Whole Genome Alignment

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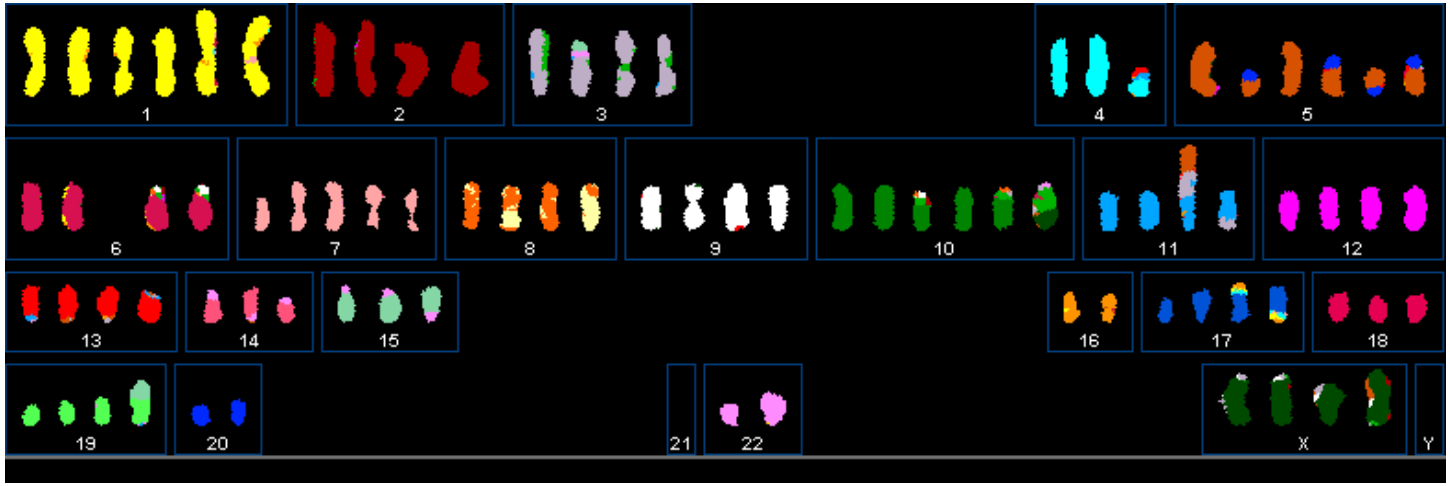
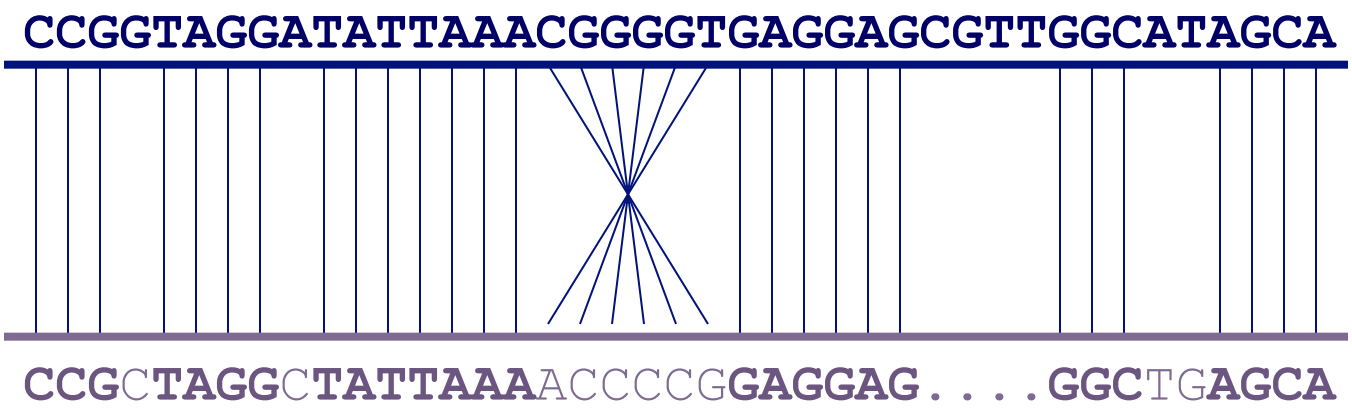
Motivation

Breast cancer karyotypes



Goal of whole-genome alignment

- For two genomes, *A* and *B*, find a mapping from each position in *A* to its corresponding position in *B*



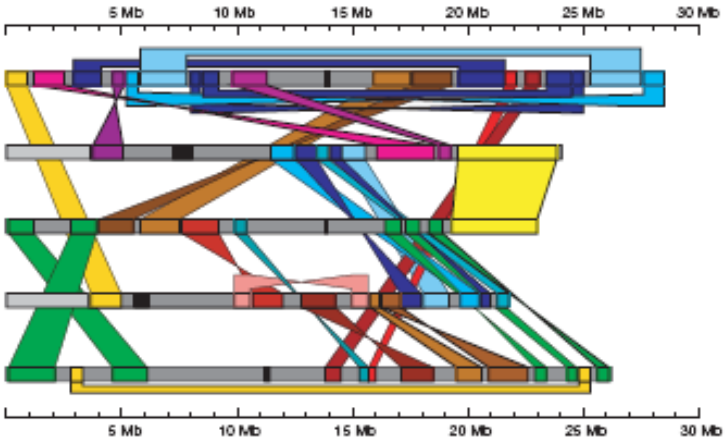
Megabase-sized sequences cannot be aligned with an O(n^2) algorithm like dynamic programming.

Global vs. Local alignments

- Global pairwise alignment

```
...AAGCTTGGCTTAGCTGCTAGGGTAGGCTTGGG...
...AAGCTGGGCTTAGTTGCTAG..TAGGCTTTGG...
          ^         ^        ^^        ^
```

- Whole genome alignment

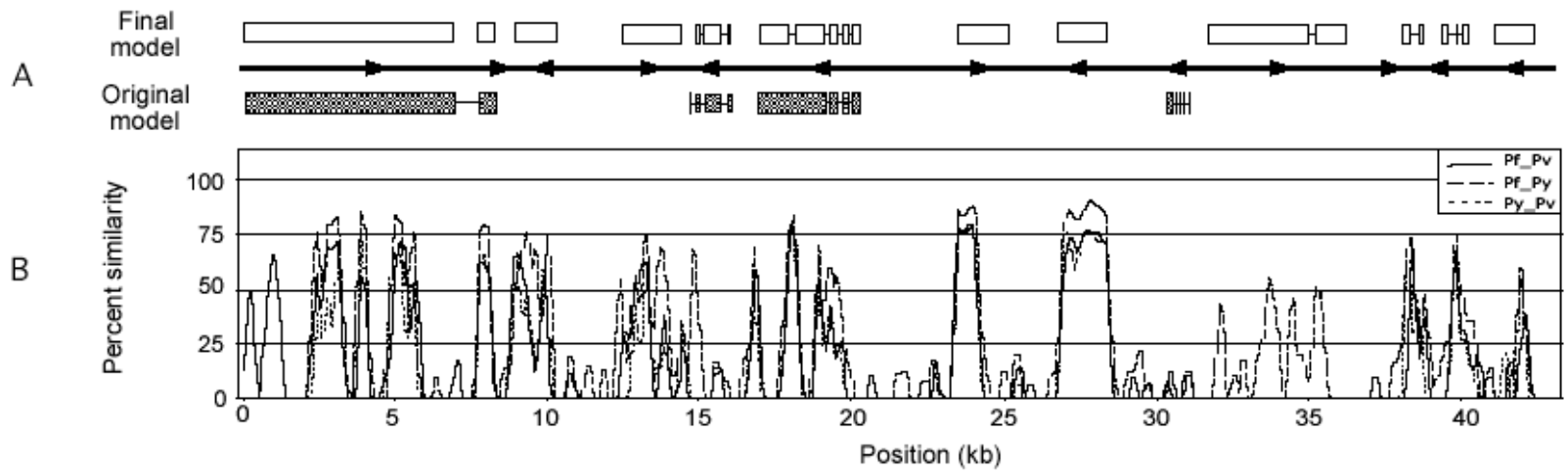


Recently had a global alignment project? What about local alignment?

Alignment Visualization

Global visualization

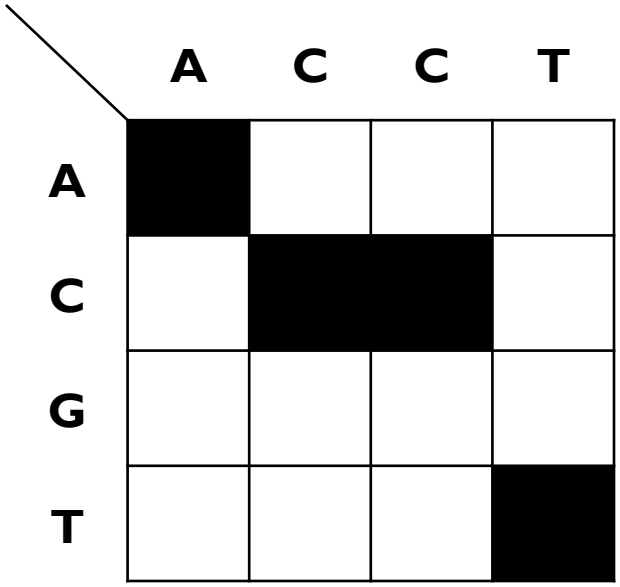
- Gene model conservation across 3 *Plasmodium* species



Genome alignment visualization

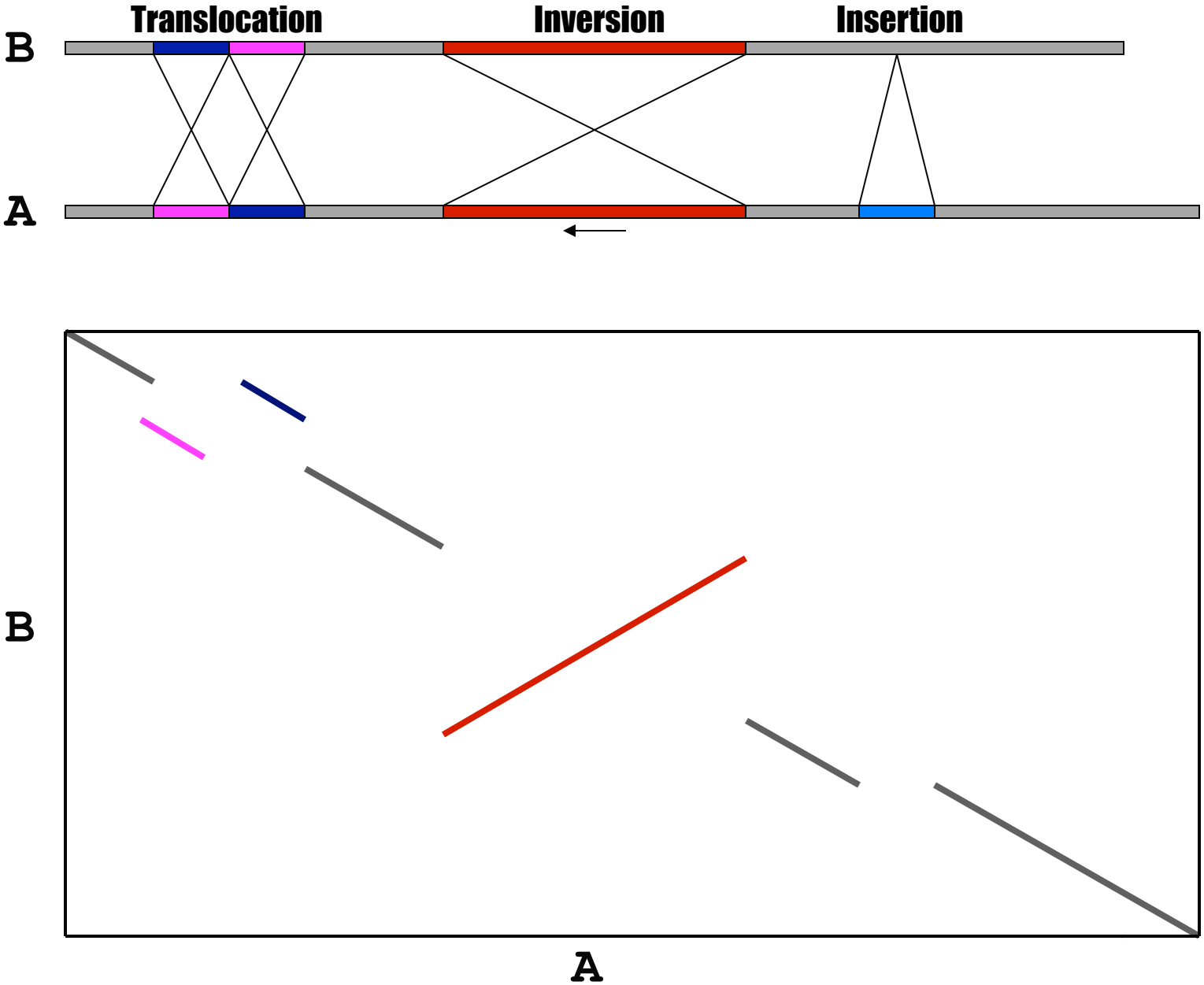
- How can we visualize *whole* genome alignments?

- With an alignment dot plot
  - *N* x *M* matrix
    - Let *i* = position in genome *A*
    - Let *j* = position in genome *B*
    - Fill cell *(i,j)* if A_i shows similarity to B_j

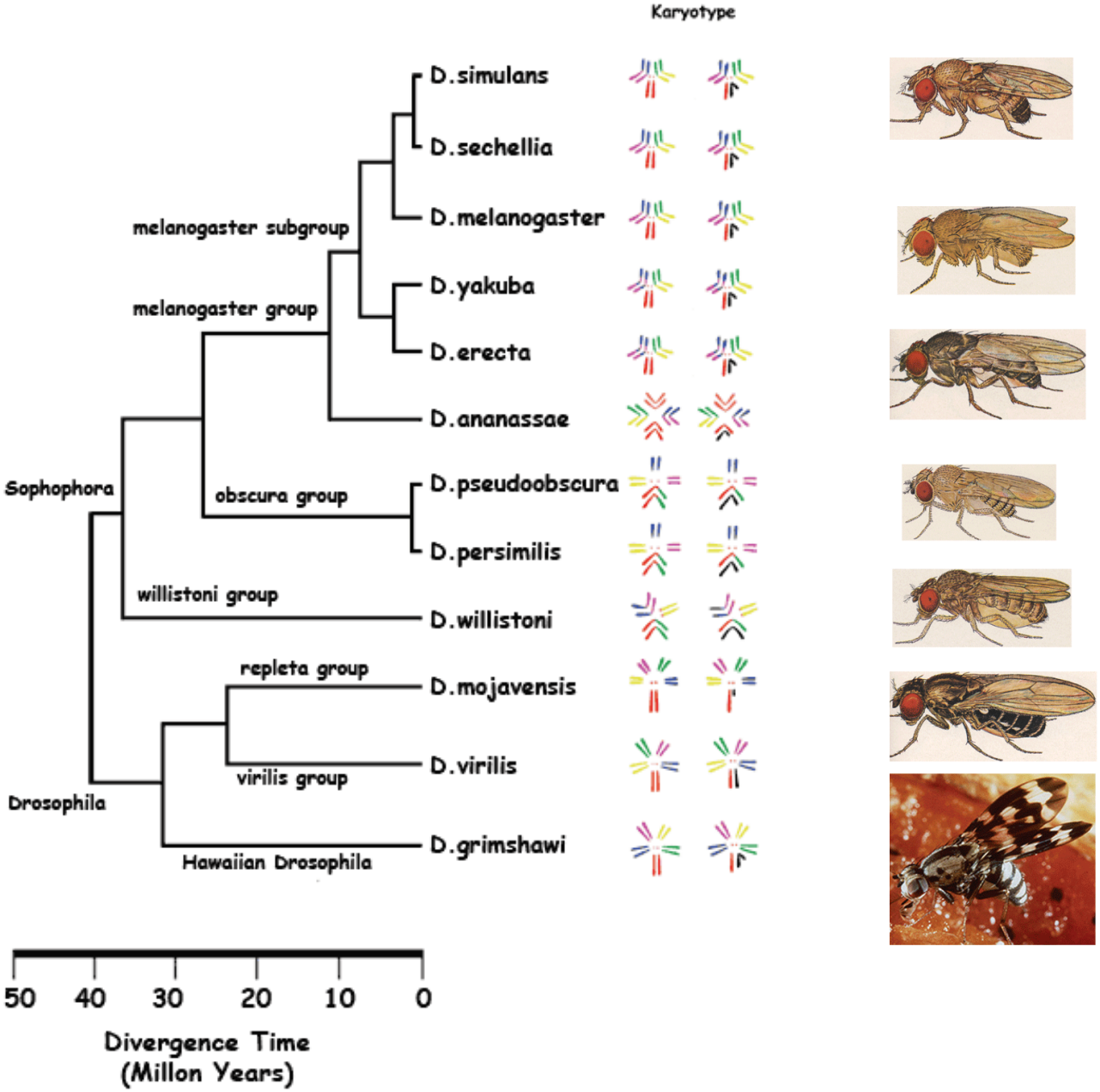


  - A perfect alignment between *A* and *B* would completely fill the positive diagonal

What does this remind you of?

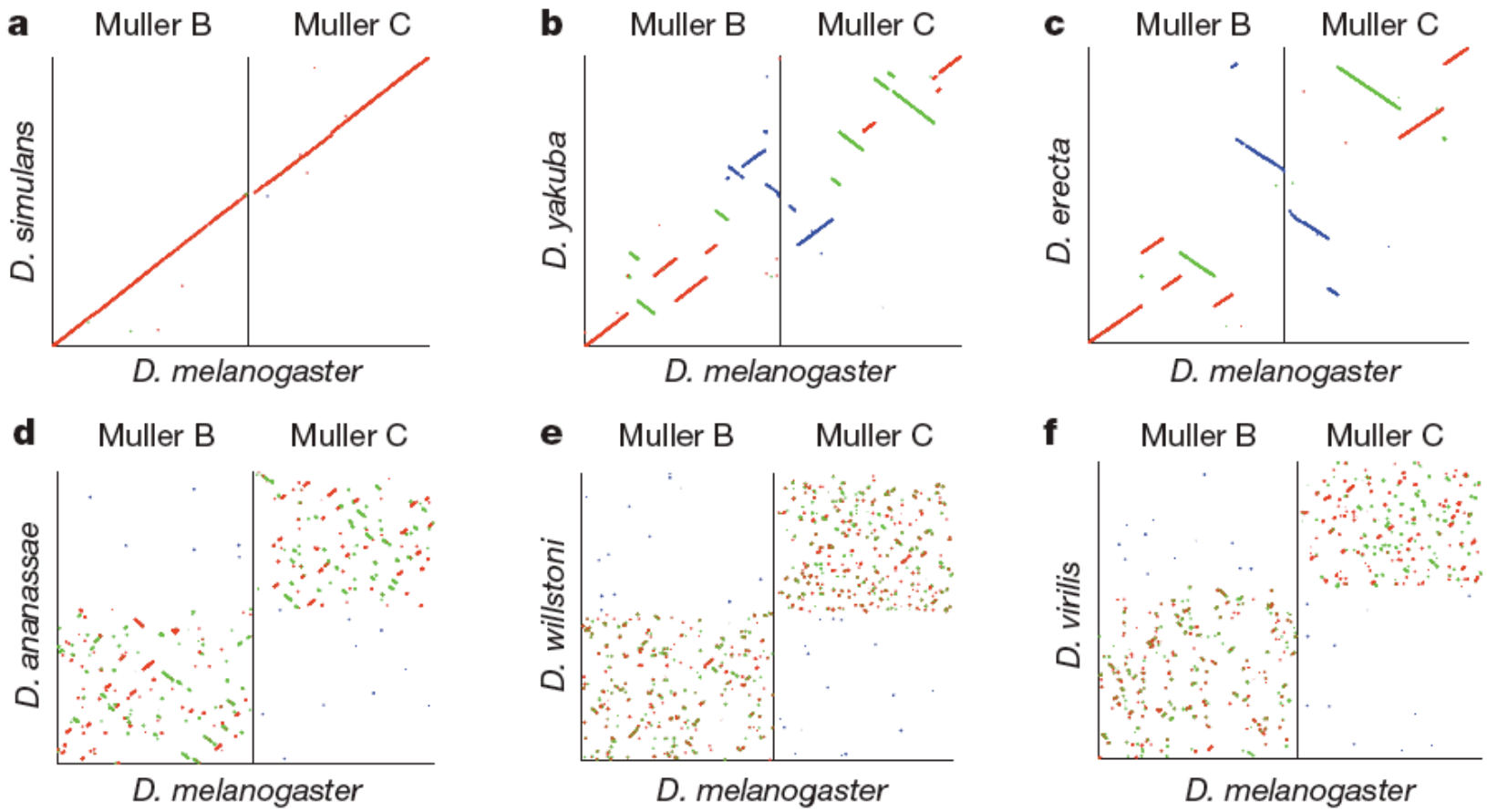


http://mummer.sourceforge.net/manual/AlignmentTypes.pdf



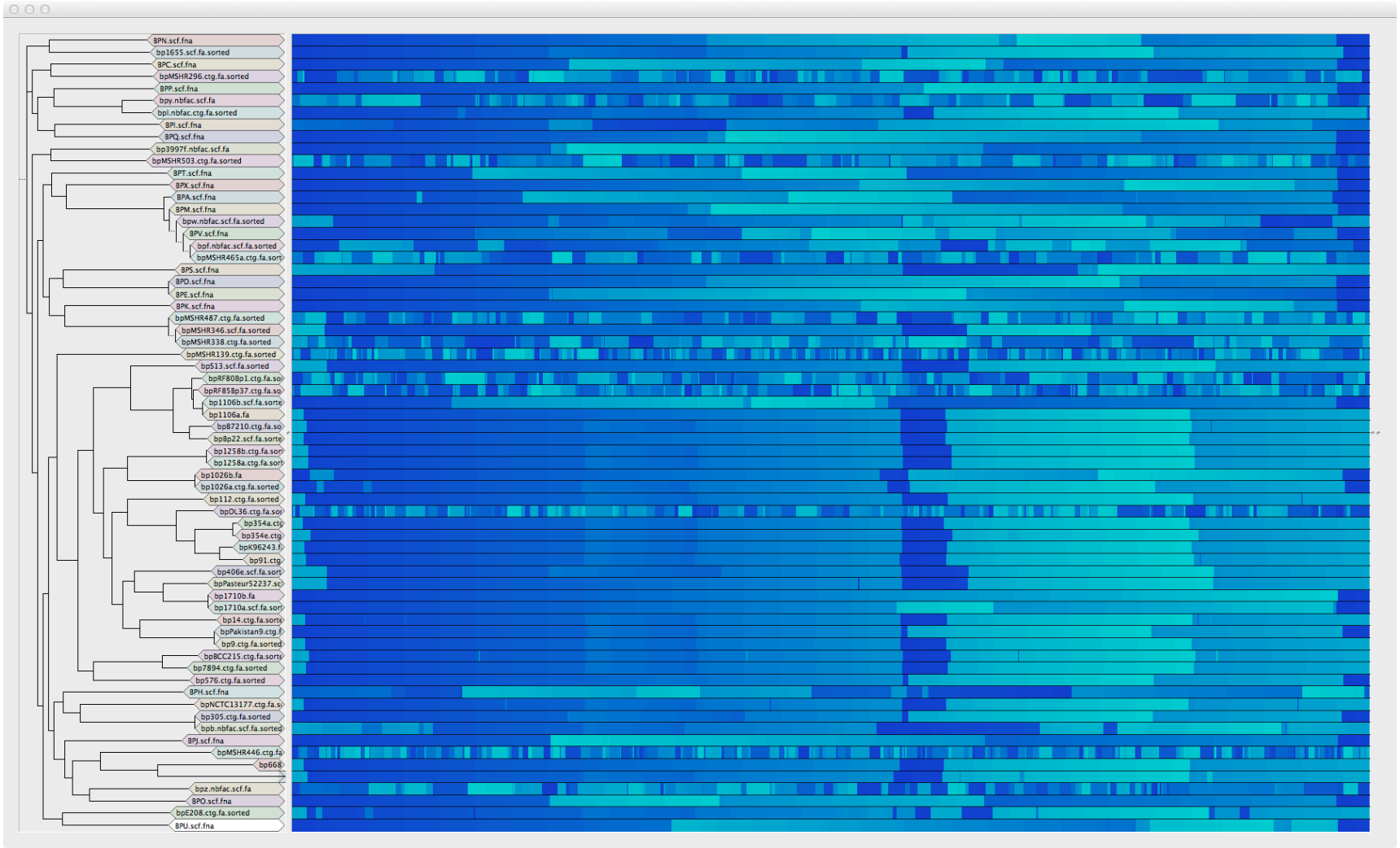
The look similar, what about their genomes?

Drosophila shuffling



- Evolution of genes and genomes on the Drosophila phylogeny. Drosophila 12 Genomes Consortium. Nature. 2007 Nov 8;450(7167):203-18.

Multiple alignment visualization



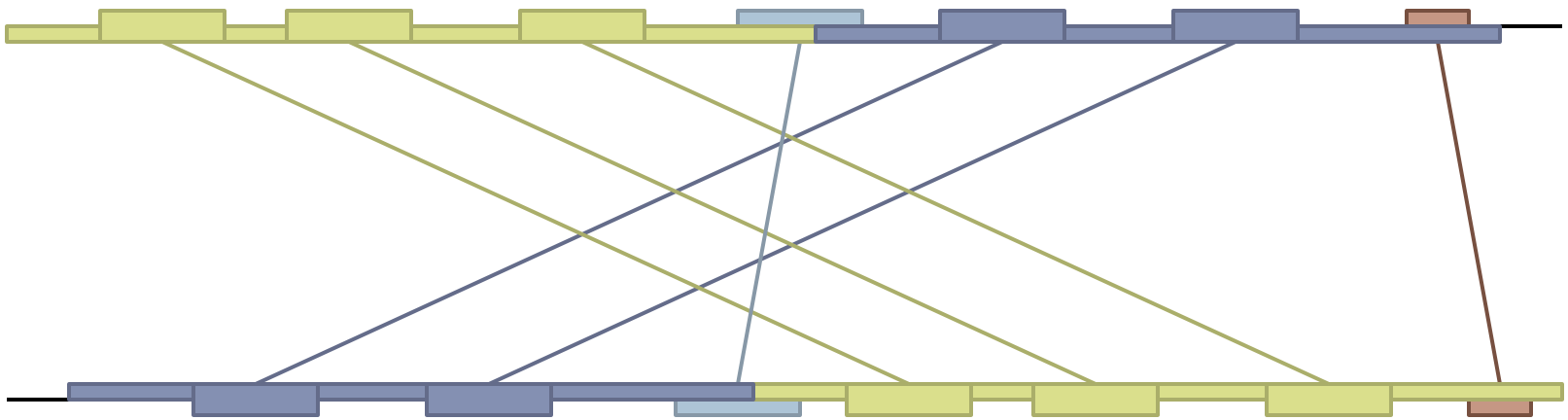
- Open problem for many genomes

MUMmer

Aligning two genomes in under a minute

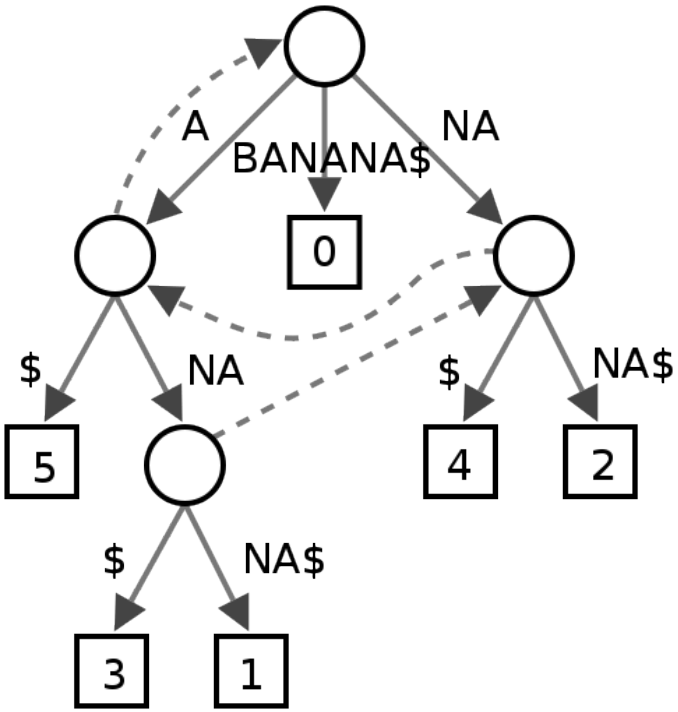
Nucmer algorithm

1. Find exact match seeds (MUMmer Suffix Tree)
2. Cluster significant matches (Union-Find)
3. Extend and combine alignments (Smith-Waterman)
4. Filter repeats (Dynamic programming)



Suffix trees

- O(n) construction
- O(n) space
- O(n+m) Longest common substring
- O(n+m+k) Find all k maximal matches



MUMmer

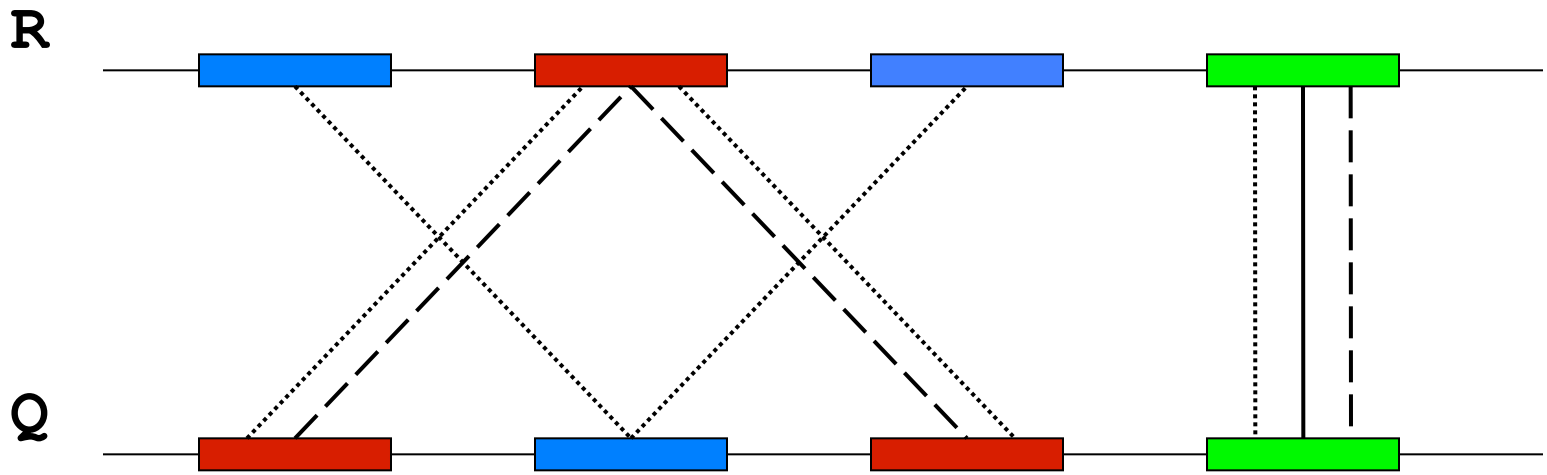
- Maximal Unique Matcher (MUM)
  - match
    - exact match of a minimum length
  - maximal
    - cannot be extended in either direction without a mismatch
  - *unique*
    - occurs only once in both sequences (MUM)
    - occurs only once in a single sequence (MAM)
    - occurs one or more times in either sequence (MEM)

Is it a MEM, MAM or MUM?

MUM : maximal unique match

MAM : maximal almost-unique match

MEM : maximal exact match



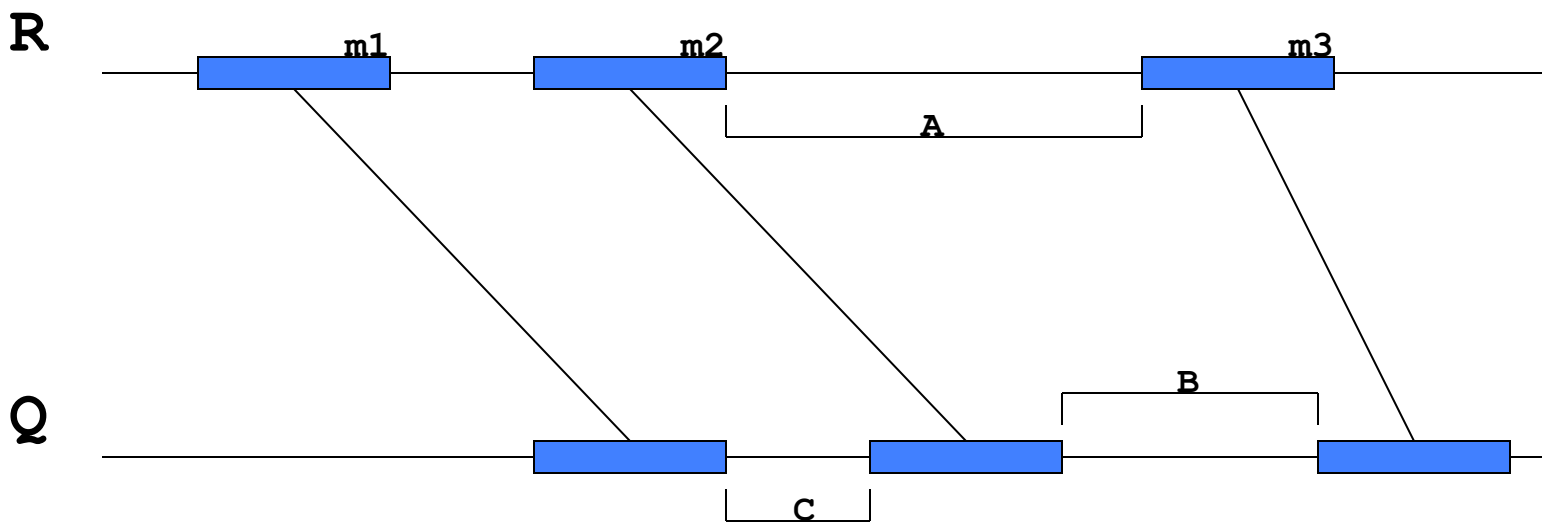
MUMs inherently avoid repetitive regions, which do not make good seeds.

Clustering

cluster length = $\sum m_i$

gap distance = C

indel difference = $|B - A|$



Banded dynamic programming

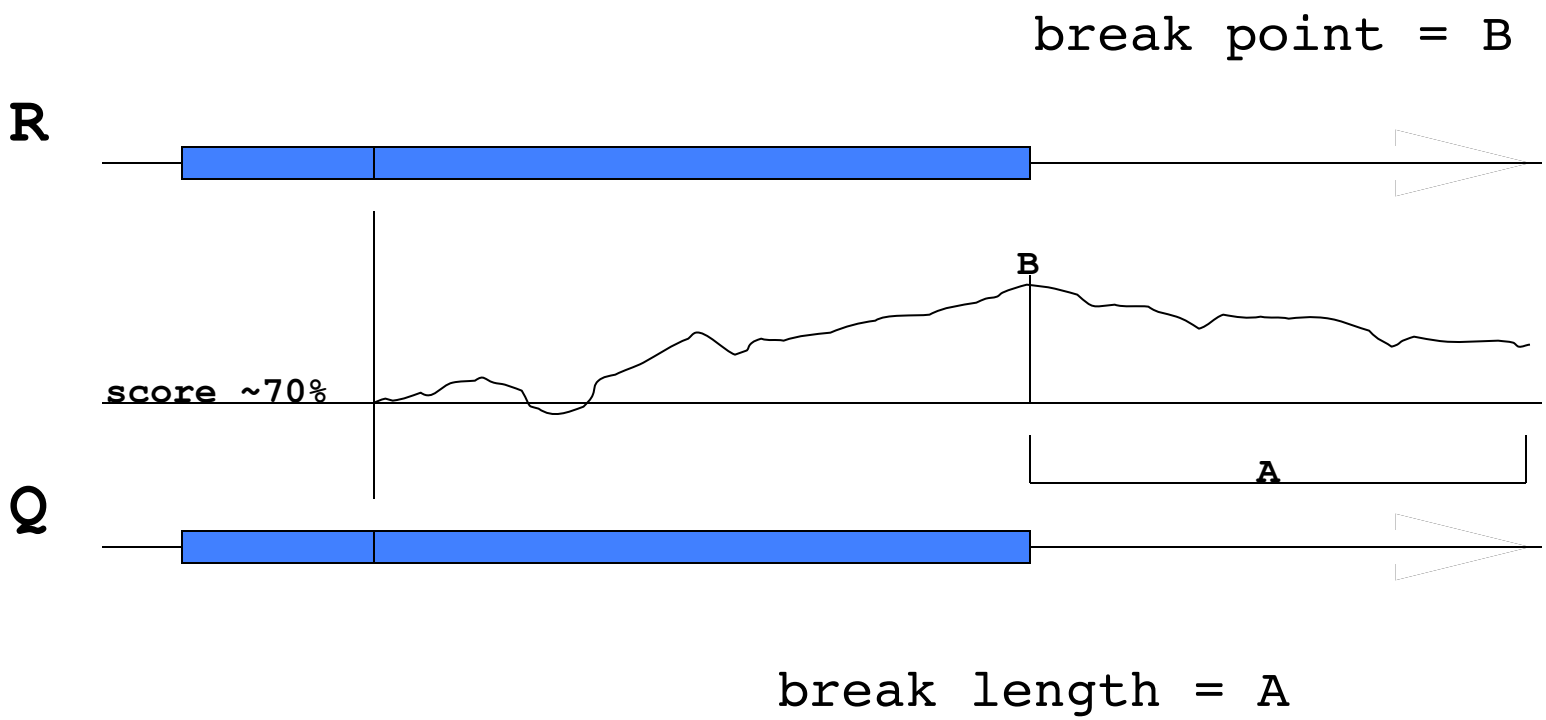
Match score 0, Edit score +1, Max edits 2

	^	T	T	G	C	A	G
^	0	1	2	3*	4	5	6
T	1	0	1	2	3	4	5
G	2	1	1	1	2	3	4
C	3*	2	2	2	1	2	3
T	4	3	2	3*	2	2	3*
G	5	4	3	2	3	3*	2

Linear time and space dynamic programming, also see Divide and Conquer

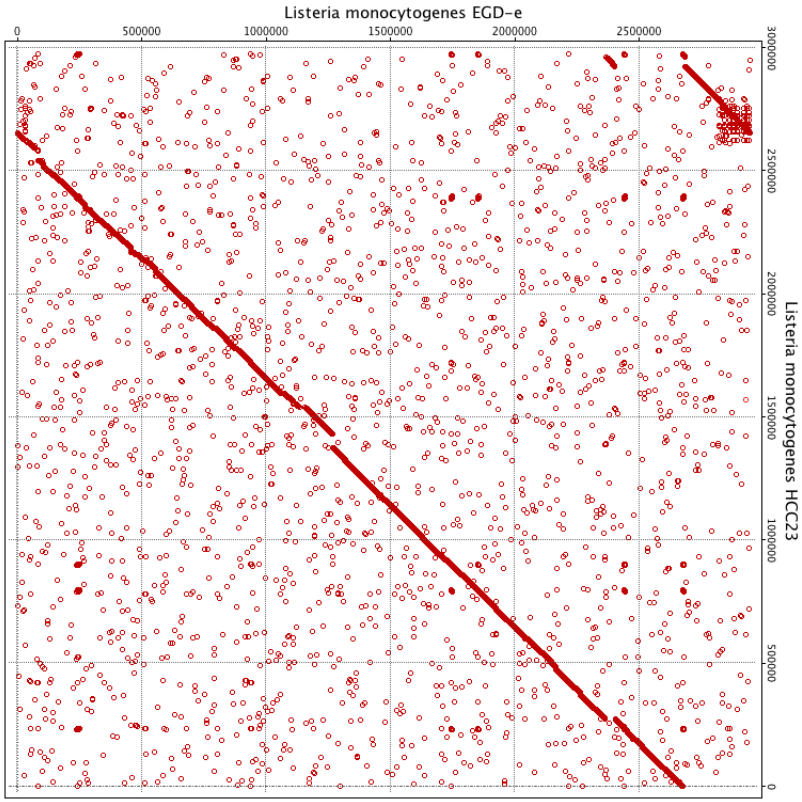
Extending

Match score +3, Edit score -7

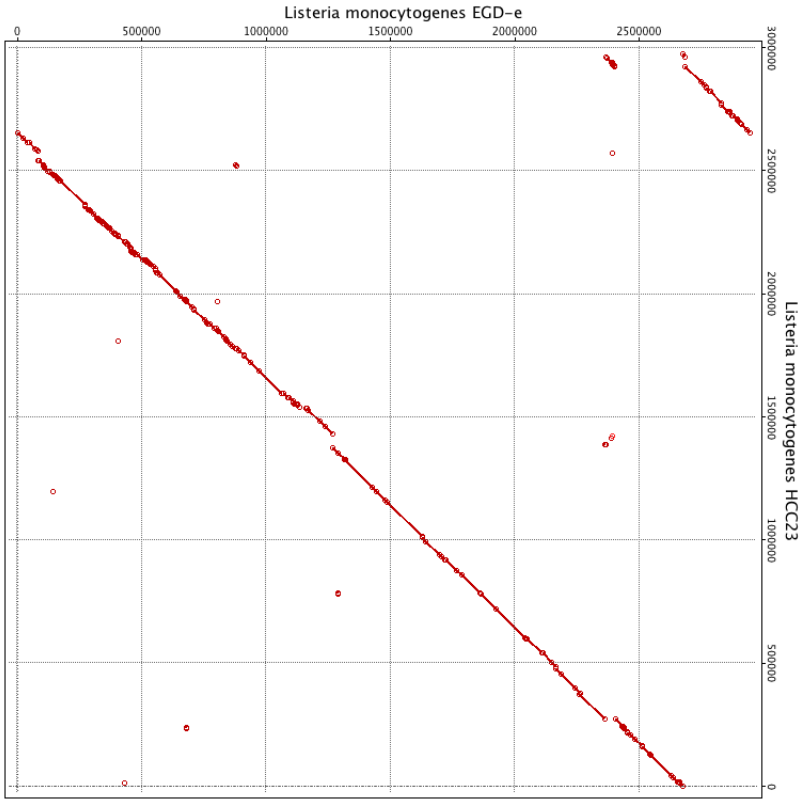


7 matches and 3 edits over a 10 bp window = 7*3-3*7 = 0

L. monocytogenes alignment



18-mer seeds



alignments

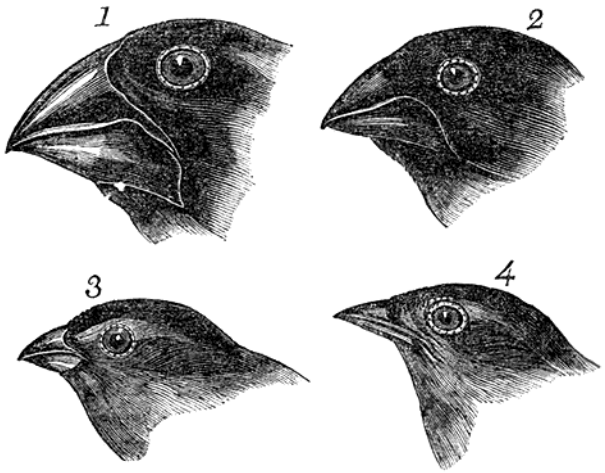
- Why isn't it a single diagonal?

Microbial Genomics

Comparative genomics

- Study genomic content and function across different taxa

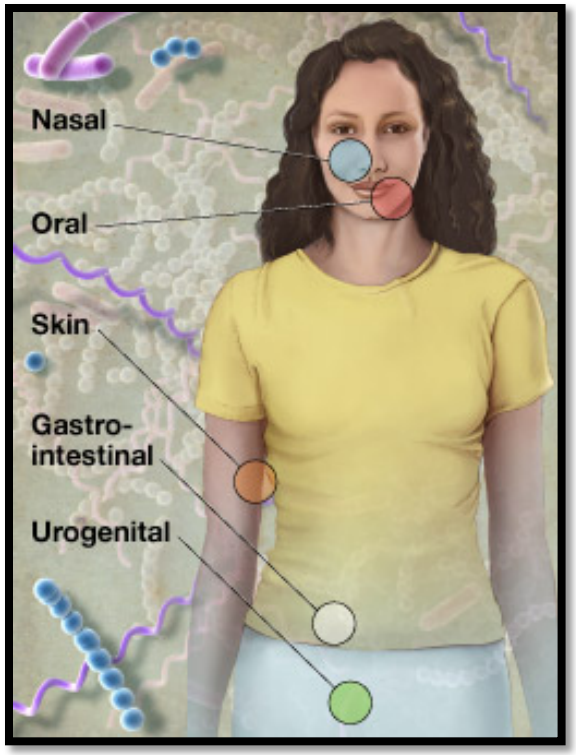
- Why?
  - study evolution
  - link phenotype with genotype
  - reveal genomic organization and function
  - transfer functional annotation



- How?
  - genome sequencing and alignment

Microbes are underappreciated

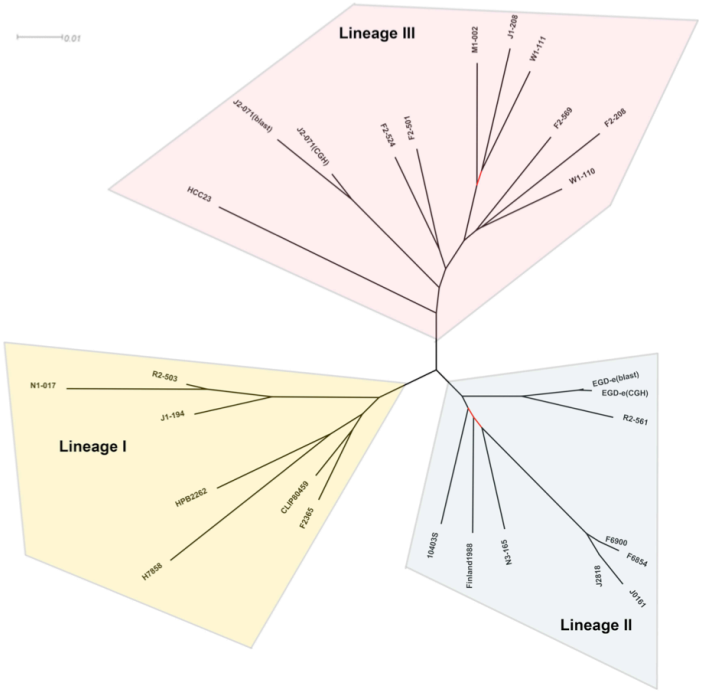
- They're everywhere
- Harmful
  - disease, spoiling
- Beneficial
  - human microbiota
  - bio-energy, bio-remediation
  - synthetic genomics
- Easy to work with
  - rapid generation time
  - small genomes
  - extremely efficient
  - simpler models

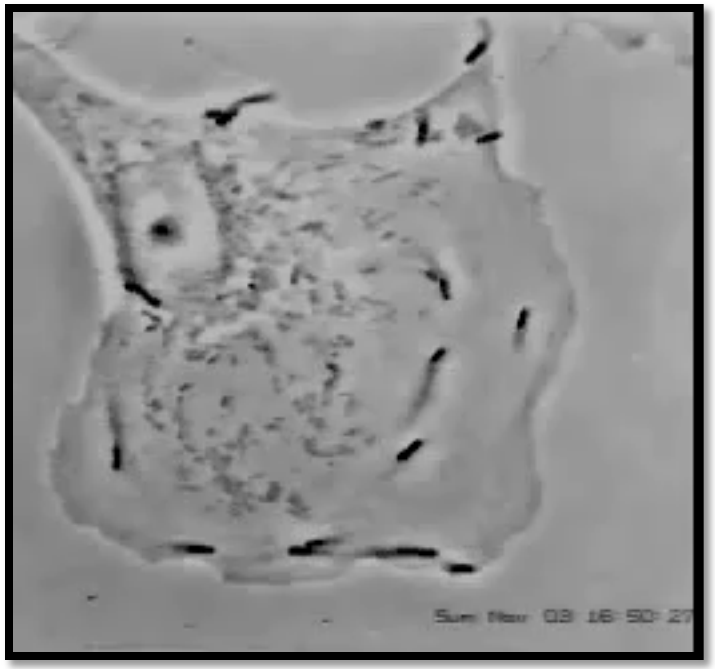


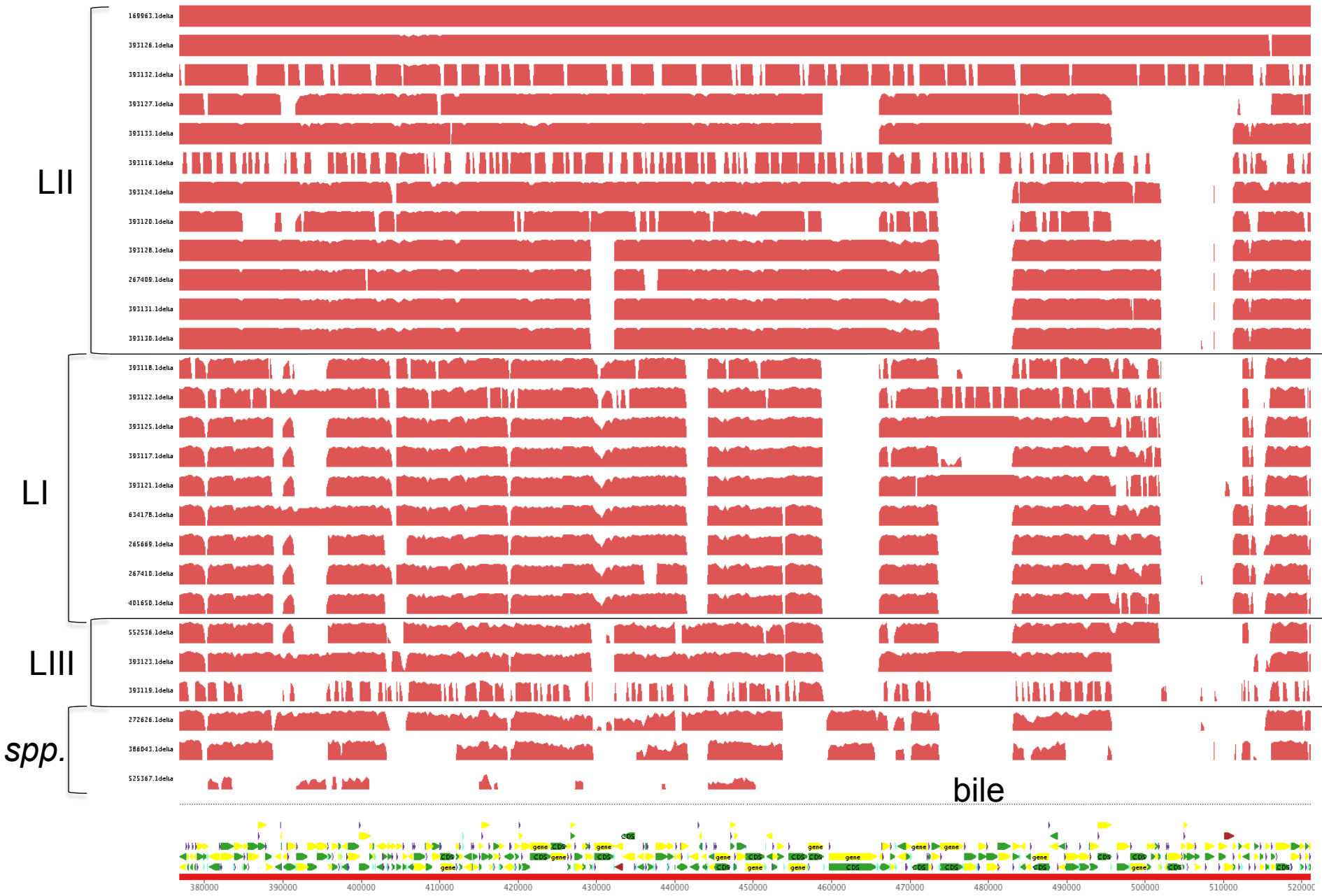
10^{14} bacterial cells vs. 10^{13} human cells

Listeria monocytogenes

- *Listeria monocytogenes*
  - Important foodborne pathogen (cheese, lunch meat, etc.)
  - 3 Mbp genome, 3 primary lineages (I,II,III*)



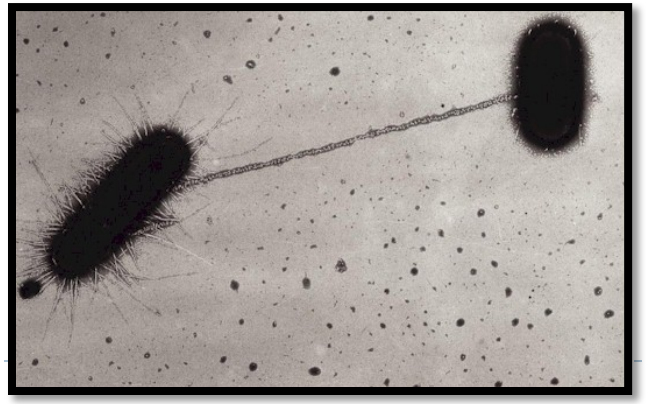




HGT bile resistance genes

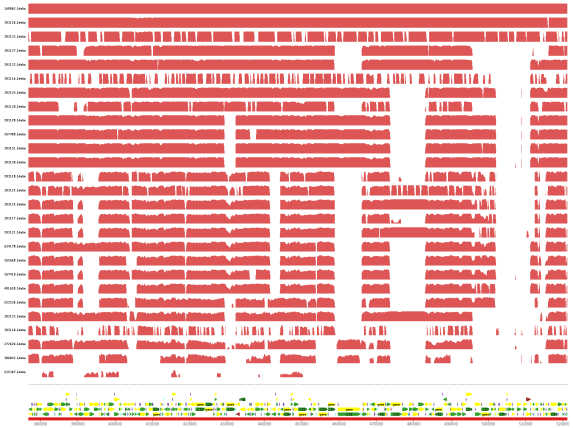
Bacteria have sex

- A few mechanisms of "horizontal gene transfer"
  - **Transformation:** the genetic alteration of a cell resulting from the introduction, uptake, and expression of foreign genetic material (DNA or RNA).
  - **Transduction:** the process in which bacterial DNA is moved from one bacterium to another by a virus (e.g. phage)
  - **Bacterial conjugation:** a process in which genetic material is transferred to another cell by cell-to-cell contact.



Wikipedia

Pan-genomics



- Core genome
  - minimal gene set necessary for survival
  - defining characteristics of the species
  - orthologs, gene groups
- Accessory genome
  - mediate adaptation to different environments
  - e.g. stress and antibiotic resistance, nutrient metabolism
- Pan genome
  - union of core and accessory genes (non-redundant)
  - defines total genetic diversity of the species

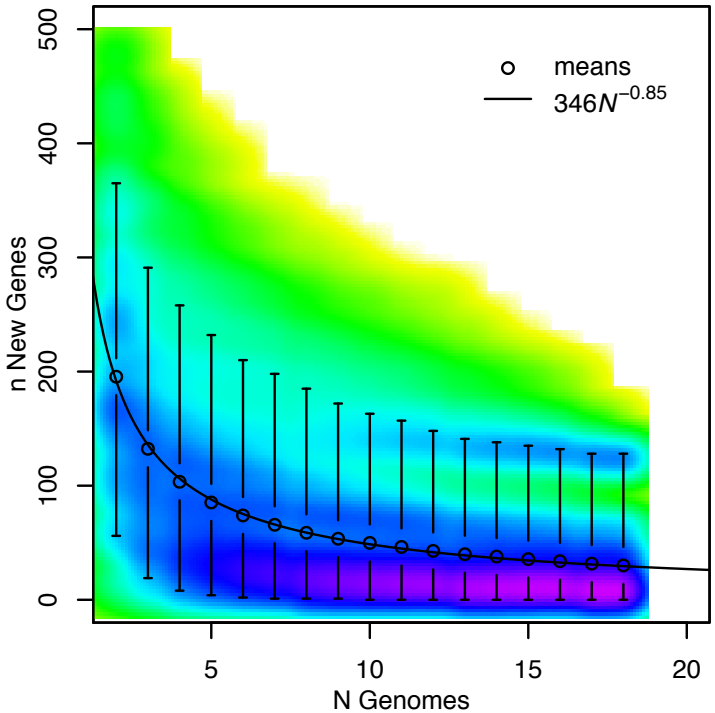
How big is a pan-genome?

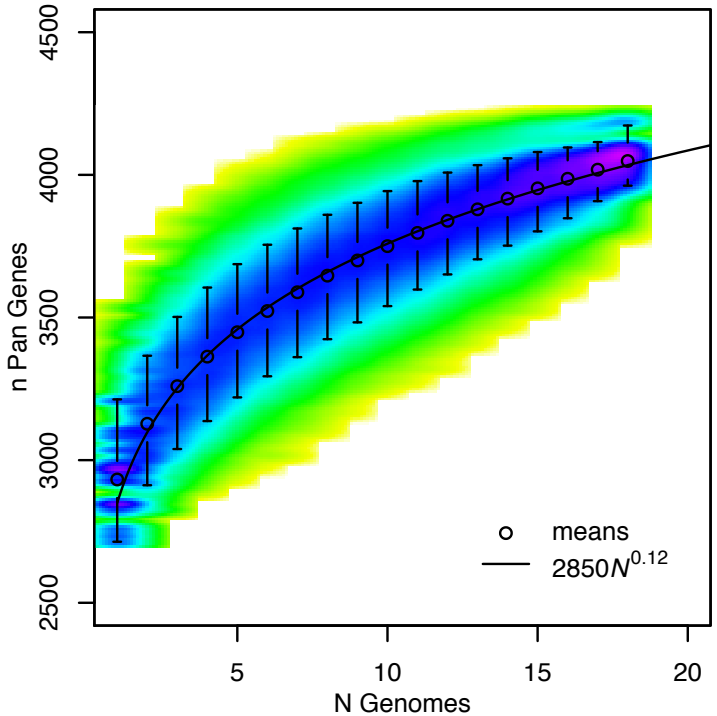
- How many new genes will be discovered in sequencing the kth genome?
  - For all k! possible permutations of k genomes
    - how many <u>new</u> genes are found in the kth genome?
  - Perform regression on the average values

```
FOR k = 1 to N
  FOR each random sample
      Randomly generate an ordered set of k genomes
      Compute # unique genes in the kth genome
  END FOR
END FOR
```

L. monocytogenes pan genome

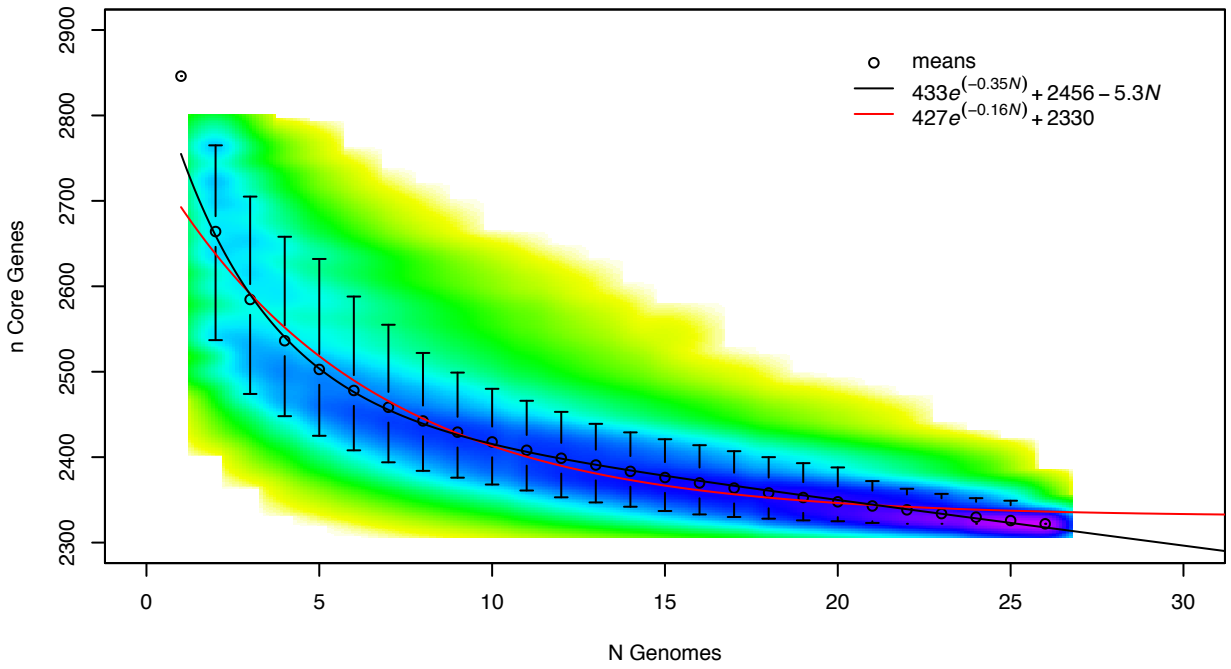
- Power law — non-linear least squares fit to means





L. monocytogenes core genome

- Exponential decay — non-linear least squares fit to means



- Draft genomes missing ~5 genes per genome