ETH zürich

Swiss National
Science Foundation

An introduction to pangenomics

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Caveat emptor

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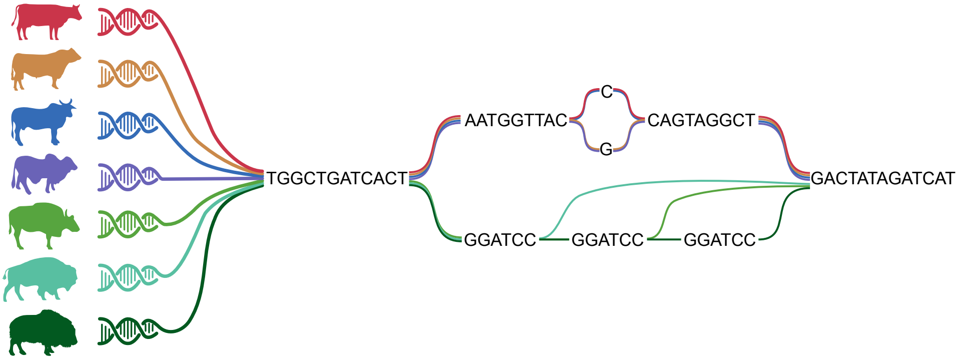

Overview

1. Introduction to pangenomics
   - Terminology
   - Graph building
   - Pangenome visualisation
2. Working with pangenomes
   - Pangenome communities
   - Pangenome validation
   - Downstream pangenomics
3. Pangenomics of the future
   - Personalised pangenomes
   - Targeted pangenomes
   - Pangenomes = biology?

What is a genome?

Encode *one* layer of information for an individual organism

Sequence of $\sim$ 1,000,000,000 nucleotides [ACTG] split into chromosomes

What is a reference genome?

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A reference sequence is an accepted representation that is used by researchers as a standard for comparison to DNA sequences generated in their studies.

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We use the **same** reference genome for these **different** cows?

Routine genome assembly

Long read sequencing has *almost* solved genome assembly

Solving a puzzle is easier with larger pieces

Jarvis, E.D., Formenti, G., Rhie, A. et al. Semi-automated assembly of high-quality diploid human reference genomes. *Nature* **611**, 519–531 (2022). https://doi.org/10.1038/s41586-022-05325-5

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Much faster **and** much cheaper **and** much easier today

What is a **pan**genome?

Almost no consensus of what a pangenome *is*

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- a reference genome with a vcf
- a set of genome assemblies
- a list of haplotypes

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- a reference genome with a vcf
- a set of genome assemblies
- a list of haplotypes
- **a graph structure representing variation across multiple assemblies**

What is a **pan**genome?

How can we integrate information from many assemblies into one structure?

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ACAGTCGCCGTCGGTCTGTCCG

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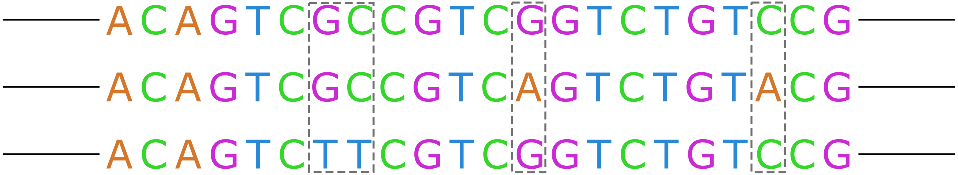

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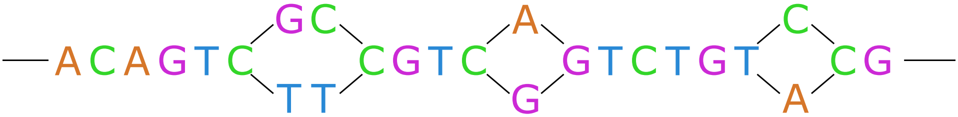

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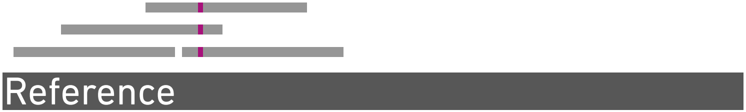

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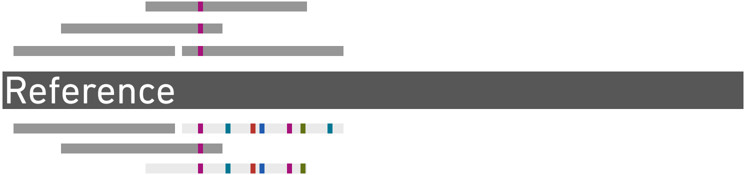

soft bias

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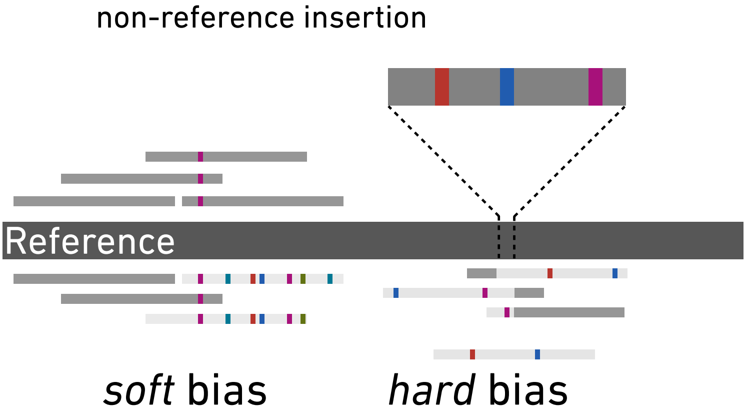

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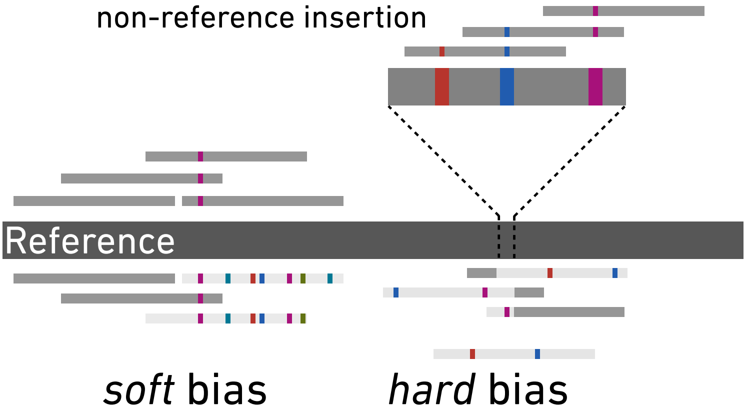

How do we represent complex variaton?

SNPs can **at worst** be quadallelic but a small SV (50 bp) can have $4^{50} \approx 1.3 \times 10^{30}$ alleles

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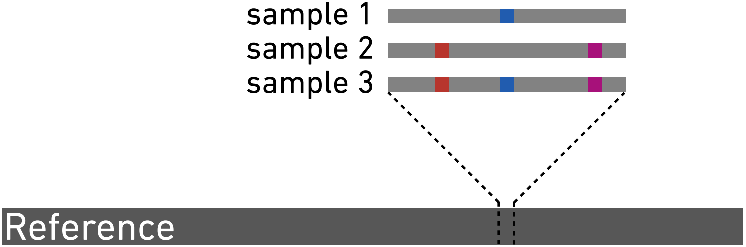

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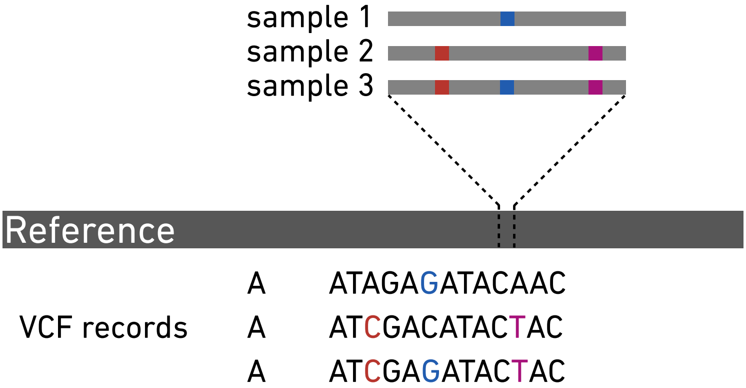

sample 1

sample 2

sample 3

Reference

VCF records

```
A    ATAGAGATACAAC
A    ATCGACATACTAC
A    ATCGAGATACTAC
```

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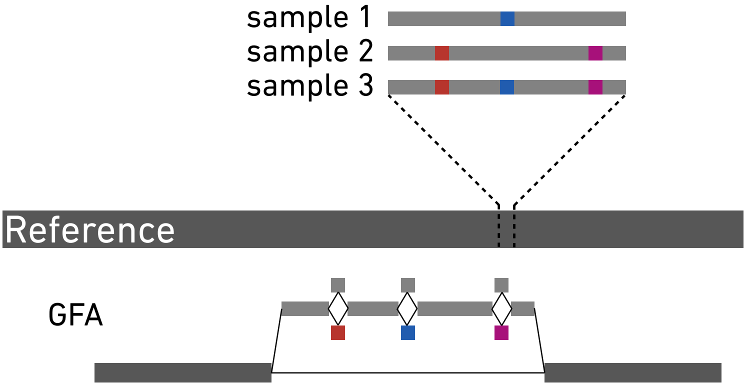

Genome file formats

Most sequencing data (or anything representing genomes) are in *fasta/q*

Sequence alignments are generally in *SAM/BAM*

Other “annotation” files like *BED*, *GFF*, etc

Pangenome terminology

How do we describe a graph-based sequence/variation pangenome?

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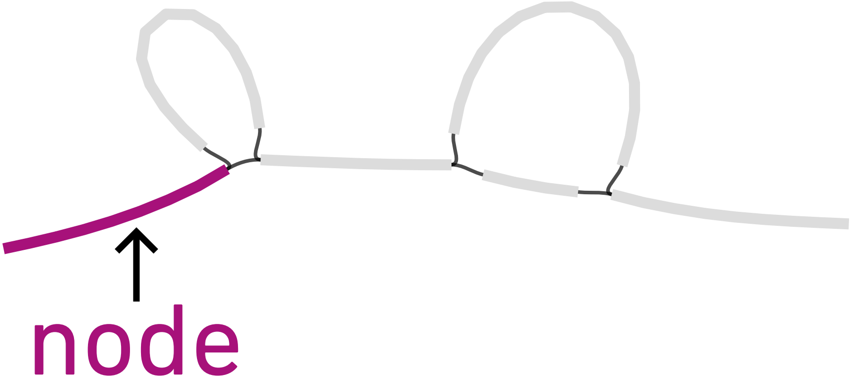

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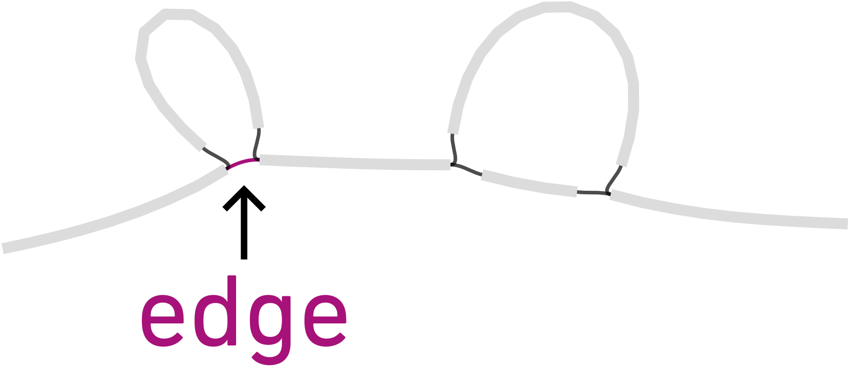

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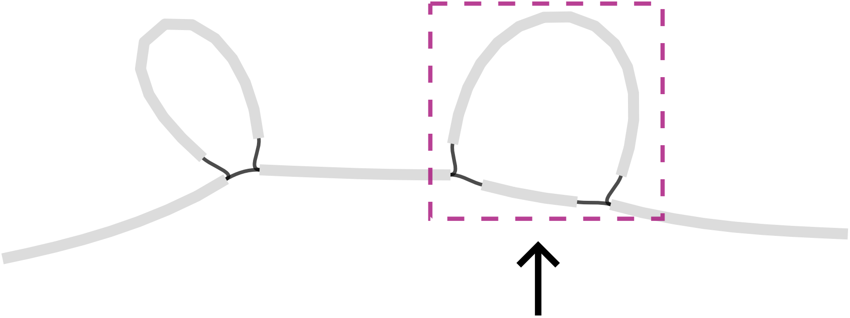

"bubble"

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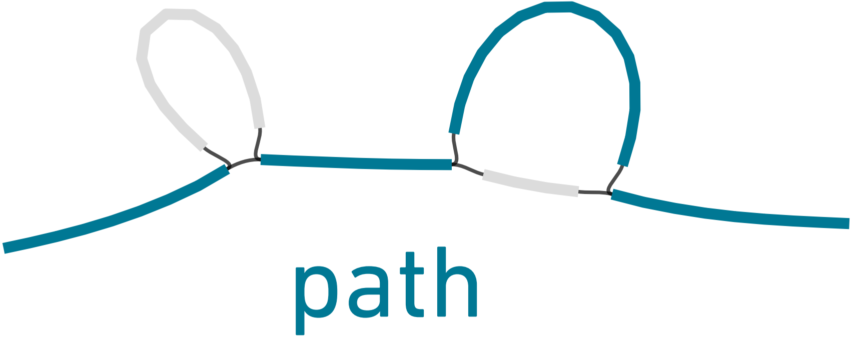

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Three main components:

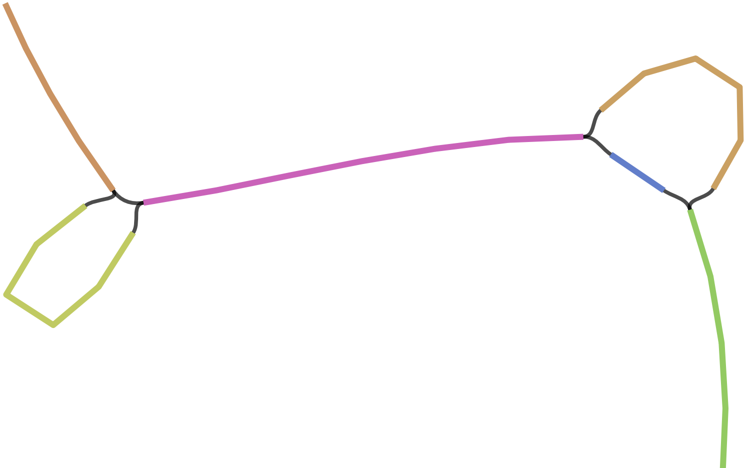
- S-lines: the sequence of the nodes
- L-lines: how the graph is connected with edges
- P-lines: how a “sample” traverses the graph (*optional*)

Pangenome file formats

```
H       VN:Z:1.0
S       1       AATTTACC
S       2       GGTAT
S       3       T
S       4       CCCGATA
S       5       GGACTA
S       6       TTAC
L       1       +       2       +       0M
L       1       +       3       +       0M
L       2       +       4       +       0M
L       3       +       4       +       0M
L       4       +       5       +       0M
L       5       +       6       +       0M
L       4       +       6       +       0M
P       Alice    1+,2+,4+,5+,6+ *
P       Bob      1+,3+,4+,6+ *
```

Pangenome file formats

That looks like



Pangenome file formats

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These graphs contain a lot of information.

GFA is human-readable, but binary formats are more compute efficient

Pangenome file formats

GAF: **G**raph **A**lignment **F**ormat

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Similar to *.sam* files, recording details on:

- which read
- where does it align
- how good was that alignment

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Similar to *.sam* files, recording details on:

- which read
- where does it align
- how good was that alignment

Likewise, this is human-readable, and so some tools prefer the binary version `.gam`.

Graph building

Building a “variation graph” starts with a set of assemblies

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We often rename chromosome names using PanSN-spec

[sample]#[haplotype]#[contig](#[fragment/subrange])

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- avoids conflicts of many e.g. “>chr1” sequences
- encodes some metadata *within* the file
- enables selectively grouping/renaming values by “classification”

minigraph

Augments a linear reference “backbone” with *sufficiently* new variation

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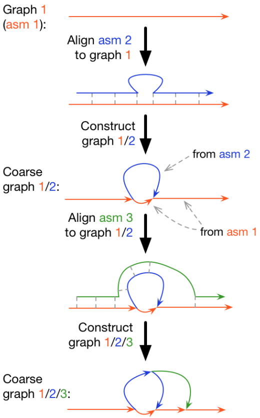

pggb

All-versus-all alignment, followed by complicated cleaning of the graph structure

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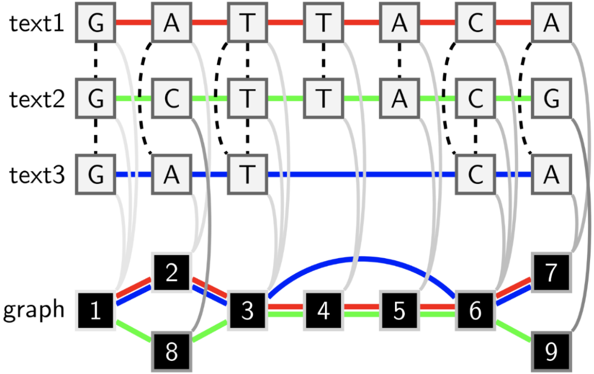

Different approaches

	≥ 50 bp	< 50 bp	Reference-based	Lossless	N+1	Compute
`minigraph`	Yes	No	Yes	No	Easy	Laptop
`cactus`	Yes	Yes	No-ish	Yes	Easy-ish	Cluster
`pggb`	Yes	Yes	No	Yes	Rebuild	Big cluster

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Pick the approach that best matches **your** research question

Other pangenome tools

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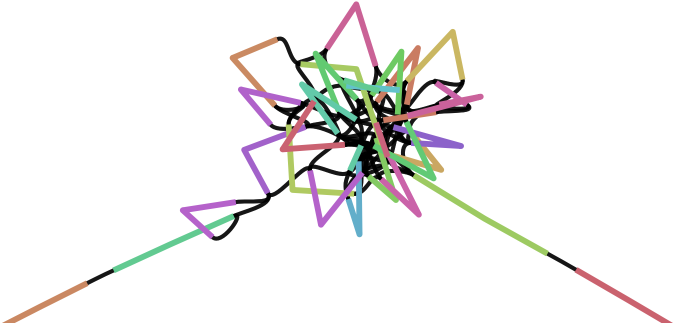

Pangenome visualisation

IGV (**I**ntegrative **G**enomics **V**iewer, https://igv.org/doc/desktop/) is a useful tool for visualising different formats of genomic data:

- read alignments
- bed files
- gene annotations

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Is there a pangenomic equivalent?

Visualising **pan**genomic data

Everything is more complicated in the pangenomic world

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Everything is more complicated in the pangenomic world

What are we trying to visualise?

- Synteny between many assemblies?
- Genic regions in a pangenome?
- Alignments to a pangenome?

Interactive visualisation

How do we visualise the *.gfa* output of pangenome construction?

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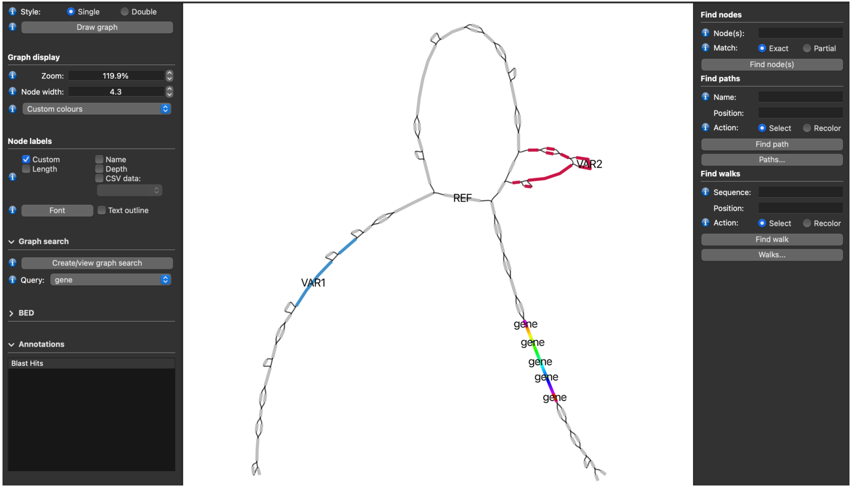
One of the most common tools is `BandageNG` (https://github.com/asl/BandageNG).

We'll explore this in the practical, but it has several advantages:

- easy to install
- quick to load small-to-moderate sized graphs
- extensive analytic functionality

Interactive visualisation



Style: ● Single ○ Double

Zoom: 119.9%

Node width: 4.3

Custom colours

☑ Custom □ Name
□ Length □ Depth
□ CSV data:

□ Text outline

Query: gene

Node(s):

Match: ● Exact ○ Partial

Name:

Position:

Action: ● Select ○ Recolor

Sequence:

Position:

Action: ● Select ○ Recolor

Static visualisation

Large graphs (many nodes and/or edges) are complex to render.

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Let the computer do the **hard** work and render a static representation!

Static visualisation

Break pangenome down into multiple linear blocks

Static visualisation

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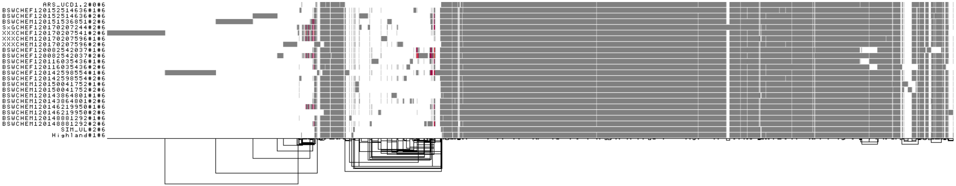

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"Optimally" lay out nodes/edges in 2D with a *Hogwild!* algorithm.

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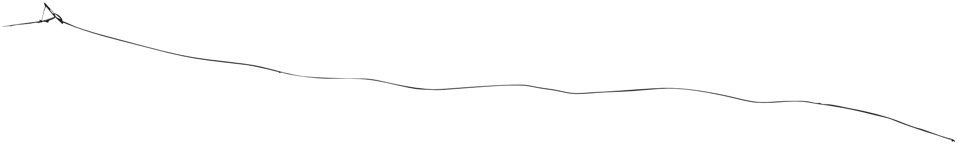

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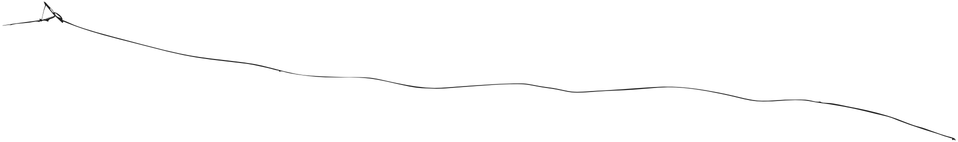

This step took ~**30%** of the entire HPRC pipeline runtime!

Pangenome communities

Building pangenomes per chromosome is much easier than genome-wide

Pangenome communities

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What if

- we care about interchromosomal events
- we don’t know how to define “per chromosome”
- we don’t have assigned chromosomes

Nonuniform karyotypes

Even “similar” species can undergo complex chromosomal evolution

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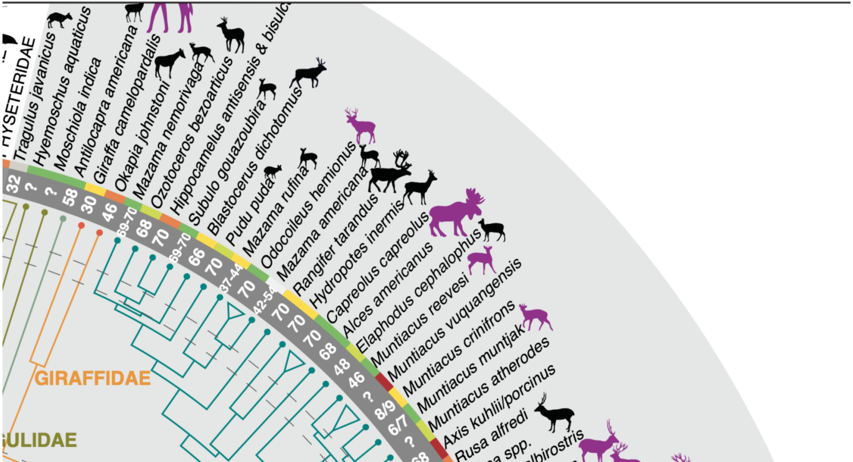

Community detection

pggb implemented community detection

- map whole genomes all-versus-all
- build a *weighted* network from all submappings
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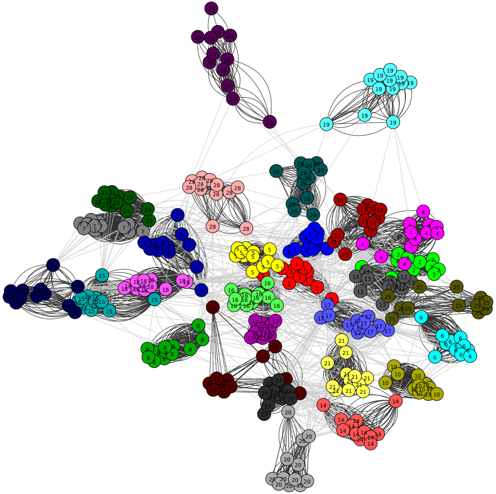
Distinguishing signal from noise is hard for small/infrequent mappings

Community detection



Pangenome validation

How do we know if the pangenome we built is any good?

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What does *good* even mean to us?

Pangenome analyses

There are several tools useful for checking pangenome construction and content

- `gfatools`
- `odgi`
- `panacus`
- `gretl`

Pangenome graph statistics

After building a graph, the simplist statistics to check are:

- total sequence length
- maxmimum and average node size
- node depth distribution

Pangenome graph statistics

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Different graphs (e.g., `pggb` versus `minigraph`) may have similar length, but very different node/edge counts.

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Different graphs (e.g., `pggb` versus `minigraph`) may have similar length, but very different node/edge counts.

Consider the average node size (pangenome length / number of nodes) or average edge degree (number of nodes / number of edges)

Should be *reasonable* values (how many bases do you expect before a SNP?)

Pangenome graph statistics

From `gfatools stat` on a large, base-level bovine pangenome of chromosome 1 (159 Mb)

```
Number of segments: 10140559
Number of links: 14371940
Number of arcs: 28743880
Total segment length: 200985993
Average segment length: 19.820
Max degree: 106924
Average degree: 1.417
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The total pangenome size should *approximately* be equal to the reference plus all variation.

Pangenome openness

How does the growth of a pangenome change with more samples?

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We can use *Heap's law* from text analysis: $N \propto n^{-\alpha}$

If $\alpha > 1$, the pangenome is **closed**, otherwise if $\alpha \leq 1$, the pangenome is **open**.

Pangenome openness

With enough samples, we can estimate α

Care is needed about how much variation is *expected* to be shared . . .

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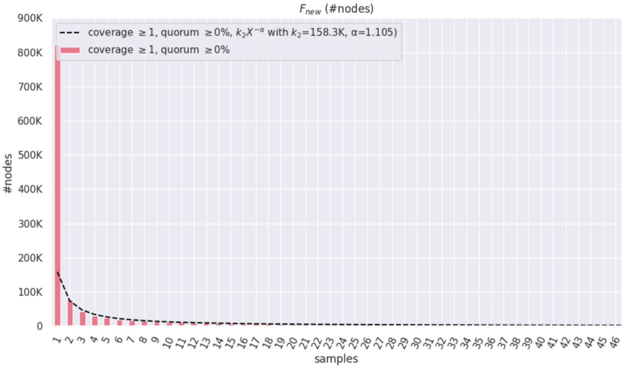

Pangenome layers

Pangenome openness effectively addresses the total unique sequence.

What about different levels of intersection?

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Pangenome openness effectively addresses the total unique sequence.
What about different levels of intersection?

We can characterise pangenome *nodes* as:

- **core**: present in all/most samples
- **shell**: present in at least two samples
- **cloud**: present in only one sample
- **flexible/dispensable**: varies, but something like shell/cloud

Pangenome layers

With enough samples, we expect minimal sequence to be “core”

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Misassemblies can also further reduce the “core”

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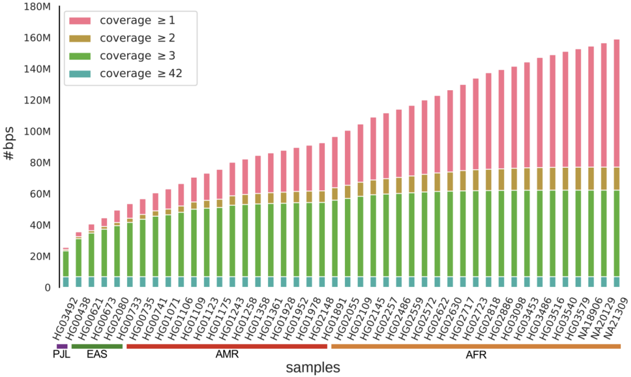

Downstream pangenomics

Once we have a “good” pangenome, what can we actually do with it?

Calling pangenome variants

We can also call variants *within* the pangenome with `vg deconstruct`

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“Project” back into linear space (losing *some* pangenomic benefits)

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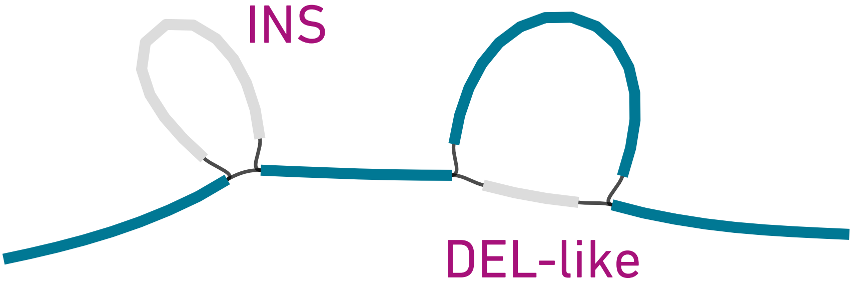

Aligning to pangenomes

Linear-reference alignment is “simple”

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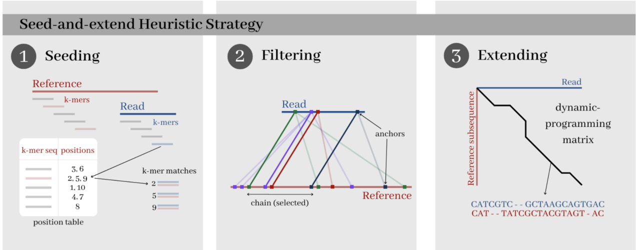

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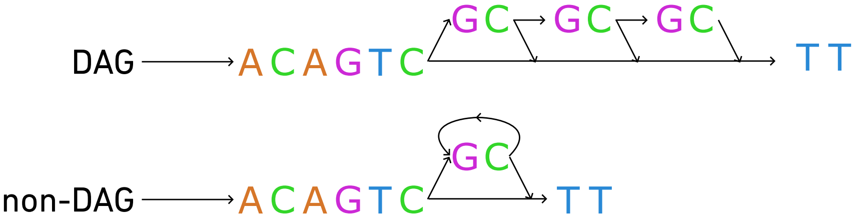

Long read alignment

Long reads span more bubbles in graphs, exponentially complicating alignment

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Currently limited number of “production” tools

- `GraphAligner`
- `vg giraffe-lr` soon!

Personalised pangenomes

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Can we “filter” out graph complexity that isn’t useful for a *given* sample?

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Given any genomic sequencing, we can easily calculate a set of *k*-mers for that sample

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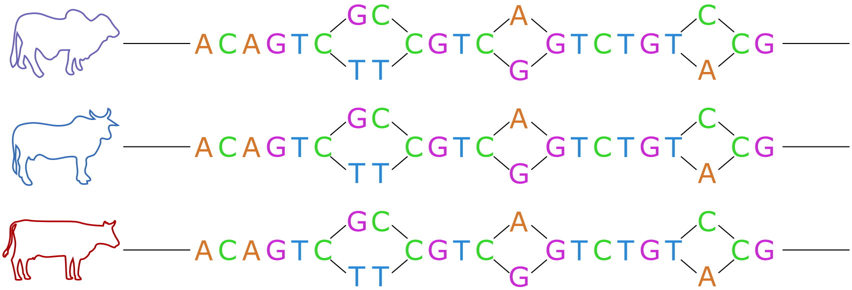

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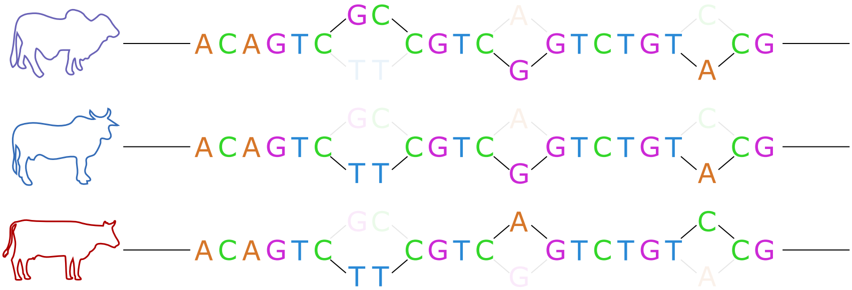

ACAGTC GC CGTC G GTCTGT A CG
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Upstream blackbox

Pangenomes can be challenging and don't always match downstream input formats

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A user could provide a complete reference pangenome and (short) reads

Inside a black box, we can then run

- `vg haplotype` (personalise the pangenome)
- `vg giraffe` (align to the pangenome)
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- e.g. `DeepVariant` (call variants as per usual)

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Improved variant calls without *direct* exposure to the pangenome

Targeted pangenomes

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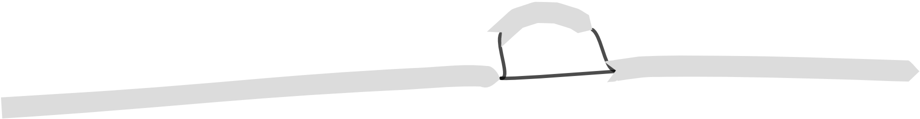

Bison specific deletion

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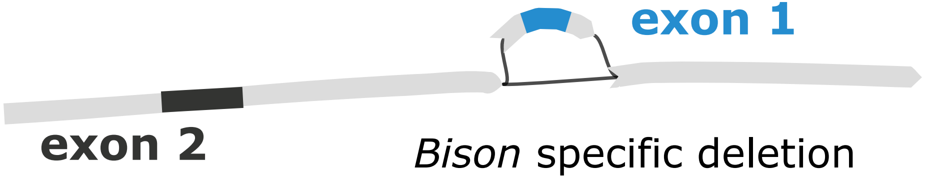

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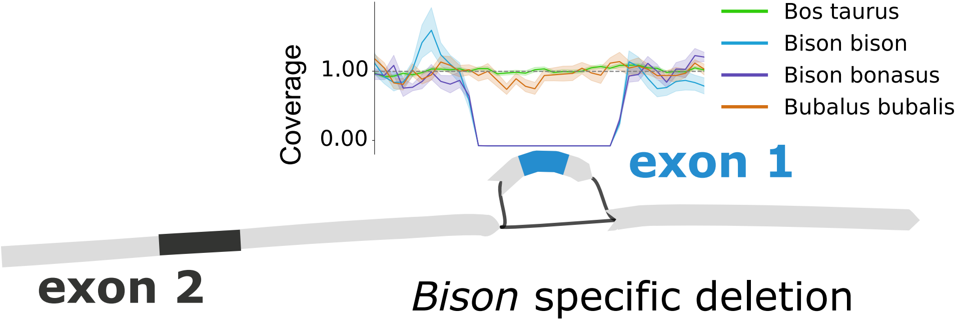

Bison specific deletion

Manual QTL pangenome

For a given reference-annotated region, we can:

Manual QTL pangenome

For a given reference-annotated region, we can:

- lift over equivalent reference coordinates into other assemblies
- extract relevant section of those assemblies
- build a pangenome from these sequences

A better approach

`impg` outlines a different approach

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- conduct the hard all-to-all mapping once
- extract *transitive* regions based on a set of coordinates
- build a pangenome from those sequences

A new whole-genome approach?

Building many small pangenomes is easier than one big pangenome

Can we go from per *chromosome* to per *window*?

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Recombine pieces into chromosome-scale graphs with `gfalace`

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Can we go from per *chromosome* to per *window*?

Recombine pieces into chromosome-scale graphs with `gfalace`

Some unresolved concerns:

- boundary conditions are poorly defined
- events spanning the "split length" might be lost
- detecting subgraph isomorphisms is hard

Acrocentric recombination

Caveat: biologists probably knew before the computer people

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Initial human pangenome construction lead to huge tangles in *some* chromosomes

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Pangenomes (at minimum) offer a new perspective on existing questions

Acrocentric recombination

Pseudo-homologous regions near centomeres drive Robertsonian translocations

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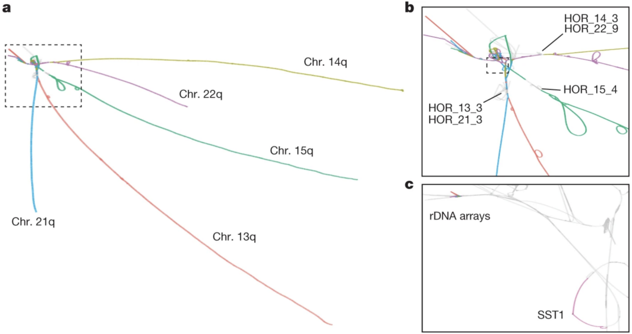

{Guarracino et al. 2023}

Braided snarls

Strange pangenomic structures are generally worrying

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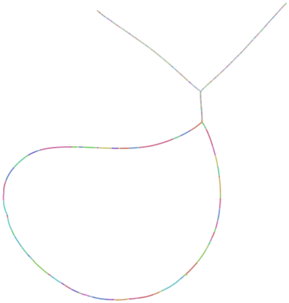

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Hyper/**Mega**/**Ultra**pangenomes?

Superpangenomes

What happens if we include many related species into a pangenome?

Superpangenomes

What happens if we include many related species into a pangenome?

- ultraconserved elements are still roughly single nodes
- species-specific variation are distinct paths through bubbles
- phylogeny-related information present in nested bubbles

Summary – starting with pangenomes

Pangenomes can integrate many genomes into one structure to mitigate reference bias

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Pangenome openess or graph statistics help us know if our graphs are “good”

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T2T assemblies and pangenomes *can* unlocking entirely new perspectives

Population-scale read alignment and “direct” pangenomic analyses are *becoming* possible

Hands on pangenomics

During the activity we'll look at

- building a small `minigraph` pangenome
- visualising that pangenome in `BandageNG`
- using `gfatools` to find regions of interest

Questions?