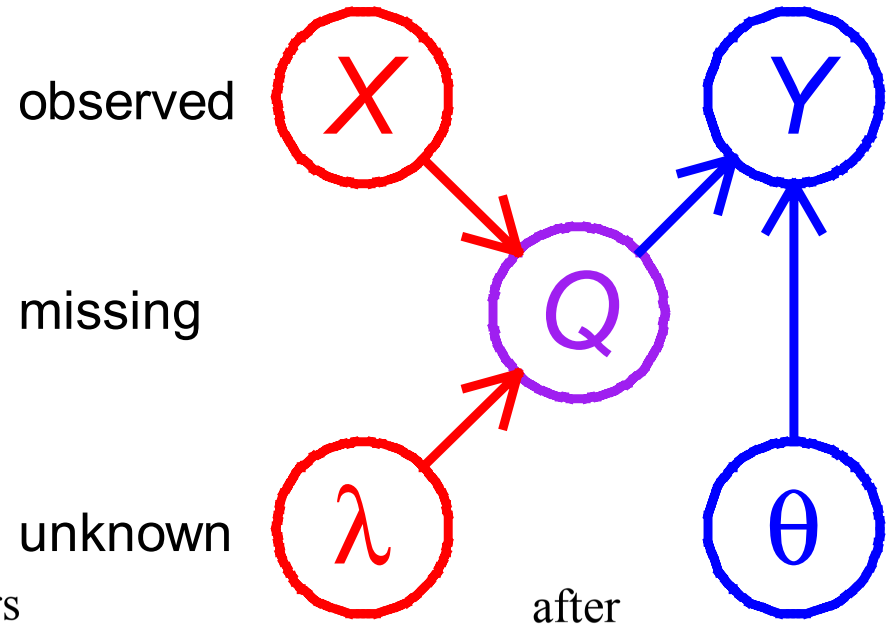
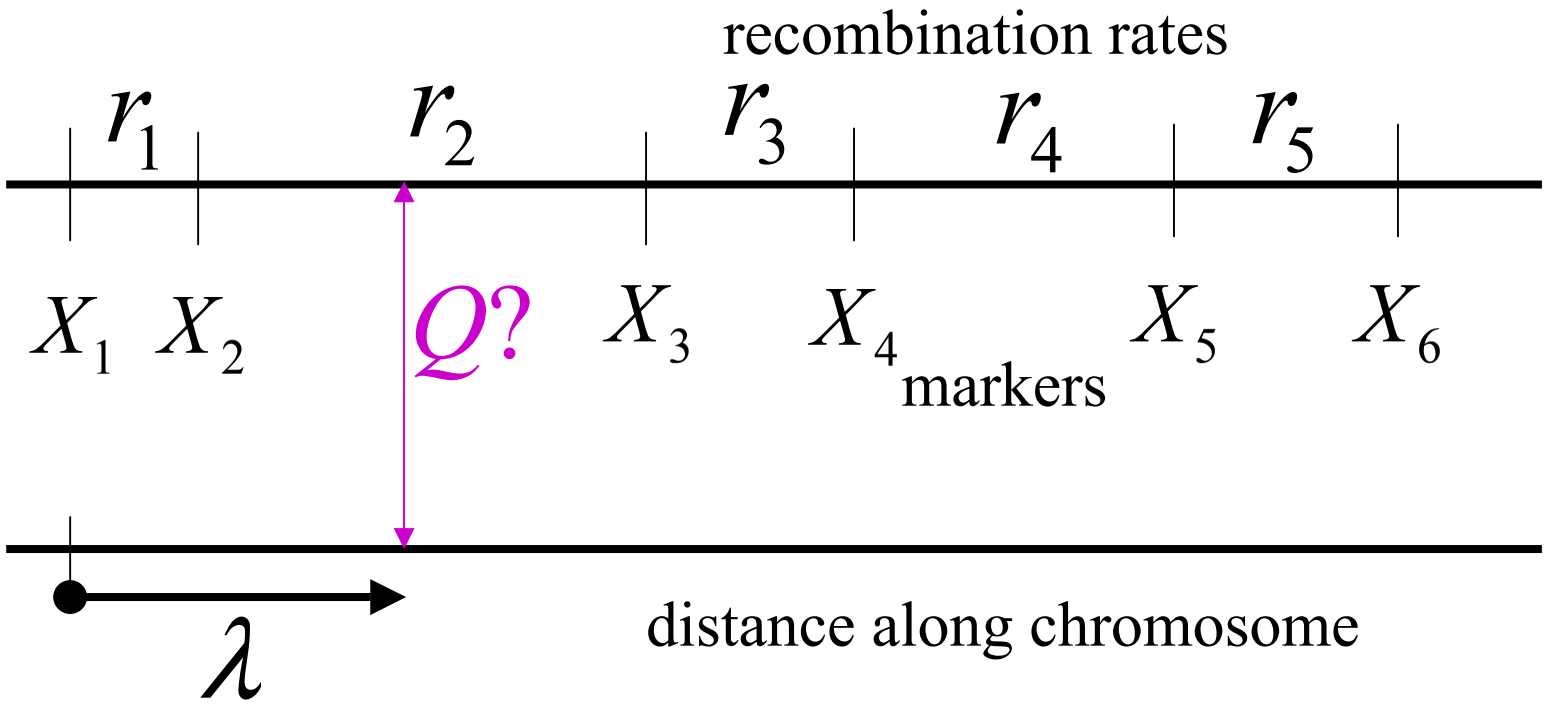
Part I: Interval Mapping Basics

- observed measurements
  - Y = phenotypic trait
  - X = markers & linkage map
    - i = individual index 1,…,n
- missing data
  - missing marker data
  - Q = QT genotypes
    - alleles QQ, Qq, or qq at locus
- unknown quantities
  - λ = QT locus (or loci)
  - θ = phenotype model parameters
- pr($Q|X,\lambda$) recombination model
  - grounded by linkage map, experimental cross
  - recombination yields multinomial for Q given X
- pr($Y|Q,\theta$) phenotype model
  - distribution shape (could be assumed normal)
  - unknown parameters θ (could be non-parametric)



after
Sen Churchill (2001)

recombination model components

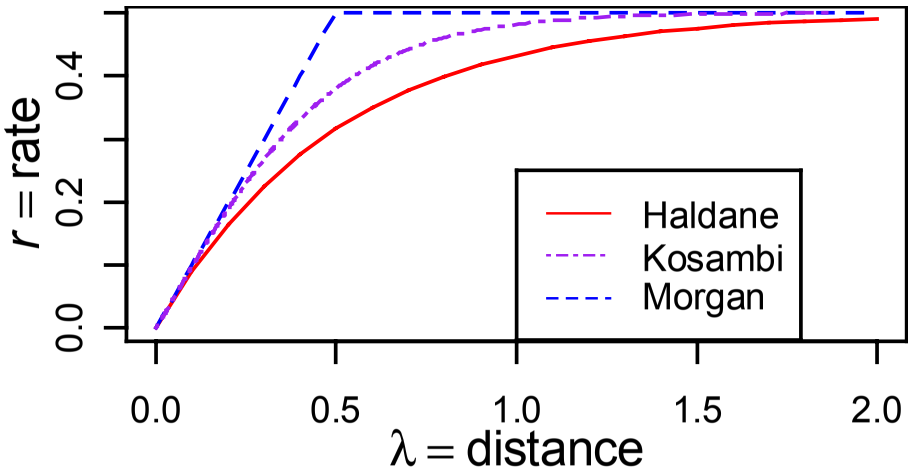


Recombination and Distance

- assume map and marker distances are known
- useful approximation for QTL linkage
  - Haldane map function: no crossover interference
  - independence implies crossover events are Poisson
- all computations consistent in approximation
  - rely on given map with known marker locations
  - 1-to-1 relation of distance to recombination
  - all map functions are approximate anyway

$$r = \frac{1}{2}\left(1 - e^{-2\lambda}\right)$$

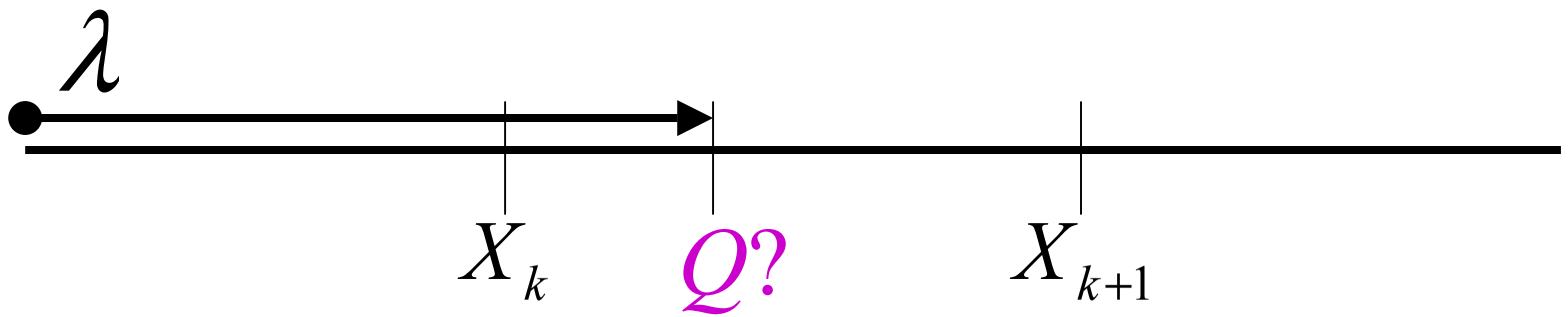
$$\lambda = -\frac{1}{2}\log(1 - 2r)$$



recombination model $\text{pr}(Q|X,\lambda)$

- locus λ is distance along linkage map
  - identifies flanking marker region
- flanking markers provide good approximation
  - map assumed known from earlier study
  - inaccuracy slight using only flanking markers
    - extend to next flanking markers if missing data
  - could consider more complicated relationship
    - but little change in results

$$\text{pr}(Q|X,\lambda) = \text{pr}(\text{geno} \mid \text{map, locus}) \approx \text{pr}(\text{geno} \mid \text{flanking markers, locus})$$



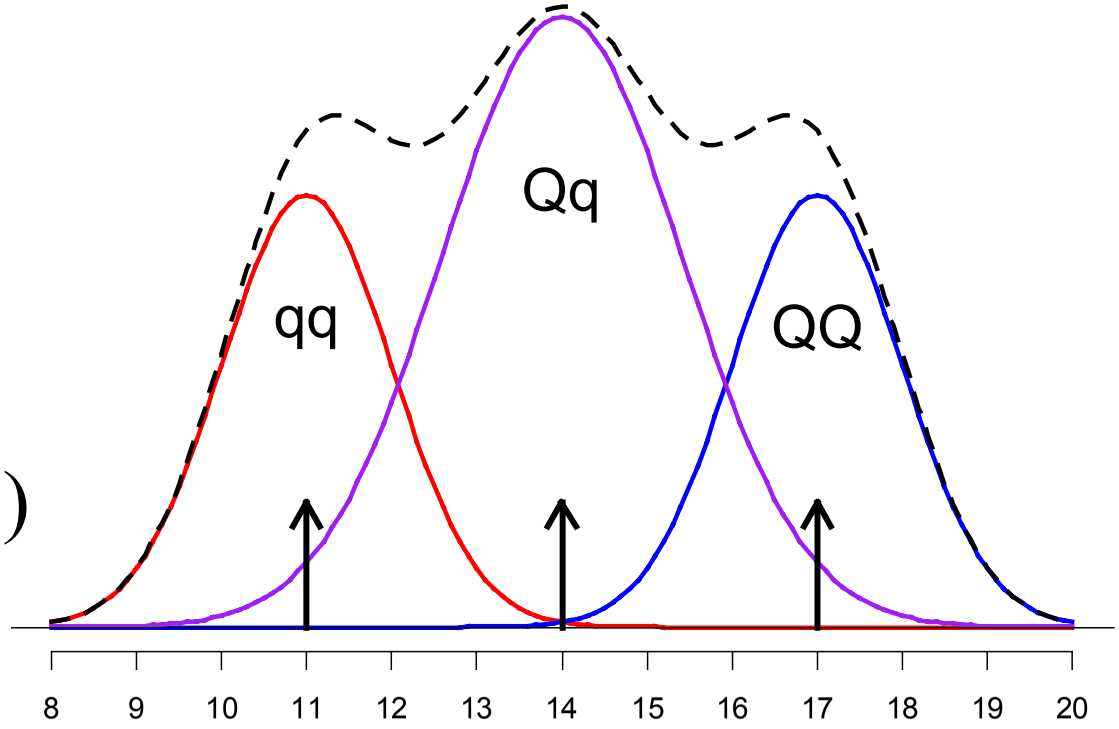
idealized phenotype model

- trait = mean + additive + error
- trait = effect_of_geno + error
- pr(trait | geno, effects)

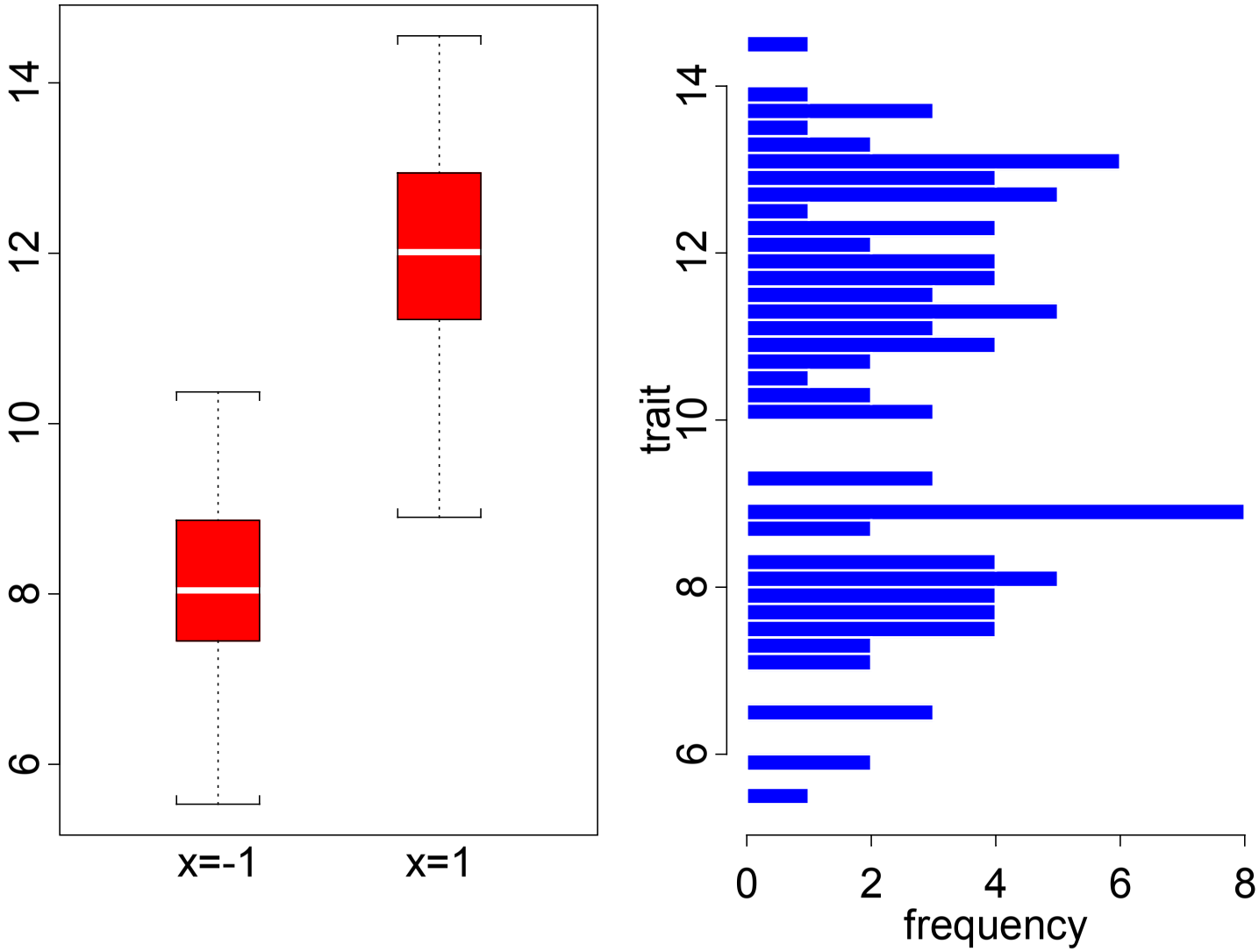
$$Y = G_Q + E$$

$$\text{pr}(Y \mid Q, \theta) =$$

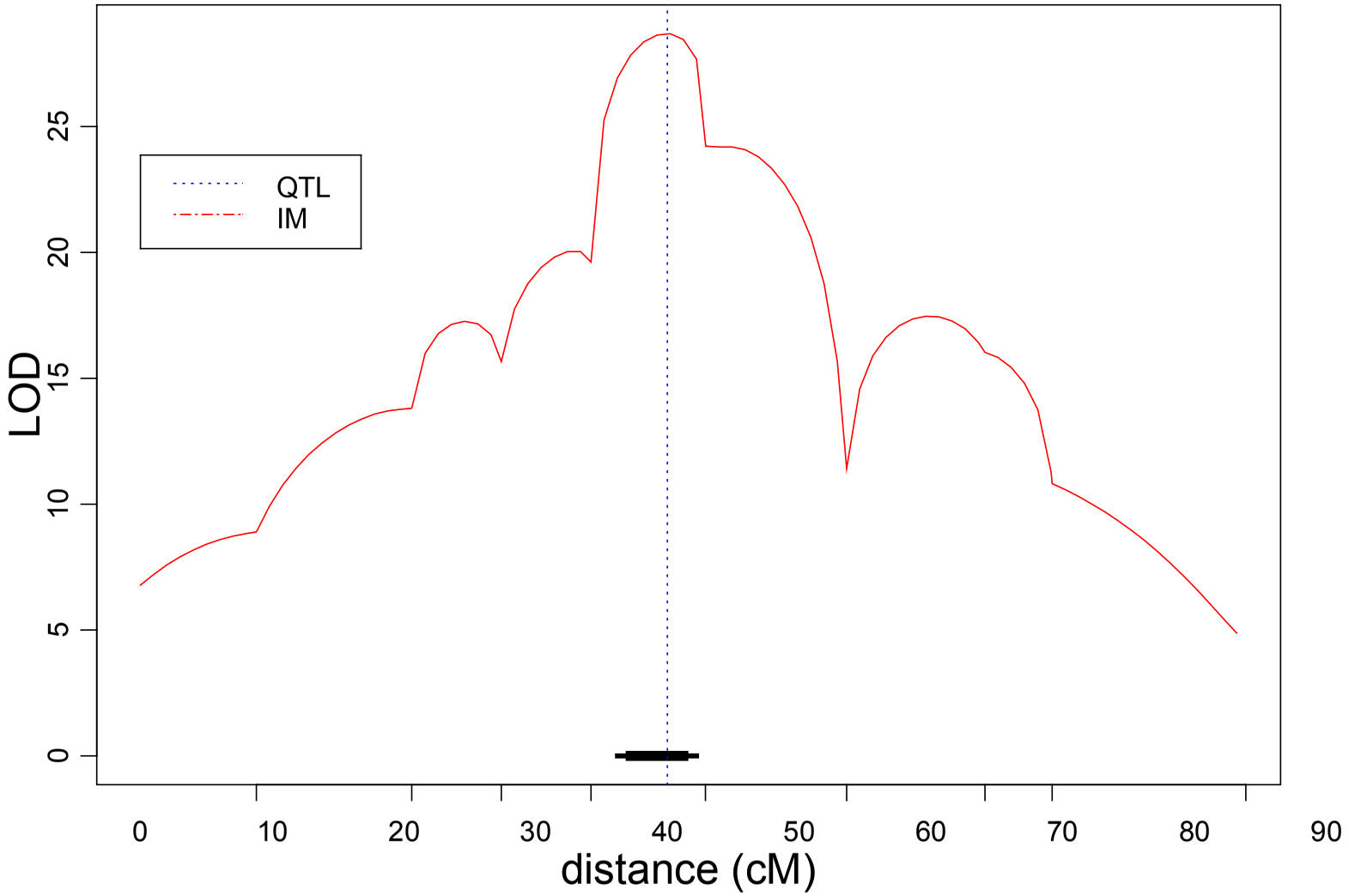
$$\text{normal}(G_Q, \sigma^2)$$



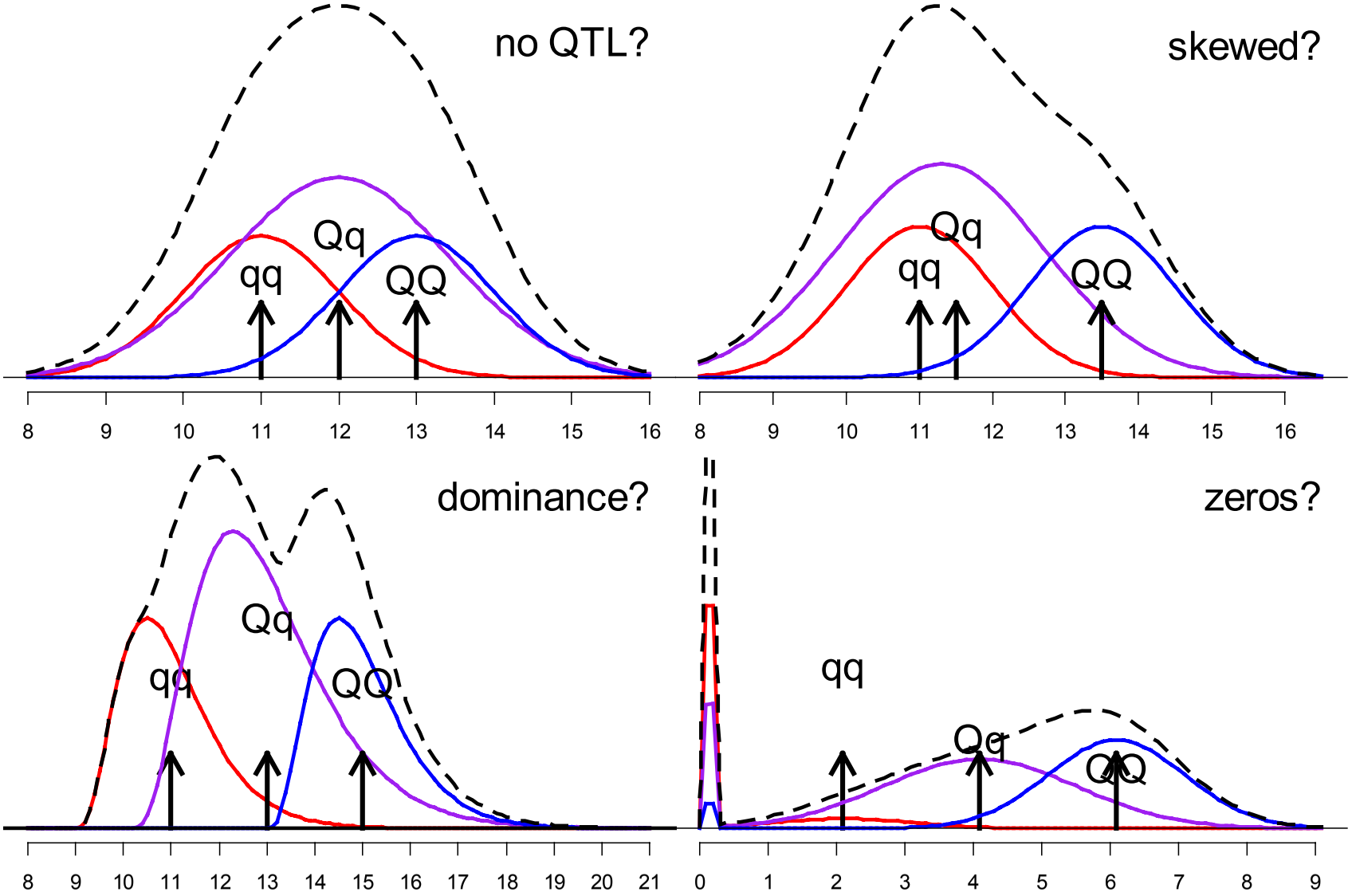
Simulated Data with 1 QTL



Profile LOD for 1 QTL

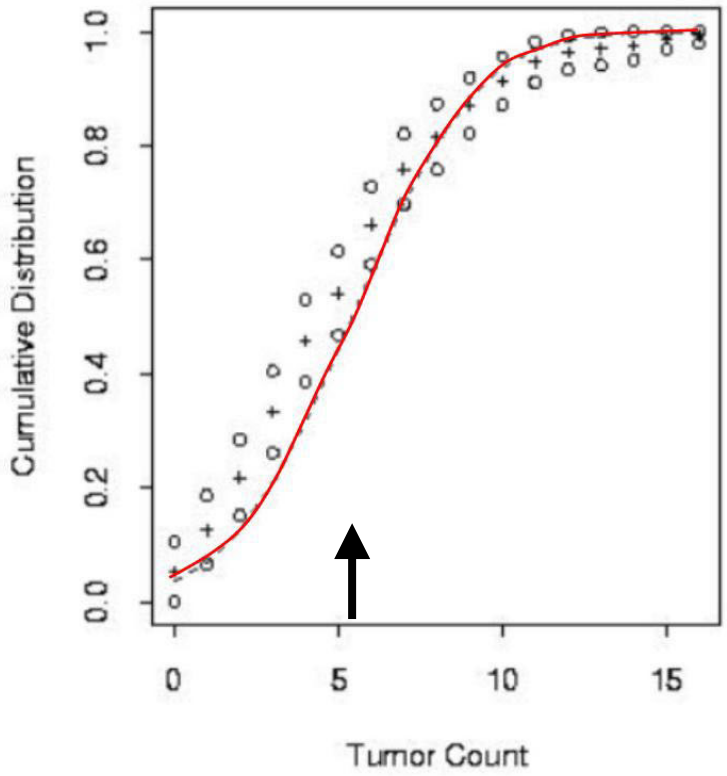


What if data are far away from ideal?

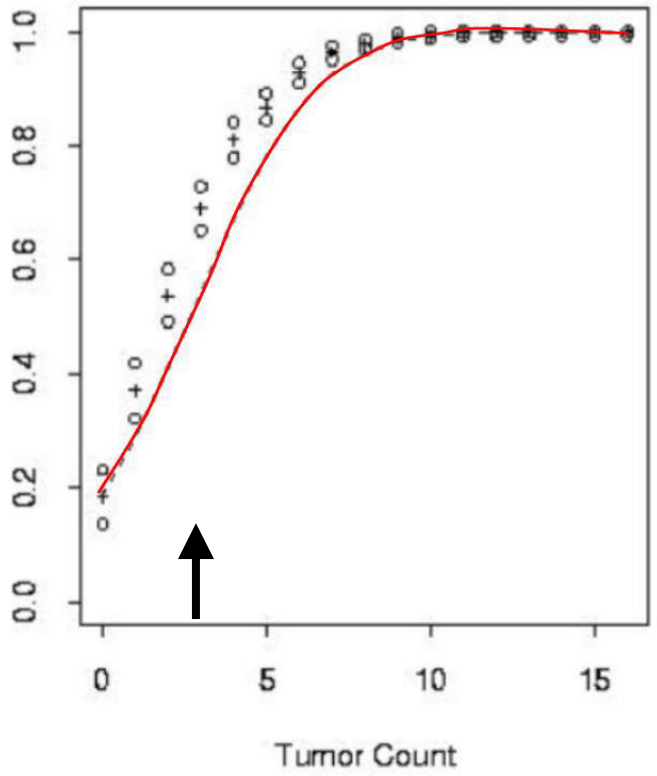


What shape histograms by genotype?

WF/WF



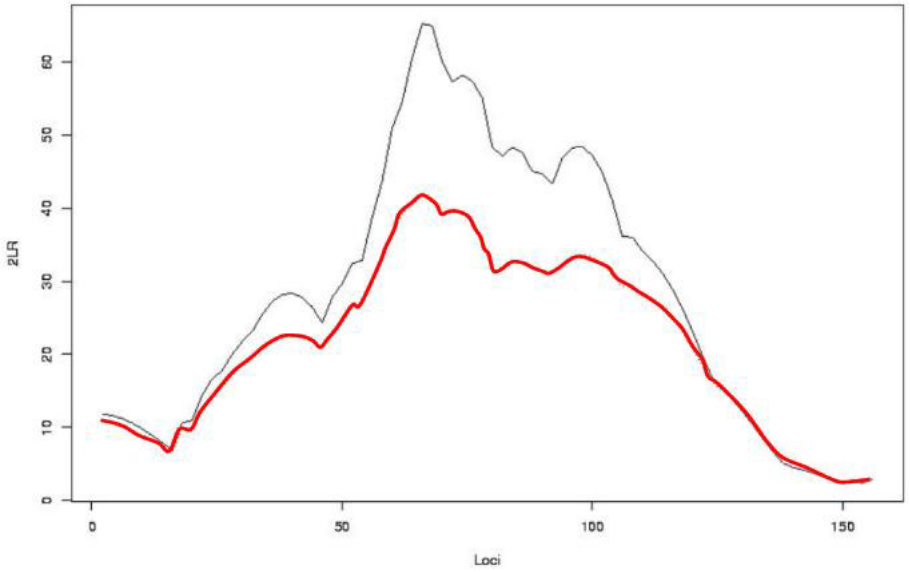
WKy/WF



line = normal, + = semi-parametric, o = confidence interval

What QTL influence flowering time? no vernalization: censored survival

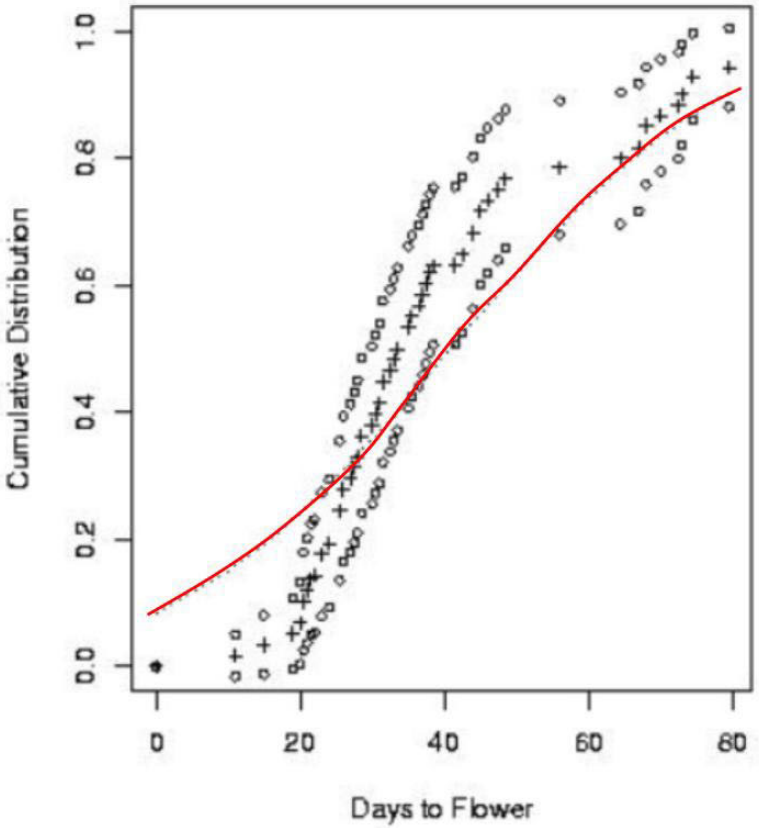
- *Brassica napus*
  - Major female
    - needs vernalization
  - Stellar male
    - insensitive
  - 99 double haploids
- *Y* = log(days to flower)
  - over 50% Major at QTL never flowered
  - log not fully effective



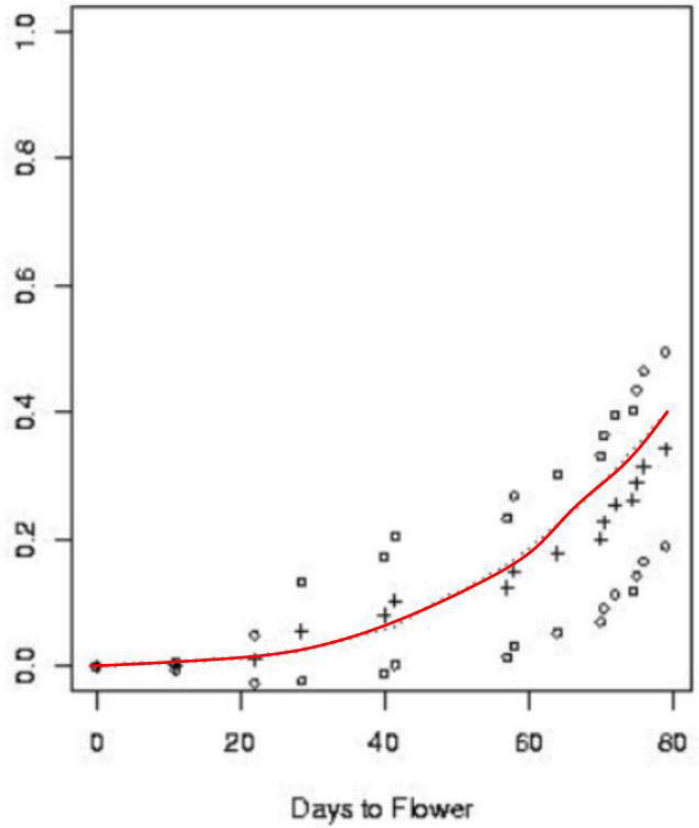
grey = normal, red = non-parametric

What shape is flowering distribution?

B. napus Stellar



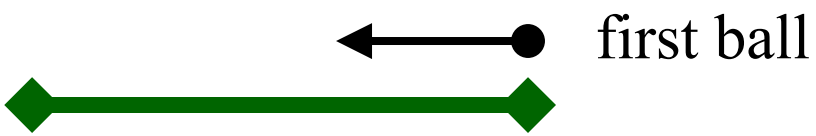
B. napus Major



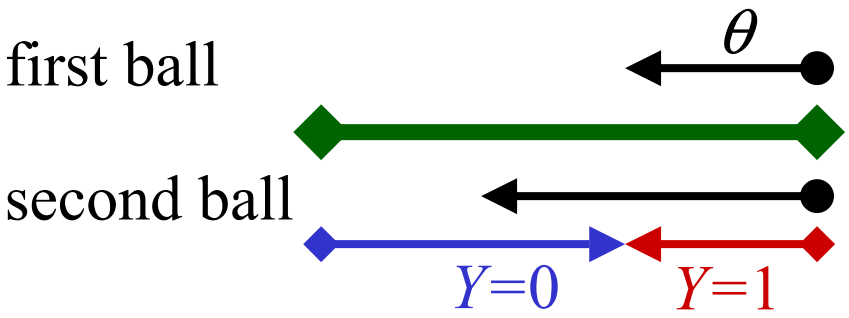
line = normal, + = non-parametric, o = confidence interval

Who was Bayes?

- Reverend Thomas Bayes (1702-1761)
  - part-time mathematician
  - buried in Bunhill Cemetary, Moongate, London
  - famous paper in 1763 *Phil Trans Roy Soc London*
    - Barnard (1958 *Biometrika*), Press (1989) *Bayesian Statistics*
    - Stigler (1986) *History of Statistics*
    - Carlin Louis (1996); Gelman et al. (1995) books
  - Was Bayes the first with this idea? (Laplace)
- billiard balls on rectangular table
  - two balls tossed at random (uniform) on table
  - where is first ball if the second is to its right (left)?



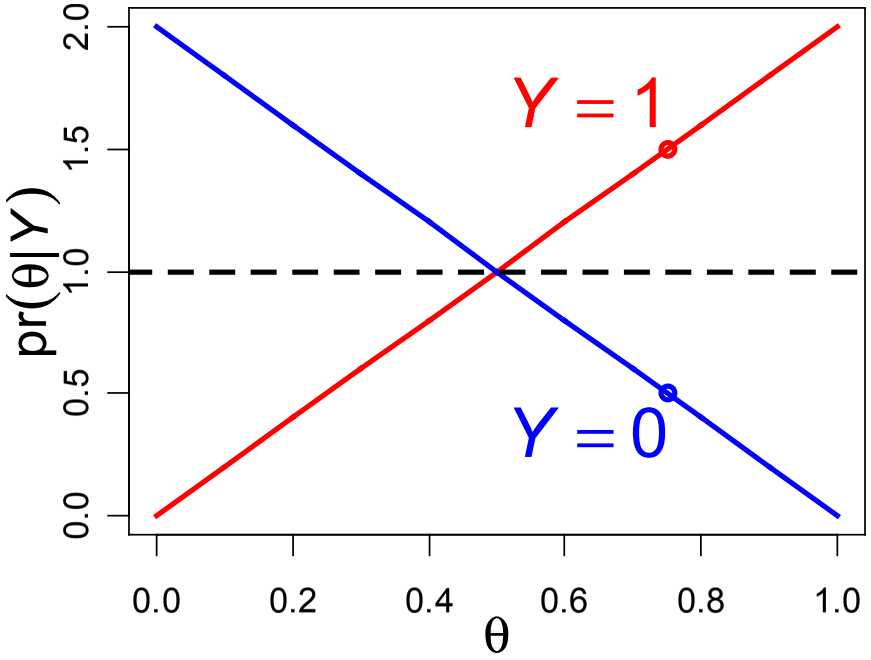
Where is the first ball?



prior $\quad \text{pr}(\theta) = 1$

likelihood $\quad \text{pr}(Y|\theta) = \theta^{Y}(1-\theta)^{1-Y}$

posterior $\quad \text{pr}(\theta|Y) = ?$



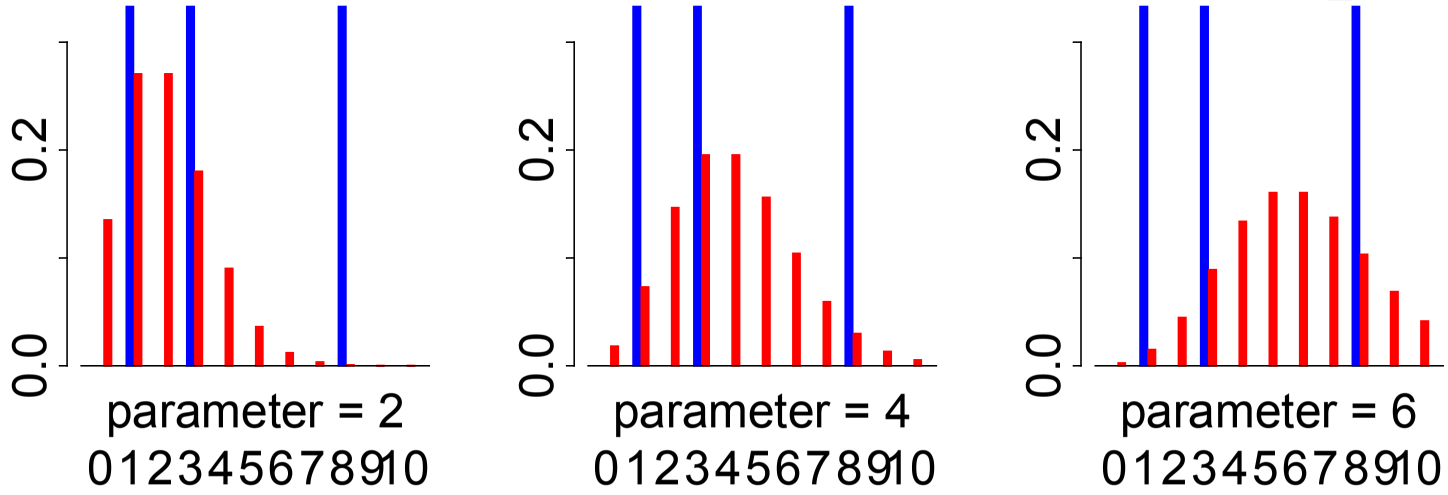
$$\text{pr}(\theta|Y) = \frac{\text{pr}(Y|\theta)\text{pr}(\theta)}{\text{pr}(Y)}$$

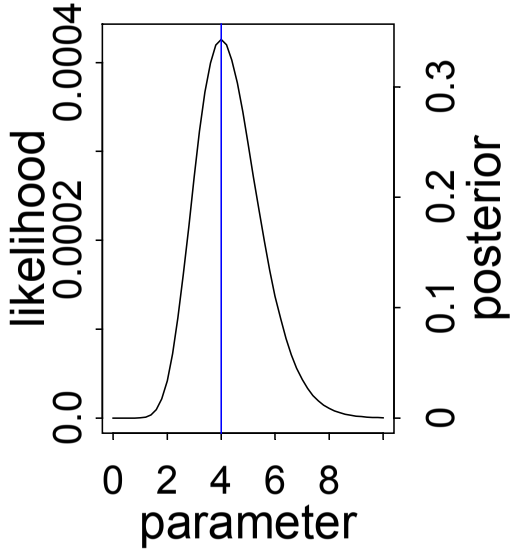
$$\text{pr}(Y) = \int_0^1 \theta^{Y}(1-\theta)^{1-Y}\,d\theta = \frac{1}{2}$$

$$\text{pr}(\theta|Y) = \begin{cases} 2\theta & Y = 1 \\ 2(1-\theta) & Y = 0 \end{cases}$$

(now throw second ball *n* times)

Likelihood and Posterior Example





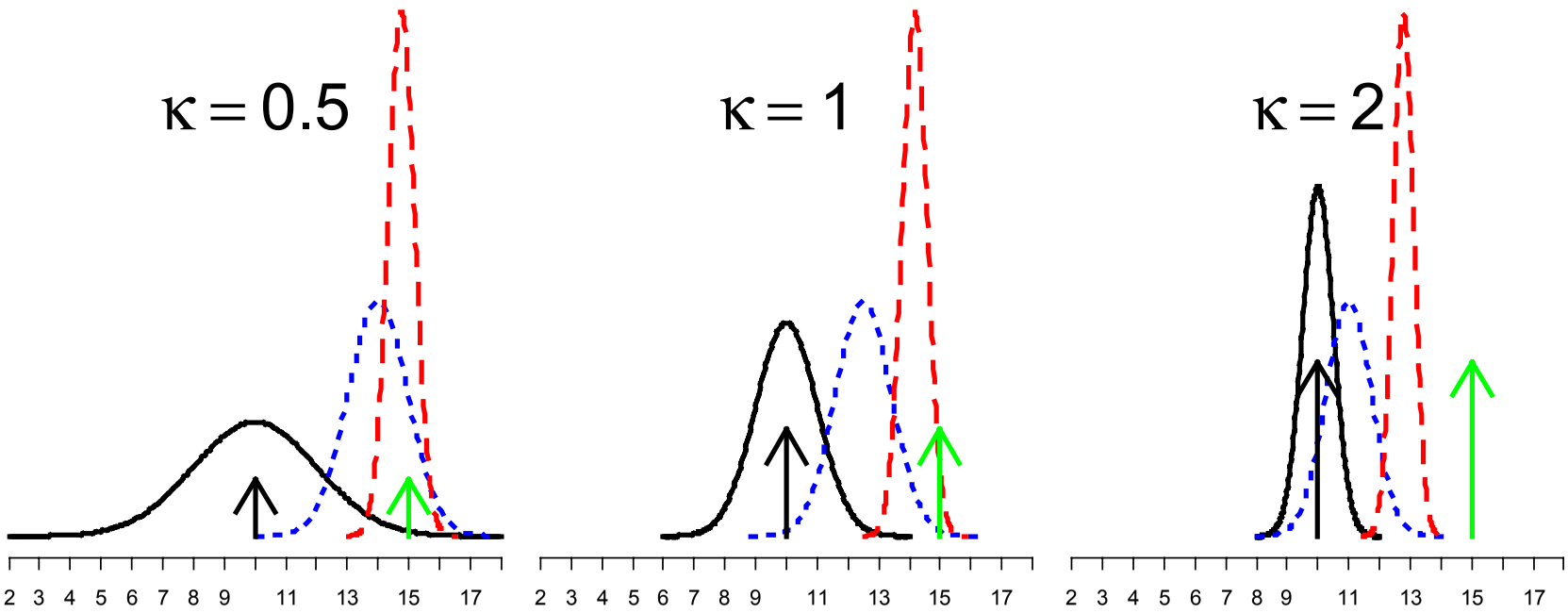
$$\text{data} : Y = 1,3,8$$

$$\text{parameter} : \theta = ?$$

$$\text{pr}(Y = y \mid \theta) = \frac{\theta^y e^{-\theta}}{y!}$$

(M. Newton, pers. comm.)

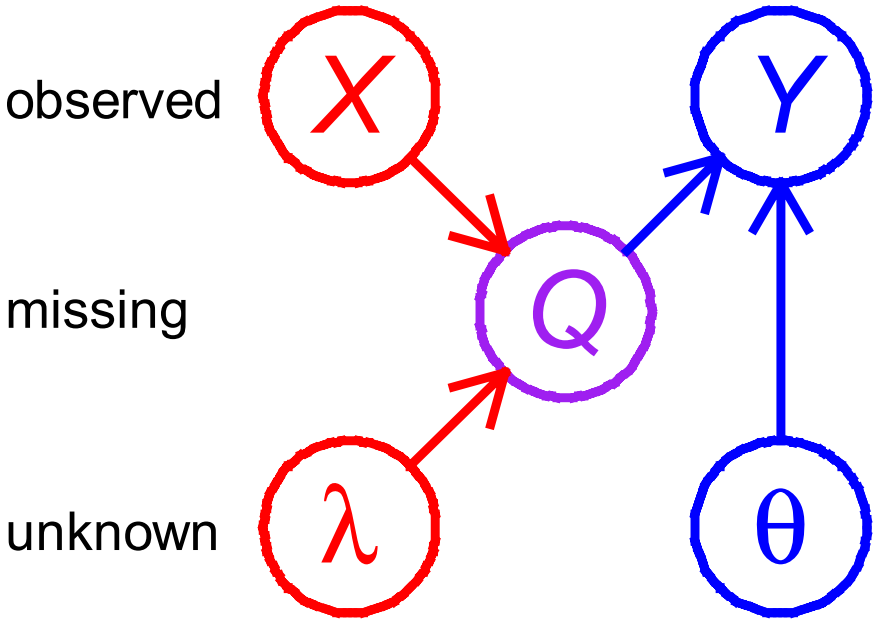
effect of prior variance on posterior



normal prior, posterior for $n = 1$, posterior for $n = 5$, true mean

Bayesian Idea for QTLs

- key idea
  - sample missing genotypes *Q*
    - using recombination model
  - phenotype model given *Q*
    - see previous slides
- methods and philosophy
  - EM & MCMC
  - Frequentists & Bayesians



- review interval maps & profile LODs
- case study: simulated single QTL