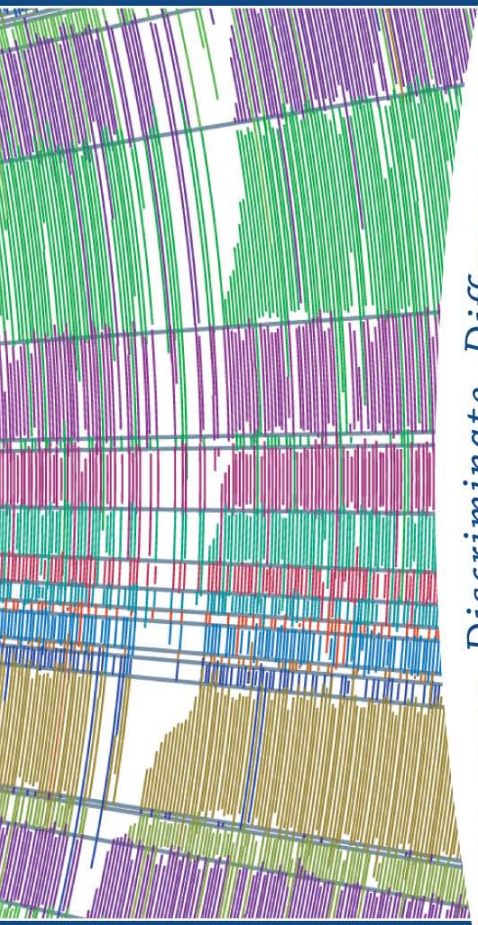

Discover. Discriminate. Differentiate.

A Software System for Validating and Orienting Sequence Contigs Using Optical Maps

Adam M Briska.

Senior Bioinformatics Scientist

OpGen Inc.

Optical Mapping

A system that generates whole-genome, ordered restriction maps.

For whole genome analysis of bacteria, yeast or fungi

- high precision
- without the cost of DNA sequencing
- without the inherent bias in microarrays

A *de novo* process...no sequence information required

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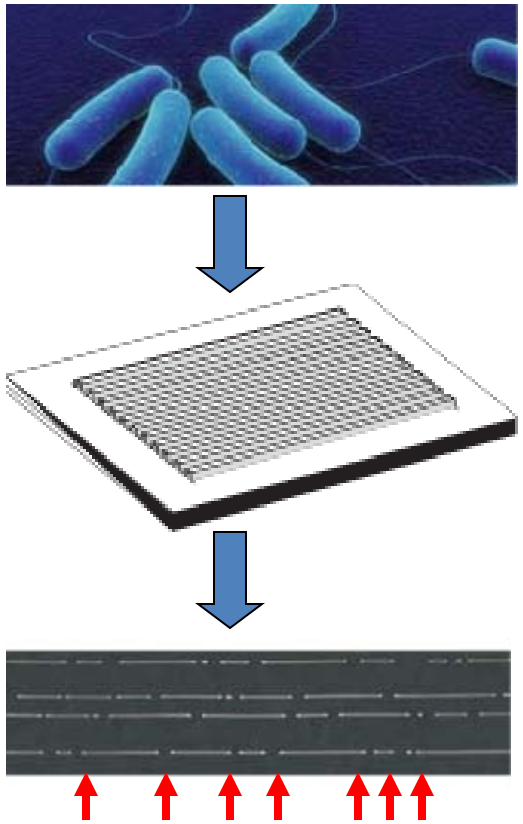
How Optical Mapping Works



Cells gently lysed to release genomic DNA

DNA captured in parallel arrays of long single DNA molecules using a microfluidic device

Restriction enzymes cleave the DNA at specific sites

Gaps in the DNA indicate location of cut sites

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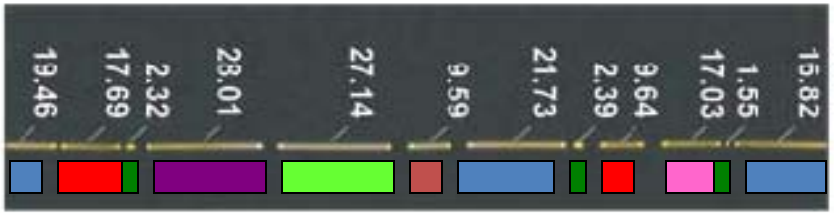
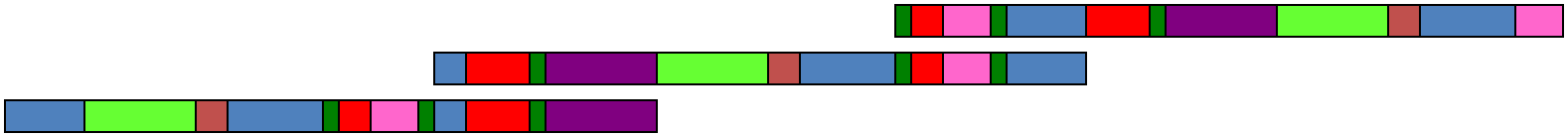
How Optical Mapping Works



The DNA is stained with fluorescent dye and image analysis measures the size and order of each fragment to create “Single Molecule Maps”.



Overlapping single molecule maps are aligned to produce a map assembly covering an entire chromosome.

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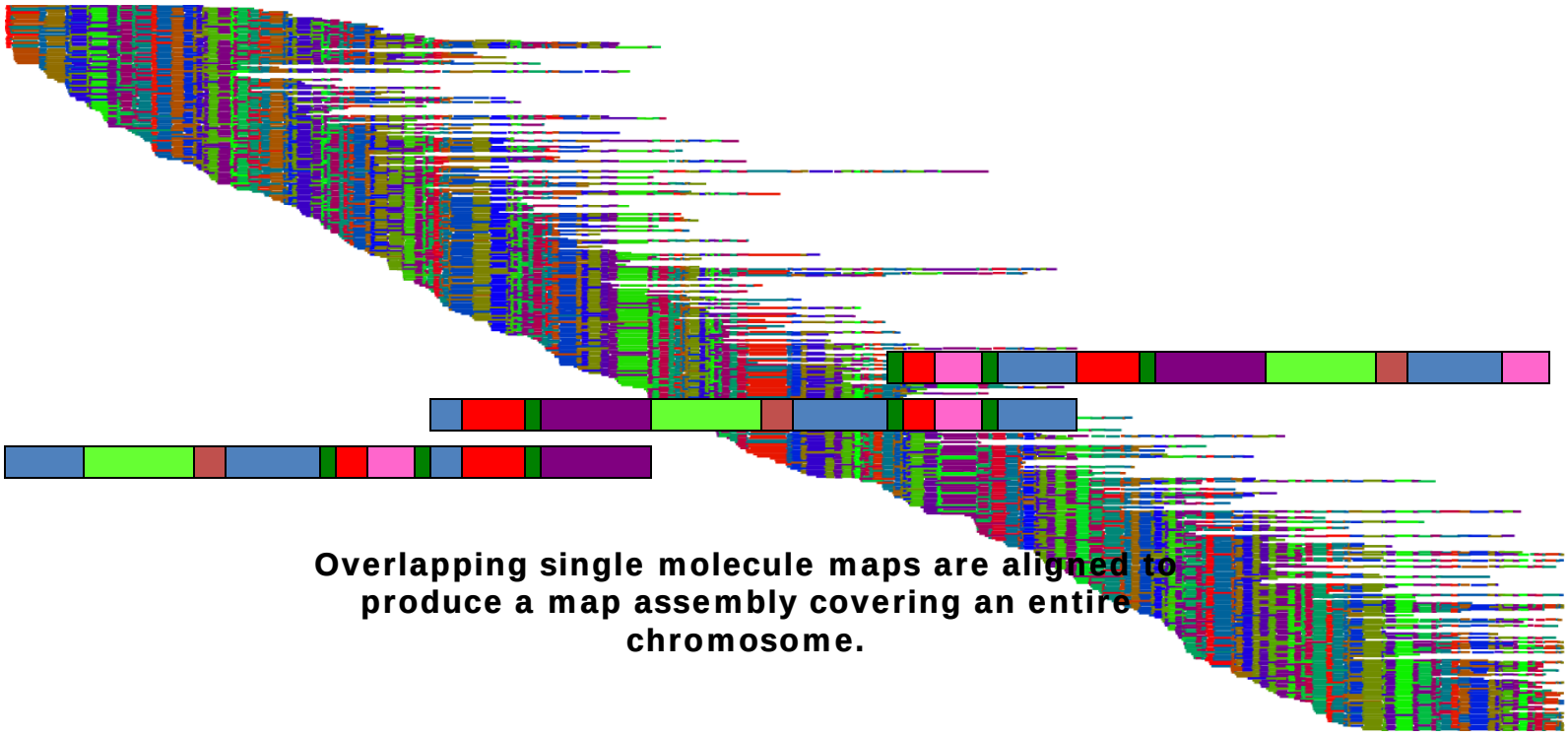
How Optical Mapping Works



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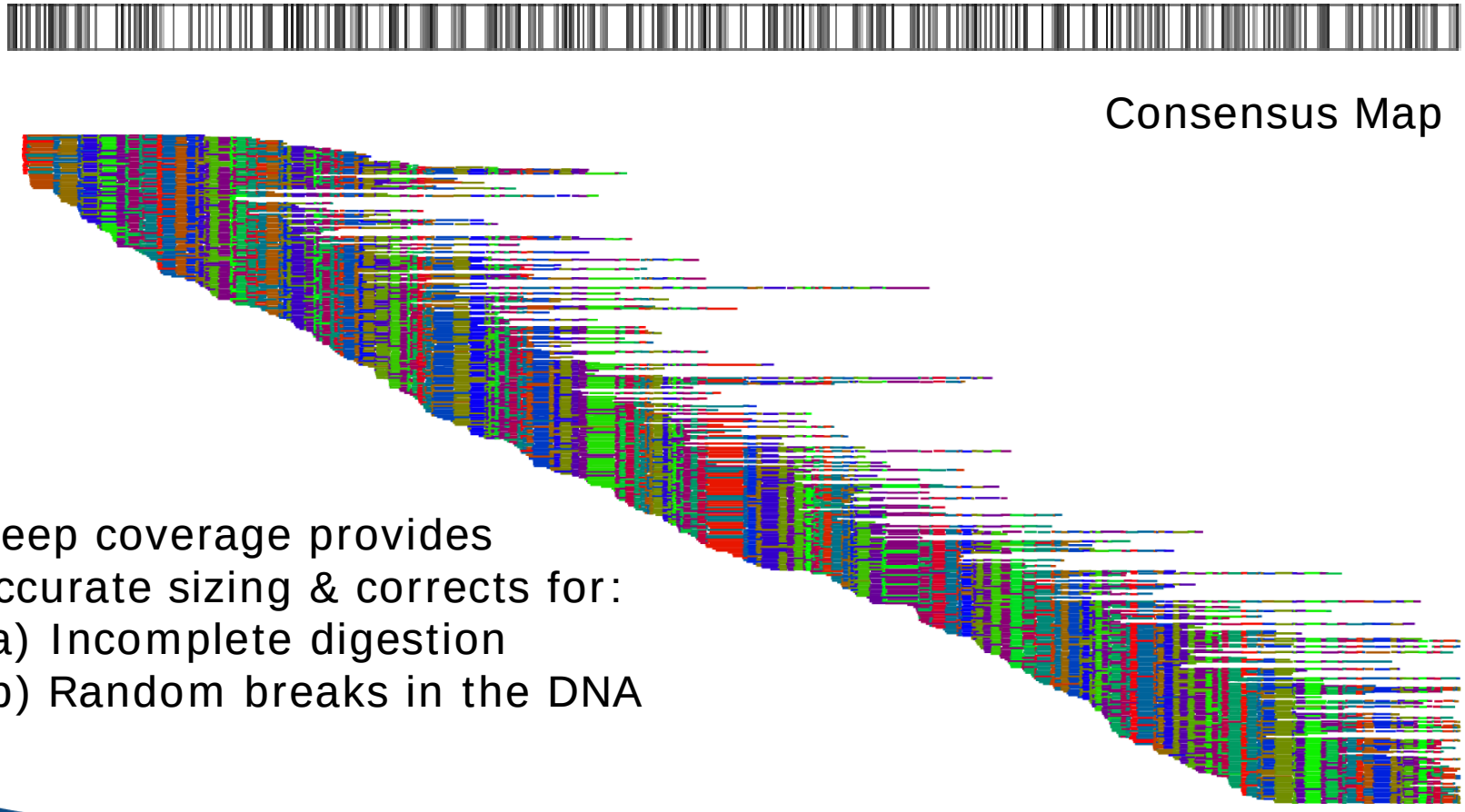

Consensus Map

Deep coverage provides
accurate sizing & corrects for:
(a) Incomplete digestion
(b) Random breaks in the DNA

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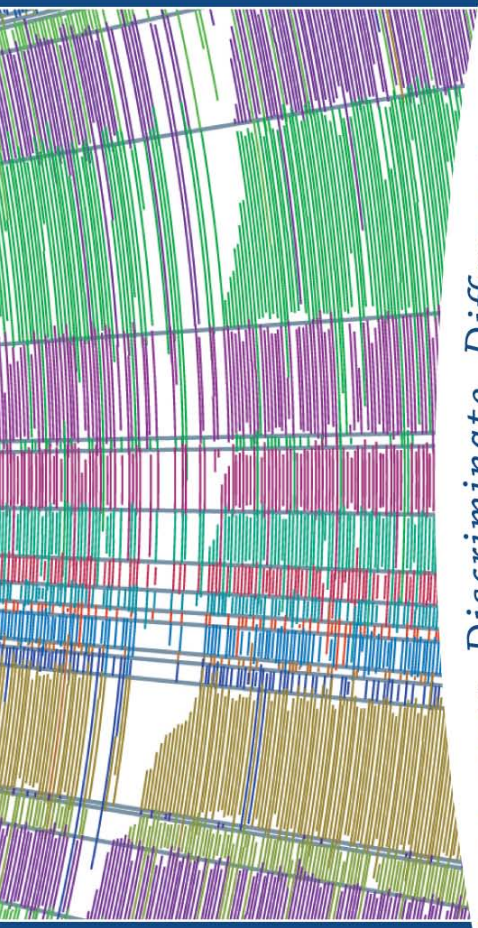

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Placing Sequence Contigs on an Optical Map

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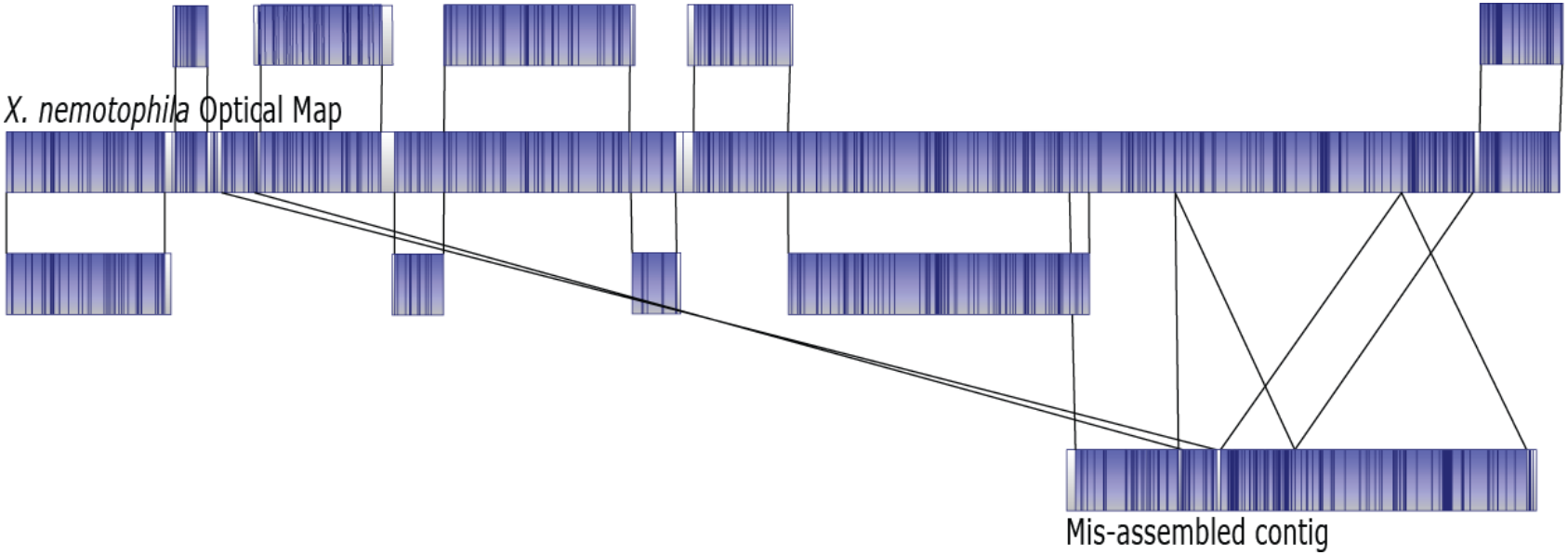
Example data



Latreille P, Norton S, Goldman BS, Henkhaus J, Miller N, Barbazuk B, Bode H, Darby G, Du Z, Forst S, Gaudriault S, Goodner B, Goodrich-Blair H, Slater S. “Optical mapping as a routine tool for bacterial genome sequence finishing.” *BMC Genomics* 2007, **8**:321.

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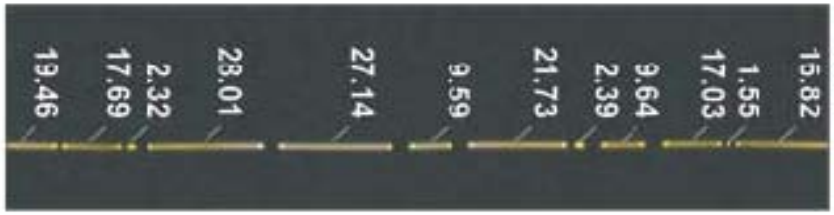
Matching Model

Sizing

Cut site mismatches

$$\max\begin{cases} 1-\dfrac{|d_M-d_S|}{N\sqrt{d_M V_M}}-C\left(c_M+c_S-\sum_{f\in f_S}e^{-fM}\right) & \text{Normal matches} \\ \max\begin{cases}0\\ d_S\end{cases} & \text{aps} \end{cases}$$



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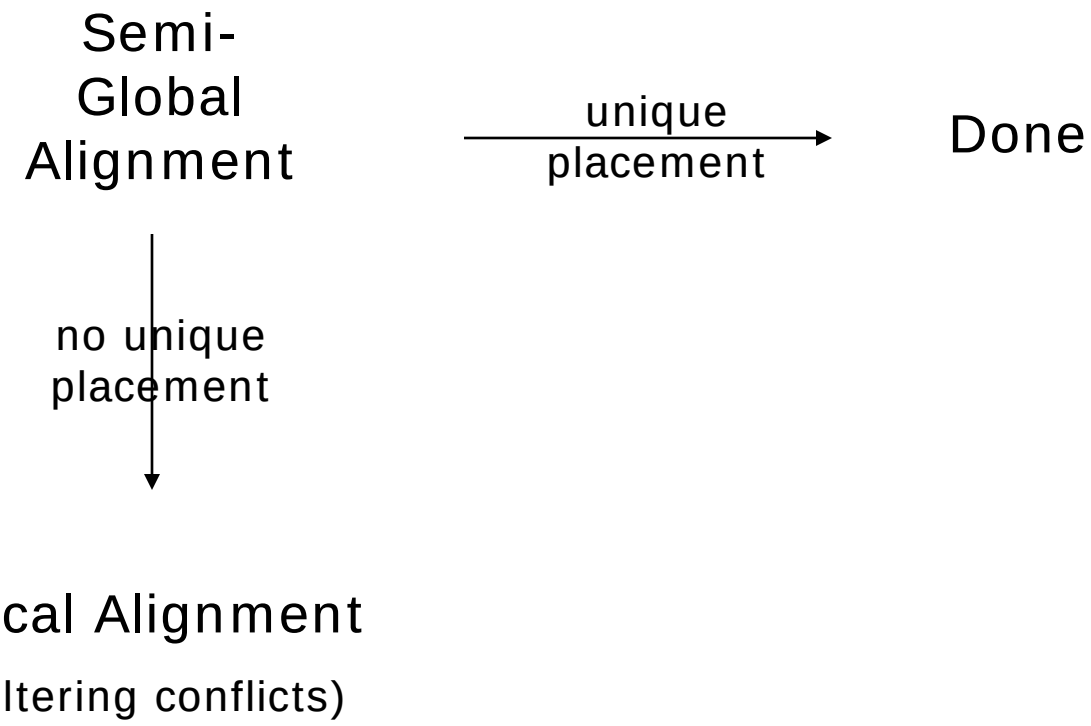
Placement logic



Simulation

3 genomes

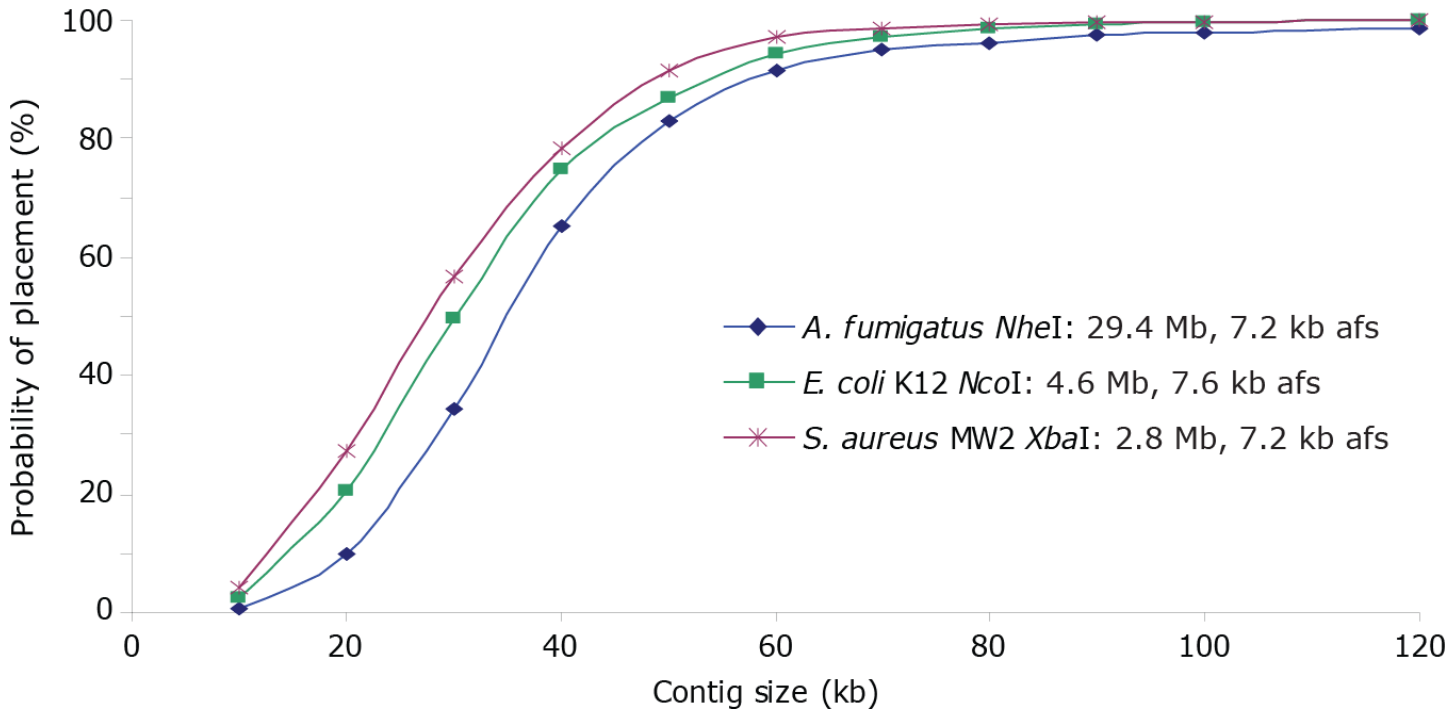
- *A. fumigatus*, *Nhe*I, 29.4 Mb, 7.2 kb afs
- *E. coli* K12, *Nco*I, 4.6 Mb, 7.6 kb afs
- *S. aureus* MW2, *Xba*I, 2.8 Mb, 7.2 kb afs

100 trials for each contig size

100 random contigs for each trial

Placement had to be in the correct location

Simulation results



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Understanding the placement

How much is this driven by number of cut sites in each contig?

Given the assumption that cut sites are randomly distributed across the genome, the number of cuts per contig is governed by a Poisson distribution:

$$\text{P(at least N cut sites)} = 1 - \sum_{k=0}^{N-1} \frac{e^{-\lambda t}(\lambda t)^k}{k!}$$

where λ is the enzyme cut rate and t is the size of the contig

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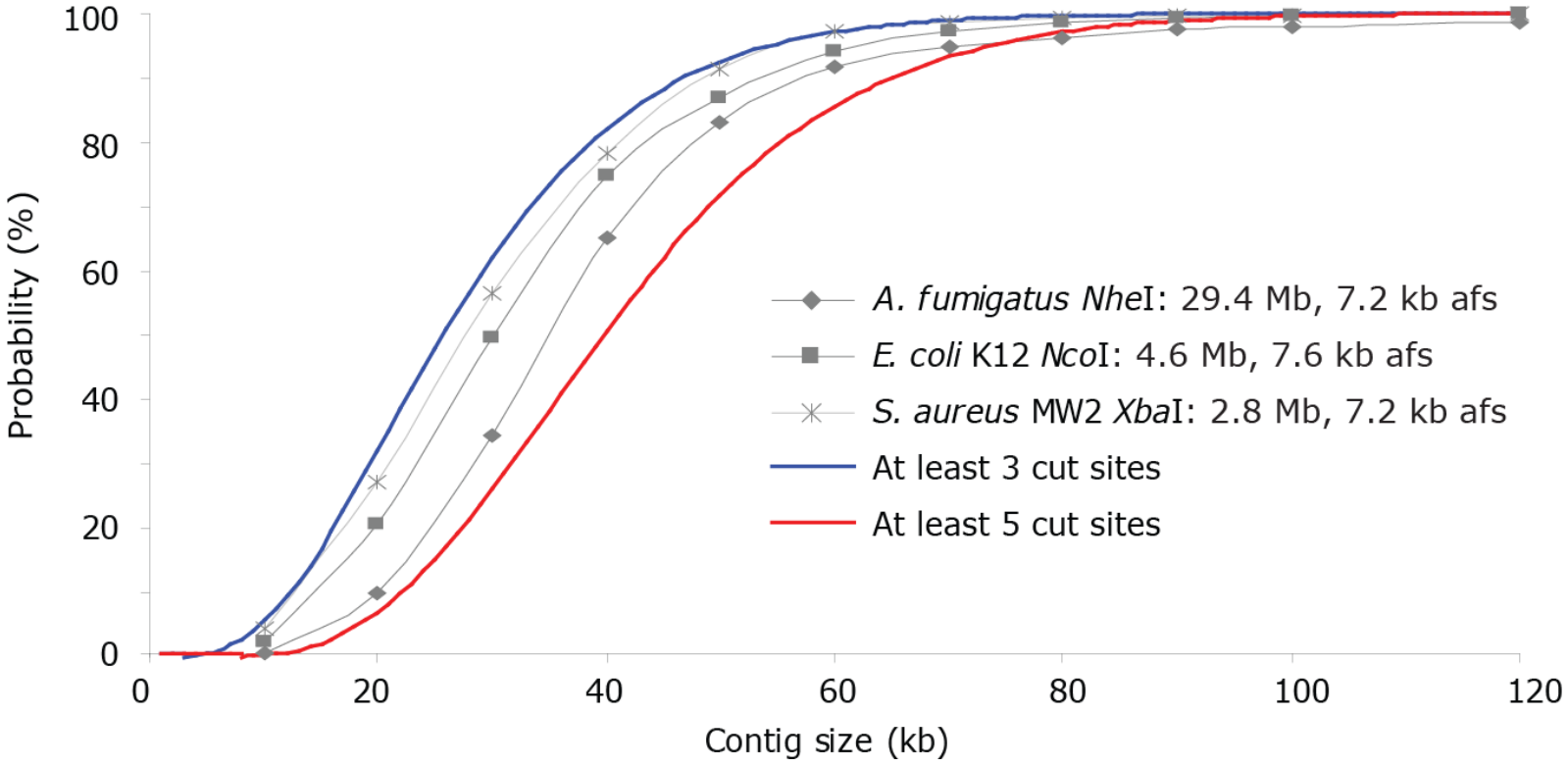
Understanding the placement



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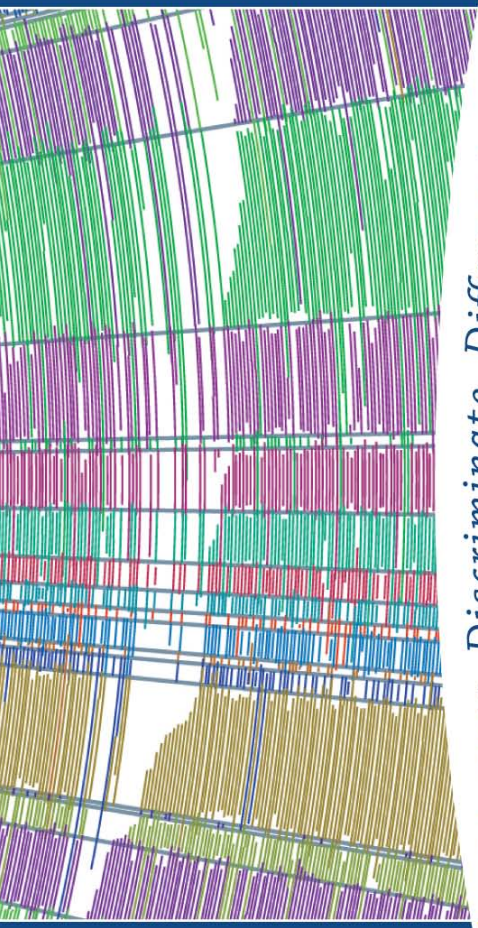

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Questions?

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