Recombine often or perish: Genome evolution in bacterial and eukaryotic pathogens

Molecular Epidemiology of Infectious Diseases
Lecture 7

February 28th, 2022

Classic population genetic models of evolution focus on changes in genotype frequencies

Evolutionary Theory 101: Selection

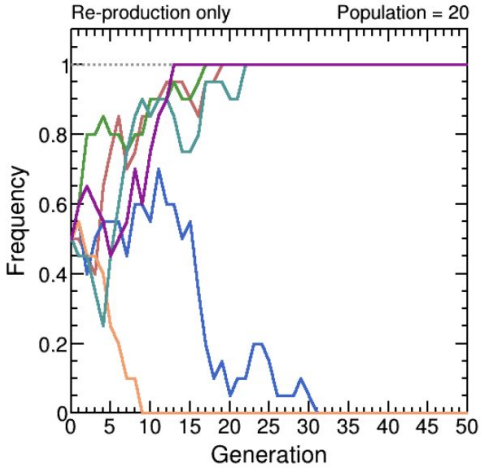
Selection “acts” on genetic variation (i.e. mutations or alleles) at one or a few loci to increase the frequency of higher fitness variants.

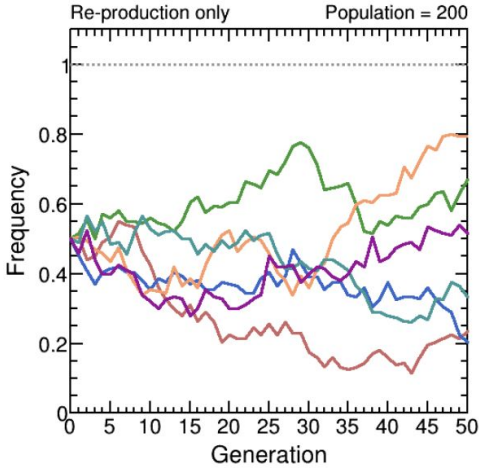
Selection can purge deleterious mutations and increase the frequency of beneficial mutations.

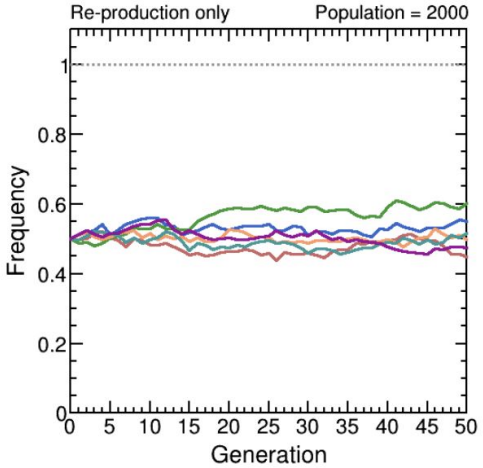
The strength of selection will depend on the fitness effects of mutations and the size of populations due to genetic drift.

Genetic drift

Genetic drift refers to stochastic fluctuations in genotype frequencies caused by random variation in reproduction and survival. Stochastic variation and drift play a larger role in smaller populations.





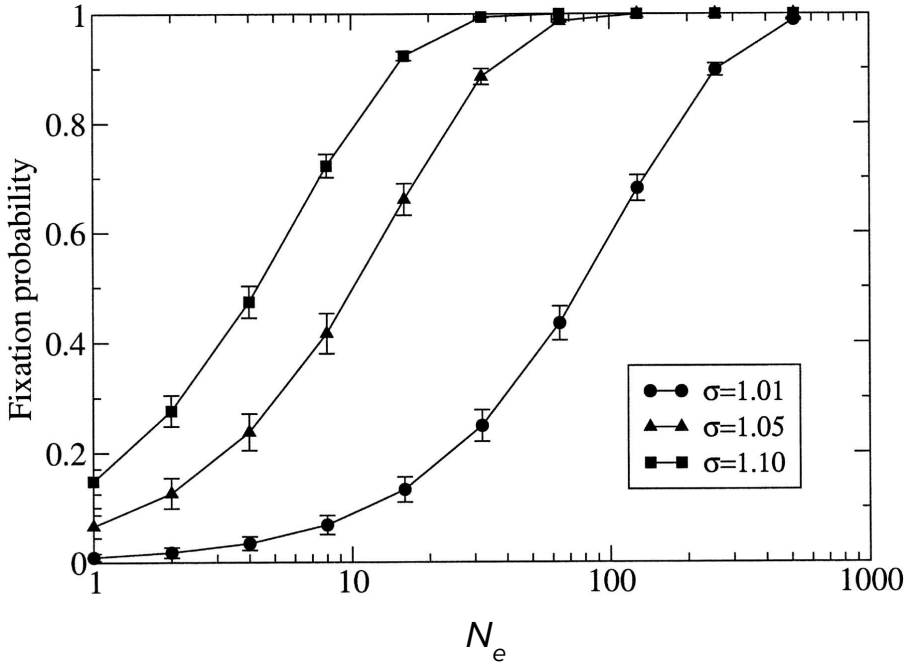


https://boundino.github.io/S188592web/drift.html

Genetic drift

The probability that a beneficial mutation reaches fixation (freq → 1.0) depends both on its selective advantage (s or σ) and the effective population size (N_e) – the number of individuals that contribute progeny to the next generation.

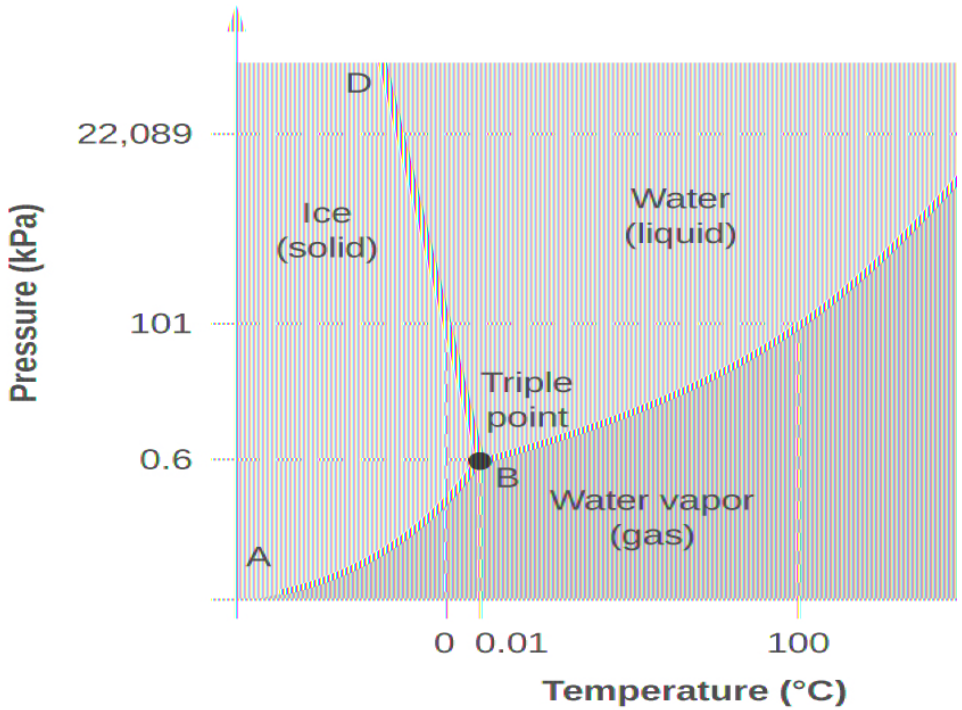
$$s = w_{mut} - w_{wt}$$



Wilke (Genetics, 2003)

Evolutionary phase diagrams

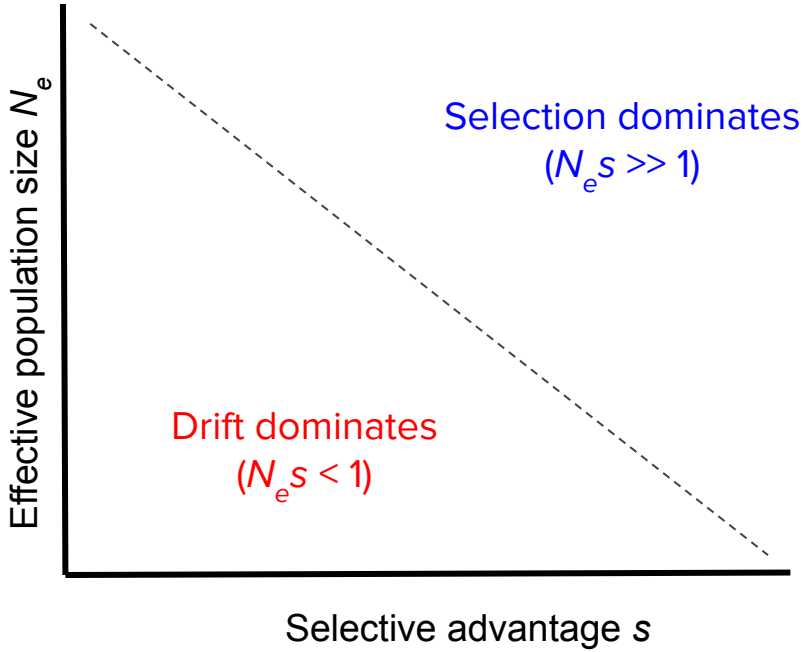
Phase diagrams describe how the large-scale properties of systems depend on key variables and identify ***critical points*** at which the qualitative behaviour of the system changes.



https://cnx.org/contents/oFoO44pW@5/Phase-Diagrams

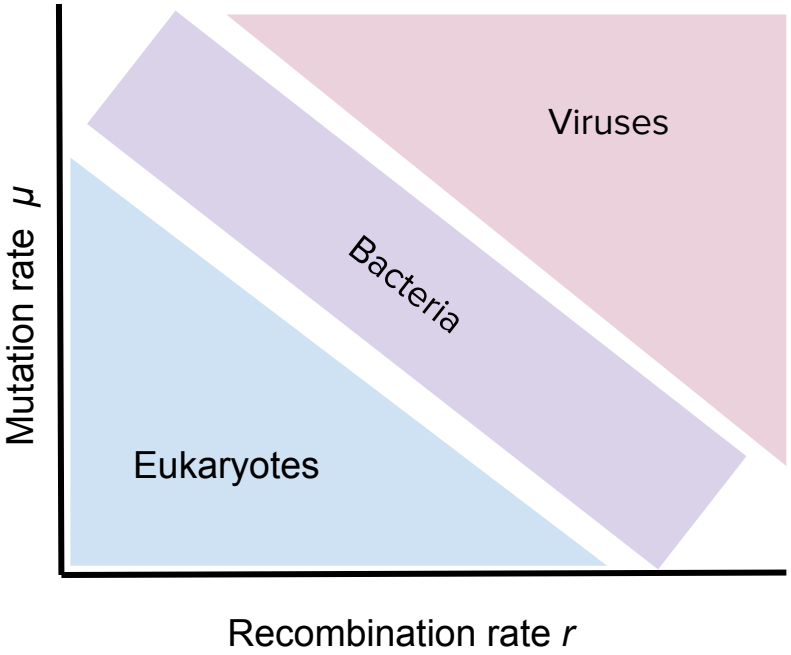
Selection vs. drift

The relative importance of selection versus drift is determined by $N_e s$



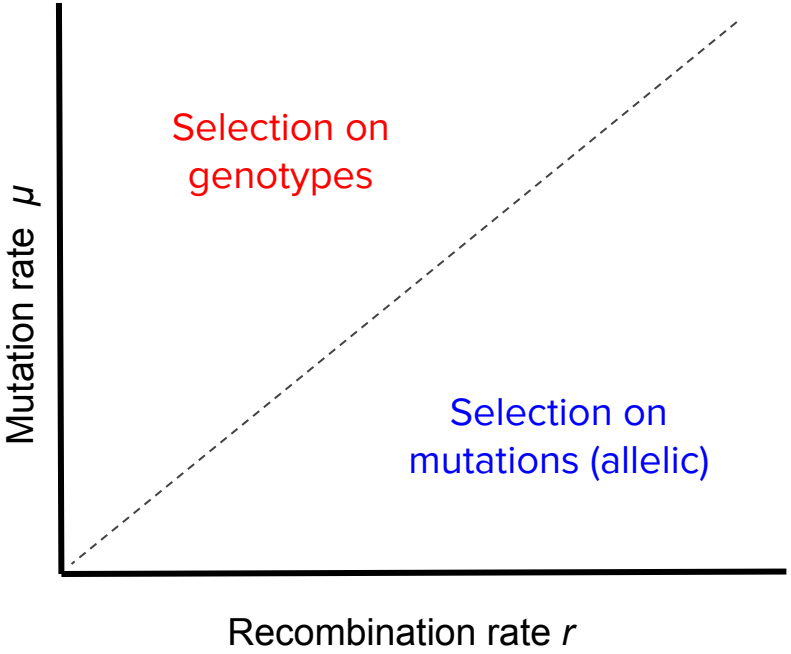
Ok, but how do pathogen genomes *actually* evolve?

Recombination vs. mutation



Recombination vs. mutation rates

The relative ratio of recombination versus mutation rates determines whether selection acts primarily on individual mutations or whole genotypes/haplotypes.



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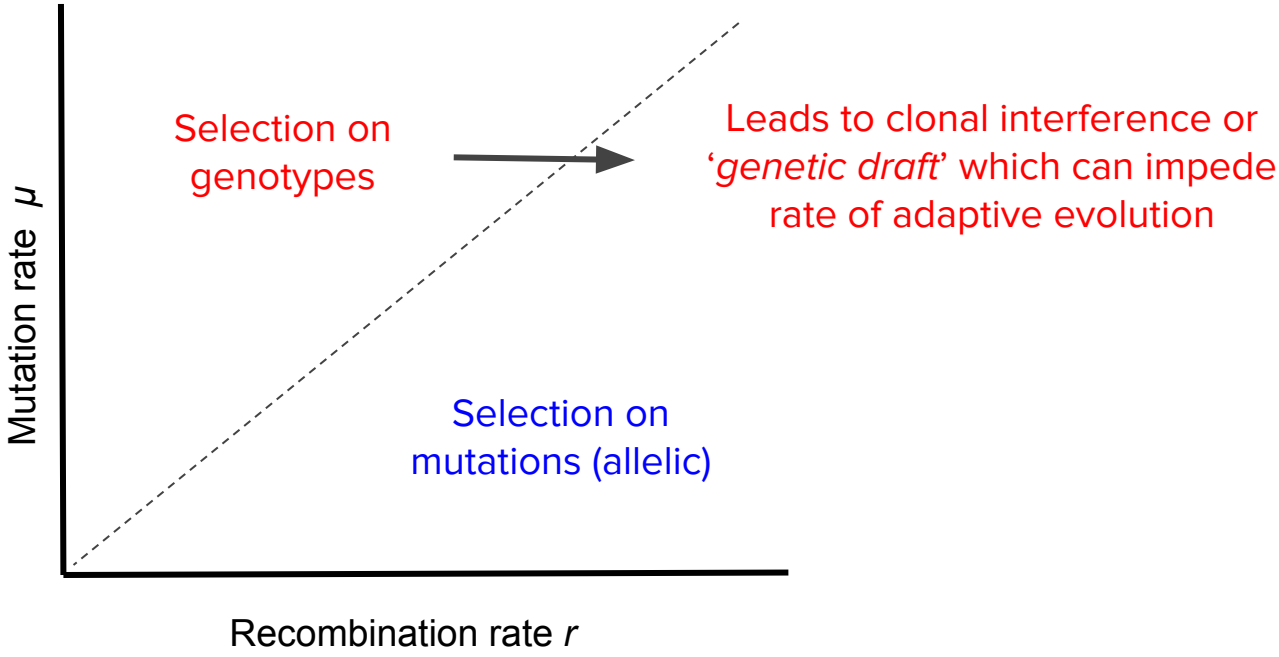


Clonal vs. horizontal evolution

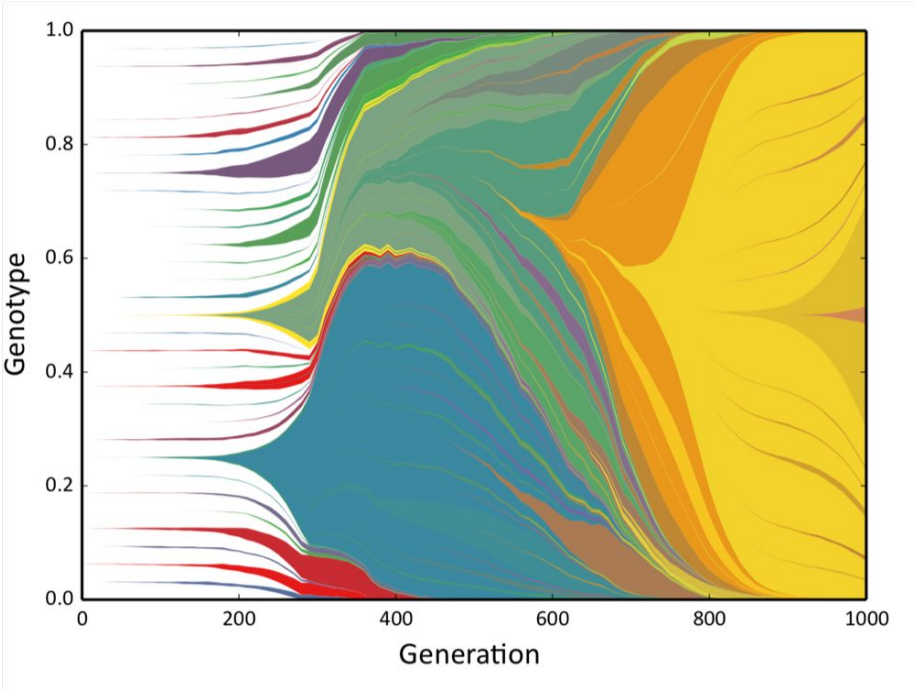
Clonal evolution occurs by vertical descent where genetic material is passed from parents to children.

In contrast, genetic material can be exchanged **horizontally** between lineages through recombination or horizontal gene transfers.

Clonal interference

Clonal interference arises in large asexual populations with high mutations rates and large population sizes.

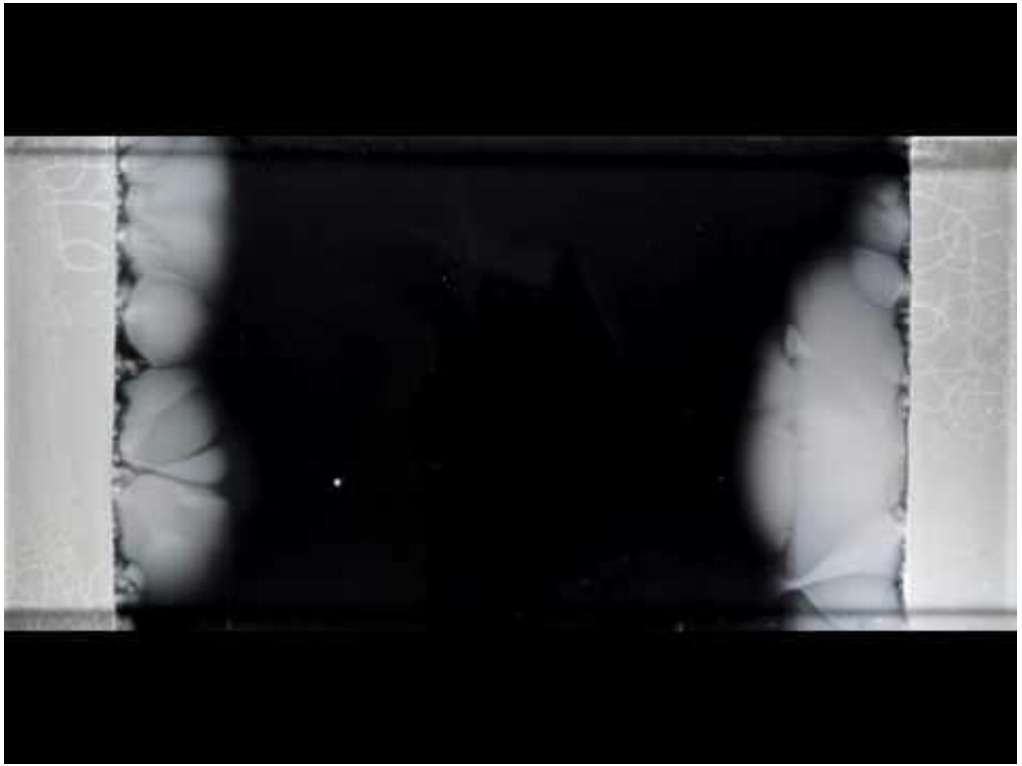
Multiple lineages with beneficial mutations compete with one another.



Cvijovic et al. (Trends in Genetics, 2018)

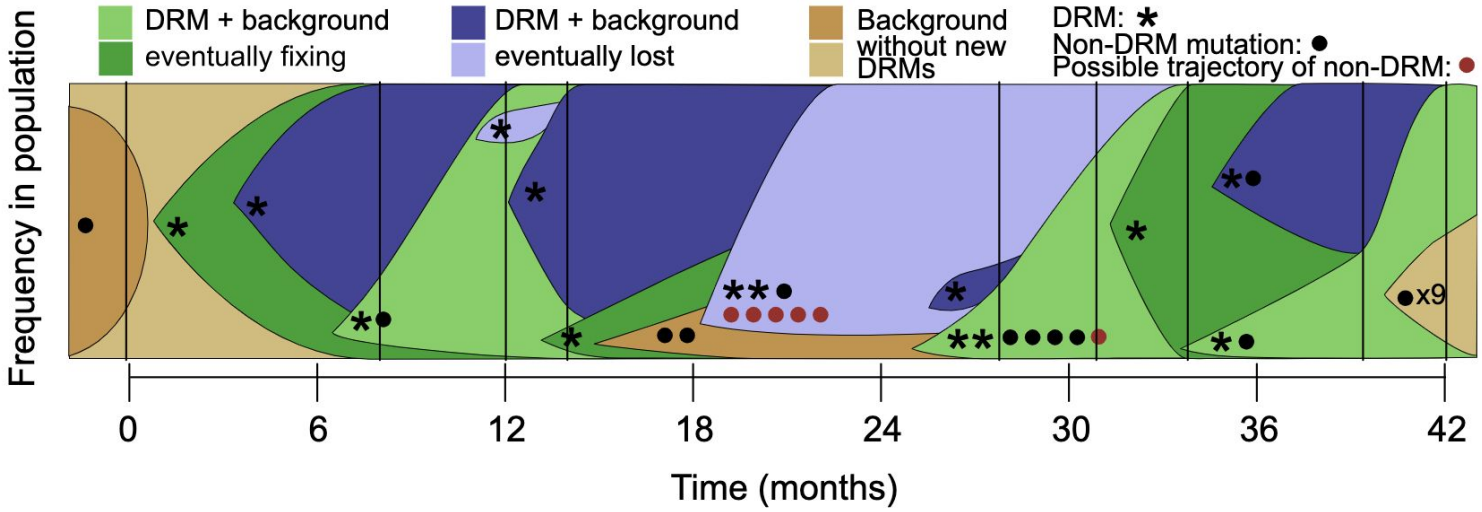
Clonal interference through competition

The Microbial Evolution and Growth Arena (MEGA) experiments show multiple strains of antibiotic resistant *E. coli* competing with one other for space.



Clonal interference in *M. tuberculosis*

Dynamics of TB clones within a host treated with a series of antibiotics.



Eldhom et al. (Genome Bio, 2014)

Clonal interference: summary

Role of genetic drift becomes negligible as competition creates strong selection for highly fit genotypes.

Increases chance that “best” genotype with the largest fitness advantage goes to fixation. This genotype may often carry multiple beneficial mutations.

However, interference can actually slow down the rate of adaptation as multiple beneficial genotypes will compete against one another.

How do multi-drug resistant bacteria evolve?

Resistance evolution in MRSA

Methicillin resistant *Staphylococcus aureus* first emerged in the 1960's and causes dangerous bloodstream infections with roughly 30% mortality.

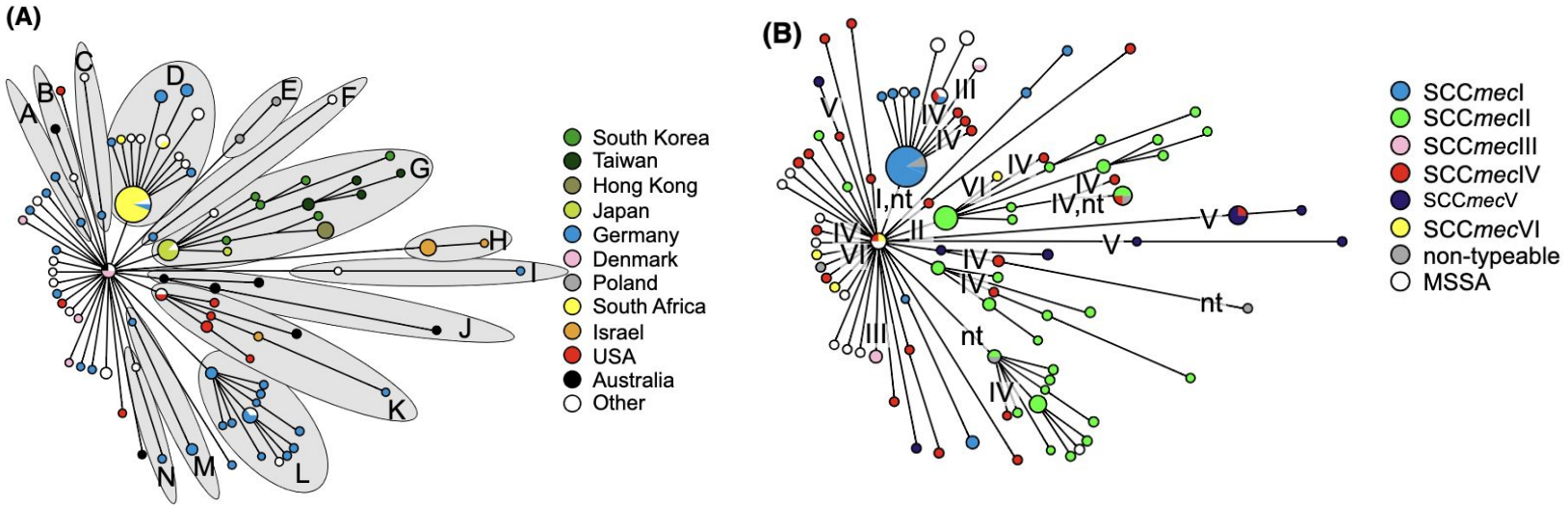
S. aureus is highly clonal with a low recombination rate and only a few lineages are responsible for most infections.

Methicillin resistance is acquired via the staphylococcal cassette chromosome *SCCmec,* a mobile genetic element that integrates a cassette of genes into the bacterial chromosome (most likely by transduction from bacteriophages).

SCCmec acquisition is a classic example of horizontal gene transfer (HGT).

Acquisition of methicillin resistance

S. aureus phylogenies show independent acquisitions of *SCCmec* cassettes in across different lineages suggesting frequent horizontal transfers.



Nübel *et al.* (PNAS, 2008)

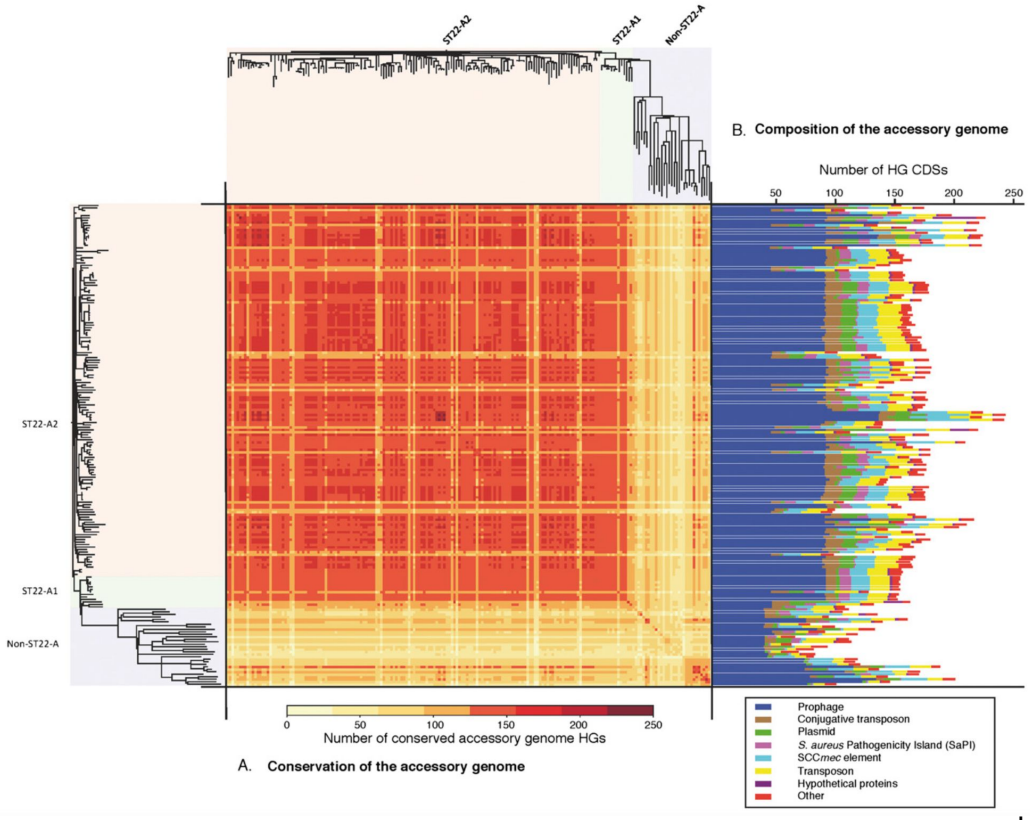
The pangenome concept

The **core genome** contains the highly conserved genes with often essential functions (i.e. DNA replication) that are present within all members of a species.

The **accessory genome** includes gene content that varies between strains including chromosomal cassettes, prophages, transposons and pathogenicity islands. These genes can be chromosomal or extrachromosomal (e.g. on plasmids).

Prokaryote populations are often characterized by extensive sharing of accessory genes due to horizontal gene transfers and subsequent gene losses.

The MRSA accessory genome



Holden *et al.* (Genome Research, 2013)

Evolution of multidrug resistant MRSA

Increased fitness of initially resistant strains leads to large clonal expansions.

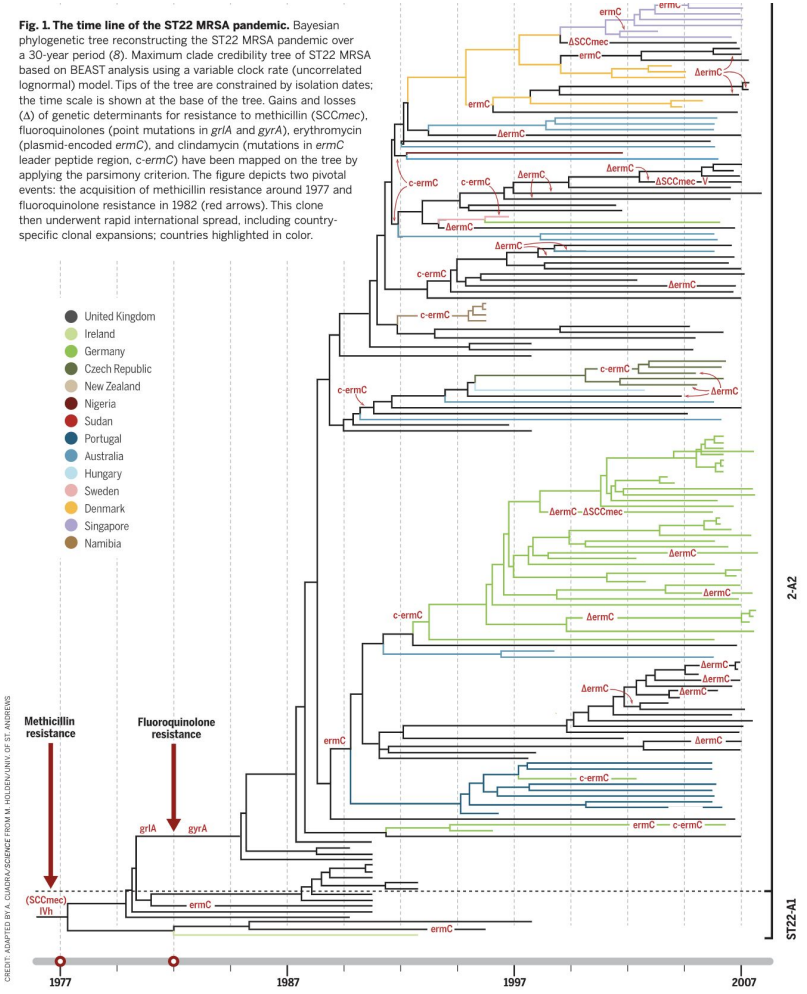
Accumulation of additional genes conferring resistance to other antibiotics occurred through further HGTs, leading to superfit multidrug resistance clones.

These multi-drug resistant (MDR) strains have acquired resistance to several major classes of antibiotics including fluoroquinolones and erythromycin.

MDR MRSA

“MRSA epitomizes a now all-too-familiar evolutionary route by which successful AMR clones emerge in response to local antimicrobial usage, undergo population expansion under selection from sustained antimicrobial exposure and then explode into pandemic spread”

Baker *et al.* (Science, 2017)



Recombine often or perish

Moderately high mutation rates but low recombination rates cause competition and clonal interference between high-fitness lineages.

Rapid adaptation to selective pressures like antimicrobials occurs by frequent horizontal transfers of beneficial genetic elements in the accessory genome.

Successful lineages therefore tend to be clones that have acquired multiple beneficial genes or other genetic elements through HGT.

“Two-speed” genomes in eukaryotes

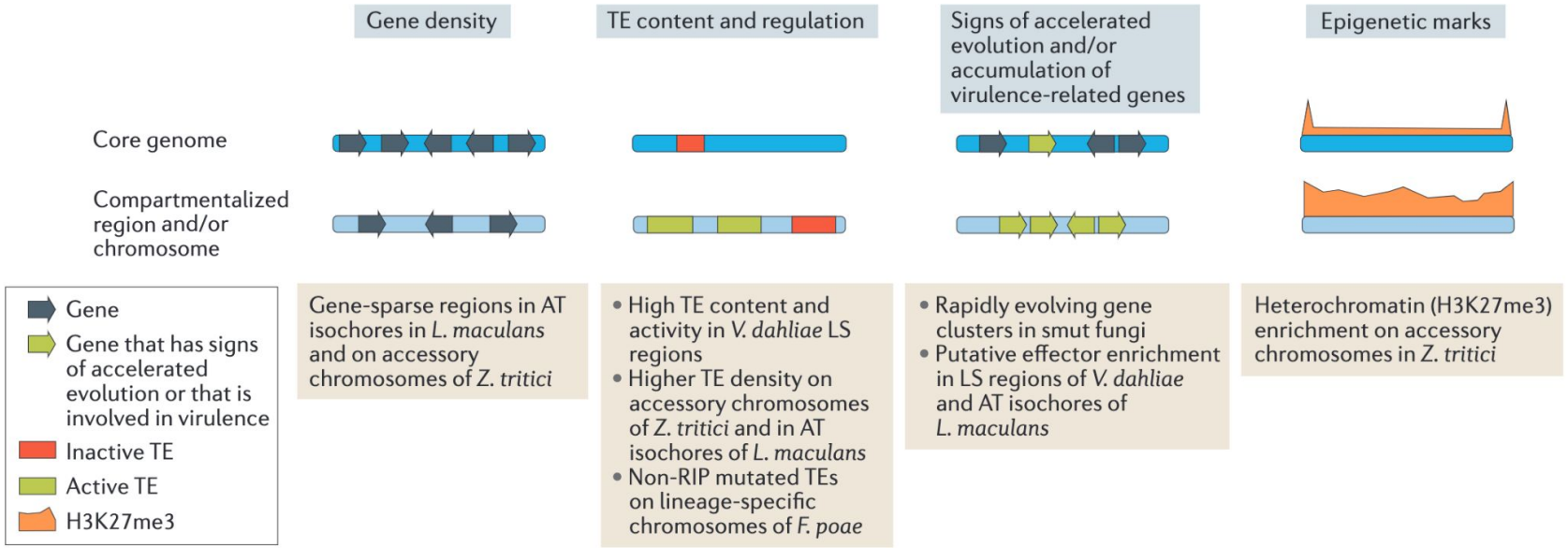
Pathogenic fungi often have virulence-related and effector genes involved in host-adaptation compartmentalized to genomic regions with elevated mutations rates and high densities of mobile genetic elements, including:

Accessory chromosomes: lineage-specific chromosomes with low gene density but high mutation rates that can move horizontally between lineages.

TE-rich compartments: regions of the core genome that are gene-sparse but highly variable due to transposable elements or other mobile genetic elements.

Dong *et al.* (2015)

Fast evolving genome compartments



Möller and Stukenbrock (Nature Rev. Micro., 2017)

How clonal are bacteria and other microbial pathogens?

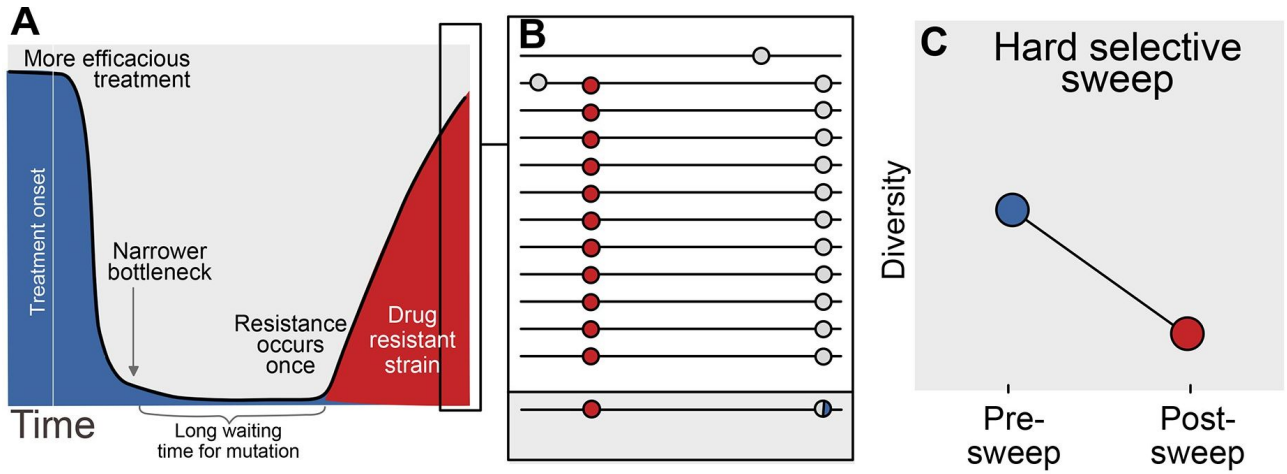
What determines clonality?

Rates of recombination and horizontal exchange have traditionally been thought of as the key determinants of clonality.

However, recombination also interacts with selection to determine how clonal a population is at any particular point in time.

Selective sweeps eliminate diversity

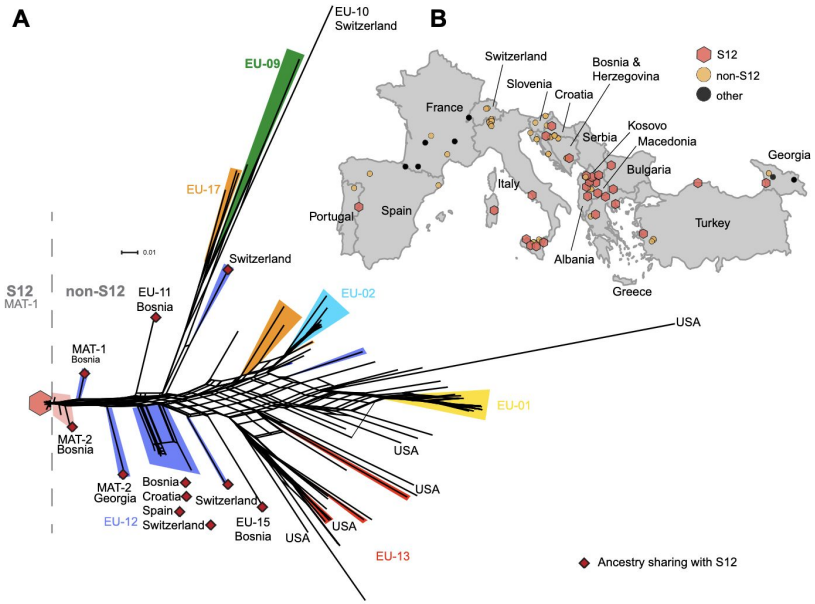
Strong selection can lead to rapid clonal expansions and genome-wide selective sweeps of linked variants.

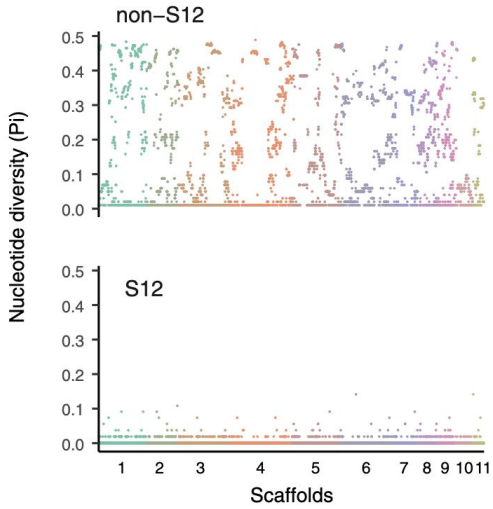


Feder *et al.* (eLife, 2016)

Clonal expansions of chestnut blight

The invasive S12 genotype is an asexual and more virulent lineage of *Cryphonectria parasitica* undergoing a clonal expansion in European chestnut trees.





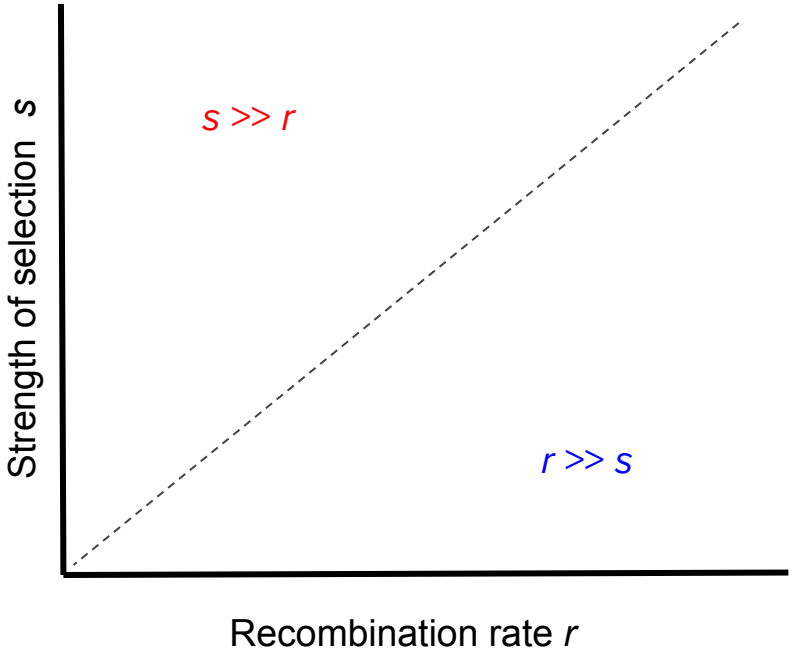
Stauber *et al.* (eLife, 2021)

Recombination vs. selection

The strength of selection relative to the recombination rate determines how selective sweeps impact diversity elsewhere in the genome.

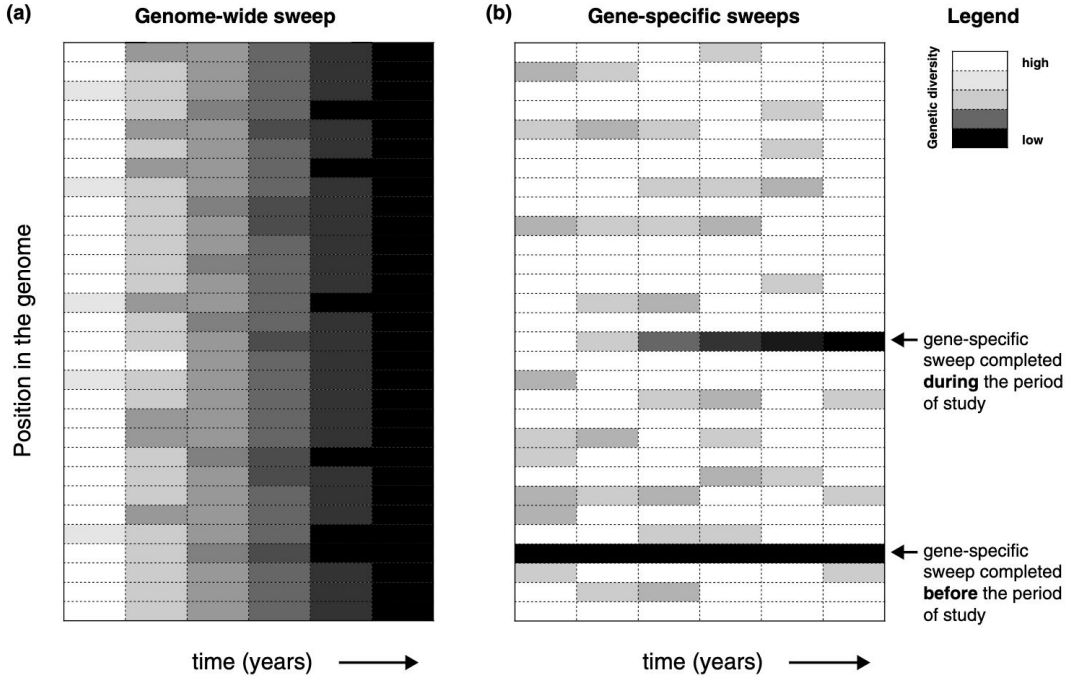
Genome-wide selective sweeps

$s = w_{mut} - w_{wt}$



Gene-specific selective sweeps

Gene-specific vs. genome-wide sweeps



Shapiro (Curr. Op. Micro., 2016)

Clonality can dynamically vary over time

Genome-wide selective sweeps increase clonality even if recombination rates were historically high.

Genomic islands, pieces of DNA that were transferred horizontally, can therefore become peninsulas linked by the conserved regions of the genome (i.e. the continents).

Continents can be broken up over time into archipelagos by recombination.

The extended island metaphor

Clonality varies considerably between different species of bacteria and may reflect their recent demographic history.

Extended island metaphors of microbial genome evolution

Geographic metaphor	Genetic unit to which the metaphor applies	Type of selective sweep experience by the unit	Dominant mode of genetic transmission	Example
Island	Gene	Gene-specific	Horizontal	Genes in the *V. cholerae* integron [22•,23]
Peninsula	Gene	Genome-wide	Vertical (clonal)	The cholera toxin gene, acquired horizontally, then linked to a clonal *V. cholerae* genome [9,21]
Continent	Genome	Genome-wide	Vertical (clonal)	Clonal expansions of *S. aureus* [28], *M. tuberculosis* [31,43]
Archipelago	Genome	Gene-specific	Horizontal	Hotspring cyanobacteria [11•], ocean vibrios [13•,14], pneumococcus [44,46•]

Shapiro (Curr. Op. Micro., 2016)

For Wednesday's discussion

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Current Opinion in Microbiology

How clonal are bacteria over time?

B Jesse Shapiro

Bacteria and archaea reproduce clonally (vertical descent), but exchange genes by recombination (horizontal transfer). Recombination allows adaptive mutations or genes to spread rapidly within (or even between) species, and reduces the burden of deleterious mutations. Clonality — defined here as the balance between vertical and horizontal inheritance — is therefore a key microbial trait, determining how quickly a population can adapt and the size of its gene pool. Here, I discuss whether clonality varies over time and if it can be considered a stable trait of a given population. I show that, in some cases, clonality is clearly not static. For example, non-clonal (highly recombining) populations can give rise to clonal expansions, often of pathogens. However, an analysis of time-course metagenomic data from a lake suggests that a bacterial population's past clonality (as measured by its genetic diversity) is a good predictor of its future clonality. Clonality therefore appears to be relatively — but not completely — stable over evolutionary time.

where a bacterial population of interest happens to fall along a spectrum of clonality can help us understand its biology, and even make predictions about its evolution.

The opposite of clonality is panmixis — a situation in which the rate of horizontal transfer is higher than the rate of vertical cell division, resulting in random association (linkage equilibrium) among loci in the genome [1,2]. However, rates of horizontal transfer (recombination) vary widely across the genome, such that a population can be mostly clonal, except for a few loci in the genome [3]. These loci came to be termed genomic islands — a metaphor I will build upon below. Some of the first islands identified were called pathogenicity islands because they contained virulence factors [4]. However, non-pathogenic environmental bacteria also contain islands, conferring adaptation to different ecological niches. For example, genes in *Prochlorococcus* genomic islands confer

Shapiro (Curr. Op. Micro., 2016)