DNA Analysis Techniques for Molecular Genealogy

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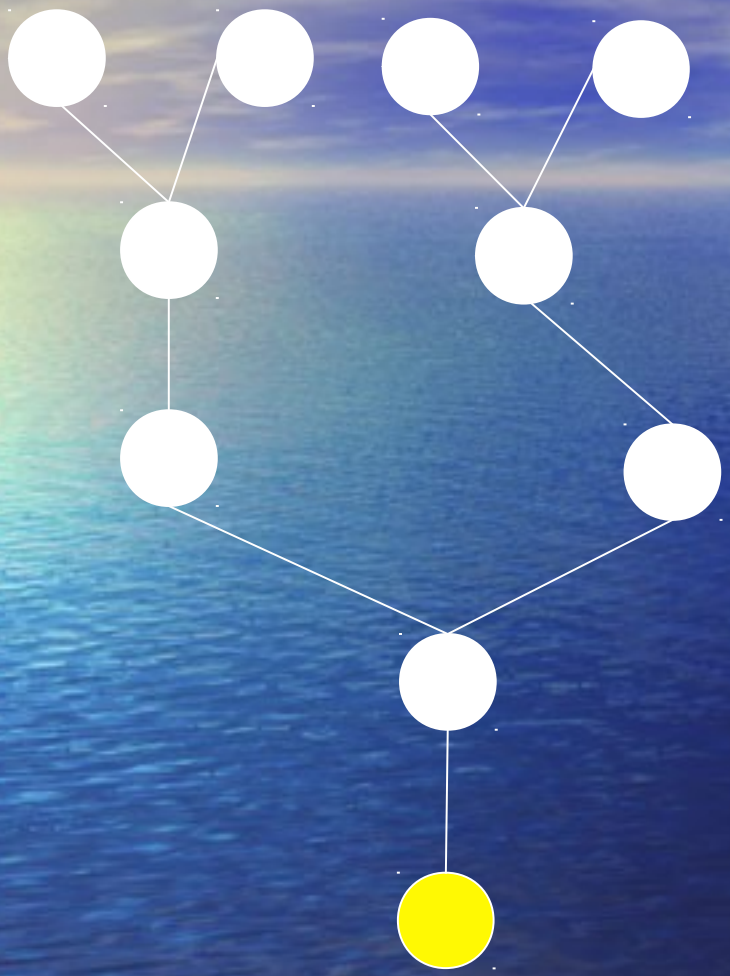
Mission:
The BYU Center for Molecular Genealogy

- *To establish the world's most comprehensive genetic and genealogical database.*
- *To create tools for reconstruction of genealogies from DNA*
- *To establish genetic links between families throughout the world.*

Molecular Genealogy: Process

- 100,000 DNA samples and genealogies are being collected from 500 different populations
- Common ancestors and population structure are inferred [population and quantitative genetics]
- A searchable database is being produced for DNA-based genealogical research



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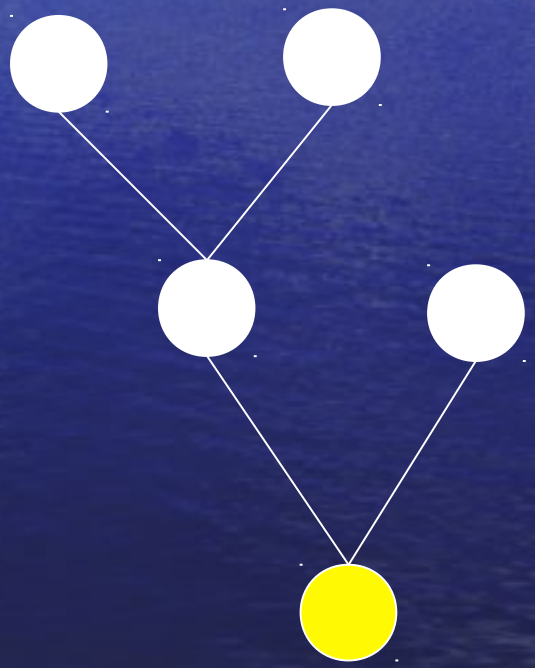
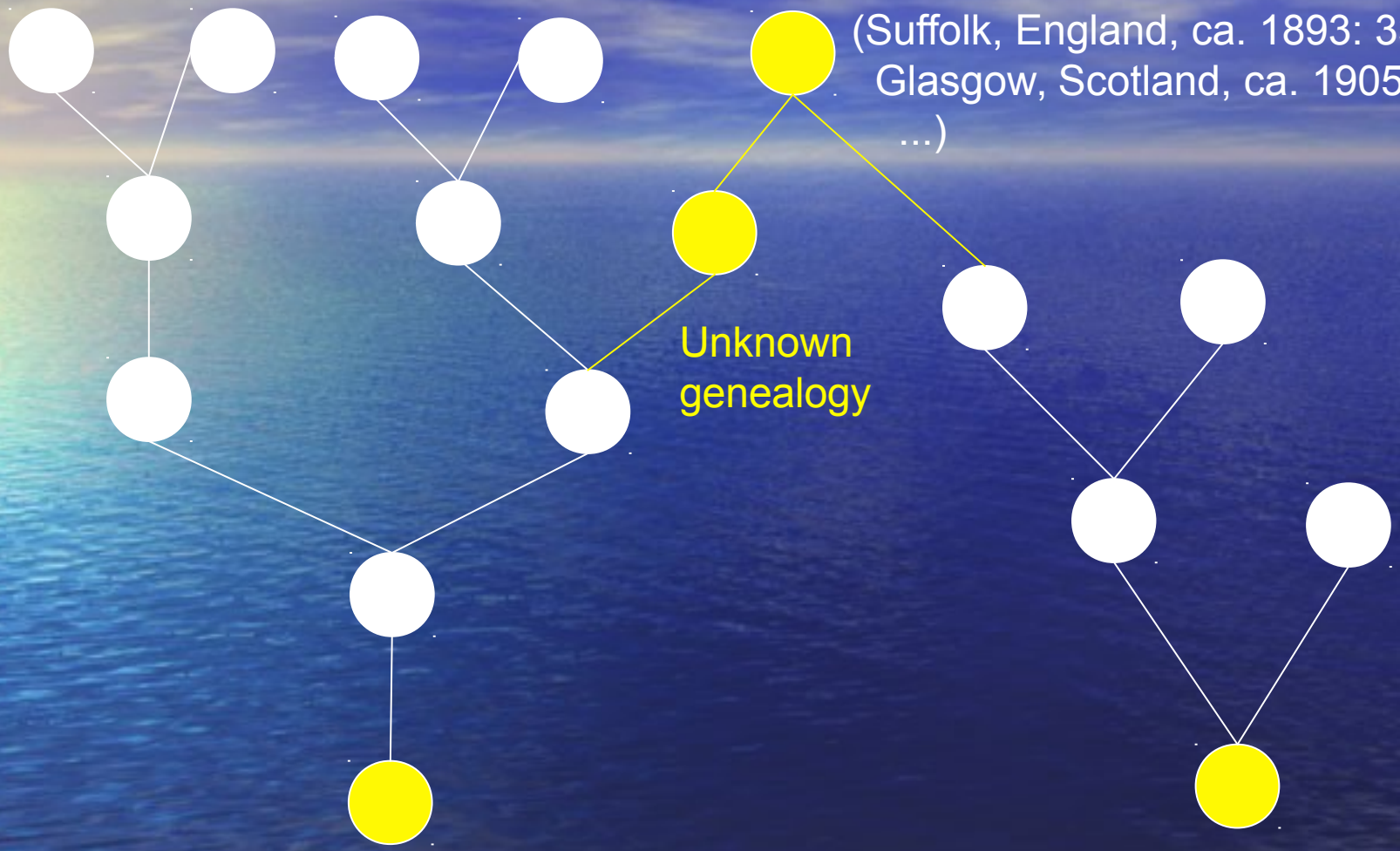
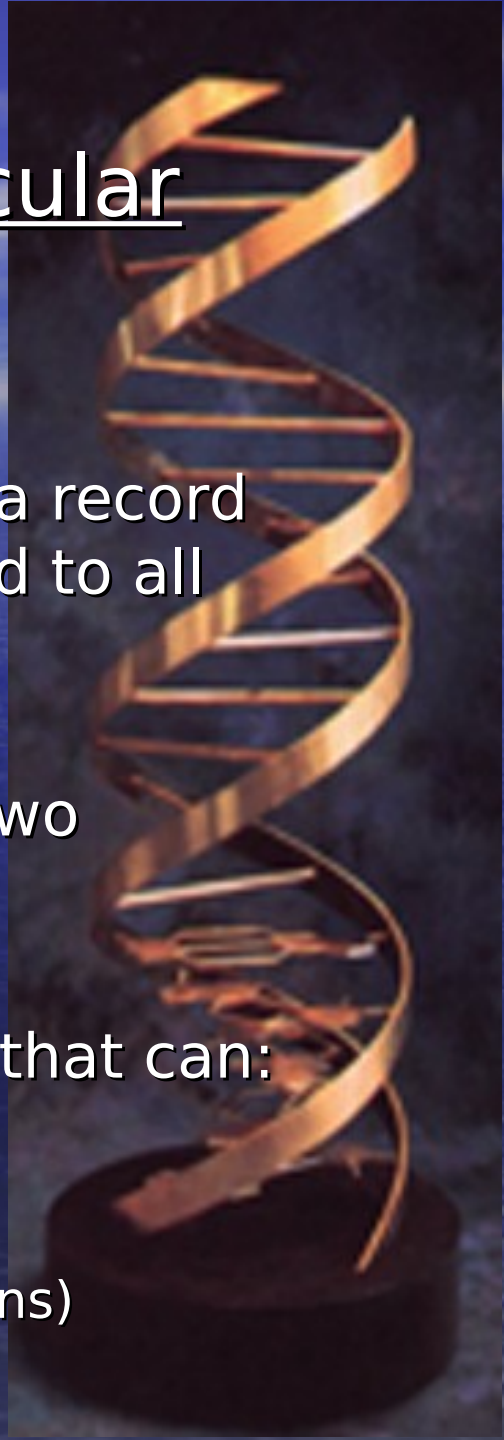


Common Ancestor



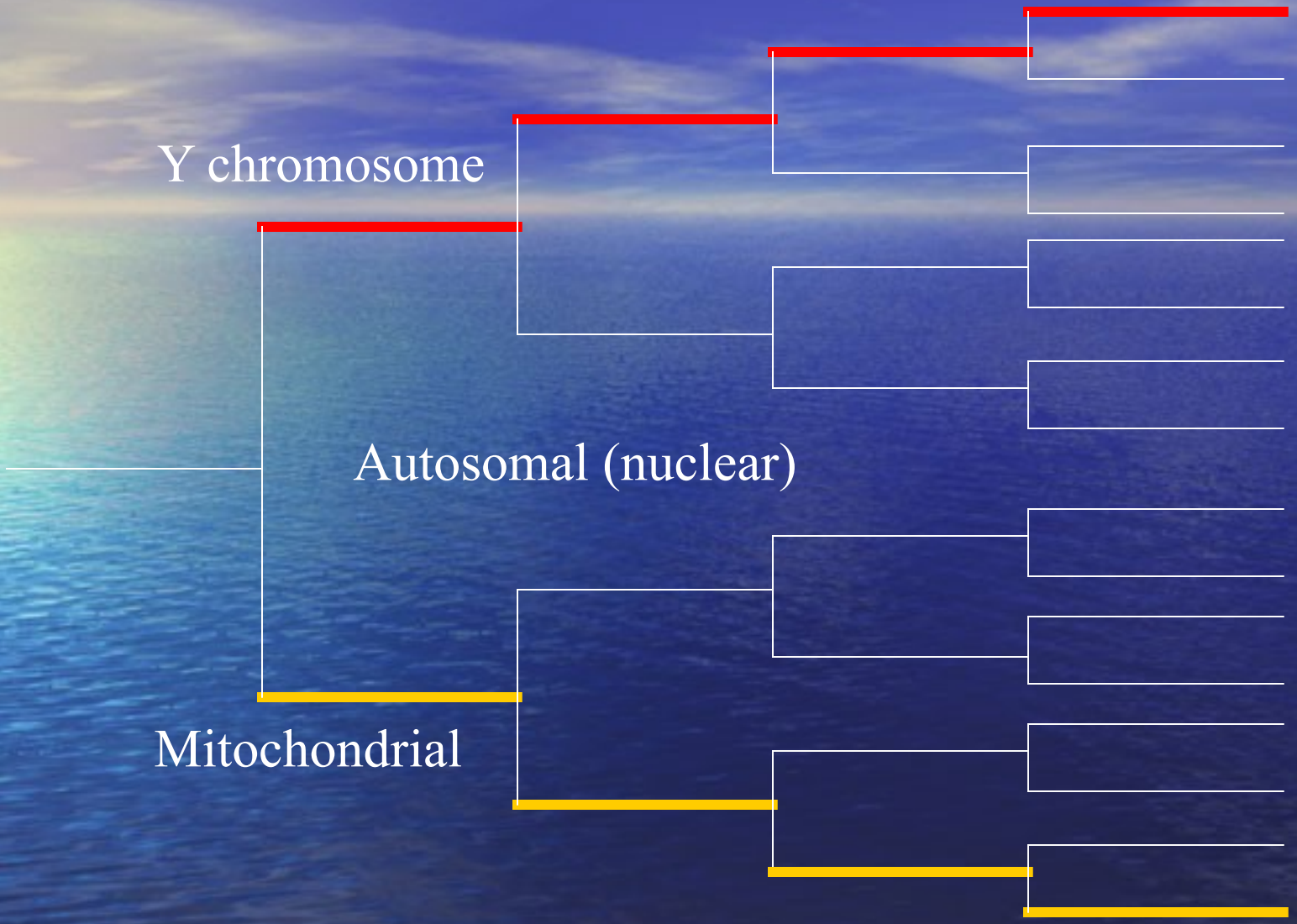
What is the Basis of Molecular Genealogy?

- Each individual carries within their DNA a record of who they are and how they are related to all other people.
- You received all of your DNA from your two parents (50% from each).
- Specific regions of DNA have properties that can:
  - Identify an individual
  - Link them to a family
  - Identify extended family groups (tribes or clans)



3 major types of genetic data

- Y Chromosome
  - Males only, paternal inheritance
  - Haploid, none or little recombination
  - 0.51% of an individual's total genetic information
- Mitochondrial DNA
  - Both males and females, maternal inheritance
  - Haploid, none or little recombination
  - 0.0006% of an individual's total genetic information
- Autosomal (Nuclear)
  - Both males and females, inherited equally from both parents
  - Diploid, undergoes recombination at each generation
  - >99% of your genetic information


Y chromosome
Autosomal (nuclear)
Mitochondrial

Genotypic and Genealogical data

8562	276	280	261	273	162	166	111	125	205	205	207	213	134	134	170	174	222	224	265	269	266	274	118	122	141	149	134	138	175	179	187	195
8563	288	291	271	275	148	160	127	127	209	211	211	223	136	150	174	178	224	224	261	273	268	268	106	120	125	133	132	138	176	178	201	203
8564	272	291	259	267	144	156	113	127	209	211	207	211	142	154	152	174	218	224	269	273	272	272	100	122	149	149	140	140	174	179	191	201
8565	291	295	263	275	148	160	123	127	207	211	217	217	134	136	174	174	220	224	269	309	262	272	106	120	143	147	136	138	171	175	191	195
8566	271	271	263	271	162	164	111	113	207	209	209	213	150	150	174	178	212	216	273	277	258	262	102	118	127	145	138	140	173	175	191	195
8567	271	283	269	275	162	164	111	127	207	209	207	217	150	156	170	178	212	216	273	309	258	270	102	104	143	145	130	138	173	175	187	191

8549	1	8	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	Unknown	0.125
8550	1	8	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125	Unknown	0.125
8551	1	8	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	Europe	0.125	Europe	0.125	NorthAmerica	0.125	NorthAmerica	0.125
8552	1	8	Europe	0.125	Europe	0.125	Unknown	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125	NorthAmerica	0.125
8553	1	8	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125
8554	1	8	PacificIsland	0.125	PacificIsland	0.125	Unknown	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125	PacificIsland	0.125

Sequence and Length polymorphisms

(a) Sequence polymorphism

--------AGA**C**TAG**A**CATT-------

--------AGA**T**TAG**G**CATT-------

(b) Length polymorphism

--------**(AATG)**(AATG)(AATG)-------

3 repeats

--------(AATG)(AATG)-------

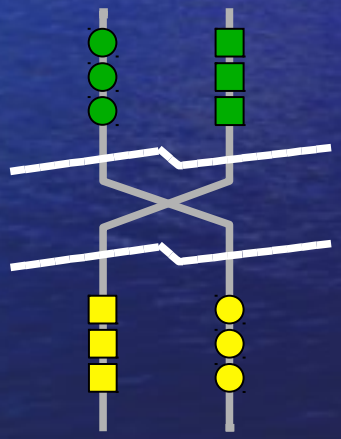
2 repeats

Types of DNA Data Extracted

- Pair of alleles (numbers of repeats) for a locus (e.g.. 121,123)
  - Linked loci (close together in chromosome)
  - Unlinked loci (distant enough from each other to be genetically unrelated, due to the high probability of a crossover occurring between the markers; the presence of one does not imply the presence of the other)

Linked Loci: “Haplotypes”

- The probability of a crossover event occurring in the middle of a haplotype is low, since the loci are tightly linked.



- Haplotypes are therefore likely to be passed down intact for many generations.

Haplotyping

- *Problem:* Correct order of the genetic information in a pair is unknown (which allele came from which parental chromosome?):

  121,123 or 123,121 ?

- The problem compounds for linked loci:

  121|123 121|123 123|121 }
  142|144 144|142 142|144 }... (x 2^3=8)
  115|119 115|119 115|119 }

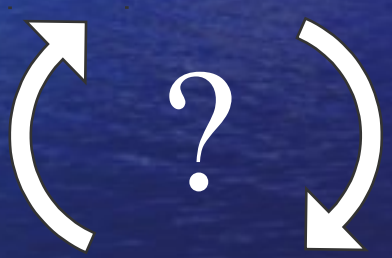
- Finding which alleles occur together on the same chromosome for linked loci (the *haplotypes) is* called *hapotyping*. The alignment is called the *phase.*

Properties of Haplotypes

- Populations which do not inter-breed each develop a distinctive distribution of haplotypes.
- Haplotypes may eventually appear (due to mutation and/or crossover) that do not exist in any other population
- Haplotypes give much more discerning power than alleles alone, since there are many possible haplotypes given a set of possible alleles at each locus

Haplotyping: A Cyclic Problem

- We could figure out the most likely phase for the alleles in a haplotype if we knew the haplotype distributions of the parent populations



- We could figure out the haplotype distributions of the parent populations if we knew the correct phase of the alleles

Haplotyping: A Cyclic Solution

- (1) First guess for phase probs: all equal (0.125)
- (3), (5), ... Estimate phase probabilities based on the current estimate of population haplotype probabilities

- (2), (4), ... Estimate population haplotype probabilities based on the current estimate of phase probabilities

Haplotyping: Results

- Convergence typically achieved in 3-7 iterations
- Difficult to judge accuracy since nobody knows how to get the true correct answer!
- Previous researchers' attempts on simulated data: 50-60% accuracy
- Our algorithm on (different) simulated data: 97%
- Our algorithm on real data (accuracy measured by 'spiking' with CEPH data): 88-93%

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