Algorithmique pour la bioinformatique

1. Modélisation stochastique et inférence probabiliste

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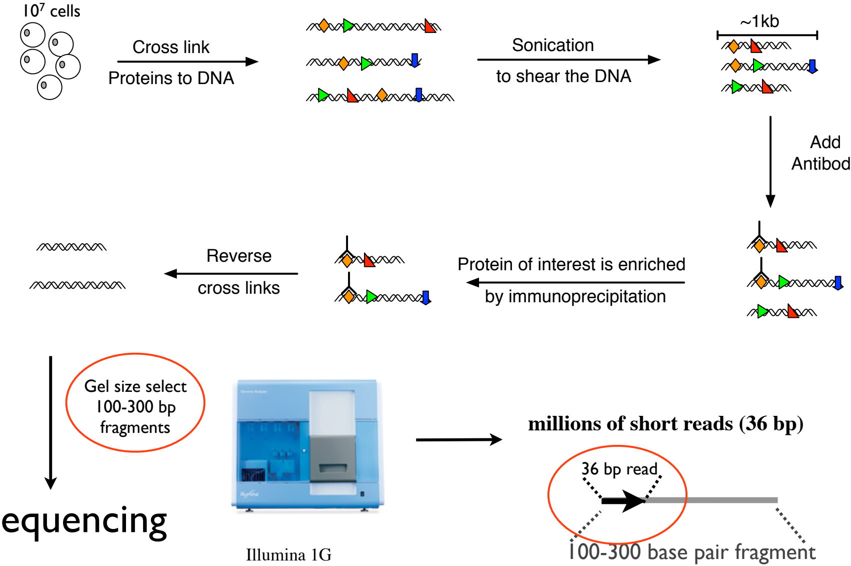
1. Introduction
2. Random variables
3. Maximum likelihood and Bayesian inference
4. Summary

La bioinformatique aujourd'hui

Exemples de problèmes et de questions

- recherche de séquences homologues (blast)
- alignement de séquences
- NGS (next generation sequencing)
- → génotypage, SNP calling, Chip-Seq

Chip-Seq



10^7 cells

Cross link

Proteins to DNA

Sonication

to shear the DNA

~1kb

Add Antibody

Protein of interest is enriched

by immunoprecipitation

Reverse

cross links

Gel size select 100-300 bp fragments

Sequencing

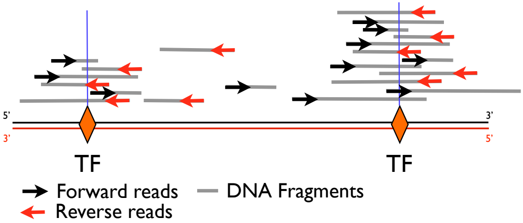
Illumina 1G

millions of short reads (36 bp)

36 bp read

100-300 base pair fragment

Chip-Seq



- binding, cross-linking: → noisy processes
- uneven coverage, small number of reads
- → stochastic signal
- alignment and sequencing errors

La bioinformatique aujourd’hui

Exemples de problèmes et de questions

- recherche de séquences homologues (blast)
- alignement de séquences
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Enjeux et défis

- calculs complexes: algorithmique sophistiquée
- données bruitées (erreurs de séquençage, d’alignement)
- problèmes complexes et imbriqués les uns dans les autres
- → modéliser les erreurs et prendre en compte l’incertitude
- → intégrer question de fond et analyse des données.

Modélisation stochastique

Modèles

- construire des modèles probabilistes qui formalisent
- les processus sous jacents (évolution, génétique, biophysique)
- le protocole d'acquisition de données (séquençage, etc)

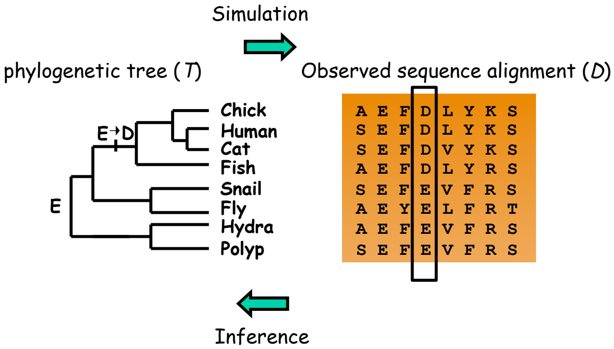
Paramètres

- certains paramètres connus
- exemple: méthodes de séquençage: taux d'erreur connus
- d'autres paramètres sont inconnus → estimation
- paramètres d'intérêt / paramètres de nuisance

Séparation des tâches

- modélisation stochastique: formaliser hypothèses sur processus
- paradigme statistique: principes d'inférence/prédiction
- algorithmes: implémenter ces principes sur ces modèles

Modèles probabilistes: simulation et inférence



A	E	F	D	L	Y	K	S
S	E	F	D	L	Y	K	S
S	E	F	D	V	Y	K	S
A	E	F	D	L	Y	R	S
S	E	F	E	V	F	R	S
A	E	Y	E	L	F	R	T
A	E	F	E	V	F	R	S
S	E	F	E	V	F	R	S

Modélisation stochastique et inférence probabiliste

- modéliser: expliciter les hypothèses quant au processus
- simuler: en prédire les conséquences observables
- estimer paramètres: ajuster simulateur → reproduire l’observé

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Heterozygosity: Bernoulli distribution

```
...AACAAATTAATACGGTACAGTCTATTGTG...
...AACGAATTAATAGGGTACTGTCGATTGTG...
...0001000000000100000100010000000...
```

- in humans, one out of 1000 positions heterozygous on average
- mean heterozygosity $\theta = 0.001$

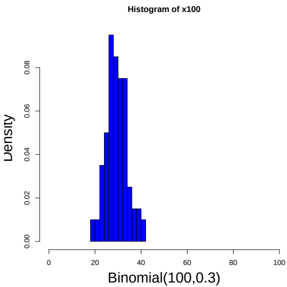
Bernoulli variable

- a position *i* is taken at random
- heterozygosity h_i
- $h_i \sim Bernoulli(\theta)$
- $h_i = 1$ with prob θ, $h_i = 0$ with prob $1 - \theta$

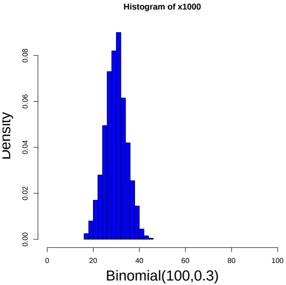
Simulating a binomial random variable

repeat N times

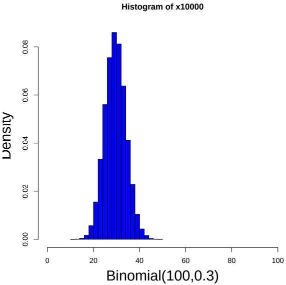
- simulate a sequence $h = (0, 1, 0, ...)$ of length n
- for each $i = 1..n$, $h_i = 1$ with prob θ and 0 with prob $1 - \theta$
- count $k =$ total number of 1's out of n



$N = 100$



$N = 1,000$



$N = 100,000$

Discrete random variable

definitions

- this program implements a *random variable* K over integers
- the value of a *draw* (or *outcome*) is denoted by a lower case k
- K is the *random variable*, and k the value that it takes
- this random variable has a *probability distribution* $p(k) = \Pr(K = k)$
- $p(k) = \lim_{N \to +\infty} f_N(k)$
- where $f_N(k)$, the frequency of outcome $K = k$

An algorithmic representation of random variables

random variable		algorithm
sampling from its distribution	$\Longleftrightarrow$	running the program
probability		asymptotic frequency over runs
expectations		averages over runs

The Bernoulli and Binomial distributions

Bernoulli distribution

- $h_i \sim \mathit{Bernoulli}(\theta)$
- $h_i = 1$ with prob θ, $h_i = 0$ with prob $1 - \theta$

- A sequence $h = (0, 1, 1, 0, \ldots)$ of n positions, k 1's and $n - k$ 0's

  $p(h \mid \theta) = (1 - \theta)\, \theta\, \theta\, (1 - \theta) \ldots = \theta^k (1 - \theta)^{n-k}$
- Number of distinct sequences with k 1's and $n - k$ 0's:

  $Q(k, n) = \binom{n}{k} = \frac{n!}{k!(n-k)!}$

Binomial distribution

probability that sequence h contains k 1's out of n

$p(k \mid \theta) = \binom{n}{k} \theta^k (1 - \theta)^{n-k}$

Heterozygosity: binomial distribution

```
...AACAAATTAATACGGTACAGTCTATTGTG...
...AACGAATTAATAGGGTACTGTCGATTGTG...
...00010000000010000010001000000...
```

- in humans, one out of 1000 positions heterozygous on average
- mean heterozygosity $\theta = 0.001$

Binomial variable

- *n* positions are considered
- *k*: number of heterozygous positions
- $k \sim \mathit{Binomial}(n, \theta)$

Heterozygosity: geometric distribution

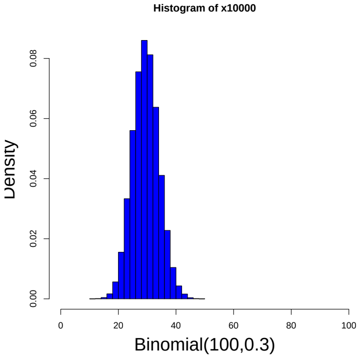
```
...AACAAATTAATACGGTACAGTCTATTGTG...
...AACGAATTAATAGGGTACTGTCGATTGTG...
...00010000000010000010001000000...
```

- in humans, one out of 1000 positions heterozygous on average
- mean heterozygosity $\theta = 0.001$

Geometric variable

- starting from position i, such that $h_i = 1$
- how many positions m until the next heterozygous position h_{i+m}?
- $m \sim Geometric(1 - \theta)$
- $p(m) = (1 - \theta)^{m-1}\theta$

Expectation



- make N draws, $(k_n)_{n=1..N}$
- define $m_N = \frac{1}{N}\sum_{n=1}^{N} k_n$
- $\lim_{N\to+\infty} m_N$?

Expectation and variance

Expectation

$$\overline{k} = E[k] = \lim \frac{1}{N} \sum_{n=1}^{N} k_n \quad = \quad \sum_k p(k)\, k$$

Variance

$$V[k] = E[(k - \overline{k})^2] = \lim \frac{1}{N-1} \sum_{n=1}^{N} (k_n - \hat{k})^2 \quad = \quad \sum_k p(k)\,(k - \overline{k})^2$$

Expectation in simple cases

- $h \sim Bernoulli(\theta)$: $E[h] = ?$
- $k \sim Binomial(n, \theta)$: $E[k] = ?$
- $m \sim Geometric(r)$: $E[m] = ?$

Expectation in simple cases

- $h \sim Bernoulli(\theta)$: $E[h] = \theta$
- $k \sim Binomial(n, \theta)$: $E[k] = n\theta$
- $m \sim Geometric(r)$: $E[m] = 1/(1 - r)$

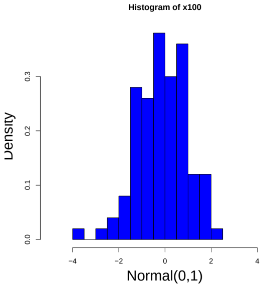
Expectation of a function g

- make N draws, $(k_n)_{n=1..N}$
- define $g_N = \frac{1}{N}\sum_{n=1}^{N} g(k_n)$
- $\lim_{N\to+\infty} g_N$?

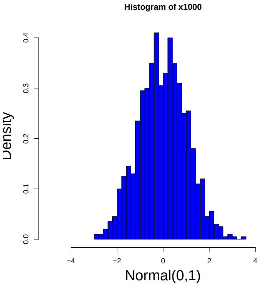
Expectation of g

$$\lim_{N\to+\infty} g_N = E[g] = \sum_k p(k)\, g(k)$$

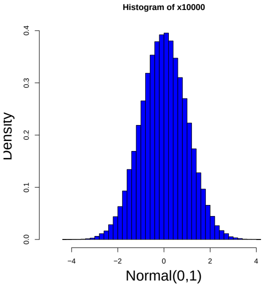
Continuous random variable (Normal)



100 draws



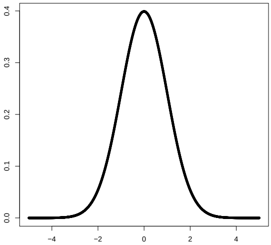
1, 000 draws



100, 000 draws

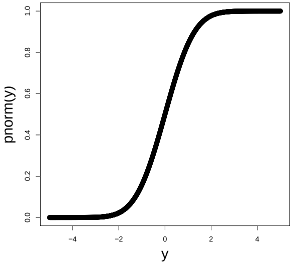
density / cumulative distributions

probability density function



$$p(x)dx = Pr(x < X < x + dx)$$

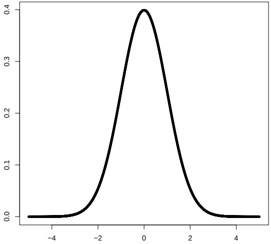
cumulative distribution function



$$F(x) = \Pr(X < x)$$

$$F(x) = \int_{-\infty}^{x} p(u)du$$

Expectation. Continuous case



- make N draws, $(x_n)_{n=1..N}$
- define $m_N = \frac{1}{N}\sum_{n=1}^{N} x_n$

Expectation of x

$$\lim_{N \to +\infty} m_N = \overline{x} = E[x] = \int_{-\infty}^{+\infty} p(x)\, x\, dx$$

Expectation and variance

Expectation

$$\overline{x} = E[x] = \lim \frac{1}{N} \sum_{n=1}^{N} x_n = \hat{x} \quad = \quad \int_{-\infty}^{+\infty} p(x)\, x \, dx$$

Variance

$$V[x] = E[(x - \overline{x})^2] = \lim \frac{1}{N-1} \sum_{n=1}^{N} (x_n - \hat{x})^2 \quad = \quad \int_{-\infty}^{+\infty} p(x)\, (x - \overline{x})^2 \, dx$$

Expectation of any function *g*

$$\lim_{N \to +\infty} g_N = E[g] = \int_{-\infty}^{+\infty} p(x)\, g(x)\, dx$$

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ML in a simple case: frequency of a neutral allele

problem

- 2 alleles at a locus: 0 and 1
- We type $n = 5$ individuals, among which $k = 3$ were of type 1.
- θ: (unknown) proportion of allele 1 in population.
- how to estimate θ?

fast estimate

- just compute the empirical frequency: $\frac{k}{n}$

maximum likelihood approach

- if θ were known, what would be the probability of $k = 3$ out of 5?
- this defines the likelihood $L(\theta) = p(k \mid \theta)$
- your estimator is the value of $\hat{\theta}$ that maximises the likelihood $L(\theta)$

The Bernoulli and Binomial distributions

- each individual has genotype 1 with prob θ (0 with prob $1 - \theta$)
- genotype is $\sim$ *Bernoulli*(θ)

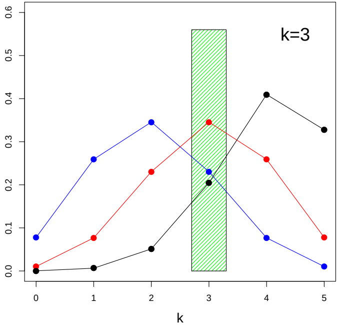
number k of individuals with genotype 1:

- $k \sim \mathit{Binomial}(n, \theta)$
- $p(k \mid \theta) = \binom{n}{k}\theta^k(1-\theta)^{n-k}$

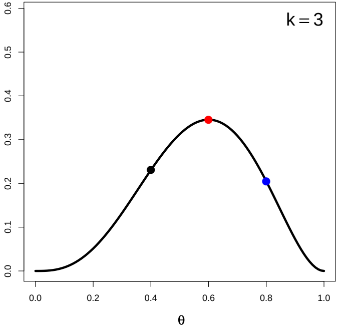
The likelihood

$$p(k \mid \theta) \propto \theta^k (1-\theta)^{n-k}$$

as a function of k, for fixed θ:

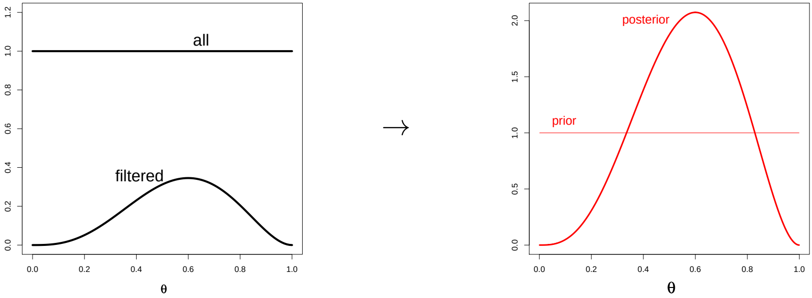


as a function of θ, for fixed k:



$p(k \mid \theta)$ is maximized for $\hat{\theta} = 0.6$.

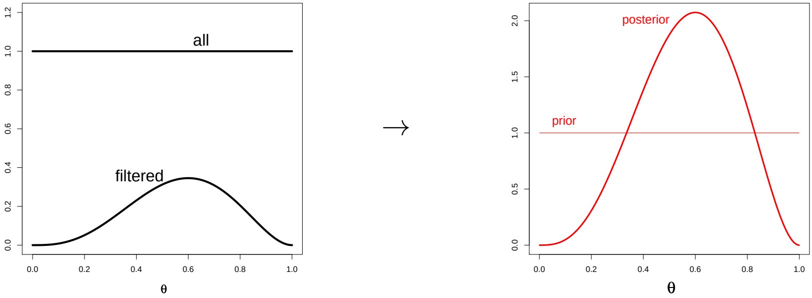
Rejection sampling: the meaning of Bayes theorem



Algorithm

- draw θ uniformly in $(0, 1)$
- given θ, draw $k \sim Binom(n, \theta)$
- keep θ only if $k = 3$, and iterate

Rejection sampling: the meaning of Bayes theorem



- distribution of all draws: prior distribution
- renormalized distribution of accepted draws: posterior distribution
- area under curve: marginal likelihood ($p(k = 3)$ regardless of θ)

Bayes theorem

Model with parameters θ. Data D

Bayes theorem

$$p(\theta \mid D) = \frac{p(D \mid \theta)p(\theta)}{p(D)}$$

$$p(\theta \mid D) \propto p(D \mid \theta)p(\theta)$$

Interpretation

$p(\theta)$: prior: our state of knowledge
before seeing D

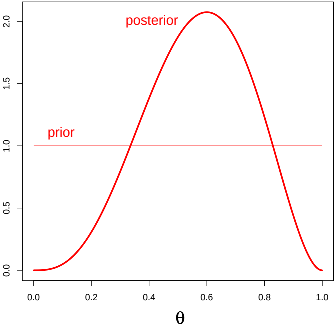
$p(D \mid \theta)$: likelihood: information contained in D about θ

$p(\theta \mid D)$: posterior: our state of knowledge
once we have observed D.

Bayesian inference on θ; uniform prior

Bayes theorem

$$p(\theta \mid k) \quad \propto \quad p(k \mid \theta) p(\theta)$$



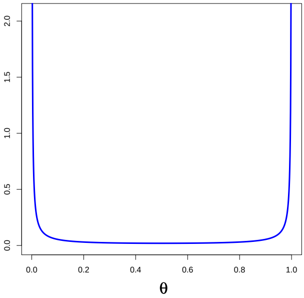
prior	$p(\theta)$	$\propto$	1
likelihood	$p(k \mid \theta)$	$\propto$	$\theta^k (1-\theta)^{n-k}$
posterior	$p(\theta \mid k)$	$\propto$	$\theta^k (1-\theta)^{n-k}$

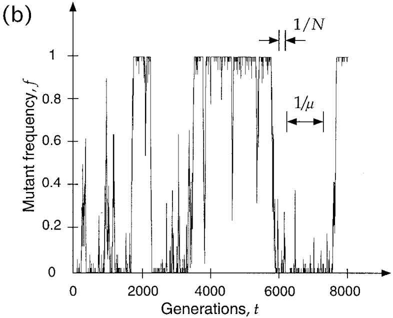
Choice of prior on θ

frequency distribution of neutral alleles under low mutation rate $\beta = 4Nu$

$$p(\theta) \quad \propto \quad \theta^{\beta-1}(1-\theta)^{\beta-1}$$

can be used as our prior

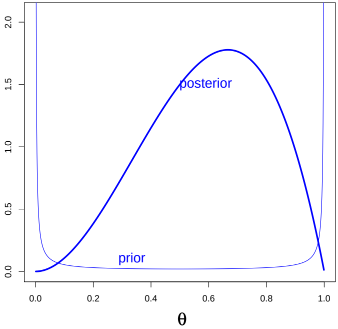




Bayesian inference on θ; neutral prior

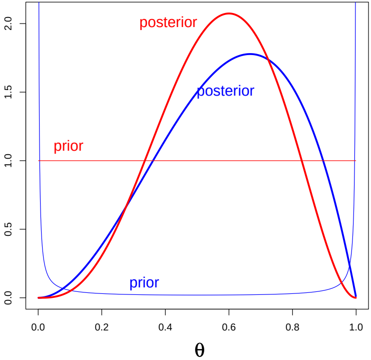
Bayes theorem

$$p(\theta \mid k) \quad \propto \quad p(k \mid \theta) p(\theta)$$



$$\begin{array}{llll} \text{prior} & p(\theta) & \propto & \theta^{\beta-1}(1-\theta)^{\beta-1} \\ \text{lik.} & p(k \mid \theta) & \propto & \theta^{k}(1-\theta)^{n-k} \\ \text{post.} & p(\theta \mid k) & \propto & \theta^{k+\beta-1}(1-\theta)^{n-k+\beta-1} \end{array}$$

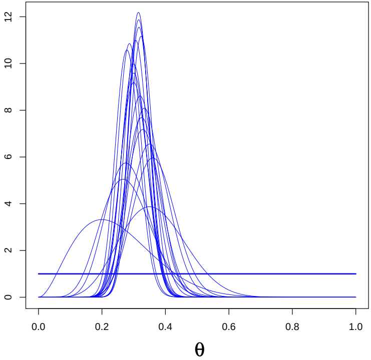
Prior sensitivity



red: uniform prior

blue: neutral prior

Increasing number of observations



- concentration of posterior around true value

Example 2: diagnostic test

The problem

- prevalence of genetic disease in population: 0.1%
- test has a false positive rate of 5%
- test has a false negative rate of 0
- I got tested and was positive
- what is the probability that I have the disease ?

Example 3. SNP calling

Data and notations

- true genotype is $S = a$, where $a = A, C, G, T$
- observed nucleotide for read k is O_k
- data: $D = (O_k)_{k=i..n}$, (n:number of reads)
- $\hat{\pi}_a$, $a = A, C, G, T$: genotype frequencies in the population (estimated over all individuals)

Model of sequence errors

- $p(O_k = a \mid S = a) = 1 - \epsilon$
- for $b \neq a$, $p(O_k = b \mid S = a) = \epsilon/3$
- reads are independent, so likelihood is: $p(D \mid S = a) = \prod_{k=1}^{n} p(O_k \mid S = a)$

Empirical Bayes probabilities for calling genotypes

- prior: $p(S = a) = \hat{\pi}_a$
- likelihood: $p(D \mid S = a) = \prod_{k=1}^{n} p(O_k \mid S = a)$
- posterior:

$$\begin{aligned} p(S = a \mid D) &\propto p(D \mid S = a)\, p(s = a) \\ &= \frac{p(D \mid S = a)\, p(s = a)}{\sum_{b=A,C,G,T} p(D \mid S = b)\, p(s = b)} \end{aligned}$$

Empirical Bayes

SNP calling using empirical Bayes posterior probabilities

- maximum a posteriori (MAP) inference of genotype
- post probs depend on parameters that are empircally estimated
- here: empirically estimated genotype frequencies in population
- post prob: gives a level of statistical confidence
- only genotypes with $pp > 0.9$ are typically considered reliable

Other frequent uses of empirical Bayes

- Hidden Markov Models (Viterbi, posterior decoding)
- SNP calling, inferring genotypes, etc
- more generally: multiple inference over
  - many nucleotide positions
  - many individuals
  - etc.

Stochastic modeling and probabilistic inference

Models

- model is defined in terms of simulation
- given parameter θ, how to simulate observable data D
- defines $p(D \mid \theta)$: probability of simulating D given θ

Inference

- Likelihood: $L(\theta) = p(D \mid \theta)$, as a function of θ
- Maximum likelihood (ML): find parameters maximising $L(\theta)$
- Bayesian inference: define prior $p(\theta)$
- posterior distribution over parameter $p(\theta \mid D) \propto p(D \mid \theta) p(\theta)$
- empirical Bayes: ML over θ, post probs for sequence annotation

Main probability distributions

- Bernouilli (tossing a coin: 0 or 1)
- Binomial (number of sucesses out of N draws)
- Geometric (number of draws before first success)
- Multinomial ($\simeq$ binomial for more than 2 outcomes)
- Exponential (waiting times of a Poisson process)
- Poisson (number of events of Poisson process over time T)