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Adapting Flint for Calculating Bacterial Replication Rates in Microbiomes

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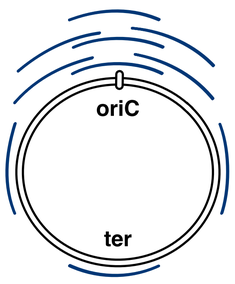
Abstract

We extend **Flint**, a **Spark-based metagenomic profiling tool**, to efficiently **measure bacterial growth rates** for large data sets. The tool **bPTR** for bacterial growth rate measurement from metagenomic samples [Brown et al., *Nat Biotech*, 2016] was adapted and integrated into Flint's **MapReduce** framework in order to take advantage of Flint's efficient read alignments and mapping, thus enabling the creation of bacterial abundance profiles that are enhanced with growth-rate information.

To show the viability of our method we analyzed whole **metagenome sequence data** from a longitudinal study of sampled preterm infants [Gibson et al., *Nat Micro*, 2016], computing the abundance profile enhanced with growth-rate information. The conclusions shed light on the new perspective obtained on antibiotics treatments and **antibiotic resistance** by looking at replication rates.

Introduction

Peak to Trough Ratio (PTR)

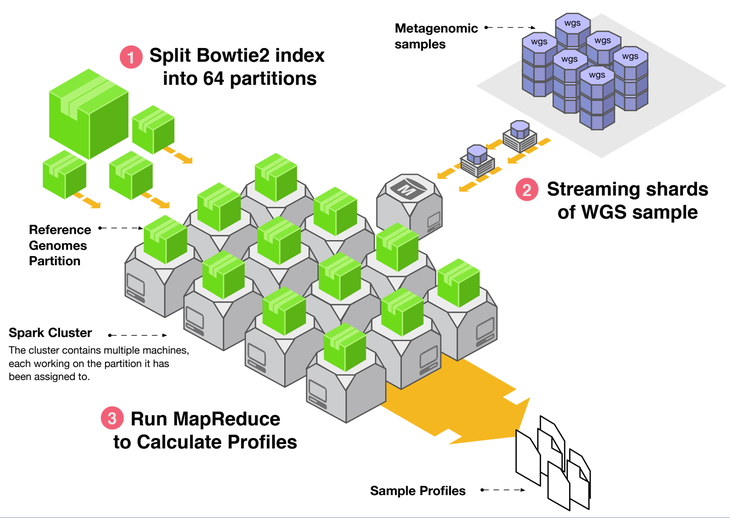


$$PTR = \frac{Coverage(oriC)}{Coverage(ter)}$$

When bacteria is replicating, coverage of reads near the origin of replication (*oriC*) is known to be higher than the coverage near the terminus (*ter*) [Korem et al., *Science*, 2015].

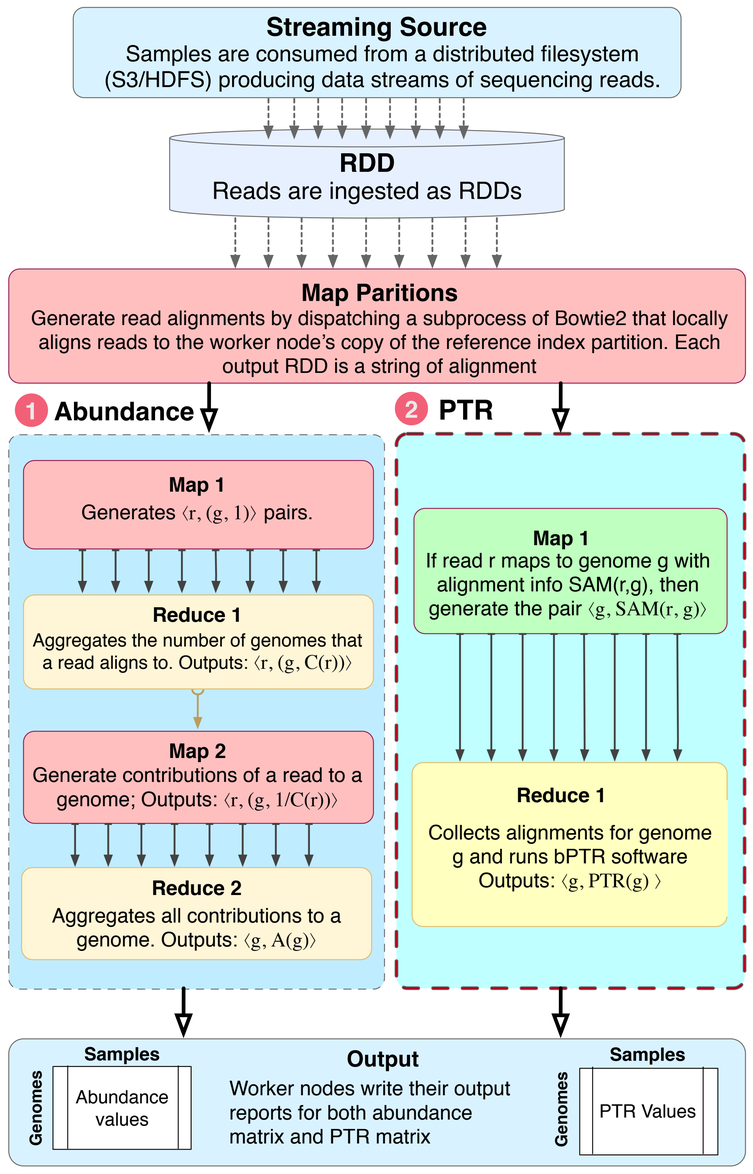
Flint

Flint is a scalable, efficient, and affordable metagenomics profiling tool that is built on top of the Apache Spark framework. Figure below describes the workflow of the Flint flamework [Valdes et al., *ISMB,* 2019].



Materials and Methods

Flint was extended to efficiently calculate bacterial growth rates by adapting bPTR software [Brown et al., *Nat Biotech*, 2016], processing aligned metagenomic reads using MapReduce. See architecture of solution below.



- ~25,000 complete bacterial, archaeal, and viral genome sequences from RefSeq v.92 database were used for the analyses.
- The experiments were executed on AWS EMR platform.
- The results were cross-referenced with computations on LSF scheduler platform.

Data Source

Metagenomic reads from 401 stool samples from 84 premature infants from a longitudinal gut microbiome study were analyzed [Gibson et al., *Nat Micro*, 2016].
All but two infants received antibiotic therapy within the first 24 hours. 61% of the infants received additional antibiotic therapies ("Antibiotic" cohort) between 1–10 weeks of life. Remaining 39% formed the "Control" group. Each therapy consisted of one or more antibiotics. A total of 2-6 samples per individual were obtained at different time points between 6-156 days.

Conclusions

A pipeline for calculating PTR using the FLINT framework for large-scale analysis was successfully implemented. The PTR values provided useful additional information about the dynamics of microbiomes.

Our results led to the following conclusions:

A. Dormancy is a survival strategy against meropenem.

Other antibiotic defense mechanisms are less effective since meropenem is highly resistant to degradation by β-lactamases or cephalosporinases.

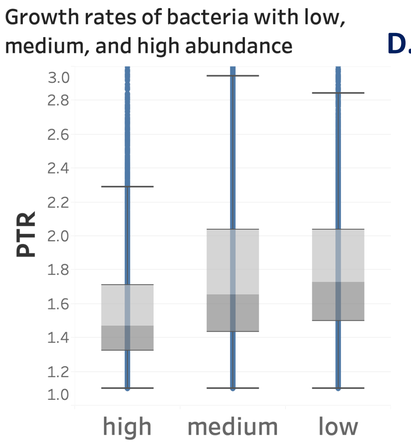
B. When relative abundance of a bacterial taxon increases upon administration of ampicillin, meropenem, or vancomycin, their replication rate tends to decrease.

Bacterial taxa often respond to antibiotic exposure by reducing replication rates. The relative abundance of a taxon increases (even if its real abundance does not) if other taxa are reduced or eliminated by an antibiotic.

C. Decrease in taxon abundance is correlated with increase in PTR.

Broad spectrum antibiotics effectively eliminate many bacterial taxa, increasing the availability of nutrients, and pushing some taxa out of stationary phase.

Growth rates of bacteria with low, medium, and high abundance



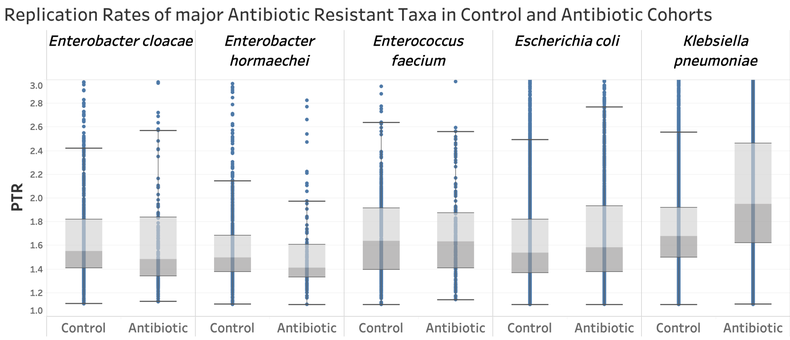
D. In general, highly abundant bacteria have lower PTR (figure on left).

One explanation is that taxa with high abundance have likely consumed a lot of the available nutrients, pushing them from exponential to stationary growth phase.

***E. Klebsiella pneumoniae* has significantly higher PTR in the "Antibiotics" group, suggesting an exponential growth after antibiotics treatment.**

Figure below shows PTR of 5 major antibiotic-resistant taxa from the "Control" and "Antibiotics" cohorts.

Replication Rates of major Antibiotic Resistant Taxa in Control and Antibiotic Cohorts



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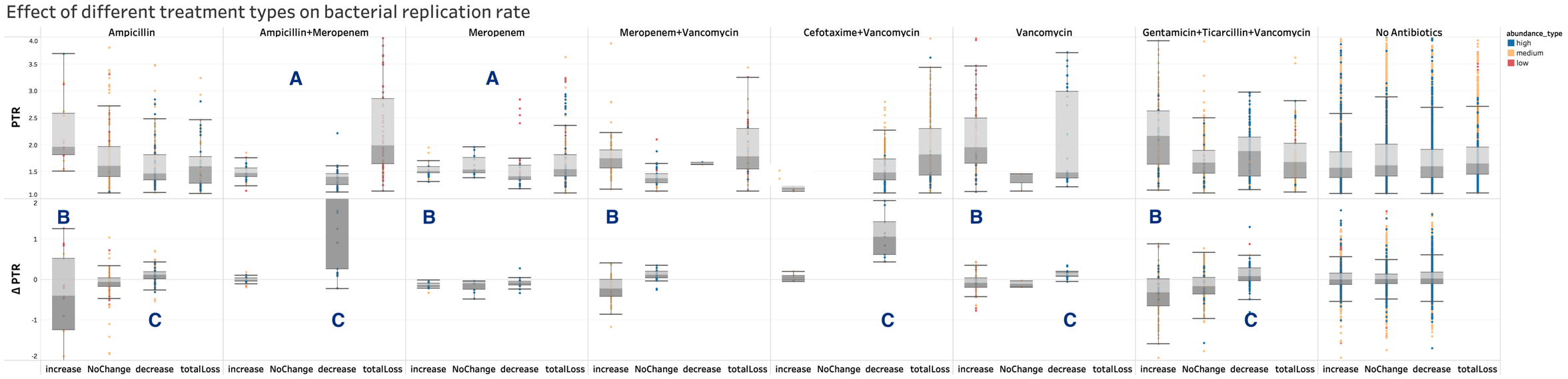
Results

A total of 31,635 PTR values were calculated. The replication rates vary with with different antibiotic treatments, and this is most likely related to different antibiotic defense mechanisms. The box and whisker plots below of PTR and ΔPTR (i.e., difference between PTR after and PTR before the specified treatment) for each of the categories (Increase, Decrease and Total Loss) broken down by treatment type. Different color points indicate different magnitudes of abundance — low (red), medium (orange), or high (blue).

Effect of different treatment types on bacterial replication rate



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