# Roadmap

- Coalescent with recombination
- Hitchhiking
- Gene surfing
- "Genetic draft" (background selection)

## One-minute responses

- Too much/not quite enough discussion time
- Where did $4Nc$ come from?

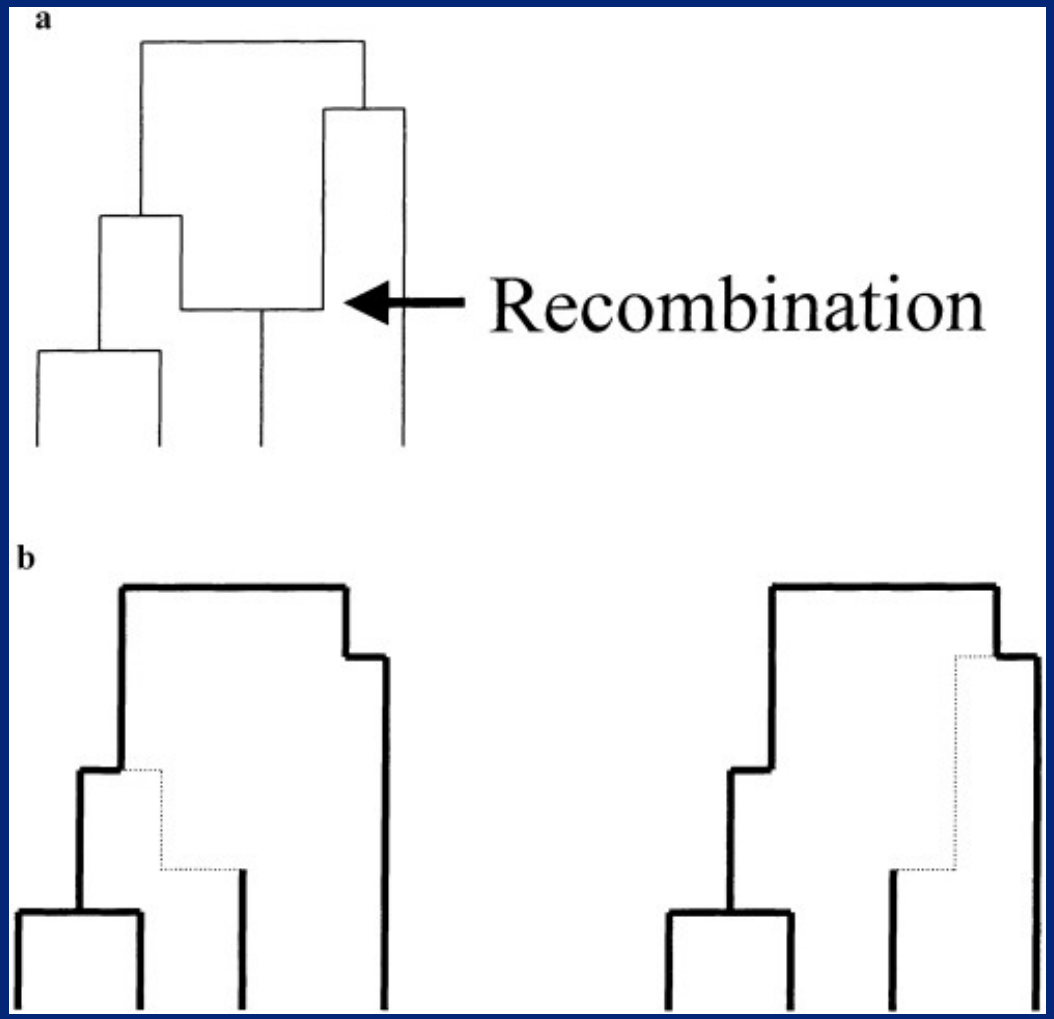
## Where did $4Nc$ come from?

- $4Nc$ and $4Nr$ are two names for the same quantity
- Time to common ancestor of a region: $4N$ generations
- Recombination chance per generation: $c$
- $c << 4N$ – few or no recombinations in haplotypes, high disequilibrium
- $c >> 4N$ – lots of recombinations, little or no disequilibrium

## Selection on two linked loci with recombination

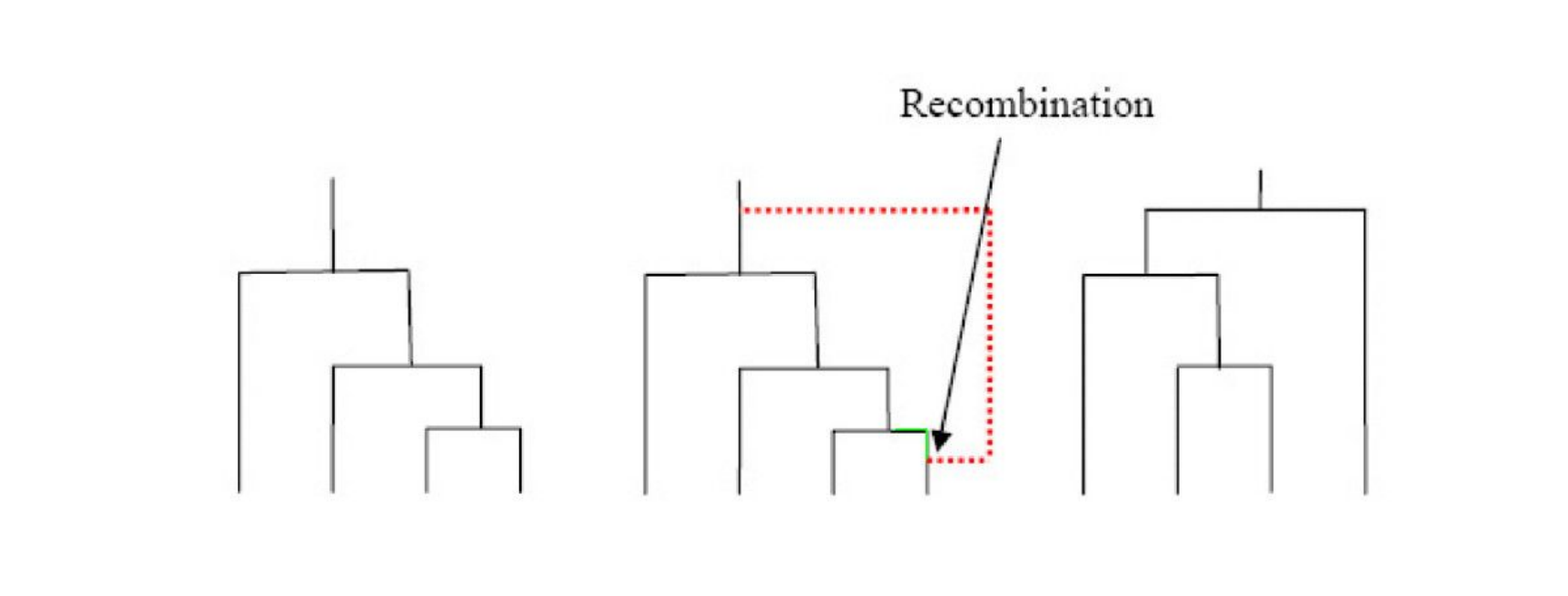
- If the loci interact (epistasis):
  - No simple equations for what happens
- If alleles with a favorable interaction start out togther, recombination *reduces* population fitness
- Predicted to lead to strongly interacting loci being clustered in the genome
  - Not much evidence for this in eukaryotes
  - HLA genes might be an example–they are tightly linked in many/most mammals
  - Alternative: they are tightly linked because they are tandem duplications

# Coalescent with recombination




With recombination, different parts of the chromosome have different (but correlated) local coalescent trees

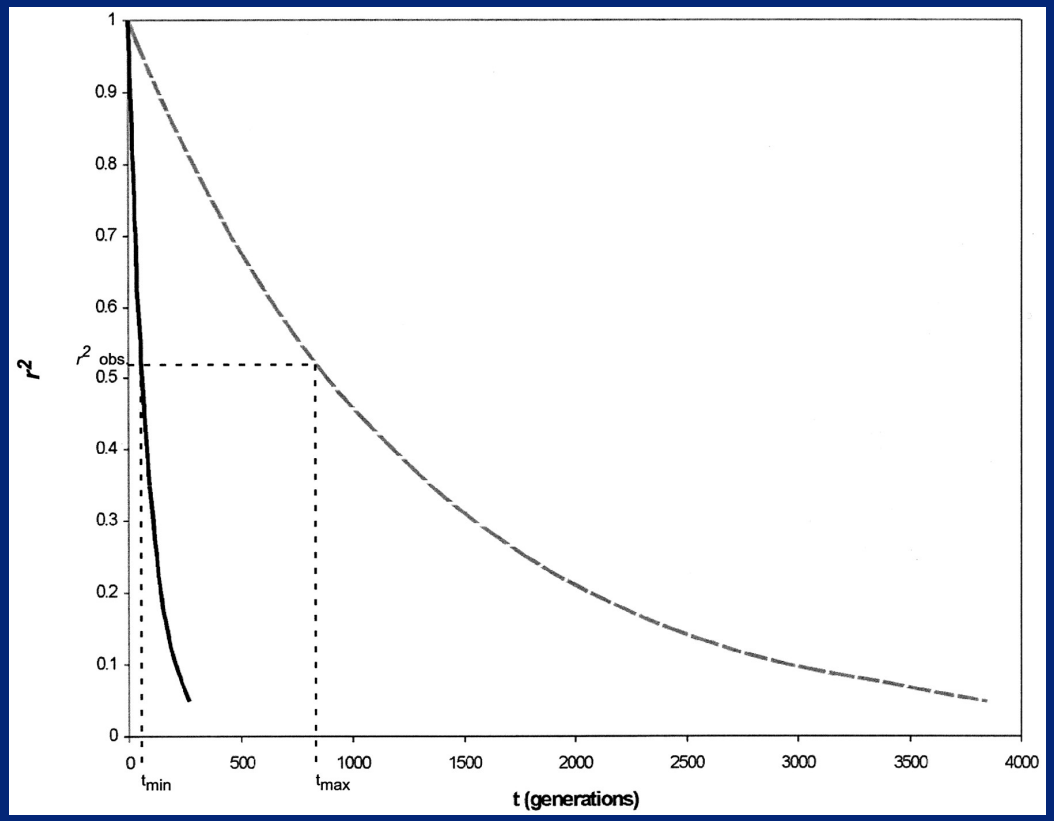
# Coalescent with recombination




A recombination can change the depth of the local coalescent tree

# Predicting allele age from LD

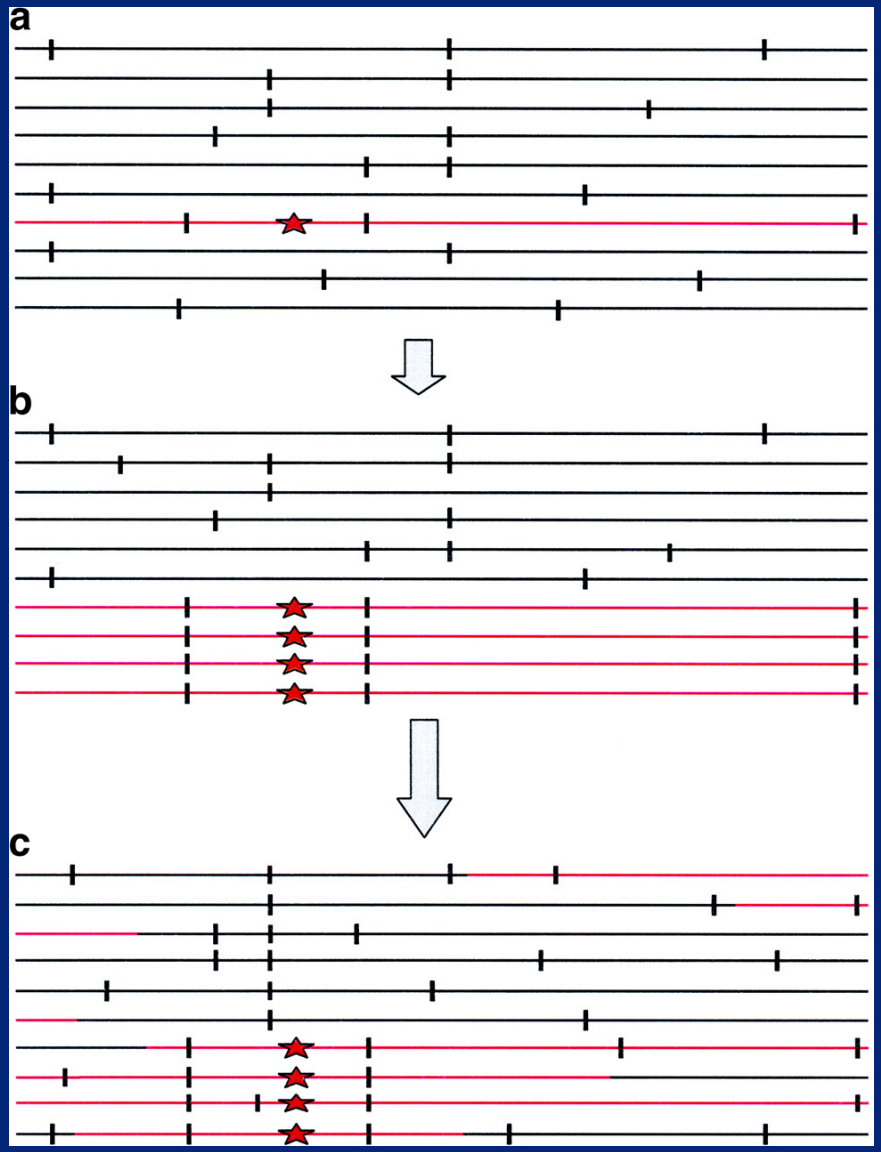
- We know rate of LD decay with time: $D_n = (1 - c)^n D_0$
- Estimate $D_0$ of newly arisen mutation
- Measure current $D$
- Estimate time back to origin of mutation




"Plot of linkage decay between G6pd (site 202) and L1cam (positions 776, 885, and 2115). The expected plot of linkage decay as measured by $r^2$ is shown over time (t) for a range of two different recombination rates [...] for the chromosomal region near G6pd and L1cam. The observed $r^2 = 0.52$ provides minimum (tmin = 58 generations) and maximum (tmax = 840 generations) ages for the G6pd A-allele.
From Saunders et al. (2002) Genetics 162: 1849-1861.

## $G6pd$ story is puzzling

- Locus is X-linked
- Hemizygous males and homozygous females have anemia
- Hemizygous males and homozygous or heterozygous females are protected against malaria
- What kind of selection is this?
  - Could be overdominant if homozygous females are fitter (with malaria) but no evidence for this
  - Could be directional, but frequency still $< 20\%$ in most of Africa; it doesn't seem able to fix
  - Fluctuating selection?
  - Interaction with other loci?
  - Gene flow?




From Saunders et al. (2002) Genetics 162: 1849-1861.

## Hazards of hitchhiking

- Fixation of good mutant will fix a large chunk of its haplotype
- This includes any nearby deleterious mutations
- Why not turn up recombination rate to avoid this?
  - Recombination can be mutagenic
  - Significant energy required
  - Breaks up epistatic allele combination
- Recombination rate varies wildly among organisms, between sexes, and across genome

# Apparently recombination is not essential

Bdelloid rotifer. The entire class is believed to have gone without sex for at least 40 million years (maybe as long as 100 million years). They are common and widespread with at least 360 different species.

## Evidence for asexuality of Bdelloids

- Chromosomes do not match up in pairs
- No males
- No meiosis; eggs produced by mitosis
- Relationships between individuals form a simple tree across the whole genome
- Strong LD across genes on different chromosomes

*What's risky about this lifestyle?*

# Muller's Ratchet–death by hitchhiking

- Population contains a range of haplotypes in different fitness classes
- Deleterious mutations can move a haplotype into a worse class
- If:
  - Population size is limited
  - Selection is weak
  - Recombination is absent
  - Favorable and back mutations are rare
- The most-fit haplotype class is prone to be lost
- Repeated, this causes deterioration of the population

# Mutational meltdown

- There can be a feedback cycle:
  - The ratchet reduces absolute fitness
  - Population size decreases
  - Small population makes ratchet click faster
  - Process accelerates until population dies out
- Interest in causing this to happen in cancer cell populations

## How can populations escape the ratchet?

- Sexual reassortment and recombination
  - Allows two mediocre haplotypes to generate a better one
- Other modes of genetic exchange:
  - Horizontal gene transfer
  - Chromosome rearrangement (suggested for mammalian Y chromosome)
- Extremely strong selection (mtDNA)

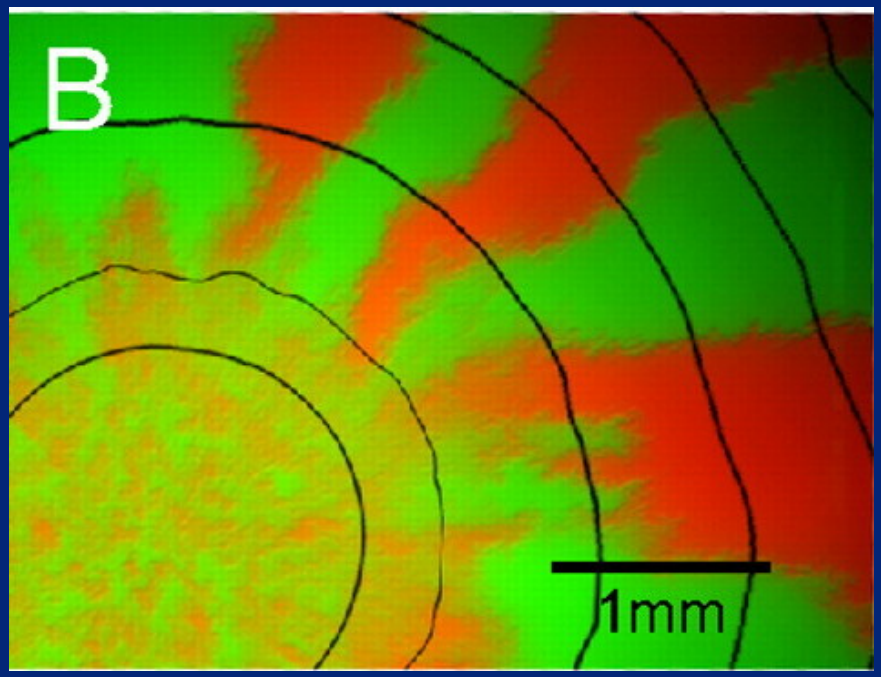
# Bdelloid scandal

- Lifestyle includes high risk of desiccation:
  - High investment in DNA repair – low mutation rate
  - Pick-up of DNA from environment
- Low mutation slows ratchet
- Horizontal gene transfer allows swapping out bad alleles

## Best paper title ever

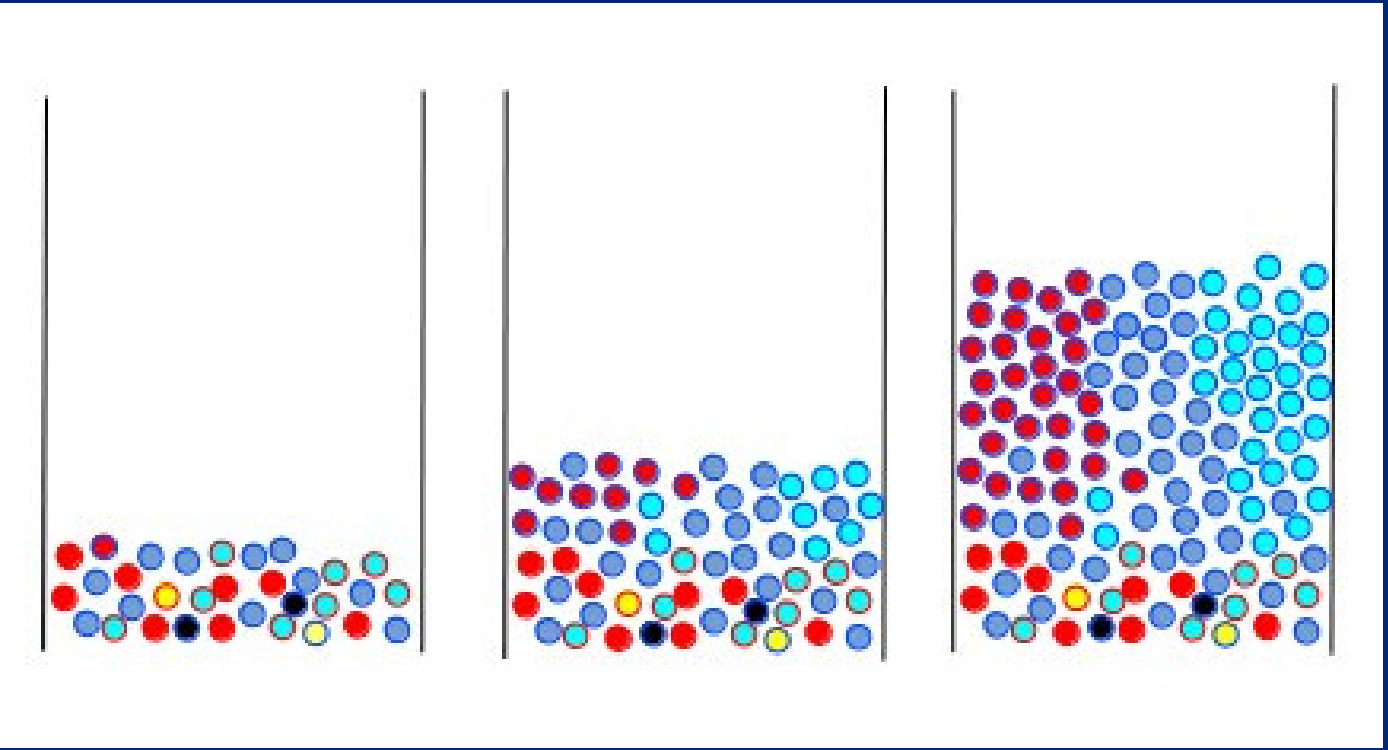
"Evolution of bacterial transformation: Is sex with dead cells ever better than no sex at all?" RJ Redfield, Genetics 119:213-331, 1988.

Why would an organism pick up environmental DNA, given that the donor is known to be dead?




Mixture of red and green fluorescent $E.\ coli$ on a plate. From Hallatschek et al. (2007) PNAS 104.

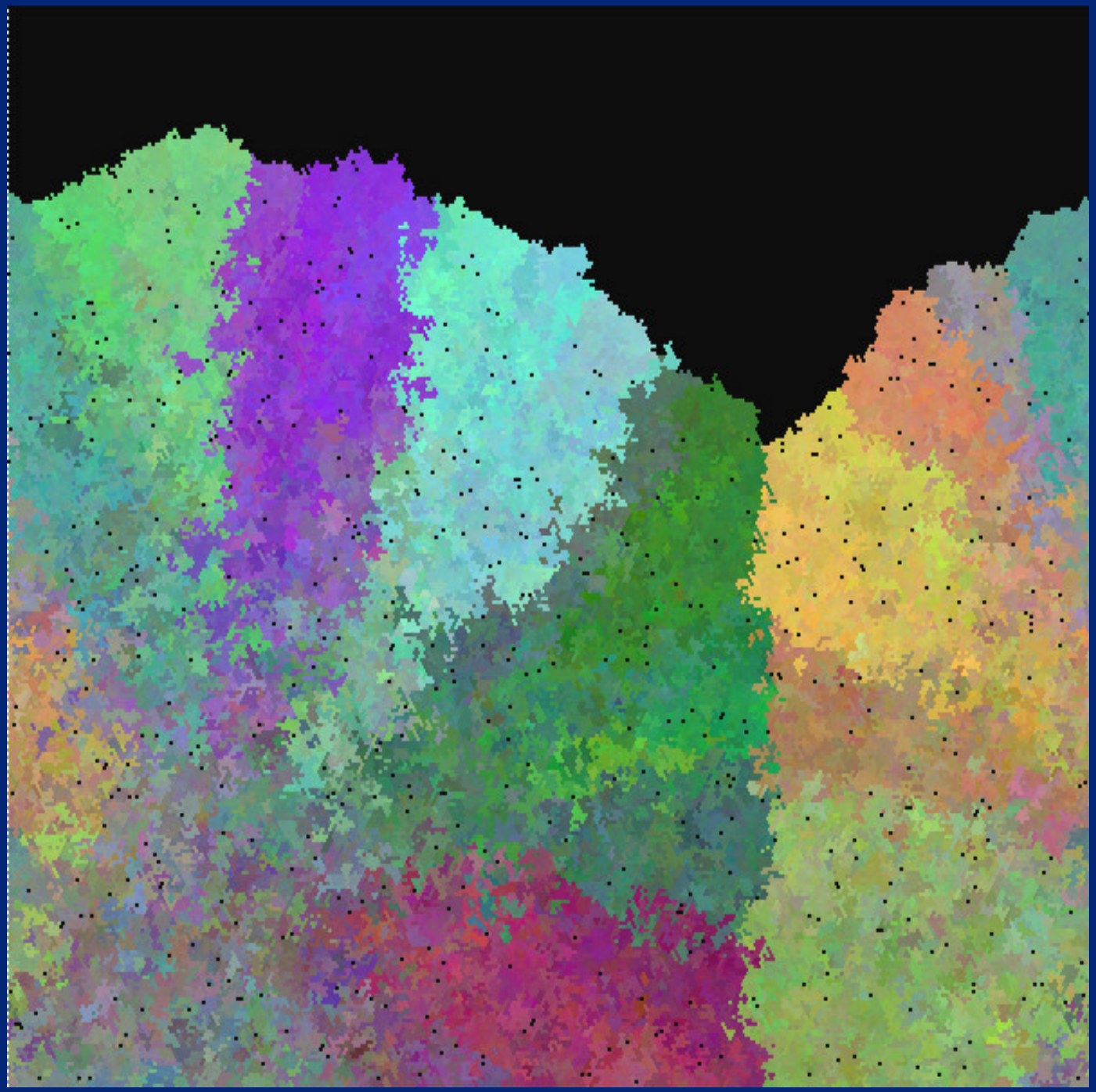
# Gene surfing



Sectors of related cells appear as population grows upward

## Gene surfing

- Happens when:
  - Population expanding rapidly in space
  - Individual mobility limited
- Intense genetic drift along leading edge of expansion
- Like hitchhiking, but on population growth rather than a sweep



## Possible gene surfing in a pre-cancer condition

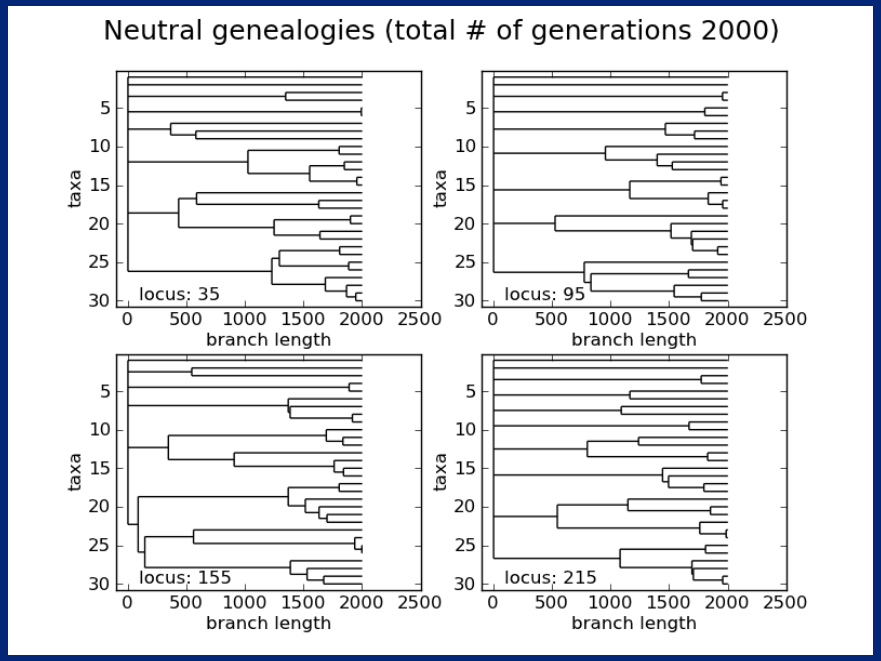
- Barrett's Esophagus (BE) – neoplasm (not yet cancer)
  - Probably grows up from bottom of esophagus
  - Intense gene surfing in simulations of this process
  - An oncogene mutation that was NOT selectively favored could still become frequent in this system

## Paradoxes

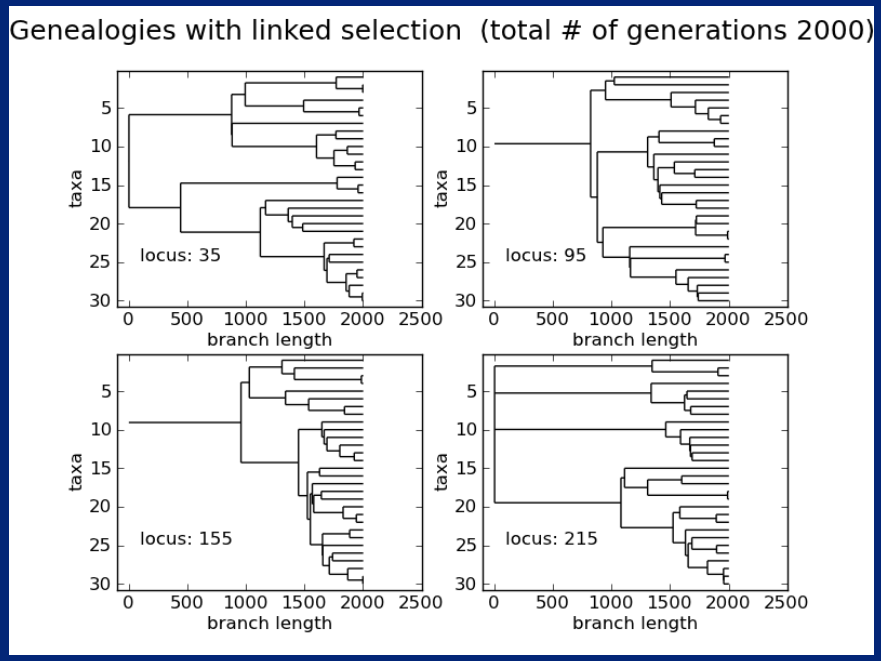
- BE paradoxes
  - Most patients never get cancer
  - Those who do get cancer do so within a few years of diagnosis
- General cancer paradox
  - Many alleles that cause cancer when inherited are seldom seen in sporadic cancers
- Possible explanation: these mutations are neutral or harmful to cells carrying them
- They need a boost to become frequent enough to matter
- Trying to get funding to look into this further

# Hitchhiking and related effects reduce $N_e$

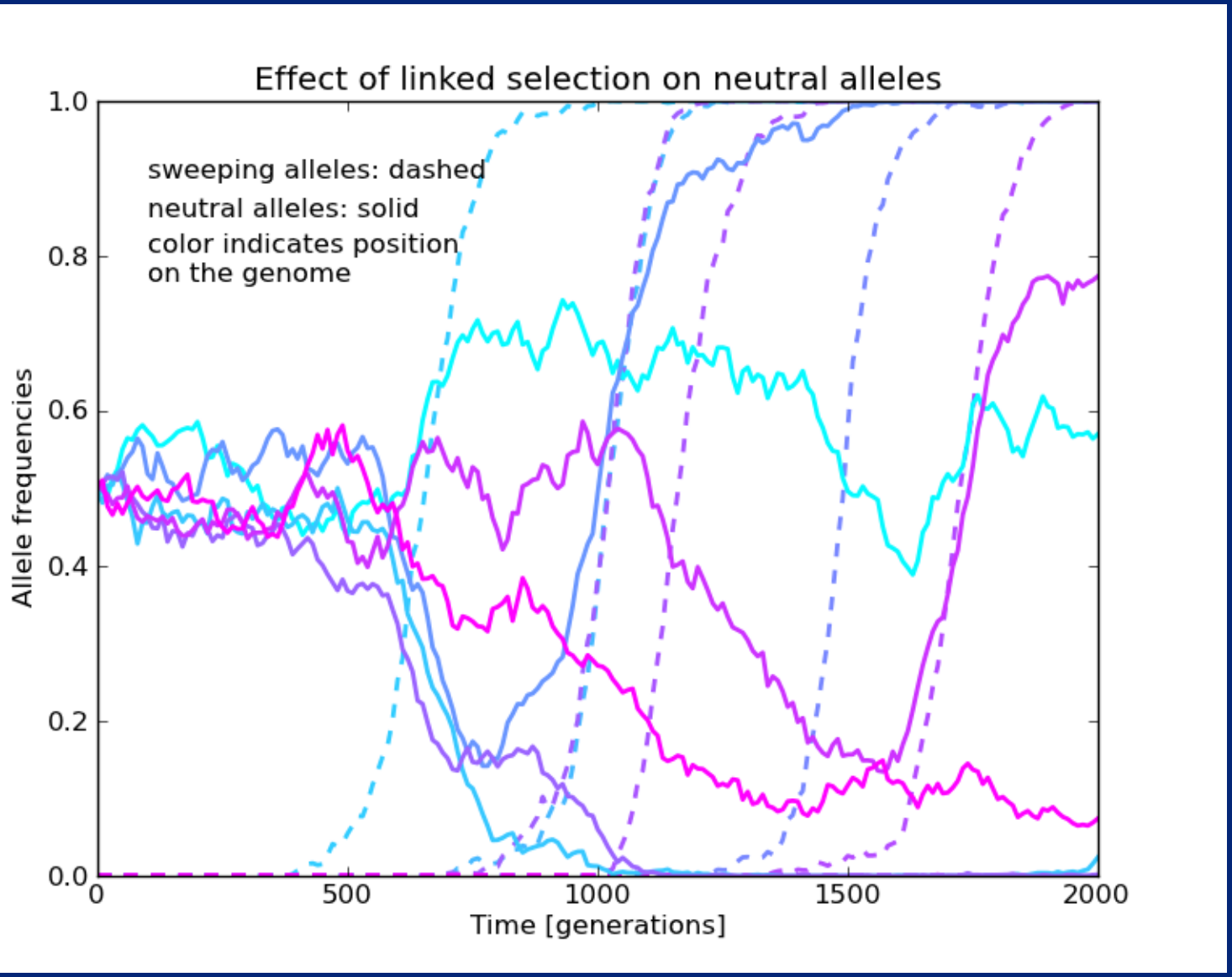
Without background selection




With background selection




Simulated data from
http://webdav.tuebingen.mpg.de/interference/draft.html


Effect of linked selection on neutral alleles
sweeping alleles: dashed
neutral alleles: solid
color indicates position
on the genome
Allele frequencies
Time [generations]
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000

## "Genetic draft"

- Both positive and negative selection reduce $N_e$ for nearby loci
- Not often considered in applications of the coalescent
- Could the anomalous low $N_e$ for red drum be due to this?

# Monday

- Population subdivision
- Gene flow
- Gene flow versus selection

## One-minute responses

- Please:
  - Tear off a slip of paper
  - Give me one comment or question on something that worked, didn't work, needs elaboration, etc.