Lecture 2. June 7 2019

Recap

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1. Generate $\theta \sim \pi(\cdot)$
2. Generate $\mathcal{D}'$ from the model with parameter θ
3. Choose a set of summary statistics S of the data
   - Compute $S \equiv S(\mathcal{D})$, and $S' = S(\mathcal{D}')$
   - Accept θ if $\rho(S', S) < \epsilon$, where
     - ρ is a metric on the space of Ss

   Return to [1.]

The connection with sufficiency

Note that

$$\rho(S(\mathcal{D}),\, S(\mathcal{D}')) = 0 \;\not\Longrightarrow\; \mathcal{D} = \mathcal{D}'$$

We are employing a dimension-reduction strategy here. There is a connection with sufficiency.

Recall that a statistic $S = S(\mathcal{D})$ is *sufficient* for the parameter θ if

$$\mathbb{P}(\mathcal{D}|S, \theta) \text{ is independent of } \theta$$

If S is sufficient for θ, then

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We are really after a notion of *approximate sufficiency*

Research Question: If we had a measure of how close S is to sufficient, we should be able to metrise the difference between $f(\theta|\mathcal{D})$ and $f(\theta|S)$.

A Normal example – 1

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For the ABC method, assume we observed $\bar{X}_0 = 0$. Then

1. Generate $\mu \sim \mathrm{U}(a, b)$
2. Generate $X_1, \ldots, X_n \sim \mathrm{N}(\mu, \sigma^2)$
3. Accept μ if $\rho(\bar{X}, \bar{X}_0 = 0) = |\bar{X}| \leq \epsilon$

A Normal example – 2

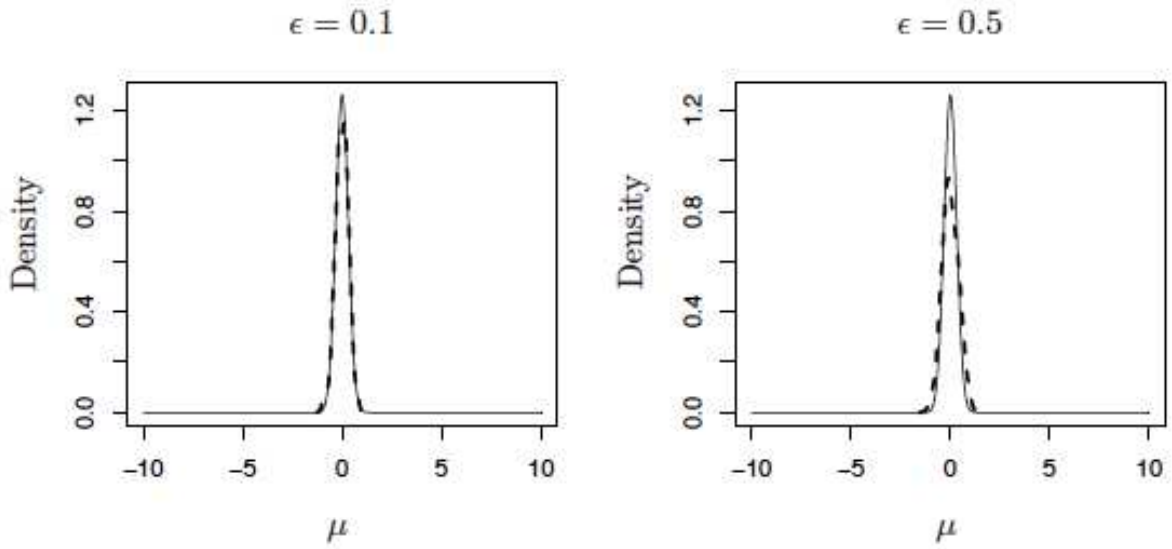

Figure 3.1: *Plots of the true posterior distribution for μ (solid line), and the ABC estimate using 1000 samples (dashed line). A value of $\sigma^2 = 1$ was used for all four plots.*

A Normal example – 3

The ABC density is proportional to

$$\mathbb{1}(a < \mu < b) \int_{-\epsilon}^{\epsilon} (2\pi\sigma^2/n)^{-1/2} \exp(-n(y-\mu)^2/2\sigma^2) dy$$

and the normalizing constant is $\int_a^b () d\mu$. We look at the case where $a \to -\infty, b \to \infty$. Then the normalising constant is 2ϵ, and the density is

$$f_\epsilon(\mu) = \frac{1}{2\epsilon} \left(\Phi\left(\frac{\epsilon - \mu}{\sigma/\sqrt{n}} \right) - \Phi\left(\frac{-\epsilon - \mu}{\sigma/\sqrt{n}} \right) \right)$$

Furthermore,

$$\mathbb{E}(\mu \,|\, |\bar{X}| \leq \epsilon) = 0, \quad \mathrm{Var}(\mu \,|\, |\bar{X}| \leq \epsilon) = \frac{\sigma^2}{n} + \frac{\epsilon^2}{3}$$

A Normal example – 4

Note that the variance shows *overdispersion*: the variance of the ABC method is larger than the true variance

Next we use a Taylor expansion to show that

$$d_{\mathrm{TV}}(f_\epsilon, f) := \frac{1}{2}\int_{-\infty}^{\infty} |f_\epsilon(\mu) - f(\mu)| d\mu \approx \frac{cn\epsilon^2}{\sigma^2} + o(\epsilon^2), \epsilon \to 0$$

Here, $c = \sqrt{\frac{2}{\pi}} e^{-1/2} \approx 0.4839$

Note: This example is from Richard Wilkinson's (2007) DAMTP PhD thesis

Relevant theory from population genetics

Population genetics principles

- Study the effects of mutation, selection, recombination . . . on the structure of genetic variation in natural populations
- Allow for demographic effects such as migration, admixture, subdivision and fluctuations in population size

With the advent of molecular data in the early 1970s, paradigm changed from prospective to retrospective

Drosophila allozyme frequency data

- *D. tropicalis* Esterase-2 locus [$n = 298$]

$$234, 52, 4, 4, 2, 1, 1$$

- *D. simulans* Esterase-C locus [$n = 308$]

$$91, 76, 70, 57, 12, 1, 1$$

What is expected under neutrality?

Sewall Wright (vol. 4, p303) argued that

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What was needed . . .

. . . the null distribution of the numbers $\boldsymbol{C}(n) = (C_1(n), \ldots, C_n(n))$ of alleles represented j times in a sample of size n

The Ewens Sampling Formula [1972]

The distribution of the counts in a sample of size n with mutation parameter θ:

$$\mathbb{P}[C_j(n) = c_j, j = 1, 2, \ldots, n]$$

$$= \frac{n!}{\theta(\theta+1)\cdots(\theta+n-1)} \prod_{j=1}^{n} \left(\frac{\theta}{j}\right)^{c_j} \frac{1}{c_j!}$$

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Its distribution can be simulated very rapidly using Chinese Restaurant Process or Feller Coupling, and a rejection method with $\theta = K/\log(n)$

Consequences

- *D. tropicalis* Esterase-2 locus [$n = 298$]

  234 52 4 4 2 1 1 $F = 0.647, 95\% \ (0.226, 0.818)$

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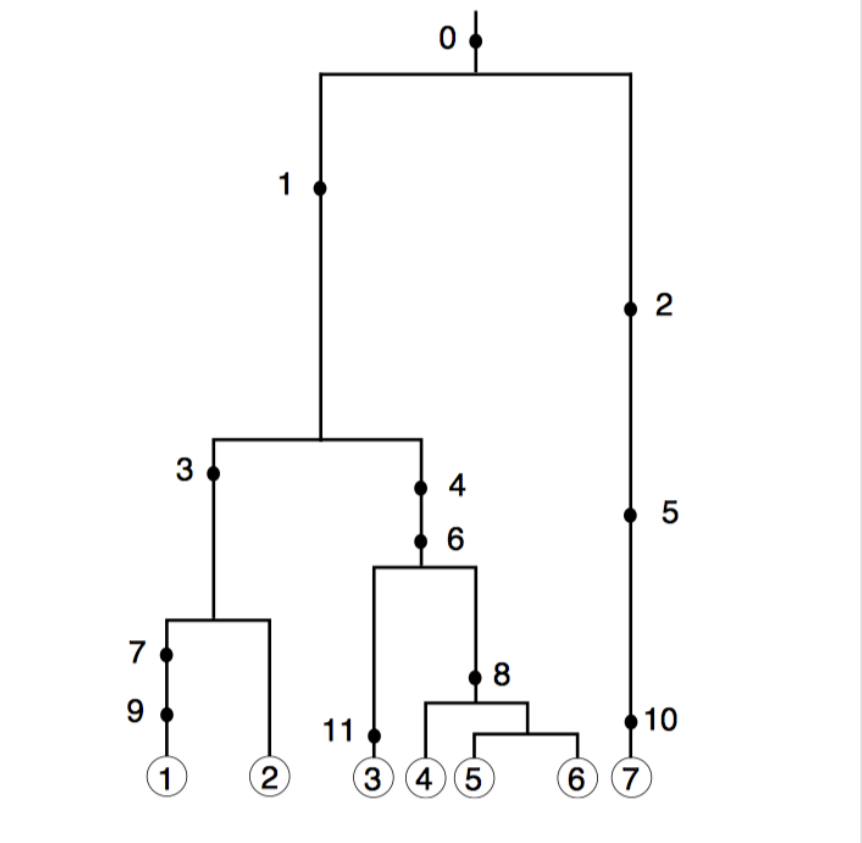
The Maximum Likelihood Estimator $\hat{\theta}_n$ of θ is asymptotically Normal with mean θ variance proportional to $1/\log n$. The slow rate is because of dependence . . .

The coalescent (Kingman 1982)

Infinitely many sites/alleles model



gene 1	(9,7,3,1,0)
gene 2	(3,1,0)
gene 3	(11,6,4,1,0)
gene 4	(8,6,4,1,0)
gene 5	(8,6,4,1,0)
gene 6	(8,6,4,1,0)
gene 7	(10,5,2,0)

What this led to . . .

- Measure-valued processes, lambda coalescents
- Inference for stochastic processes, including ABC
- Coalescent (and related branching process) simulators
- Applications to statistical genetics, human disease, evolutionary biology
- Non-parametric Bayesian inference, clustering
- Useful paradigm for cancer, in which the individuals are cells (and we model cell division)

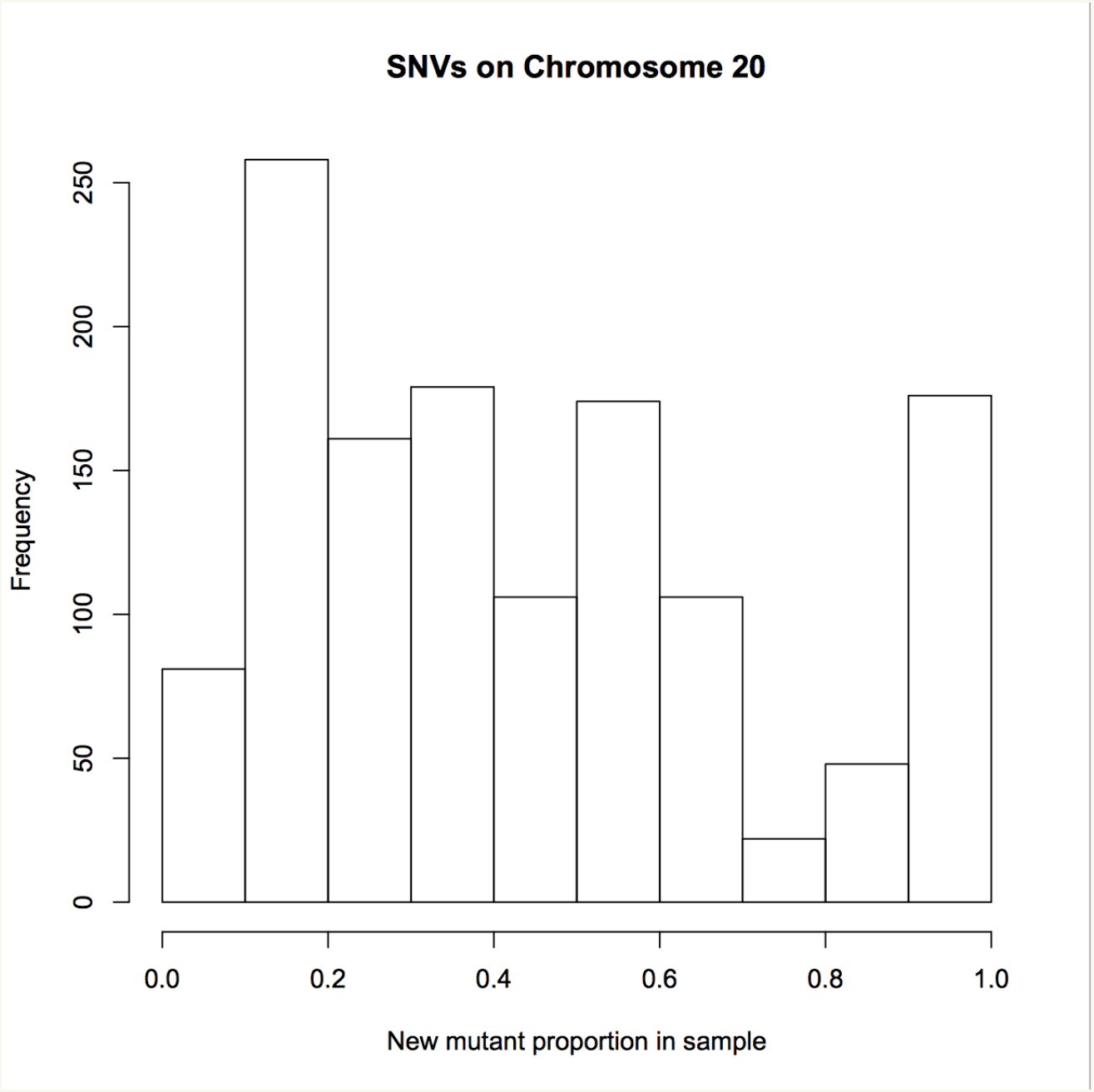
A substantive example from the cancer genomics world (in progress)

Cancer data: Nik-Zainal et al, *Cell*, 2012

Full data: number of SNVs s = 27,719 (the read counts have been processed to provide allele frequency estimates at each SNV)

chr	1	2	3	4	5	6	
#snv	1110	4885	4032	1728	3725	27	
chr	8	9	10	12	13	14	16
#snv	5	164	2702	1	1	3	1253
chr	17	18	19	20	21	22	X
#snv	1286	320	1387	1311	232	243	3304

Binned site frequency spectrum



Another look at sequence data

$$
\begin{array}{c}
 & \begin{array}{ccccccc} m_1 & m_2 & m_3 & m_4 & m_5 & \cdots & m_s \end{array} \\
\begin{array}{c} h_1 \\ h_2 \\ h_3 \\ h_4 \\ \vdots \\ h_n \end{array} &
\left[\begin{array}{ccccccc}
0 & 1 & 1 & 0 & 0 & \cdots & 0 \\
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0 denotes ancestral type, 1 the mutant type

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f_i = number of mutant copies at ith site (known)

K = number of *distinct* haplotypes (not known)

The site frequency spectrum (SFS)

$$
\begin{array}{c}
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$$

Compute

$$
\begin{aligned}
M_b &= \text{number of sites carrying } b \text{ copies of the mutant} \\
&= \#\{l | f_l = b\}, b = 1, 2, \ldots, n-1
\end{aligned}
$$

$\boldsymbol{M}(n) = (M_1, M_2, \ldots, M_{n-1})$ is the observed SFS

Some theory

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For many settings, including most branching processes, simulation is required

Some theory

For the SFS, there are corresponding results, the simplest of which is

$$\mathbb{E}M_b = \frac{\theta}{b}, b = 1, 2, \ldots, n-1$$

and many papers have discussed other features of the counts. For example, Dahmer and Kersting (2015) showed that

$$\boldsymbol{M}(n) \Rightarrow (P_1, P_2, \ldots) \quad \text{as } n \to \infty$$

where the P_i are independent Poisson random variables with $\mathbb{E}(P_i) = \theta/i$.

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We do this in a Bayesian setting (is there any other way?)

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The combinatorics are not simple here, and explicit results seem hard to come by ...

Back to cancer sequencing: some challenges

- Pooled samples of cells of mixed type are sequenced – a mixture of tumor and non-tumor cells
  - Experiments are rather like Pool-Seq, but the sample size n is not known

- Want to know about number of clones in the sample (akin to K)

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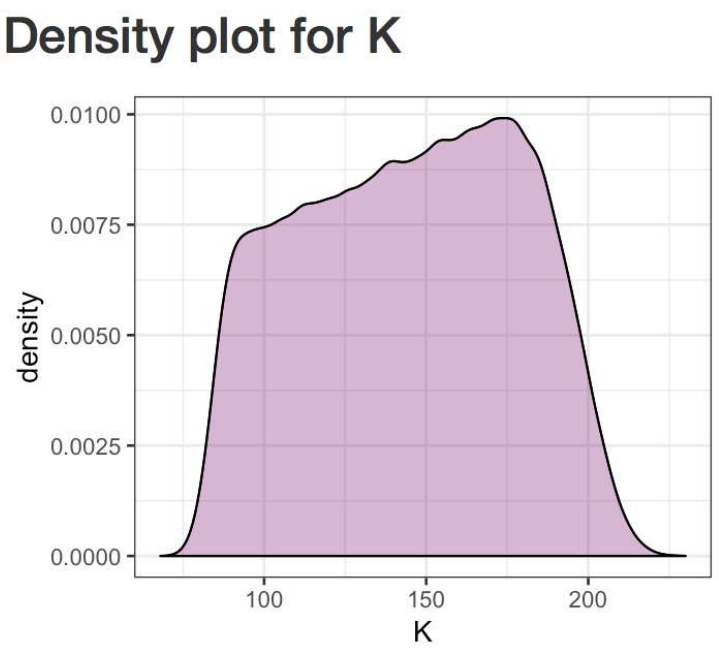
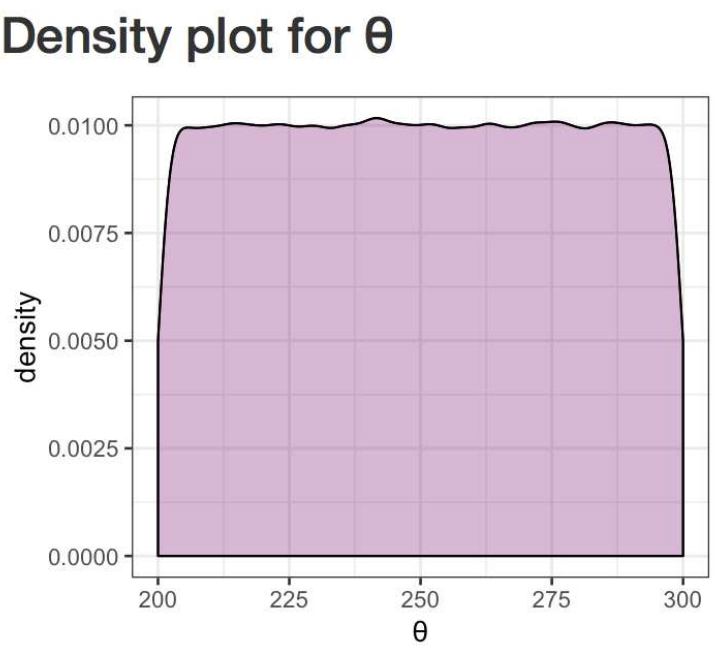
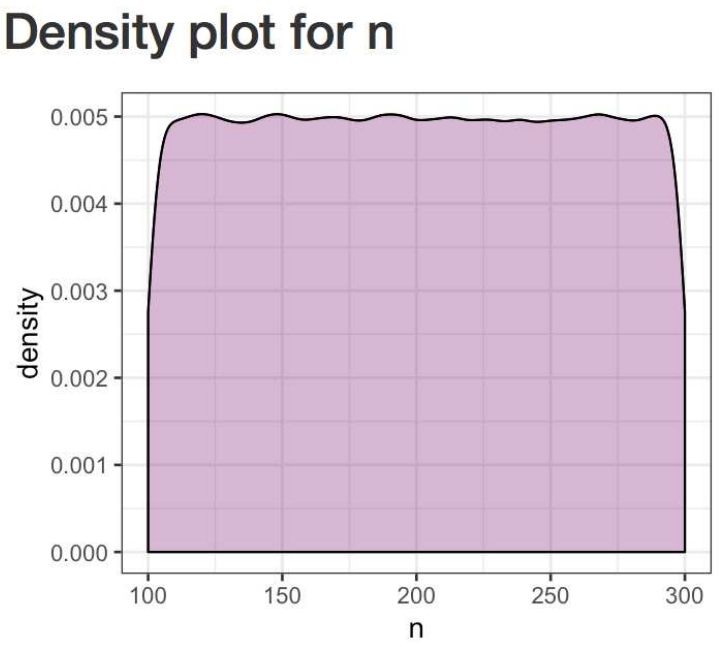
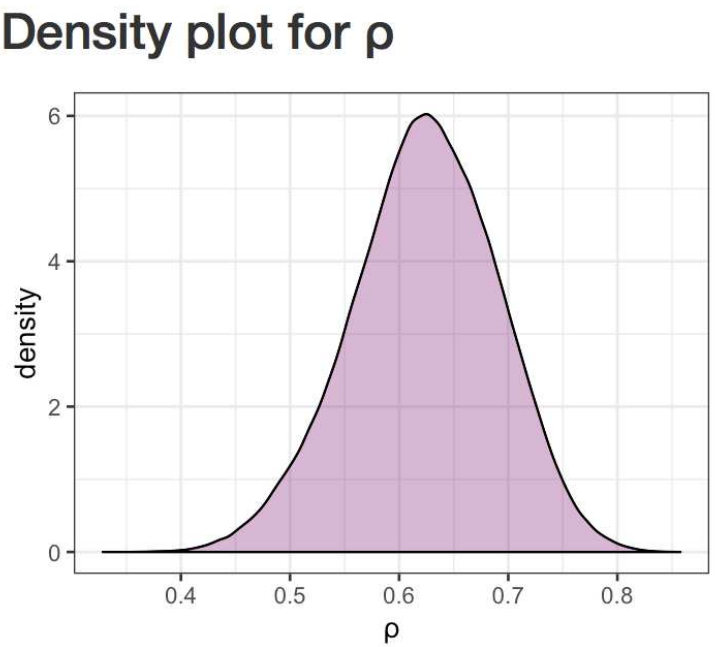
- Want $\mathcal{L}(K, n, \theta \mid (p_1, \ldots, p_{10}))$
  - Generated 500,000 samples
  - The 1% point of ρ values is 0.46

What happened? . . . priors

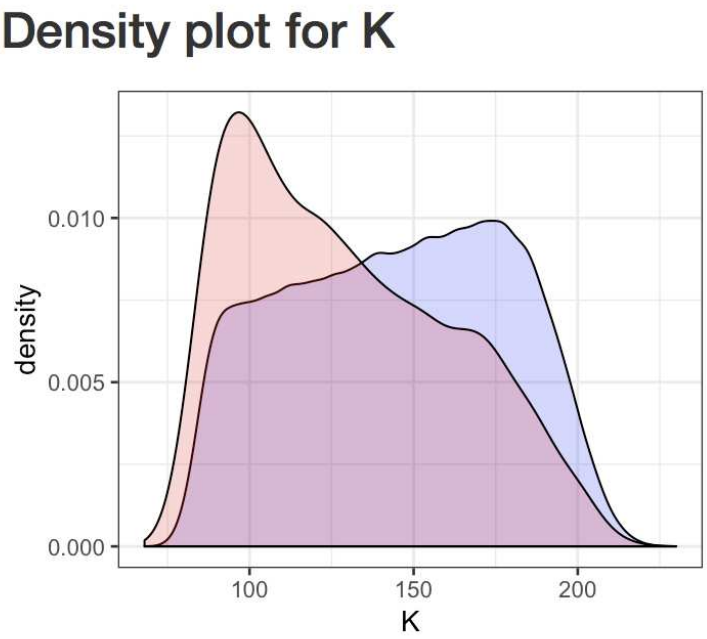


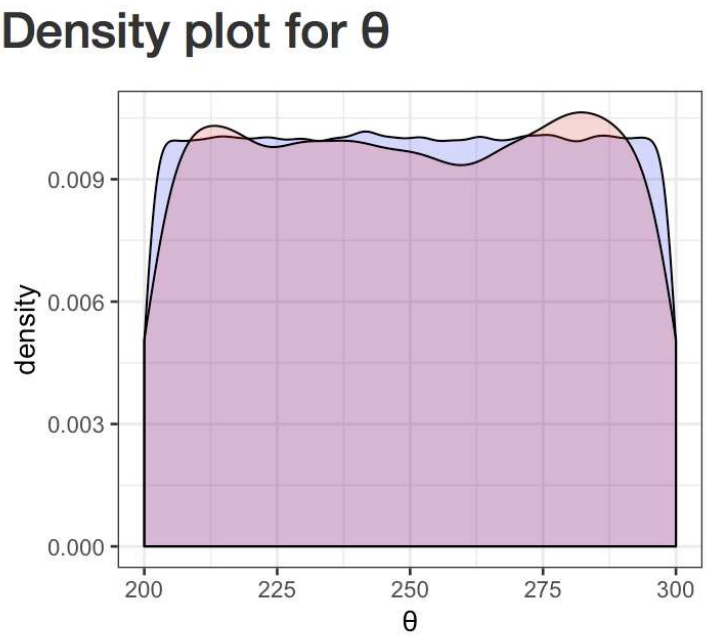


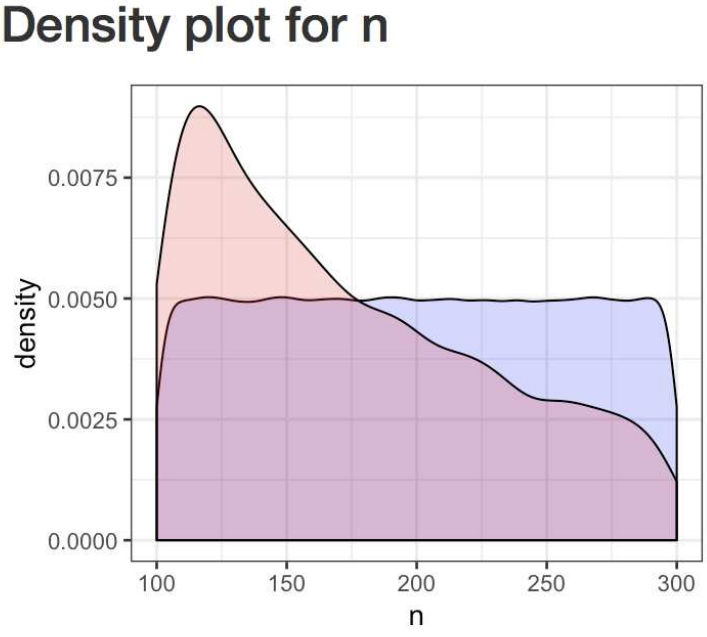


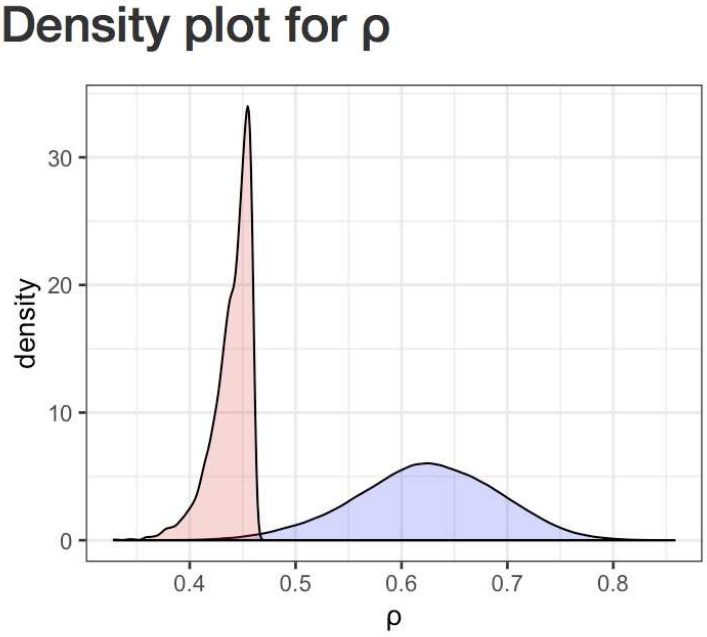


What happened? . . . posteriors









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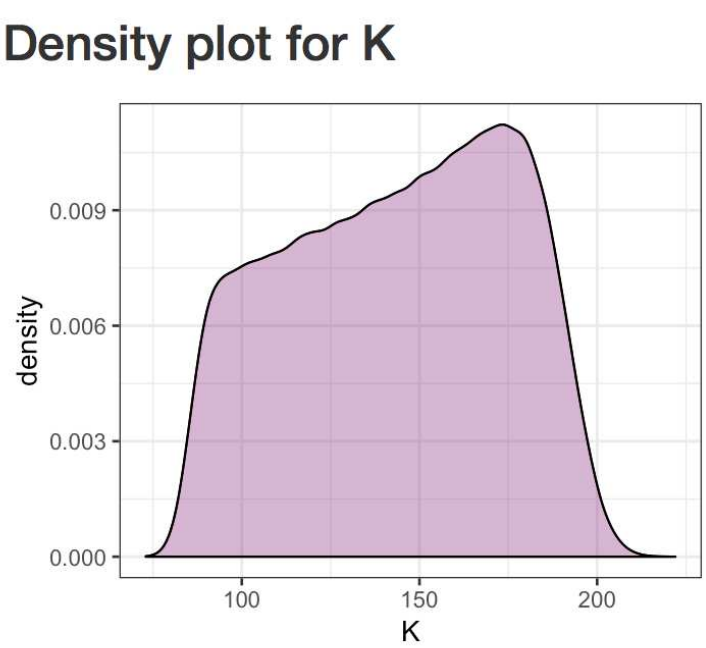
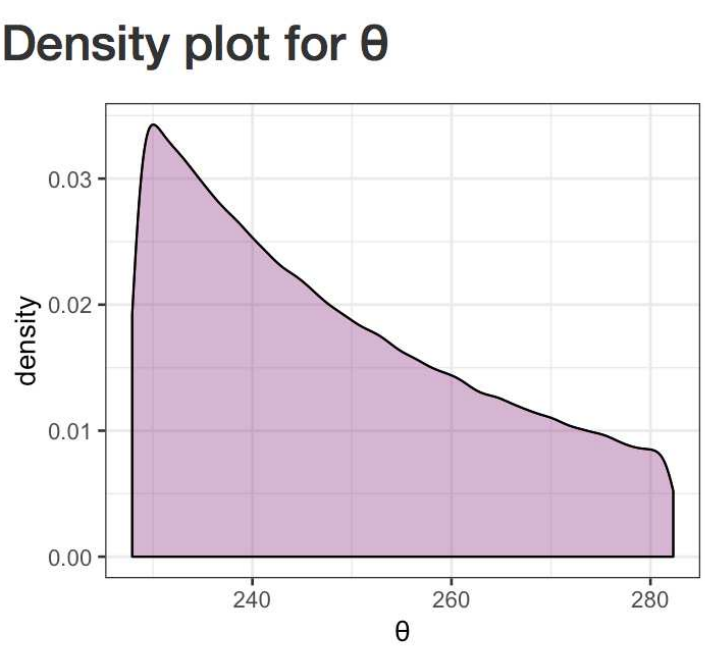
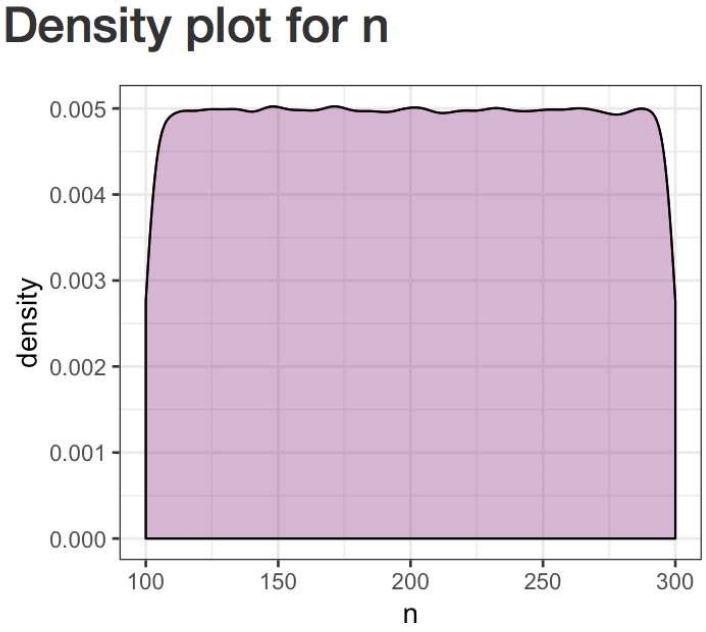
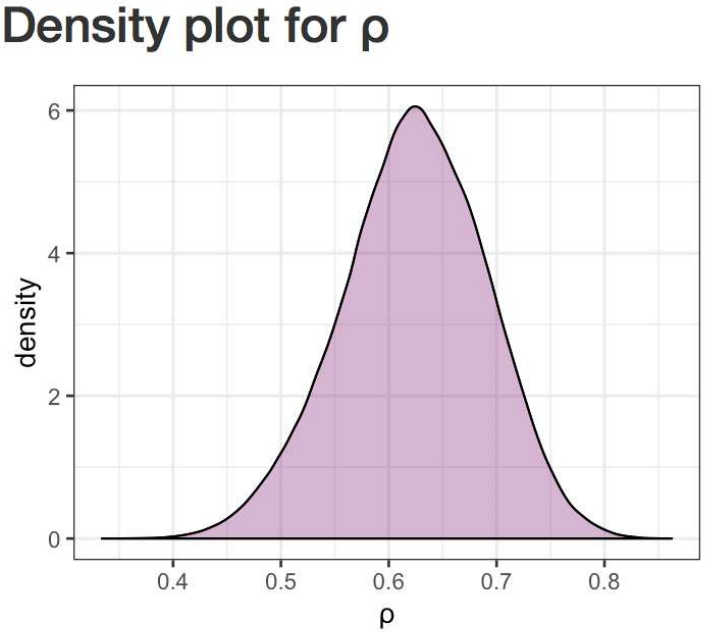
- $s \approx 1300$
- Prior for n: uniform on (100,300)
- $\theta = s/\log(n)$

What happened? . . . priors









What happened? . . . posteriors