## Probabilistic Methods in Algorithms with Applications to Computational Biology

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## Outline - What I'll try to cover...

- The basic bounds: Bernstein, Chernoff, Hoeffding, Azuma-Hoeffding, McDiarmid. How to create your own bound....
- The Monte-Carlo method and MCMC
- The curse of too many questions: the multi-hypothesis problem and genome-wide association studies
- Two computational biology applications: HotNet and Dendrix

## It's (almost) all in the book:



Expanded second edition coming soon.

## Large Deviation Bounds for CS Analysis:

- Bernstein Inequality: the basic scheme
- Chernoff bound: independent, Bernoulli random variables
- Hoeffding bound: independent, bounded r.v.'s
- Azuma-Hoeffding bound: non-independent, bounded, martingale sequence
- McDiarmid bound: a Doob martingale on a function with bounded variation.

## Why Special Probabilistic Tools for CS?

A typical probability theory statement:

#### Theorem (The Central Limit Theorem)

Let  $X_1, \ldots, X_n$  be independent identically distributed random variables with common mean  $\mu$  and variance  $\sigma^2$ . Then

$$\lim_{n\to\infty} \Pr(\frac{\sum_{i=1}^n X_i - n\mu}{\sigma\sqrt{n}} \le z) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^z e^{-t^2/2} dt.$$

#### A typical CS probabilistic tool:

#### Theorem (Chernoff Bound)

Let  $X_1, ..., X_n$  be independent Bernoulli random variables such that  $Pr(X_i = 1) = p_i$ , then

$$Pr(\sum_{i=1}^n X_i \ge (1+\delta)\sum_{i=1}^n p_i) \le e^{-\mu\delta^2/3}.$$

## We build on Basic Probability Theory

Reminder:

Theorem (Markov Inequality)

If a random variable X is non-negative ( $X \ge 0$ ) then

$$Prob(X \ge a) \le \frac{E[X]}{a}.$$

Theorem (Chebyshev's Inequality)

For any random variable X.

$$Prob(|X - E[X]| \ge a) \le \frac{Var[X]}{a^2}$$

Both bound are general but relatively weak.

## The Basic Idea of Large Deviation Bounds:

For any random variable X, by Markov inequality we have: For any t > 0,

$$Pr(X \ge a) = Pr(e^{tX} \ge e^{ta}) \le \frac{\mathsf{E}[e^{tX}]}{e^{ta}}.$$

Similarly, for any t < 0

$$Pr(X \leq a) = Pr(e^{tX} \geq e^{ta}) \leq \frac{\mathsf{E}[e^{tX}]}{e^{ta}}$$

## The General Scheme:

We obtain specific bounds for particular conditions/distributions by

- **1** computing  $E[e^{tX}]$
- optimizing

$$Pr(X \ge a) \le \min_{t>0} \frac{\mathbf{E}[e^{tX}]}{e^{ta}}$$
$$Pr(X \le a) \le \min_{t<0} \frac{\mathbf{E}[e^{tX}]}{e^{ta}}.$$



## Moment Generating Function

#### Definition

The moment generating function of a random variable X is defined for any real value t as

 $M_X(t) = \mathbf{E}[e^{tX}].$ 

#### Theorem

Let X be a random variable with moment generating function  $M_X(t)$ . Assuming that exchanging the expectation and differentiation operands is legitimate, then for all  $n \ge 1$ 

 $\mathbf{E}[X^n] = M_X^{(n)}(0),$ 

where  $M_{\chi}^{(n)}(0)$  is the *n*-th derivative of  $M_{\chi}(t)$  evaluated at t = 0.

#### Proof.

$$M_X^{(n)}(t) = \mathbf{E}[X^n e^{tX}].$$

Computed at t = 0 we get

 $M_X^{(n)}(0) = \mathbf{E}[X^n].$ 

#### Theorem

Let X and Y be two random variables. If

 $M_X(t) = M_Y(t)$ 

for all  $t \in (-\delta, \delta)$  for some  $\delta > 0$ , then X and Y have the same distribution.

#### Theorem

If X and Y are independent random variables then

 $M_{X+Y}(t) = M_X(t)M_Y(t).$ 

#### Proof.

## $M_{X+Y}(t) = \mathbf{E}[e^{t(X+Y)}] = \mathbf{E}[e^{tX}]\mathbf{E}[e^{tY}] = M_X(t)M_Y(t).$

## Chernoff Bound for Sum of Bernoulli Trials

Let  $X_1, \ldots, X_n$  be a sequence of independent Bernoulli trials with  $Pr(X_i = 1) = p_i$ . Let  $X = \sum_{i=1}^n X_i$ , and let

$$\mu = \mathbf{E}[X] = \mathbf{E}\left[\sum_{i=1}^{n} X_i\right] = \sum_{i=1}^{n} \mathbf{E}[X_i] = \sum_{i=1}^{n} p_i.$$

For each  $X_i$ :

$$egin{array}{rcl} \mathcal{M}_{X_i}(t) &=& {\sf E}[e^{tX_i}] \ &=& p_i e^t + (1-p_i) \ &=& 1+p_i(e^t-1) \ &\leq& e^{p_i(e^t-1)}. \end{array}$$

$$M_{X_i}(t) = \mathbf{E}[e^{tX_i}] \le e^{p_i(e^t-1)}.$$

Taking the product of the *n* generating functions we get for  $X = \sum_{i=1}^{n} X_i$ 

$$egin{array}{rcl} M_X(t) &=& \prod_{i=1}^n M_{X_i}(t) \ &\leq& \prod_{i=1}^n e^{p_i(e^t-1)} \ &=& e^{\sum_{i=1}^n p_i(e^t-1)} \ &=& e^{(e^t-1)\mu} \end{array}$$

$$M_X(t) = \mathbf{E}[e^{tX}] = e^{(e^t - 1)\mu}$$

Applying Markov's inequality we have for any t > 0

$$\begin{aligned} \Pr(X \ge (1+\delta)\mu) &= & \Pr(e^{tX} \ge e^{t(1+\delta)\mu}) \\ &\leq & \frac{\mathsf{E}[e^{tX}]}{e^{t(1+\delta)\mu}} \\ &\leq & \frac{e^{(e^t-1)\mu}}{e^{t(1+\delta)\mu}} \end{aligned}$$

For any  $\delta > 0$ , we can set  $t = \ln(1 + \delta) > 0$  to get:

$${\it Pr}({\it X} \geq (1+\delta)\mu) \leq \left(rac{{\it e}^{\delta}}{(1+\delta)^{(1+\delta)}}
ight)^{\mu}.$$

#### Theorem

Let  $X_1, \ldots, X_n$  be independent Bernoulli random variables such that  $Pr(X_i = 1) = p_i$ .

• For any  $\delta > 0$ ,

$$\Pr(X \ge (1+\delta)\mu) \le \left(rac{e^{\delta}}{(1+\delta)^{1+\delta}}
ight)^{\mu}.$$
 (1)

• For  $0 < \delta \leq 1$ ,

$$\Pr(X \ge (1+\delta)\mu) \le e^{-\mu\delta^2/3}.$$
 (2)

(3)

• For  $R \ge 6\mu$ ,  $Pr(X \ge R) \le 2^{-R}$ .

$$M_X(t) = \mathbf{E}[e^{tX}] = e^{(e^t - 1)\mu}$$

Applying Markov's inequality we have for any t > 0

$$egin{aligned} & extsf{Pr}(X \geq (1+\delta)\mu) &= & extsf{Pr}(e^{tX} \geq e^{t(1+\delta)\mu}) \ & \leq & rac{\mathbf{E}[e^{tX}]}{e^{t(1+\delta)\mu}} \ & \leq & rac{e^{(e^t-1)\mu}}{e^{t(1+\delta)\mu}} \end{aligned}$$

For any  $\delta > 0$ , we can set  $t = \ln(1 + \delta) > 0$  to get:

$${\it Pr}(X \geq (1+\delta)\mu) \leq \left(rac{e^{\delta}}{(1+\delta)^{(1+\delta)}}
ight)^{\mu}.$$

This proves (1).

We show that for  $0 < \delta < 1$ ,

$$rac{e^{\delta}}{(1+\delta)^{(1+\delta)}} \leq e^{-\delta^2/3}$$

or that  $f(\delta) = \delta - (1 + \delta) \ln(1 + \delta) + \delta^2/3 \le 0$ in that interval. Computing the derivatives of  $f(\delta)$  we get

$$\begin{aligned} f'(\delta) &= 1 - \frac{1+\delta}{1+\delta} - \ln(1+\delta) + \frac{2}{3}\delta = -\ln(1+\delta) + \frac{2}{3}\delta, \\ f''(\delta) &= -\frac{1}{1+\delta} + \frac{2}{3}. \end{aligned}$$

 $f''(\delta) < 0$  for  $0 \le \delta < 1/2$ , and  $f''(\delta) > 0$  for  $\delta > 1/2$ .  $f'(\delta)$  first decreases and then increases over the interval [0, 1]. Since f'(0) = 0 and f'(1) < 0,  $f'(\delta) \le 0$  in the interval [0, 1]. Since f(0) = 0, we have that  $f(\delta) \le 0$  in that interval. This proves (2).



that proves (3).

#### Theorem

Let  $X_1, \ldots, X_n$  be independent Bernoulli random variables such that  $Pr(X_i = 1) = p_i$ . Let  $X = \sum_{i=1}^n X_i$  and  $\mu = \mathbf{E}[X]$ . For  $0 < \delta < 1$ :

$$Pr(X \leq (1-\delta)\mu) \leq \left(\frac{e^{-\delta}}{(1-\delta)^{(1-\delta)}}\right)^{\mu}.$$
 (4)

$$\Pr(X \leq (1-\delta)\mu) \leq e^{-\mu\delta^2/2}.$$
 (5)

Using Markov's inequality, for any t < 0,

$$egin{aligned} & extsf{Pr}(X \leq (1-\delta)\mu) &= & extsf{Pr}(e^{tX} \geq e^{(1-\delta)t\mu}) \ & \leq & rac{\mathbf{E}[e^{tX}]}{e^{t(1-\delta)\mu}} \ & \leq & rac{e^{(e^t-1)\mu}}{e^{t(1-\delta)\mu}} \end{aligned}$$

For  $0 < \delta < 1$ , we set  $t = \ln(1 - \delta) < 0$  to get:

$$\Pr(X \leq (1-\delta)\mu) \leq \left(rac{e^{-\delta}}{(1-\delta)^{(1-\delta)}}
ight)^{\mu}$$

This proves (4). We need to show:

$$f(\delta)=-\delta-(1-\delta)\ln(1-\delta)+rac{1}{2}\delta^2\leq 0.$$

We need to show:

$$f(\delta) = -\delta - (1-\delta)\ln(1-\delta) + \frac{1}{2}\delta^2 \le 0.$$

Differentiating  $f(\delta)$  we get

$$f'(\delta) = \ln(1-\delta) + \delta,$$
  
$$f''(\delta) = -\frac{1}{1-\delta} + 1.$$

Since  $f''(\delta) < 0$  for  $\delta \in (0, 1)$ ,  $f'(\delta)$  decreasing in that interval. Since f'(0) = 0,  $f'(\delta) \le 0$  for  $\delta \in (0, 1)$ . Therefore  $f(\delta)$  is non increasing in that interval. f(0) = 0. Since  $f(\delta)$  is non increasing for  $\delta \in [0, 1)$ ,  $f(\delta) \le 0$  in that interval, and (5) follows.

## Example: Coin flips

Let X be the number of heads in a sequence of n independent fair coin flips.

$$\Pr\left(\left|X - \frac{n}{2}\right| \ge \frac{1}{2}\sqrt{6n\ln n}\right)$$
$$= \Pr\left(X \ge \frac{n}{2}\left(1 + \sqrt{\frac{6\ln n}{n}}\right)\right)$$
$$+\Pr\left(X \le \frac{n}{2}\left(1 - \sqrt{\frac{6\ln n}{n}}\right)\right)$$

$$\leq e^{-\frac{1}{3}\frac{n}{2}\frac{6\ln n}{n}} + e^{-\frac{1}{2}\frac{n}{2}\frac{6\ln n}{n}} \leq \frac{2}{n}.$$

Markov Inequality gives

$$\Pr\left(X \ge \frac{3n}{4}\right) \le \frac{n/2}{3n/4} \le \frac{2}{3}.$$

Using the Chebyshev's bound we have:

$$Pr\left(\left|X-\frac{n}{2}\right|\geq\frac{n}{4}\right)\leq\frac{4}{n}.$$

Using the Chernoff bound in this case, we obtain

$$Pr\left(\left|X-\frac{n}{2}\right| \ge \frac{n}{4}\right) = Pr\left(X \ge \frac{n}{2}\left(1+\frac{1}{2}\right)\right)$$
$$+ Pr\left(X \le \frac{n}{2}\left(1-\frac{1}{2}\right)\right)$$
$$\le e^{-\frac{1}{3}\frac{n}{2}\frac{1}{4}} + e^{-\frac{1}{2}\frac{n}{2}\frac{1}{4}}$$
$$< 2e^{-\frac{n}{24}}.$$

## Example: Estimating a Parameter

- Evaluating the probability that a particular DNA mutation occurs in the population.
- Given a DNA sample, a lab test can determine if it carries the mutation.
- The test is expensive and we would like to obtain a relatively reliable estimate from a minimum number of samples.
- *p* = the unknown value;
- n = number of samples,  $\tilde{p}n$  had the mutation.
- Given sufficient number of samples we expect the value p to be in the neighborhood of sampled value p
  p, but we cannot predict any single value with high confidence.

## **Confidence Interval**

Instead of predicting a single value for the parameter we give an *interval* that is *likely* to contain the parameter.

#### Definition

A 1 - q confidence interval for a parameter T is an interval  $[\tilde{p} - \delta, \tilde{p} + \delta]$  such that

 $Pr(T \in [\tilde{p} - \delta, \tilde{p} + \delta]) \ge 1 - q.$ 

We want to minimize  $2\delta$  and q, with minimum n. Using  $\tilde{p}n$  as our estimate for pn, we need to compute  $\delta$  and q such that

 $Pr(p \in [\tilde{p} - \delta, \tilde{p} + \delta]) = Pr(np \in [n(\tilde{p} - \delta), n(\tilde{p} + \delta)]) \ge 1 - q.$ 

- The random variable here is the interval [p̃ − δ, p̃ + δ] (or the value p̃), while p is a fixed (unknown) value.
- $n\tilde{p}$  has a binomial distribution with parameters n and p, and  $\mathbf{E}[\tilde{p}] = p$ . If  $p \notin [\tilde{p} \delta, \tilde{p} + \delta]$  then we have one of the following two events:
  - 1 If  $p < \tilde{p} \delta$ , then  $n\tilde{p} \ge n(p+\delta) = np\left(1 + \frac{\delta}{p}\right)$ , or  $n\tilde{p}$  is larger than its expectation by a  $\frac{\delta}{p}$  factor.
  - 2 If  $p > \tilde{p} + \delta$ , then  $n\tilde{p} \le n(p \delta) = np\left(1 \frac{\delta}{p}\right)$ , and  $n\tilde{p}$  is smaller than its expectation by a  $\frac{\delta}{p}$  factor.

$$\begin{aligned} & \Pr(p \notin [\tilde{p} - \delta, \tilde{p} + \delta]) \\ &= \Pr\left(n\tilde{p} \le np\left(1 - \frac{\delta}{p}\right)\right) + \Pr\left(n\tilde{p} \ge np\left(1 + \frac{\delta}{p}\right)\right) \\ &\le e^{-\frac{1}{2}np\left(\frac{\delta}{p}\right)^2} + e^{-\frac{1}{3}np\left(\frac{\delta}{p}\right)^2} \\ &= e^{-\frac{n\delta^2}{2p}} + e^{-\frac{n\delta^2}{3p}}. \end{aligned}$$

But the value of p is unknown, A simple solution is to use the fact that  $p \leq 1$  to prove

$$\mathsf{Pr}(p \not\in [\widetilde{p} - \delta, \widetilde{p} + \delta]) \leq e^{-rac{n\delta^2}{2}} + e^{-rac{n\delta^2}{3}}.$$

Setting  $q = e^{-\frac{n\delta^2}{2}} + e^{-\frac{n\delta^2}{3}}$ , we obtain a tradeoff between  $\delta$ , n, and the error probability q.

$$q = e^{-\frac{n\delta^2}{2}} + e^{-\frac{n\delta^2}{3}}$$

If we want to obtain a 1 - q confidence interval  $[\tilde{p} - \delta, \tilde{p} + \delta]$ ,

$$n \geq \frac{3}{\delta^2} \ln \frac{2}{q}$$

samples are enough.

### Chernoff's vs. Chebyshev's Inequality

Assume for all *i* we have  $p_i = p$ ;  $1 - p_i = q$ .

 $\mu = \mathbf{E}[X] = np$ 

Var[X] = npq

If we use Chebyshev's Inequality we get

$$Pr(|X - \mu| > \delta\mu) \le \frac{npq}{\delta^2 \mu^2} = \frac{npq}{\delta^2 n^2 p^2} = \frac{q}{\delta^2 \mu}$$

Chernoff bound gives

$$Pr(|X - \mu| > \delta\mu) \le 2e^{-\mu\delta^2/3}.$$

## Set Balancing

Given an  $n \times n$  matrix  $\mathcal{A}$  with entries in  $\{0, 1\}$ , let

$$\begin{pmatrix} a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & a_{22} & \dots & a_{2n} \\ \dots & \dots & \dots & \dots \\ a_{n1} & a_{n2} & \dots & a_{nn} \end{pmatrix} \begin{pmatrix} b_1 \\ b_2 \\ \dots \\ \dots \\ b_n \end{pmatrix} = \begin{pmatrix} c_1 \\ c_2 \\ \dots \\ \dots \\ b_n \end{pmatrix}.$$

Find a vector  $\overline{b}$  with entries in  $\{-1,1\}$  that minimizes

 $||\mathcal{A}\bar{b}||_{\infty} = \max_{i=1,\dots,n} |c_i|.$ 

#### Theorem

For a random vector  $\overline{b}$ , with entries chosen independently and with equal probability from the set  $\{-1, 1\}$ ,

$$\Pr(||\mathcal{A}\overline{b}||_{\infty} \geq \sqrt{4n\ln n}) \leq \frac{2}{n}.$$

The  $\sum_{i=1}^{n} a_{j,i} b_i$  (excluding the zero terms) is a sum of independent -1, 1 random variable. We need a bound on such sum.

# Chernoff Bound for Sum of $\{-1, +1\}$ Random Variables

#### Theorem

Let  $X_1, ..., X_n$  be independent random variables with

$$Pr(X_i = 1) = Pr(X_i = -1) = \frac{1}{2}$$

Let  $X = \sum_{i=1}^{n} X_i$ . For any a > 0,

$$Pr(X \geq a) \leq e^{-\frac{a^2}{2n}}.$$

de Moivre – Laplace approximation: For any k, such that  $|k - np| \le a$ 

$$\binom{n}{k} p^k (1-p)^{n-k} \approx \frac{1}{\sqrt{2\pi n p (1-p)}} e^{-\frac{a^2}{2np(1-p)}}$$

For any t > 0,

$$\mathbf{E}[e^{tX_i}] = \frac{1}{2}e^t + \frac{1}{2}e^{-t}.$$

$$e^t = 1 + t + \frac{t^2}{2!} + \dots + \frac{t^i}{i!} + \dots$$

$$e^{-t} = 1 - t + \frac{t^2}{2!} + \dots + (-1)^i \frac{t^i}{i!} + \dots$$

Thus,

$$\mathbf{E}[e^{tX_i}] = \frac{1}{2}e^t + \frac{1}{2}e^{-t} = \sum_{i \ge 0} \frac{t^{2i}}{(2i)!}$$

$$\le \sum_{i \ge 0} \frac{(\frac{t^2}{2})^i}{i!} = e^{t^2/2}$$

$$\mathsf{E}[e^{tX}] = \prod_{i=1}^{n} \mathsf{E}[e^{tX_i}] \le e^{nt^2/2},$$

$$Pr(X \ge a) = Pr(e^{tX} > e^{ta}) \le \frac{\mathsf{E}[e^{tX}]}{e^{ta}} \le e^{t^2n/2-ta}.$$

Setting t = a/n yields

$$Pr(X \ge a) \le e^{-\frac{a^2}{2n}}$$

By symmetry we also have

#### Corollary

Let  $X_1, ..., X_n$  be independent random variables with

$$Pr(X_i = 1) = Pr(X_i = -1) = \frac{1}{2}$$

Let  $X = \sum_{i=1}^{n} X_i$ . Then for any a > 0,

 $Pr(|X| > a) \leq 2e^{-\frac{a^2}{2n}}.$ 

## Application: Set Balancing

#### Theorem

For a random vector  $\overline{b}$ , with entries chosen independently and with equal probability from the set  $\{-1, 1\}$ ,

$$\Pr(||\mathcal{A}\bar{b}||_{\infty} \ge \sqrt{4n\ln n}) \le \frac{2}{n} \tag{6}$$

- Consider the *i*-th row  $\bar{a}_i = a_{i,1}, \dots, a_{i,n}$ .
- Let *k* be the number of 1's in that row.
- $Z_i = \sum_{j=1}^k a_{i,i_j} b_{i_j}$ .
- If  $k \leq \sqrt{4n \ln n}$  then clearly  $Z_i \leq \sqrt{4n \ln n}$ .

If  $k > \sqrt{4n \log n}$ , the k non-zero terms in the sum  $Z_i$  are independent random variables, each with probability 1/2 of being either +1 or -1. Using the Chernoff bound:

 $\Pr\left\{|Z_i| > \sqrt{4n\log n}\right\} \le 2e^{-4n\log n/(2k)} \le \frac{2}{n^2},$ 

where we use the fact that  $n \ge k$ . The result follows by union bound (*n* rows).

## Hoeffding's Inequality

Large deviation bound for more general random variables:

Theorem (Hoeffding's Inequality)

Let  $X_1, ..., X_n$  be independent random variables such that for all  $1 \le i \le n$ ,  $E[X_i] = \mu$  and  $Pr(a \le X_i \le b) = 1$ . Then

$$\Pr(|rac{1}{n}\sum_{i=1}^n X_i - \mu| \ge \epsilon) \le 2e^{-2n\epsilon^2/(b-a)^2}$$

#### Lemma

(Hoeffding's Lemma) Let X be a random variable such that  $Pr(X \in [a, b]) = 1$  and E[X] = 0. Then for every  $\lambda > 0$ ,

 $\mathbf{E}[E^{\lambda X}] \le e^{\lambda^2 (a-b)^2}/8.$ 

## Proof of the Lemma

Since  $f(x) = e^{\lambda x}$  is a convex function, for any  $\alpha \in (0, 1)$  and  $x \in [a, b]$ ,

 $f(X) \leq \alpha f(a) + (1 - \alpha)f(b).$ 

Thus, for  $\alpha = \frac{b-x}{b-a} \in (0,1)$ ,

$$e^{\lambda x} \leq rac{b-x}{b-a}e^{\lambda a} + rac{x-a}{b-a}e^{\lambda b}.$$

Taking expectation, and using E[X] = 0, we have

$$E[e^{\lambda X}] \leq rac{b}{b-a}e^{\lambda a} + rac{a}{b-a}e^{\lambda b} \leq e^{\lambda^2(b-a)^2/8}.$$

## Proof of the Bound

Let  $Z_i = X_i - \mathbf{E}[X_i]$  and  $Z = \frac{1}{n} \sum_{i=1}^n X_i$ .

$$\Pr(Z \ge \epsilon) \le e^{-\lambda \epsilon} \mathbf{E}[e^{\lambda Z}] \le e^{-\lambda \epsilon} \prod_{i=1}^{n} \mathbf{E}[e^{\lambda X_i/n}] \le e^{-\lambda \epsilon + \frac{\lambda^2 (b-a)^2}{8n}}$$

Set  $\lambda = \frac{4n\epsilon}{(b-a)^2}$  gives

$$Pr(|\frac{1}{n}\sum_{i=1}^{n}X_{i}-\mu|\geq\epsilon)=Pr(Z\geq\epsilon)\leq 2e^{-2n\epsilon^{2}/(b-a)^{2}}$$

## A More General Version

#### Theorem

Let  $X_1, ..., X_n$  be independent random variables with  $\mathbf{E}[X_i] = \mu_i$ and  $Pr(B_i \le X_i \le B_i + c_i) = 1$ , then

$$\Pr(|\sum_{i=1}^n X_i - \sum_{i=1}^n \mu_i| \ge \epsilon) \le e^{-\frac{2\epsilon^2}{\sum_{i=1}^n c_i^2}}$$