Everything You Ever Wanted to Know about Splines...

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Overview

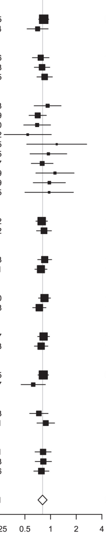
Introduction

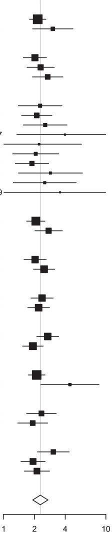
- Splines are a flexible class of models that can be helpful for representing dose-response relationships in epidemiology
- In this course we will be using spline models extensively.
- However, spline models are widely misunderstood.
- The purpose of this lecture is to give a conceptual background on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

Outline

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

	TSH				Tg			
	Cases/ controls	OR	95% CI	OR (95%CI)	Cases/ controls	OR	95% CI	OR (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/m^2								
<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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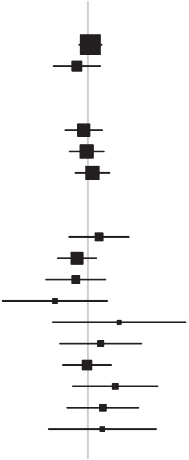


Statisticians against categorization

- 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

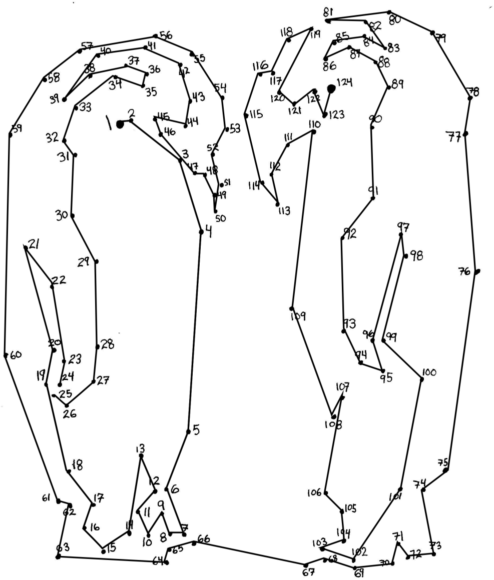
Rose, G. (1992) The Strategy of Preventive Medicine

- 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.

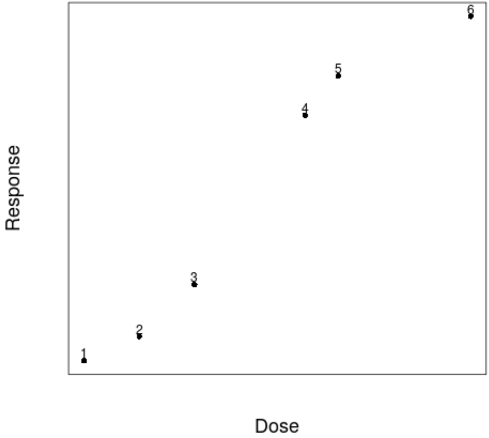
Outline

Join the dots

Join the dots

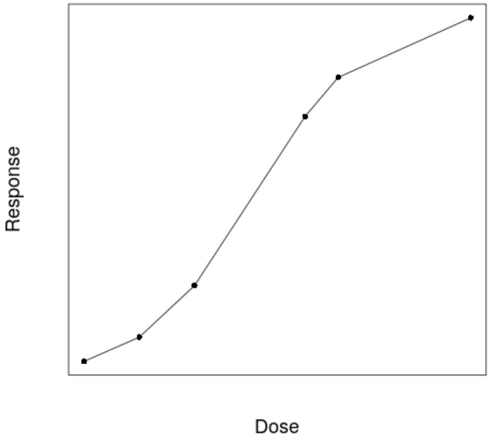


Linear interpolation



- 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

Linear interpolation



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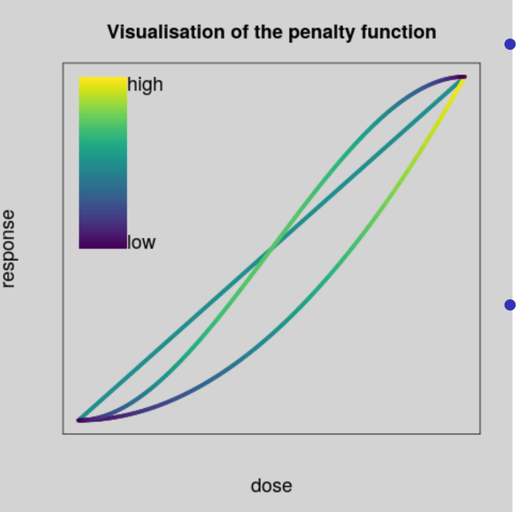
- We can fill in the gaps (interpolate) by drawing a straight (linear) line between adjacent points

Why linear interpolation?

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

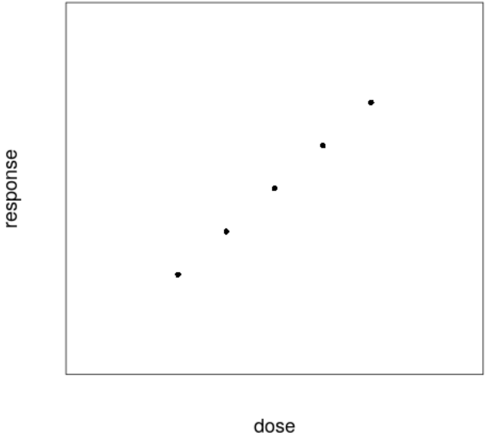
$$\int \left(\frac{\partial f}{\partial x}\right)^2 dx$$

What does the penalty mean?



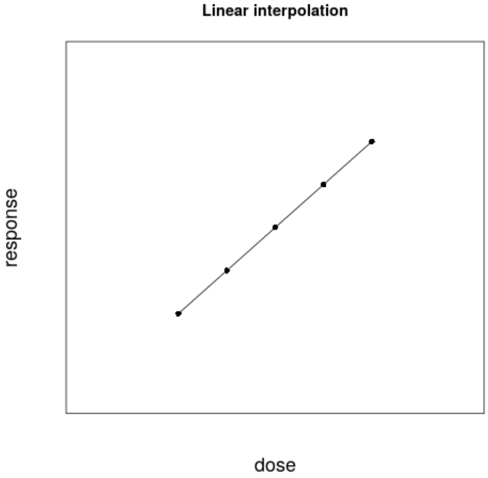
- The contribution to the penalty at each point depends on the steepness of the curve (represented by a colour gradient)
- Any deviation from a straight line between the two fixed points will incur a higher penalty overall.

Extrapolation



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

Extrapolation



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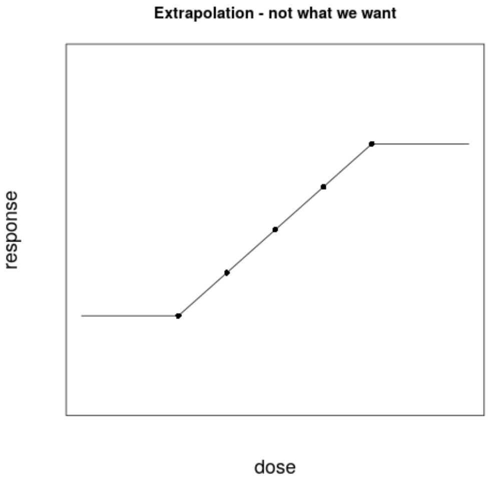

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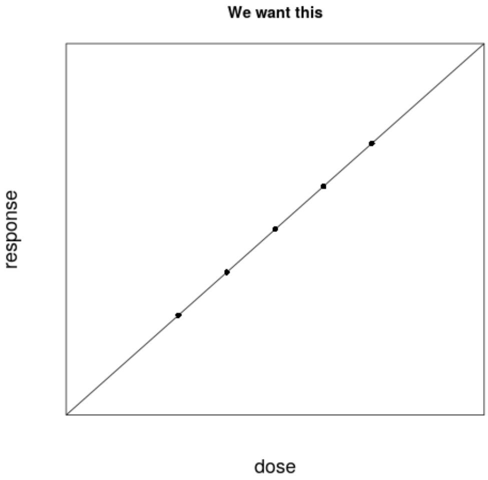

- Linear interpolation fits a linear dose-response curve exactly
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Why does linear interpolation break down?

- 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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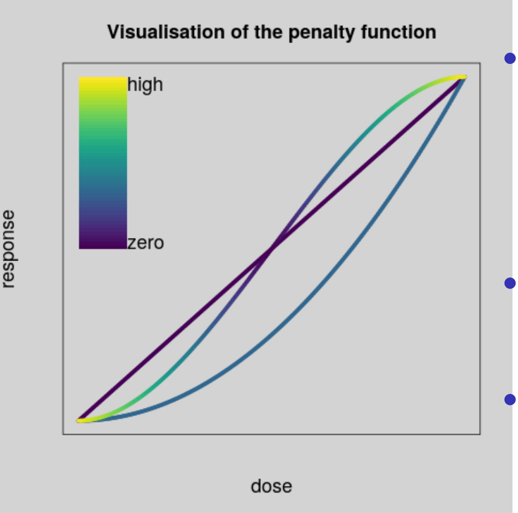
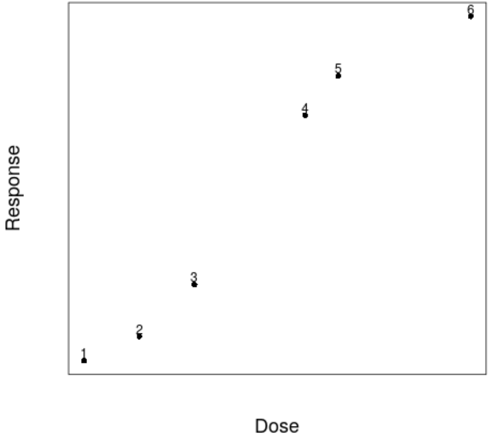
What does the roughness penalty mean?



- 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



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

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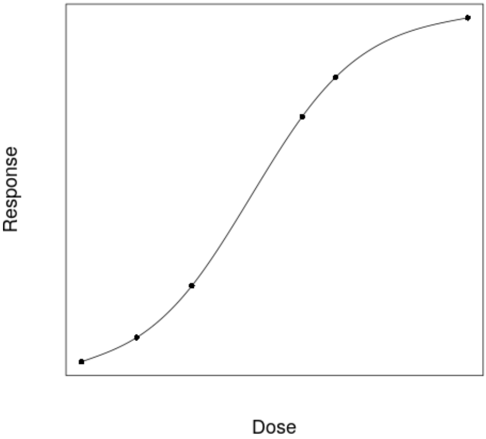

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Properties of cubic splines

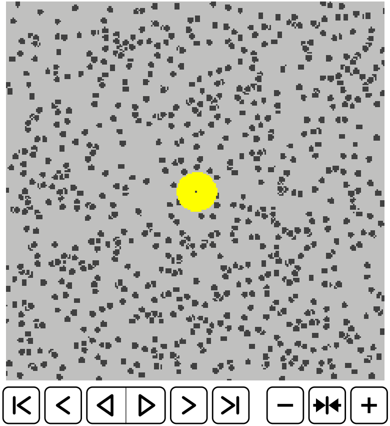
- A cubic spline consists of a sequence of curves of the form

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

  for some coefficients a, b, c, d, in between each observed point.
- The cubic curves are joined at the observed points (knots)
- The cubic curves match where they meet at the knots
  - Same value $f(x)$
  - Same slope $\partial f / \partial x$
  - Same curvature $\partial^2 f / \partial x^2$

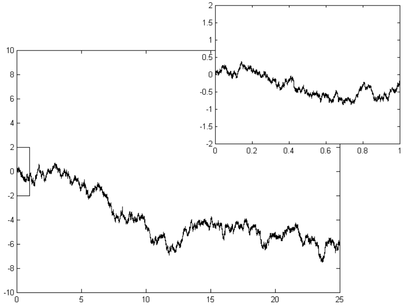
Outline

Brownian motion



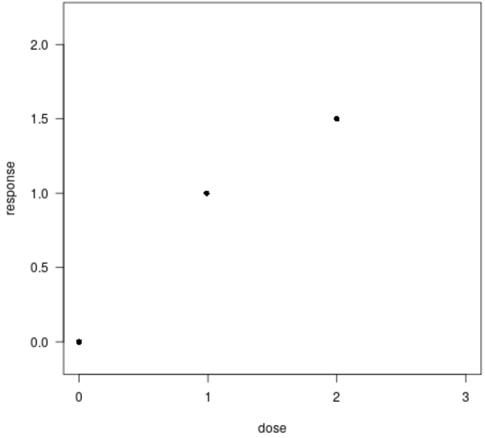
- In 1827, botanist Robert Brown observed particles under the microscope moving randomly
- Theoretical explanation by Einstein (1905) in terms of water molecules
- Verified by Perrin (1908). Nobel prize in physics 1927.

Evolution of 1-dimensional Brownian motion with time



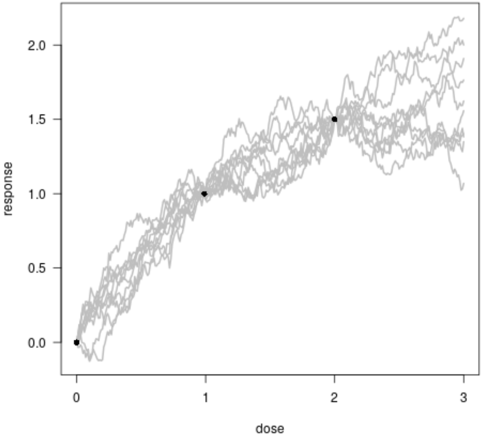
- In mathematics a Brownian motion is a stochastic process that randomly goes up or down at any time point
- Also called a Wiener process after American mathematician Norbert Wiener.
- A Brownian motion is fractal – it looks the same if you zoom in and rescale

A partially observed Brownian motion



- Suppose we observe a Brownian motion at three points
- Grey lines show a sample of possible paths through the points
- The black line shows the average over all paths

A partially observed Brownian motion



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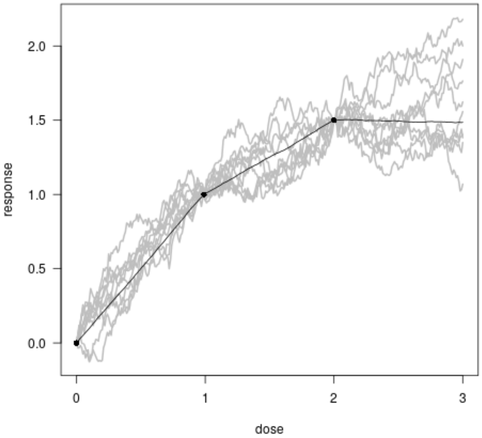

- Suppose we observe a Brownian motion at three points
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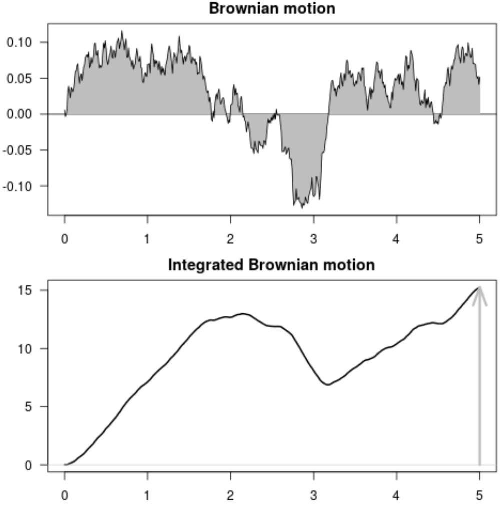
Statistical model for linear interpolation

- Suppose the curve f is generated by the underlying model

$$f(x) = \alpha + \sigma W(x)$$

  where W (for Wiener process) is a Brownian motion
- Then given points $(x_1, f(x_1)) \dots (x_n, f(x_n))$ the *expected value* of f is the curve we get from linear interpolation.

Integrated Brownian motion



- The value of an integrated Brownian motion is the area under the curve (AUC) of a Brownian motion up to that point.
- AUC goes down when the Brownian motion takes a negative value.

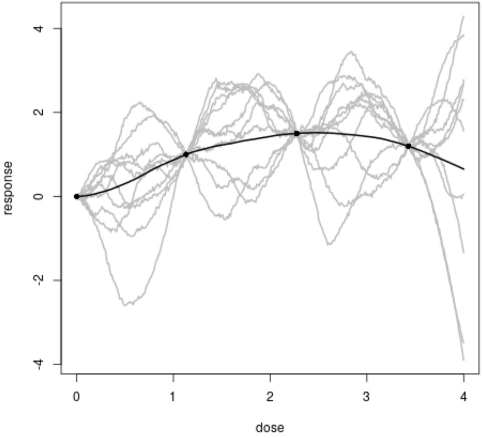
Integrated Brownian motion with drift

Add a mean parameter and a linear trend (drift) to the integrated Brownian motion:

$$f(x) = \alpha + \beta x + \sigma \int_0^x W(z) dz$$

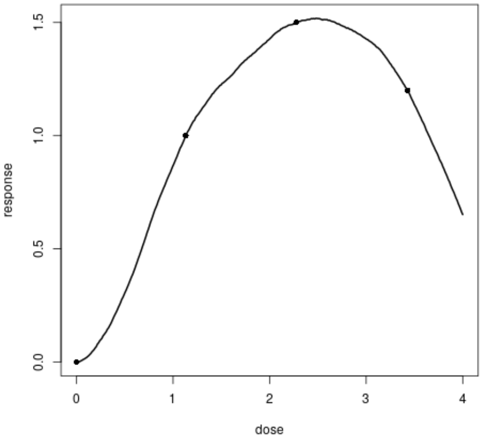
This more complex model is capable of modelling smooth curves.

A partially observed integrated Brownian motion with drift



- Grey lines show a sample of possible paths through the points
- The black line shows the average over all paths

Zoom on the expected value



- The expected value is a cubic spline.
- Extrapolation beyond the boundary of the points is linear (natural spline).

The smoothness paradox

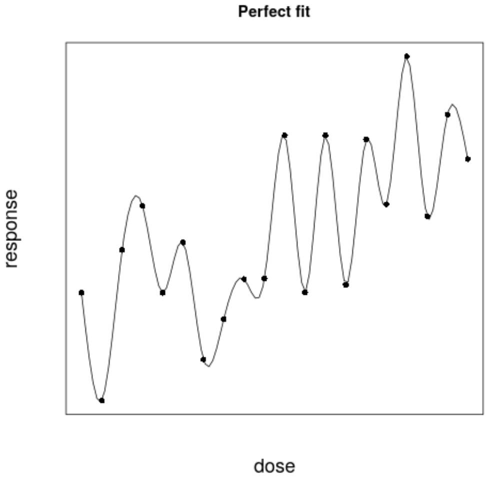
- A cubic natural spline is the smoothest curve that goes through a set of points.
- But the underlying random process $f(x)$ is nowhere smooth.
- $f(x)$ is constantly changing its slope based on the value of the underlying Brownian motion.

The knot paradox

- There are no knots in the underlying model for a cubic natural spline.
- Knots are a result of the observation process.

Outline

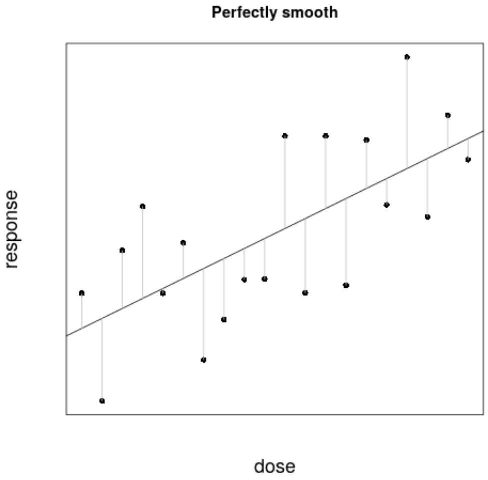
Dose response with error



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



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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

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

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

How to choose the tuning parameter λ

This is a statistical problem. There are various statistical approaches:

- Restricted maximum likelihood (REML)
- Cross-validation
- Bayesian approach (with prior on smoothness)

At least the first two should be available in most software.

Outline

Spline models done badly

- Choose number and placement of knots
- Create a spline bases
- Use spline basis as the design matrix in a generalized linear model.

- Without penalization, model will underfit (too few knots) or overfit (too many knots)
- Placement of knots may create artefacts in the dose-response relationship

Spline models done well

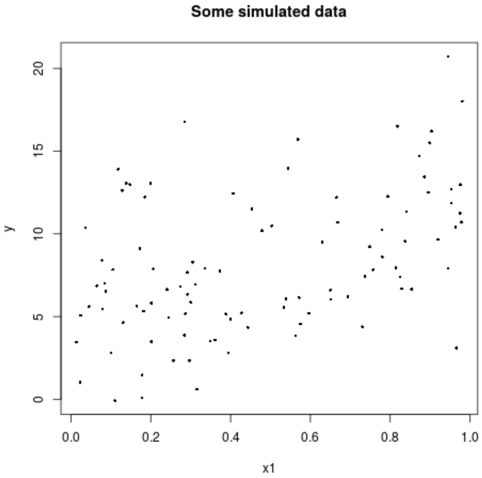
- A knot for every observed value (remember: knots are a product of the observation process).
- Use penalization: find the right compromise between model fit and model complexity.

- In practice we can get a good approximation to this "ideal" model with fewer knots.
- This assumption should be tested

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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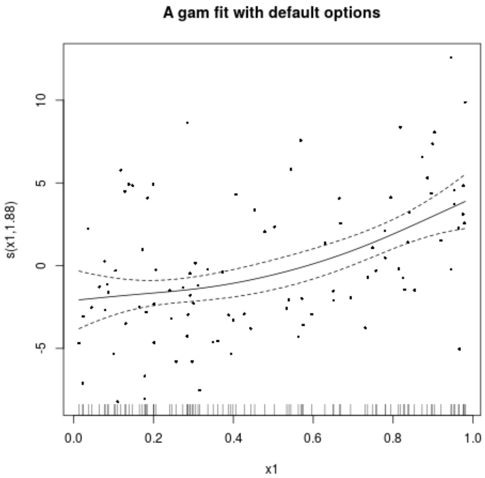

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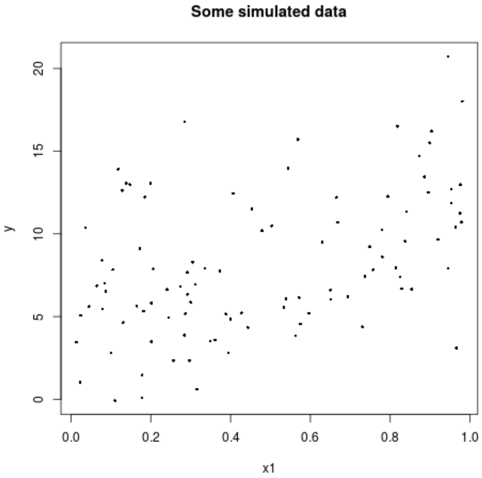
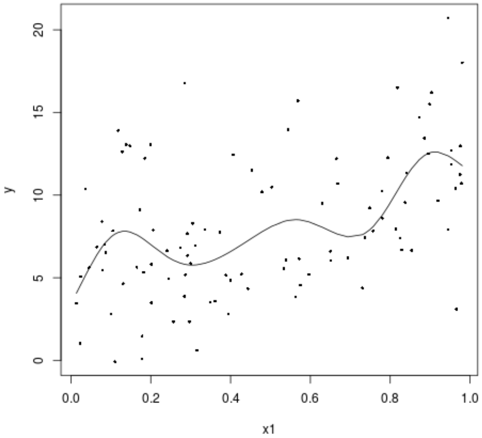
Unpenalized spline



- An unpenalized spline using the same spline basis as the gam fit.
- Model has 9 degrees of freedom

Unpenalized spline



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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