DAYZERO DIAGNOSTICS

Democratizing Sequencing for Infection Control: A Scalable, Automated Pipeline for WGS Analysis for Outbreak Detection

Mohamad Sater, Timothy Farrell, Febriana Pangestu, Ian Herriott, Melis Anahtar, Doug Kwon, Erica Shenoy, David Hooper, Miriam Huntley

Background

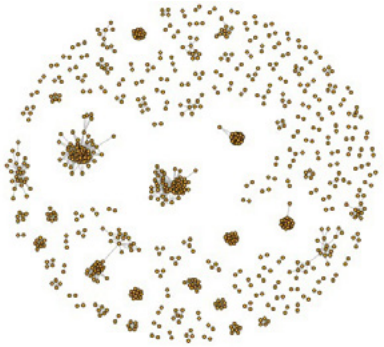
Whole genome sequencing (WGS) is well established as a high-resolution method for measuring bacterial relatedness to better understand infection transmission in cases of healthcare associated infections (HAIs). Yet sequencing is still rarely used in HAI investigations due to a lack of access to computational analysis platforms with actionable turnaround times. Single nucleotide polymorphism (SNP) analysis is typically used to determine bacterial relatedness. However, SNP-based methods often require a suite of bioinformatics tools that can be difficult to use and interpret without the expertise of a trained computational biologist. These obstacles become more significant in the case of prospective, real-time surveillance of HAIs which can require analyzing a large number of isolates. To enable the use of WGS for proactive determination of infection outbreaks, a rapid, automated method that can scale to large datasets is required.

Methods

Here we demonstrate the capabilities of *ksim*, a novel automated algorithm to determine the clonality of bacterial samples using WGS. *ksim* measures the number of shared *k*mers (genomic subsequences of length k) between bacterial samples to determine their relatedness. *ksim* also filters out accessory genomic regions such as plasmids which can confound genetic relatedness estimates. We benchmarked the accuracy and speed of *ksim* relative to a SNP-based pipeline on simulated datasets, with sequencing reads generated in-silico, and on 9 clinical cluster datasets - 6 publicly-available, and 3 real-time datasets from Massachusetts General Hospital (MGH). We also used *ksim* to determine the relatedness of >5,000 historical clinical bacterial isolates from MGH, collected between 2015-2019.

Results

ksim first preprocesses raw sequencing data to generate a common data structure, after which it computes the genomic distance between bacterial samples in ~0.2 seconds in simple cases, and ~4 seconds in complex cases when accessory genome filtering is required. In simulations across five species, *ksim* determined clonality (defined as <40 SNPs) with high accuracy (sensitivity: 99.7%, specificity: 99.6%). *ksim*performance on 9 clinical HAI datasets found it had sensitivity 99.4% and specificity: 90.8% compared to a SNP-based pipeline. *ksim* efficiently analyzed >5,000 clinical samples from MGH, and found previously unidentified transmission clusters.



***ksim* clustering of >3000 *E. coli* clinical samples.**
Patient clusters based on isolate genomic clonality identified by *ksim*. Each yellow circle represents a patient, an edge between two circles denotes an *E. coli* clonal pair, non-clonal pairs not shown.

Conclusion

ksim shows promise for rapid clonality determination in HAI outbreaks and the potential to scale to tens of thousands of samples. This method enables infection control teams to use WGS for prospective outbreak detection via an automated computational pipeline, without the need for specialized computational biology training.

