

# Chapter 26

## Loess and Spline Modeling (90 Patients)

### 1 General Purpose

Plasma concentration time curves are the basis of pharmacokinetics. If traditional nonlinear models do not fit the data well, spline and loess (locally weighted scatter plot smoothing) modeling will provide a possible solution.

### 2 Schematic Overview of Type of Data File

Outcome predictor (time)	
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### 3 Primary Scientific Question

Does loess and spline modeling produce a better fit model for the plasma concentration – time relationships of medicines than traditional curvilinear estimations (Chap. 25).

### 4 Data Example

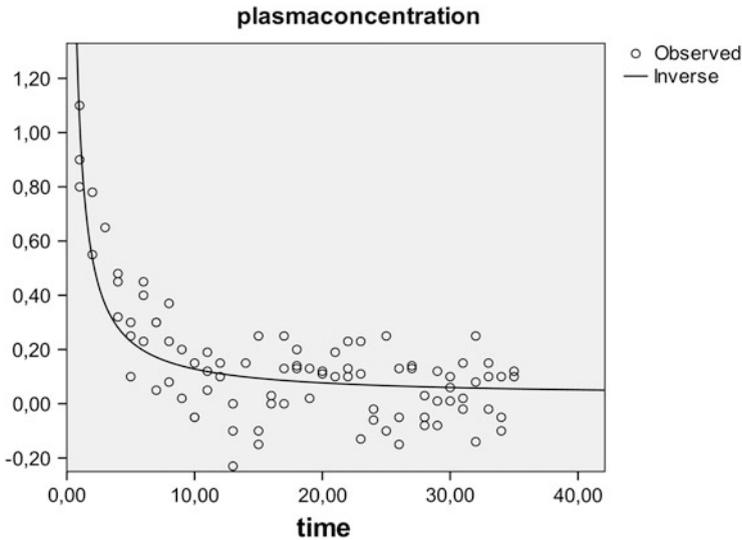
In 90 patient a plasma concentration time curve study of intravenous administration of zoledronic acid (ng/ml) was performed.

Conc	Time
1,10	1,00
,90	1,00
,80	1,00
,78	2,00
,55	2,00
,65	3,00
,48	4,00
,45	4,00
,32	4,00
,30	5,00

conc = plasma concentration  
of zoledromic acid (ng/ml)  
time = hours

### 5 Some Background Information

Usually, the relationship between plasma concentration and time of a drug is described in the form of an exponential model. This is convenient, because it enables to calculate pharmacokinetic parameters like plasma half-life and equations for clearance. Using the Non-Mem program of the University of San Francisco a non linear mixed effect model of the data is produced (= multi-exponential model). The underneath figure of the data shows the exponential model. There is a wide spread in the data, and, so, the pharmacokinetic parameters derived from the model do not mean too much.



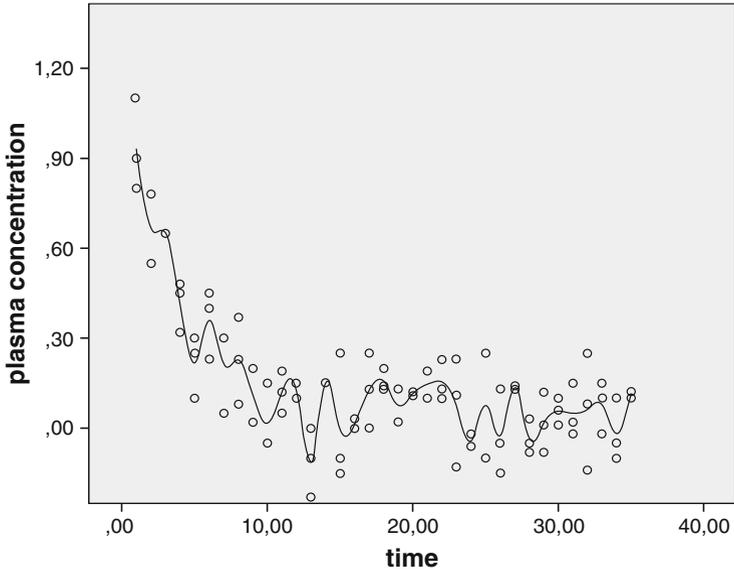
## 6 Spline Modeling

If the traditional models do not fit your data very well, you may use a method called spline modeling. The term spline stems from thin flexible wooden splines formerly used by shipbuilders and cardesigners to produce smooth shapes. A spline model consists of 4, 5 or more intervals with different cubic curves (= third order polynomes, like  $y = a + bx^3$ , see also Chap. 25) that have the same y-value, slope, and curvature at the junctions.

Command:

Graphs. . .Chart Builder. . .click Scatter/Dot. . .click in Simple Scatter and drag to Chart Preview. . . click plasma concentration and drag to the Y-Axis. . .click time and drag to the X-Axis. . .OK. . .double-click in GGraph . . .Chart Editor comes up. . .click Elements. . .click Interpolation. . .dialog box Properties. . . mark Spline. . .click Apply. . .click Edit. . .click Copy Chart.

The underneath figure shows the best fit spline model of the above data.



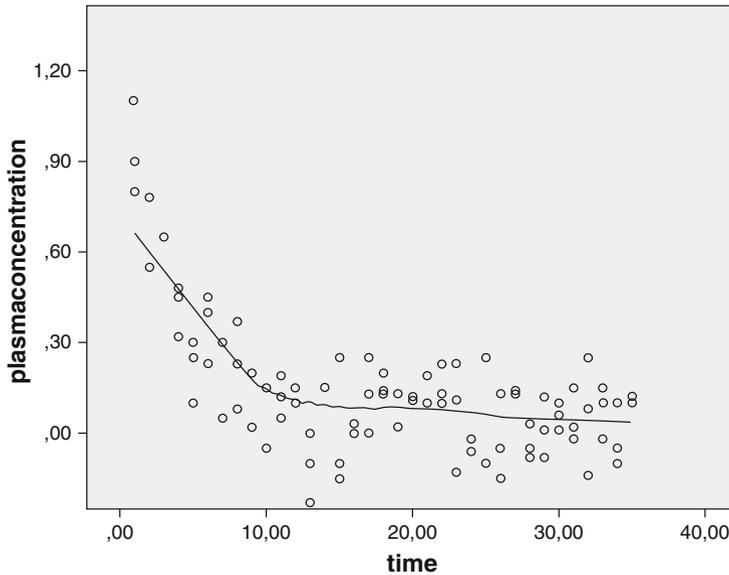
## 7 Loess (Locally Weighted Scatter Plot Smoothing) Modeling

Also loess modeling works with cubic curves (third order polynomes), but unlike spline modeling it does not work with junctions, but, instead, it chooses the best fit cubic curves for each value with outlier data given less weight.

Command:

Graphs...Chart Builder...click Scatter/Dot...click in Simple Scatter and drag to Chart Preview... click plasma concentration and drag to the Y-Axis...click time and drag to the X-Axis...OK...double-click in GGraph...Chart Editor comes up...click Elements...Fit Line at Total...in dialog box Properties... mark: Loess...click: Apply... click Edit...click Copy Chart.

The underneath figure shows the best fit Loess model of the above data.



## 8 Conclusion

Both spline and loess modeling are computationally very intensive methods that do not produce simple regression equations like the ones given in the Chap. 25 on curvilinear regression. They also require fairly large, densely sampled data sets in order to produce good models. For making predictions from such models direct interpolations / extrapolations from the graphs can be made, and, given the mathematical refinement of these methods, these predictions should, generally, give excellent precision. We conclude.

1. Both spline and loess modeling are computationally intensive models that are adequate, if the data plot leaves you with no idea about the relationship between the y- and x-values.
2. They do not produce simple regression equations like the ones given in Chap. 25 on curvilinear regression.
3. For making predictions from such models direct interpolations / extrapolations from the graphs can be made, and, given the mathematical refinement of these methods, these predictions generally give excellent precision.
4. Maybe, the best fit for many types of nonlinear data is offered by loess.

## 9 Note

More background, theoretical, and mathematical information of loess and spline modeling is given in *Statistics applied to clinical studies* 5th edition, Chap. 24, Springer Heidelberg Germany, 2012, from the same authors.