Everything you ever wanted to know about splines but were too afraid to ask

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University of Warwick

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Overview

Categorization and its discontents

Join the dots

Smoothing splines

Splines in R

Introduction

- Splines are a flexible class of models that can be helpful for representing dose-response relationships in epidemiology
- In this course we will be using spline models extensively.
- However, spline models are widely misunderstood.
- The purpose of this lecture is to give a conceptual background on where spline models come from.

Outline

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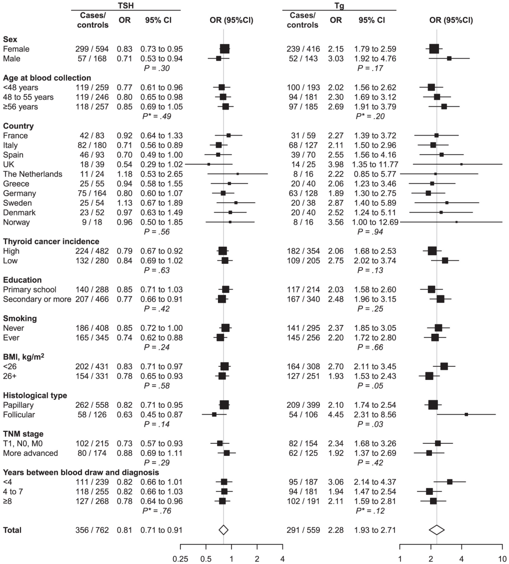
Rinaldi et al, JNCI. 2014 Jun;106(6):dju097



	TSH Cases/controls	TSH OR	TSH 95% CI	Tg Cases/controls	Tg OR	Tg 95% CI
Sex						
Female	299 / 594	0.83	0.73 to 0.95	239 / 416	2.15	1.79 to 2.59
Male	57 / 168	0.71	0.53 to 0.94	52 / 143	3.03	1.92 to 4.76
			P = .30			*P* = .17
Age at blood collection						
<48 years	119 / 259	0.77	0.61 to 0.96	100 / 193	2.02	1.56 to 2.62
48 to 55 years	119 / 246	0.80	0.65 to 0.98	94 / 181	2.30	1.69 to 3.12
≥56 years	118 / 257	0.85	0.69 to 1.05	97 / 185	2.69	1.91 to 3.79
			*P** = .49			*P** = .20
Country						
France	42 / 83	0.92	0.64 to 1.33	31 / 59	2.27	1.39 to 3.72
Italy	82 / 180	0.71	0.56 to 0.89	68 / 127	2.11	1.50 to 2.96
Spain	46 / 93	0.70	0.49 to 1.00	39 / 70	2.55	1.56 to 4.16
UK	18 / 39	0.54	0.29 to 1.02	14 / 25	3.98	1.35 to 11.77
The Netherlands	11 / 24	1.18	0.53 to 2.65	8 / 16	2.22	0.85 to 5.77
Greece	25 / 55	0.94	0.58 to 1.55	20 / 40	2.06	1.23 to 3.46
Germany	75 / 164	0.80	0.60 to 1.07	63 / 128	1.89	1.30 to 2.75
Sweden	25 / 54	1.13	0.67 to 1.89	20 / 38	2.87	1.40 to 5.89
Denmark	23 / 52	0.97	0.63 to 1.49	20 / 40	2.52	1.24 to 5.11
Norway	9 / 18	0.96	0.50 to 1.85	8 / 16	3.56	1.00 to 12.69
			P = .56			*P* = .94
Thyroid cancer incidence						
High	224 / 482	0.79	0.67 to 0.92	182 / 354	2.06	1.68 to 2.53
Low	132 / 280	0.84	0.69 to 1.02	109 / 205	2.75	2.02 to 3.74
			P = .63			*P* = .13
Education						
Primary school	140 / 288	0.85	0.71 to 1.03	117 / 214	2.03	1.58 to 2.60
Secondary or more	207 / 466	0.77	0.66 to 0.91	167 / 340	2.48	1.96 to 3.15
			P = .42			*P* = .25
Smoking						
Never	186 / 408	0.85	0.72 to 1.00	141 / 295	2.37	1.85 to 3.05
Ever	165 / 345	0.74	0.62 to 0.88	145 / 256	2.20	1.72 to 2.80
			P = .24			*P* = .66
BMI, kg/m²						
<26	202 / 431	0.83	0.71 to 0.97	164 / 308	2.70	2.11 to 3.45
26+	154 / 331	0.78	0.65 to 0.93	127 / 251	1.93	1.53 to 2.43
			P = .58			*P* = .05
Histological type						
Papillary	262 / 558	0.82	0.71 to 0.95	209 / 399	2.10	1.74 to 2.54
Follicular	58 / 126	0.63	0.45 to 0.87	54 / 106	4.45	2.31 to 8.56
			P = .14			*P* = .03
TNM stage						
T1, N0, M0	102 / 215	0.73	0.57 to 0.93	82 / 154	2.34	1.68 to 3.26
More advanced	80 / 174	0.88	0.69 to 1.11	62 / 125	1.92	1.37 to 2.69
			P = .29			*P* = .42
Years between blood draw and diagnosis						
<4	111 / 239	0.82	0.66 to 1.01	95 / 187	3.06	2.14 to 4.37
4 to 7	118 / 255	0.82	0.66 to 1.03	94 / 181	1.94	1.47 to 2.54
≥8	127 / 268	0.78	0.64 to 0.96	102 / 191	2.11	1.59 to 2.81
			*P** = .76			*P** = .12
Total	356 / 762	0.81	0.71 to 0.91	291 / 559	2.28	1.93 to 2.71

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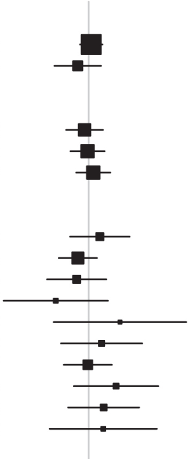

Statisticians against categorization

- Greenland S (1995) Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis, Epidemiology, **6**, 450–454.
- Senn S (2005) Dichotomania: an obsessive compulsive disorder that is badly affecting the quality of analysis of pharmaceutical trials.
- Bennette C, and Vickers A, (2012), Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. BMC Medical Research Methodology 12:21

Epidemiologists against categorization

Rose, G. (1992) The Strategy of Preventive Medicine

- Many diseases are not discrete. Instead there is an underlying continuum of increasing severity (e.g. hypertension).
- In medicine, we tend to conflate a clinical action (treat vs. do not treat) with the presence/absence of disease.
- Disease prevention efforts are best targeted at shifting the distribution of risk for the whole population instead of trying to identify and target a "high risk" group.

Outline

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Join the dots

Smoothing splines

Splines in R

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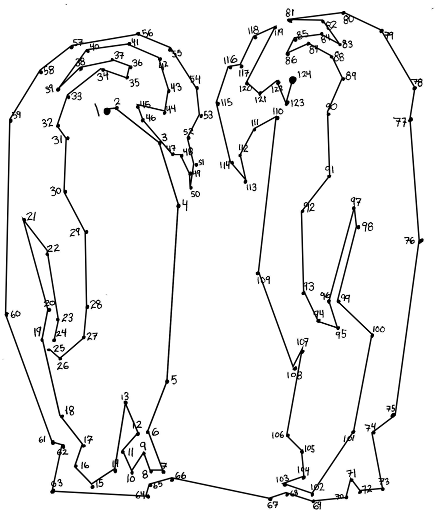
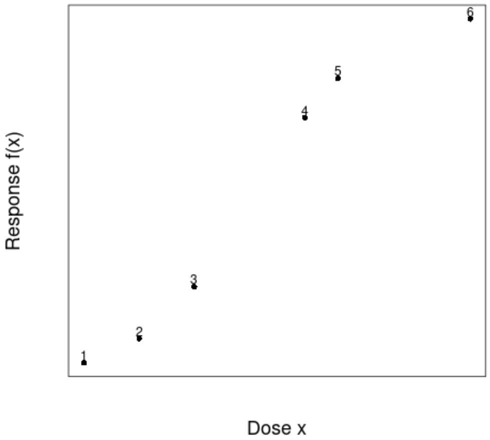
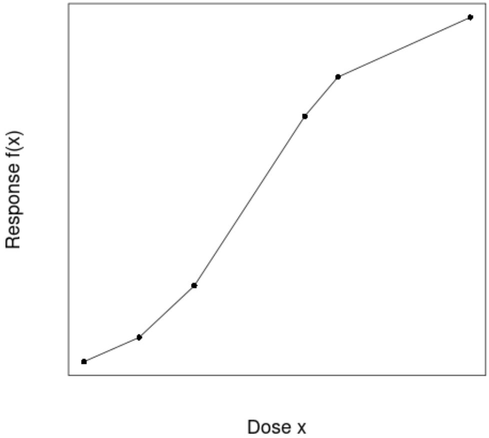


Linear interpolation



- Suppose a dose response curve is known exactly at certain points
- We can fill in the gaps (interpolate) by drawing a straight (linear) line between adjacent points
- This creates a mathematical function $f()$ which gives a response value $f(x)$ for every dose value x.

Linear interpolation



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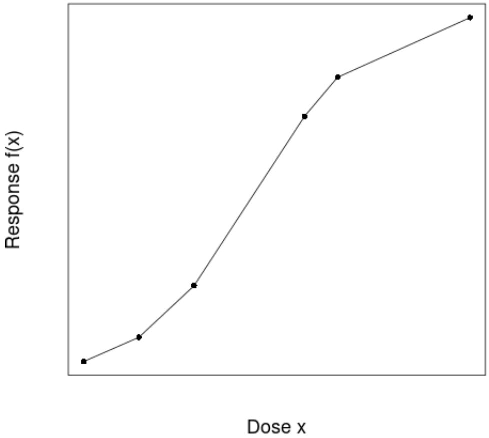

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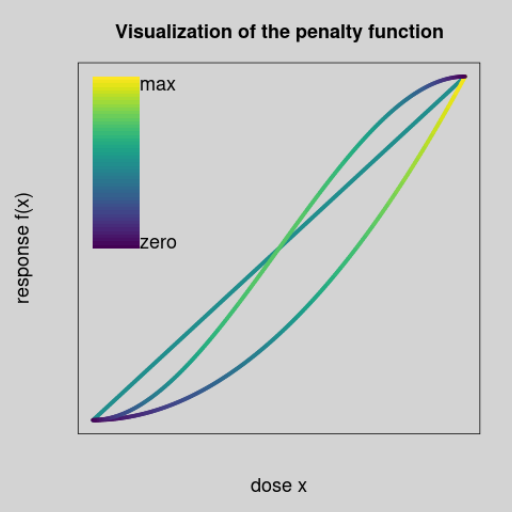
Why linear interpolation?

Out of all possible curves that go through the observed points, linear interpolation is the one that minimizes the penalty function

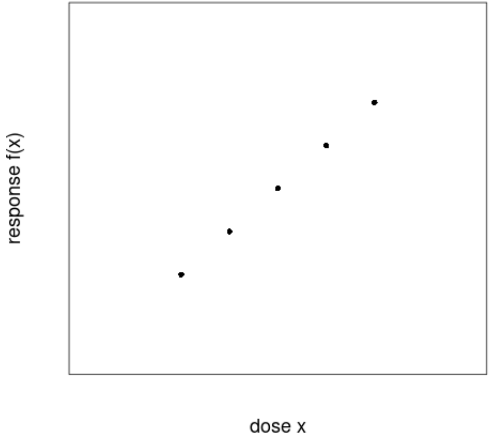
$$\int \left(\frac{\partial f}{\partial x} \right)^2 dx$$

What does the penalty mean?



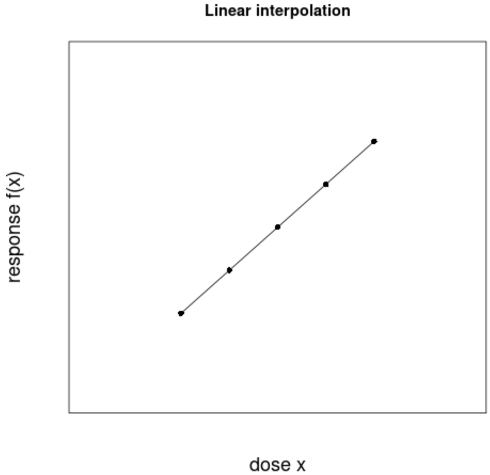
- The contribution to the penalty at each point depends on the steepness of the curve (represented by a colour gradient)
- Any deviation from a straight line between the two fixed points will incur a higher penalty overall.

Extrapolation



- Linear interpolation fits a linear dose-response curve exactly.
- But it breaks down when we extrapolate.

Extrapolation



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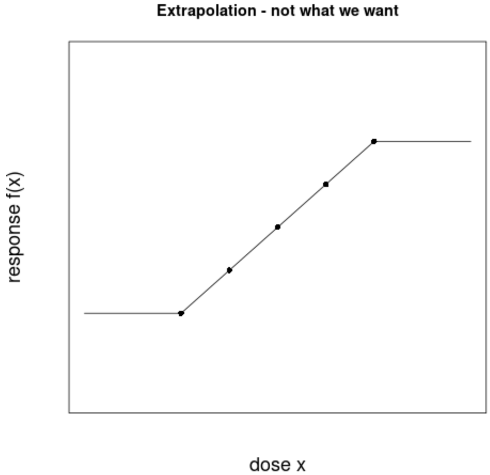

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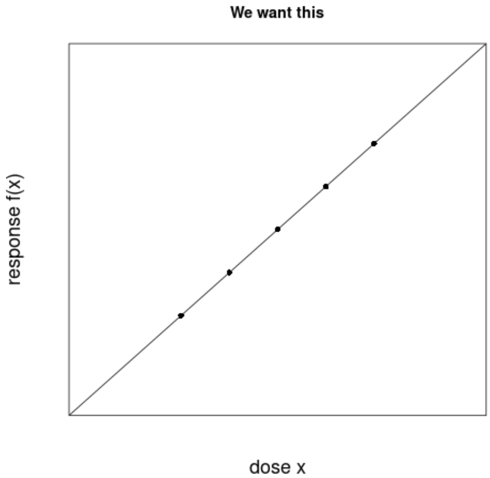

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Why does linear interpolation break down?

- The penalty function

$$\int \left(\frac{\partial f}{\partial x}\right)^2 dx$$

  penalizes the steepness of the curve
- Minimizing the penalty function gives us gives us the "flattest" curve that goes through the points.
  - In between two observations the flattest curve is a straight line.
  - Outside the range of the observations the flattest curve is completely flat.

A roughness penalty

- If we want a fitted curve that extrapolates a linear trend then we want to minimize the curvature.

$$\int \left(\frac{\partial^2 f}{\partial x^2} \right)^2 dx$$

- Like the first penalty function but uses the second derivative of f (i.e. the curvature).
- This is a roughness penalty.

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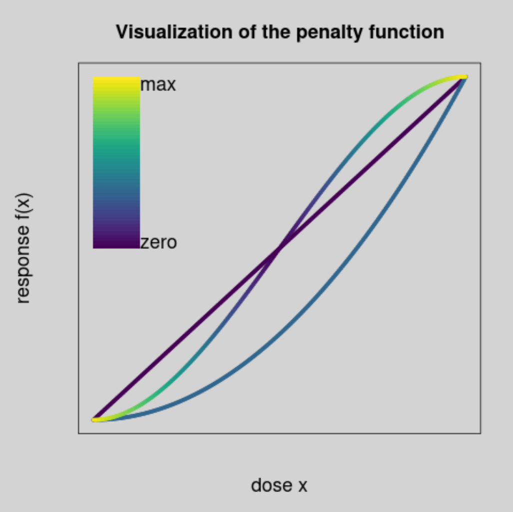
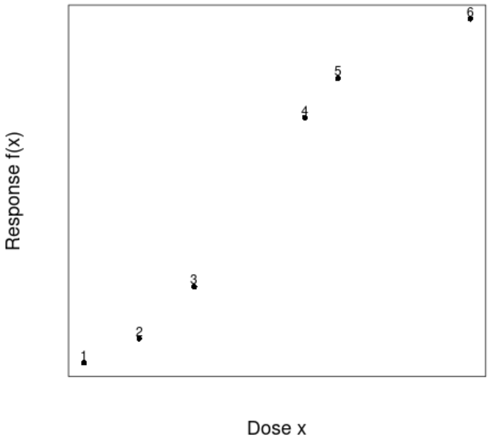
What does the roughness penalty mean?



- The contribution to the penalty at each point depends on the curvature (represented by a colour gradient)
- A straight line has no curvature, hence zero penalty.
- Sharp changes in the slope are heavily penalized.

An interpolating cubic spline



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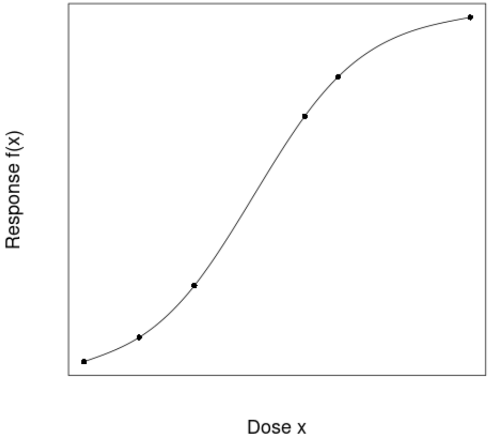


- The smoothest curve that goes through the observed points is a cubic spline.

What is a cubic spline?

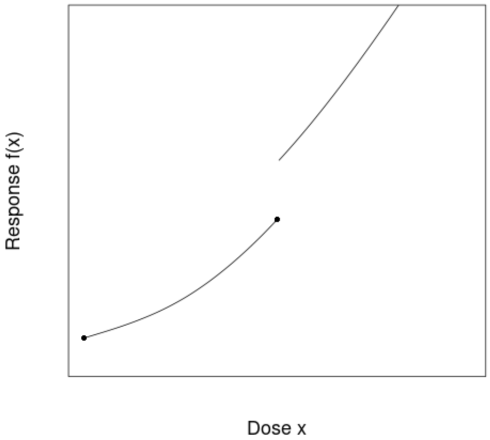
Splines are piecewise cubic curves

- Every observed point is a knot.
- The knots divide the curve into sections
- Each section is a cubic function

$$f(x) = a + bx + cx^2 + dx^3$$

- The parameters a, b, c, d are different for different sections

Boundary conditions



Sections need to join up smoothly.

- Both sides must go through the knot.
- The slope cannot change at a knot
- The curvature cannot change at a knot

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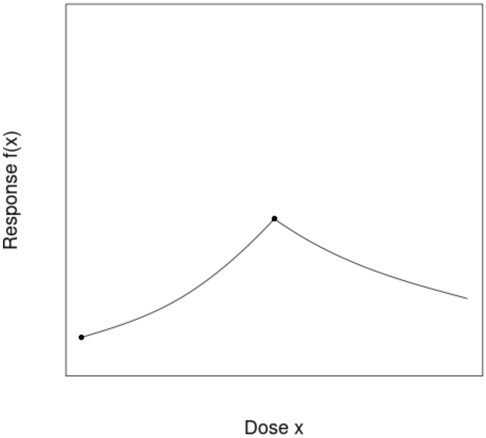

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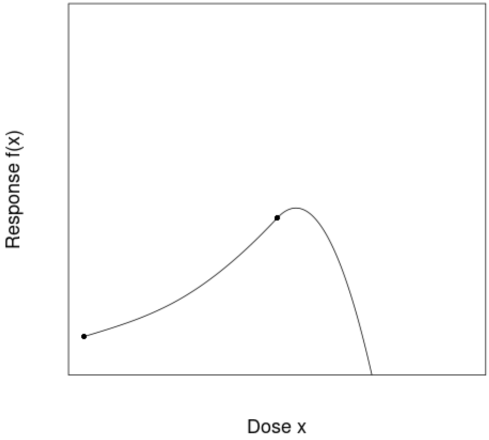

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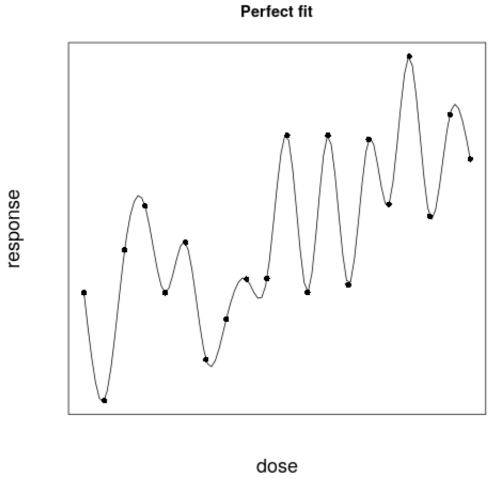
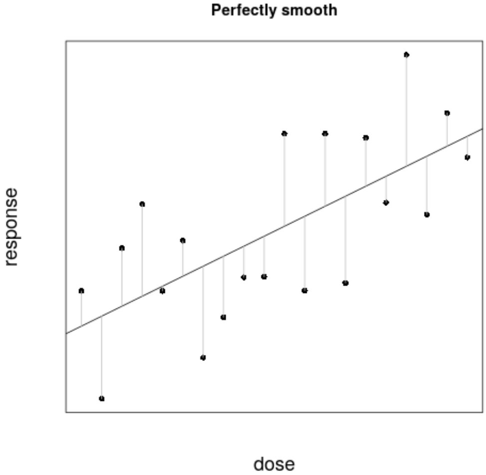
Dose response with error



In practice we never know the dose response curve exactly at any point but always measure with error. A spline model is then a compromise between

- Model fit
- Smoothness of the spline

Dose response with error



In practice we never know the dose response curve exactly at any point but always measure with error. A spline model is then a compromise between

- Model fit
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Fitting a smoothing spline

Minimize

$$\sum_i [y_i - f(x_i)]^2 + \lambda \int \left(\frac{\partial^2 f}{\partial x^2} \right)^2 dx$$

Or, more generally

$$\text{Deviance } + \lambda \times \text{Roughness penalty}$$

Size of tuning parameter λ determines compromise between model fit (small λ) and smoothness (large λ).

Smoothing and degrees of freedom

Software will choose the smoothing parameter λ for you automatically using cross-validation.

The smoothing parameter is adapted to the data.

Smoothness of the model can be measured with the *effective degrees of freedom* (EDF)

- Linear model: maximally smooth
  - EDF=2 (intercept + slope parameter)
- Intepolating mode: best fit
  - EDF=n (one parameter for every observation)

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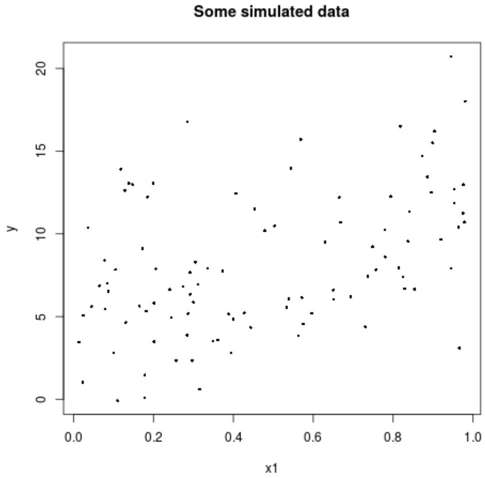
Spline models in R

- Do not use the splines package.
- Use the `gam` function from the mgcv package to fit your spline models.
- The `gam` function chooses number and placement of knots for you and estimates the size of the tuning parameter λ automatically.
- You can use the `gam.check` function to see if you have enough knots. Also re-fit the model explicitly setting a larger number of knots (e.g. double) to see if the fit changes.

Penalized spline



- A gam fit to some simulated data
- Model has 9 degrees of freedom
- Smoothing reduces this to 2.88 effective degrees of freedom

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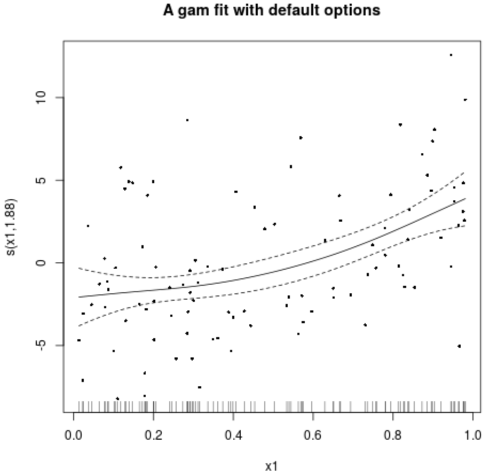

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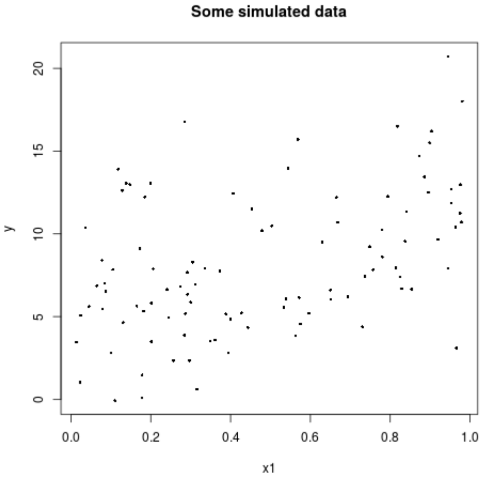
Unpenalized spline



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- Model has 9 degrees of freedom

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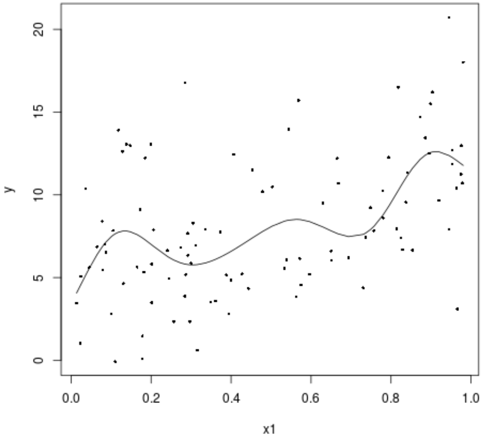

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- Model has 9 degrees of freedom

Conclusions

- Epidemiologists like to turn continuous variables into categories.
- Statisticians do not like categorization because it loses information.
- Splines are a flexible class of models that avoid categorization but also avoid making strong assumptions about the shape of a dose-response relationship.
- Penalized regression splines are based on compromise between goodness-of-fit and smoothness.
- Most of the decisions in fitting a penalized regression spline can be made for you
  - Degree of smoothing
  - Number of knots
  - Placement of knots