Biomedical Applications of Time Series Analysis

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Introduction

Spectral analysis (analysis in the frequency domain)

Analysis of time series in the time domain

Concluding remarks

Introduction

Spectral analysis (analysis in the frequency domain)

- Fourier analysis
- Wavelet analysis
- Filtering and smoothing

Analysis of time series in the time domain

- General considerations
- Analysis of longitudinal data: GLS
- Analysis of longitudinal data: mixed effects models
- Applications in epidemiology

Concluding remarks

What is a time series? Why they are important to us?

- „Observations made over time” (i.e. they are ordered)
- As a sample vs. in the population (stochastic process)
- Many-many (and important!) biomedical data are available as time series
- Traditional methods can be applied – but the nature of time series must be taken into account
- Many special methods too

Main aims today (why is it a tutorial?)

- Maximum number of areas with minimum detail on each
- Practical, real-life examples for all methods
- All calculation is made with R
  - Free and open source (http://www.r-project.org/)
  - Enthusiastic, extremely active community; incredible number of packages at CRAN
  - (There is an R package for any statistical task you can think of... and for many that you can't even think of)
  - It includes packages making complex operations one-liners, streamlining entire analysis workflows (like Frank Harrell's wonderful `rms` for regression)
  - A powerful IDE called RStudio (http://www.rstudio.org/) is freely available
  - Extremely good at visualization (this presentation will use `lattice`), report generation, reproducible research too (just like this presentation!)
- Whole source code of this presentation is available at https://github.com/tamas-ferenci/BiomedicalApplicationsOfTimeSeriesAnalysis

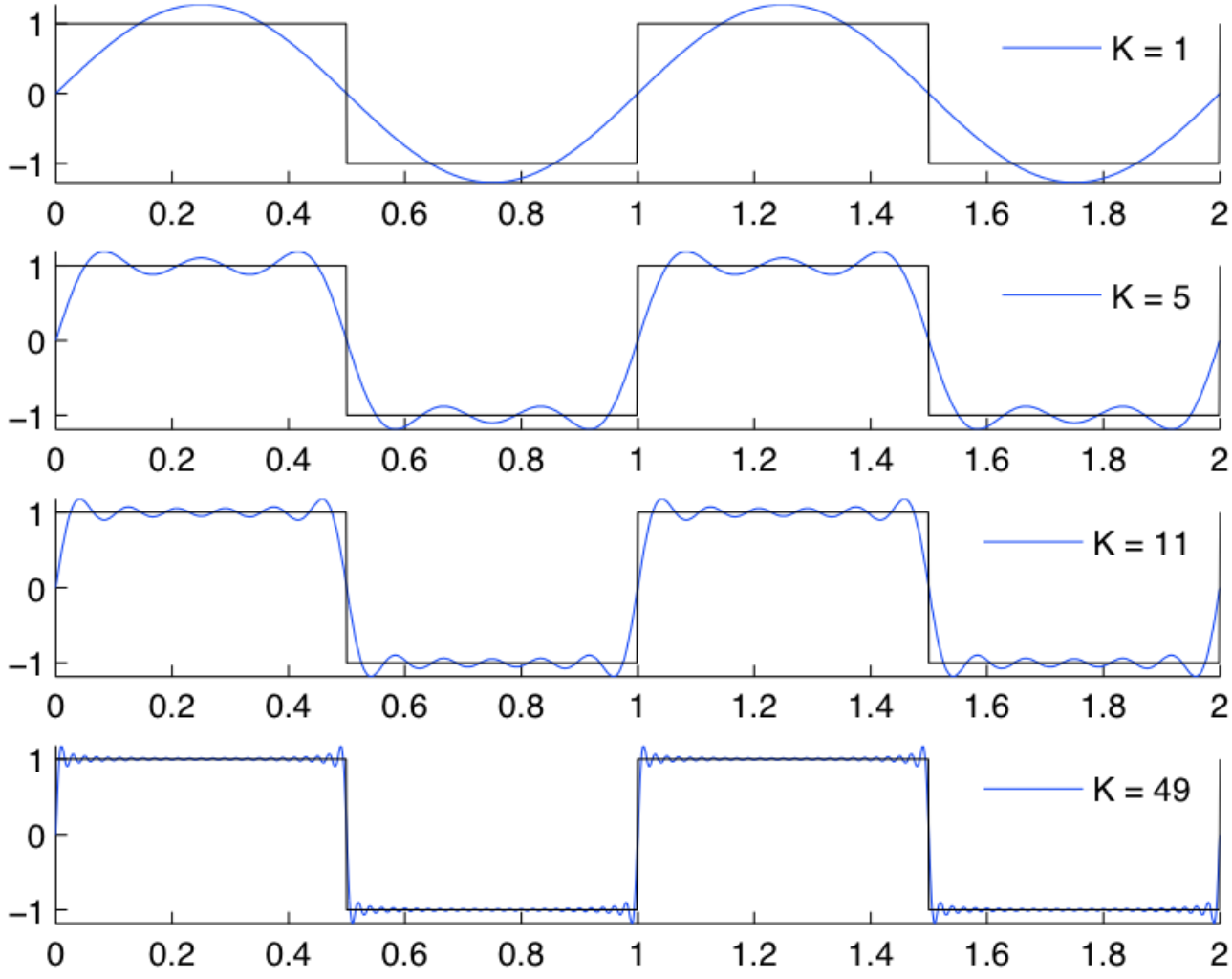
Methods applied in the analysis of biomedical time series

- It is somewhat ill-defined what can be considered „time series analysis”
- I now try to be as broad as possible
- Therefore, a rough (and very subjective) categorization:
  - Analysis of data that are only meaningful when collected over time: typically biomedical signals such as ECG or EEG
  - Analysis of data that are meaningful cross-sectionally, but measurements are repeated to obtain information on the time dimension too: typical in longitudinal studies, analysis of growth curves
  - Analysis of epidemiologic data with time dimension: typically incidence of diseases

Fourier analysis

- Fundamental idea: every periodic function can be represented as a weighted sum of sinusoidals (sine waves)
- We may need infinite number of sinusoidals, but still countable many (of course, we are trying to reconstruct a continuous function – the reason why we can do this, is its periodicity)
- If the function is non-periodic, it still works (quite universally), but we will need infinitely many terms

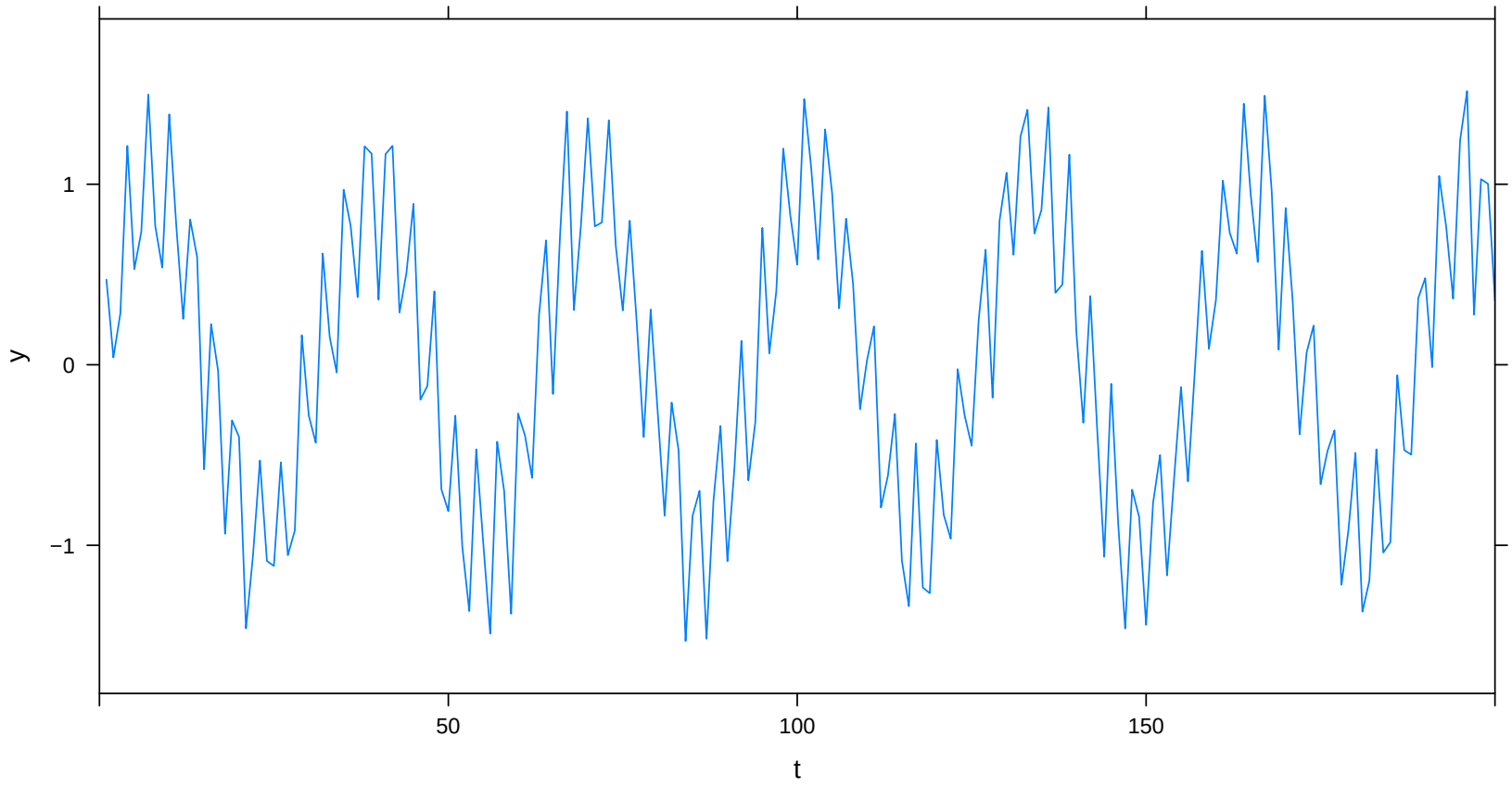
An example of Fourier analysis



Why is is it useful?

It gives a picture of what frequencies ''create" the signal:

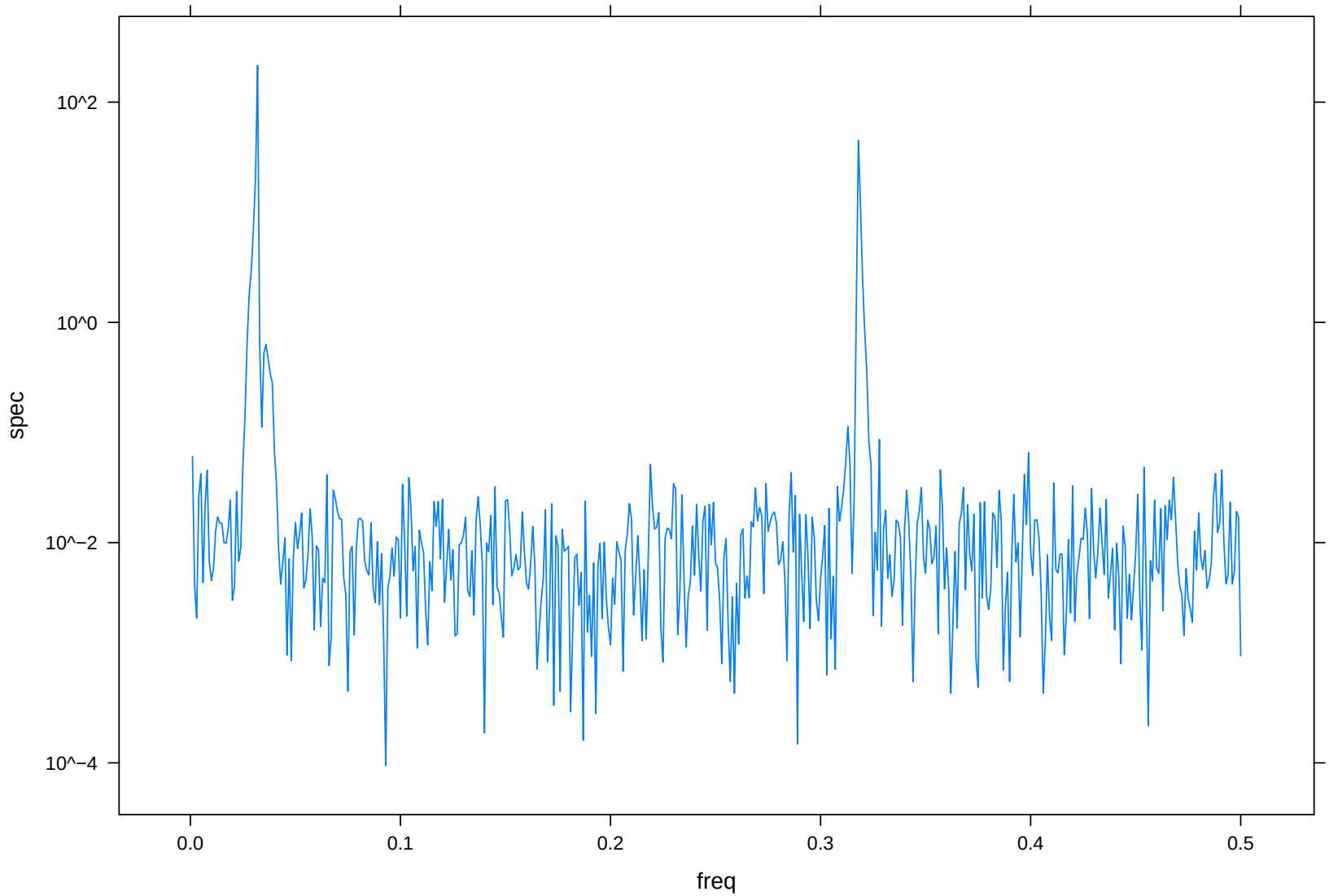
```
SimDataFourier <- data.frame( t = 1:1000 )
SimDataFourier <- transform( SimDataFourier, y = 0.5*sin( t*2 ) + sin( t/10*2 ) +
                                rnorm( length( t ), 0, 0.1 ) )
xyplot( y ~ t, data = SimDataFourier, type = "l", xlim = c( 0, 200 ) )
```



Why is is it useful?

It gives a picture of what frequencies ''create" the signal:

```
xyplot( spec ~ freq, data = spectrum( SimDataFourier$y, plot = FALSE ), type = "l",
        scales = list( y = list( log = 10 ) ) )
```



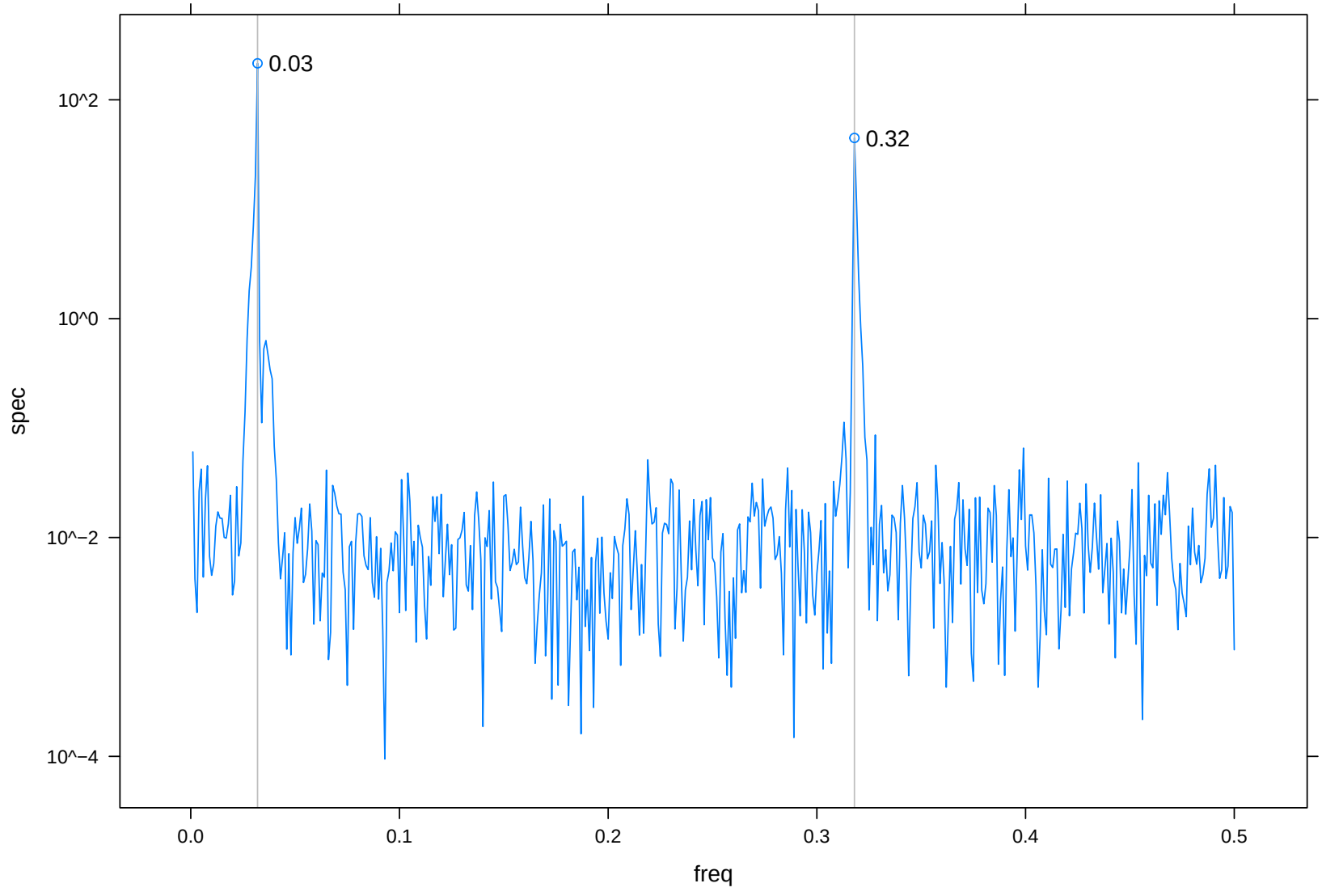
Why is is it useful?

(Sidenote) Custom plotting:

```
locmaxpanel <- function( x, y, width, maxmeddiff = 1, rounddigit = 2, ... ) {
  if( width%%2==0 )
    width <- width+1
  panel.xyplot( x, y, ... )
  maxs <- zoo::rollapply( y, width, function(x) (which.max(x)==(width+1)/2)&
                            (max(x)-median(x)>maxmeddiff),
                          align = "center", fill = NA )
  panel.abline( v = x[ maxs ], col = "gray" )
  panel.points( x[ maxs ], y[ maxs ] )
  panel.text( x[ maxs ], y[ maxs ], round( x[ maxs ], rounddigit ), pos = 4 )
}
```

Why is is it useful?

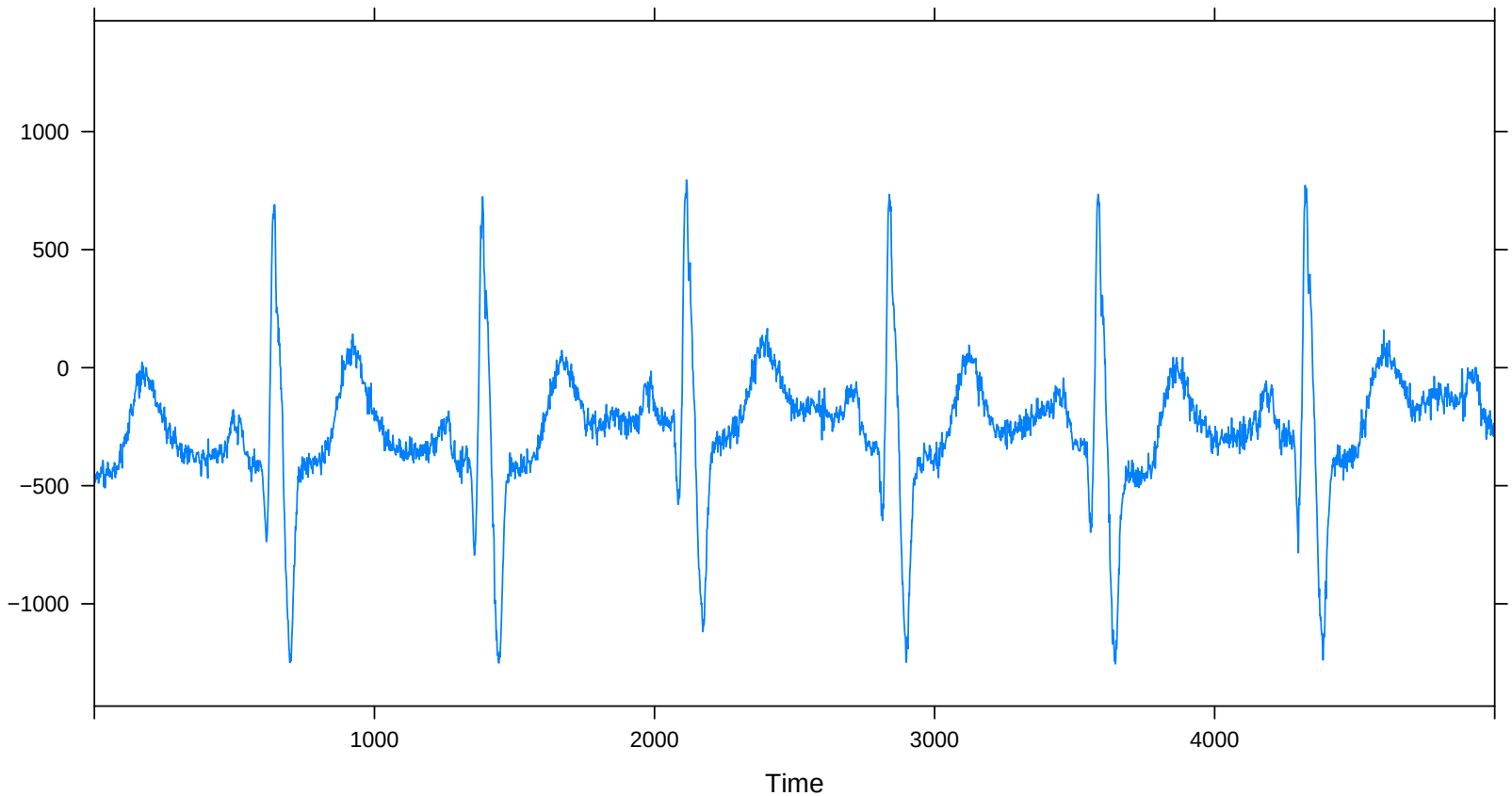
```
xyplot( spec ~ freq, data = spectrum( SimDataFourier$y, plot = FALSE ), type = "l",
        scales = list( y = list( log = 10 ) ), panel = locmaxpanel, width = 21, maxmeddiff = 2 )
```



Case study: ECG analysis

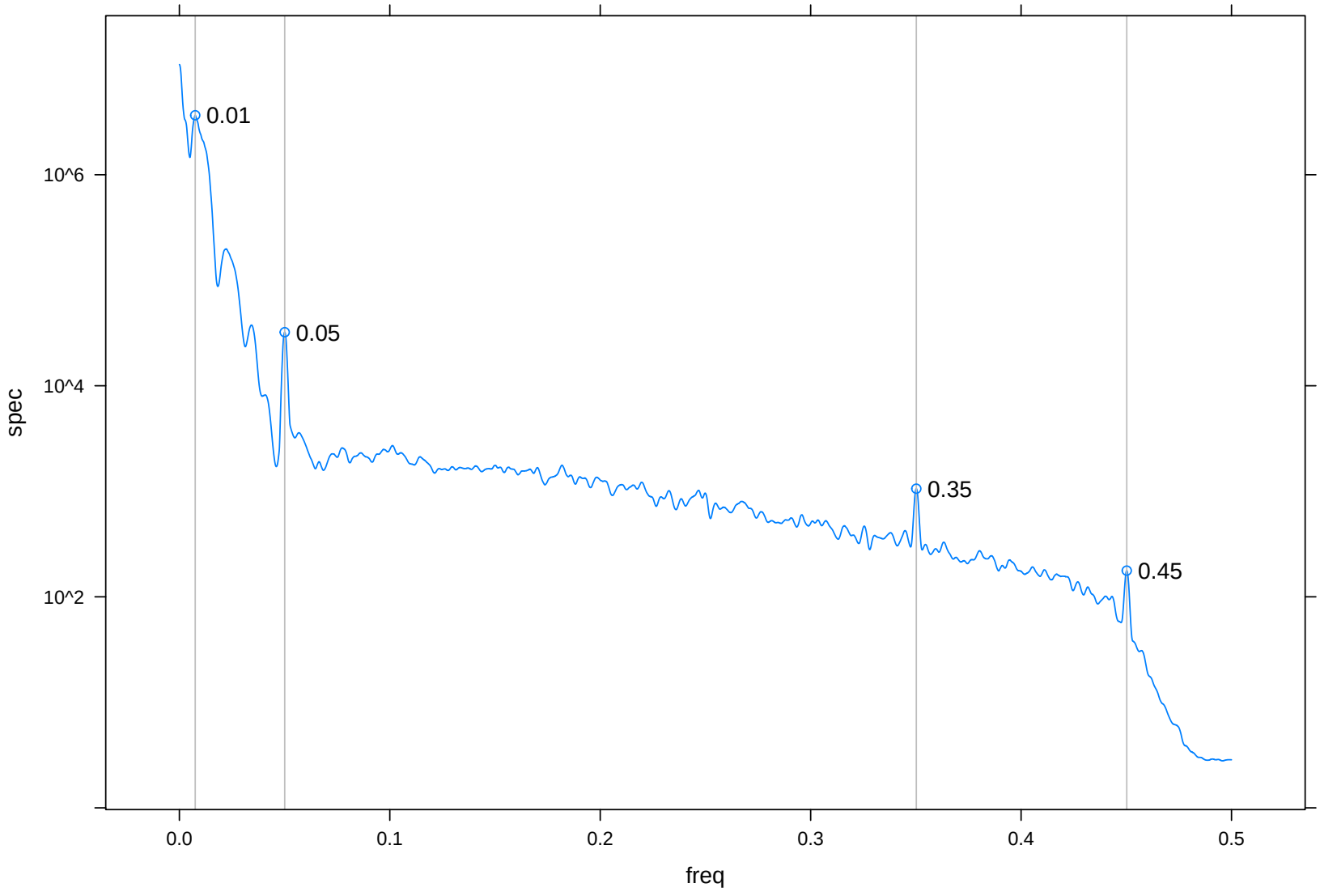
```
## require( tuneR ) ## require( pastecs ) ## devtools::install_github( "mkfs/r-physionet-ptb" )
## https://www.physionet.org/physiobank/database/ptbdb/
library( r.physionet.ptb )
## system2( system.file( "exec", "download_ptb.sh", package = "r.physionet.ptb" ) )
## system2( system.file( "exec", "ptb_patient_to_json.rb", package = "r.physionet.ptb" ),
## args="patient001" )

ptb <- ptb.from.file( "patient001.json" )
ptbecg <- ptb.extract.lead( ptb, "i" )$`1-10010`
xyplot( ptbecg~seq_along( ptbecg ), type = "l", xlim = c( 0, 5000 ), xlab = "Time", ylab = "" )
```



Case study: ECG analysis

```
xyplot( spec ~ freq, data = spectrum( ptbecg, plot = FALSE, span = rep( 201, 3 ) ), type = "l",
        scales = list( y = list( log = 10 ) ), panel = locmaxpanel, width = 21,
        maxmeddiff = 2e-4 )
```



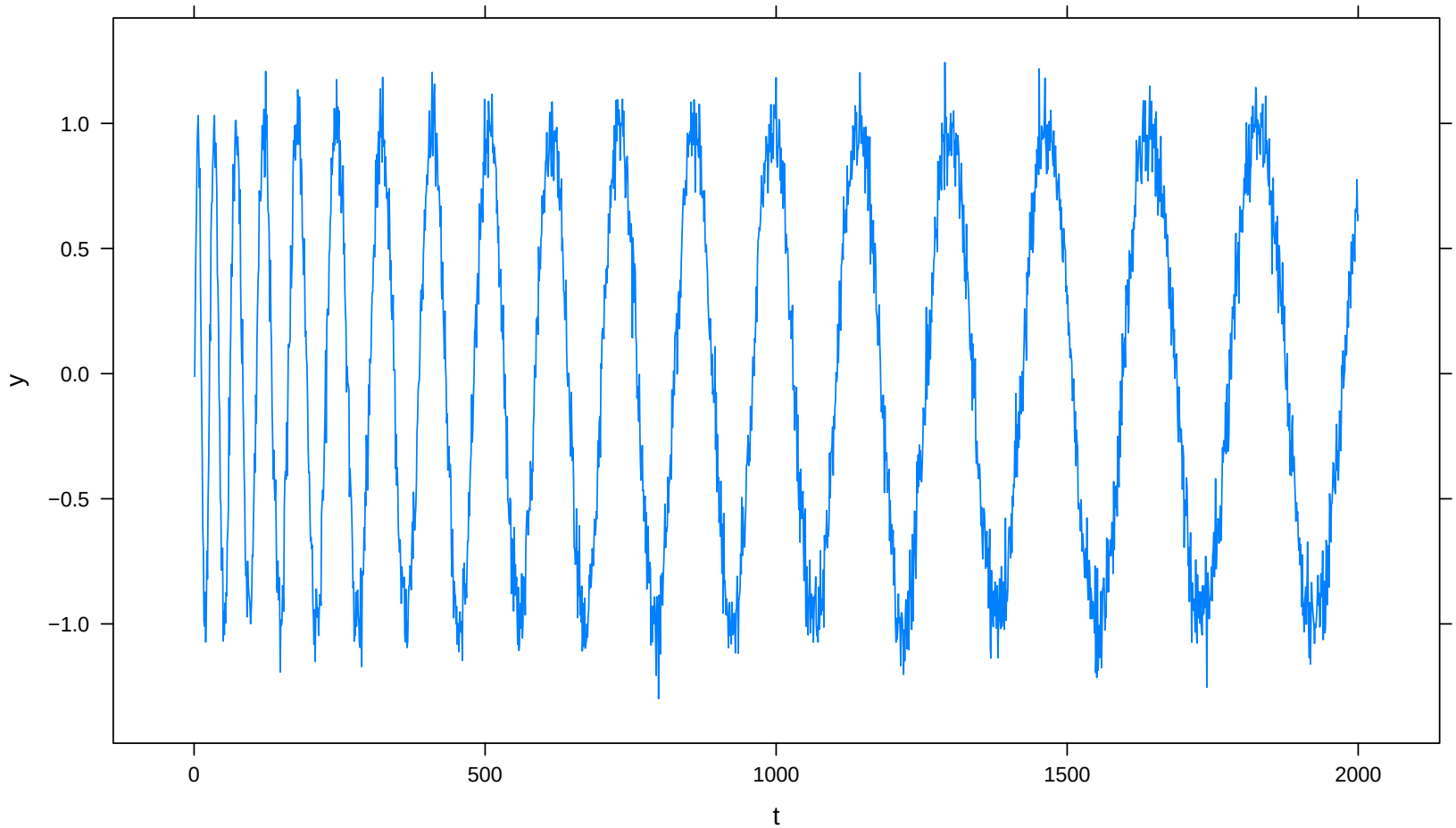
Problems of spectral analysis (and possible solutions)

- Assumes that the spectrum is constant over time: no change in this sense
- One possible way to relax this: windowed analyis (short-term Fourier transform, STFT)
- Trade-off between time-resolution and frequency resolution
- An alternative modern method: wavelet analysis
- Roughly speaking: we perform (a) a local search (b) everywhere (c) with many different frequencies

Problems of spectral analysis (and possible solutions)

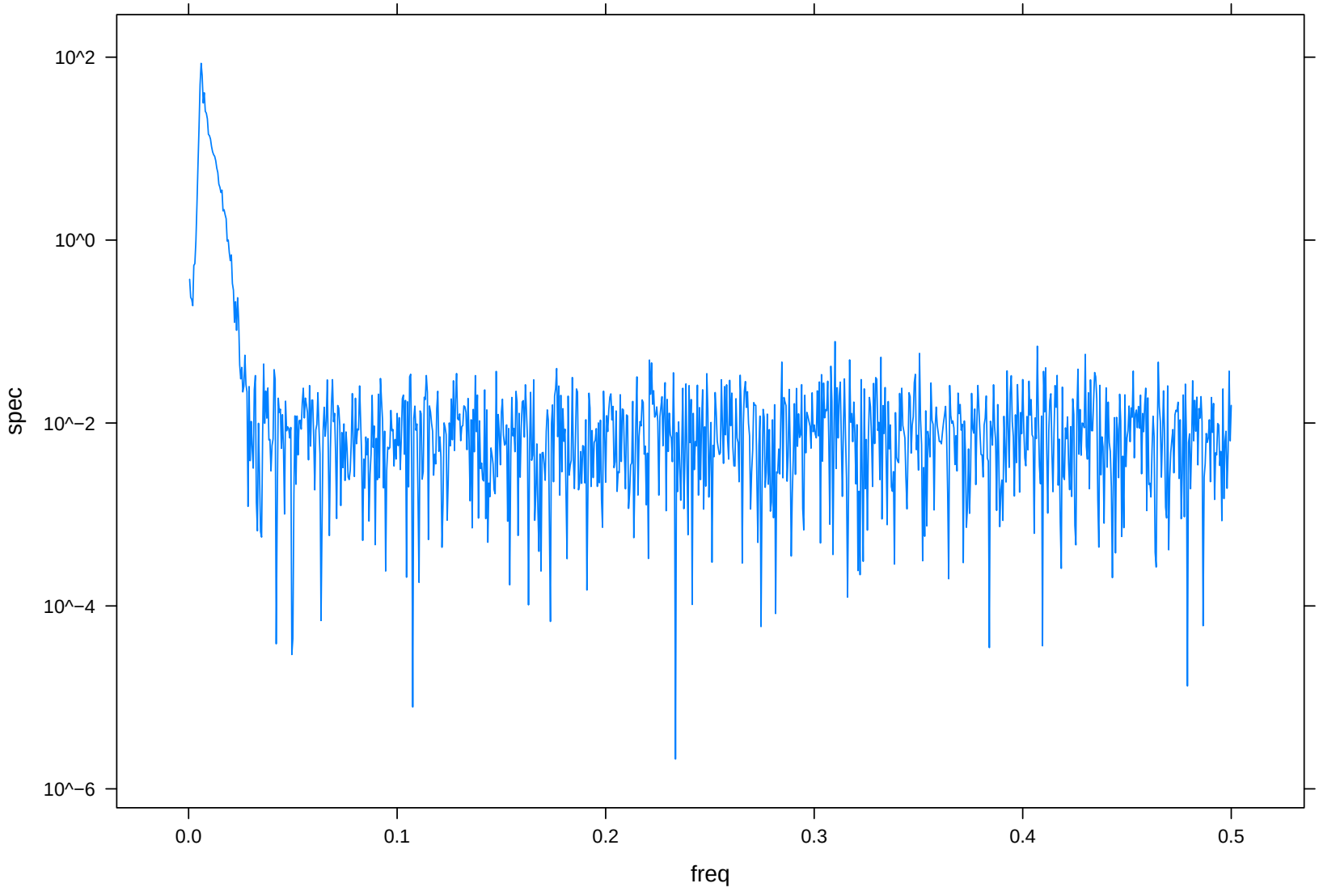
```
library( WaveletComp )

SimDataWavelet <- data.frame( t = 1:2000 )
SimDataWavelet <- transform( SimDataWavelet,
                             y = periodic.series( start.period = 20, end.period = 200,
                                                  length = length( t ) ) +
                               0.1*rnorm( length( t ) ) )
xyplot( y ~ t, data = SimDataWavelet, type = "l" )
```



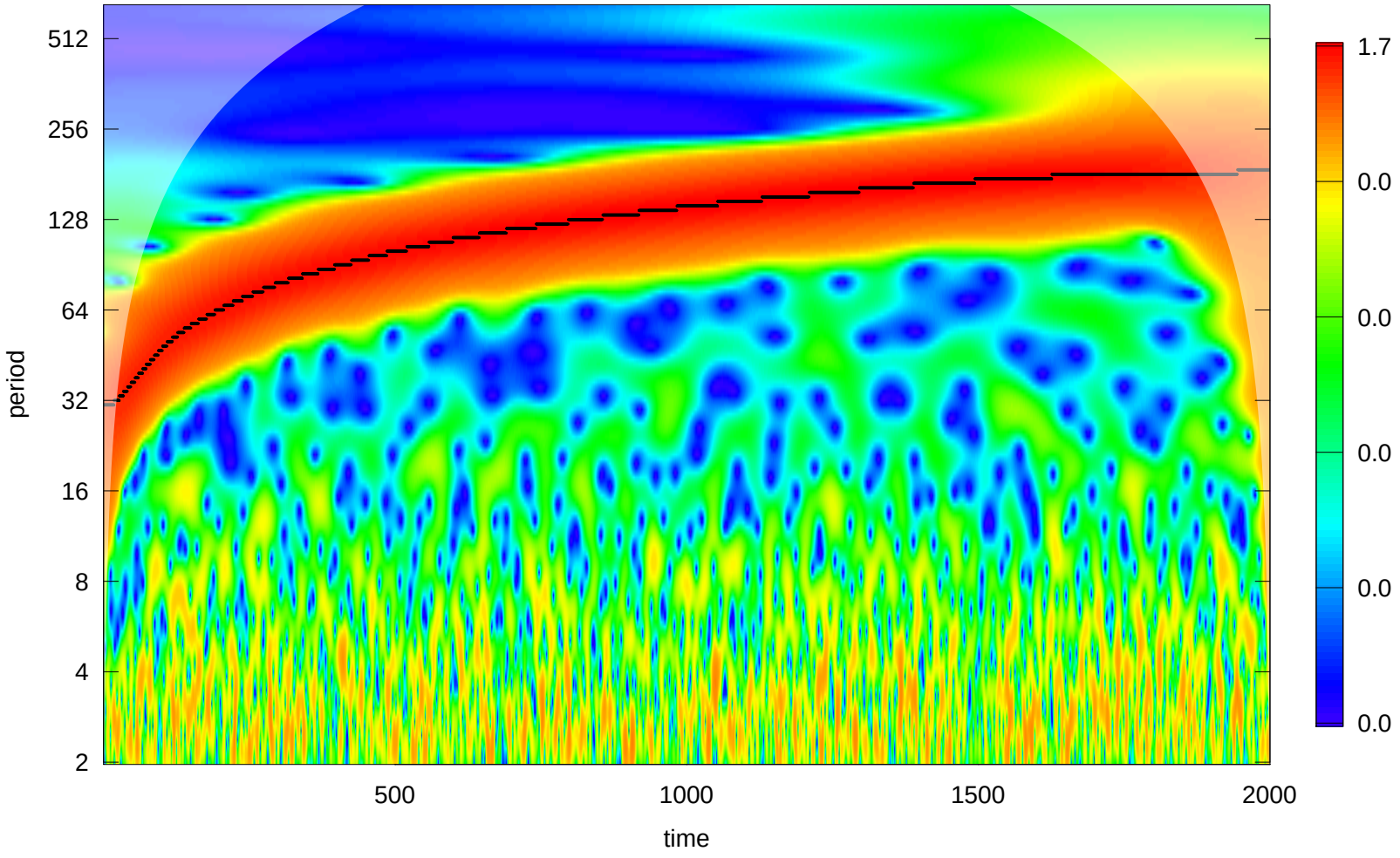
Problems of spectral analysis (and possible solutions)

```
xyplot( spec ~ freq, data = spectrum( SimDataWavelet$y, plot = FALSE ), type = "l",
        scales = list( y = list( log = 10 ) ) )
```



Result of wavelet transform

```
wt.image( analyze.wavelet( SimDataWavelet, "y", verbose = FALSE, make.pval = FALSE ) )
```



Case study for wavelet analysis: pertussis incidence

(Sidenote) A bit of data scraping:

```
library( XLConnect )
library( plyr )

tmpfile <- tempfile( fileext = ".xlsx" )
download.file( url = paste0( "https://www.gov.uk/government/uploads/system/uploads/",
                             "attachment_data/file/339410/NoidsHistoricAnnualTotals.xlsx" ),
               destfile = tmpfile, mode = "wb" )
res1 <- loadWorkbook( tmpfile )
setMissingValue( res1, value = c( "*" ) )
res1 <- do.call( rbind.fill, lapply( getSheets( res1 ), function( s ) {
  temp <- readWorksheet( res1, sheet = s, startRow = 4 )
  temp <- temp[ , grep( "Disease", colnames( temp ) ):ncol( temp ) ]
  temp <- temp[ 1:( if( sum( is.na( temp$Disease ) )==0 ) nrow( temp ) else
    which( is.na( temp$Disease ) )[ 1 ]-1 ), ]
  for( i in 2:ncol( temp ) )
    temp[ , i ] <- as.numeric( gsub( "[[:space:].,‡†]", "", temp[ , i ] ) )
  temp2 <- as.data.frame( t( temp[ , - 1 ] ) )
  colnames( temp2 ) <- temp[ , 1 ]
  temp2$Year <- as.numeric( substring( rownames( temp2 ), 2, 5 ) )
  temp2
} ) )
unlink( tmpfile )
```

Case study for wavelet analysis: pertussis incidence

(Sidenote) A bit of data scraping:

```
tmpfile <- tempfile( fileext = ".xlsx" )
download.file( url = paste0( "https://www.gov.uk/government/uploads/system/uploads/",
                             "attachment_data/file/664864/",
                             "Annual_totals_from_1982_to_2016.xlsx" ),
               destfile = tmpfile, mode = "wb" )
res2 <- loadWorkbook( tmpfile )
setMissingValue( res2, value = c( "--" ) )
res2 <- do.call( rbind.fill, lapply( getSheets( res2 )[ -1 ], function( s ) {
  temp <- readWorksheet( res2, sheet = s, startRow = 5 )
  temp <- temp[ 1:( nrow( temp )-1 ), ]
  temp2 <- as.data.frame( t( temp[ , - 1 ] ) )
  colnames( temp2 ) <- temp[ , 1 ]
  temp2$Year <- as.numeric( substring( rownames( temp2 ), 2, 5 ) )
  temp2
} ) )
unlink( tmpfile )
```

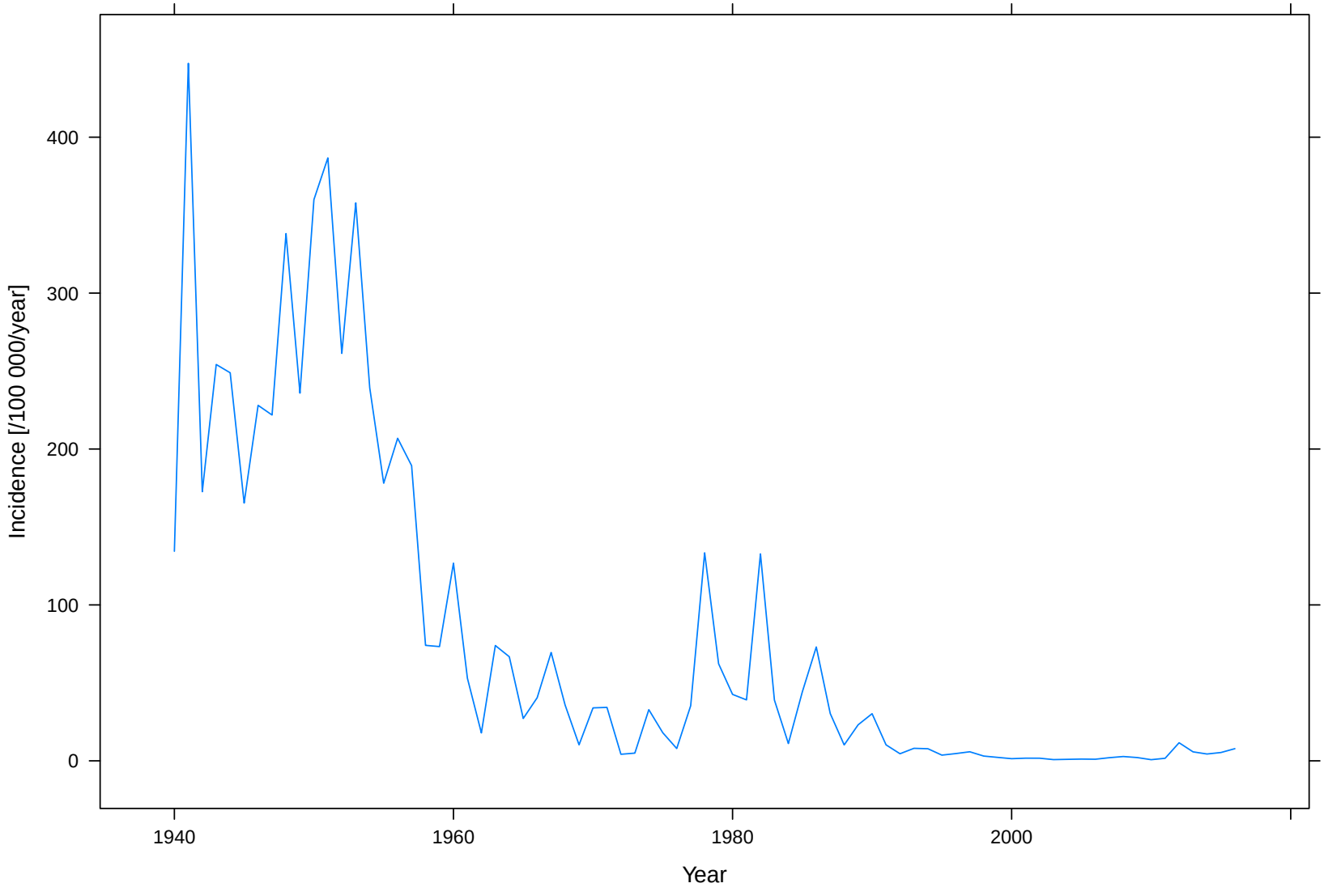
Case study for wavelet analysis: pertussis incidence

(Sidenote) A bit of data scraping:

```
tmpfile <- tempfile( fileext = ".xls" )
download.file( url = paste0( "https://www.ons.gov.uk/file?uri=/",
                             "peoplepopulationandcommunity/populationandmigration/",
                             "populationestimates/adhocs/",
                             "004358englandandwalespopulationestimates1838to2014/",
                             "englandandwalespopulationestimates18382014tcm77409914.xls" ),
               destfile = tmpfile, mode = "wb" )
res3 <- readWorksheetFromFile( tmpfile, sheet = "EW Total Pop 1838-2014", startRow = 2,
                               endRow = 179 )
unlink( tmpfile )
names( res3 )[ 1 ] <- "Year"
res3$Persons <- ifelse( res3$Persons < 100000, res3$Persons*1000, res3$Persons )
res3 <- res3[ , c( "Year", "Persons" ) ]
res4 <- read.csv( paste0( "https://www.ons.gov.uk/generator?format=csv&uri=/",
                          "peoplepopulationandcommunity/populationandmigration/",
                          "populationestimates/timeseries/ewpop/pop" ), skip = 7 )
names( res4 ) <- c( "Year", "Persons" )
res4 <- res4[ res4$Year>=2015, ]
UKEpid <- merge( rbind.fill( res1, res2 ), rbind( res3, res4 ) )
UKPertussis <- UKEpid[ , c( "Year", "Whooping cough", "Persons" ) ]
UKPertussis$Inc <- UKPertussis$`Whooping cough`/UKPertussis$Persons*100000
UKPertussis <- UKPertussis[ !is.na( UKPertussis$`Whooping cough` ), ]
```

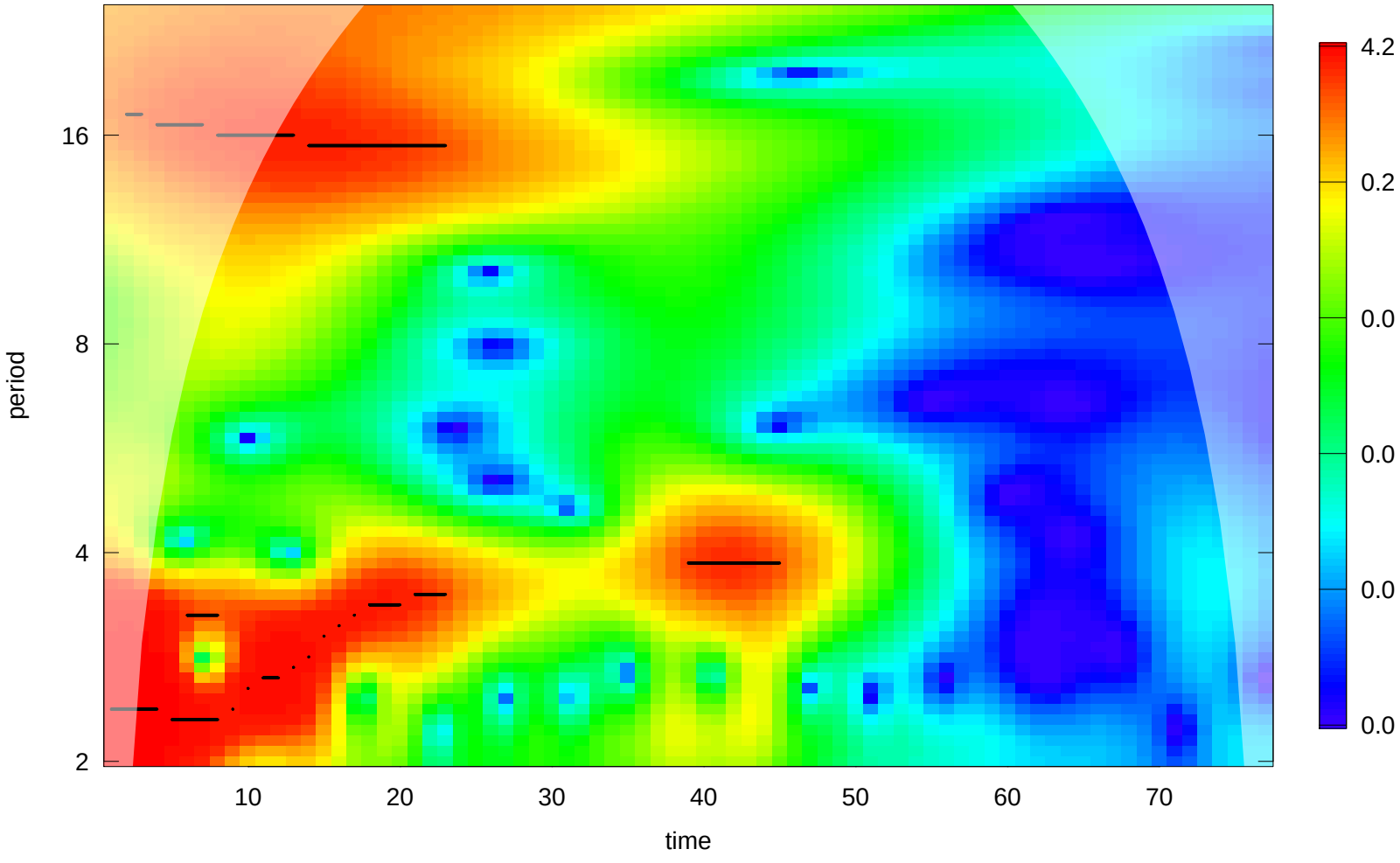
Case study for wavelet analysis: pertussis incidence

```
xyplot( Inc ~ Year, data = UKPertussis, type = "l", ylab = "Incidence [/100 000/year]" )
```



Case study for wavelet analysis: pertussis incidence

```
wt.image( analyze.wavelet( UKPertussis, "Inc", verbose = FALSE, make.pval = FALSE ) )
```



Filtering (and its interpretation in the frequency domain)

- Filter: we create another time series from the investigated one
- Consider the well-known moving average filter:

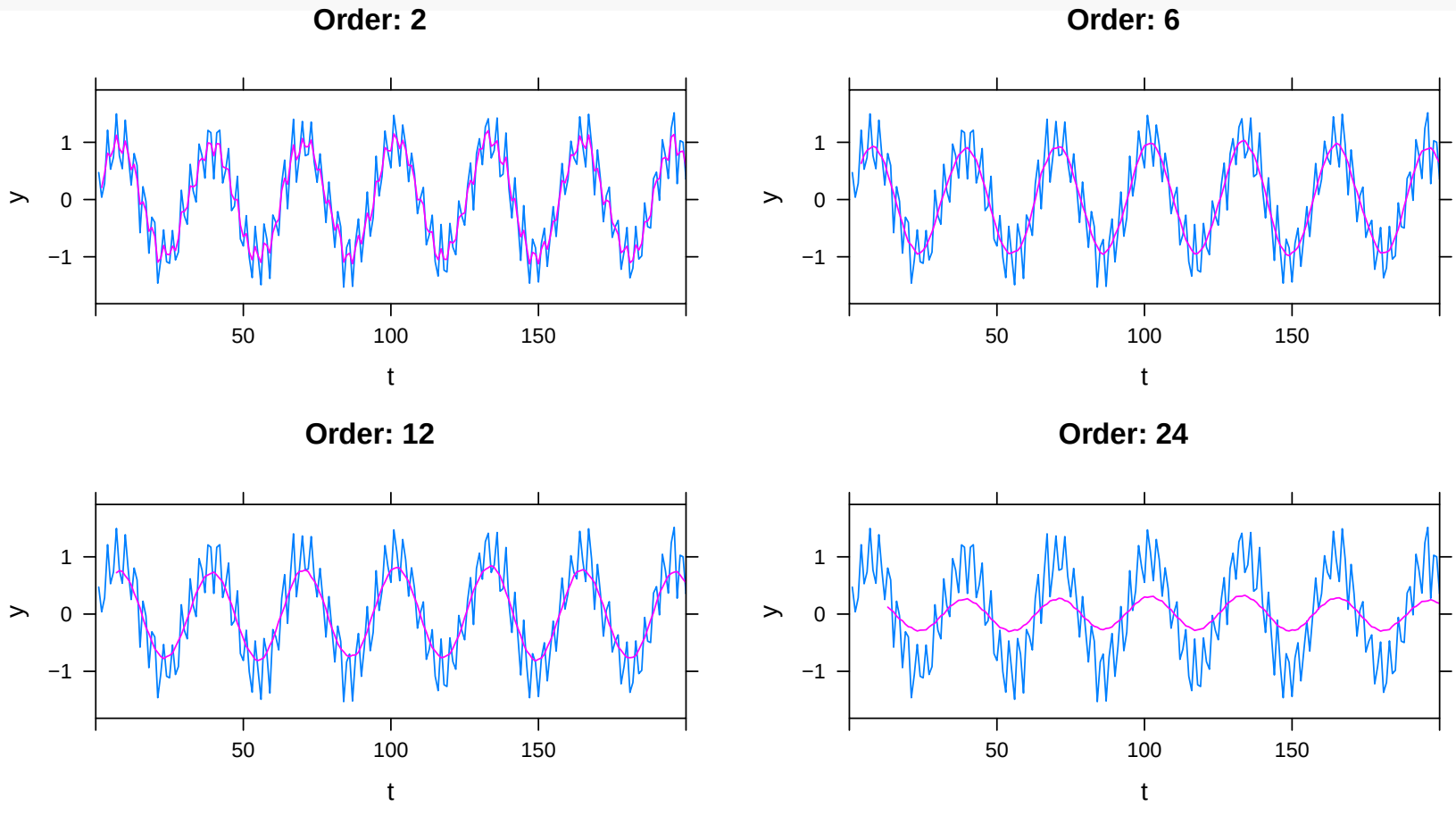
$$y'(t) = \frac{y_t + y_{t-1} + y_{t-2} + \ldots + y_{t-(p-1)}}{p}$$

- Traditionally used to ''filter noise"
- But its operation can actually be best understood in frequency domain: it filters out high-frequency components (and retains low-frequency)!

Filtering (and its interpretation in the frequency domain)

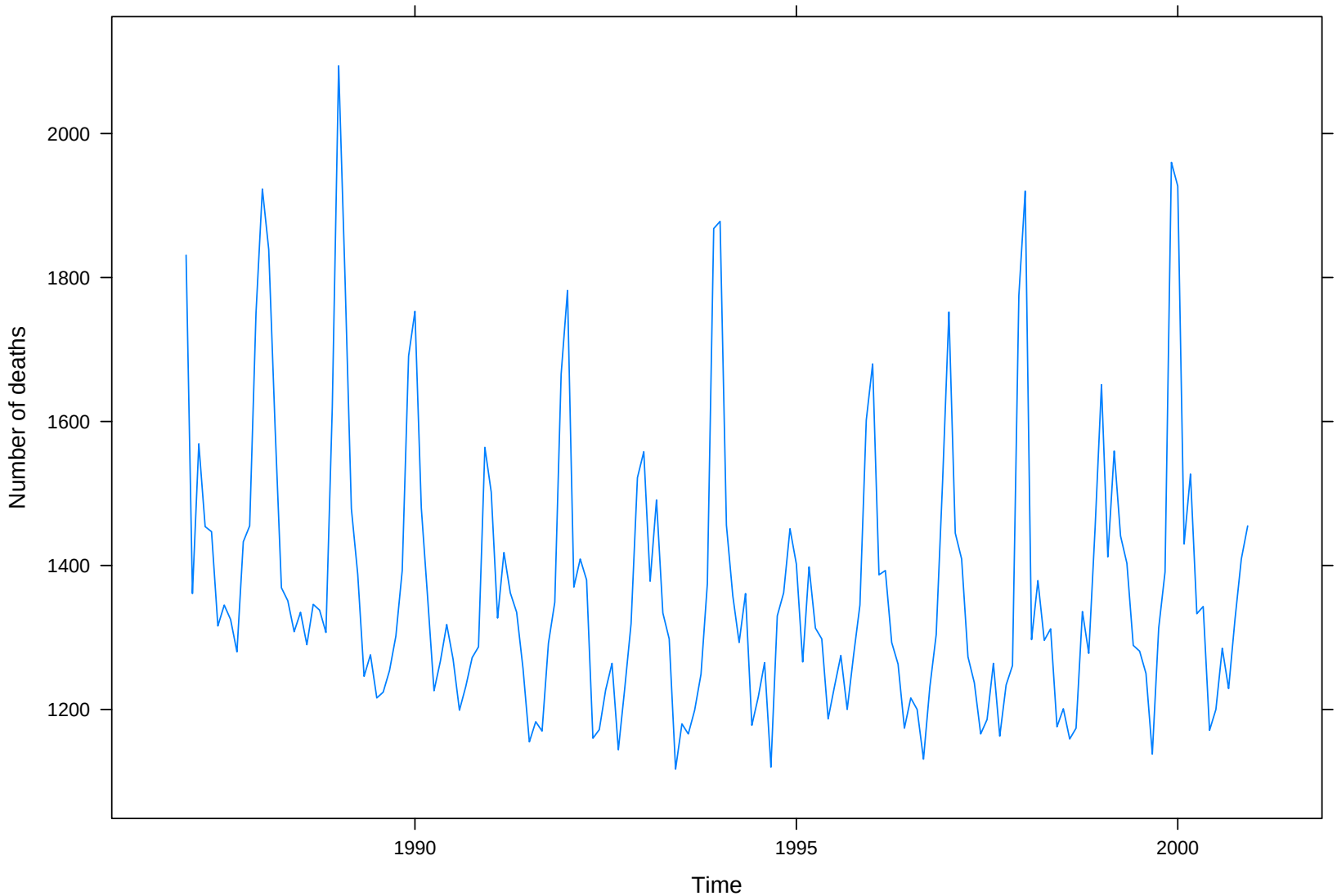
```
library( forecast )

do.call( grid.arrange, lapply( c( 2, 6, 12, 24 ), function( o ) {
  xyplot( y ~ t, groups = grp, data = rbind( data.frame( grp = "data", SimDataFourier ),
                                             data.frame( grp = "smooth", t = SimDataFourier$t,
                                                         y = ma( SimDataFourier$y, o ) ) ),
          type = "l", xlim = c( 0, 200 ), main = paste0( "Order: ", o ) )
} ) )
```



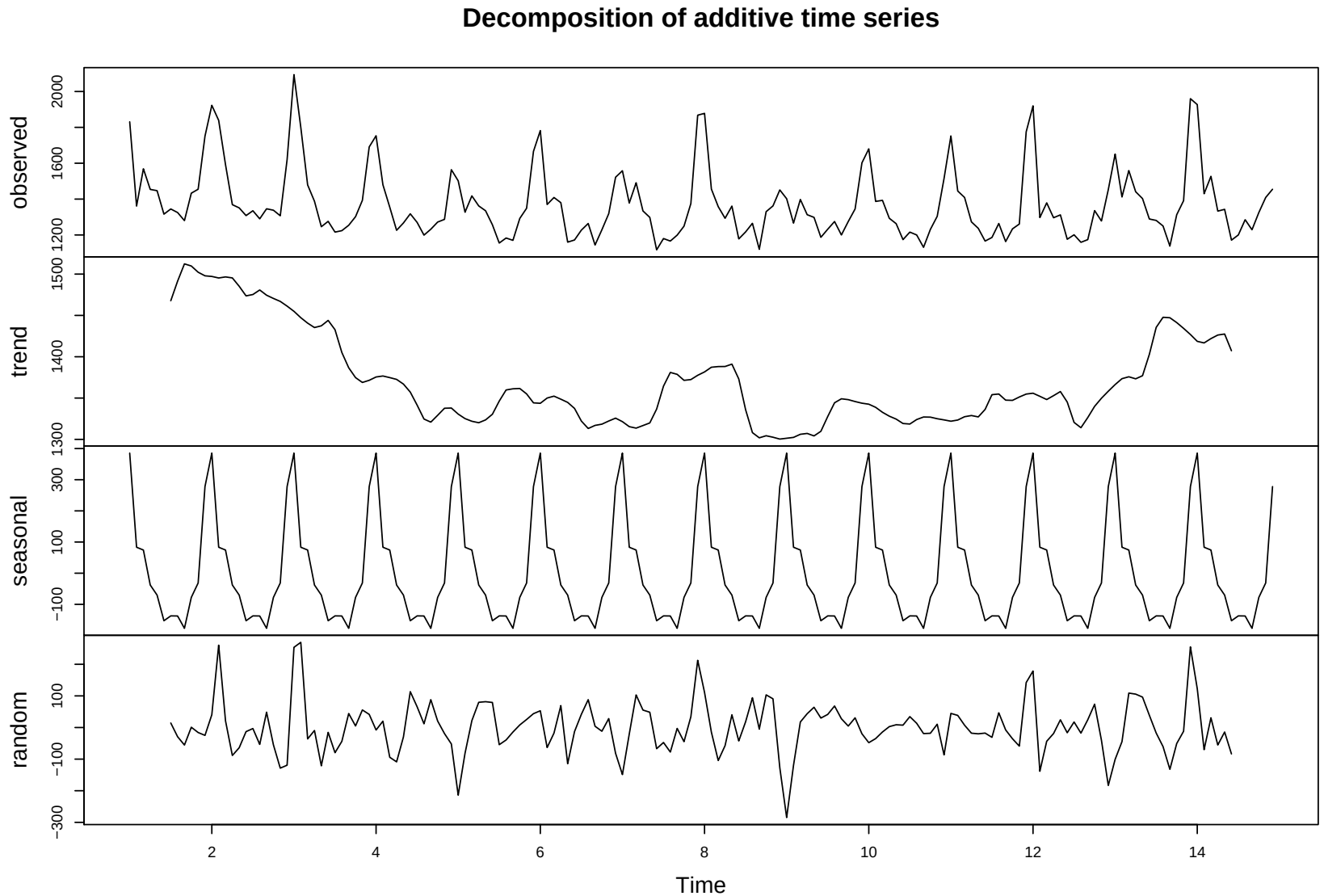
Case study: CV mortality in elderly in Los Angeles from 1987 to 2000

```
data( "CVD", package = "season" )
xyplot( cvd ~ yrmon, data = CVD, type = "l", xlab = "Time", ylab = "Number of deaths" )
```



Case study: CV mortality in elderly in Los Angeles from 1987 to 2000

```
plot( decompose( ts( data = CVD$cvd, frequency = 12 ) ) )
```



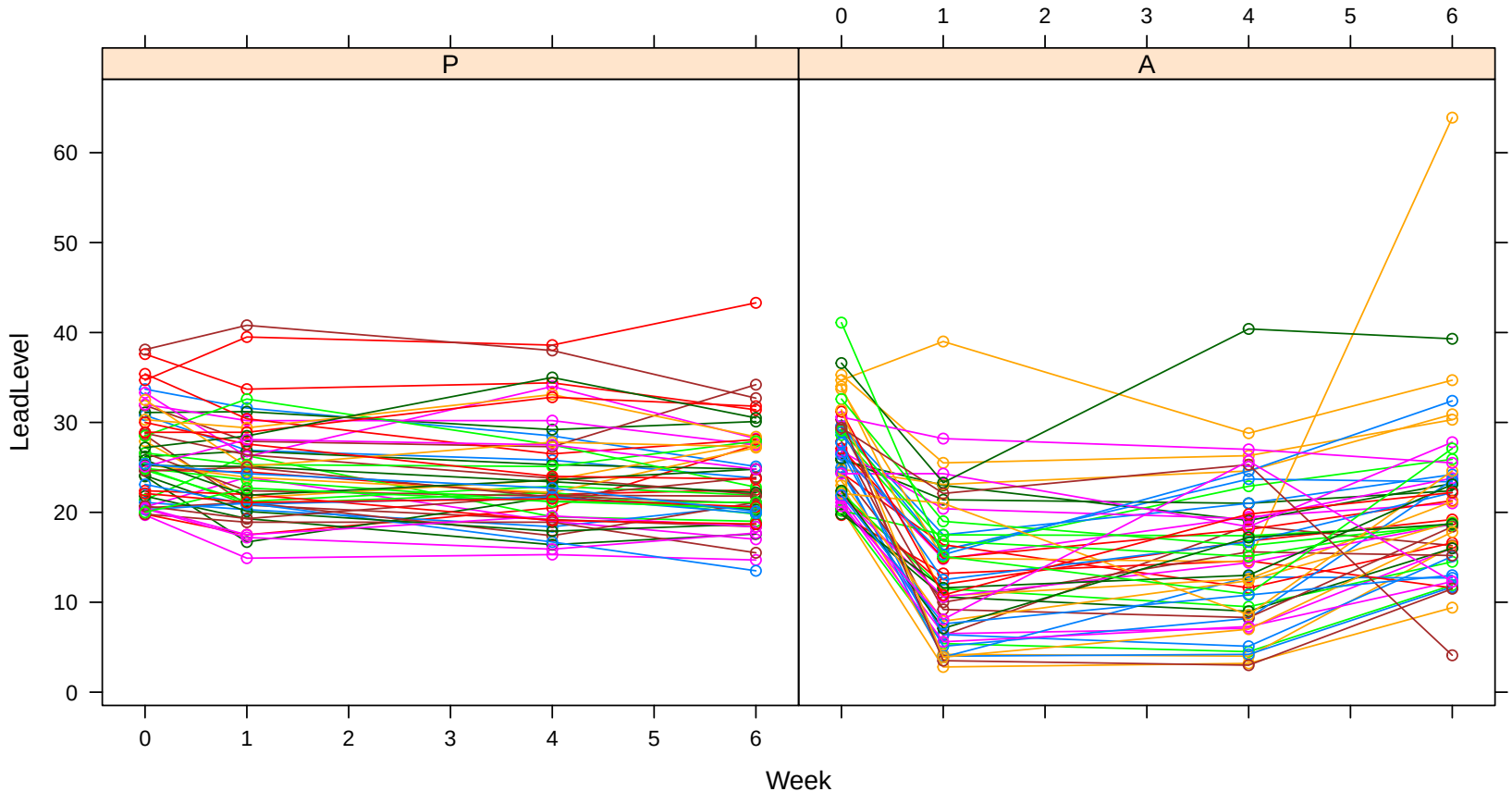
Repeated measures data (longitudinal studies)

- Same variables measured again and again over time, for the same subjects
- Typical questions: effect of an intervention, or natural history (growth curve)
- Usual tool: regression models, usual problem: intra-individual correlation (clustered data)
- Mostly obsolote solutions: RM-ANOVA (has many assumptions that are hard to test, and are usually not met in practice), pairwise tests (multiple comparisons problem, no interpolation possible, etc.), summary statistics (data are reduced to a few parameters in the first step, dramatic loss of information among others)
- Usual solutions:
  - Cluster-robust standard errors or GLS (works only for continuous responses)
  - Mixed effects models (can handle hiearchical models, parameters can be different for each subject)
  - Generalized Estimating Equations (marginal model)

Case study: Treatment of Lead Exposed Children Trial

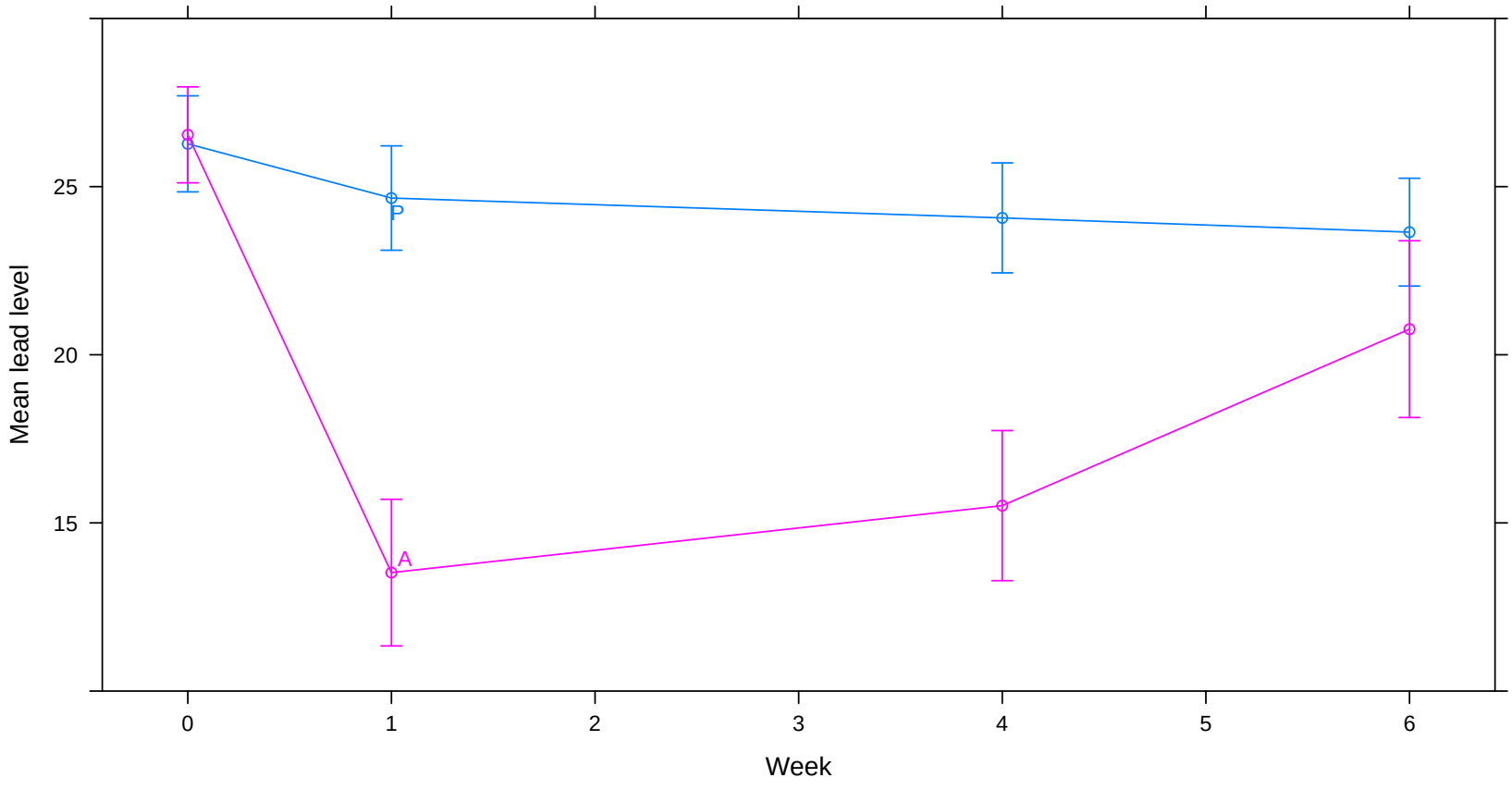
```
library( nlme )

TLCData <- read.table( "https://content.sph.harvard.edu/fitzmaur/ala2e/tlc-data.txt",
                       col.names = c( "ID", "Trt", paste0( "Wk", c( 0, 1, 4, 6 ) ) ) )
TLCData <- reshape( TLCData, varying = paste0( "Wk", c( 0, 1, 4, 6 ) ), v.names = "LeadLevel",
                    timevar = "Week", times = c( 0, 1, 4, 6 ), idvar = "ID", direction = "long" )
TLCData$Trt <- relevel( TLCData$Trt, ref = "P" )
TLCData$Week.f <- as.factor( TLCData$Week )
xyplot( LeadLevel ~ Week | Trt, groups = ID, data = TLCData, type = "b" )
```



Case study: Treatment of Lead Exposed Children Trial

```
TLCData <- data.table( TLCData )
TLCData$Time <- as.numeric( TLCData$Week.f )
dd <- datadist( TLCData )
options( datadist = "dd" )
xYplot( Cbind( mean, lwr, upr ) ~ Week, groups = Trt, type = "b",
        data = TLCData[ , .( mean = mean( LeadLevel ),
                             lwr = t.test( LeadLevel )$conf.int[1],
                             upr = t.test( LeadLevel )$conf.int[2] ) , .( Trt, Week ) ],
        ylim = c( 10, 30 ), ylab = "Mean lead level" )
```



Case study: Treatment of Lead Exposed Children Trial

```
ols( LeadLevel ~ Week.f*Trt, data = TLCData )
```

```
## Linear Regression Model
##
##  ols(formula = LeadLevel ~ Week.f * Trt, data = TLCData)
##
##                  Model Likelihood     Discrimination
##                     Ratio Test           Indexes
##  Obs     400    LR chi2    159.22    R2       0.328
##  sigma6.6257    d.f.            7    R2 adj   0.316
##  d.f.    392    Pr(> chi2) 0.0000    g        4.920
##
##  Residuals
##
##      Min       1Q  Median      3Q     Max
##  -16.662  -4.620  -0.993   3.673  43.138
##
##
##                    Coef     S.E.   t     Pr(>|t|)
##  Intercept          26.2720 0.9370 28.04 <0.0001
##  Week.f=1           -1.6120 1.3251 -1.22 0.2245
##  Week.f=4           -2.2020 1.3251 -1.66 0.0974
##  Week.f=6           -2.6260 1.3251 -1.98 0.0482
##  Trt=A               0.2680 1.3251  0.20 0.8398
##  Week.f=1 * Trt=A  -11.4060 1.8740 -6.09 <0.0001
##  Week.f=4 * Trt=A   -8.8240 1.8740 -4.71 <0.0001
##  Week.f=6 * Trt=A   -3.1520 1.8740 -1.68 0.0934
##
```

Case study: Treatment of Lead Exposed Children Trial

```
fit <- Gls( LeadLevel ~ Week.f*Trt, data = TLCData, corr = corSymm( form = ~ Time | ID ),
     weights = varIdent( form = ~ 1 | Week.f ) )
fit
```

```
## Generalized Least Squares Fit by REML
##
##  Gls(model = LeadLevel ~ Week.f * Trt, data = TLCData, correlation = corSymm(form = ~Time |
##      ID), weights = varIdent(form = ~1 | Week.f))
##
##
##  Obs 400         Log-restricted-likelihood-1208.04
##  Clusters100     Model d.f.  7
##  g 4.920         sigma  5.0225
##                  d.f.      392
##
##                    Coef     S.E.   t      Pr(>|t|)
##  Intercept          26.2720 0.7103  36.99 <0.0001
##  Week.f=1           -1.6120 0.7919  -2.04 0.0425
##  Week.f=4           -2.2020 0.8149  -2.70 0.0072
##  Week.f=6           -2.6260 0.8885  -2.96 0.0033
##  Trt=A               0.2680 1.0045   0.27 0.7898
##  Week.f=1 * Trt=A -11.4060 1.1199 -10.18 <0.0001
##  Week.f=4 * Trt=A  -8.8240 1.1525  -7.66 <0.0001
##  Week.f=6 * Trt=A  -3.1520 1.2566  -2.51 0.0125
##
##  Correlation Structure: General
##   Formula: ~Time | ID
##   Parameter estimate(s):
##   Correlation:
##    1     2     3
##  2 0.571
##  3 0.570 0.775
##  4 0.577 0.582 0.581
##  Variance function:
##   Structure: Different standard deviations per stratum
##   Formula: ~1 | Week.f
```

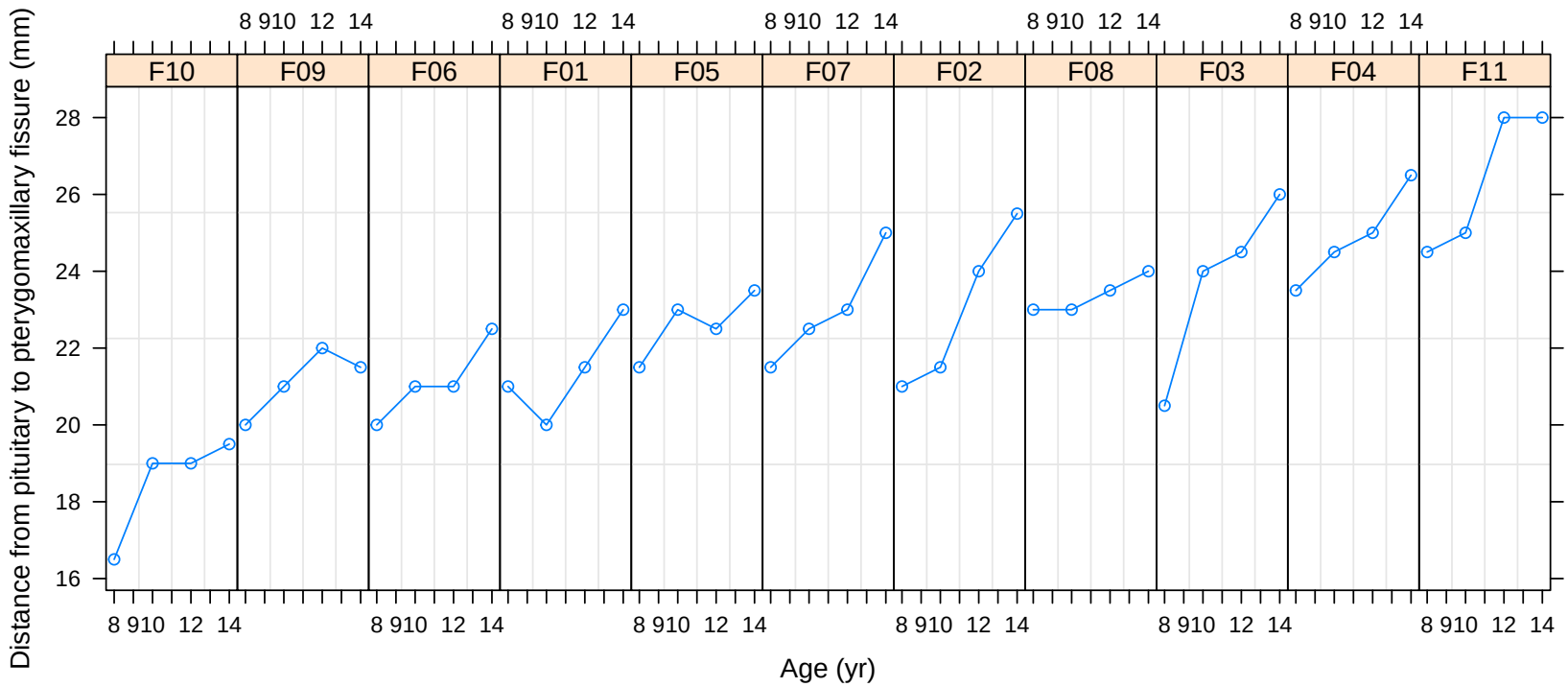
Case study: Treatment of Lead Exposed Children Trial

```
summary( fit )
```

```
##              Effects              Response : LeadLevel
##
##  Factor       Low High Diff. Effect S.E.    Lower 0.95 Upper 0.95
##  Week.f - 1:0 1   2    NA    -1.612 0.79192 -3.1641    -0.059866
##  Week.f - 4:0 1   3    NA    -2.202 0.81491 -3.7992    -0.604810
##  Week.f - 6:0 1   4    NA    -2.626 0.88852 -4.3675    -0.884530
##  Trt - A:P    1   2    NA     0.268 1.00450 -1.7008     2.236800
##
## Adjusted to: Week.f=0 Trt=P
```

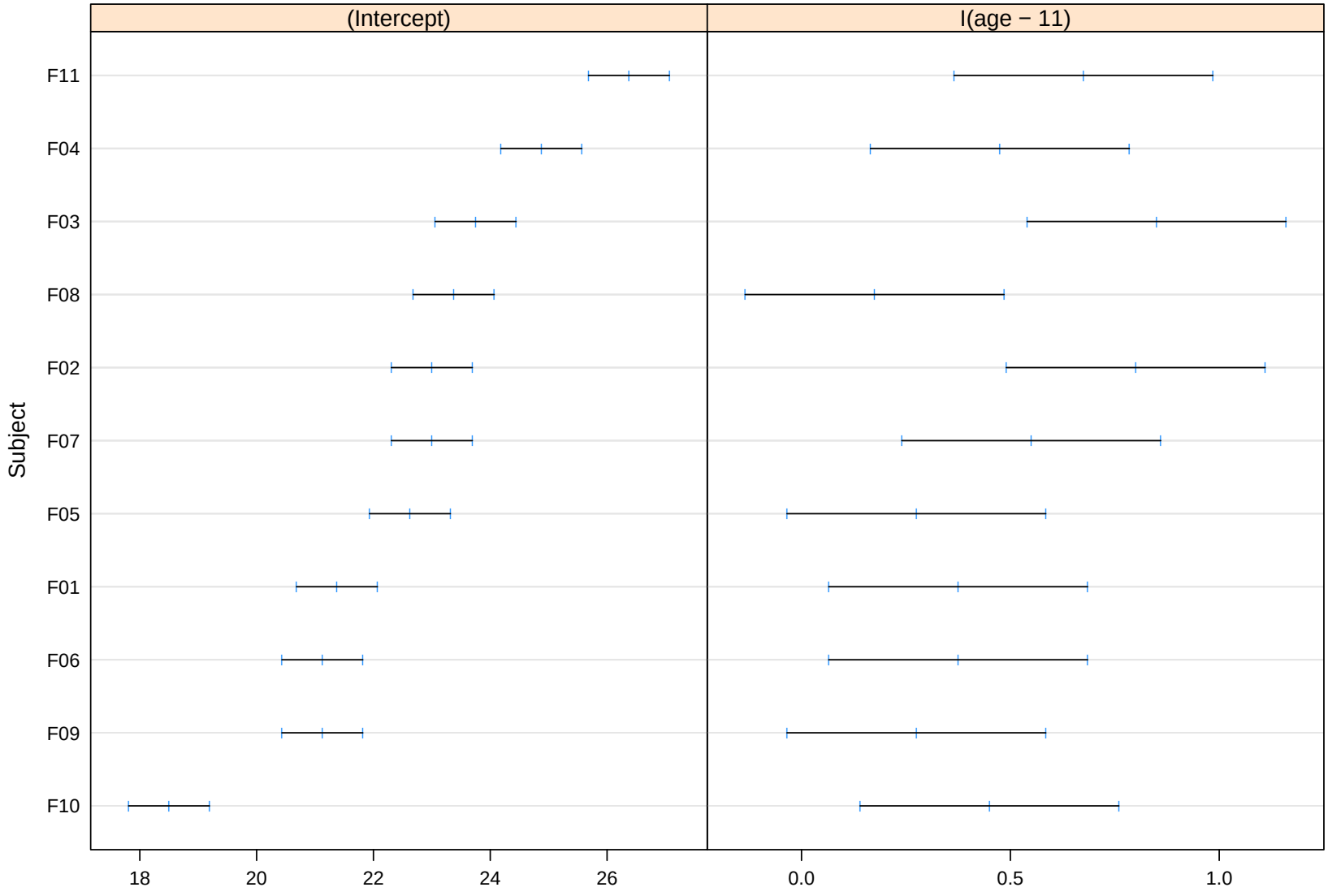
Case study: human skull growth

```
data( "Orthodont" )
OrthoFem <- Orthodont[ Orthodont$Sex=="Female", ]
plot( OrthoFem )
```



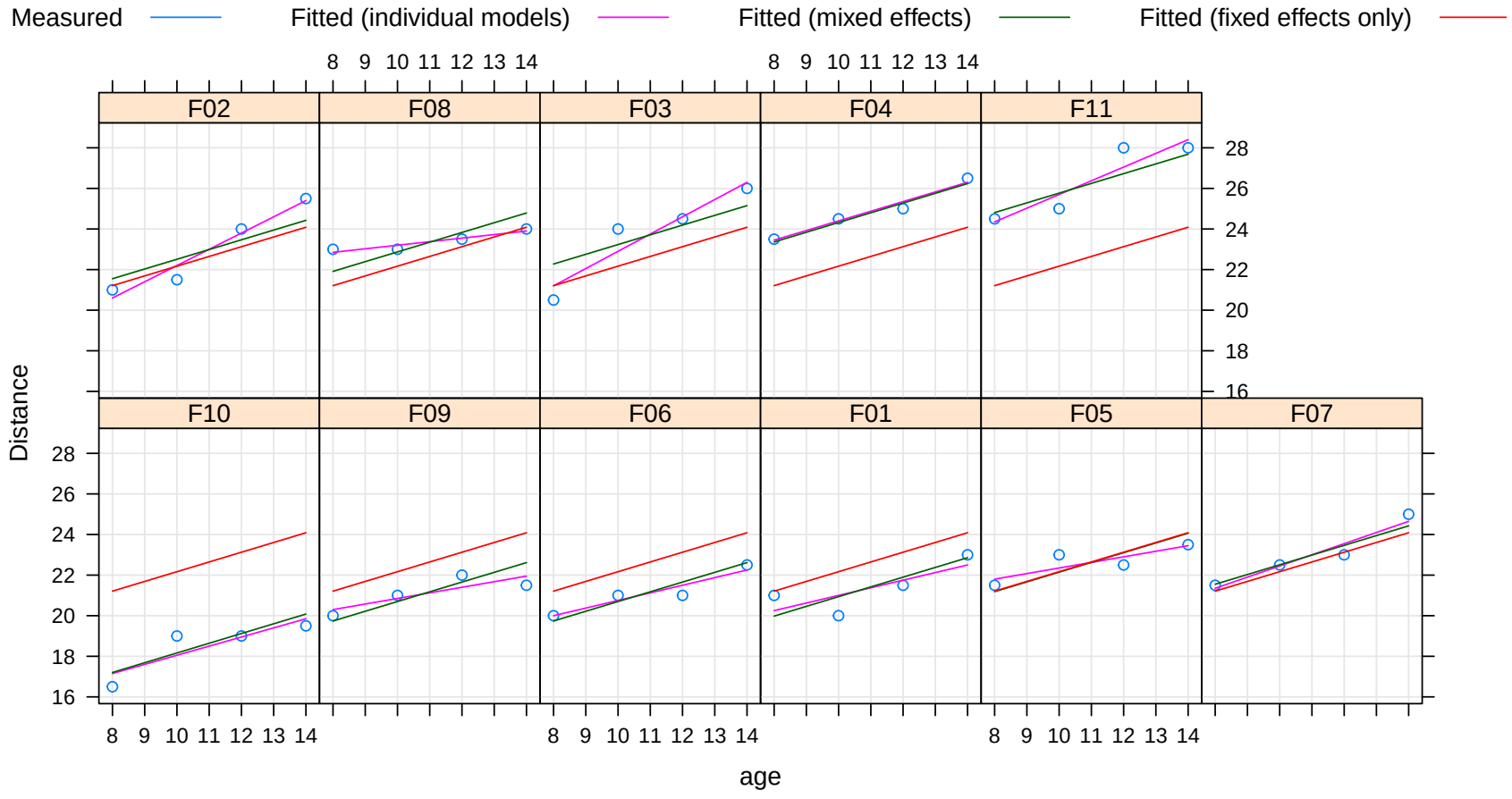
Case study: human skull growth

```
fit1 <- lmList( distance ~ I( age - 11 ), data = OrthoFem )
plot( intervals( fit1 ) )
```



Case study: human skull growth

```
fit2 <- lme( distance ~ age, data = OrthoFem, random = ~1|Subject )
xyplot( distance + fitted( fit1 ) + fitted( fit2, level = 1 ) +
          fitted( fit2, level = 0 ) ~ age | Subject, data = OrthoFem,
        type = c( "p", "l", "l", "l" ), distribute.type = TRUE, ylab = "Distance", grid = TRUE,
        auto.key = list( text = c( "Measured", "Fitted (individual models)",
                                   "Fitted (mixed effects)", "Fitted (fixed effects only)" ),
                         columns = 4, points = FALSE, lines = TRUE ) )
```

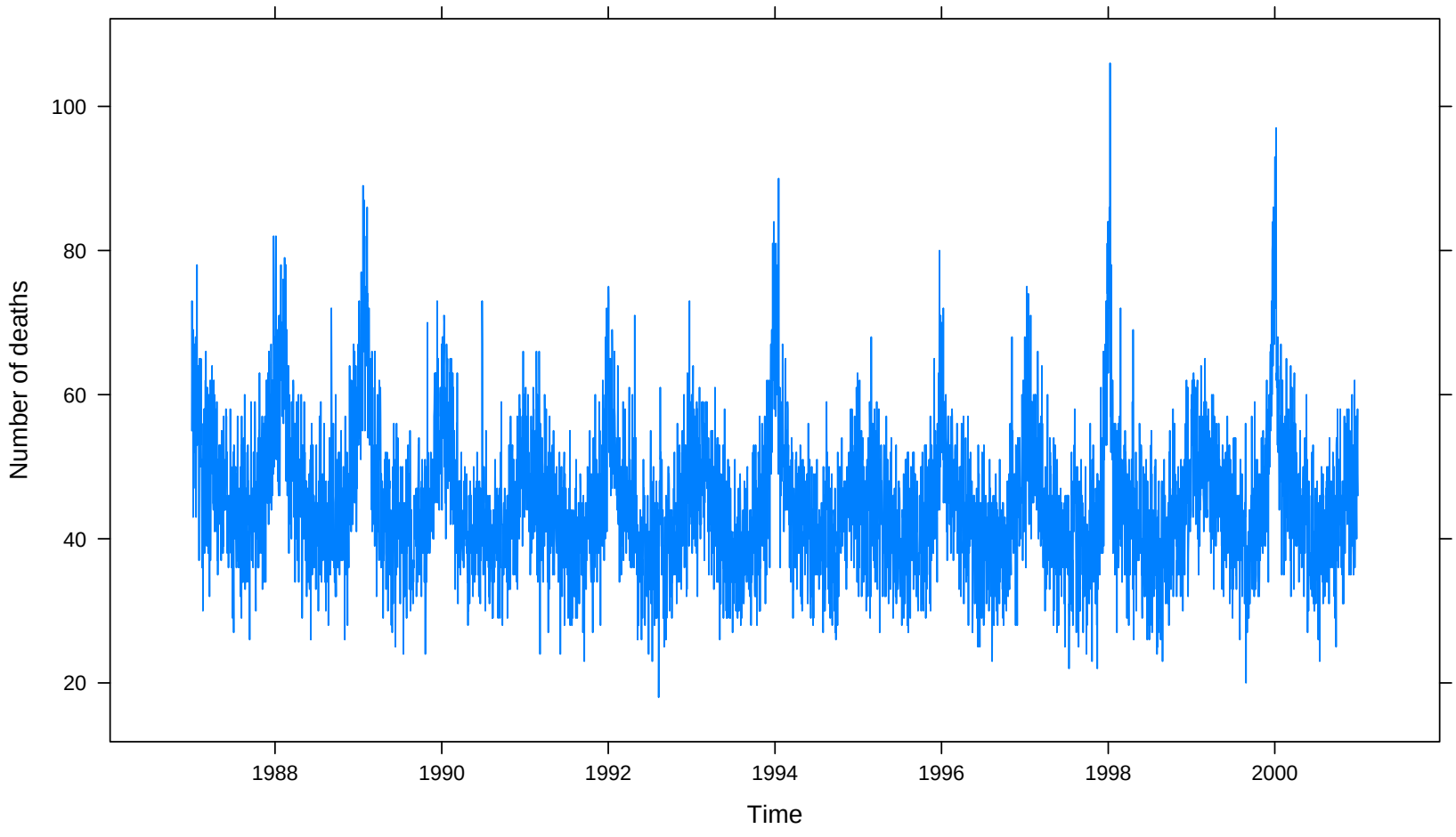


Regression modelling in time series analysis

- Perhaps *the* most powerful tool
- With appropriate measures taken to account for the nature of the data
- This of course gives rise to all usual issues of regression models (model specification such as the question of non-linearities, model diagnostics etc.)
- Mostly models with exogeneous regressors are used, stochastic models are employed much less often

Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```
data( "CVDdaily", package = "season" )
rownames( CVDdaily ) <- NULL
xyplot( cvd ~ date, data = CVDdaily, type = "l", xlab = "Time", ylab = "Number of deaths" )
```



Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```
library( lubridate )
CVDdaily$year <- year( CVDdaily$date )
CVDdaily$wday <- as.factor( wday( CVDdaily$date, week_start = 1 ) )
CVDdaily$yday <- yday( CVDdaily$date )/yearDays( CVDdaily$date )
head( CVDdaily[ , c( "date", "year", "wday", "yday", "cvd" ) ] )
```

date	year	wday	yday	cvd
1987-01-01	1987	4	0.0027397	55
1987-01-02	1987	5	0.0054795	73
1987-01-03	1987	6	0.0082192	64
1987-01-04	1987	7	0.0109589	57
1987-01-05	1987	1	0.0136986	56
1987-01-06	1987	2	0.0164384	65

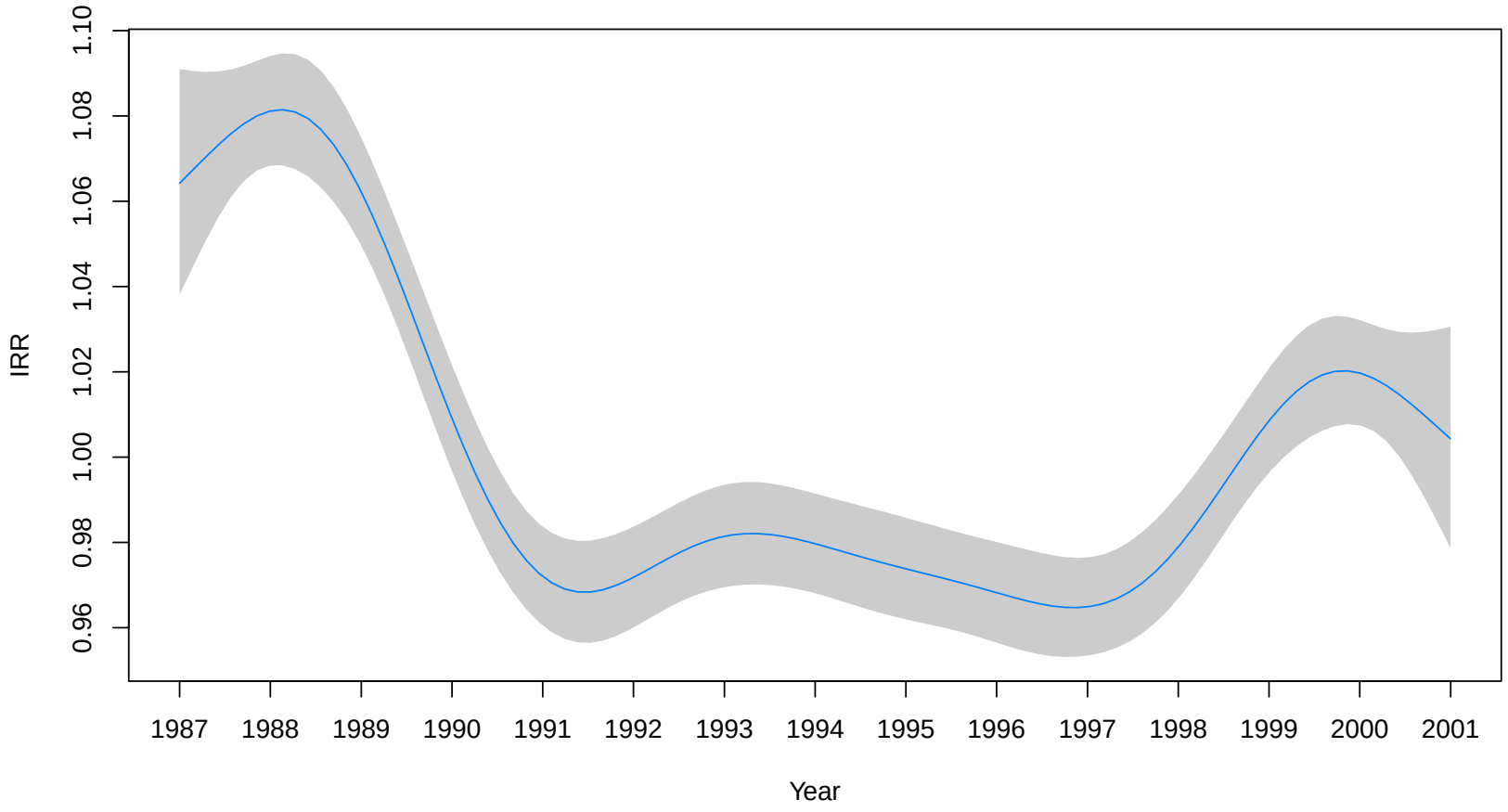
Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```r
library( mgcv )
fit <- gam( cvd ~ s( as.numeric( date ) ) + wday + s( yday, bs = "cc" ), data = CVDdaily,
            family = nb( link = log ) )
summary( fit )
```

```
##
## Family: Negative Binomial(177.091)
## Link function: log
##
## Formula:
## cvd ~ s(as.numeric(date)) + wday + s(yday, bs = "cc")
##
## Parametric coefficients:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)  3.820888   0.006137 622.550  < 2e-16 ***
## wday2       -0.007799   0.008687  -0.898 0.369335
## wday3       -0.028719   0.008724  -3.292 0.000995 ***
## wday4       -0.025035   0.008714  -2.873 0.004065 **
## wday5       -0.015468   0.008697  -1.778 0.075323 .
## wday6       -0.022458   0.008709  -2.579 0.009920 **
## wday7       -0.038679   0.008738  -4.427 9.57e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##                        edf Ref.df Chi.sq p-value
## s(as.numeric(date)) 7.696  8.568  254.4  <2e-16 ***
## s(yday)             7.771  8.000 2732.5  <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =  0.377   Deviance explained = 37.6%
```

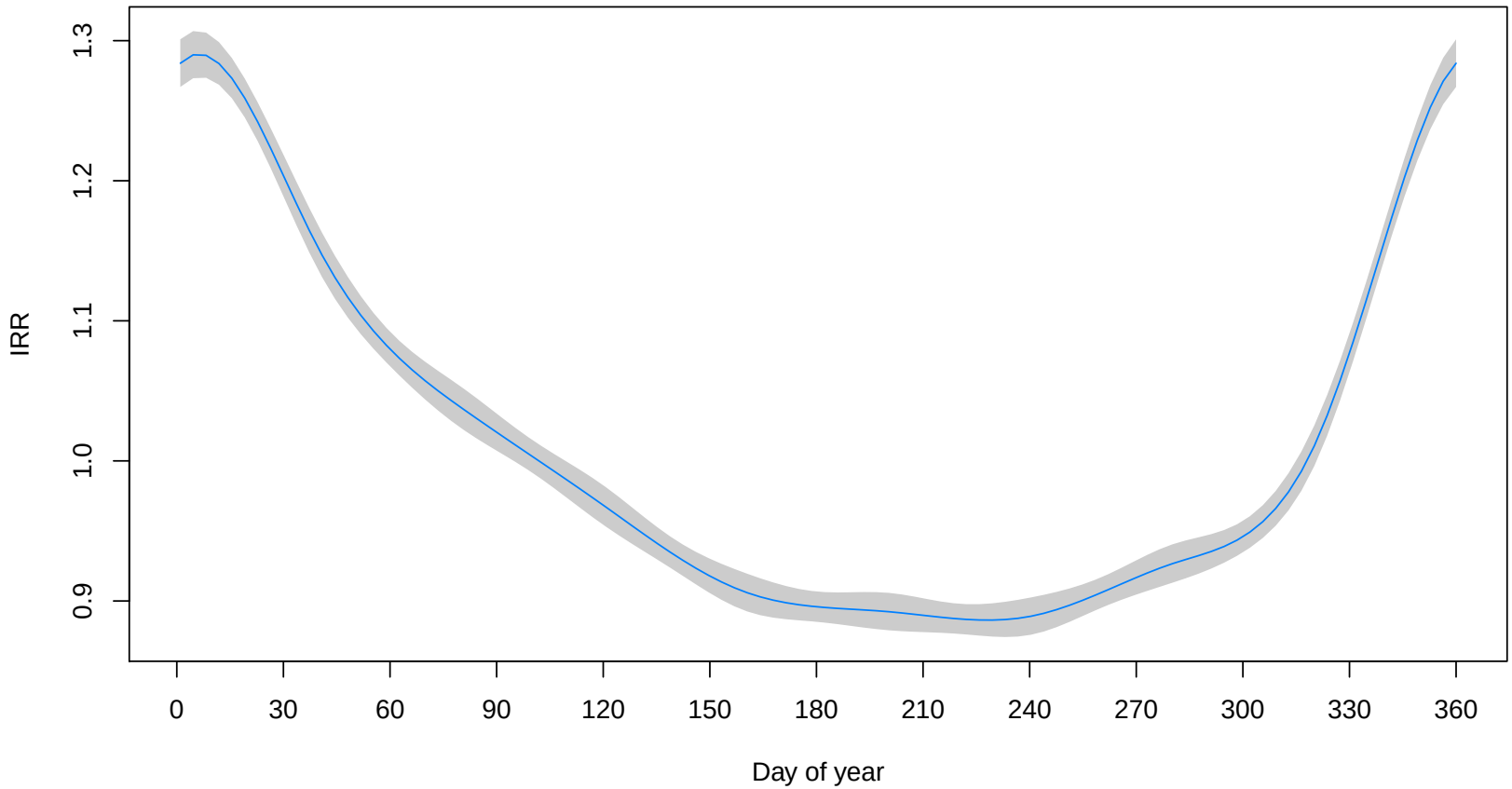
Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```
plot( fit, select = 1, scale = 0, rug = FALSE, trans = exp, shade = TRUE,
      col = trellis.par.get()$superpose.line$col[1], xaxt = "n", xlab = "Year", ylab = "IRR" )
axis( 1, at = seq( CVDdaily$date[1], tail( CVDdaily$date, 1 )+1, by = "year" ),
      labels = year( CVDdaily$date[1] ):year( tail( CVDdaily$date, 1 )+1 ) )
```



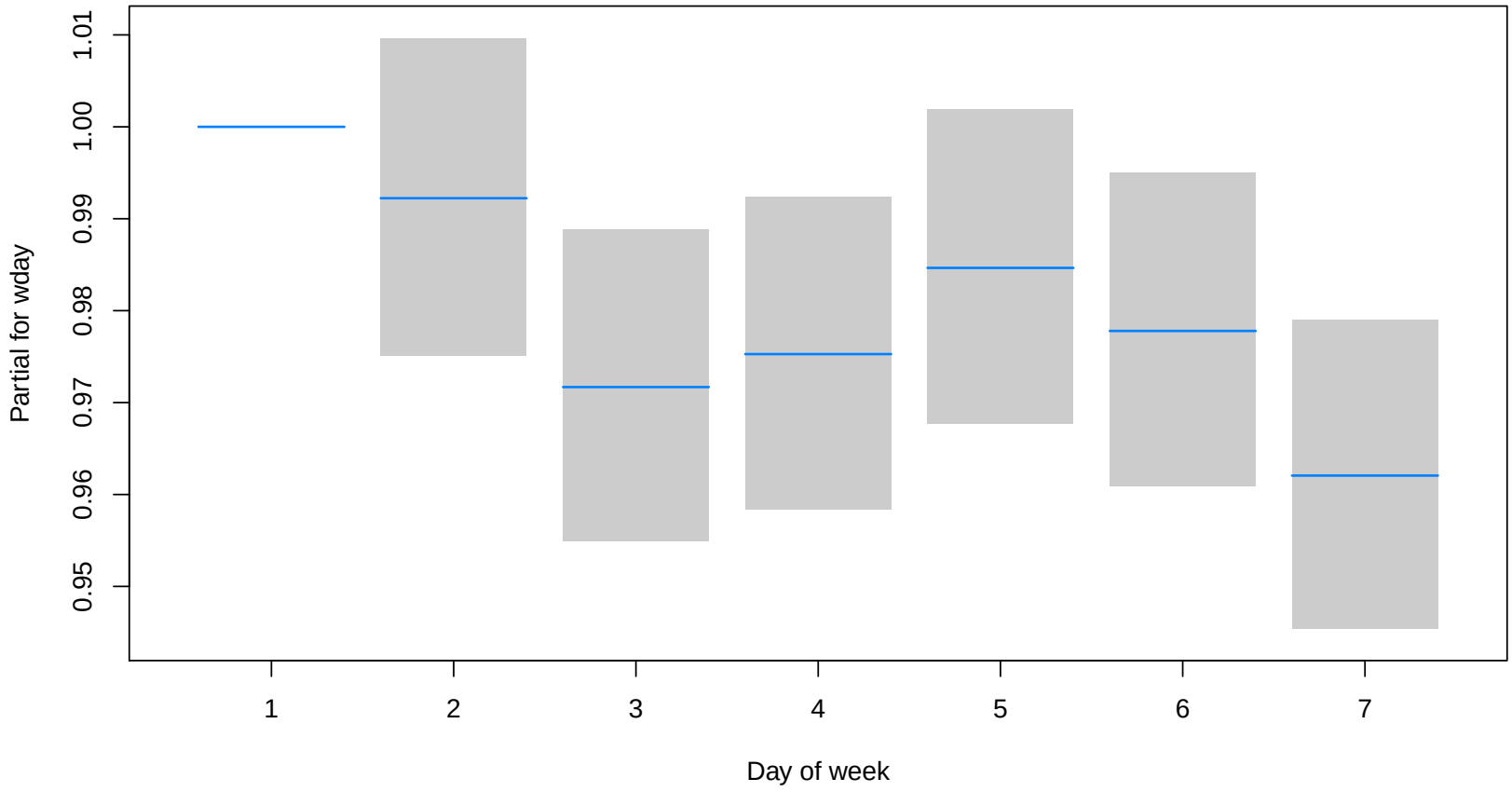
Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```
plot( fit, select = 2, scale = 0, rug = FALSE, trans = exp, shade = TRUE,
      col = trellis.par.get()$superpose.line$col[1], xaxt = "n", xlab = "Day of year",
      ylab = "IRR" )
axis( 1, at = seq( 0, 1, 1/12 ), labels = seq( 0, 1, 1/12 )*30*12 )
```



Case study: CV mortality in elderly in Los Angeles from 1987 to 2000 revisited

```
source( "https://pastebin.com/raw/hBmStX4Y" )
termplot2( fit, terms = "wday", se = TRUE, yscale = "exponential",
           col.term = trellis.par.get()$superpose.line$col[1],
           col.se = "gray80", se.type = "polygon", xlab = "Day of week" )
```



A few words on what we did not cover

- (Non-parametric) filtering and smoothing (LOESS, weighted moving average, Holt-Winters etc.)
- Multivariate time series (coherence, cross-correlation, VAR models etc.)
- Tools of stochastic modelling (autocorrelation function, ARMA models etc.)
- Long-range memory
- State-space models
- Regime switching models
- etc. etc. etc.

Role of time series analysis

- The biomedical application of time series data is getting more and more intensive
- They have role from basic science through clinical investigations to policymaking
- Understanding and – sound! – application of time series methods is of huge importance therefore
- This is not a problem of a selected few specialists: everyone working on biomedical field benefits from having basic knowledge about time series analysis

Some useful references I

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