Nearly-neutral dynamics: when is selection not selective?

Daniel Lawson

Bioinformatics and Statistics Scotland

Macaulay Institute, Aberdeen

work with:

Henrik Jeldtoft Jensen

Imperial College London

Question: is evolution really stochastic?

- Focus on Bacteria

- Large population sizes (>10^{10})

- Weak selection acts on <u>whole</u> genome
  - Stability of protein folding (Aita, Ota and Usimi, 2003, JTB 221:599-613)
  - Gene regulation (Ohta, 2002, PNAS 99:5916134-16137)
  - Non coding DNA! (Ohta, 1997, Gene 205:261-267)
  - Genome length, reading fidelity, etc…

- How small should selection be for this not to matter?

Standard approach

- Consider allele A and mutant type a
  - Fitness of A is 1. Fitness of a is 1-s
  - Population size N
  - Initial population of a is 1

- Gamblers ruin:
  - Probability of winning relative to neutral case
    $$p(s)/p(0) = 1 - Ns + O([Ns]^2)$$

- Therefore s* ~ 1/N

Standard approach

- Selection $O(10^{-10})$ is important!

- Theory: Bacteria shouldn't evolve neutrally

- Genetics data: neutral evolution occurs
  - Neutral at some loci
  - Neutral phylogenetic tree

- Also: genetic inference relies on this!

- Theory or data interpretation is wrong
  - Inappropriate to apply theory?
  - Stochastic interpretation of evolution?

- Bacteria perhaps are more selected?
  - ~50% of genes are selected in bacteria (Charlesworth and Eyre-Walker, 2006, Mol. Biol. Evol. 23:1348-1356)
  - 0-30% in apes

Are bacteria special?

- Form colonies: lower effective population

- High mutation rates: high diversity

- (mostly) clonal: gene interactions important

Fitness and reproduction

- "Fitness" concept
  - Doesn't exist!
- Fitness assigned to genes?
  - Only when recombination is high
- Fitness assigned to whole types?
  - Better when recombination is low
- Difference between asexual and sexual reproduction

High mutation rates

- Create a distribution of many types
- Types don't have to be very good to mutate again
- Gene interactions:
  - Impact of mutation depends on genotype
  - Multiple bad mutations can produce fit type
- How does this distribution effect evolution?

Evolution model

- N individuals reproduce clonally in a type space
    - Chosen randomly for death
    - Chosen proportionally to fitness for reproduction
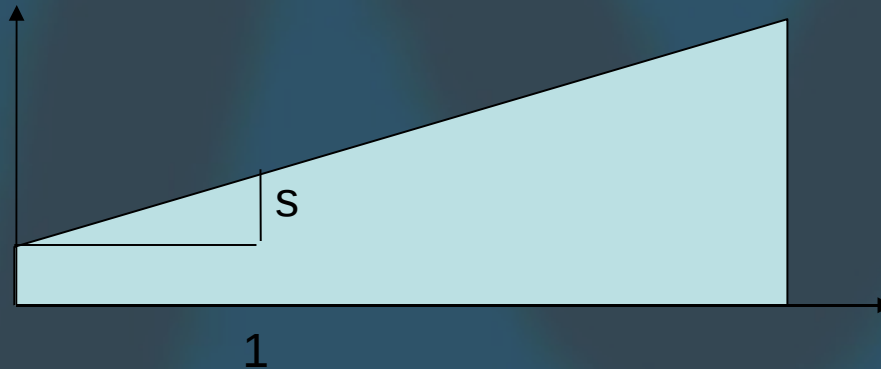   - Mutation: change at a single locus

- Mutation: maximum change in fitness = s
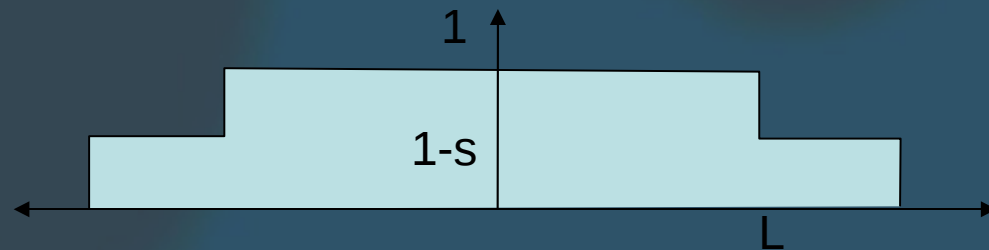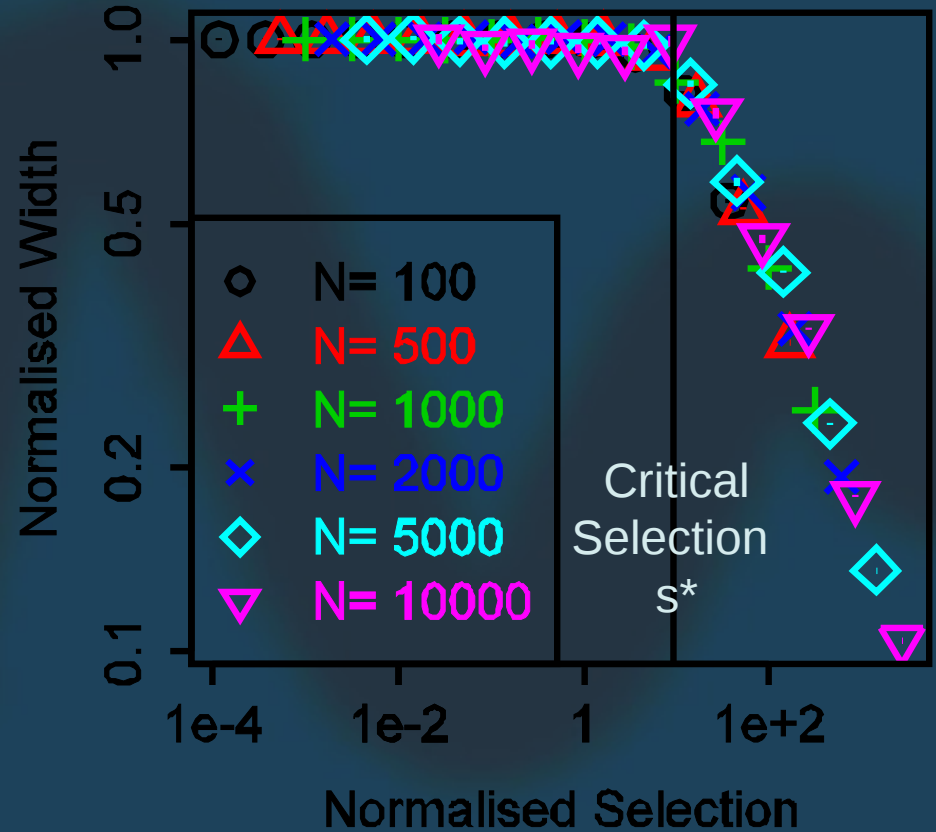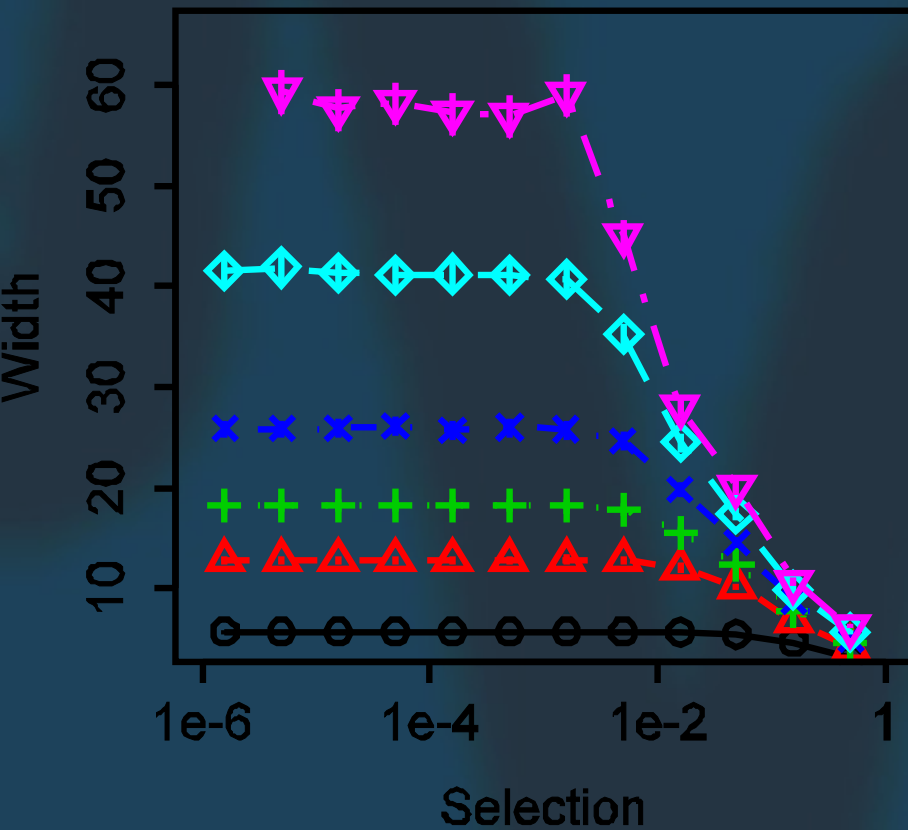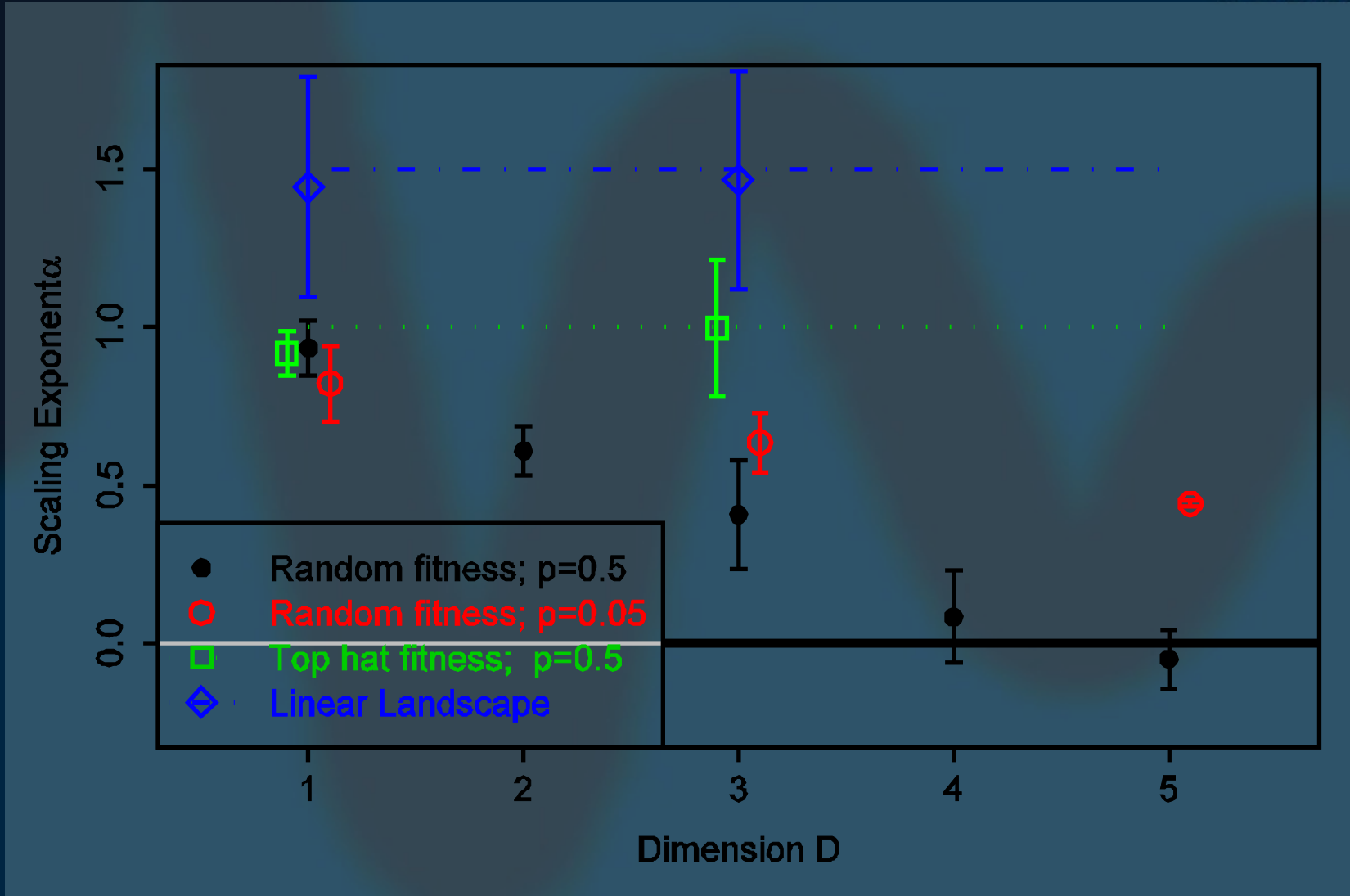
Fitness Landscapes

- Random

- Linear

- Top hat

Results

Width: standard deviation of genetic distribution
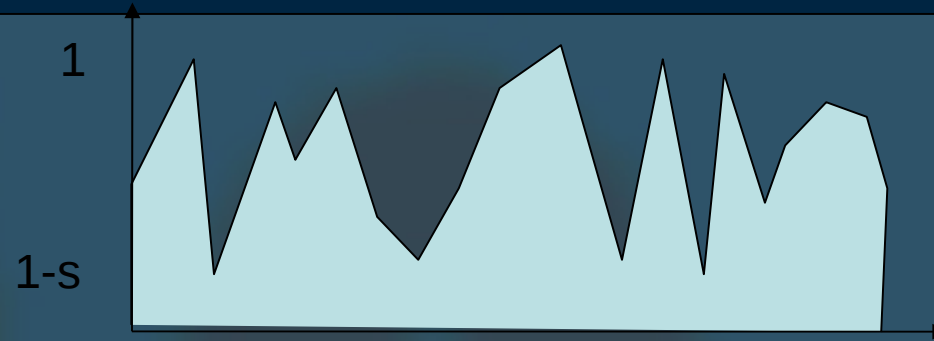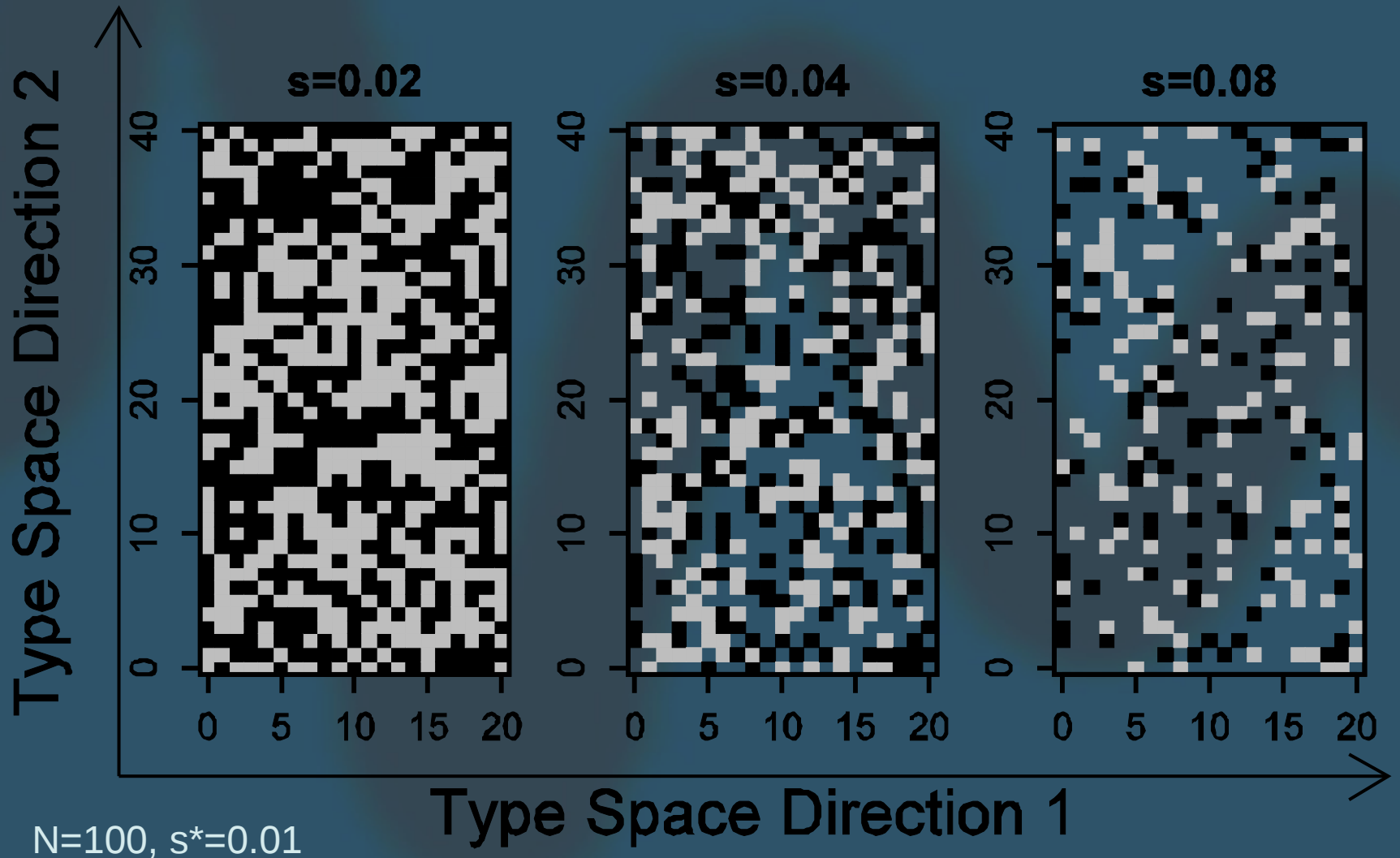
$$S^* \sim N^{-\alpha}$$

Results

Summary of Results

- Neutral region size:
  - Linear landscape: large region ($\alpha = 1.5$)
  - Top hat: as low mutation case ($\alpha = 1$)
  - Random fitness:
    - $\alpha \rightarrow 1$ as $p_{mutation} \rightarrow 0$ or dimension $D \rightarrow 0$
    - $\alpha \rightarrow 0$ as dimension $D \rightarrow \infty$
    - When $\alpha = 0$ an infinitely large population can still be neutral!

Why neutral evolution?

Real evolution

- Selection "weaker" in large populations if:
    - Gene interaction is strong
    - Mutation rates per generation high
- Can form "Neutral Network"
    - Not all mutations are neutral
    - But population overcomes bad mutations by chance
- MAY apply to sexual population if gene interactions strong enough (NK landscape)

Caveats

- "Fitness Landscapes" don't really exist
- Model not explicitly for DNA
- Only mutations with weak effect count as "dimensions"

Conclusion

- Combination of
  - High mutation rates
  - Gene interactions important over evolutionary time
  - Large space of possible mutations
- Allows statistically neutral evolution even when selection is present
- Occurring on neutral networks
- This happens all the time!

Implications

- Recombining/non-recombining regions and phenotypes/genotypes evolve differently

- Stochastic evolution in large populations is reasonable

  - Current genetic inference techniques supported!

- Selection at single mutation DOES NOT imply selection in population!

Further reading

This work:

"The role of weak selection and high mutation rates in nearly neutral evolution"

Daniel John Lawson and Henrik Jeldtoft Jensen

(to appear)

Cited Literature:

Charlesworth and Eyre-Walker, 2006, Mol. Biol. Evol. 23:1348-1356

Aita, Ota and Uusimi, 2003, JTB 221:599-613)

Ohta, 2002, PNAS 99:5916134-16137

Ohta, 1997, Gene 205:261-267

Nearly neutral tree