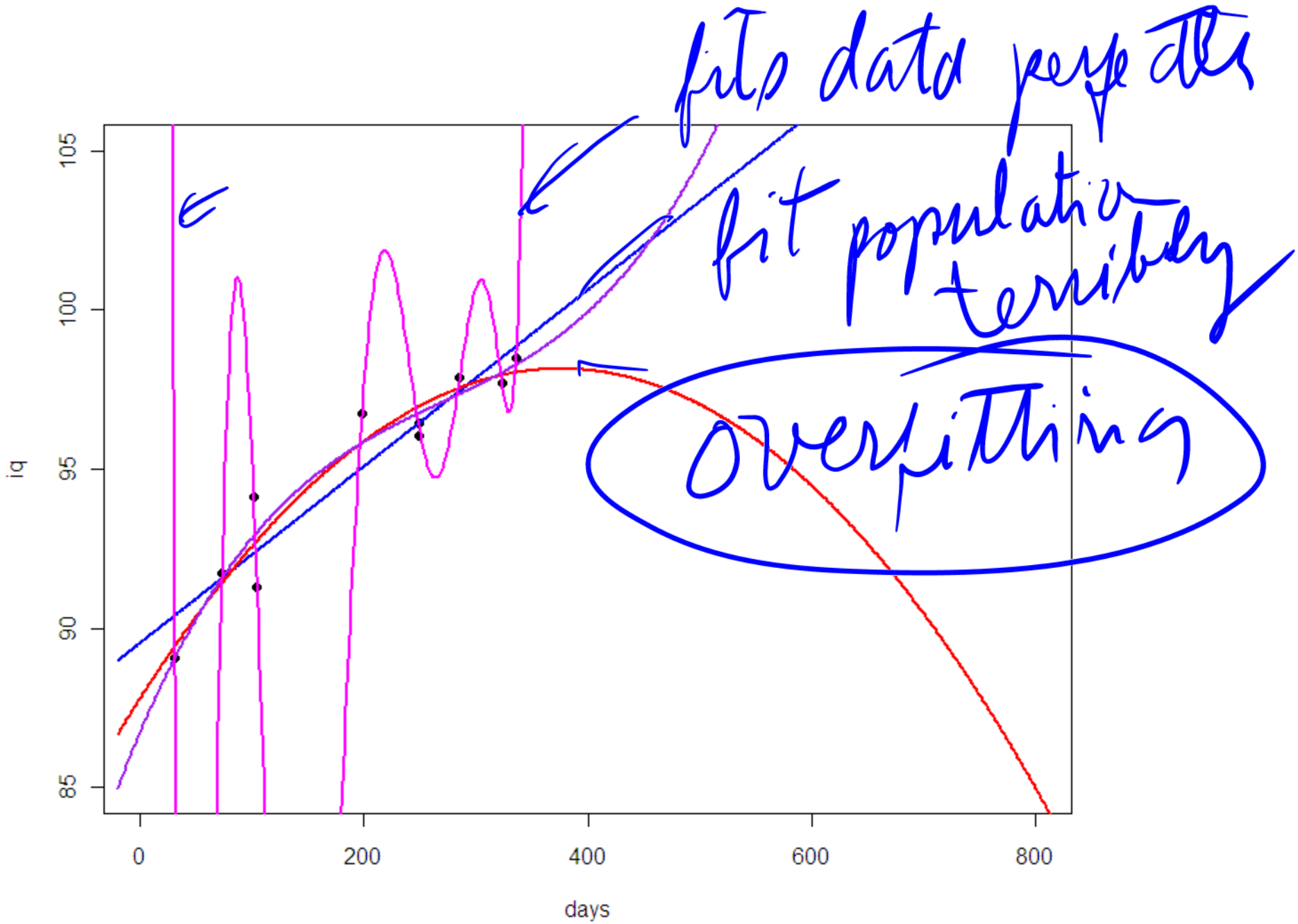
Exasperated we decided to go all the way with a polynomial of degree 8:

Thanks to John, this option is available

```
>  p8 <- function( x ) poly( x, 8, raw = TRUE)
>  fit.high <- lm( iq ~ p8( days ), iqsim )
>  summary(fit.high)   # look at R-Squared!!
.  .  .  .
Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.314e+03  1.665e+02   7.889   0.0803 .
p8(days)1   -9.135e+01  1.238e+01  -7.381   0.0857 .
p8(days)2    2.548e+00  3.436e-01   7.414   0.0854 .
p8(days)3   -3.596e-02  4.829e-03  -7.447   0.0850 .
p8(days)4    2.878e-04  3.846e-05   7.482   0.0846 .
p8(days)5   -1.362e-06  1.811e-07  -7.518   0.0842 .
p8(days)6    3.777e-09  4.999e-10   7.555   0.0838 .
p8(days)7   -5.674e-12  7.476e-13  -7.590   0.0834 .
p8(days)8    3.567e-15  4.679e-16   7.624   0.0830 .
---
Residual standard error: 0.2871 on 1 degrees of freedom
Multiple R-squared: 0.9991,     Adjusted R-squared: 0.9921
F-statistic: 142.8 on 8 and 1 DF,  p-value: 0.06463
```

An almost perfect fit!

18


fits data perfectly
fit population terribly
overfitting
iq
105
100
95
90
85
0
200
400
600
800
days

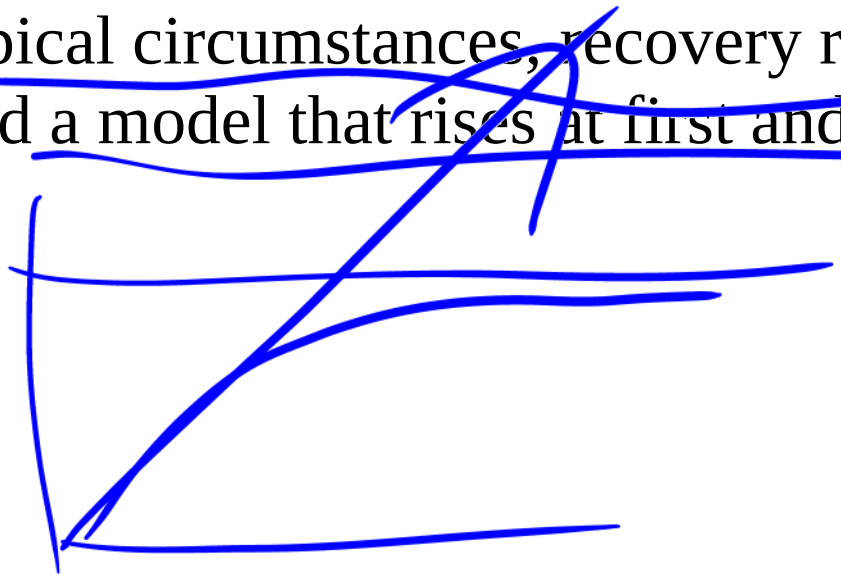
19

- A perfect fit to the data
- But a very poor fit to the 'population'
- An example of overfitting and loss of validity

The remedy:

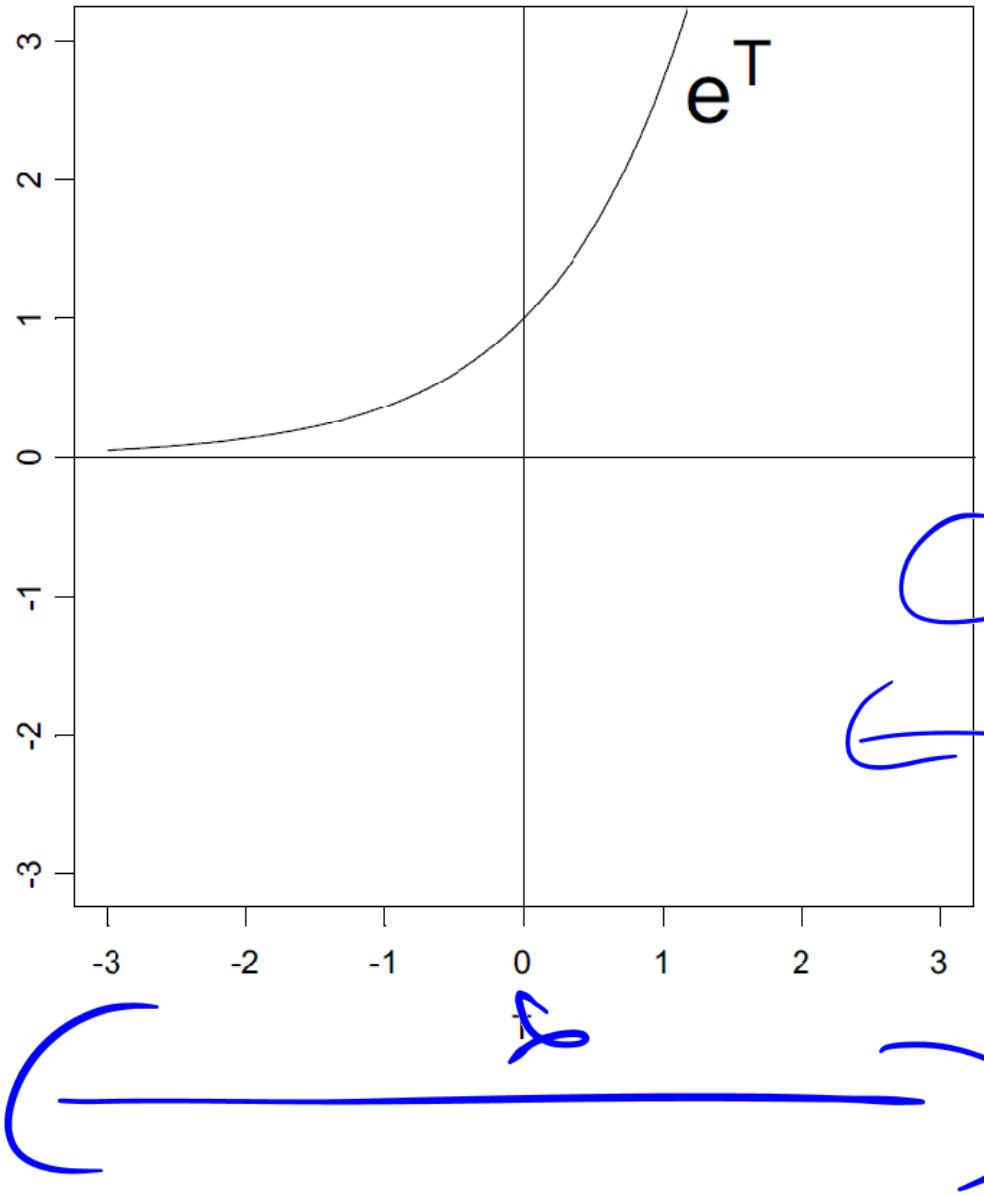
Use a model that captures characteristics of the process under study. Don't just use a high order polynomial to get a good empirical fit.

Presumably, under typical circumstances, recovery reaches a plateau after a while. We need a model that rises at first and then flattens out.

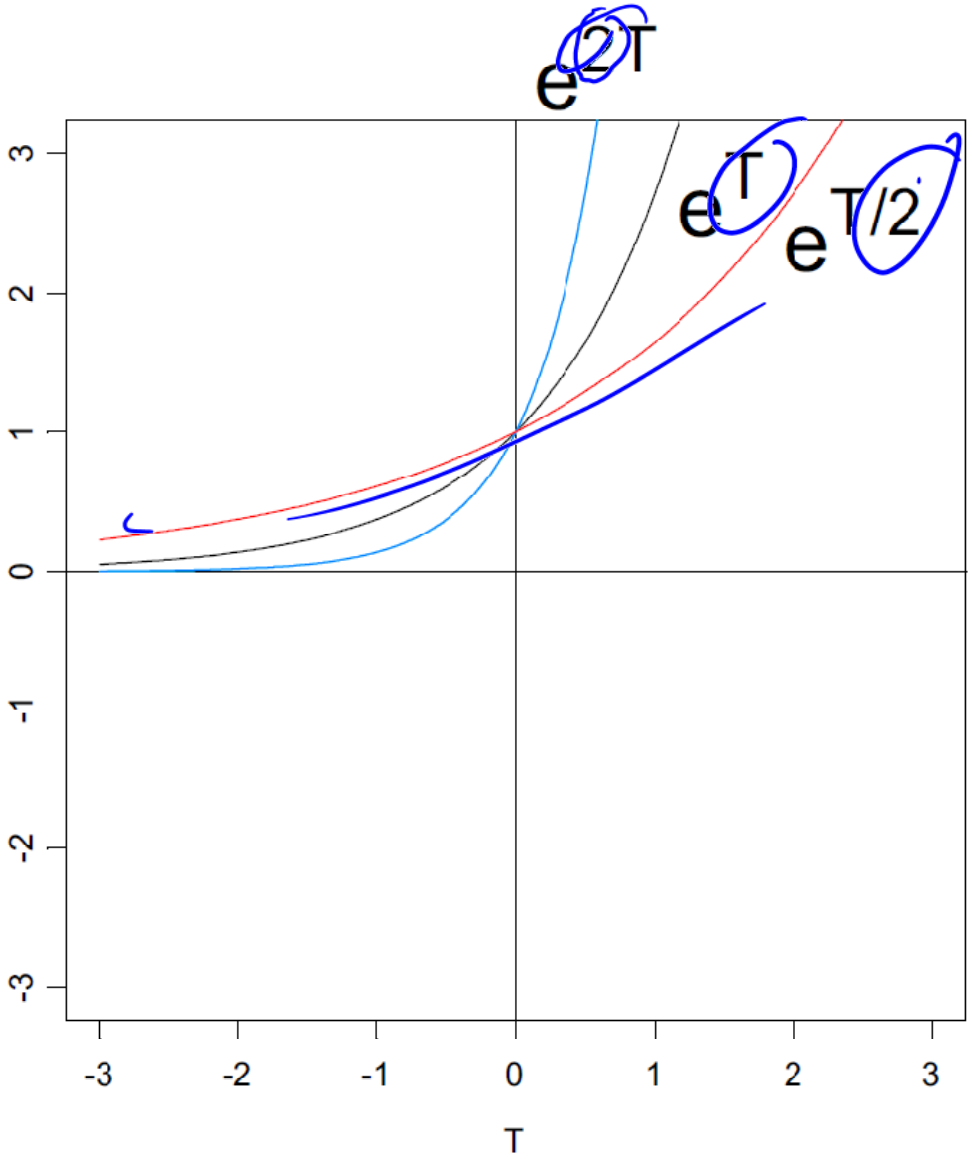


20

Exponential growth or decay



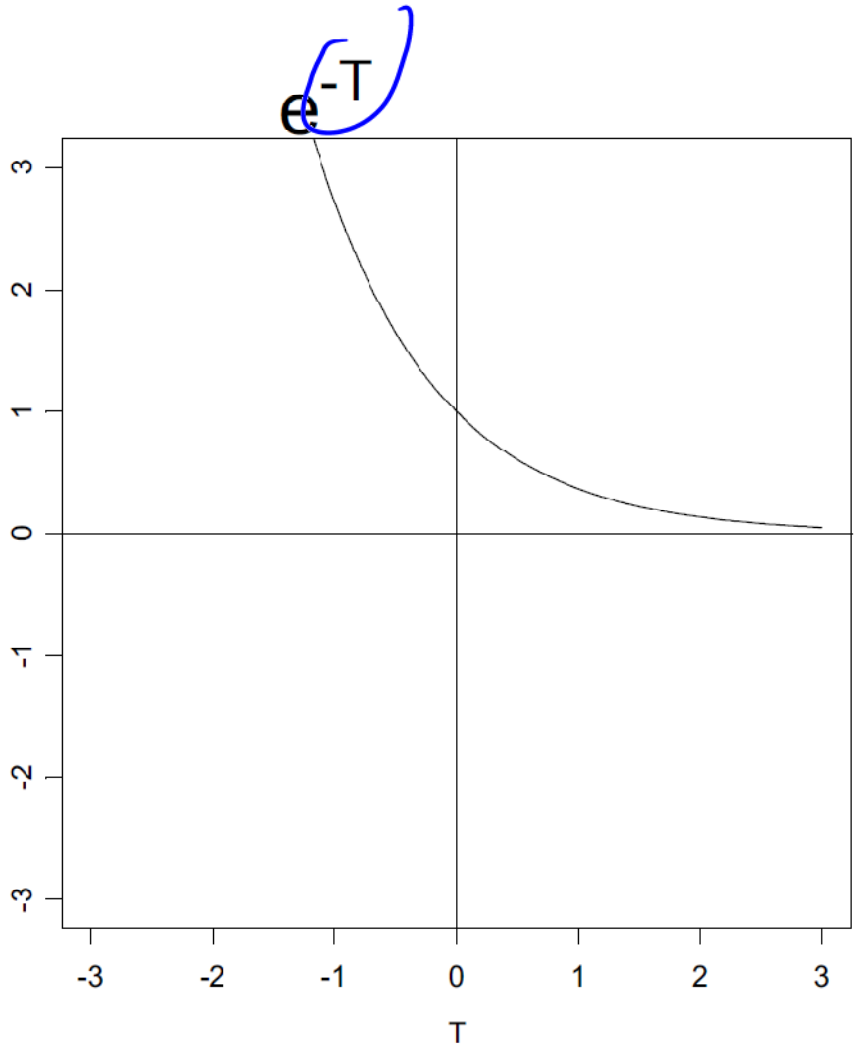
21

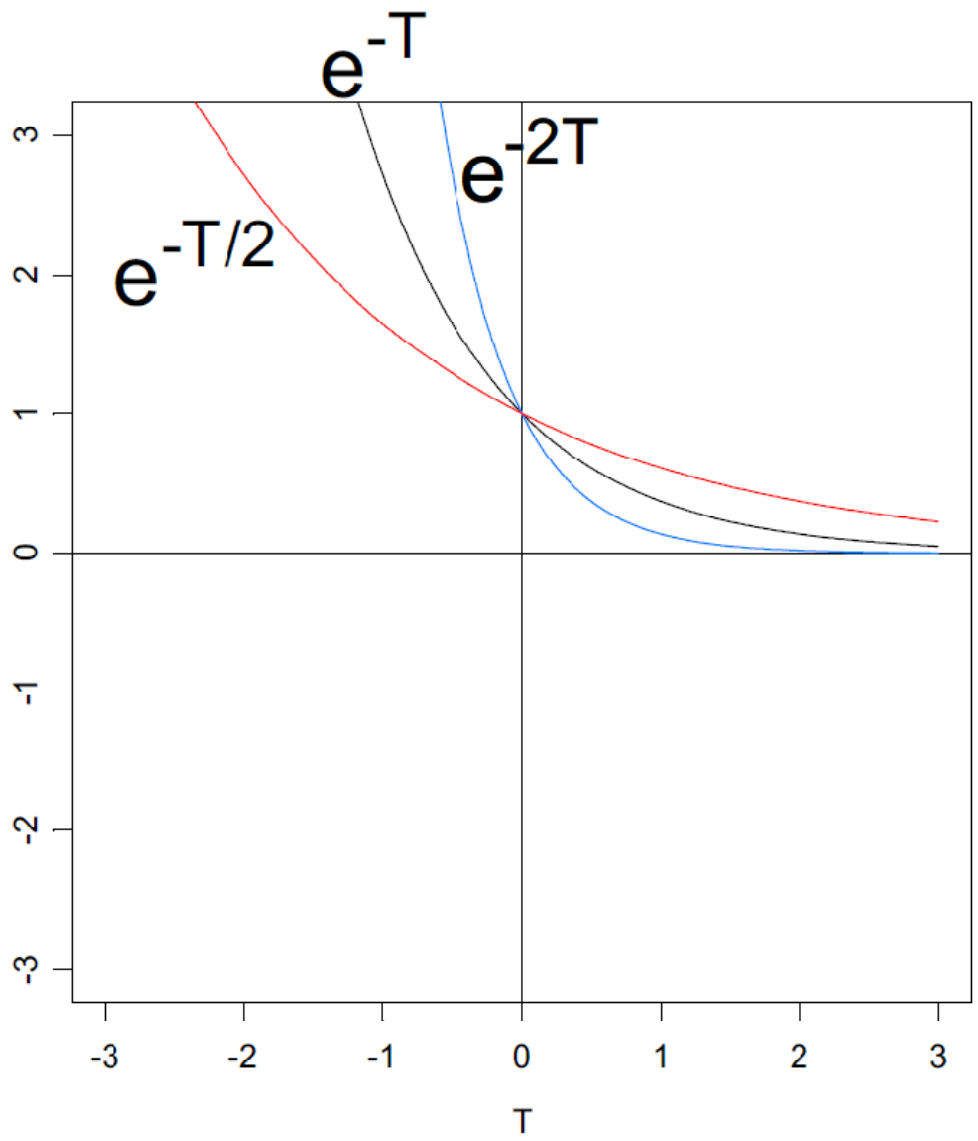


22

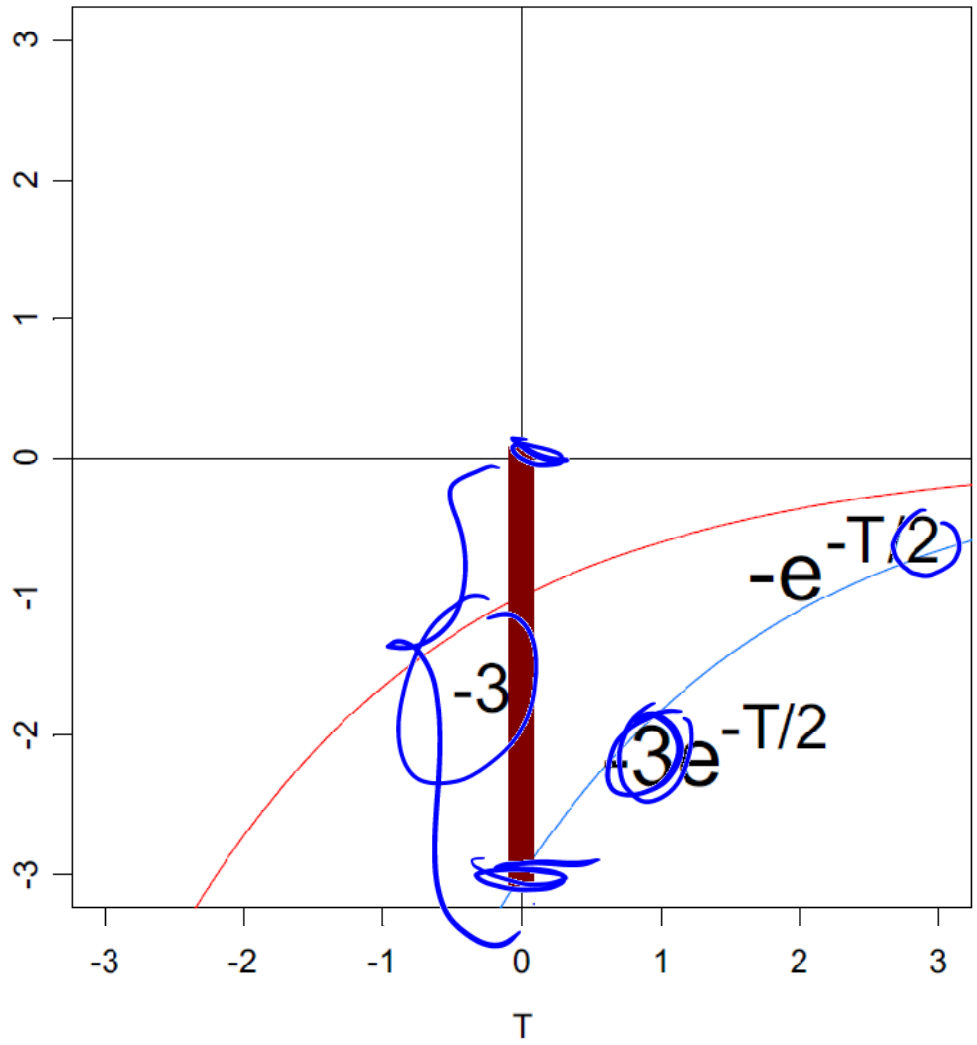
23

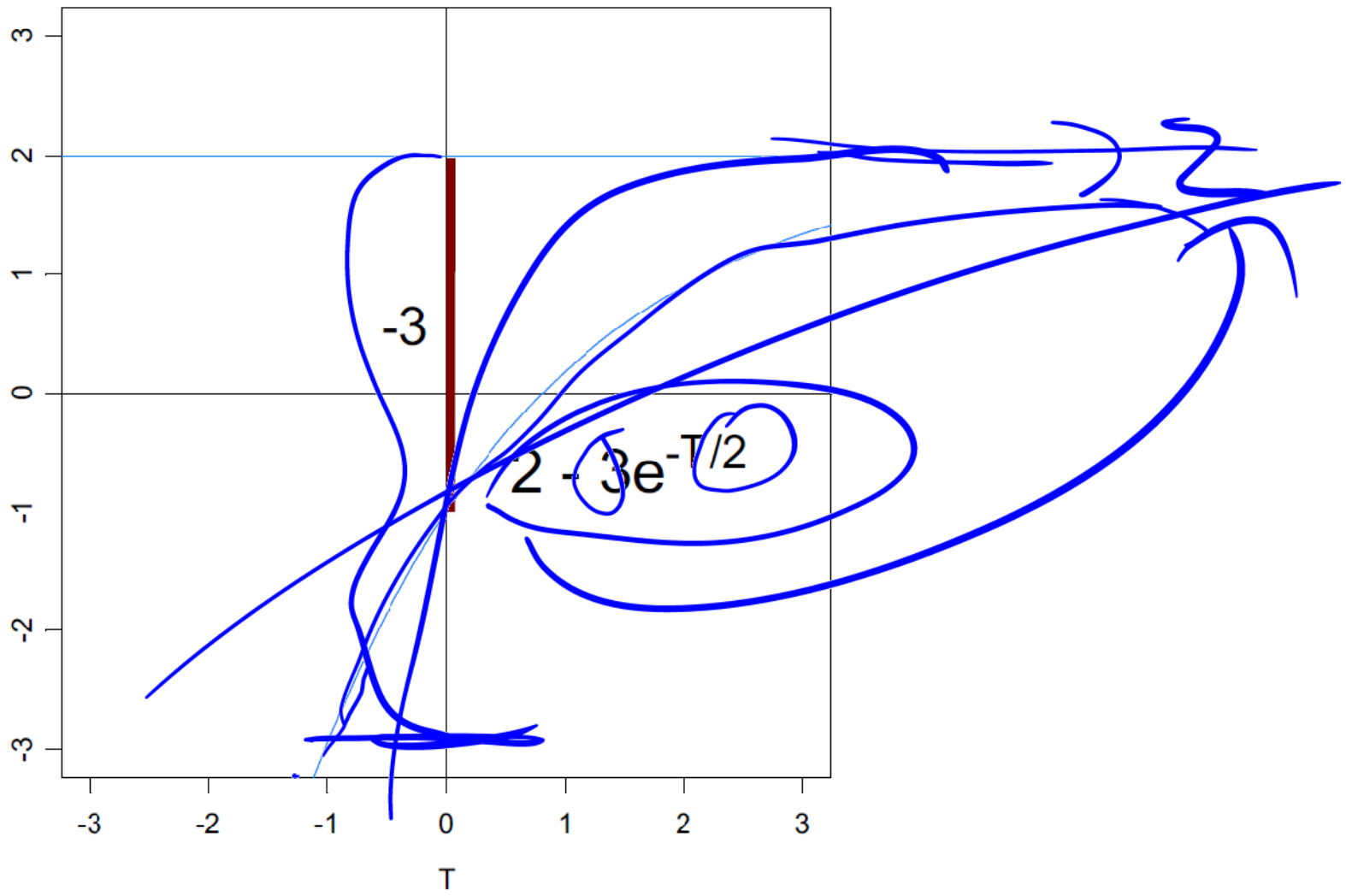
Exponential decay

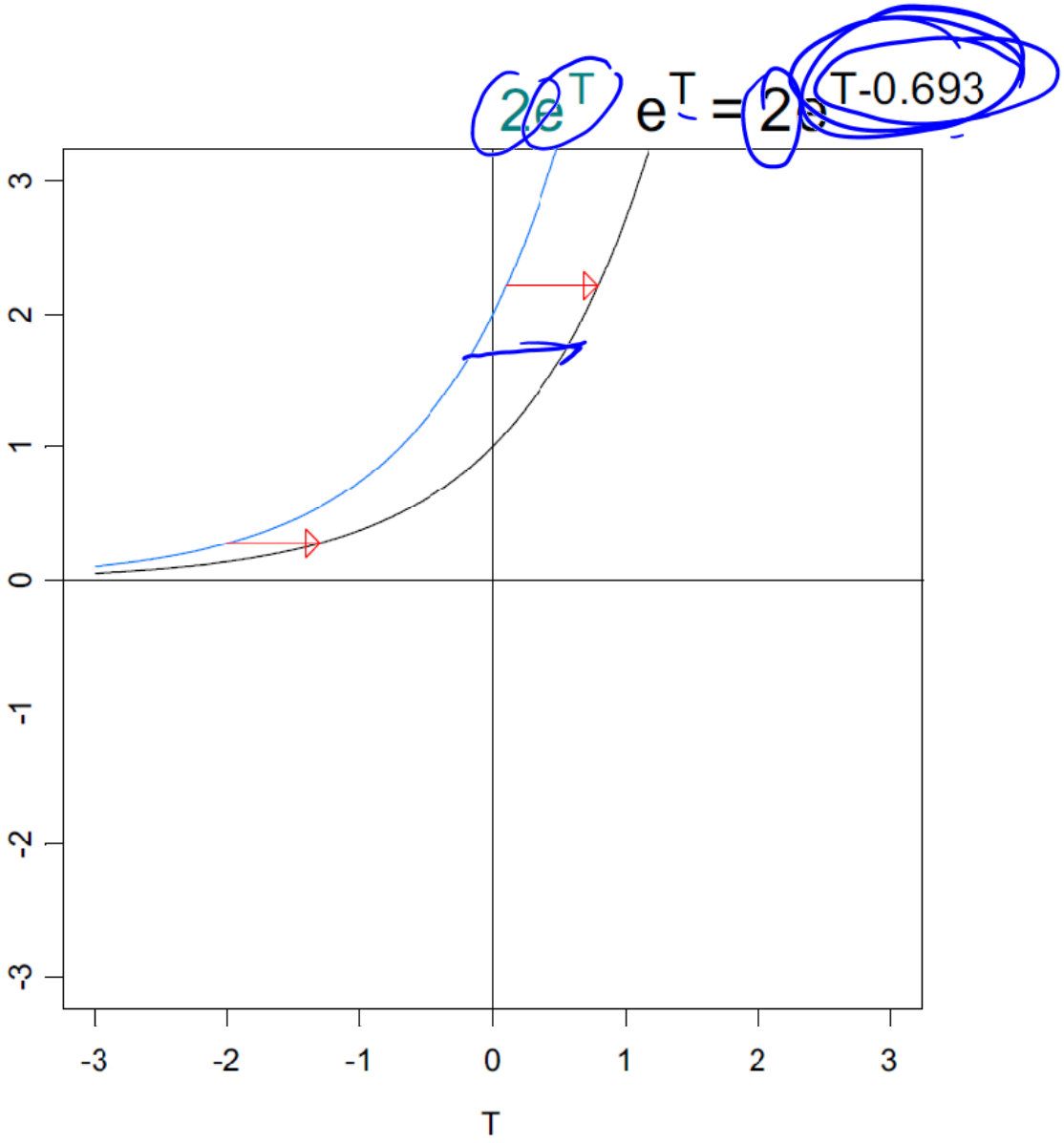


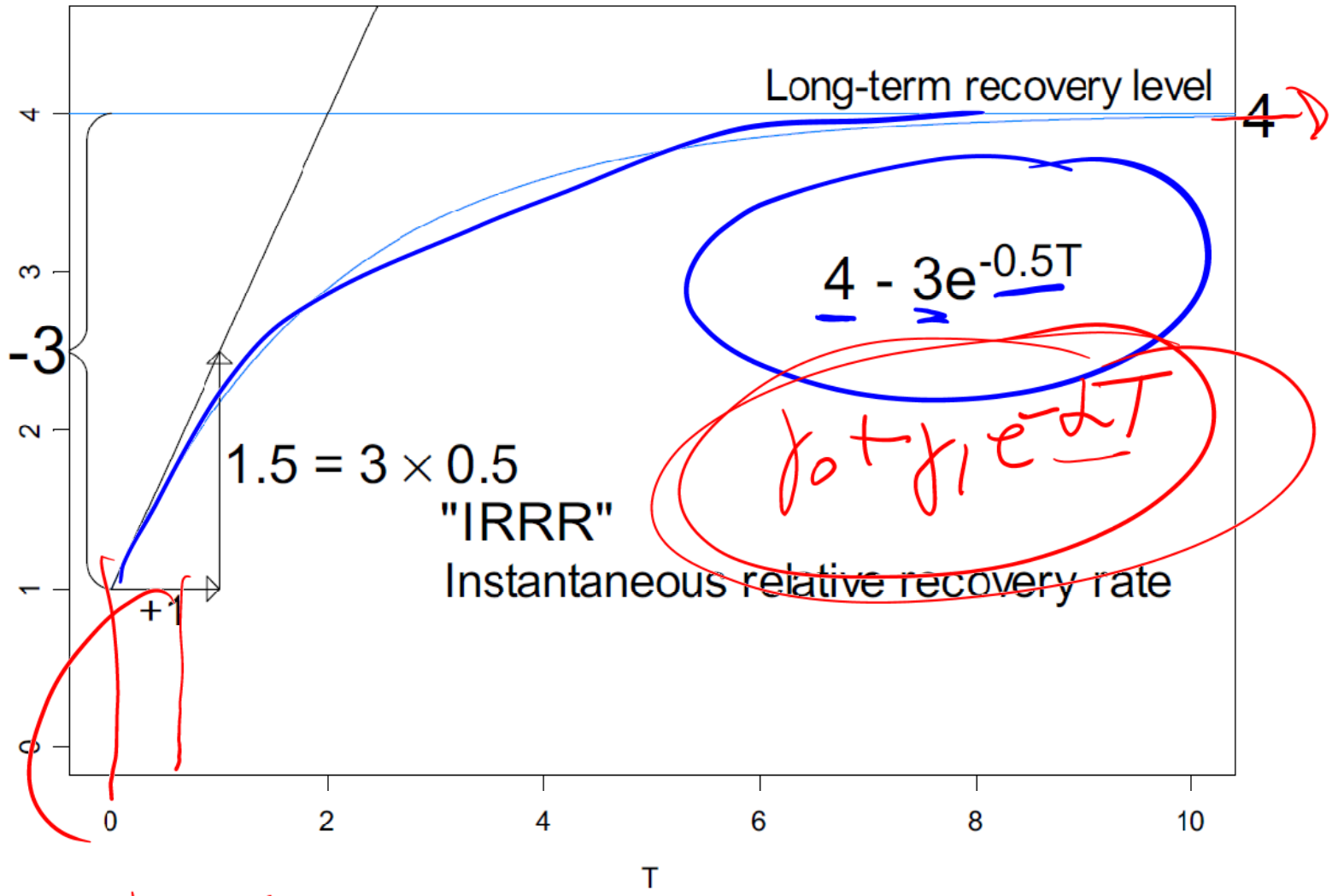

e-T
e-2T
e-T/2
3
2
1
0
-1
-2
-3
-3
-2
-1
0
1
2
3
T

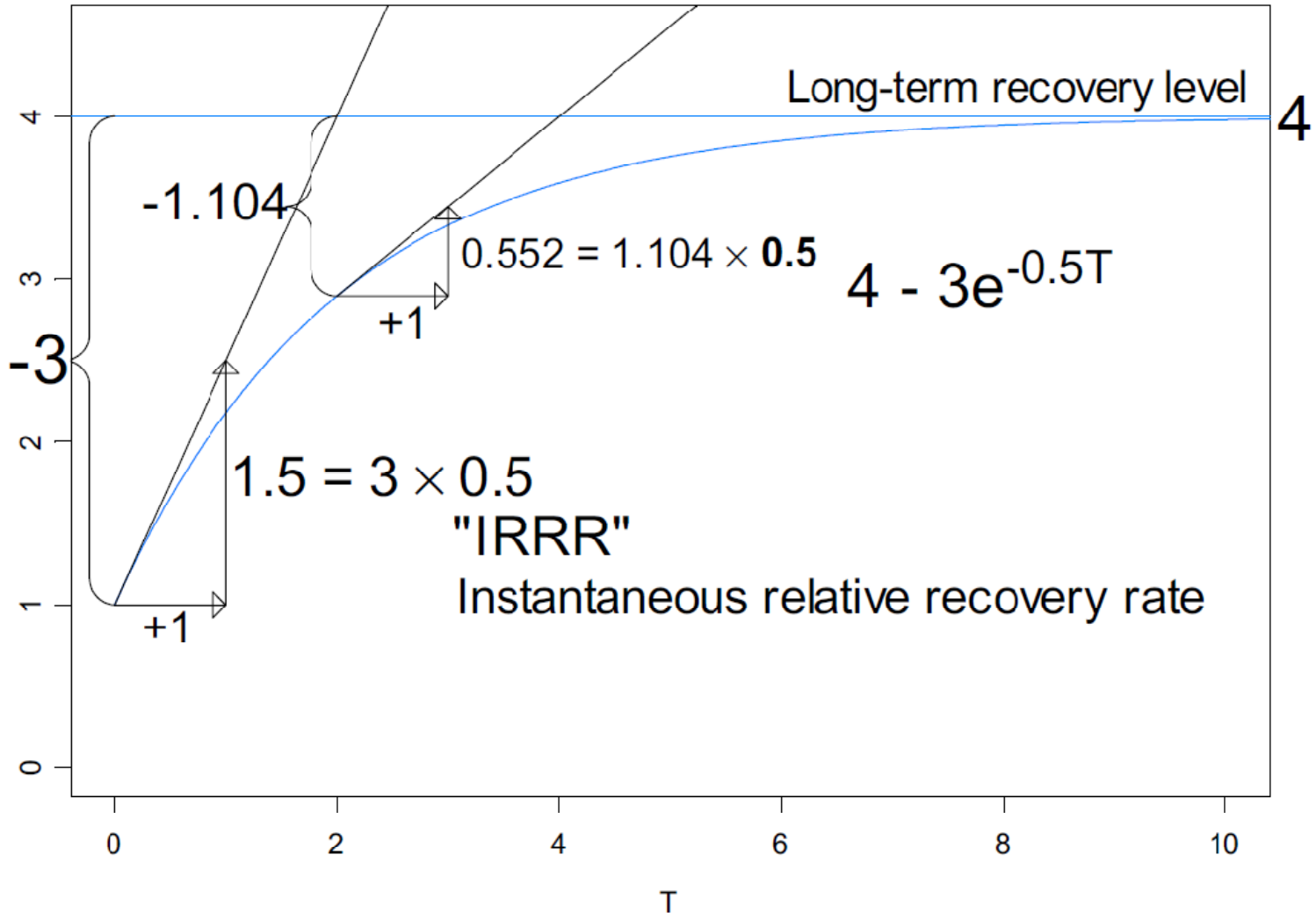
Exponential asymptotic growth


3
2
1
0
-1
-2
-3
-3
-2
-1
0
1
2
3
T
-e-T/2
-3
3e-T/2

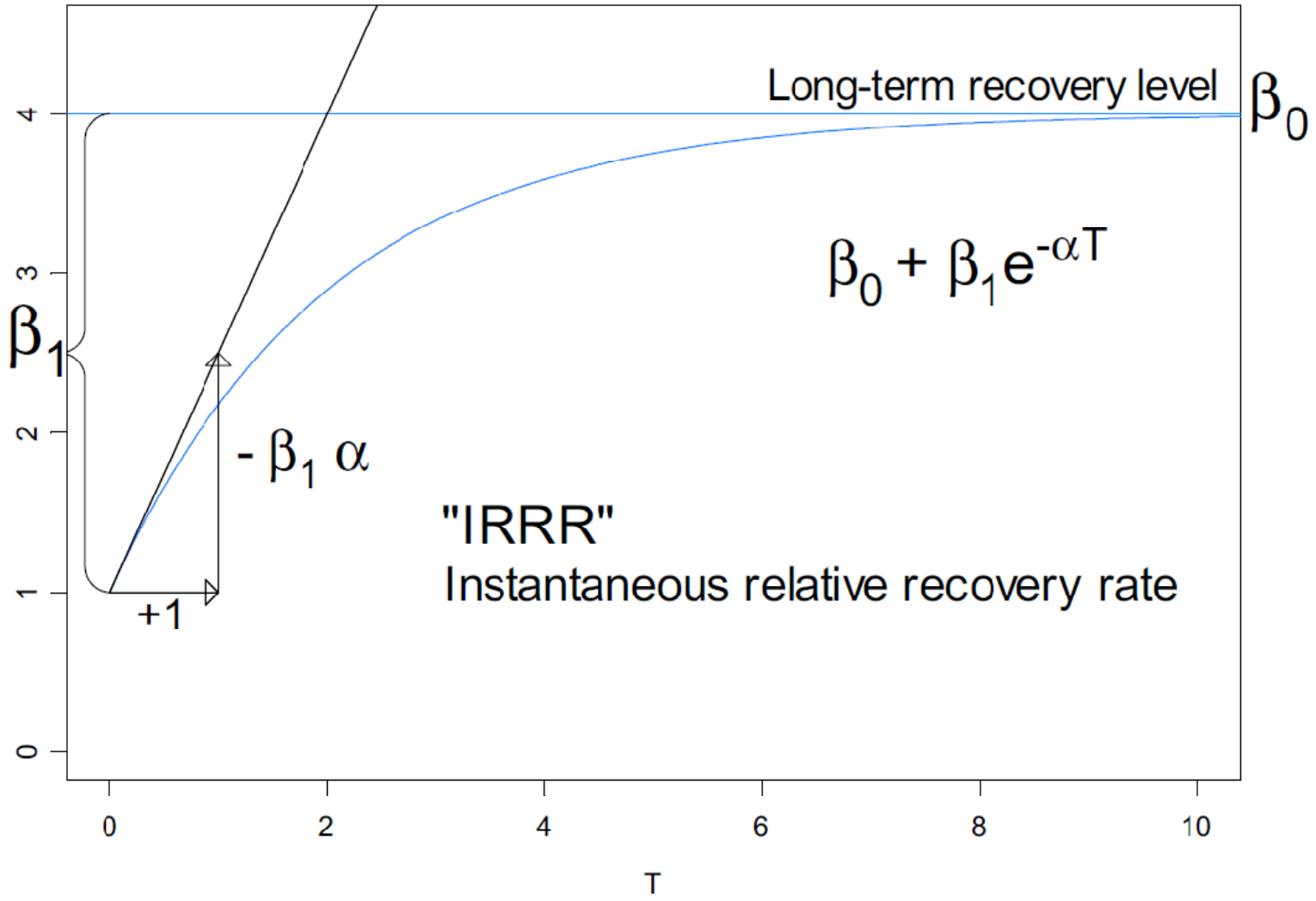

-3
2 - 3e^-T/2
3
2
1
0
-1
-2
-3
-3
-2
-1
0
1
2
3
T

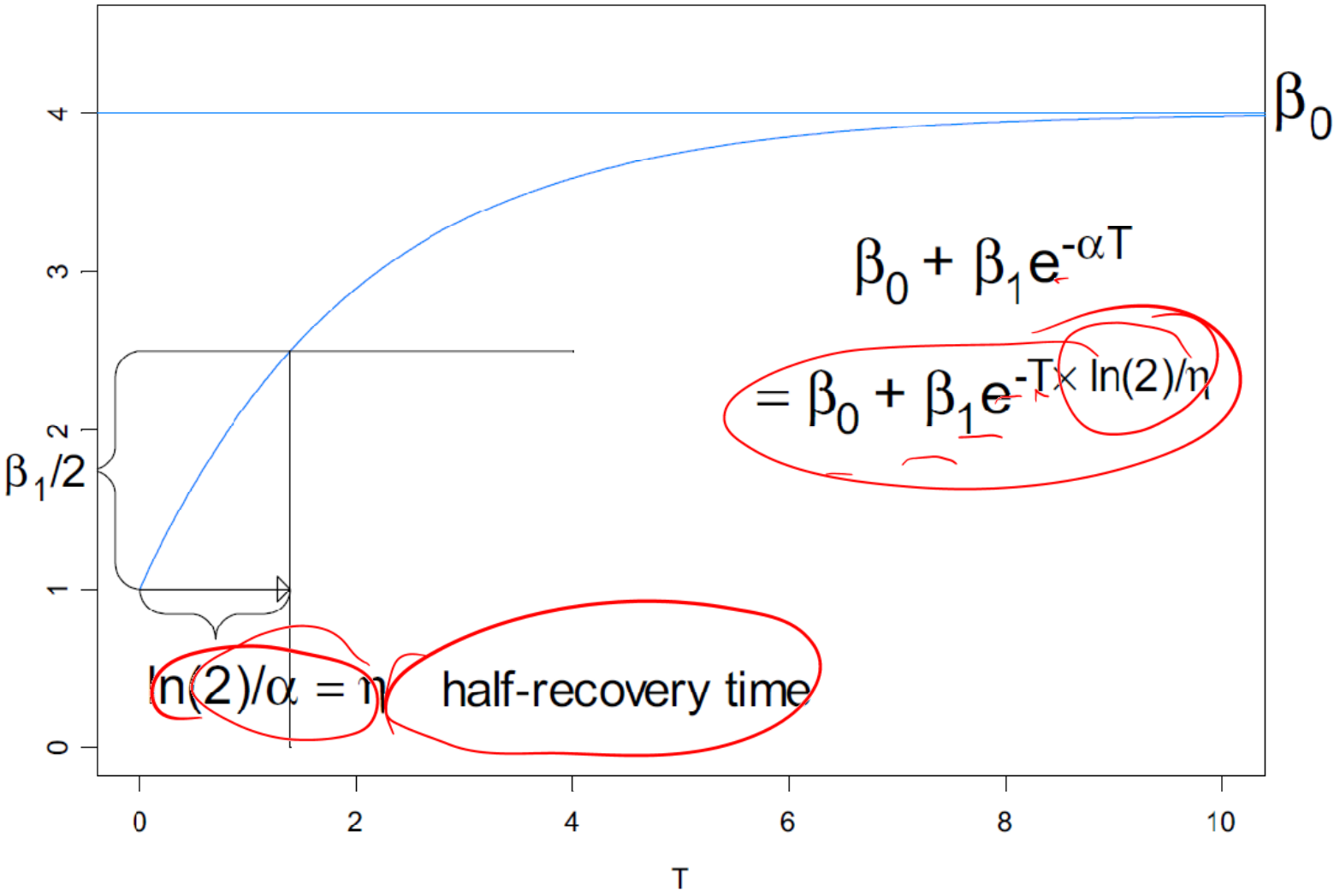

$2e^T$
$e^T = 2e^{T-0.693}$
3
2
1
0
-1
-2
-3
-3
-2
-1
0
1
2
3
T


Long-term recovery level
4
4 - 3e^-0.5T
-3
1.5 = 3 × 0.5
"IRRR"
Instantaneous relative recovery rate
+1
0
1
2
3
4
0
2
4
6
8
10
T


Long-term recovery level
4
-1.104
0.552 = 1.104 × 0.5
4 - 3e-0.5T
+1
-3
1.5 = 3 × 0.5
"IRRR"
Instantaneous relative recovery rate
+1
0
1
2
3
4
0
2
4
6
8
10
T

Using half-recovery time instead (half-life)




β_0
$\beta_0 + \beta_1 e^{-\alpha T}$
$= \beta_0 + \beta_1 e^{-T \times \ln(2)/\eta}$
$\beta_1/2$
$\ln(2)/\alpha = \eta$
half-recovery time
0
1
2
3
4
0
2
4
6
8
10
T

Fitting a non-linear growth curve model:

$$Y_t = \beta_0 + \beta_1 \exp(-\alpha T_i) + \varepsilon_i \qquad \varepsilon_i \text{ independent } N(0, \sigma^2)$$

Later we will use nlme for longitudinal data with more that one subject. With just one subject we use 'nls', which is to 'nlme' what 'lm' is to 'lme'.

The syntax for fitting a non-linear model is very similar to that for a linear model with three differences.

1. With a linear model we only need to specify the ***predictors***. We don't need to say anything about the ***parameters*** because it is understood that there is exactly one parameter for each regressor (some predictors will have more than one regressor) and each parameter multiplies its regressor. The ***non-linear model formula*** for a non-linear model needs to specify both

the parameters and the regressor.

2. The algorithm for fitting is iterative and needs starting values which you generally need to supply.

3. In non-linear mixed effects models – with `nlme` – parameters in the non-linear model are themselves be modeled through linear models potentially based on other predictors. This allows the non-linear model to be simpler since it only needs to capture the essentially non-linear aspects of the model. Another advantage is that this formulation is easier to fit numerically, i.e. it's less work for the computer.

Growth curve model:

$$Y_i = \beta_0 + \beta_1 \exp\left(-\alpha T_i\right) + \varepsilon_i \qquad \varepsilon_i \text{ i.i.d. } N(0, \sigma^2)$$

Non-linear model formula:

```
iq ~ b0 + b1*exp(-alpha*days)
```

The formula contains references to data: `iq, days` that will be found in the `iq` data frame.

Parameters: `b0, b1, alpha` that need starting values.

Finding starting values: best way: sketch and undertand your model and infer plausible parameters.

From graphs I would guess:

```
list( b0 = 100, b1 = -20, alpha = 0.005 )
```

How did we get these values?

`b0` is the long-run level, `b1` is the relative deficit at time 0, `alpha` is the daily proportion of lost iq recovered. It looks like it might take 100 days for a half recovery of 0.5, so dividing by 100 suggests roughly 0.005 per day.

Call in R:

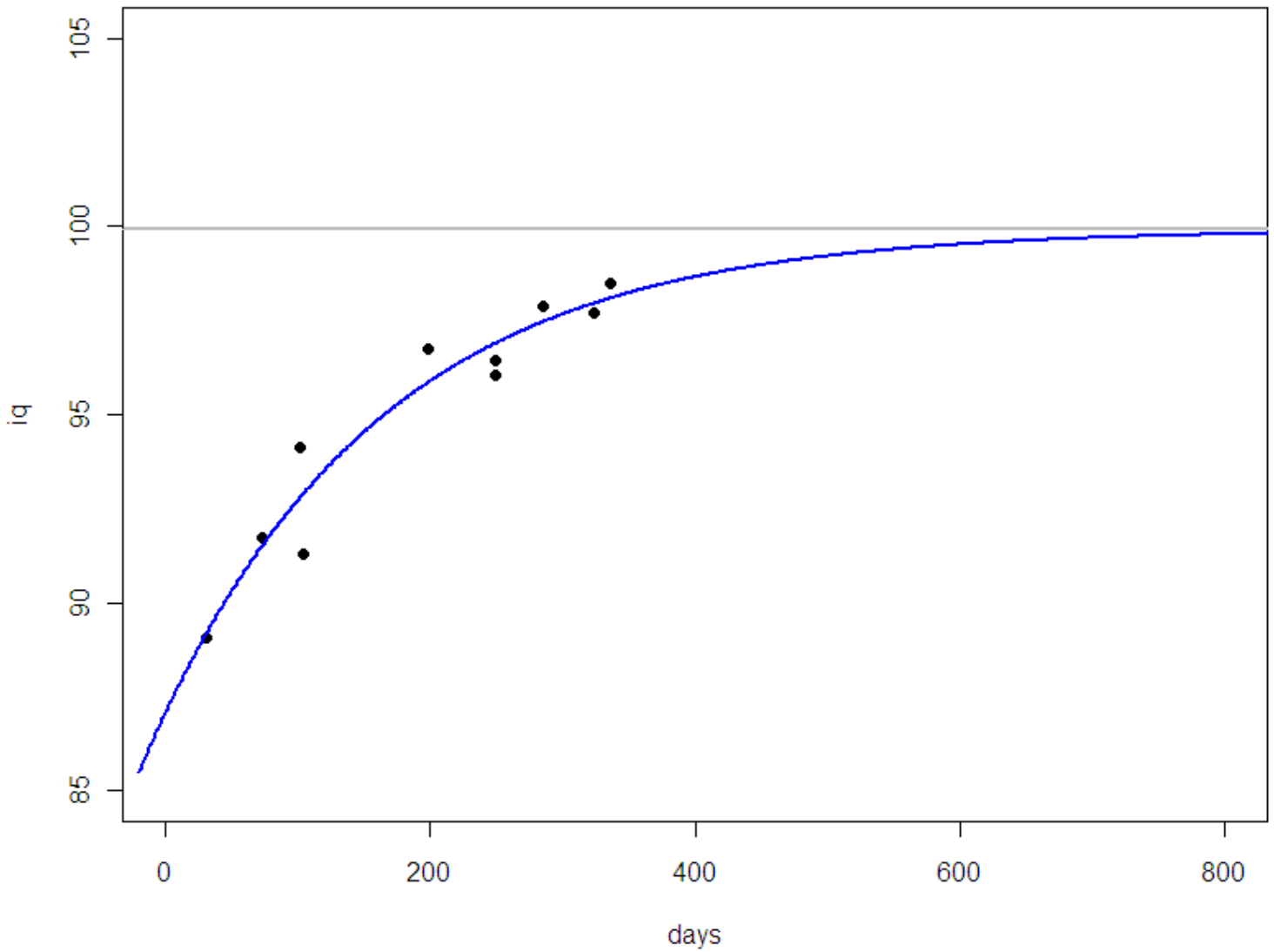
```
nls( iq ~ b0 + b1*exp(-alpha*days), iqsim,
  start = list(  b0 = 100, b1 = -20,
       alpha = 0.005 ) )
```

R code and output:

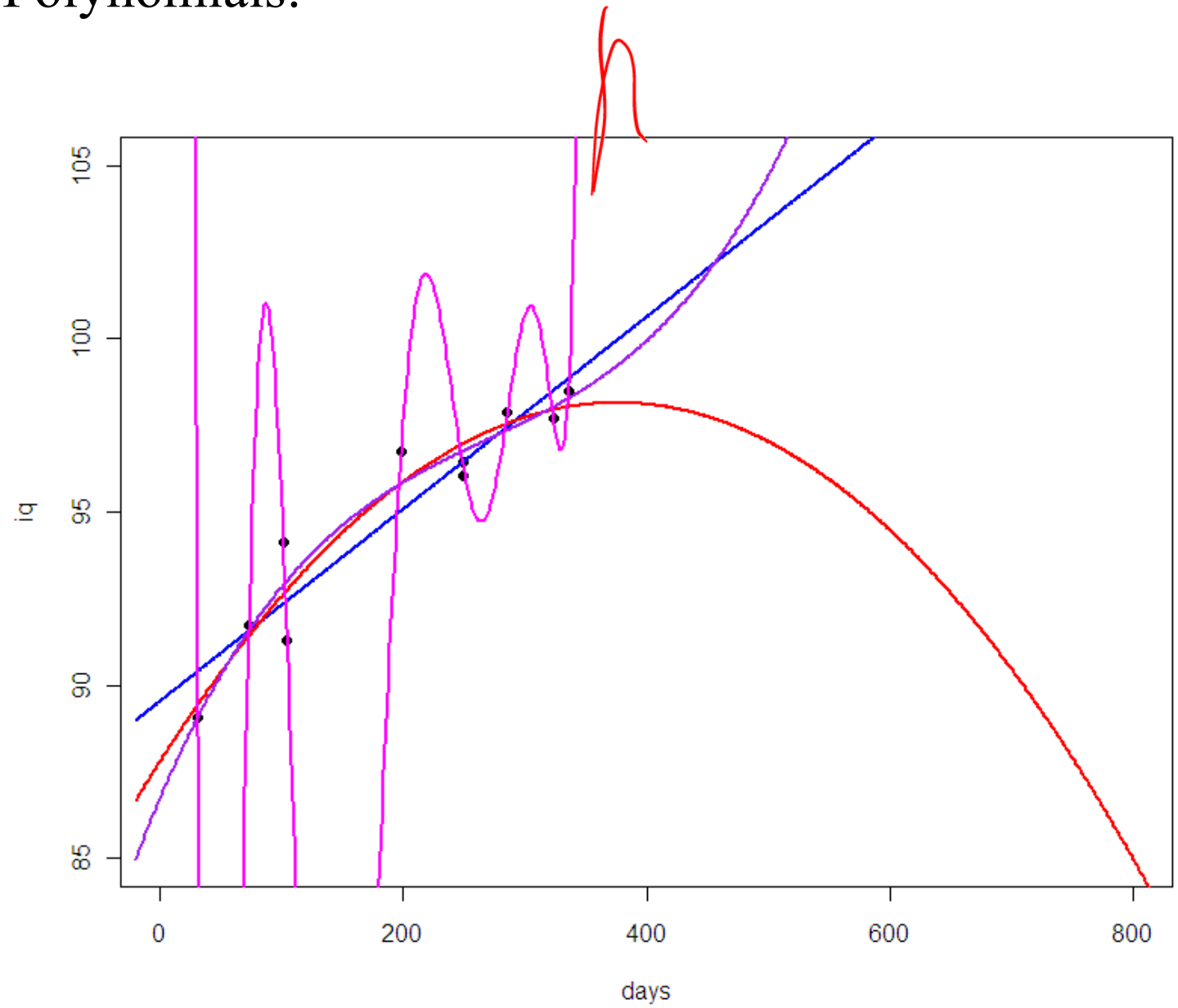
```
>  fit.nl <-nls ( iq ~ b0 + b1*exp( -a*days ), iqsim,
+           start= list(b0 = 100, b1 = -30, a = .01))
>  summary( fit.nl )

Formula: iq ~ b0 + b1 * exp(-a * days)

Parameters:
     Estimate Std. Error t value Pr(>|t|)
b0  99.906891   2.393470  41.741 1.18e-09 ***
b1 -12.847352   1.620520  -7.928 9.66e-05 ***
a    0.005820   0.002956   1.969   0.0897 .
---
Residual standard error: 0.9738 on 7 degrees of freedom

Number of iterations to convergence: 4
Achieved convergence tolerance: 7.917e-06
```

```
> pred$iq.nl <- predict( fit.nl, pred )
> plot( iq ~ days , iqsim, pch = 16,
+     xlim = c(0,800), ylim = c(85,105) )
> lines( iq.nl ~ days , pred, col = 'black', lwd = 2)
> coef( fit.nl )
           b0            b1             a
 99.906891397 -12.847351723   0.005819758
>    abline( h = coef(fit.nl)[1], col = 'gray', lwd = 2)
```

Asymptotic growth curve:



Polynomials:



40

Alternative: Transforming Time

What difference does it make if we turn our non-linear model into a linear model by transforming time:

$$\text{ttime} = \exp\{-0.0056 \times \text{days}\}$$

As days $\to \infty$, ttime(days) $\to 0$, as days $\to 0$, ttime(days) $\to 1$

```
>    ttime <- function( x ) exp( -0.0058 * x)
>    fit.lin <- lm( iq ~ ttime( days ), iqsim)
>    summary(fit.lin)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   99.9224     0.5628  177.54 1.13e-15
ttime(days) -12.8535     1.2508  -10.28 6.92e-06

Residual standard error: 0.9109 on 8 degrees of freedom
Multiple R-squared: 0.9296,     Adjusted R-squared: 0.9208
F-statistic: 105.6 on 1 and 8 DF,  p-value: 6.922e-06
```

Compare coefficients from tranformed fit and from non-linear fit:

```
Coefficients: (transformed)
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   99.9224   0.5628  177.54 1.13e-15
ttime(days) -12.8535   1.2508  -10.28 6.92e-06

Parameters: (non-linear)
     Estimate Std. Error t value Pr(>|t|)
b0  99.906891   2.393470  41.741 1.18e-09 ***
b1 -12.847352   1.620520  -7.928 9.66e-05 ***
a    0.005820   0.002956   1.969   0.0897 .
```

- The **estimated parameters** are almost the same but the linear fit using transformed time reports **much smaller SEs** than the non-linear fit.
- Why? The linear fit is not taking into account the uncertainty stemming from the fact that **a** is not known.
- Note that the biggest difference in SE occurs for the asymptote. Unless you have data well into the asymptote – where the curve gets very flat – the estimate of the asymptote depends heavily on the estimate of curvature.
- When reviewing work that used transformations consider whether a non-linear approach might have been more honest. Note that the transformation is free if it is an intentional change in the scale: e.g. log(Salary).

Summary:

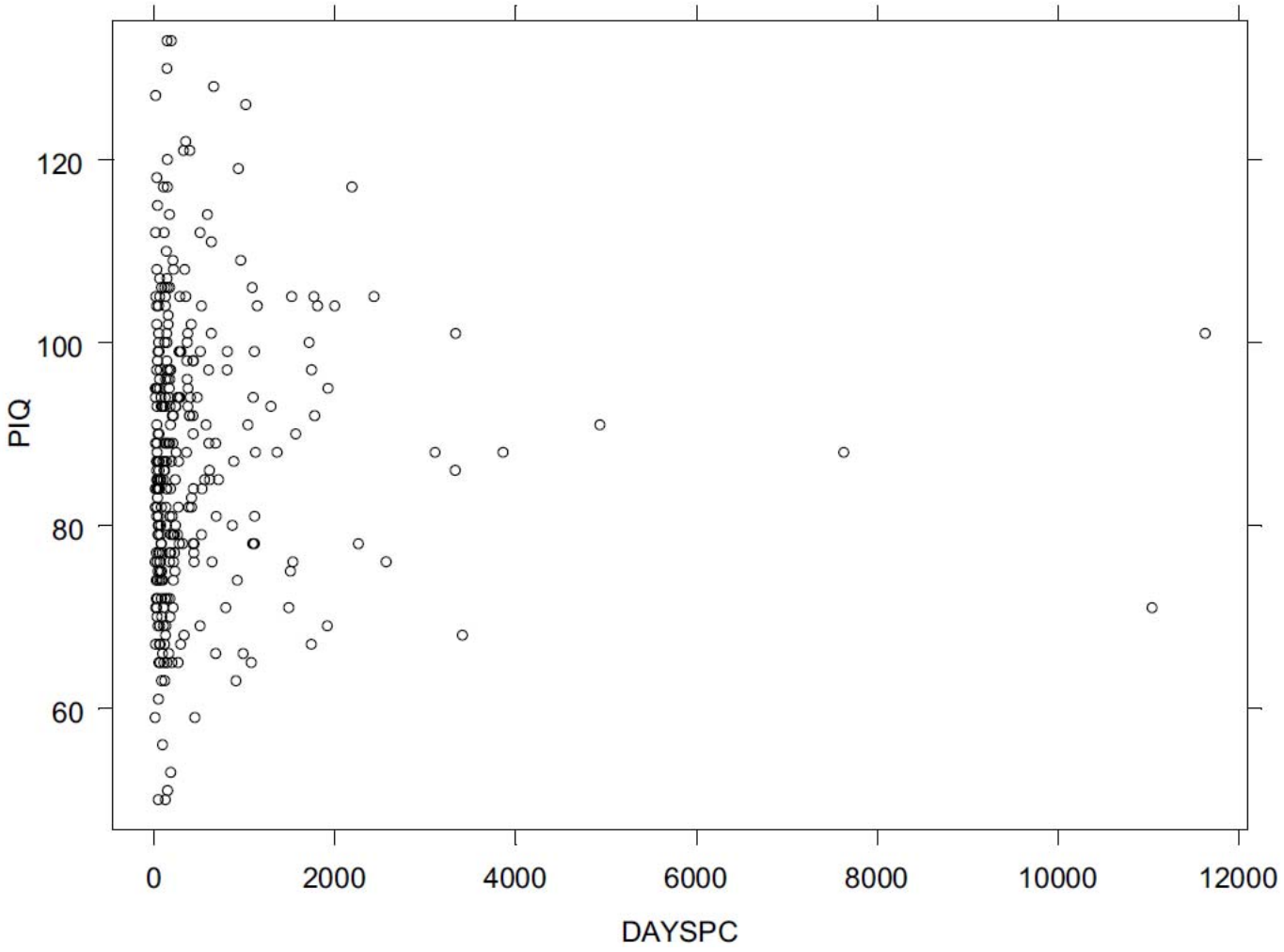
We fit an asymptotic non-linear growth curve to PIQ as a function of Days post Coma.

We then try the same model with VIQ in the hope of comparing the two models, but the VIQ model does not converge. We explore causes and remedies of non convergence and eventually decide on a mild reparametrization. It works! We then use the same model on PIQ and compare the two models.

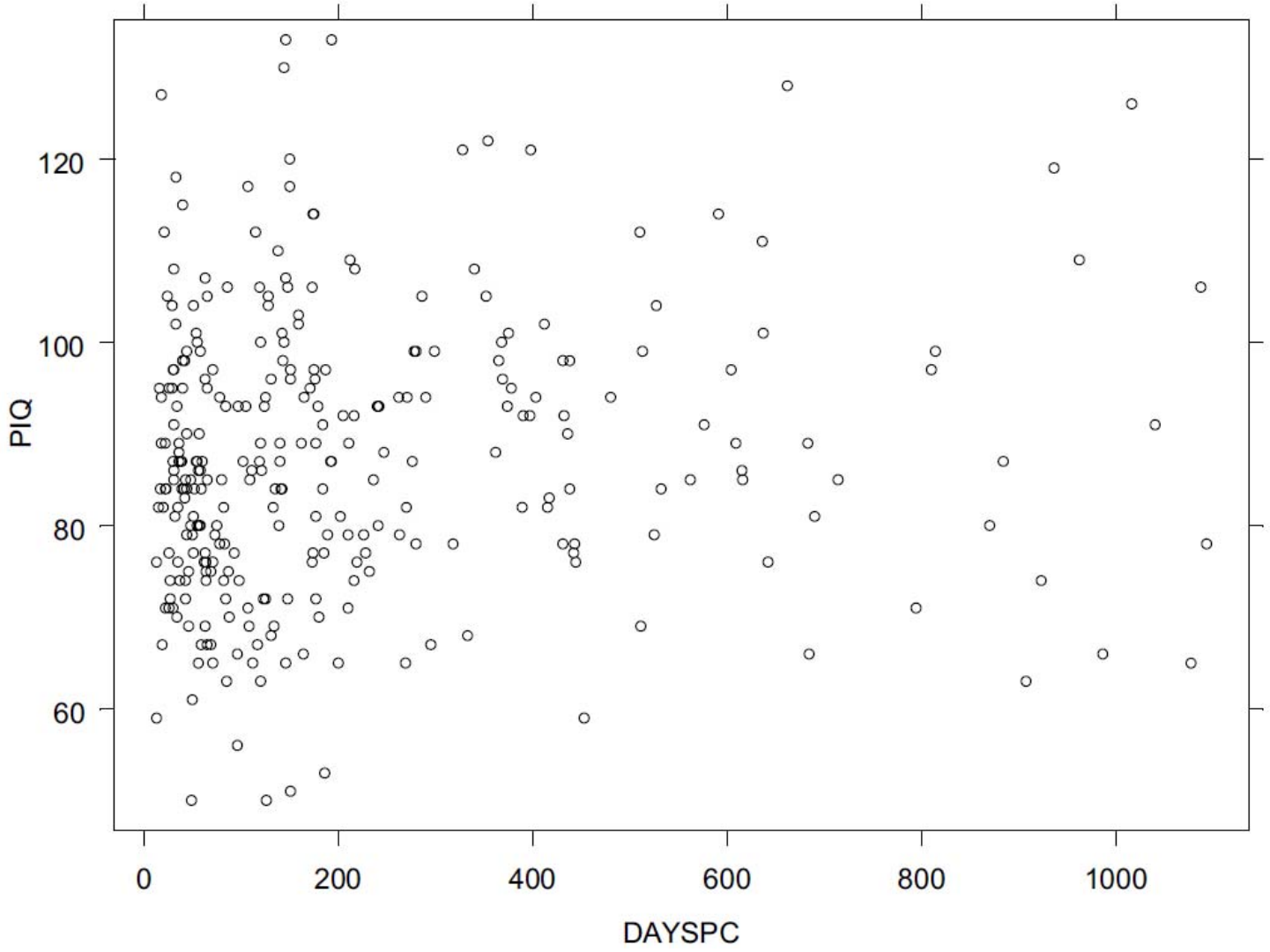
These two models are 'univariate' multivariate models, looking at one response at a time. To get p-values in the comparison of the models for the two responses, we need to do more. One possibility is bootstrapping which we don't explore. The other is to exploit multilevel (with 3 levels) modeling in nlme to fit something close to (but not exactly) a multivariate model. This is done at the end of the Lab script.

Recovery of post-coma IQ

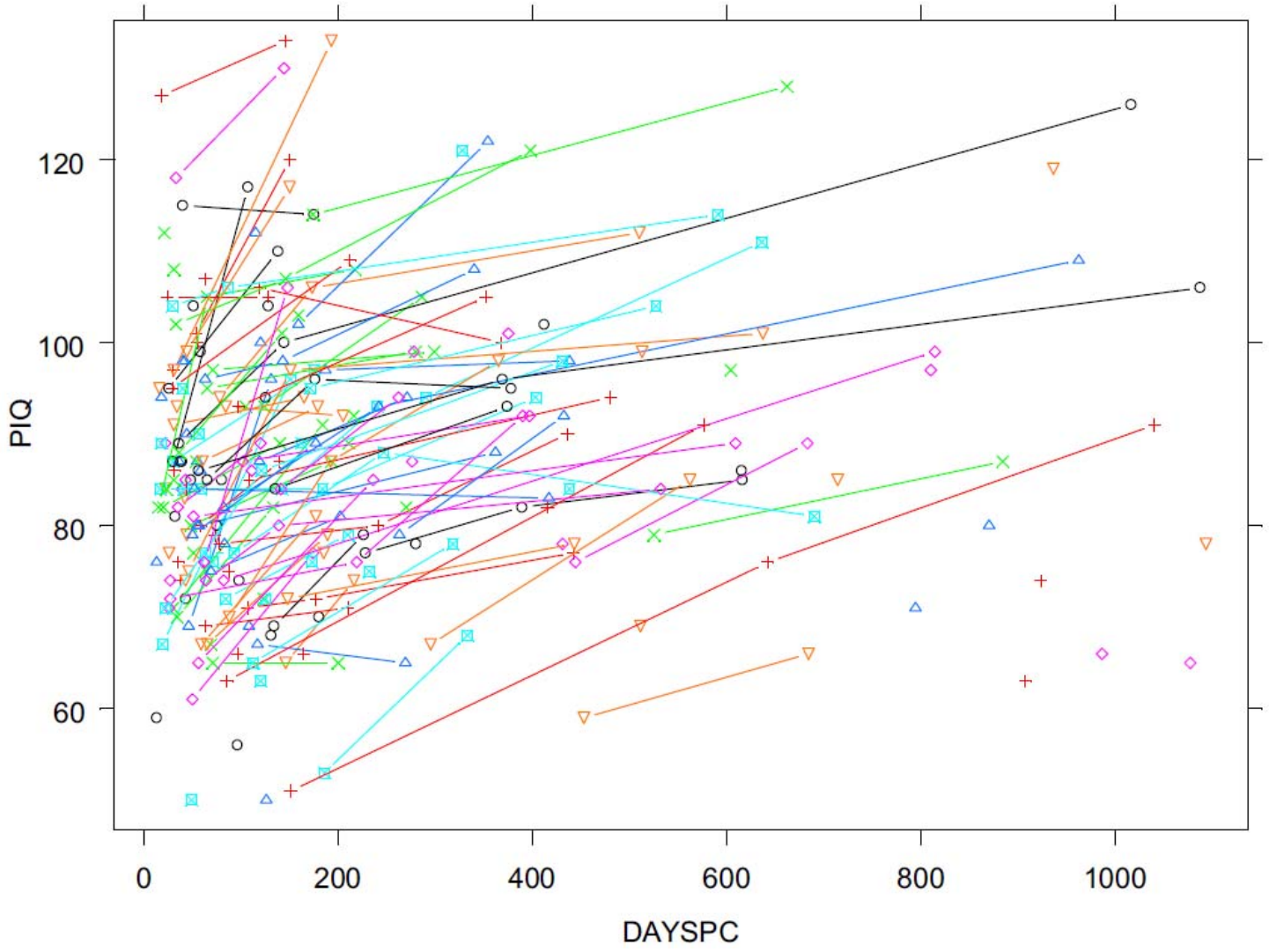
76



First 3 years:



45


120
100
80
60
PIQ
0
200
400
600
800
1000
DAYSPC

Using nlme

The nlme model is specified like a hierarchical model, except that you can mix variable levels.

Example:

```
nlme( piq ~ b0 + b1*exp(-a*dayspc),
   data = iq,
   fixed = list( b0 ~ 1+sqrt( dcoma ),
      b1 ~ 1,
      a ~ 1),
   random = list( id = b0 ~ 1),
   start = list( fixed = c(
      100, 0,-20.,.05)),
    control = list( maxIter = 100,
      returnObject = TRUE),
    verbose = T)
```

The code one line at a time:

```
piq ~ b0 + b1*exp(-a*dayspc)
```

A ***non-linear model formula*** with ***regressors*** and parameters. In this example, it's the Level 1 model. In general, you could have Level 2 ***regressors*** in this model. If you want to use a factor you need to use it through its dummies: e.g.

```
b.sex * (sex=="Female")
```

where `b.sex` is the parameter multiplying the indicator for Female.

```
data = iq,
```

data frame as usual

```
fixed = list(
        b0 ~ 1+sqrt( dcoma ),
        b1 ~ 1+sqrt( dcoma ),,
        a ~ 1)
```

A list of ***linear model formulas***, one for each parameter. Here, the parameter `a` is assumed to have the same value across the population, `b0` and `b1` are assumed to depend through a linear model on `sqrt(dcoma)`. This transformation incorporates an assumption that an extra day of coma after, say, 3 days has a greater impact than an extra day after 50 days. The sqrt transformation was chosen by examining visual plots. It is somewhat arbitrary. Also it is an oversimplification to assume that `a` is a constant across the population.

```
random = list( id = list( b0 ~ 1, b1 ~ 1 )
```

Specify the parameters that are assumed to vary randomly from id to id. Note that **b0** is the asymptotic level but it is also a constant added to all observations.

```
start = list( fixed =
   c( 100, -10, -20.,-1,.05)))
```

This is the challenging part that rewards a good understanding of the paramters of the model. Recall the fixed portion of the model above:

```
        fixed = list(
                b0 ~ 1+sqrt( dcoma ),
                b1 ~ 1+sqrt( dcoma ),,
                a ~ 1)
```

The starting values are listed in the same order as the regressors of the 'fixed' portion of the model. Generally, it is good enough to have plausible starting values. Draw a sketch and make educated guesses Here, our starting model is:

```
      b0 = 100 - 10 * sqrt(dcoma)
      b1 = -20 - 1 * sqrt(dcoma)
      a = 0.05
```

```
control = list( maxIter = 100,
        returnObject = TRUE)
```

Increases the default number of iterations from 50 to 100 and returns the last fit even if there is no convergence. We'll see how to use this shortly.

```
verbose = T
```

This shows information on each **PNLS** and **LME** step. Type Ctrl-W in the R console to get unbuffered output and you can watch a frequently exciting show.

Fitting the model:

```
> fit.nlme <- nlme(
+      piq ~ b0 + b1*exp(-a*dayspc),
+      data = iq,
+      fixed = list(
+            b0 ~ 1 + sqrt(dcoma) ,
+            b1 ~ 1 + sqrt(dcoma) ,
+            a ~ 1),
+      random = list( id  = list( b0 ~ 1, b1~ 1 )),
+      control = list( maxIter = 200, returnObject = T),
+      start = list(
+             fixed = c(100, -10, -10, 0,.05)),
+      control = list( maxIter = 100, returnObject = T),
+      verbose = TRUE)
```

```
. . . . [Omitting Output on Iterations 1 to 3]
**Iteration 4
LME step: Loglik: -1287.679 , nlm iterations: 1
reStruct  parameters:
      id1       id2       id3
 1.515913  0.949715 23.921793

PNLS step: RSS =  15018.94
 fixed effects:97.0948  -1.24521  -11.1453  -3.24829  0.00825027
 iterations: 7

Convergence:
       fixed     reStruct
1.312661e-06 7.021607e-04
```

This was pretty quick convergence

```
> summary( fit.nlme )
Nonlinear mixed-effects model fit by maximum likelihood
  Model: piq ~ b0 + b1 * exp(-a * dayspc)
 Data: iq
       AIC      BIC    logLik
  2593.358 2627.577 -1287.679
```

```
Random effects:
 Formula: list(b0 ~ 1, b1 ~ 1)
 Level: id
 Structure: General positive-definite, Log-Cholesky parametrization
               StdDev    Corr
b0.(Intercept) 13.769293 b0.(I)
b1.(Intercept)  2.605835 -0.994
Residual        6.736055
```

worries me a bit
I might try to reparametrize

```
Fixed effects: list(b0 ~ 1 + sqrt(dcoma), b1 ~ 1 +
sqrt(dcoma), a ~ 1)
                     Value Std.Error  DF  t-value p-value
b0.(Intercept)  97.09476  2.036582 127 47.67536  0.0000
b0.sqrt(dcoma)  -1.24521  0.480486 127 -2.59157  0.0107
b1.(Intercept) -11.14530  3.208072 127 -3.47414  0.0007
b1.sqrt(dcoma)  -3.24829  1.076749 127 -3.01676  0.0031
a                0.00825  0.001651 127  4.99579  0.0000
```

```
 Correlation:
                  b0.(I) b0.s() b1.(I) b1.s()
b0.sqrt(dcoma) -0.724
b1.(Intercept) -0.596  0.463
b1.sqrt(dcoma)  0.463 -0.455 -0.789
a              -0.309  0.013  0.092 -0.380
```

```
Standardized Within-Group Residuals:
         Min           Q1          Med           Q3          Max
-3.332408193 -0.365688335  0.009002275  0.382738703  2.303114344

Number of Observations: 331
Number of Groups: 200
```

> ***An interesting calculation:***

Between subject SD of 'true' IQ	13.769
Within subject between test SD of IQ	6.736
Population SD of IQ	$\sqrt{13.769^2 + 6.736^2} = 15.329$
Test-retest reliability of IQ $= \dfrac{\text{Variance in True Score}}{\text{Variance of Observed Score}}$	$\dfrac{13.769^2}{15.328^2} = 0.807$

How does fitting work?

See Pinheiro and Bates (2000) and Lindstrom and Bates (1990) for a description. It's a clever blend of available tools. Bates and Watts (1988) *Non-linear regession analysis and its applications* deals with non-linear models for independent data which can be adapted to situation where the variance-covariance is known.
So we have we have tools for non-linear models when the variance is known. And we have tools for linear mixed models (lme). If we have estimates of parameters in a non-linear model we can construct an approximating linear model.

The algorithm keeps repeating 2 steps until convergence:

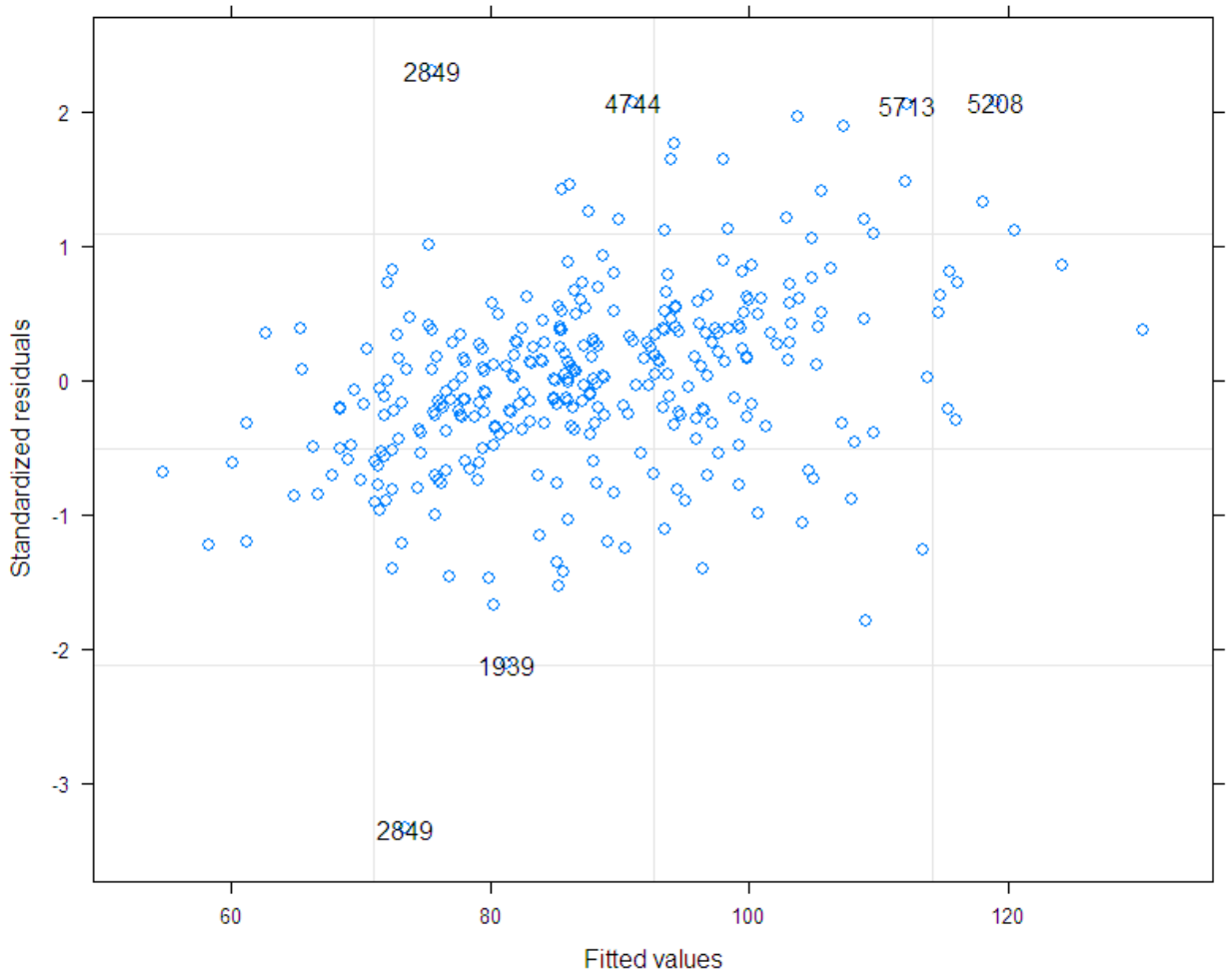
1) PNLS step: Given an estimate of G and R, estimate fixed parameters and random effects using a ***p***enalized ***n***on-linear ***l***east-***s***quares algorithm.

2) LME step: Given estimates of fixed parameters and random effects, construct an approximating linear model and estimate G and R with lme.

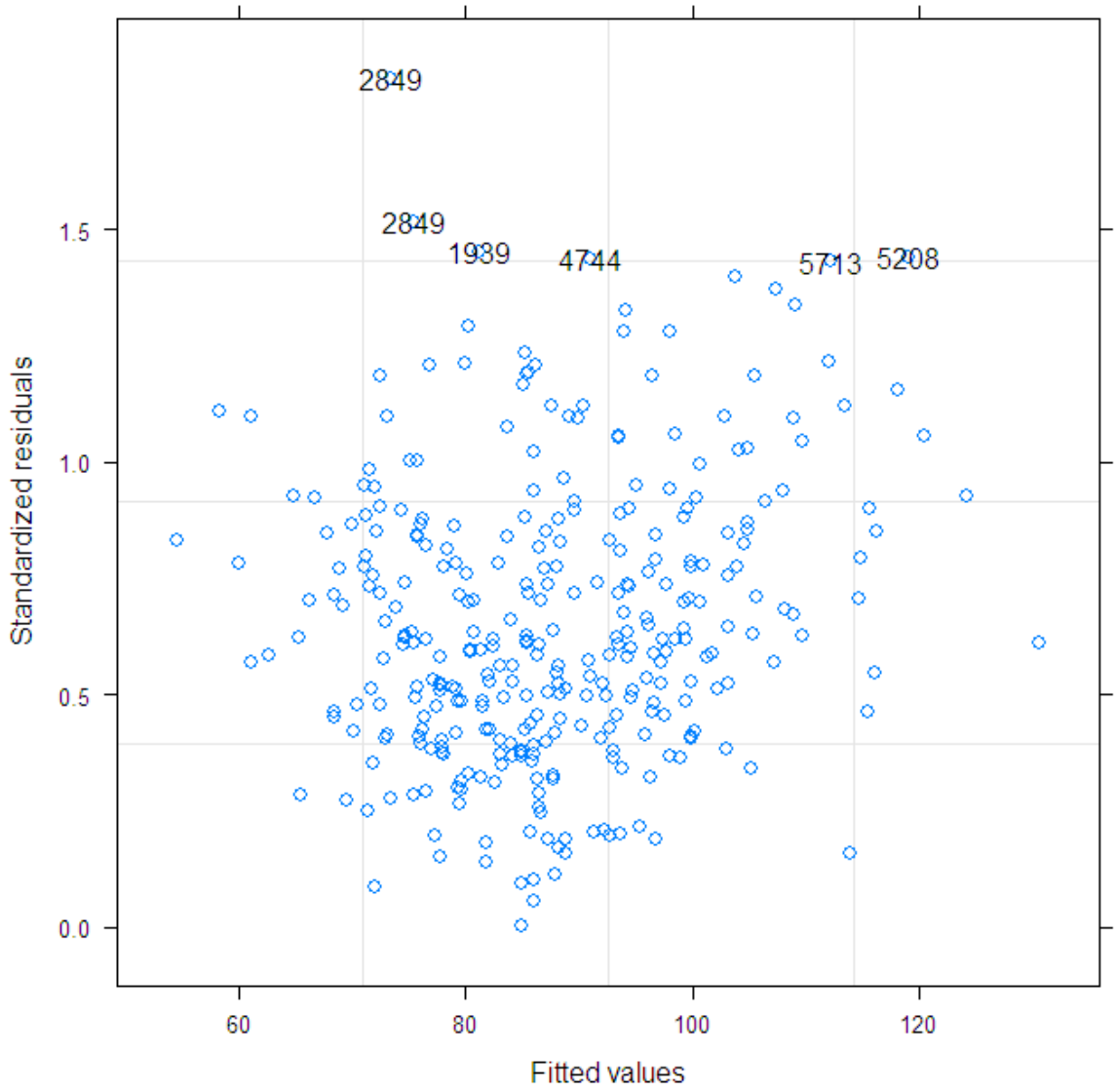
Keep repeating (1) and (2) until the estimates don't change much.

Some diagnostics for PIQ

```
> plot( fit.nlme, resid(. , type = 'p') ~ fitted(.),
+           id = .05)
```



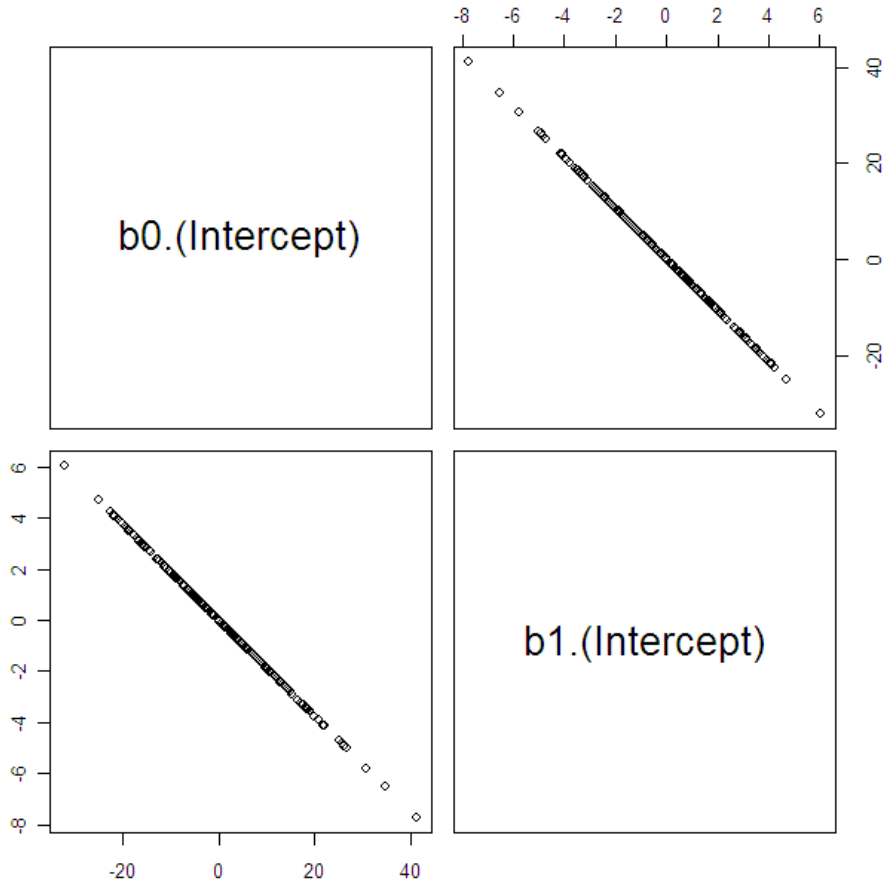
```
> plot( fit.nlme, sqrt( abs( resid(. ,type='p')))
+         ~fitted(.), id = .05)
```




```
>  plot( ranef( fit.nlme )) # output omitted
```

60

```
> pairs( ranef( fit.nlme ))
```



This plot shows the near singularity of the G matrix shown earlier in the strong correlation between **b0** and **b1**. It suggests that long-term recovery level, possibly related to pre-trauma intelligence does not confer so large a benefit in the early stages of recovery.

Fitting VIQ

```
> fit.nlme.viq <- nlme(
+    viq ~ b0 + b1*exp(-a*dayspc),
+    data = iq,
+    fixed = list( b0 ~ 1 + sqrt(dcoma) ,
+                  b1 ~ 1 + sqrt(dcoma) ,
+                  a ~ 1),
+    random = list( id  =
+        list( b0 ~ 1, b1~ 1 )),
+    start = list(
+        fixed = c(100, -.3, -10, -5,.01)),
+    control = list( maxIter = 100,
+        returnObject = T),
+    verbose = T)
```

```
**Iteration 1

LME step: Loglik: -1246.109 , nlm iterations: 20
reStruct  parameters:
        id1         id2         id3
-0.31704425 -0.03919651  1.58004210

PNLS step: RSS =  8190.372
 fixed effects:98.3784  -0.398053  -11.1171  -3.81443  0.02529
 iterations: 7

Convergence:
    fixed  reStruct
0.6045864 0.3340419
```

We hope these numbers will get very small

Then it repeats:

```
**Iteration 2
LME step: Loglik: -1242.047 , nlm iterations: 10
reStruct  parameters:
       id1         id2         id3
-0.6005839 -1.1484260  0.3314853

PNLS step: RSS =  29302.31
```

```
 fixed effects:93.3904  -0.500735  -2.79404  -5.93326  0.0384955
 iterations: 7

Convergence:
   fixed reStruct
2.978855 2.355074
```

Much, much later:

```
**Iteration 97
LME step: Loglik: -1223.248 , nlm iterations: 11
reStruct  parameters:
       id1        id2        id3
-0.3076645 -0.9642632  0.4746019

PNLS step: RSS =  13520.03
 fixed effects:96
 iterations: 7

Convergence:
    fixed  reStruct
0.6185455 1.3370712
```

64

```
**Iteration 98
LME step: Loglik: -1239.934 , nlm iterations: 11
reStruct  parameters:
       id1        id2        id3
-0.6920771 -0.9315449  0.3989076

PNLS step: RSS =  9035.715
 fixed effects:98.3663  -0.345367  -8.12821  -2.46351  0.0134667
 iterations: 7

Convergence:
   fixed reStruct
1.619486 0.572147

**Iteration 99
LME step: Loglik: -1223.284 , nlm iterations: 11
reStruct  parameters:
       id1        id2        id3
-0.3084674 -0.9647008  0.4741239

PNLS step: RSS =  13512.85
 fixed effects:96.0224  -0.381974  -9.02973  -5.45431  0.0352635
 iterations: 7
```

These are the estimated fixed effects at iteration 98

```
Convergence:
    fixed  reStruct
0.6181109 1.3332673

**Iteration 100
LME step: Loglik: -1239.936 , nlm iterations: 11
reStruct  parameters:
       id1        id2        id3
-0.6921102 -0.9316034  0.3988804

PNLS step: RSS =  9033.863
 fixed effects:98.3667  -0.345443  -8.13618  -2.46378  0.0134763
 iterations: 7

Convergence:
    fixed  reStruct
1.6167060 0.5714619
Warning message:
In nlme.formula(viq ~ b0 + b1 * exp(-a * dayspc), data = iq, fixed
= list(b0 ~  :
  Maximum number of iterations reached without convergence
```

These numbers are just bouncing around and not getting smaller

Have a close look at what these number have been doing for the past few iterations

Our model didn't converge.

What to do?

Looking carefully at the output we notice that:

1) The convergence criteria are not slowly getting smaller, they're bouncing around, and
2) Some of the fixed parameters are stuck in an oscillation of period 2.

Possible actions:

1) Increase maxIter and come back much later. In this case it won't help,
2) Simplify the model, particularly the RE model. Here we could – and it would work – but it would require making assumptions we would prefer to avoid for now.
3) Consider whether the model is well identified. Are there parameters whoses estimates are far from expected? Or that are constantly changing in a given direction as iterations increase?

3) When the process is stuck in a cycle, as it is here, which parameters oscillate and how do they oscillated together? Try to visualize what this implies about the fitted surface. A cycle can mean that the leverage and residuals of some points oscillate from iteration to iteration. Such points pull the fit towards themselves in one iteration but in the new fit they lose leverage and let go of the fitted surface for the next iteration. This can't happen with OLS because leverage does not depend on the fit. But the linear approximation in non-linear models depends on the previous fit so leverage can change from one fit to the next. The points involved tend to be outliers.

Finding problematic points:

1) Use maxIter to stop the iteration at each point in the cycle, with a 2-cycle, use an odd iteration and an even iteration. Save the fitted object in each case. Plot the residuals of one fit against the

residuals of the other. The points with very different residuals are likely to be the culprits. You can also compare the fits to see how each fit attempts to approximate the data.

2) Use your knowledge of the data to isolate some known outliers.

We note that the distribution of **dcoma** is highly skewed and we'll try dropping anyone with **dcoma > 100**. Note dcoma is a between subject variable and extreme values are likely to have high leverage. With the asymptotic model for **dayspc**, influence may be reversed with small values being very influential and large values less so. After further experimenting we also see that **b1**, the deficit at **dayspc = 0** is bound with the estimate of **a**. A larger value for **a** produces a very negative value of **b1**. This leads us to the realization that attempting to estimate deficit immediately upon arousal is not feasible since there is little IQ data that early. We can easily move the origin to say one month after arousal by simply

changing **dayspc** to **dayspc – 30** in the non-linear formula. If this works we can do the same for PIQ to have comparable results.

```
> fit.nlme.viq2 <-nlme( viq ~ b0 + b1*exp(-a*(dayspc-30)),
+          data = iq,
+          fixed = list( b0 ~ 1 + sqrt(dcoma) ,
+                        b1 ~ 1 + sqrt(dcoma) ,
+                        a ~ 1),
+          random = list( id  = list( b0 ~ 1, b1~ 1 )),
+          start = list(
+          fixed = c(100, -.3, -10, 0,.3)),
+          control = list( maxIter = 100, returnObject = T),
+          verbose = T,
+          subset = dcoma < 100)
```

which converges in 3 iterations:

. . . . . .

```
**Iteration 3
LME step: Loglik: -1225.668 , nlm iterations: 1
reStruct  parameters:
       id1        id2        id3
-0.8286352 12.2429072 59.7420069

PNLS step: RSS =  9725.302
 fixed effects:99.2084  -0.561859  -6.79895  -1.87309
0.0214789
 iterations: 7

Convergence:
       fixed     reStruct
1.054542e-07 1.588532e-01
>
> summary( fit.nlme.viq2 )
Nonlinear mixed-effects model fit by maximum
likelihood
```

```
  Model: viq ~ b0 + b1 * exp(-a * (dayspc - 30))
 Data: iq
  Subset: dcoma < 100
       AIC      BIC    logLik
  2469.336 2503.363 -1225.668

Random effects:
 Formula: list(b0 ~ 1, b1 ~ 1)
 Level: id
 Structure: General positive-definite, Log-Cholesky
parametrization
                 StdDev       Corr
b0.(Intercept) 1.254731e+01 b0.(I)
b1.(Intercept) 2.640292e-05 0
Residual       5.478719e+00
```

```
Fixed effects: list(b0 ~ 1 + sqrt(dcoma), b1 ~ 1 +
sqrt(dcoma), a ~ 1)
                    Value Std.Error  DF  t-value p-value
b0.(Intercept) 99.20845 1.7262297 196 57.47117  0.0000
b0.sqrt(dcoma) -0.56186 0.4940133 123 -1.13734  0.2576
b1.(Intercept) -6.79895 2.2442154 123 -3.02954  0.0030
b1.sqrt(dcoma) -1.87309 0.7804948 123 -2.39987  0.0179
a               0.02148 0.0044938 123  4.77971  0.0000


 Correlation:
                b0.(I) b0.s() b1.(I) b1.s()
b0.sqrt(dcoma) -0.777
b1.(Intercept) -0.418  0.332
b1.sqrt(dcoma)  0.312 -0.343 -0.860
a              -0.148 -0.057  0.096 -0.058

Standardized Within-Group Residuals:
         Min           Q1          Med           Q3          Max
-2.157276598 -0.389534045  0.007514936  0.366479340  1.903012142

Number of Observations: 324
```

```
Number of Groups: 197
```

We have no evidence of a long-term effect of duration of coma and only weak evidence of an effect at the end of 30 days.

Refitting PIQ with a similar model:

```
>  fit.nlme.piq2 <-nlme( piq ~ b0 + b1*exp(-a*(dayspc-30)),
+      data = iq,
+      fixed = list( b0 ~ 1 + sqrt(dcoma) ,
+                    b1 ~ 1 + sqrt(dcoma) ,
+                    a ~ 1),
+      random = list( id  = list( b0 ~ 1, b1~ 1 )),
+      start = list(
+             fixed = c(100, -.3, -10, 0,.1)),
+      control = list( maxIter = 100, returnObject = T),
+      verbose = T,
+      subset = dcoma < 100)
```

which also converges quickly.

```
> summary( fit.nlme.piq2 )
. . . .
Random effects:
 Formula: list(b0 ~ 1, b1 ~ 1)
 Level: id
 Structure: General positive-definite, Log-Cholesky
parametrization
                  StdDev       Corr
b0.(Intercept) 1.303845e+01 b0.(I)
b1.(Intercept) 1.288991e-04 0.001
Residual       6.640711e+00

Fixed effects: list(b0 ~ 1 + sqrt(dcoma), b1 ~ 1 +
sqrt(dcoma), a ~ 1)
                    Value Std.Error  DF  t-value p-value
b0.(Intercept)  98.45118 2.1594531 123 45.59079  0.0000
b0.sqrt(dcoma)  -1.52286 0.5784392 123 -2.63270  0.0096
b1.(Intercept) -10.71808 2.6410052 123 -4.05833  0.0001
b1.sqrt(dcoma)  -2.06639 0.8298037 123 -2.49022  0.0141
a                0.00707 0.0014827 123  4.76892  0.0000
```

These results contrast interestingly with VIQ.

***EXERCISE*:** Note that `b1` has very small variability in both models. What happens if you refit without a random effect for `b1`.

Comparison of half-recovery times

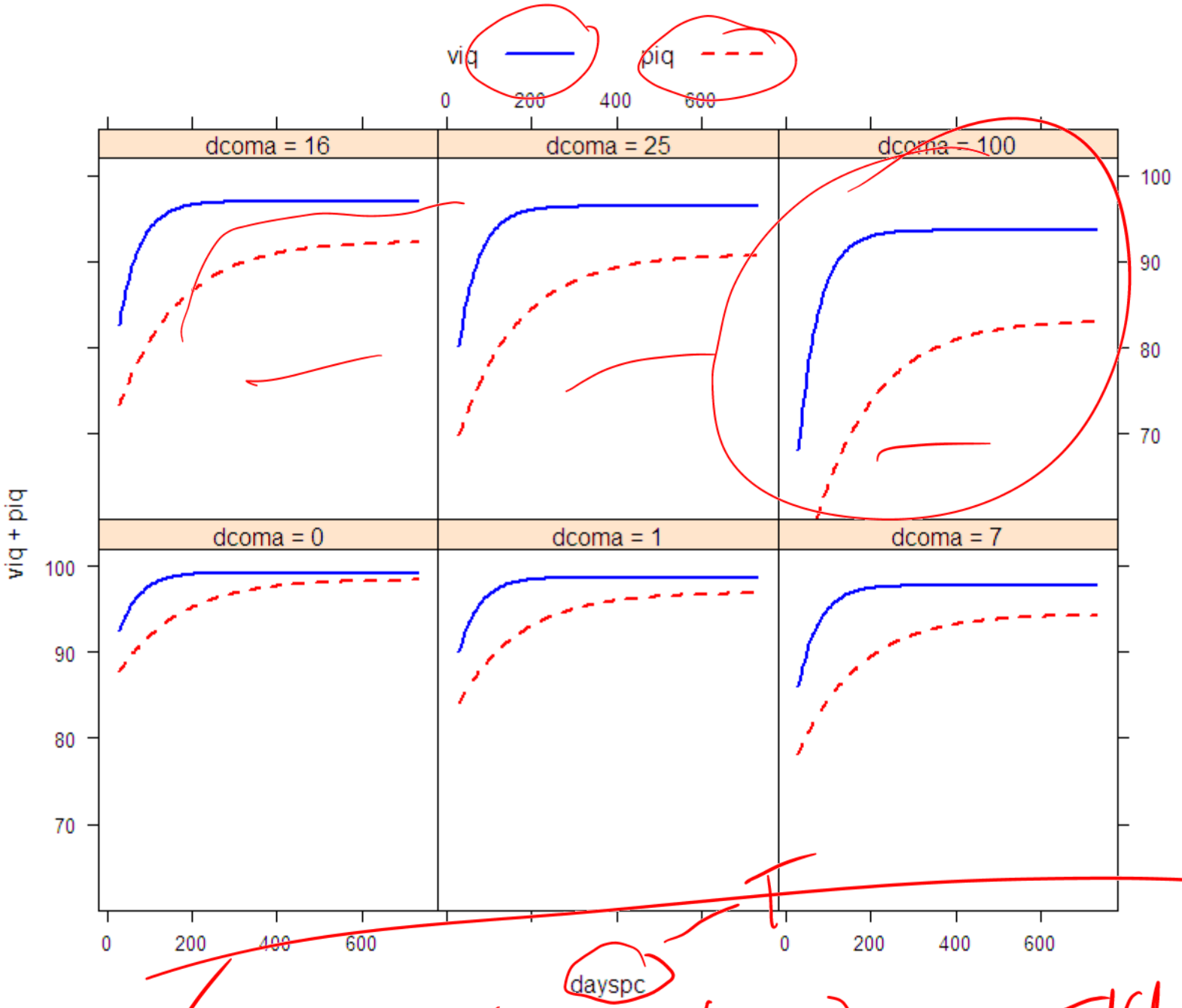
$$\text{Half-recovery time} = \frac{1}{\alpha \times \ln(2)}$$

IQ	α	half-recovery time
VIQ	0.02148	67 days
PIQ	0.00707	204 days

EXERCISE: Reparametrize the non-linear model formula to use half-life instead of IRRR in the model. Are the results consistent?

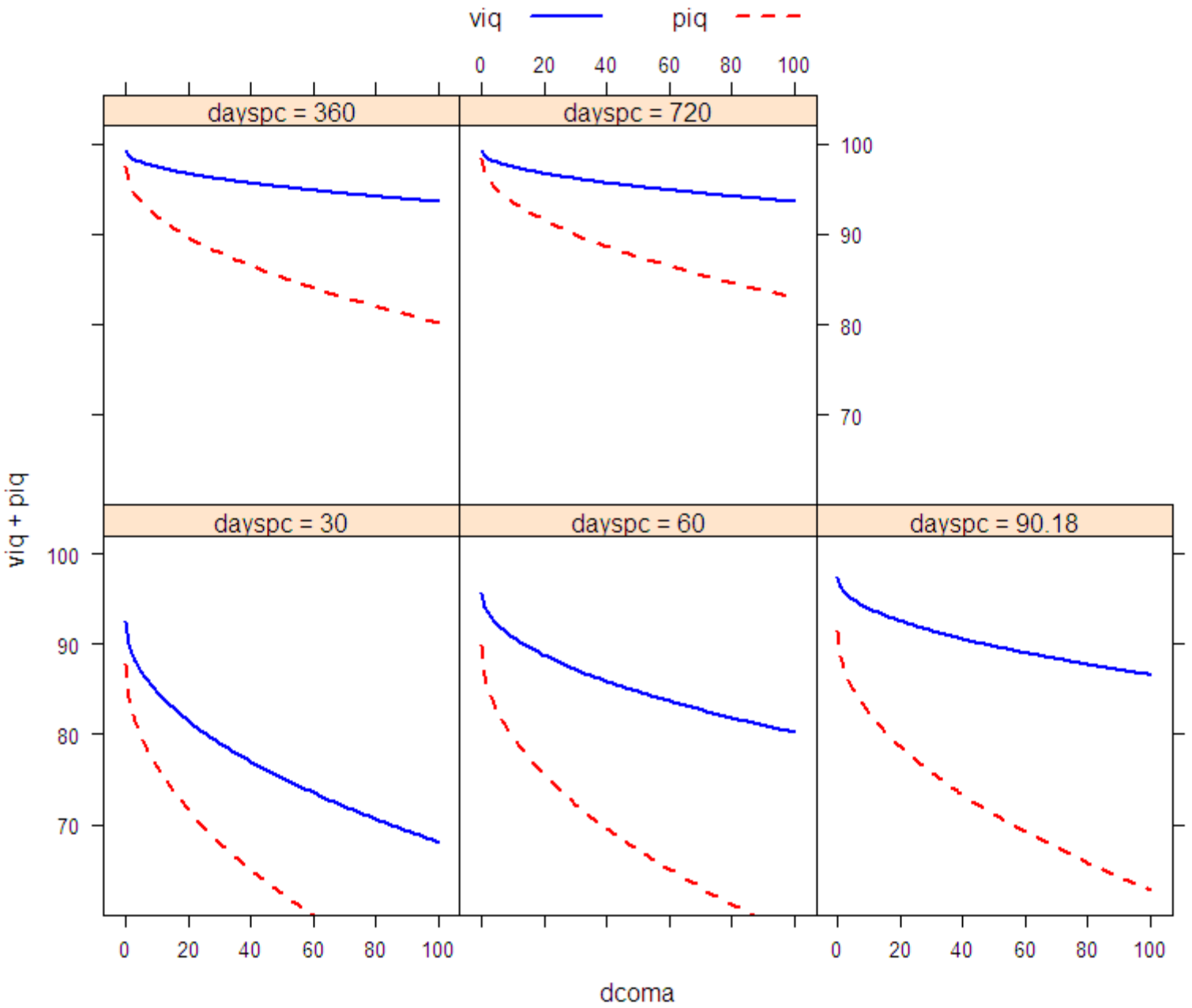
Visual comparisons of PIQ and VIQ

```
#

windows( height = 7, width = 8.5)

pred <- expand.grid( dcoma = c(0,1,7,16,25,100),
                     dayspc = seq(30,365*2,5))
pred$piq <- predict( fit.nlme.piq2, pred, level = 0 )
pred$viq <- predict( fit.nlme.viq2, pred, level = 0 )

zz <- factor( paste( 'dcoma =', pred$dcoma))
pred$dcoma.lab <- reorder( zz, pred$dcoma)

td( col = c('blue','red'), lwd = 2)
xyplot( viq + piq ~ dayspc | dcoma.lab, pred, type = 'l',
    ylim = c(60,102),
    lwd = 2, auto.key = list(columns = 2, points = F, lines = T))
```



$$y = \gamma_0 + \gamma_1 \exp(-\alpha T) + \gamma_2 \operatorname{sqrt}(\text{dcoma}) + \varepsilon$$

```
pred2 <- expand.grid( dcoma = 0:100,
                      dayspc = c(30,60,90.180,360,720))
pred2$piq <- predict( fit.nlme.piq2, pred2, level = 0 )
pred2$viq <- predict( fit.nlme.viq2, pred2, level = 0 )

zz <- factor( paste( 'dayspc =', pred2$dayspc))
pred2$dayspc.lab <- reorder( zz, pred2$dayspc)


xyplot( viq + piq ~ dcoma | dayspc.lab, pred2, type = 'l',
          ylim = c(60,102),
          lwd = 2,
          auto.key = list(columns = 2, points = F, lines = T))
```

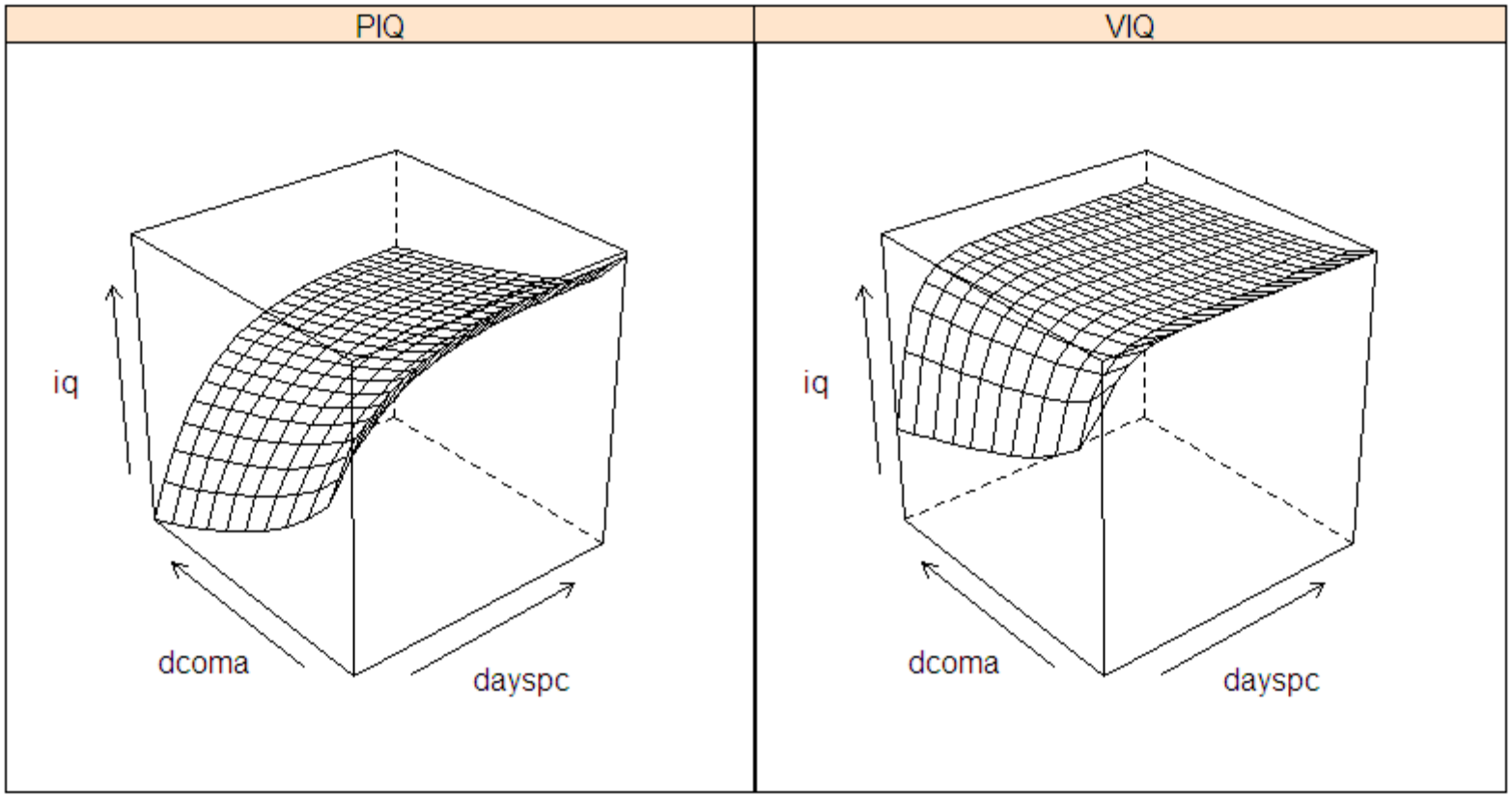

viq
piq
dayspc = 360
dayspc = 720
dayspc = 30
dayspc = 60
dayspc = 90.18
viq + piq
dcoma
0
20
40
60
80
100
70
90

80

```
predviq <- expand.grid( dcoma = seq(0,100,10),
                        dayspc = seq(30,720,30))
predpiq <- predviq
predviq $ iq <- predict( fit.nlme.viq2, predviq, level = 0)
predpiq $ iq <- predict( fit.nlme.piq2    , predpiq, level = 0)
predpiq$type <- factor( "PIQ" )
predviq$type <- factor( "VIQ" )
```

```
wireframe( iq ~ dayspc + dcoma | type, Rbind( predpiq, predviq))
```

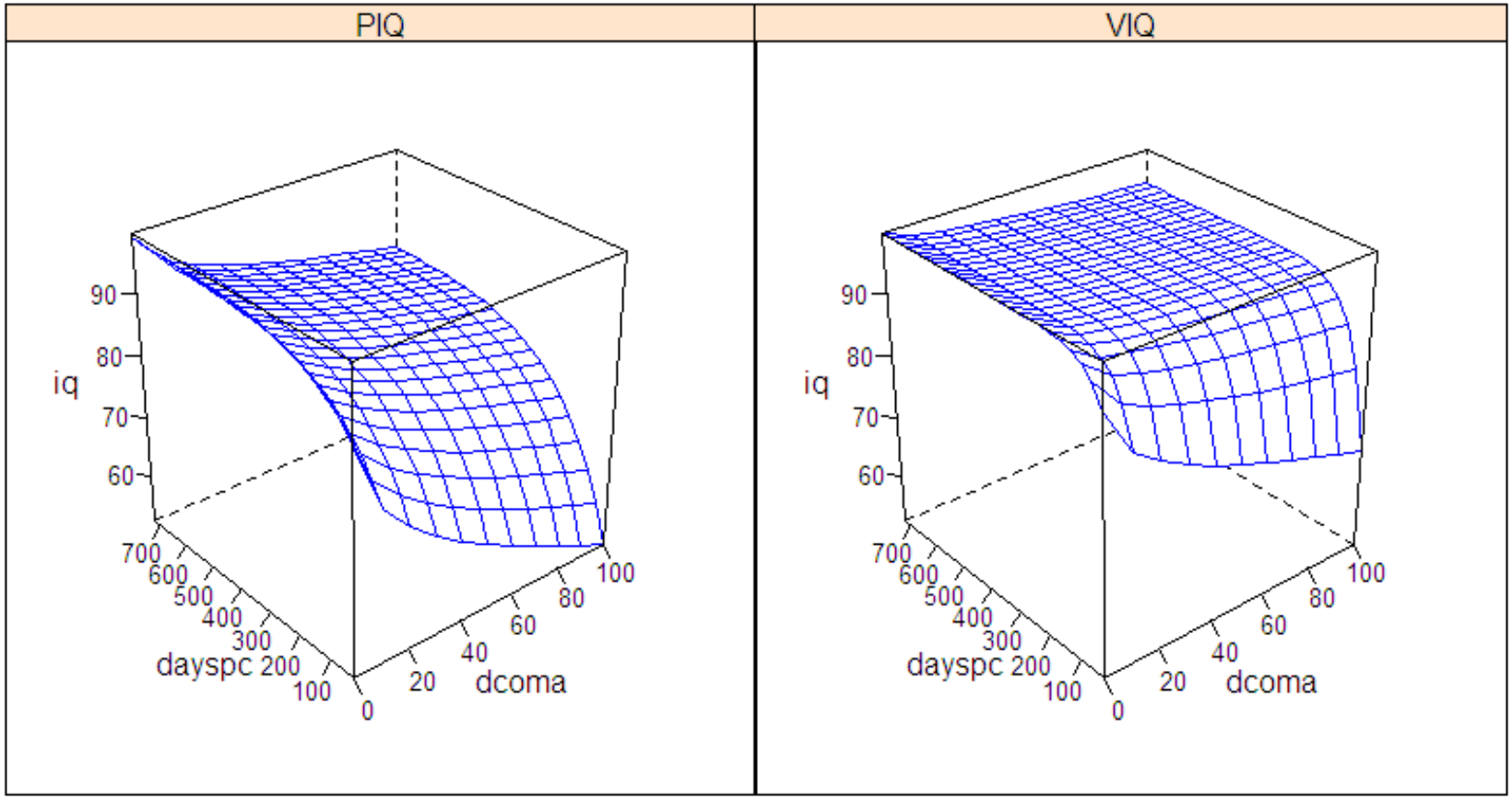
Default options and orientation for a wireframe plot:


PIQ
VIQ
iq
dcoma
dayspc
iq
dcoma
dayspc

```
wireframe( iq ~ dcoma + dayspc | type, Rbind( predpiq, predviq),
          scales = list( arrows = F), col = 'blue')
```

Exchange axes for a more natural presentation of dayspc (Level 1 variable) and dcoma (Level 2)

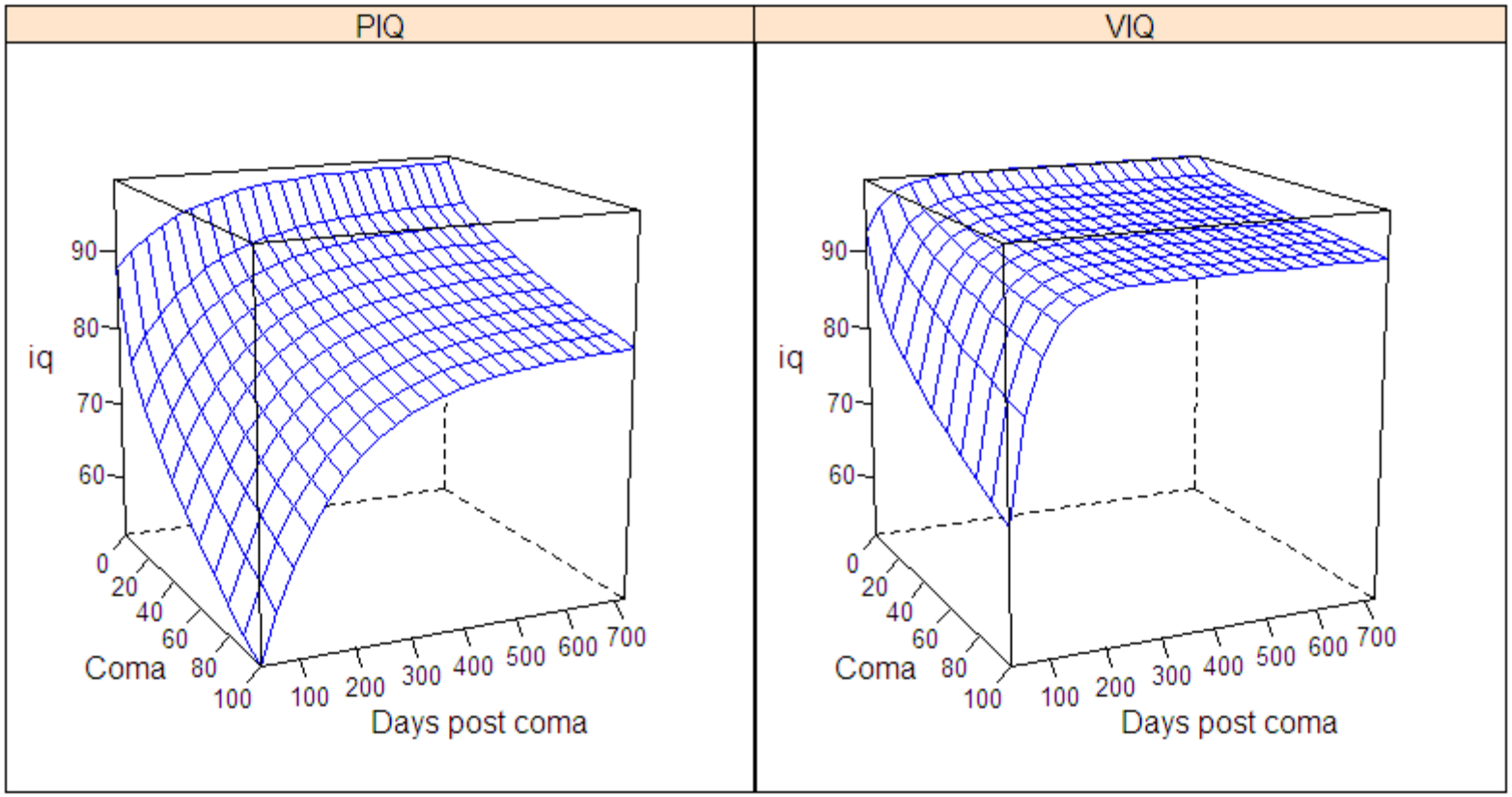
Suppress arrows and get axis with values and tickmarks.


PIQ
VIQ
iq
90
80
70
60
dayspc
700
600
500
400
300
200
100
0
dcoma
0
20
40
60
80
100

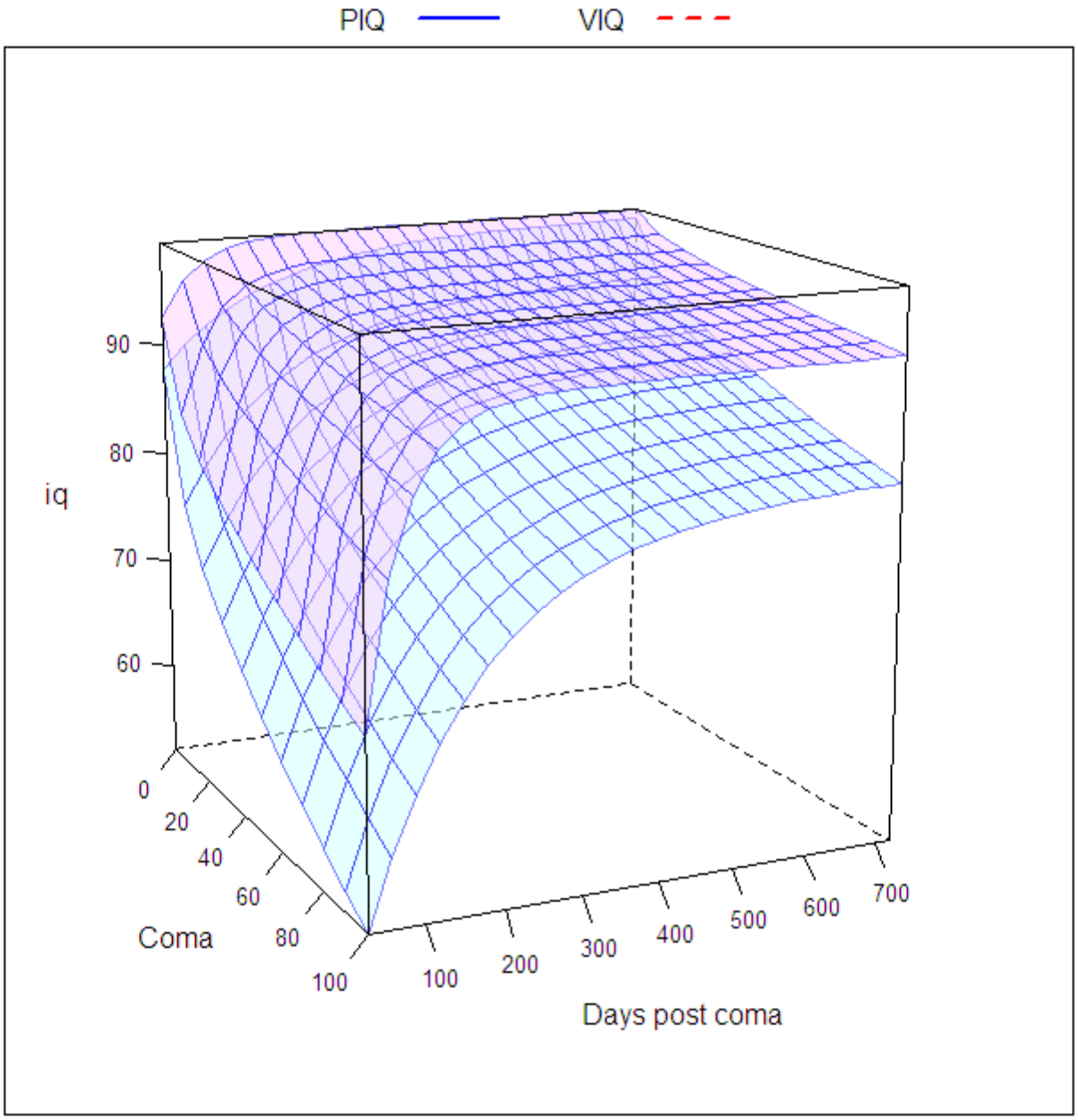
```
wireframe( iq ~ dcoma + dayspc | type, Rbind(predpiq, predviq),
          scales = list( arrows = F), col = 'blue',
          xlab = 'Coma',
          ylab = 'Days post coma',
          screen = list( z = -65, x = -75 ))
```

With the 'screen' parameter, you can control the orientation of the graph. Here, the z axis is tha vertical axis, the x axis, the horizontal axis in the surface of the screen and y, the horizontal axis straight into the screen.

Rotation in the z axis of -65 degrees results in clockwise rotation of +65 degrees from the top and x-axis rotation of -75, tilts the graph up by 75 degrees.


PIQ
VIQ
iq
90
80
70
60
Coma
0
20
40
60
80
100
100
200
300
400
500
600
700
Days post coma

```
wireframe( iq ~ dcoma + dayspc , Rbind(predpiq, predviq),
          groups = type,
          scales = list( arrows = F), col = 'blue',
          xlab = 'Coma',
          ylab = 'Days post coma',
          screen = list( z = -65, x = -75 ),
          auto.key = list(columns=2, lines = T, points = F),
          alpha = .5)
```


PIQ
VIQ
iq
90
80
70
60
0
20
40
60
80
100
Coma
100
200
300
400
500
600
700
Days post coma

88

See the Non-Linear Lab script for a multivariate model that compares the parameters for PIQ and VIQ.