Maximum Likelihood Estimation for Allele Frequencies

Biostatistics 666

Lecture 7

Last Three Lectures: Introduction to Coalescent Models

- Computationally efficient framework
  - Alternative to forward simulations
- Predictions about sequence variation
  - Number of polymorphisms
  - Frequency of polymorphisms

Coalescent Models: Key Ideas

- Proceed backwards in time
- Genealogies shaped by
  - Population size
  - Population structure
  - Recombination rates
- Given a particular genealogy ...
  - Mutation rate predicts variation

Next Series of Lectures

- Estimating allele and haplotype frequencies from genotype data
  - Maximum likelihood approach
  - Application of an E-M algorithm
- Challenges
  - Using information from related individuals
  - Allowing for non-codominant genotypes
  - Allowing for ambiguity in haplotype assignments

Objective: Parameter Estimation

- Learn about **population** characteristics
  - E.g. allele frequencies, population size
- Using a specific **sample**
  - E.g. a set sequences, unrelated individuals, or even families

Maximum Likelihood

- A general framework for estimating model parameters
- Find the set of parameter values that maximize the probability of the observed data
- Applicable to many different problems

Example: Allele Frequencies

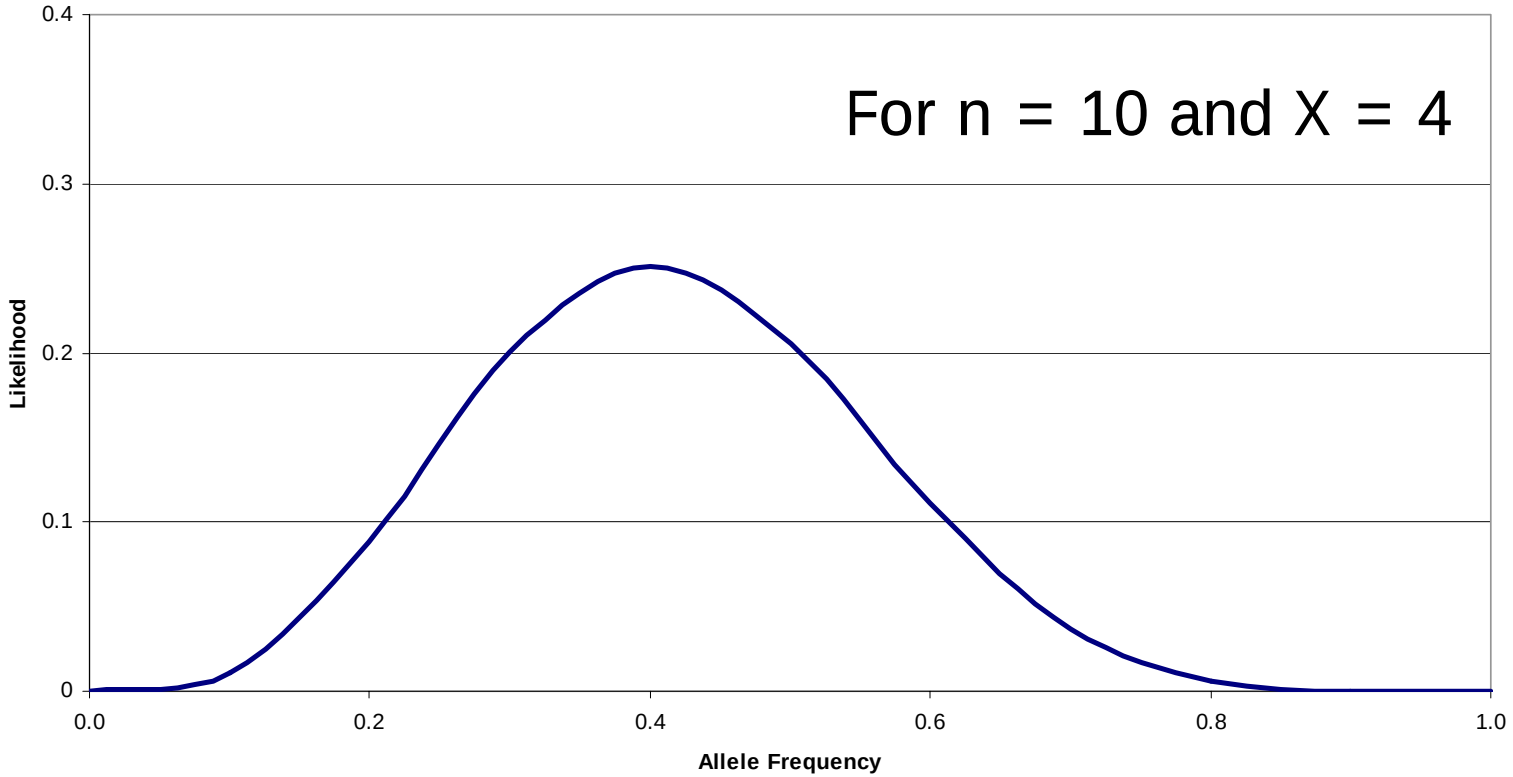
- Consider…
  - A sample of *n* chromosomes
  - *X* of these are of type “a”
  - Parameter of interest is allele frequency…

$$L(p \mid n, X) = \binom{n}{X} p^{X} (1-p)^{n-X}$$

Evaluate for various parameters

p	1-p	L
0.0	1.0	0.000
0.2	0.8	0.088
0.4	0.6	0.251
0.6	0.4	0.111
0.8	0.2	0.006
1.0	0.0	0.000

Likelihood Plot



In this case

- The likelihood tells us the data is most probable if $p = 0.4$
- The likelihood curve allows us to evaluate alternatives…
  - Is $p = 0.8$ a possibility?
  - Is $p = 0.2$ a possibility?

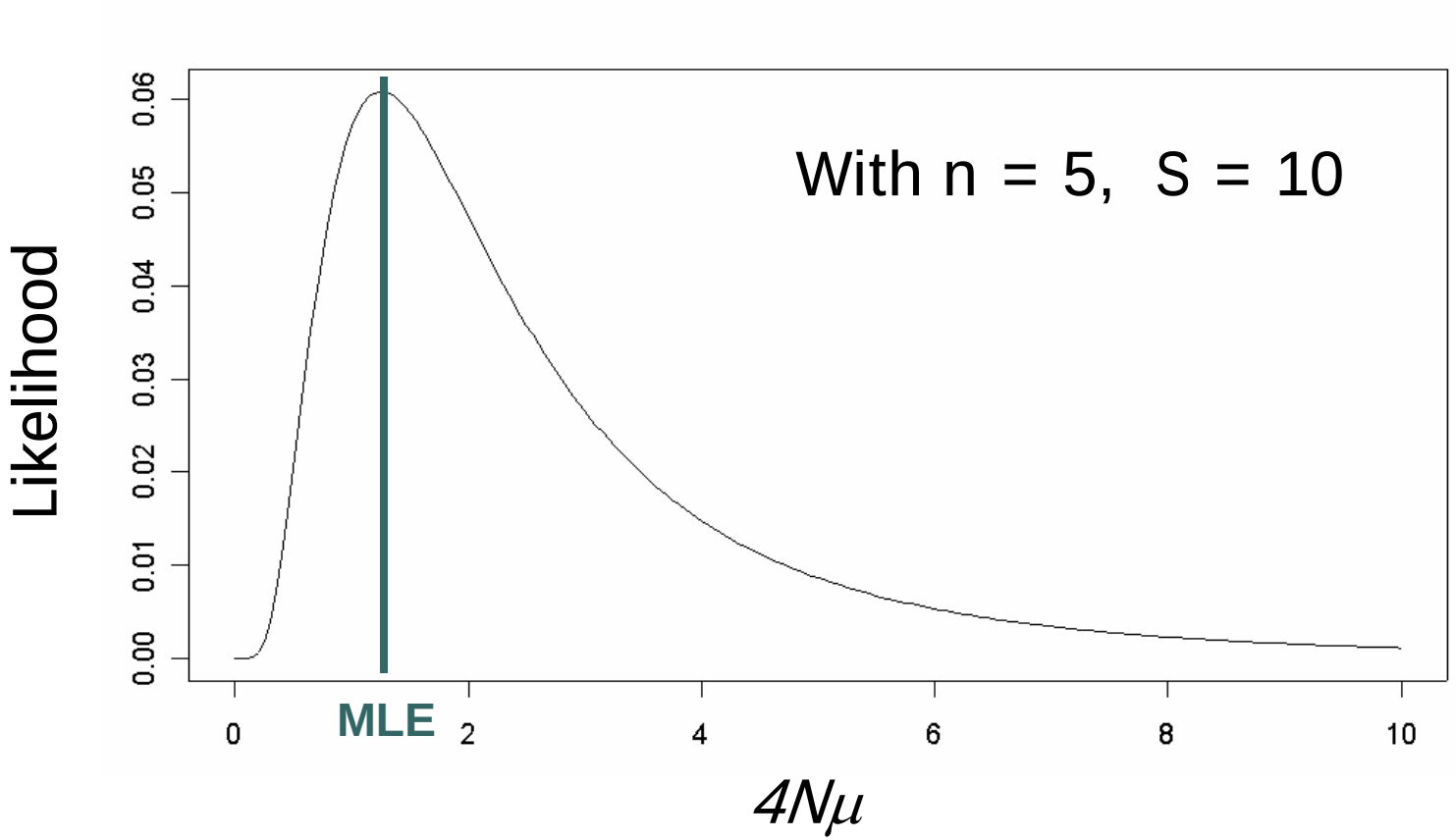
Example: Estimating $4N\mu$

- Consider *S* polymorphisms in sample of *n* sequences…

$$L(\theta \mid n, S) = P_n(S \mid \theta)$$

- Where P_n is calculated using the Q_n and P_2 functions defined previously

Likelihood Plot



Maximum Likelihood Estimation

- Two basic steps…

  a) Write down likelihood function

  $$L(\theta \mid x) \propto f(x \mid \theta)$$

  b) Find value of $\hat{\theta}$ that maximizes $L(\theta \mid x)$

- In principle, applicable to any problem where a likelihood function exists

MLEs

- Parameter values that maximize likelihood
  - θ where observations have maximum probability
- Finding MLEs is an optimization problem
- How do MLEs compare to other estimators?

Comparing Estimators

- How do MLEs rate in terms of …
  - **Unbiasedness**
  - **Consistency**
  - **Efficiency**

- For a review, see Garthwaite, Jolliffe, Jones (1995) *Statistical Inference*, Prentice Hall

Analytical Solutions

- Write out log-likelihood …

$$\ell(\theta \mid data) = \ln L(\theta \mid data)$$

- Calculate derivative of likelihood

$$\frac{d\ell(\theta \mid data)}{d\theta}$$

- Find zeros for derivative function

Information

- The second derivative is also extremely useful

$$I_\theta = -E\left[\frac{d^2\ell(\theta \mid data)}{d\theta^2}\right]$$

$$V_{\hat{\theta}} = \frac{1}{I_\theta}$$

- The speed at which log-likelihood decreases
- Provides an asymptotic variance for estimates

Allele Frequency Estimation …

- When individual chromosomes are observed this does not seem tricky…
- What about with genotypes?
- What about with parent-offspring pairs?

Coming up …

- We will walk through allele frequency estimation in three distinct settings:
  - Samples single chromosomes …
  - Samples of unrelated Individuals …
  - Samples of parents and offspring …

I. Single Alleles Observed

- Consider…
  - A sample of *n* chromosomes
  - *X* of these are of type “a”
  - Parameter of interest is allele frequency…

$$L(p \mid n, X) = \binom{n}{X} p^{X} (1-p)^{n-X}$$

Some Notes

- The following two likelihoods are just as good:

$$L(p;X,n)=\binom{n}{X}p^{X}(1-p)^{n-X}$$

$$L(p;x_1,x_2\ldots x_n,n)=\prod_{i=1}^{n}p^{x_i}(1-p)^{1-x_i}$$

- For ML estimation, constant factors in likelihood don't matter

Analytic Solution

- The log-likelihood

$$\ln L(\theta \mid n, X) = \ln \binom{n}{X} + X \ln p + (n - X) \ln(1 - p)$$

- The derivative

$$\frac{d \ln L(p \mid X)}{dp} = \frac{X}{p} - \frac{n - X}{1 - p}$$

- Find zero …

Samples of Individual Chromosomes

- The natural estimator (where we count the proportion of sequences of a particular type) and the MLE give identical solutions

- Maximum likelihood provides a justification for using the “natural” estimator

II. Genotypes Observed

Genotypes				
Genotype	**A_1A_1**	**A_1A_2**	**A_2A_2**	**Total**
Observed	n_{11}	n_{12}	n_{22}	$n=n_{11}+n_{12}+n_{22}$
Frequency	p_{11}	p_{12}	p_{22}	1.0

Alleles			
Genotype	**A_1**	**A_2**	**Total**
Observed	$n_1=2n_{11}+n_{12}$	$n_2=2n_{22}+n_{12}$	$2n=n_1+n_2$
Frequency	$p_1=n_1/2n$	$p_2=n_2/2n$	1.0

Consider a Set of Genotypes…

- Use notation n_{ij} to denote the number of individuals with genotype i / j

- Sample of n individuals

	Genotypes			
Genotype	**A_1A_1**	**A_1A_2**	**A_2A_2**	**Total**
Observed	n_{11}	n_{12}	n_{22}	$n=n_{11}+n_{12}+n_{22}$
Frequency	p_{11}	p_{12}	p_{22}	1.0

Allele Frequencies by Counting…

- A natural estimate for allele frequencies is to calculate the proportion of individuals carrying each allele

	Alleles		
Genotype	**A_1**	**A_2**	**Total**
Observed	$n_1=2n_{11}+n_{12}$	$n_2=2n_{22}+n_{12}$	$2n=n_1+n_2$
Frequency	$p_1=n_1/2n$	$p_2=n_2/2n$	1.0

MLE using genotype data...

- Consider a sample such as ...

	Genotypes			
Genotype	**A_1A_1**	**A_1A_2**	**A_2A_2**	**Total**
Observed	n_{11}	n_{12}	n_{22}	$n=n_{11}+n_{12}+n_{22}$

- The likelihood as a function of allele frequencies is ...

$$L(p;n) = \frac{n!}{n_{11}!n_{12}!n_{22}!}\left(p^2\right)^{n_{11}}\left(2pq\right)^{n_{12}}\left(q^2\right)^{n_{22}}$$

Which gives…

- Log-likelihood and its derivative

$$\ell = \ln L = \left(2n_{11} + n_{12}\right)\ln p_1 + \left(2n_{22} + n_{12}\right)\ln(1 - p_1) + C$$

$$\frac{d\ell}{dp_1} = \frac{2n_{11} + n_{12}}{p_1} - \frac{2n_{22} + n_{12}}{(1 - p_1)}$$

- Giving the MLE as …

$$\hat{p}_1 = \frac{\left(2n_{11} + n_{12}\right)}{2\left(n_{11} + n_{12} + n_{22}\right)}$$

Samples of Unrelated Individuals

- Again, natural estimator (where we count the proportion of alleles of a particular type) and the MLE give identical solutions

- Maximum likelihood provides a justification for using the “natural” estimator

III. Parent-Offspring Pairs

	Child			
Parent	A_1A_1	A_1A_2	A_2A_2	
A_1A_1	a_1	a_2	0	a_1+a_2
A_1A_2	a_3	a_4	a_5	$a_3+a_4+a_5$
A_2A_2	0	a_6	a_7	a_6+a_7
	a_1+a_3	$a_2+a_4+a_6$	a_5+a_7	N pairs

Probability for Each Observation

	Child			
Parent	A_1A_1	A_1A_2	A_2A_2	
A_1A_1				
A_1A_2				
A_2A_2				
				1.0

Probability for Each Observation

	Child			
Parent	A_1A_1	A_1A_2	A_2A_2	
A_1A_1	p_1^3	$p_1^2p_2$	0	p_1^2
A_1A_2	$p_1^2p_2$	p_1p_2	$p_1p_2^2$	$2p_1p_2$
A_2A_2	0	$p_1p_2^2$	p_2^3	p_2^2
	p_1^2	$2p_1p_2$	p_2^2	1.0

Which gives...

$$\ln L =$$

$$p_2 = 1 - p_1$$

$$B = 3a_1 + 2(a_2 + a_3) + a_4 + (a_5 + a_6)$$

$$C = (a_2 + a_3) + a_4 + 2(a_5 + a_6) + 3a_7$$

$$\hat{p}_1 = \frac{B}{(B + C)}$$

Which gives...

$$\begin{aligned}\ln \mathrm{L} &= a_1 \ln p_1^3 + (a_2 + a_3)\ln(p_1^2 p_2) + a_4 \ln(p_1 p_2) \\ &\quad + (a_5 + a_6)\ln(p_1 p_2^2) + a_7 \ln p_2^3 + \text{constant} \\ &= B \ln p_1 + C \ln(1 - p_1)\end{aligned}$$

$$\begin{aligned}p_2 &= 1 - p_1 \\ B &= 3a_1 + 2(a_2 + a_3) + a_4 + (a_5 + a_6) \\ C &= (a_2 + a_3) + a_4 + 2(a_5 + a_6) + 3a_7\end{aligned}$$

$$\hat{p}_1 = \frac{B}{(B + C)}$$

Samples of Parent Offspring-Pairs

- The natural estimator (where we count the proportion of alleles of a particular type) and the MLE no longer give identical solutions

- In this case, we expect the MLE to be more accurate

Comparing Sampling Strategies

- We can compare sampling strategies by calculate the information for each one

$$I_\theta = -E\left[\frac{d^2\ell(\theta \mid data)}{d\theta^2}\right]$$

$$V_{\hat{\theta}} = \frac{1}{I_\theta}$$

- Which one to you expect to be most informative?

How informative is each setting?

- Single chromosomes $Var(p) = \frac{pq}{N}$
- Unrelated individuals $Var(p) = \frac{pq}{2N}$
- Parent offspring trios $Var(p) = \frac{pq}{3N - a_4}$

Other Likelihoods

- Allele frequencies when individuals are…
  - Diagnosed for Mendelian disorder
  - Genotyped at two neighboring loci
  - Phenotyped for the ABO blood groups
- Many other interesting problems…
- … but some have no analytical solution

Today's Summary

- Examples of Maximum Likelihood
- Allele Frequency Estimation
  - Allele counts
  - Genotype counts
  - Pairs of Individuals

Take home reading

- Excoffier and Slatkin (1996)

- Introduces the E-M algorithm
- Widely used for maximizing likelihoods in genetic problems

Properties of Estimators

For Review

Unbiasedness

- An estimator is unbiased if

$$E(\hat{\theta}) = \theta$$

$$bias(\hat{\theta}) = E(\hat{\theta}) - \theta$$

- Multiple unbiased estimators may exist
- Other properties may be desirable

Consistency

- An estimator is consistent if

$$P\left(|\hat{\theta}-\theta|>\varepsilon\right)\rightarrow 0 \text{ as } n\rightarrow\infty$$

- for any ε

- Estimate converges to true value in probability with increasing sample size

Mean Squared Error

- MSE is defined as

$$MSE(\hat{\theta}) = E\left[\left\{(\hat{\theta} - \bar{\theta}) + (\bar{\theta} - \theta)\right\}^2\right]$$

$$= \text{var}(\hat{\theta}) + \text{bias}(\hat{\theta})^2$$

- If $MSE \to 0$ as $n \to \infty$ then the estimator must be consistent
  - The reverse is not true

Efficiency

- The relative efficiency of two estimators is the ratio of their variances

$$\text{if } \frac{\text{var}(\hat{\theta}_2)}{\text{var}(\hat{\theta}_1)} > 1 \text{ then } \hat{\theta}_1 \text{ is more efficient}$$

- Comparison only meaningful for estimators with equal biases

Sufficiency

- Consider…
  - Observations $X_1, X_2, \ldots X_n$
  - Statistic $T(X_1, X_2, \ldots X_n)$
- T is a sufficient statistic if it includes all information about θ in the sample
  - Distribution of X_i conditional on T is independent of θ
  - Posterior distribution of θ conditional on T is independent of X_i

Minimal Sufficient Statistic

- There can be many alternative sufficient statistics.
- A statistic is a minimal sufficient statistic if it can be expressed as a function of every other sufficient statistic.

Typical Properties of MLEs

- **Bias**
  - Can be biased or unbiased
- **Consistency**
  - Subject to regularity conditions, MLEs are consistent
- **Efficiency**
  - Typically, MLEs are asymptotically efficient estimators
- **Sufficiency**
  - Often, but not always
- Cox and Hinkley, 1974

Strategies for Likelihood Optimization

For Review

Generic Approaches

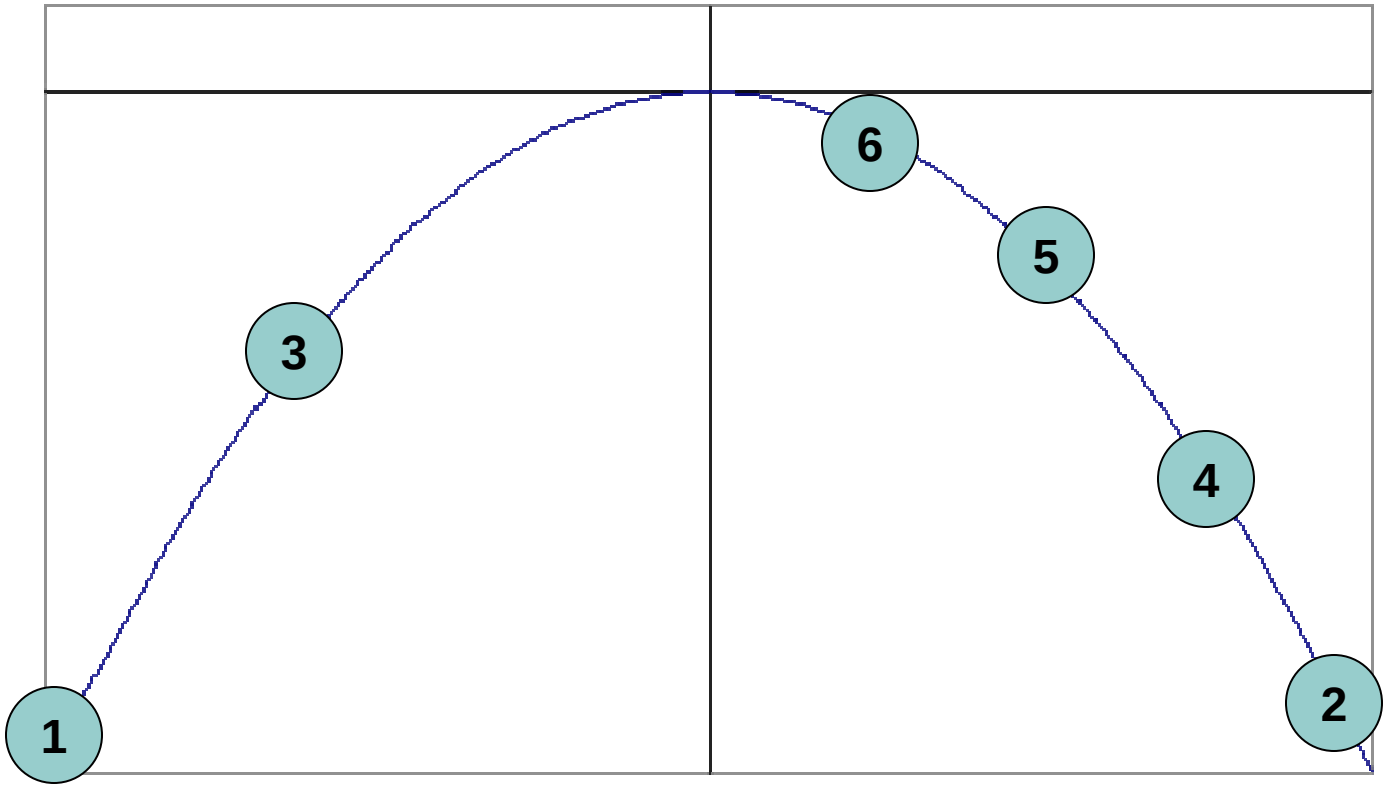
- Suitable for when analytical solutions are impractical

- Bracketing
- Simplex Method
- Newton-Rhapson

Bracketing

- Find 3 points such that
  - $\theta_a < \theta_b < \theta_c$
  - $L(\theta_b) > L(\theta_a)$ and $L(\theta_b) > L(\theta_c)$
- Search for maximum by
  - Select trial point in interval
  - Keep maximum and flanking points

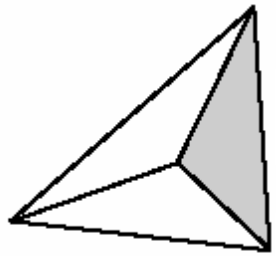
Bracketing



The Simplex Method

- Calculate likelihoods at simplex vertices
  - Geometric shape with k+1 corners
  - E.g. a triangle in k = 2 dimensions
- At each step, move the high vertex in the direction of lower points

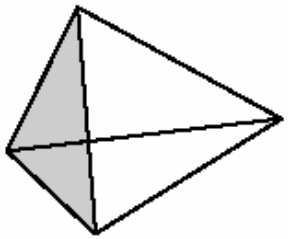
The Simplex Method II



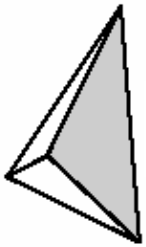
high

low

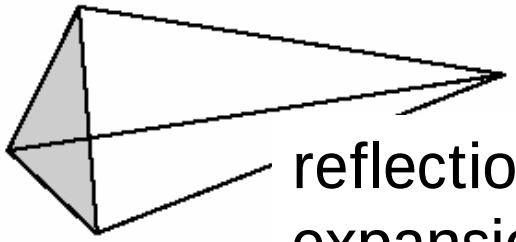
Original Simplex



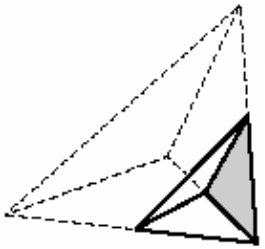
reflection



contraction



reflection and
expansion

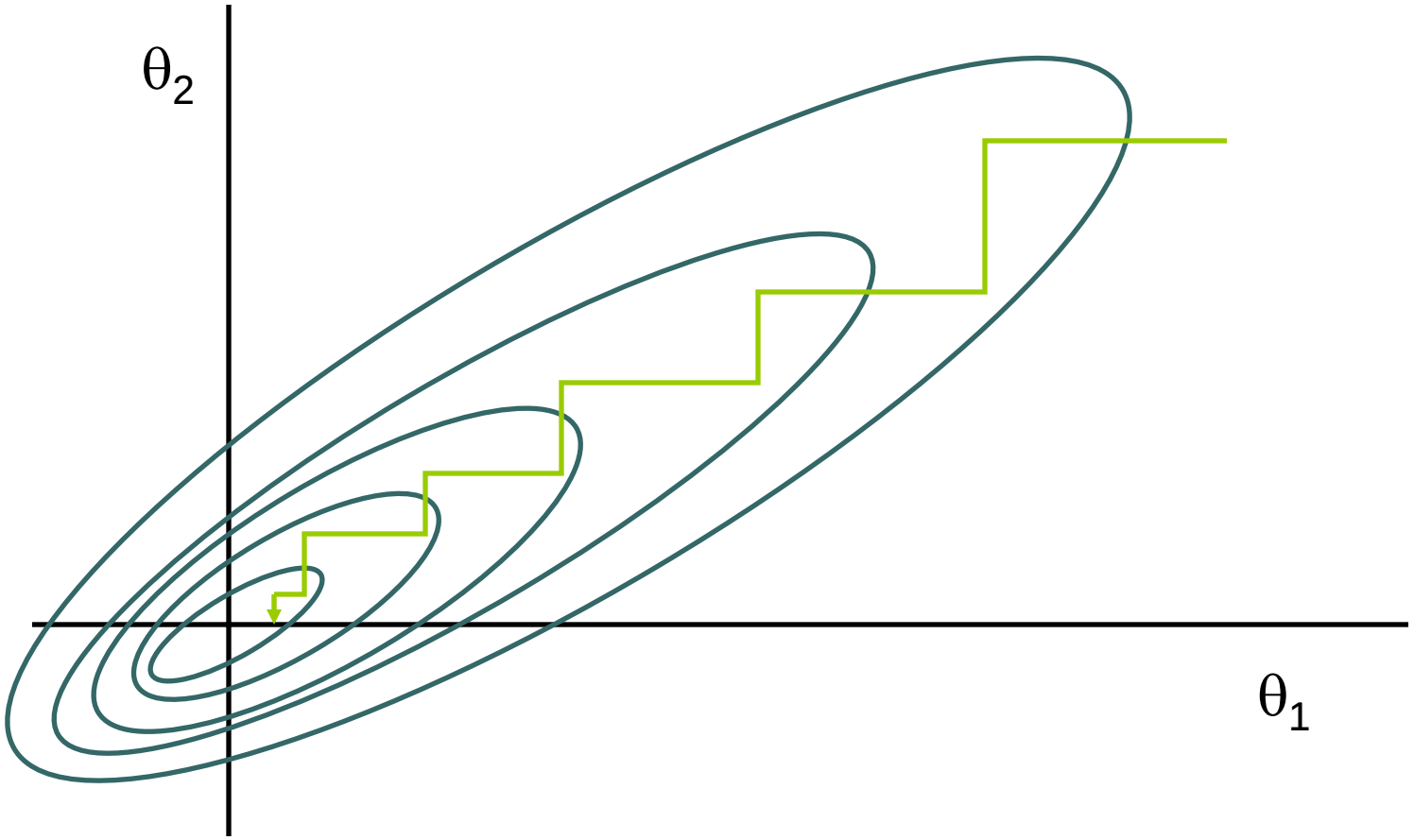


multiple
contraction

One parameter maximization

- Simple but inefficient approach
- Consider
  - Parameters $\theta = (\theta_1, \theta_2, \ldots, \theta_k)$
  - Likelihood function $L(\theta; x)$
- Maximize θ with respect to each θ_i in turn
  - Cycle through parameters

The Inefficiency...



Steepest Descent

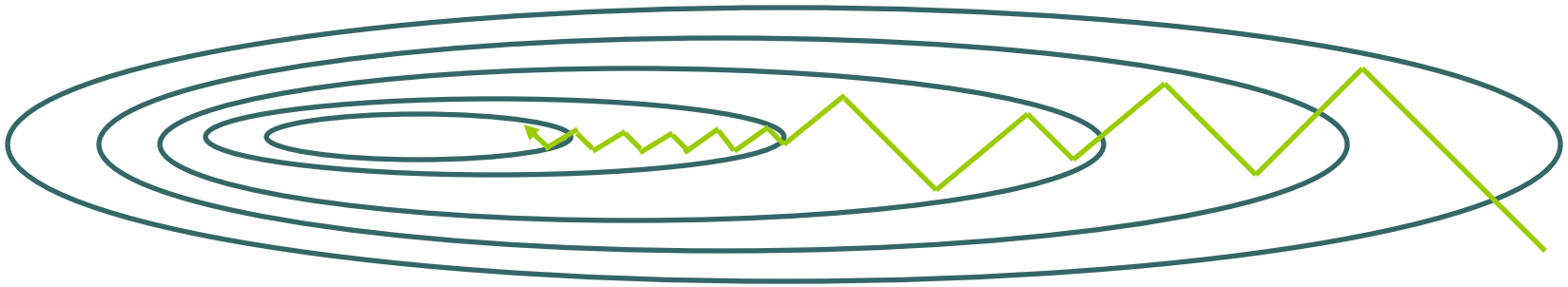
- Consider
  - Parameters $\theta = (\theta_1, \theta_2, \ldots, \theta_k)$
  - Likelihood function $L(\theta; x)$

- Score vector

$$S = \frac{d \ln(L)}{d\theta} = \left(\frac{d \ln(L)}{d\theta_1}, \quad \ldots, \quad \frac{d \ln(L)}{d\theta_k} \right)$$

  - Find maximum along $\theta + \delta S$

Still inefficient...



Consecutive steps are perpendicular!

Local Approximations to Log-Likelihood Function

In the neighboorhood of $\boldsymbol{\theta}_i$

$$\ell(\boldsymbol{\theta}) \approx \ell(\boldsymbol{\theta}_i) + S(\boldsymbol{\theta} - \boldsymbol{\theta}_i) - \tfrac{1}{2}(\boldsymbol{\theta} - \boldsymbol{\theta}_i)^t \mathbf{I}_\theta (\boldsymbol{\theta} - \boldsymbol{\theta}_i)$$

where

$\ell(\boldsymbol{\theta}) = \ln L(\boldsymbol{\theta})$ is the loglikelihood function

$\mathbf{S} = d\ell(\boldsymbol{\theta}_i)$ is the score vector

$\mathbf{I}_\theta = -d^2\ell(\boldsymbol{\theta}_i)$ is the observed information matrix

Newton's Method

Maximize the approximation

$$\ell(\boldsymbol{\theta}) \approx \ell(\boldsymbol{\theta}_i) + \mathbf{S}(\boldsymbol{\theta} - \boldsymbol{\theta}_i) - \tfrac{1}{2}(\boldsymbol{\theta} - \boldsymbol{\theta}_i)^t \mathbf{I}(\boldsymbol{\theta} - \boldsymbol{\theta}_i)$$

by setting its derivative to zero...

$$\mathbf{S} - \mathbf{I}(\boldsymbol{\theta} - \boldsymbol{\theta}_i) = \mathbf{0}$$

and get a new trial point

$$\boldsymbol{\theta}_{i+1} = \boldsymbol{\theta}_i + \mathbf{I}^{-1}\mathbf{S}$$

Fisher Scoring

- Use expected information matrix instead of observed information:

$$E\left[-\frac{d^2\ell(\theta)}{d\theta^2}\right]$$

instead of

$$-\frac{d^2\ell(\theta \mid data)}{d\theta^2}$$

Compared to Newton-Rhapson:

Converges faster when estimates are poor.

Converges slower when close to MLE.