

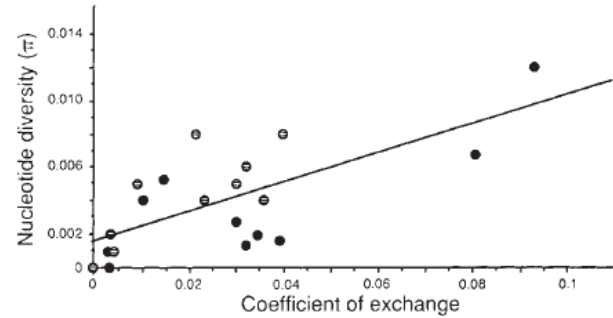
Background selection!



An alternative explanation for why π and recombination rate are correlated...
...and a continuing, heated debate!

A positive view of the world...

- Beneficial mutations around the genome cause the association of recombination rate to π !
- Advocates:



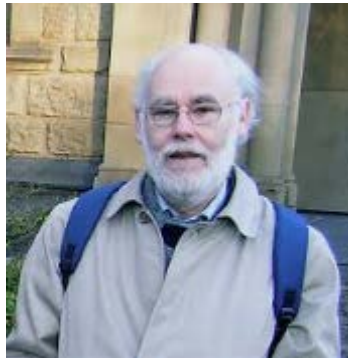
But what if beneficial mutations *very* rare?



... won't see a strong overall trend:
many low recombination regions
may still have high π .

An alternative hypothesis:

- “Bad” mutations are very common.
- When a bad mutation happens, it dooms the alleles near it to *eventual* death.
- The size of the doomed window varies with recombination rate.
- “Background selection”



Background selection low/ no recombination

GCATGCTAGTCGATTGCGGAATTTT**T**G
GCATG**A**GAGTCGATTGCGG**C**ATTTTCG
GCATGCTAGT**T**GATTGCGG**C**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG
GCATGC**G**AGTCGATTGCT**T**G**C**ATTTTCG
GCATGCTAG**G**CGATTGCGG**C**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG
G**A**ATGC**G**AGTCGATTGCGG**A**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG

Background selection low/ no recombination

Persisting chromosome segments

GCATGCTAGTCGATTGCGGAATTTT**T**G
GCATG**A**GAGTCGATTGCGG**C**ATTTTCG
GCATGCTAGT**T**GATTGCGG**C**ATTTTCG
→ GCATGCTAGTCGATTGCGG**C**ATTTTCG
GCATGC**G**AGTCGATTGCT**T**G**C**ATTTTCG
GCATGCTAG**G**CGATTGCGG**C**ATTTTCG
→ GCATGCTAGTCGATTGCGG**C**ATTTTCG
G**A**ATGC**G**AGTCGATTGCGG**A**ATTTTCG
→ GCATGCTAGTCGATTGCGG**C**ATTTTCG

Background selection low/ no recombination

Persisting chromosome segments

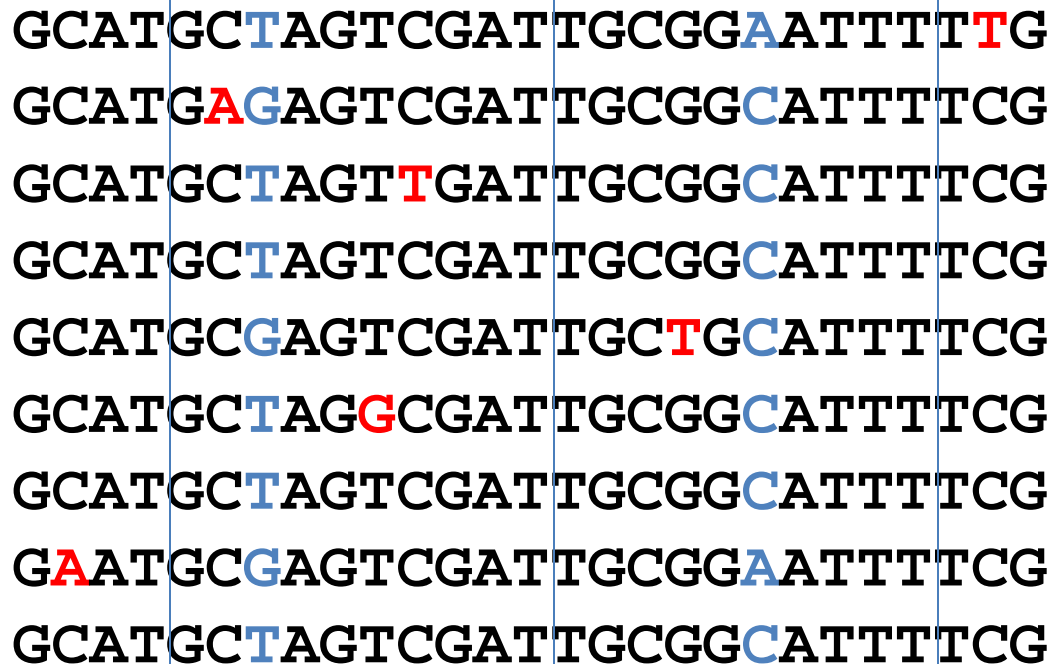


GCATGCTAGTCGATTGCGGCATTTTCG

GCATGCTAGTCGATTGCGGCATTTTCG

GCATGCTAGTCGATTGCGGCATTTTCG

Background selection high recombination



GCATGCTAGTCGATTGCGGAATTTT**T**G
GCATG**A**GAGTCGATTGCGG**C**ATTTTCG
GCATGCTAGT**T**GATTGCGG**C**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG
GCATGC**G**AGTCGATTGCT**T**G**C**ATTTTCG
GCATGCTAG**G**CGATTGCGG**C**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG
G**A**ATGC**G**AGTCGATTGCGG**A**ATTTTCG
GCATGCTAGTCGATTGCGG**C**ATTTTCG

The diagram illustrates background selection with high recombination. It shows a DNA sequence with three vertical lines representing recombination events. Mutations are highlighted in red and blue. The sequence is as follows:

| Position | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | | | | | | | |
|------------|---|----------|---|---|---|----------|----------|---|---|----------|----|----|----|----|----|----|----|----------|----------|----------|---|---|---|---|----------|---|---|
| Sequence 1 | G | C | A | T | G | C | T | A | G | T | C | G | A | T | T | G | C | G | A | A | T | T | T | T | T | G | |
| Sequence 2 | G | C | A | T | G | A | G | A | G | T | C | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | |
| Sequence 3 | G | C | A | T | G | C | T | A | G | T | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | | |
| Sequence 4 | G | C | A | T | G | C | T | A | G | T | C | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | |
| Sequence 5 | G | C | A | T | G | C | G | A | G | T | C | G | A | T | T | G | C | T | G | C | A | T | T | T | T | C | G |
| Sequence 6 | G | C | A | T | G | C | T | A | G | G | C | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | |
| Sequence 7 | G | C | A | T | G | C | T | A | G | T | C | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | |
| Sequence 8 | G | A | A | T | G | C | G | A | G | T | C | G | A | T | T | G | C | G | A | A | T | T | T | T | C | G | |
| Sequence 9 | G | C | A | T | G | C | T | A | G | T | C | G | A | T | T | G | C | G | C | A | T | T | T | T | C | G | |

Background selection high recombination

Persisting chromosome segments

The diagram illustrates DNA sequences with three vertical blue lines representing recombination events. The sequences are as follows:

| Sequence |
|-------------------------------------|
| GCATGCTAGTCGATTGCGGAATTT |
| GCAT TGCGGCATTTTCG |
| GCAT TGCGGCATTTTCG |
| GCATGCTAGTCGATTGCGGCATTTTCG |
| GCATGCGAGTCGAT TCG |
| GCAT TGCGGCATTTTCG |
| GCATGCTAGTCGATTGCGGCATTTTCG |
| GCAGAGTCGATTGCGGAATTTTCG |
| GCATGCTAGTCGATTGCGGCATTTTCG |

Background selection high recombination

Persisting chromosome segments

GCATGCTAGTCGATTGCGGAATTT
GCAT TGCGGCATTTTCG
GCAT TGCGGCATTTTCG
GCATGCTAGTCGATTGCGGCATTTTCG
GCATGCGAGTCGAT TCG
GCAT TGCGGCATTTTCG
GCATGCTAGTCGATTGCGGCATTTTCG
GCAGAGTCGATTGCGGAATTTTCG
GCATGCTAGTCGATTGCGGCATTTTCG

A lot more variability is retained because bad mutations can be lost without
“dragging away” so much of the rest of the chromosomes

Background selection prediction

- Depends on high rates of bad mutation
- Regions of high recombination (close hotspots) will preserve more variation (high π)
 - Exactly the same prediction as hitchhiking!



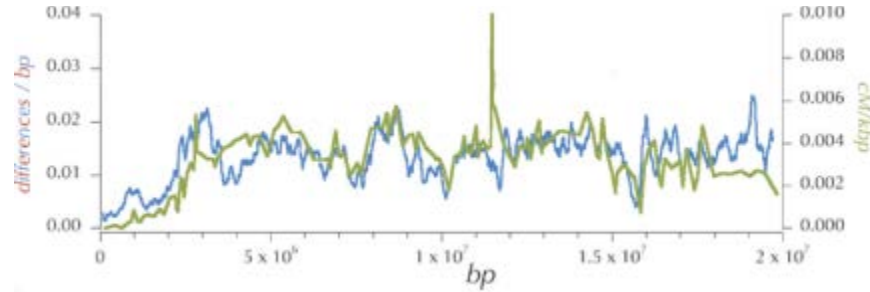
“The big debate...”

- Could be **selective sweeps & hitchhiking**
 - New *advantageous* variants arise frequently, and their fixation takes away variation
 - Neutral theory says these are very rare.
- Could be **background selection**
 - New *bad* mutations arise very frequently, and their elimination takes away variation
 - Neutral theory has no problem with this.
- Very much an area of active research today!!!

Big debate and much continued disagreement...

- Whole genome analyses show positive associations of π and recombination rate:

Drosophila simulans-

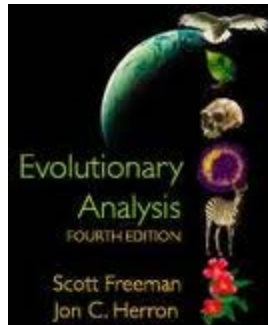


- Begun** argues it's mostly from hitchhiking, and some beneficial mutations have been found
- Charlesworth** argues that we know of WAY more cases of bad mutation



Perspectives

- Evolutionary Analysis, Freeman & Herron, 4th ed:
“The current consensus is that hitchhiking is probably responsible for the most dramatic instances of reduced polymorphism in linked regions- for example, where sequence variation is entirely eliminated- while background selection causes the less extreme cases.” -page 263



Begun reply

- E-mail 28 February 2012:

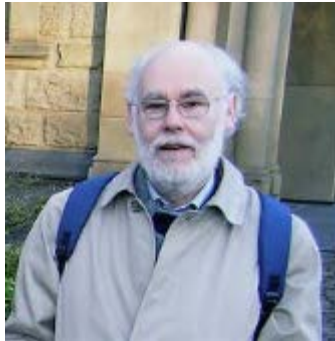
“There is no convincing evidence that background selection is a significant factor in Drosophila genome evolution!”



Charlesworth reply

- E-mail 15 March 2011:

*“Bulls**t! Look at the paper by Vera Kaiser and me in the 2009 Trends in Genetics ... I think we make a reasonable case that the reduced variability on the ... Y and the [fourth] chromosome can be explained by background selection.”*





Still unsettled...

- *“The controversy surrounding the relative significance of strongly beneficial and deleterious mutations in evolution has stimulated research activities for almost a decade. Despite efforts from many theorists and empiricists, fundamental questions are still open, in particular for the population genetics of regions of reduced recombination.”* Stephan, 2010



Image Credits, Unit 14-4

- Drosophila simulans recombination rate, © 2007 Begun et al, CC by 2.5, "Population Genomics: Whole-Genome Analysis of Polymorphism and Divergence in Drosophila simulans", www.plosbiology.org
- Puzzled chimp, © 2005 Kabir Bakie, CC by 2.5, en.wikipedia.org