Predicting the (very near) future: forecasting pathogen evolution

Molecular Epidemiology of Infectious Diseases

Lecture 13

April 18th, 2022

“No scientific theory is worth anything unless it enables us to predict something which is actually going on. Until that is done, theories are a mere game of words, and not such a good game as poetry”

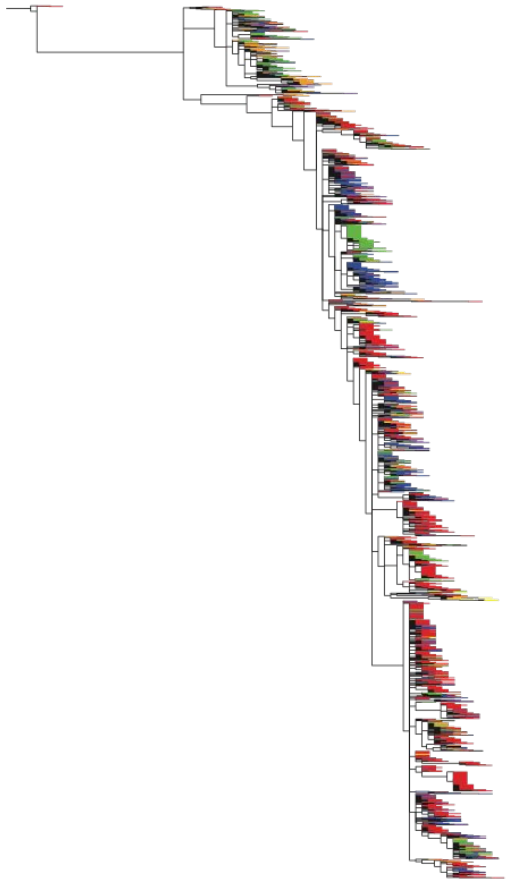
J.B.S Haldane (Adventures of a Biologist, 1937)

Most of the approaches we've considered are retrospective... can we say anything about the future?

Influenza A (H3N2)

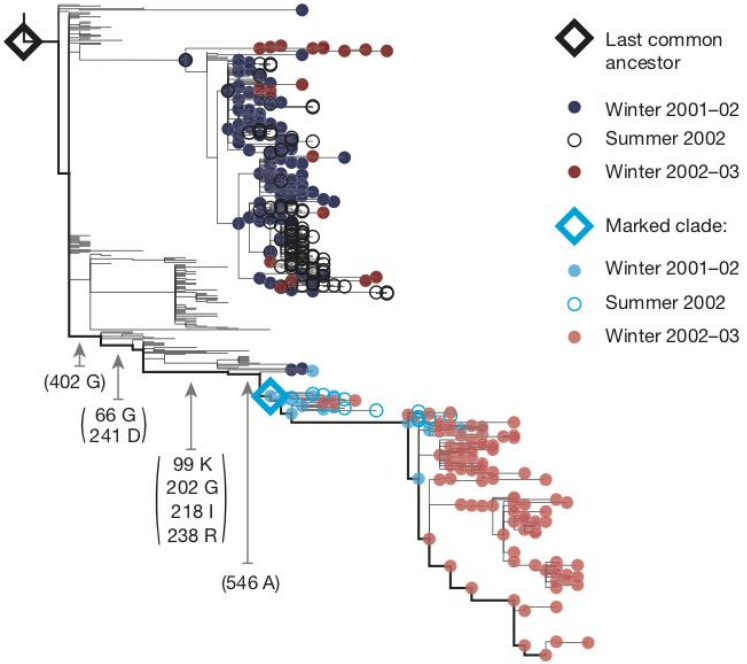
New antigenic variants periodically replace older strains:

- New antigenic variants emerge and escape antibody-based immunity against earlier strains.
- **Antigenic drift** leads to a ladder-like structure with a trunk lineage
- Flu vaccines need to be updated yearly to avoid antigenic mismatch.



Russell *et al.* (Science, 2008)

Forecasting short-term flu evolution



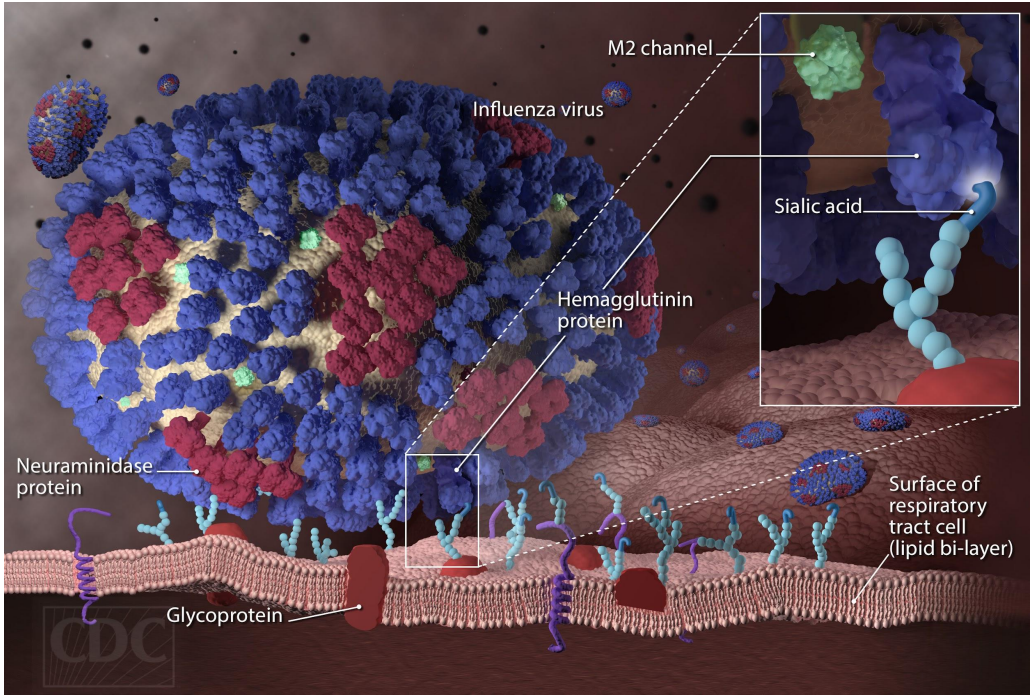
Consider the evolution dynamics of different influenza *clades*

The frequency X_v of a particular clade can be predicted based on the fitness f_i of individual strains i in a clade:

$$\hat{X}_v(t+1) = \sum_{i:v,t} x_i \exp(f_i)$$

Luskza & Lassig (Nature, 2014)

Influenza hemagglutinin and cell entry



Forecasting short-term flu evolution

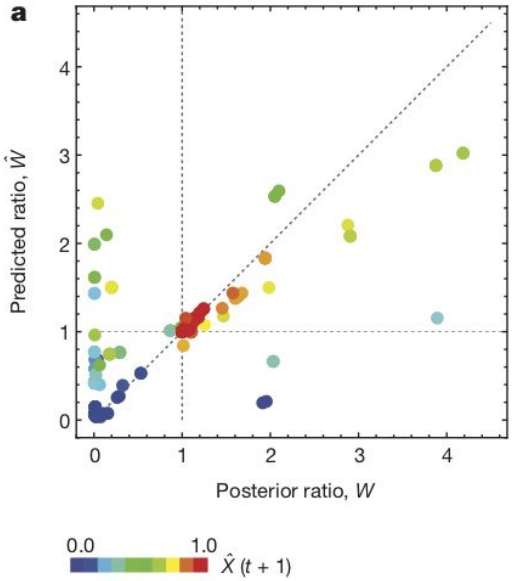
Luskza & Lassig (2014) consider two main factors that influence the fitness $\boldsymbol{f_i}$ of a strain:

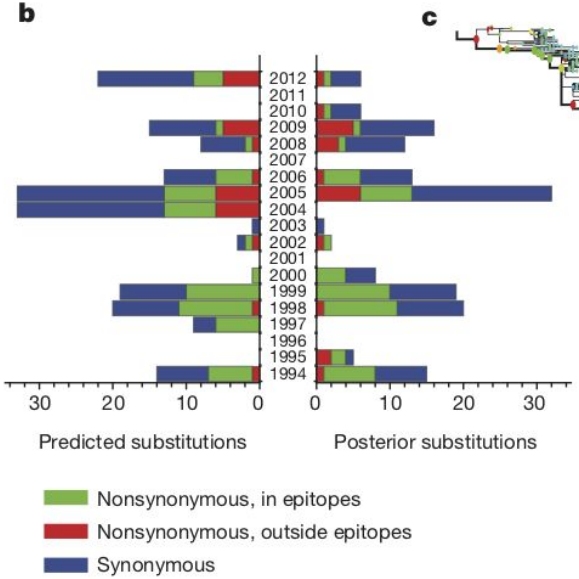
1) The amplitude of cross-immunity $\mathbf{C(a_i,a_j)}$ between strain *i* and all other strains *j* that have previously circulated in the host population
2) The fitness cost $\mathbf{L(a_i)}$ of deleterious mutations at non-antigenic sites

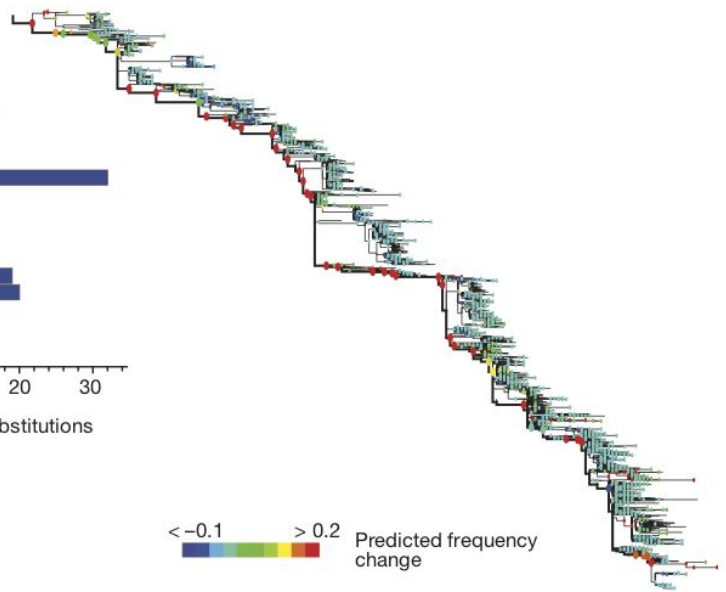
Their overall fitness mapping function is:

$$f_i = f_0 - \mathcal{L}(\mathbf{a}_i) - \sum_{j:\, t_j < t_i} x_j \, \mathcal{C}(\mathbf{a}_i, \mathbf{a}_j)$$

Forecasting short-term flu evolution





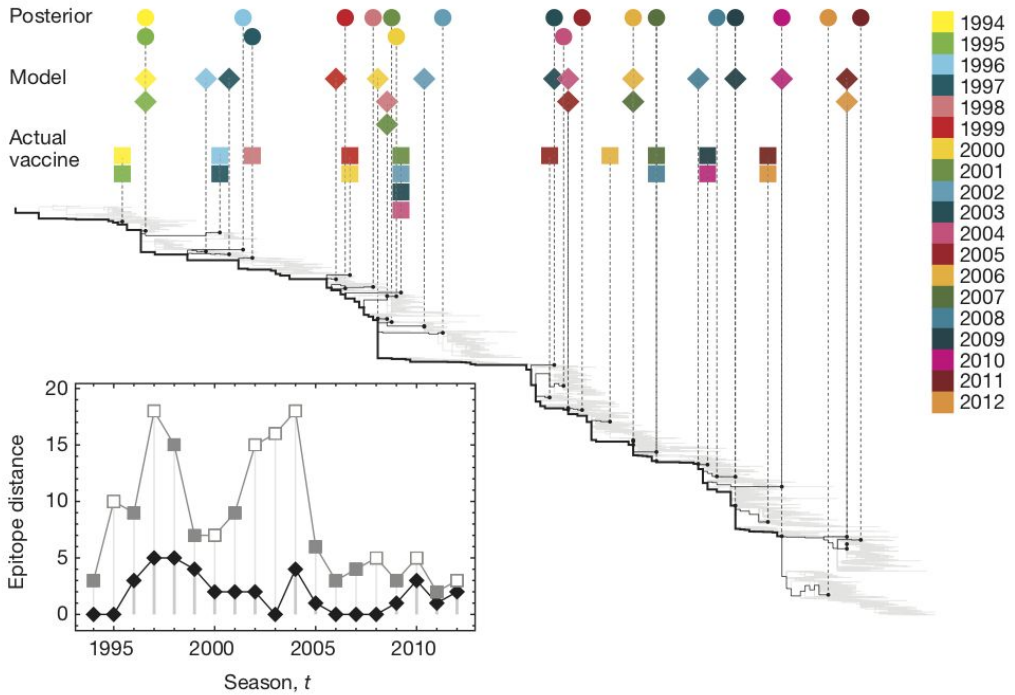


$$W_v = \frac{X_v(t+1)}{X_v(t)}$$

Luskza & Lassig (Nature, 2014)

Forecasting short-term flu evolution

Evolutionary predictions can aid design of vaccines with optimal immunity to dominant strains in the next flu season.



Luskza & Lassig (Nature, 2014)

Can we predict pathogen evolution more generally?

What do we need to know?

What mutations/genotypes are available?

Will the fate of new variants be determined by selection or drift?

How do genotypes map to fitness-related phenotypes?

How does fitness translate to epidemic potential at the population level?

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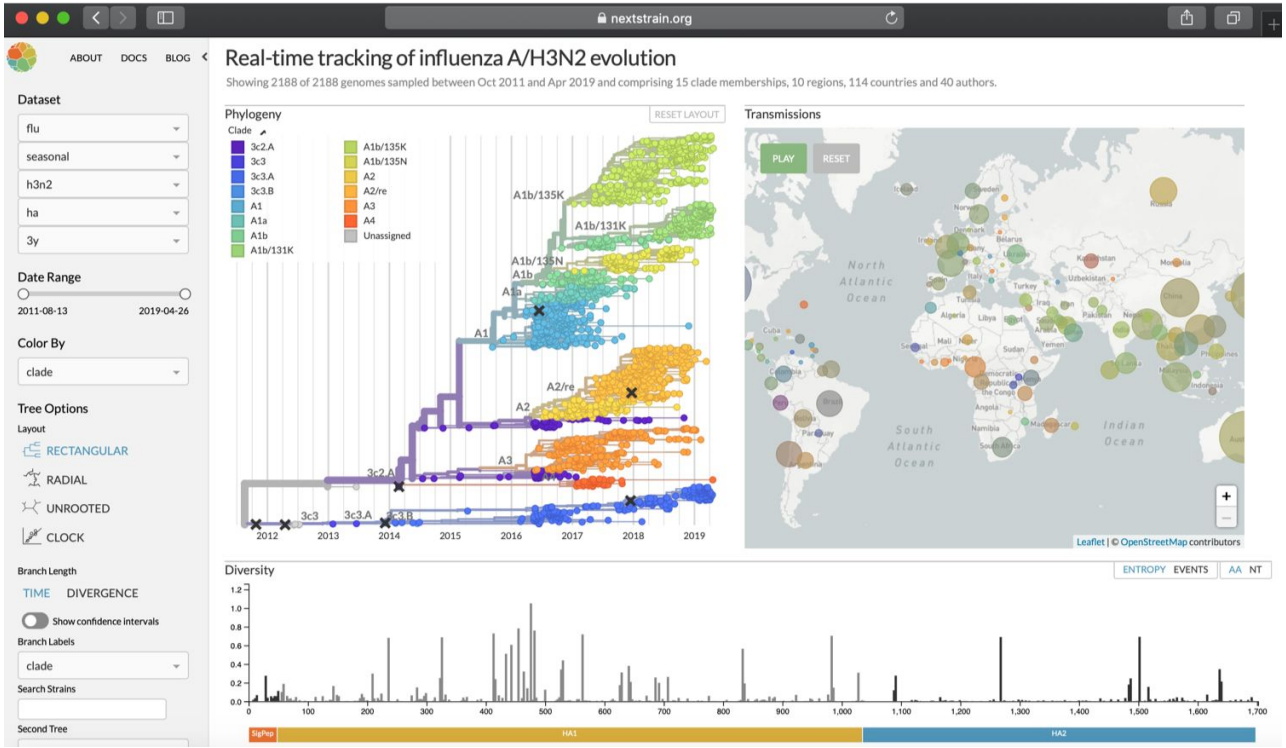
Mutational limits on prediction

At the very least, we need to know what mutations/genotypes are in a population to be able to predict anything about evolution

Genomic surveillance



Mutational limits on prediction

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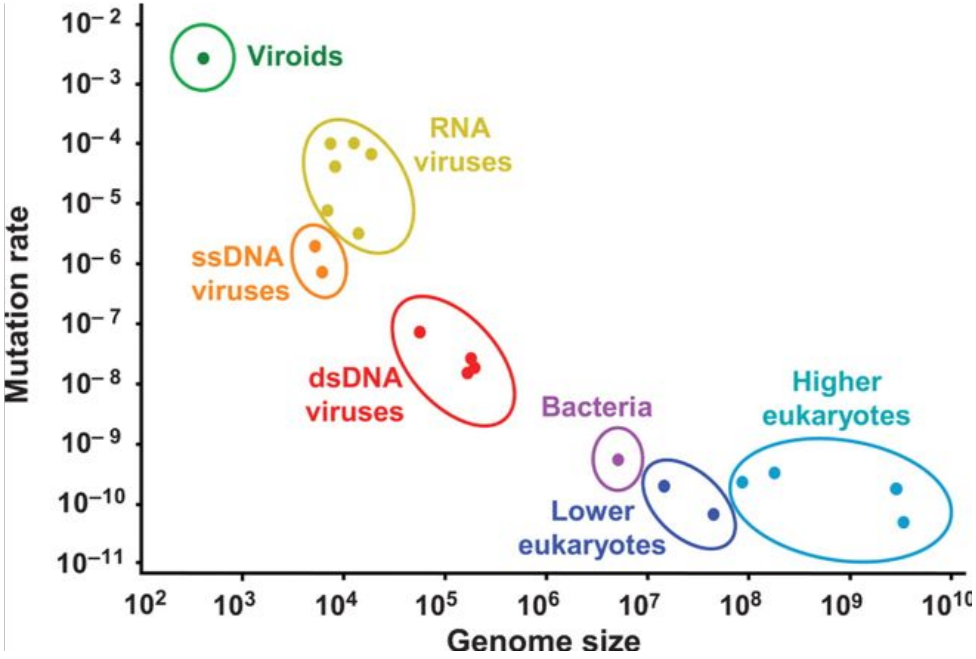
Meaningful predictions are probably limited to short-term predictions about standing genetic variation (or immediately accessible mutations).

Rapidly mutating microbes

Microbial evolution is often not mutation limited - high mutation rates and large population sizes often ensure that all possible mutations occur on relatively short timescales.

Evolutionary predictions may then be extended to all locally accessible genotypes (e.g. genotypes one mutation away from existing strains).



Gago et al. (Science, 2009)

Mutational limits on prediction

At the very least, we need to know what mutations/genotypes are in a population to be able to predict anything about evolution

Meaningful predictions are probably limited to short-term predictions about standing genetic variation (or immediately accessible mutations).

Long-term predictions are limited by the stochastic nature of the mutation process and what mutations will enter a population

What do we need to know?

What mutations/genotypes are available?

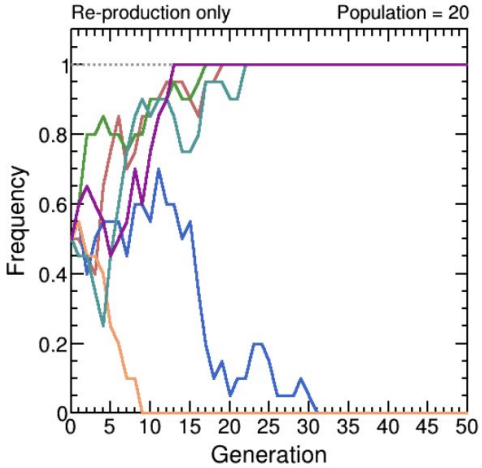
Will the fate of new variants be determined by selection or drift?

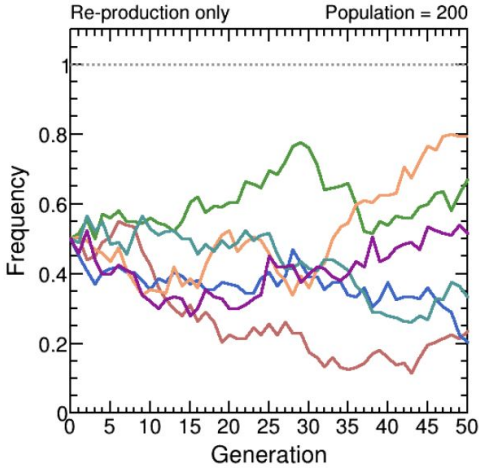
How do genotypes map to fitness-related phenotypes?

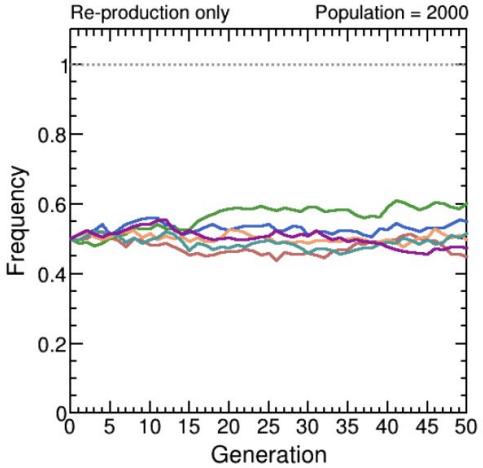
How does fitness translate to epidemic potential at the population level?

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.





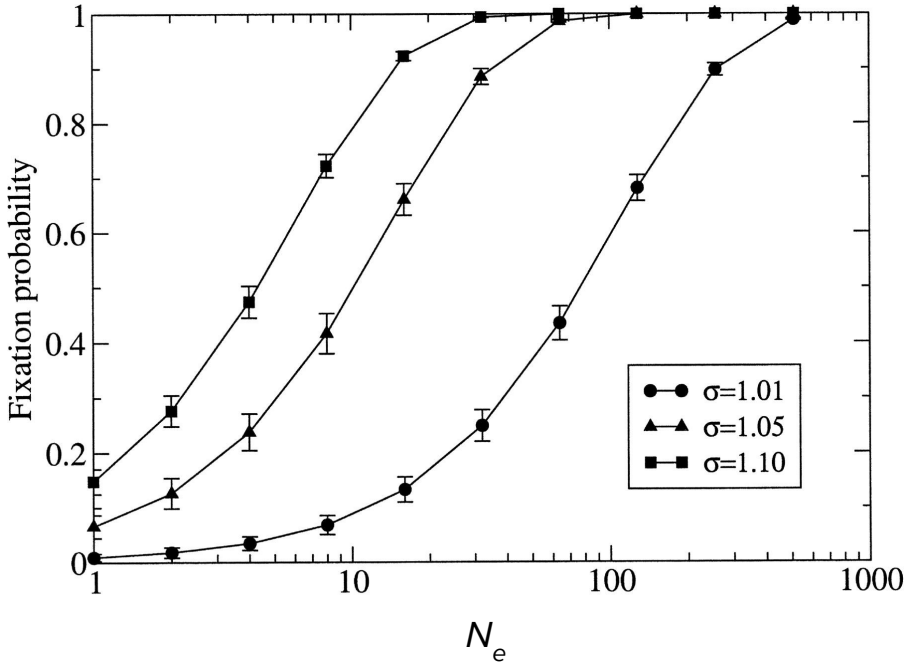


https://boundino.github.io/S188592web/drift.html

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.

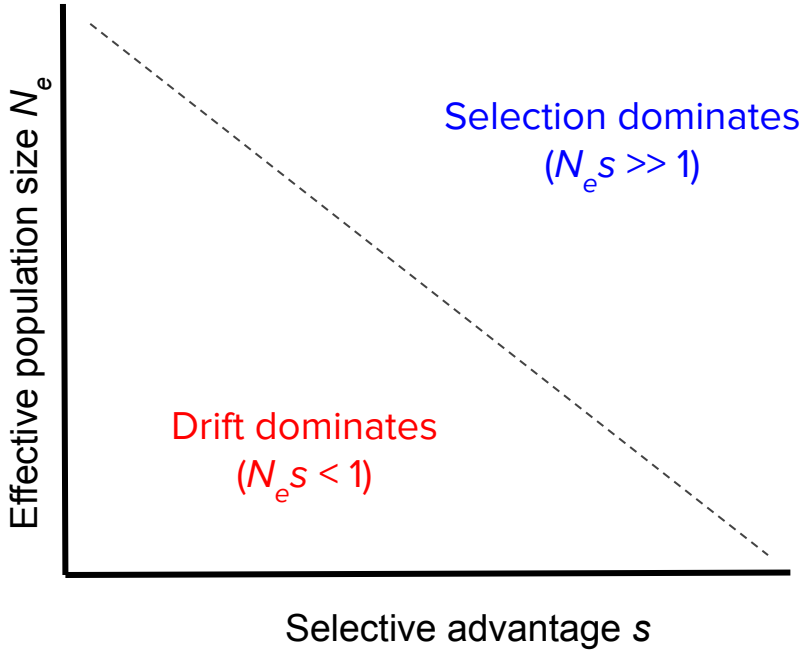
$$s = w_{mut} - w_{wt}$$



Wilke (Genetics, 2003)

Selection vs. drift

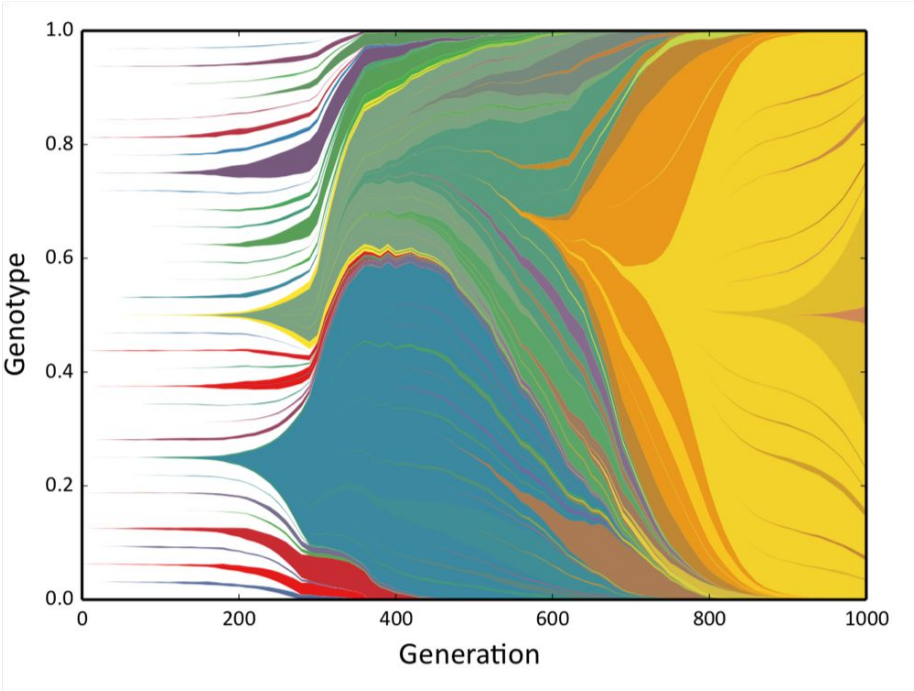
The relative importance of selection versus drift is determined by $N_e s$



Clonal interference

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

Multiple lineages with beneficial mutations compete with one another.



Cvijovic et al. (Trends in Genetics, 2018)

Clonal interference

Clonal interference enhances overall predictability:

Increases odds of evolution finding most fit genotype even if this requires multiple mutations.

Role of genetic drift becomes negligible.

Increases chances that “best” genotype with the largest fitness advantages goes to fixation.

What do we need to know?

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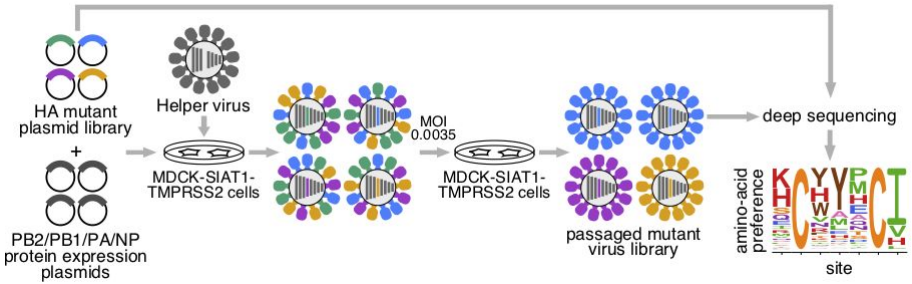
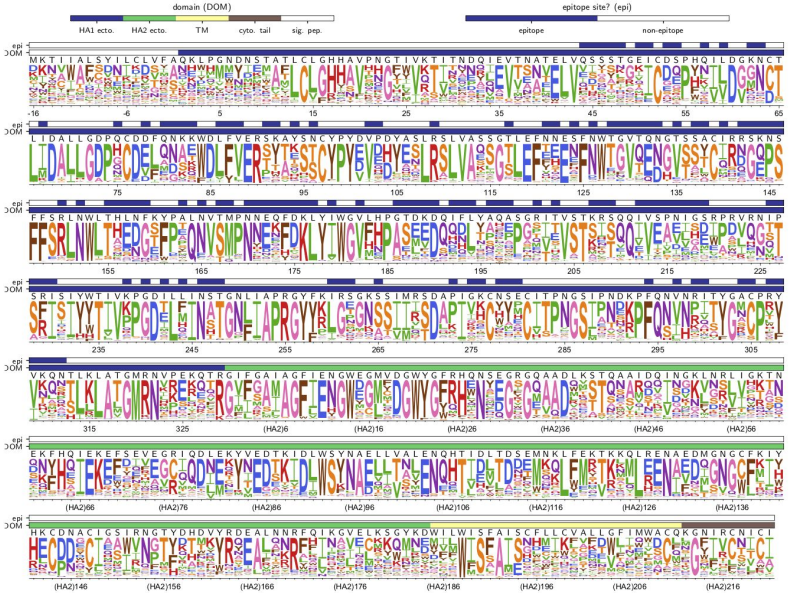
Deep mutational scanning

Reverse genetics approaches can be used to systematically explore the genotype to phenotype map using large libraries of mutants.



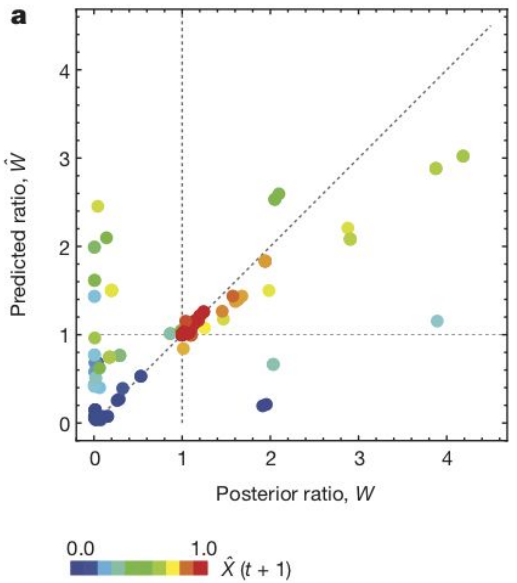


Lee et al. (PNAS, 2018)

But genetic context matters too

Luskza and Lassig found the models that only consider “adaptive” changes in epitope regions are 40% less accurate than models that all consider changes in background fitness due to deleterious mutations in other parts of the genome.

$$f_i = f_0 - \mathcal{L}(\mathbf{a}_i) - \sum_{j:\, t_j < t_i} x_j \mathcal{C}(\mathbf{a}_i, \mathbf{a}_j)$$



Luskza & Lassig (Nature, 2014)

Context dependence

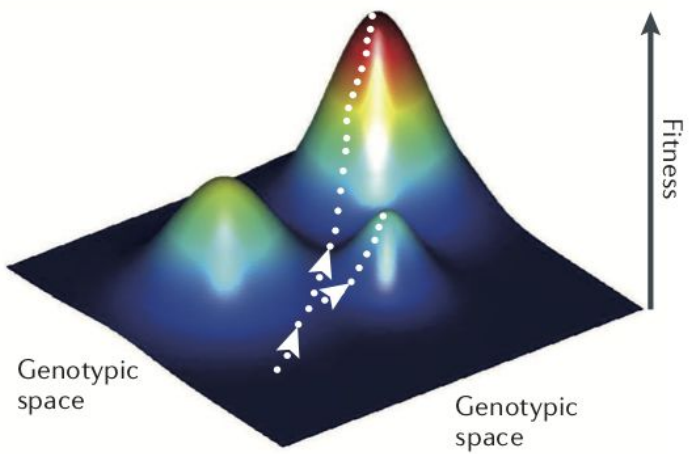
How predictable phenotypes are based on genotypes largely depends on whether phenotypes are context dependent:

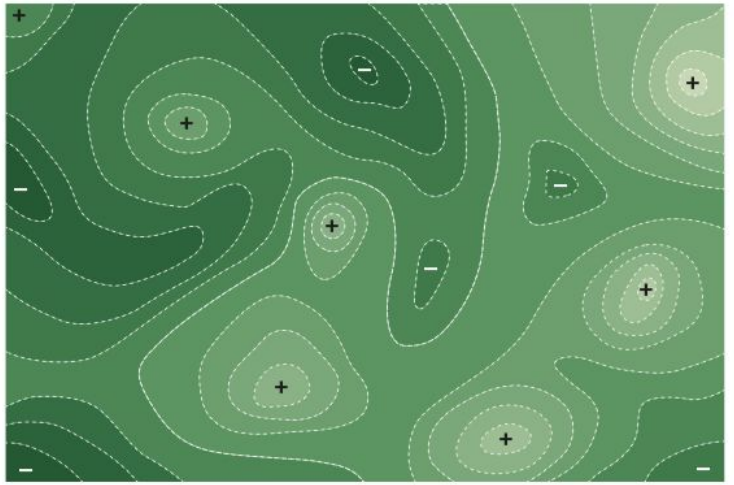
Epistasis: dependence on genetic background including interactions among mutations

Pleiotropy: the effects of mutations on multiple traits or the same trait across different environments.

Epistasis in fitness landscapes

Epistasis largely controls the smoothness/ruggedness of the fitness landscape.



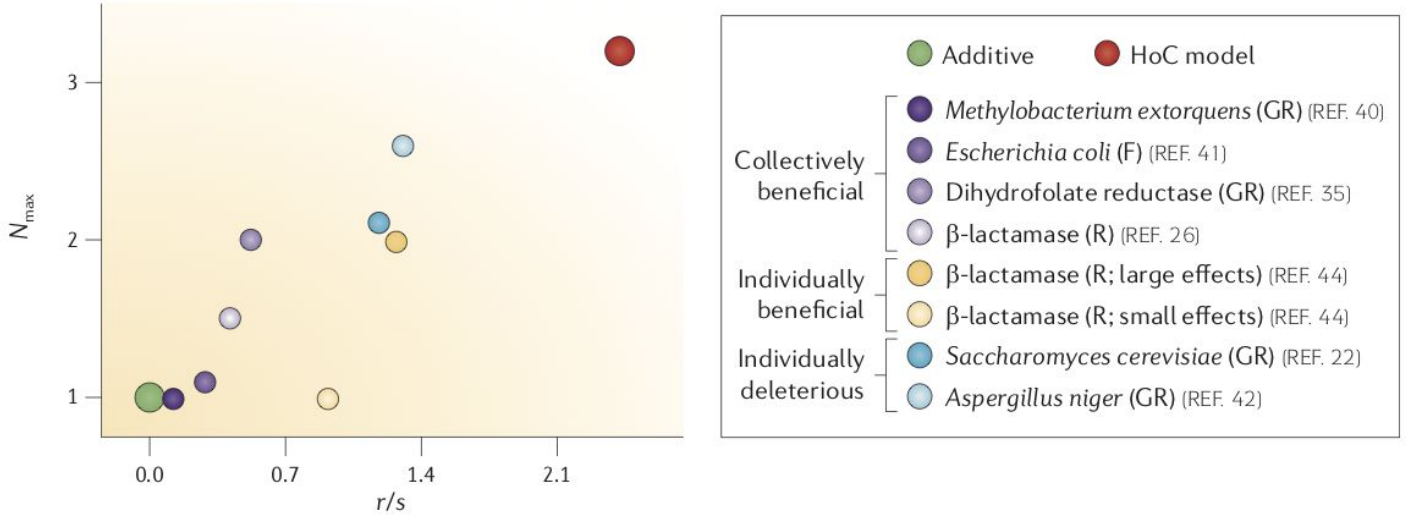


de Visser *et al*. (Nature Rev. Genetics, 2014)

Epistasis in fitness landscapes

How rugged are empirical fitness landscapes?

Number of peaks

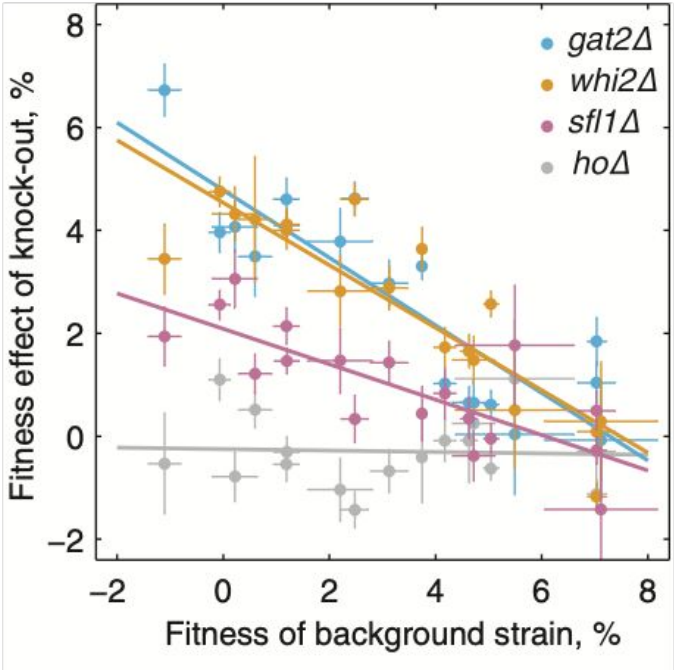


Ruggedness (local / global slope)

de Visser *et al*. (Nature Rev. Genetics, 2014)

Global epistasis

Mutations often exhibit ***global epistasis*** where their fitness effects depend on starting fitness but are “independent of the specific identify of mutations present in the background”.

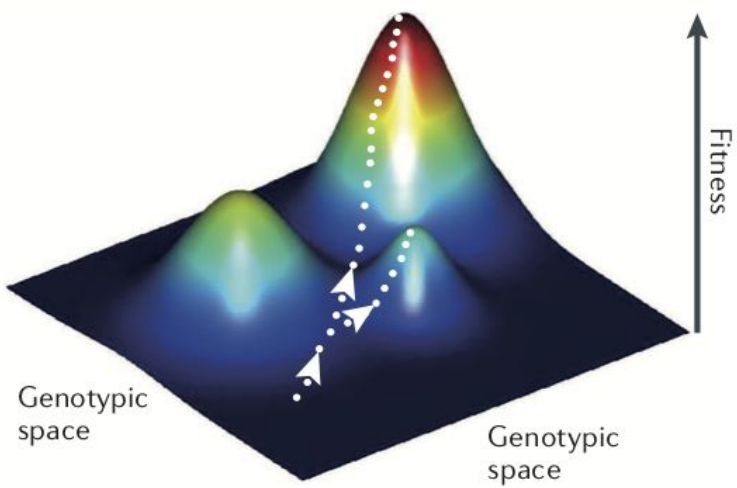


Kryazhimskiy *et al*. (Science, 2014)

Global epistasis

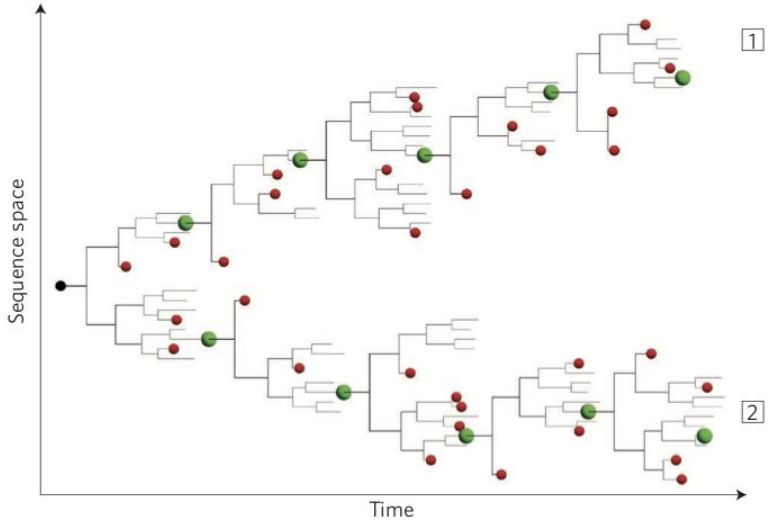
Mutations often exhibit ***global epistasis*** where their fitness effects depend on starting fitness but are “independent of the specific identify of mutations present in the background”.

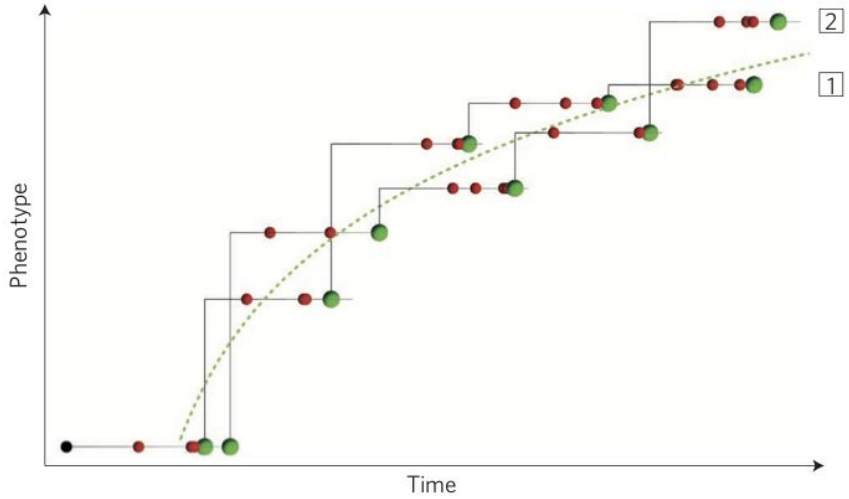
This is often seen as “diminishing returns” on the effects of beneficial mutations in already fit genotypes.



Can we predict phenotypic evolution?

Phenotypic evolution may be predictable even if genotypic evolution has a low degree of repeatability or predictability.





Lässig et al. (Nat. Ecol Evol, 2017)

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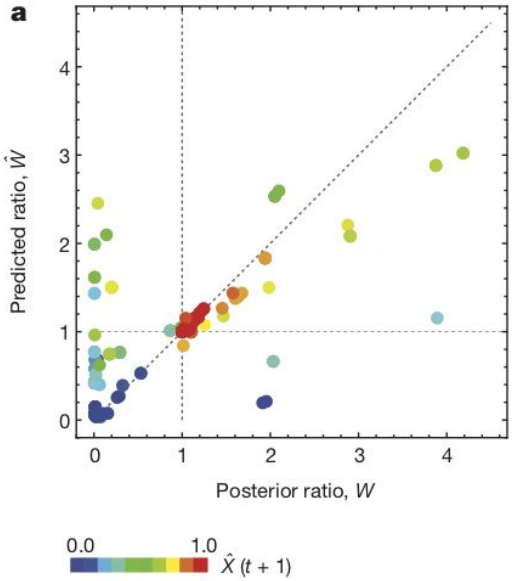
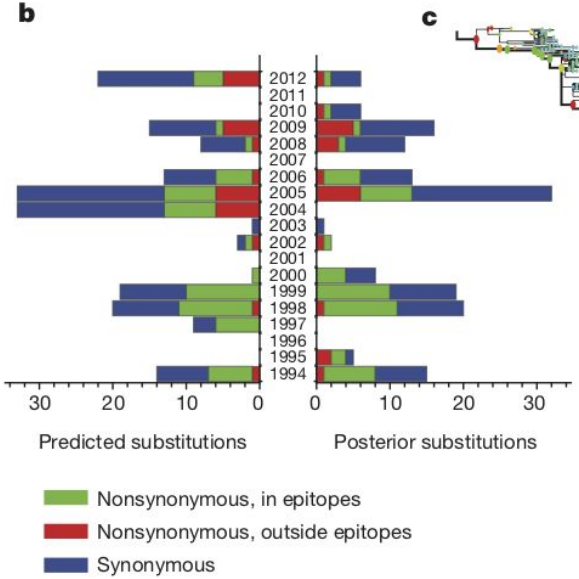
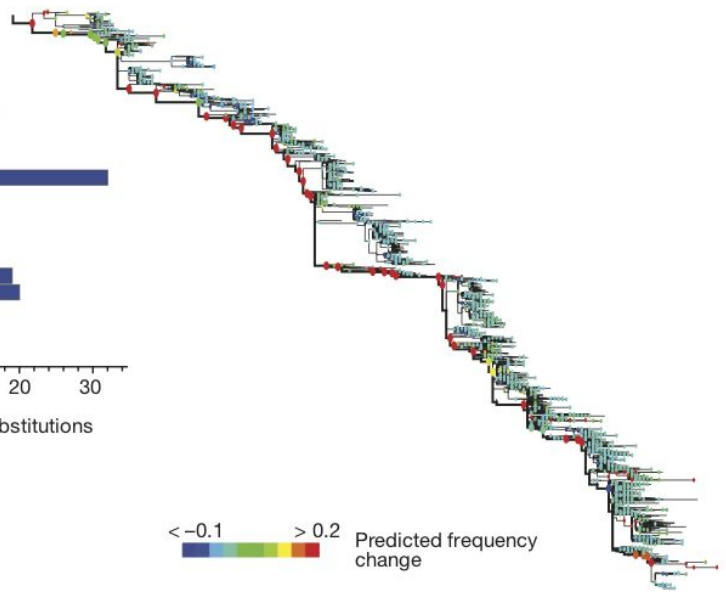
Forecasting short-term flu evolution







$$W_v = \frac{X_v(t+1)}{X_v(t)}$$

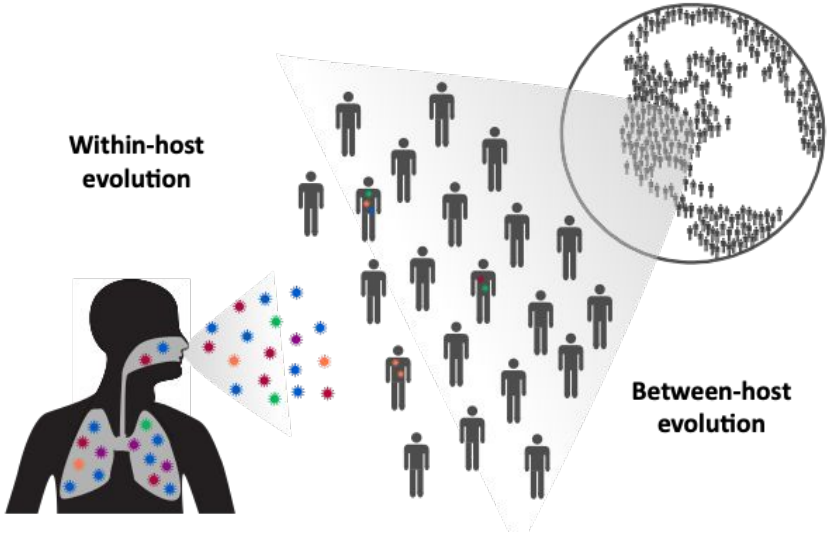
Luskza & Lassig (Nature, 2014)

“Any prediction of evolution is essentially an estimate of fitness differences between strains”

Luksza & Lassig (2014)

Translating between scales

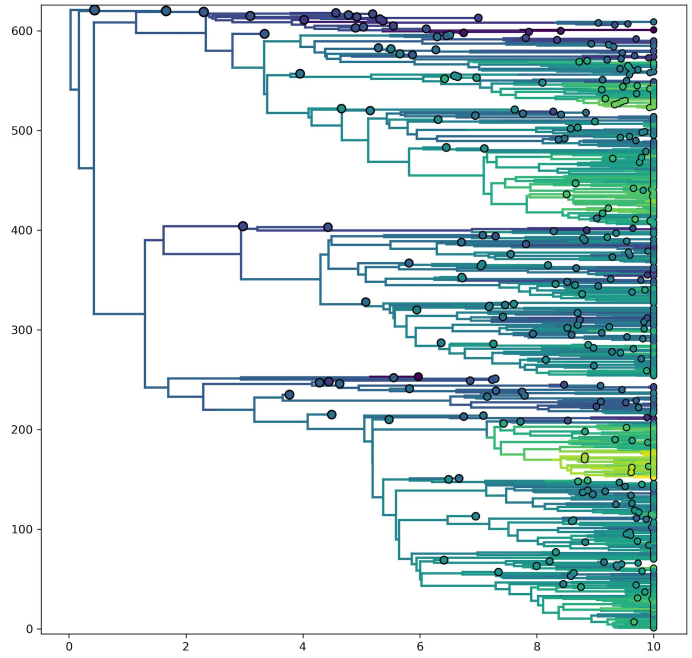
To make accurate predictions we need to know how pathogen phenotypes related to within-host fitness translate to population-level fitness between hosts.



Fitness shapes pathogen phylogenies

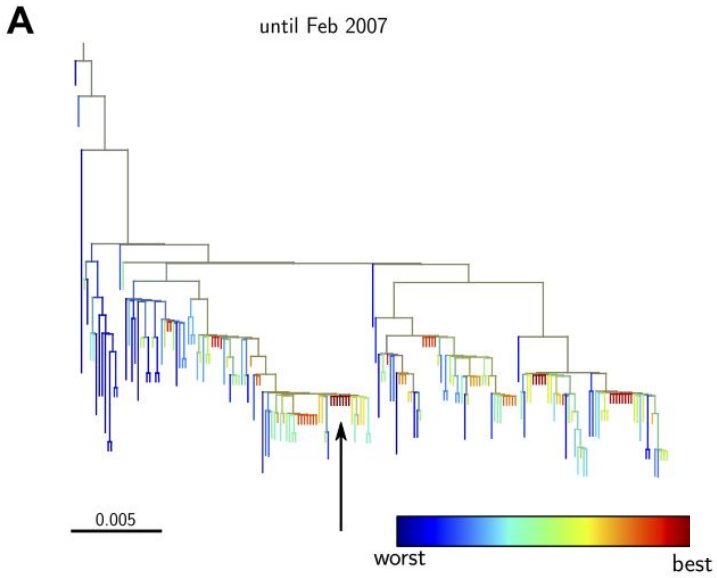
More fit lineages will have higher growth rates and therefore branch more often... leaving behind more sampled descendents in a phylogeny.

branching = birth/transmission events



Predicting evolution from tree shape

Branching rates in pathogen phylogenies correlate strongly with fitness



Neher et al. (*eLife*, 2014)

Predicting evolution from tree shape

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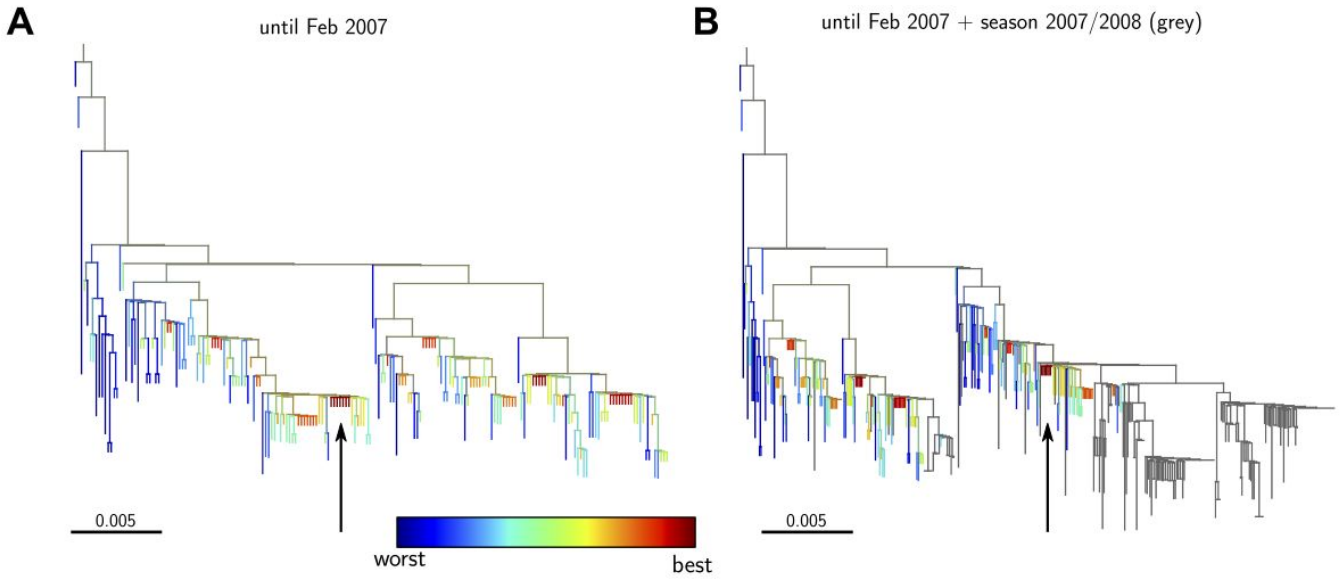
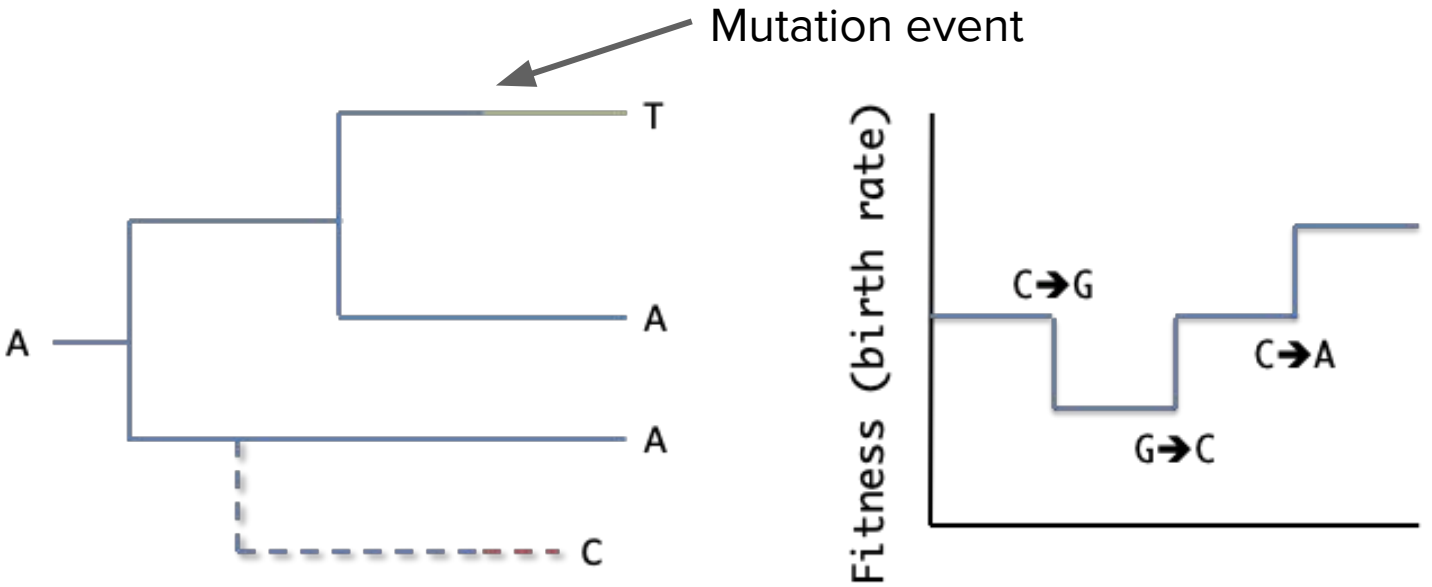


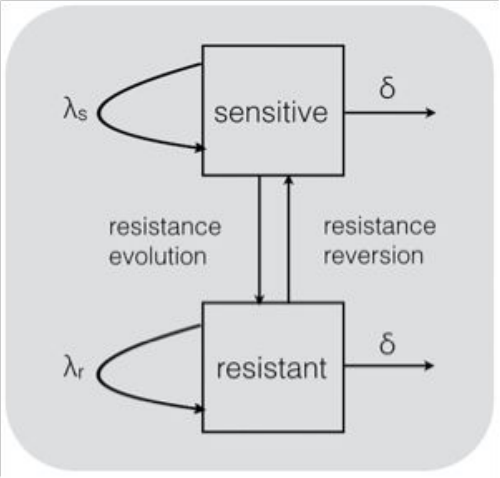
Neher et al. (*eLife*, 2014)

Multi-type birth-death models

Allows for different types of individuals (e.g. genotypes) that can vary in their birth or death rates and therefore their fitness values.



Fitness of HIV drug resistance mutations



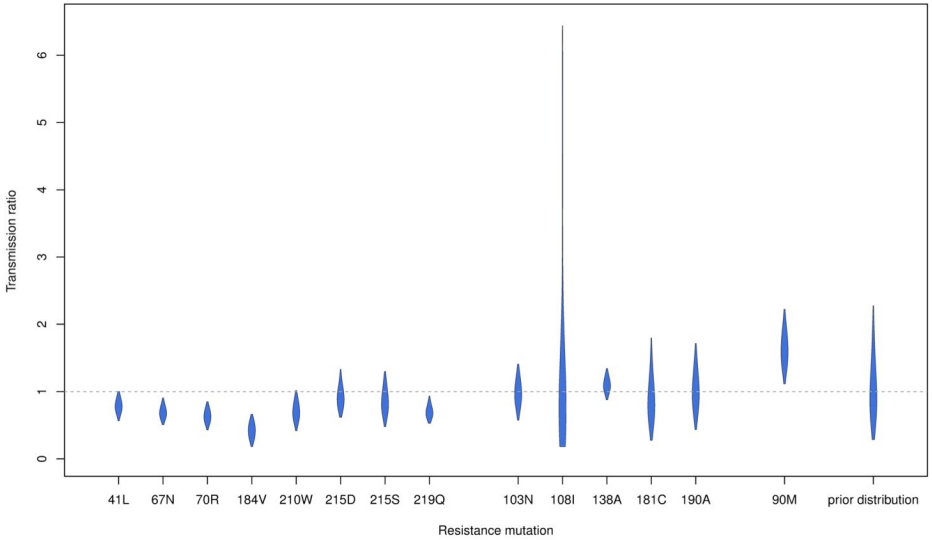


Table 1. Resistance mutations with numbers of corresponding clusters and samples, related drugs and drug usage dates within Switzerland.

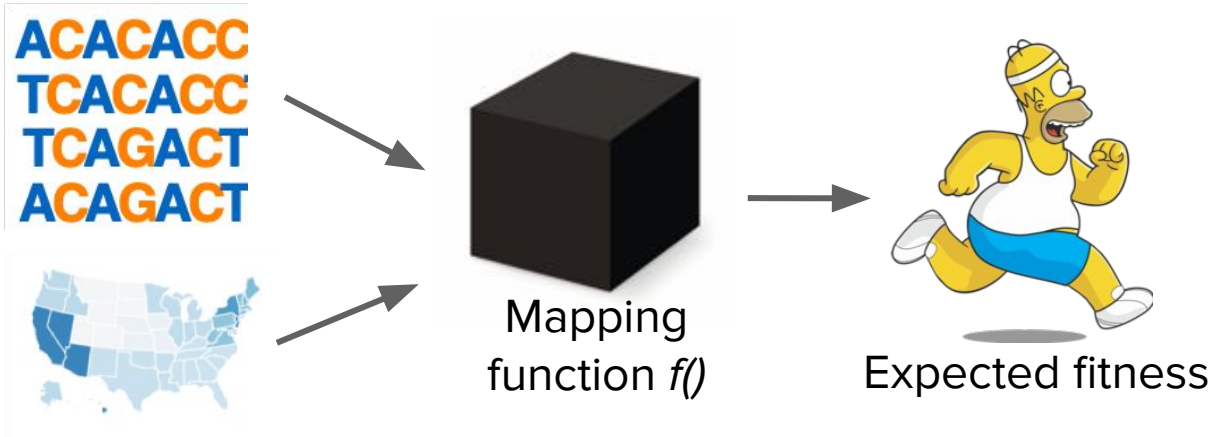
	nRTI									NNRTI					PI
Resistance mutation	41L	67N	70R	184V	210W	215D	215S	215Y	219Q	103N	108I	138A	181C	190A	90M
Number (#) of clusters of size ≥ 2	56	23	19	35	18	18	16	25	20	25	10	46	8	8	14
# Sequences in clusters	927	667	712	1011	481	569	494	807	605	725	334	1014	329	311	389
# Resistant samples in clusters	93	39	26	44	26	41	31	28	28	38	11	109	10	12	38
Drug (SHCS drug codes)	AZT D4T	AZT D4T	AZT D4T	3TC ABC FTC	AZT D4T	AZT D4T	AZT D4T	AZT D4T	AZT D4T	NVP EFV	NVP EFV	RPV	NVP EFV ETV RPV	NVP EFV	NFV SQV
Drug usage ≥ 1%	1987	1987	1987	1995.5	1987	1987	1987	1987	1987	1997	1997	2013	1997	1997	1996
Drug usage < 1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2008

Kühnert *et al.* (PLoS Pathogens, 2018)

A pathogen's fitness is a composite phenotype determined by many different intrinsic and extrinsic factors.

Mapping pathogen features to fitness

We want to learn how many different ***features*** including a pathogen's genotype and environment determine its fitness



Goal: learn the ***fitness mapping function*** that predicts a pathogen's expected fitness given its features (i.e. predictor variables).

SARS-CoV-2 workflow

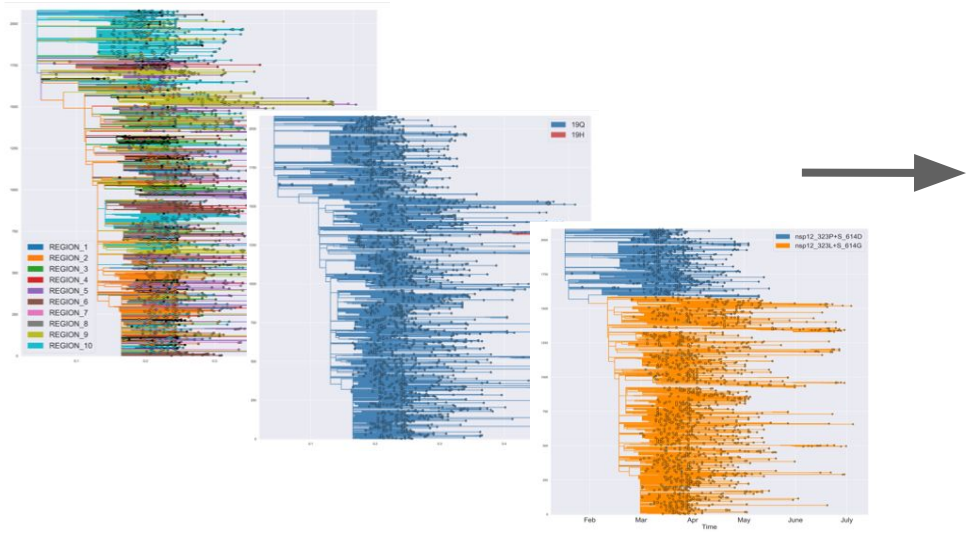
Sequences download from GISAID (n = 88,000)

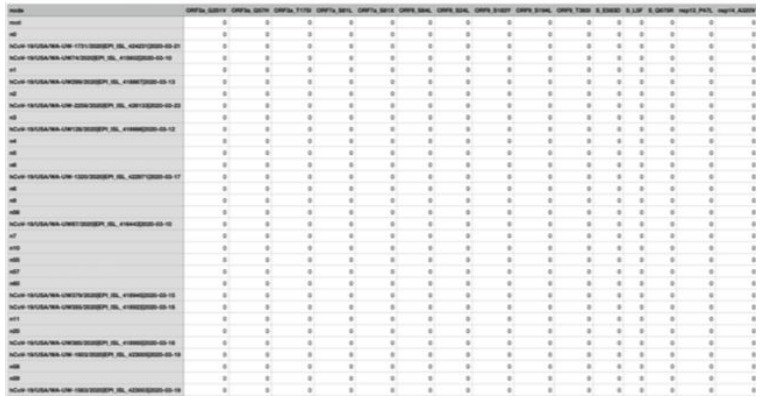
Phylogenetic reconstruction (RAxML)

Least squares dating (LSD)

Ancestral feature reconstruction (PastML)

Features encoded as binary predictor variables





SARS-CoV-2 fitness predictors

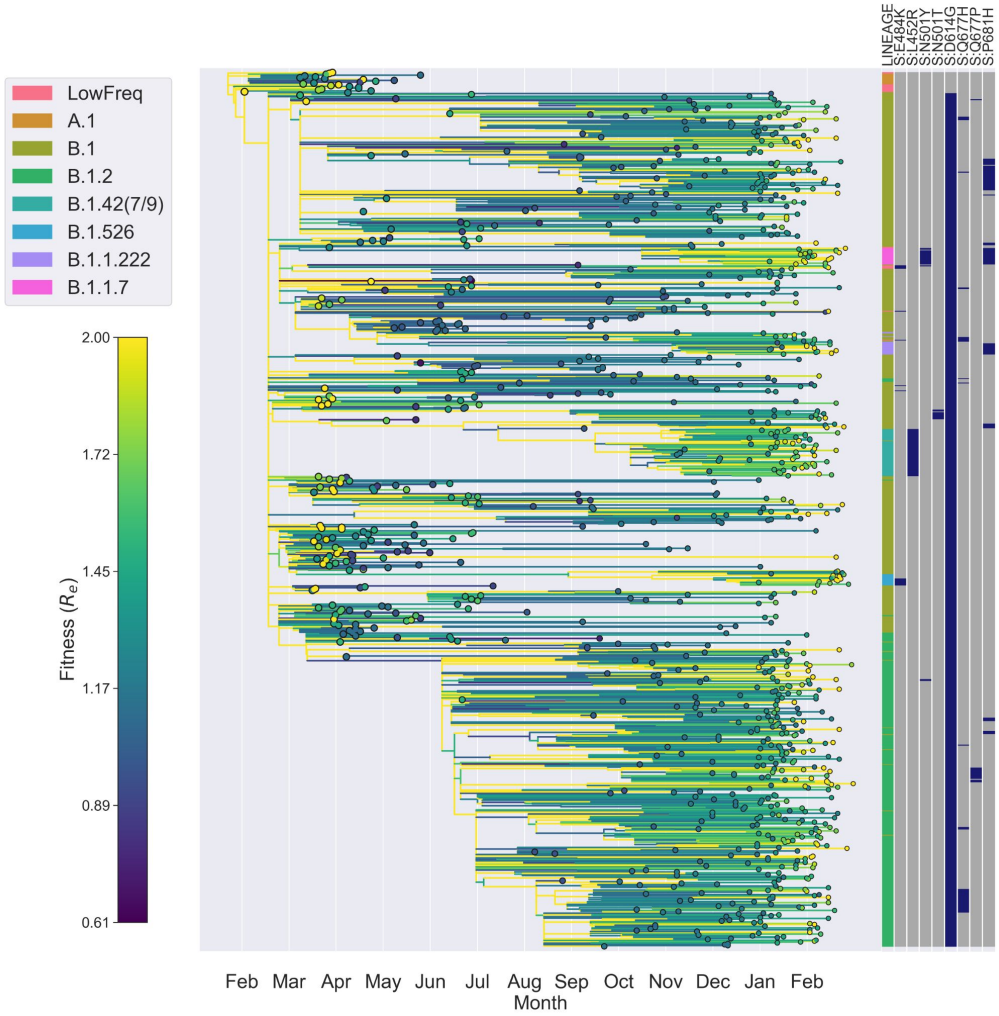
110 amino acid variants that reached a sampling frequency of at least 0.5%.

Geographic location of lineages at the level of US states and DHHS regions.

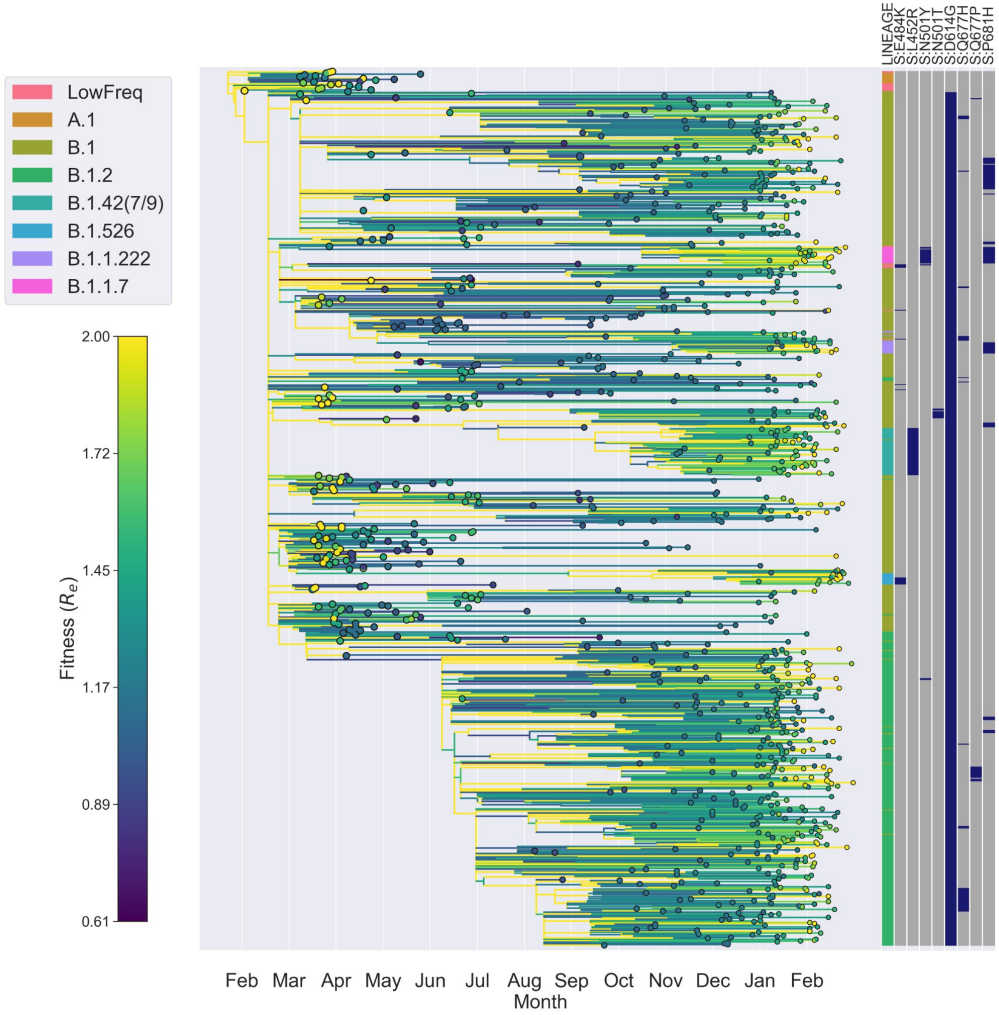
Other predictors such as aggregate mobility data (Google Mobility Trends) but some did not improve model fit.

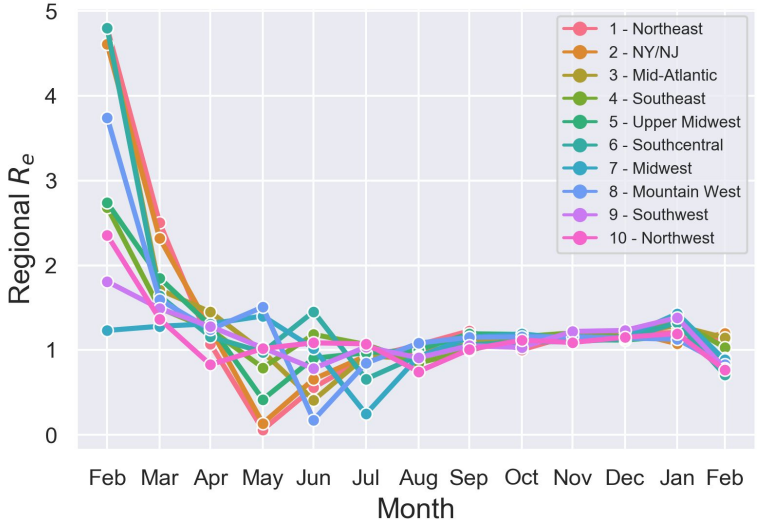
Fitness mapping function:

$$\log(F(x)) = \sum_{i \in \mathcal{X}} \log(\beta_i) x_{n,i} + \log(u_n).$$

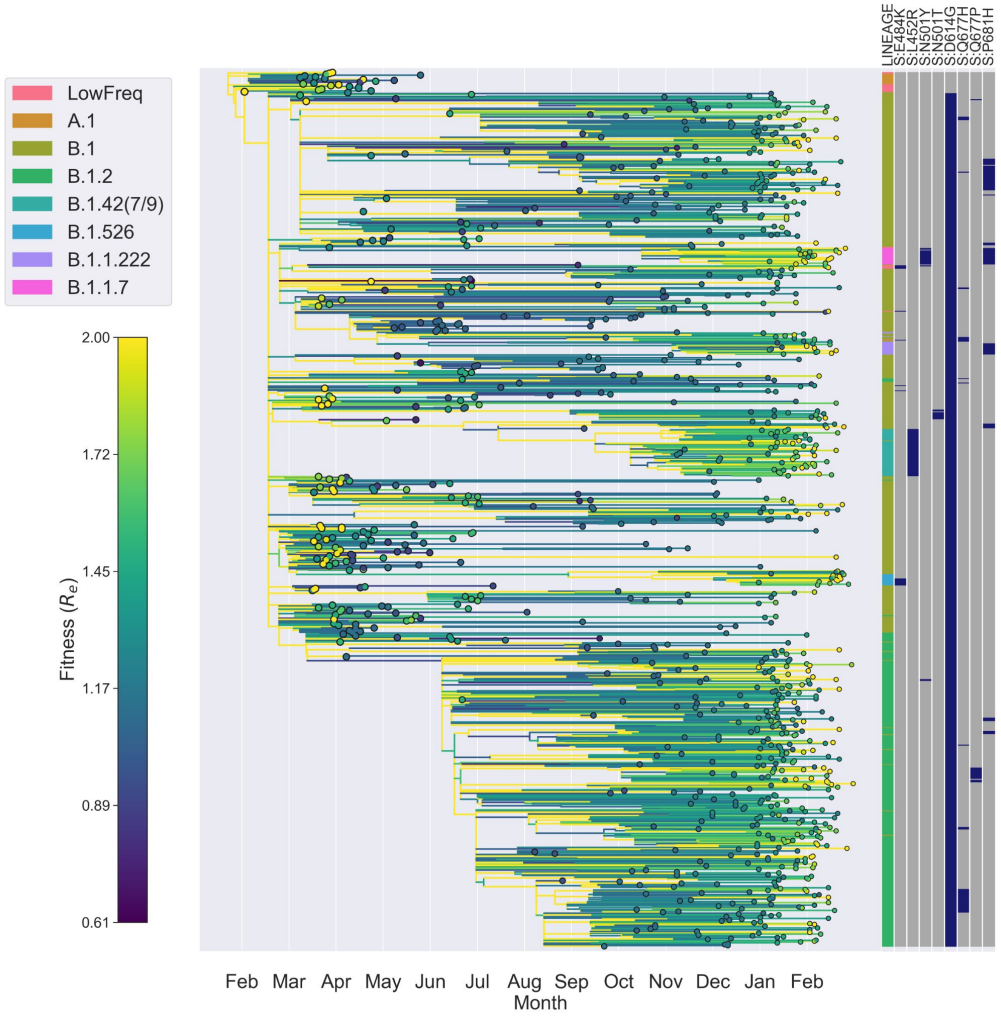


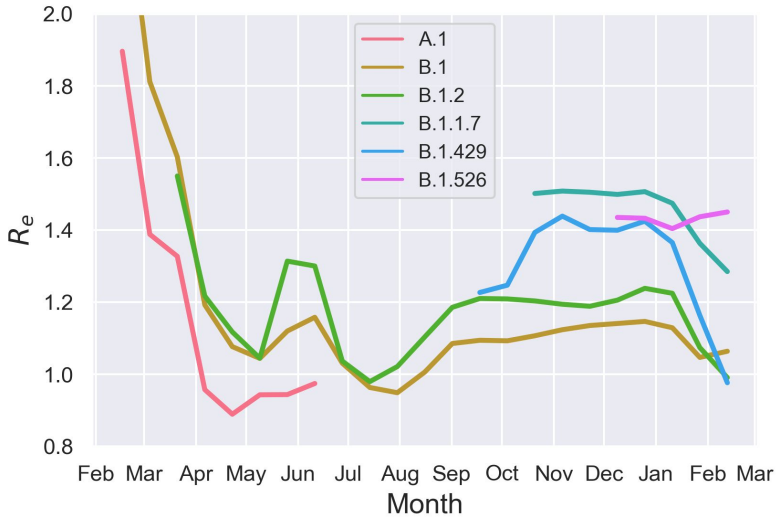
Kepler *et al.* (Virus Evo, 2021)





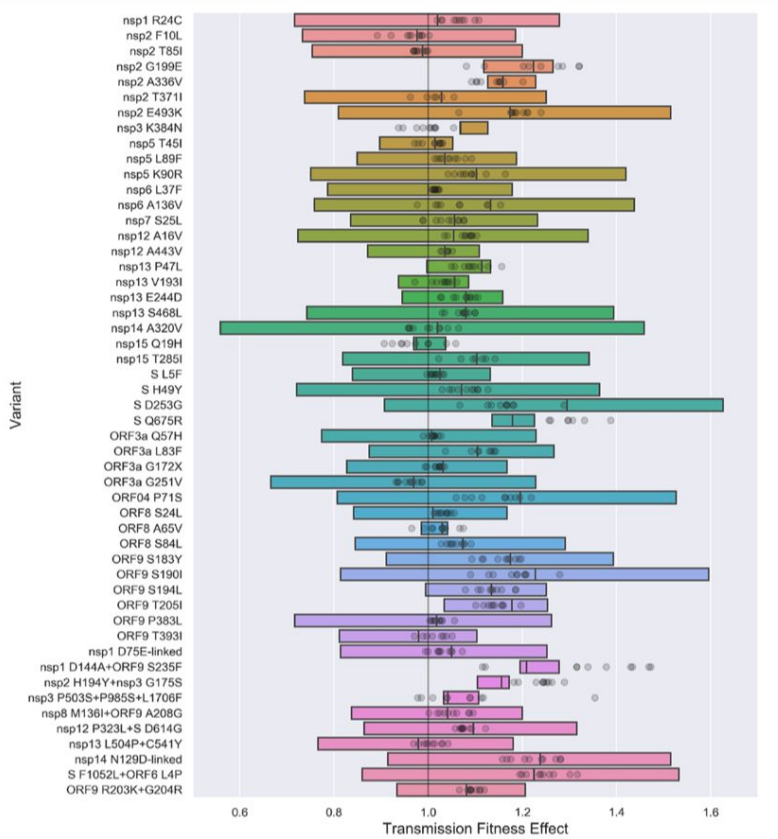
Kepler *et al.* (Virus Evo, 2021)





Kepler *et al.* (Virus Evo, 2021)

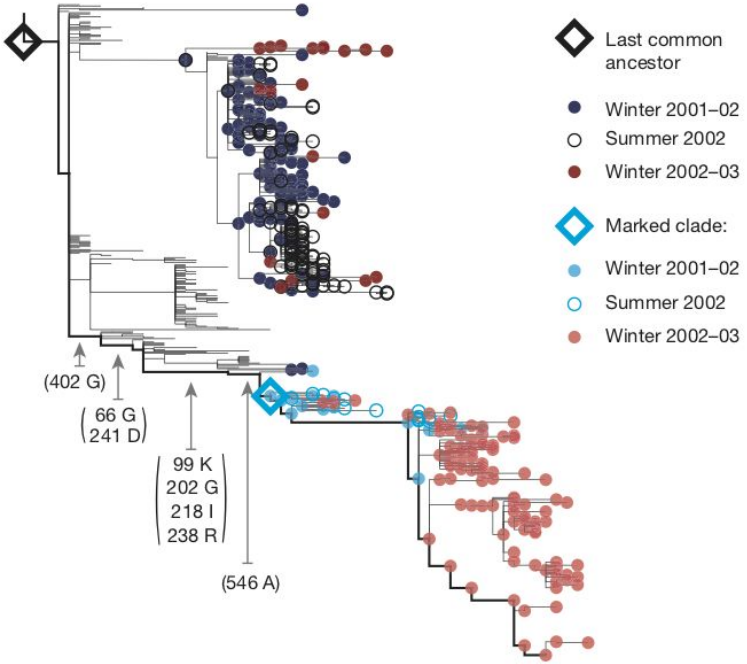
Fitness effects of amino acid variants



Variant	MLE	95% CI	Frequency
nsp3 K384N	1.057	1.05-1.07	0.016
nsp3 T1189I	1.057	1.03-1.06	0.012
nsp3 G1300D	1.052	1.05-1.07	0.023
nsp4 T429I	1.093	1.04-1.13	0.019
nsp13 Q88H	1.077	1.04-1.14	0.012
nsp14 V381L	1.06	1.05-1.07	0.014
ORF3a T151I	1.074	1.07-1.11	0.015
ORF3a D155Y	1.053	1.04-1.06	0.018
ORF3a T223I	1.053	1.04-1.06	0.033
ORF3a E226G	1.124	1.12-1.15	0.014
ORF9 D3L	1.068	1.03-1.08	0.015
ORF9 P207S	1.063	1.05-1.07	0.015
ORF9 M234I	1.063	1.03-1.086	0.054
ORF9 E378Q	1.055	1.05-1.08	0.012

Kepler *et al.* (Virus Evo, 2021)

Forecasting short-term flu evolution



Consider the evolution dynamics of different influenza *clades*

The frequency X_v of a particular clade can be predicted based on the fitness f_i of individual strains i in a clade:

$$\hat{X}_v(t+1) = \sum_{i:v,t} x_i \exp(f_i)$$

Luskza & Lassig (Nature, 2014)

What do we need to know?

What mutations/genotypes are available?

Will the fate of new variants be determined by selection or drift?

How do genotypes map to fitness-related phenotypes?

How does fitness translate to epidemic potential at the population level?

Analogy: Forecasting the weather

Despite the fact that the physical models required to predict the weather were developed in the 19th century, it still took another hundred years for reliable forecasts to emerge because of the need for massive amounts of atmospheric data and computing power.

But once short-term forecasts could be made, methods could be iteratively tested and improved, and forecasting advanced remarkably quickly.

A brief history of weather forecasting: https://www.newyorker.com/magazine/2019/07/01/why-weather-forecasting-keeps-getting-better

The future of evolutionary predictions

We have the theory, methods and data to predict short-term evolution

- Predictive genotype-to-fitness models
- High-throughput phenotypic data
- Genomic surveillance data and molecular epidemiological methods

We will likely get it wrong many times before we get it right but the fact that we can repeatedly test predictions on short timescales means that we can iteratively and rapidly improve our evolutionary forecasts.

In class discussion on Wednesday

Please read these two papers for class on Wednesday:

Łuksza, M., & Lässig, M. (2014). A predictive fitness model for influenza. Nature, 507(7490), 57-61.

Morris, D. H., Gostic, K. M., Pompei, S., Bedford, T., Łuksza, M., Neher, R. A., ... & McCauley, J. W. (2018). Predictive modeling of influenza shows the promise of applied evolutionary biology. Trends in Microbiology, 26(2), 102-118.

In class discussion on Wednesday

After you read these papers, please think about and be prepared to discuss:

1. How predictable is evolution in your favorite host-pathogen system?
2. What information is needed to make accurate predictions?
3. What is the time horizon of predictability?
4. What factors promote or limit predictability?
5. What is the biggest source of uncertainty surrounding predictions?