E. coli genomes, big data, and messy biology

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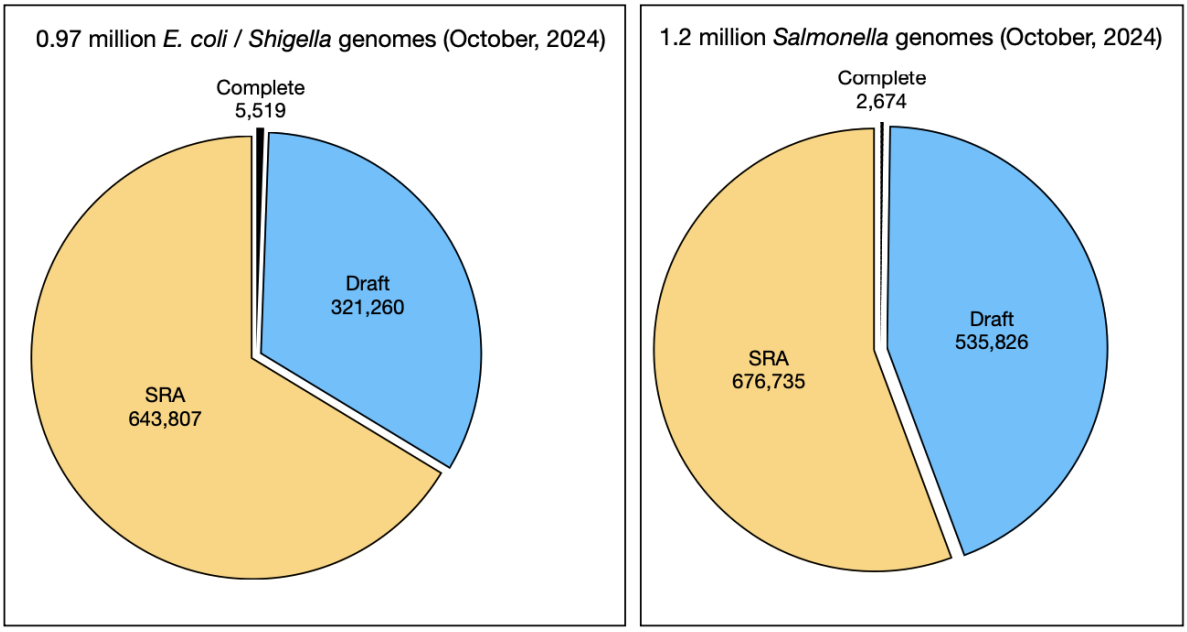

Here, David Ussery from the Department of BioMedical Informatics, UAMS, details *E. coli* genome diversity, big data, and messy biology. New methods, we discover, allow for the comparison of millions of bacterial genomes in a few days and the confident assignment of taxonomic clusters

Escherichia coli was first described in 1885 [(1)] and is one of the best-studied model organisms as both a commensal [(2)] and a pathogen. [(3)] The diversity of *E. coli* is enormous. We have compared more than 10,000 *E. coli* genomes and found more than a hundred thousand different gene families distributed in the 'pan-genome'. [(4)] Since then, the number of sequenced *E. coli* genomes has continued to grow and is now close to a million.

Where are we now? *E. coli* diversity is vast!

At the time of writing this article (October, 2024), there are just under a million *E. coli* genome sequences available in the NCBI database, with more than 5,000 complete *E. coli*/ Shigella genomes, and another 321,260 draft genomes; in addition, there are nearly twice as many genomes in the Sequence Read Archive (SRA) database, bringing the total to more than 970,000 *E. coli* genomes, as shown in Figure 1; there are likely more than a million different gene families found in this set of *E. coli* genomes, although any individual E. coli contains about 5,000 genes.

How did we get here? A brief history of *E. coli* genomics Sometimes, fact can be stranger than fiction. Who would have thought that it is possible for one bacterial species to have more than a million different proteins? The first *E. coli* genome was sequenced in 1997 from a laboratory strain, with about 4,300 genes. [5] At the time, the vast genomic diversity of this organism was not appreciated. Around this time, we developed the 'genome atlas' for *E. coli*, a way to view the entire chromosome as one circular plot. [6,8]

A few years later, the second *E. coli* genome sequence (this time from a pathogenic strain), with about 5,500 genes; many were surprised that this contained more than a thousand extra genes not found in the first *E. coli* genome. [9] A microarray with four different *E. coli* genomes soon became available [10], followed by microarrays with seven [11] and then thirty-two *E. coli* genomes [12].

A comparison of 61 *E. coli* genomes found a pan-genome with more than 15,000 different *E. coli* gene families, and a core of only 960 gene families [13]. Two years later, the number of E. coli genomes had more than doubled [14], and as more genomes were compared, we realized that the presence of low-quality draft genomes was causing the core to drop to near zero, so we re-defined 'core' genes as being present in at least 95% of the genomes. This resulted in a stable core of roughly 3,000 gene families found in 400 *E. coli* genomes [15], and then 2,000 *E. coli* genomes [16].

Since then, the number of *E. coli* genomes (and the diversity) has steadily grown with time. More recently, we have compared more than 10,000 *E. coli* genomes and found a core of about 2,800 gene families, and most of the genomes are clustered into 14 phylogroups that include many Shigella species [4].

Where are we headed in the future of 'big data in biology'?

E. coli genomics now requires dealing with large amounts of messy data. I see two areas of concern: scalable and reproducible methods for comparing millions of genomes with consistent organism names and getting the organism names right. Making predictions is difficult – especially predictions about the future. The Enterobacteriaceae family ("*E. coli* and friends") has been well-studied and heavily sequenced; there are more than 1.2 million Salmonella genomes, as well as more than another hundred thousand other genomes from the Enterobacteriaceae family.

Currently, we have found that the Mash program [17] seems to give reproducible and consistent yields and scales well. For example, we have recently clustered more than a million Salmonella genomes (see Figure 1) into a dozen phylogroups, as we've done for 100,000 *E. coli* genomes [4], which took less than a week, using a small cluster. Having said that, getting the data from the SRA is not easy.

Originally, we estimated it would take about 14 months to download the 600,000 Salmonella genomes in the SRA. Fortunately, another research group had assembled all the bacterial genomes (18), and we could download all the Salmonella genomes in less than one day. However, we found that about 8% of the 'Salmonella' genomes clustered with *E.coli* (Sudip Panday and Dave Ussery, unpublished results).

Since the time of Aristotle, biologists have been naming things, and more recently, there has been a rush to assign names to bacteria based on their genome sequence. New names for bacterial species are being proposed daily, and about 80% of the names of bacterial species have been changed in the past two years . In early versions of the Genome Taxonomy Database, many stains of *E. coli* were given new names (19). For example*, E. coli* K-12 was renamed 'Escherichia flexneri', since this sequence was close to Shigella flexneri. The idea of changing the name of one of the most well-known and studied organisms was met with resistance, and for now the 'rose' of *E. coli* is still being called a 'rose' [(20)].

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