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From genomics to metagenomics: benchmark of variation graphs

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Background

In the metagenomics field, the classical approach for quantitative analysis of sequencing data consists in aligning sequence reads to a non redundant reference gene catalogue that represents a specific ecosystem [1]. However this approach lacks flexibility and exhaustiveness. To overcome those biases, the reads should be aligned to a more informative reference structure covering the variants encountered in the population and also more complete with a full genome catalogue. Recently, the pangenome concept has been increasingly used as it opens new ways to investigate multiple genomes of close individuals, as for characterizing the different strains of a species. Erik Garrison et al. have developed “vg”, a toolkit for creating variation graphs, bidirected DNA sequence graphs that represents multiple genomes, including their genetic variation [2]. With a perspective towards metagenomics, we foresee vg as a tool enabling to build a catalogue of pangenomes from metagenomic samples.

Objectives

As a proof of concept, we constructed a pangenome graph for *Escherichia coli* with three main objectives: evaluating time complexity to take it into consideration for future scaling, defining paths (successive nodes) in the graph corresponding to strains, and identifying and quantifying strains in a sample by mapping its reads on the graph.

Graph construction and time complexity

Data

- Inputs: 6 strains of *E. coli* → O157:H7, IA139, BL21, SE15, O104:H4, K-12
- Graph construction using VG

Graph construction

- Complete genomes as inputs:
  - Execution time with increasing number of genomes was recorded (left).
  - Time linear, 20 minutes for constructing the graph from 6 genomes.
- Contigs as inputs:
  - Complete genomes of two of the strains were cut into parts (“contigs”). Parts were overlapping on 20 kbp to ensure there was no ambiguity on the order of the parts.
  - Execution time with increasing number of cuts was recorded (right).
  - Time linear, 4 hours using both genomes cut in 100 parts each.

Assigning reads to paths and counting

- A read is assigned to a path if the whole read matches a set of successive nodes belonging to the same path.
- Three different ways of counting the number of reads assigned to a path:
  - Total Count (read is counted for each path it is assigned to)
  - Unique Count (read is counted if it is assigned to a unique path)
  - Adjusted Count (Unique Count is used to define the relative abundance of the strains in the sample, this ratio is then applied to Total Count)

Results on simulated data: 100 000 reads of length 200 bp were generated without errors using a mix of O104:H4 and IA139 *E. coli* strains at different ratios and then mapped on the graph.

Mapping and counting using simulated data

Results on real data: 2 samples randomly selected from a collection after the German outbreak of Shiga-toxigenic *E. coli* (STEC) O104:H4 in 2011 mapped on the graph → 1 sample positive for STEC (STEC+) where O104:H4 is expected and 1 negative (STEC−) where O104:H4 should be absent.

Mapping and counting using real data

The strains and their original abundance are correctly identified.

References