

Lecture 4: Influenza virus

Recap: Evolutionary contingency

Can evolution be predicted?

$$\frac{dq}{dt} = \sigma q(1 - q)$$

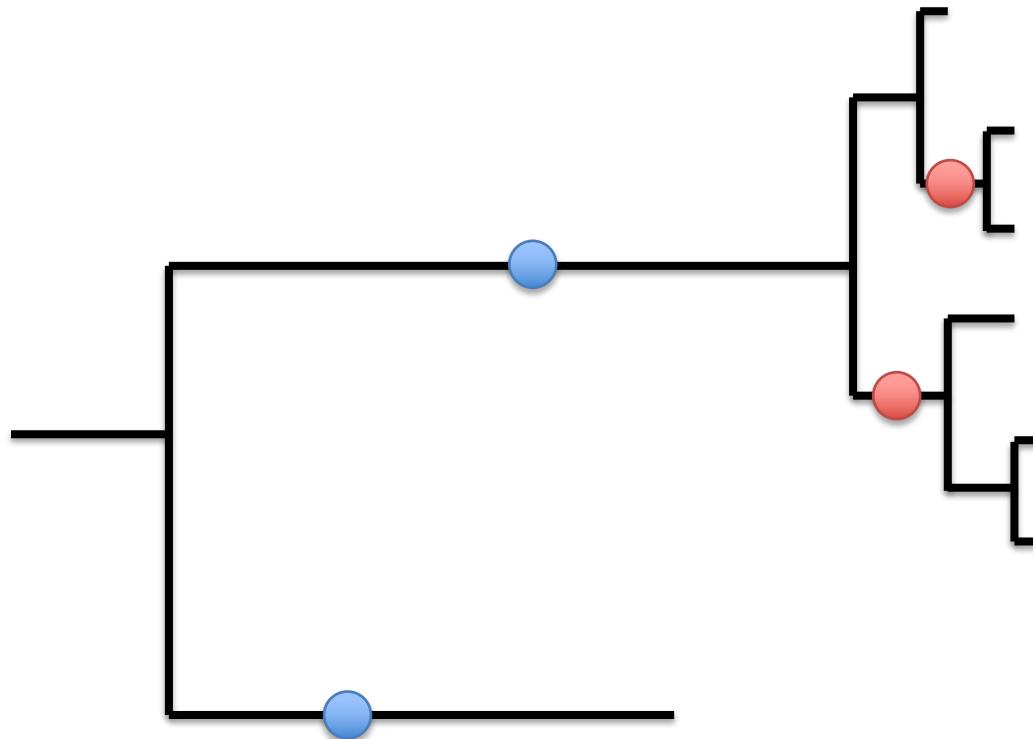
1. Use data to infer selection
2. Use knowledge of selection to predict evolution?

Phylogenetics

Phylogenetic models

Given a set of sequences, how are they related?

Aiming to retrieve a phylogeny: sequences connected by ‘relatedness’.

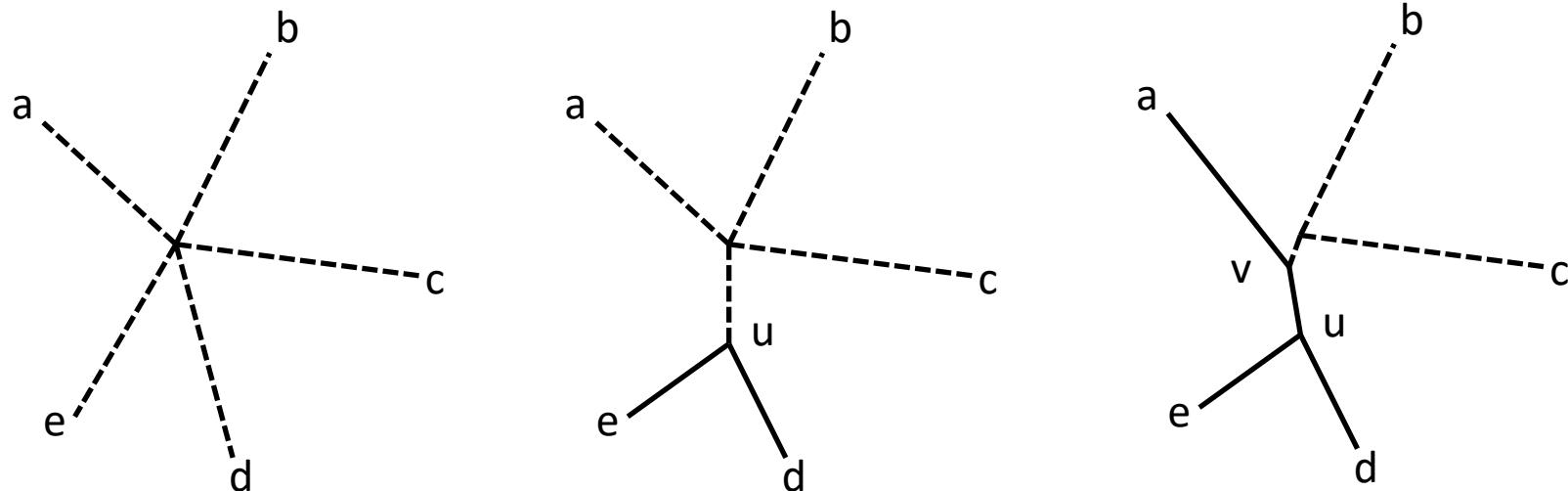


Phylogenetic models

Neighbour joining methods

Calculate a metric of genetic distances between sequences.

Join in a pairwise fashion by creating internal nodes

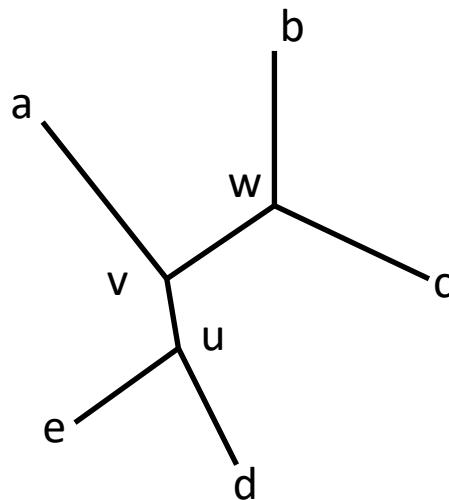
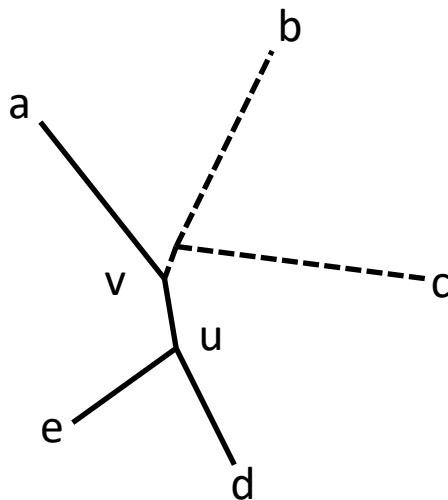


Phylogenetic models

Neighbour joining methods

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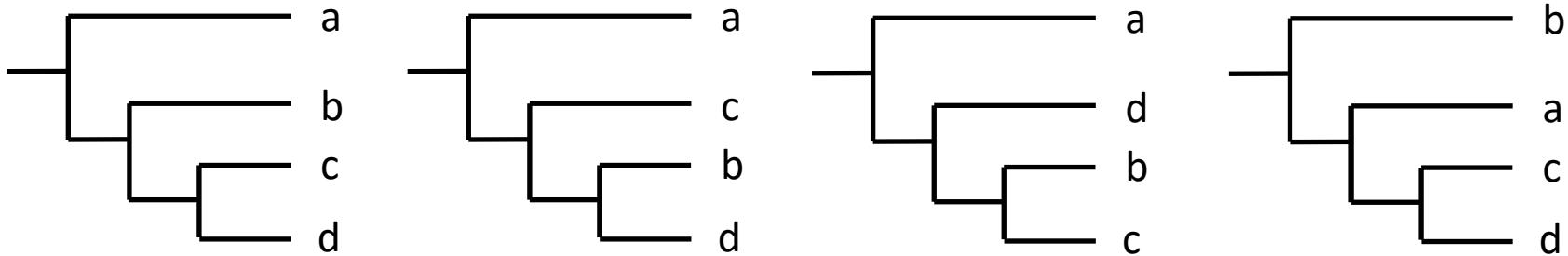
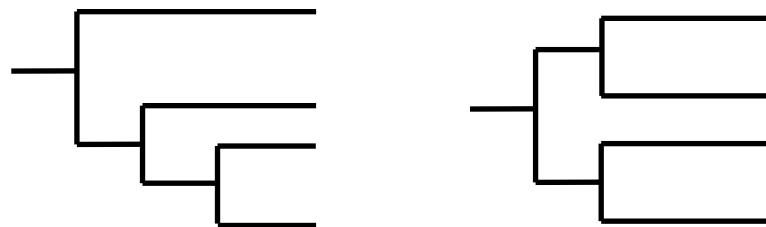


Phylogenetic models

Maximum parsimony method

Identify the network requiring the minimum number of substitutions to produce the observed outcome

Can be done by systematic search where there are few sequences



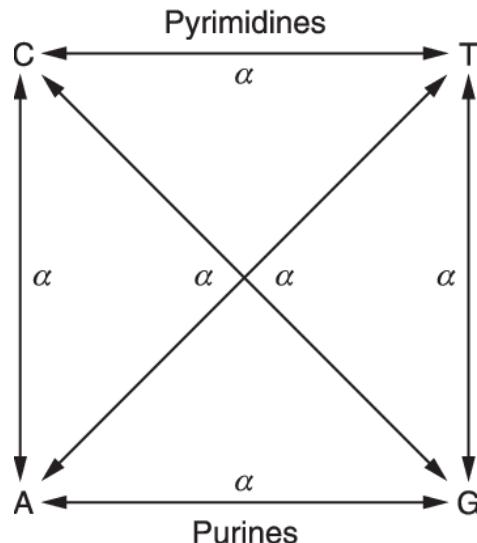
Phylogenetic models

Maximum likelihood method

Calculate the likelihood of a tree given a model which describes the rate of substitutions in the population.

Models described by a transition matrix: Probability of mutating from one nucleotide to another.

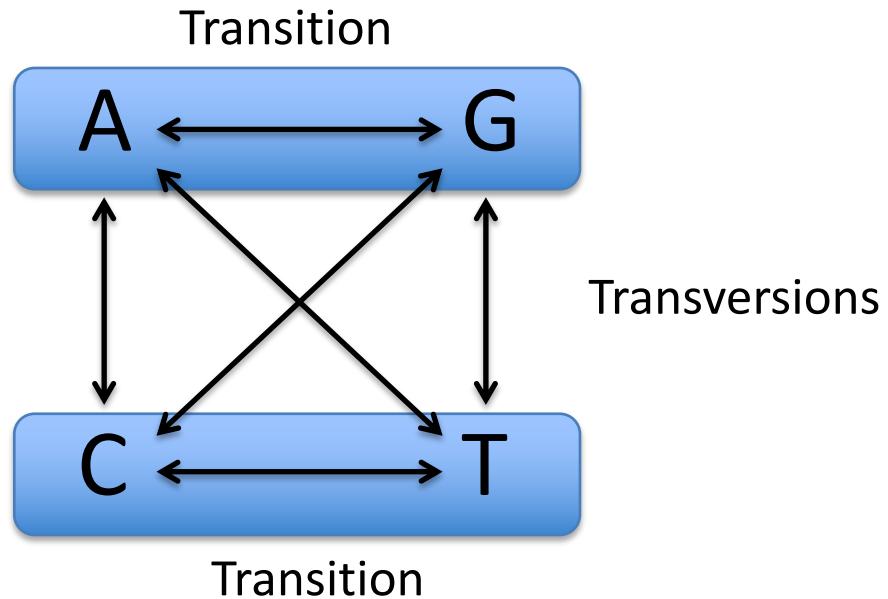
Jukes-Cantor: All mutations between A, C, G, T are equal. Allele frequencies are equal.



Phylogenetic models

Models of substitution define mutation rates

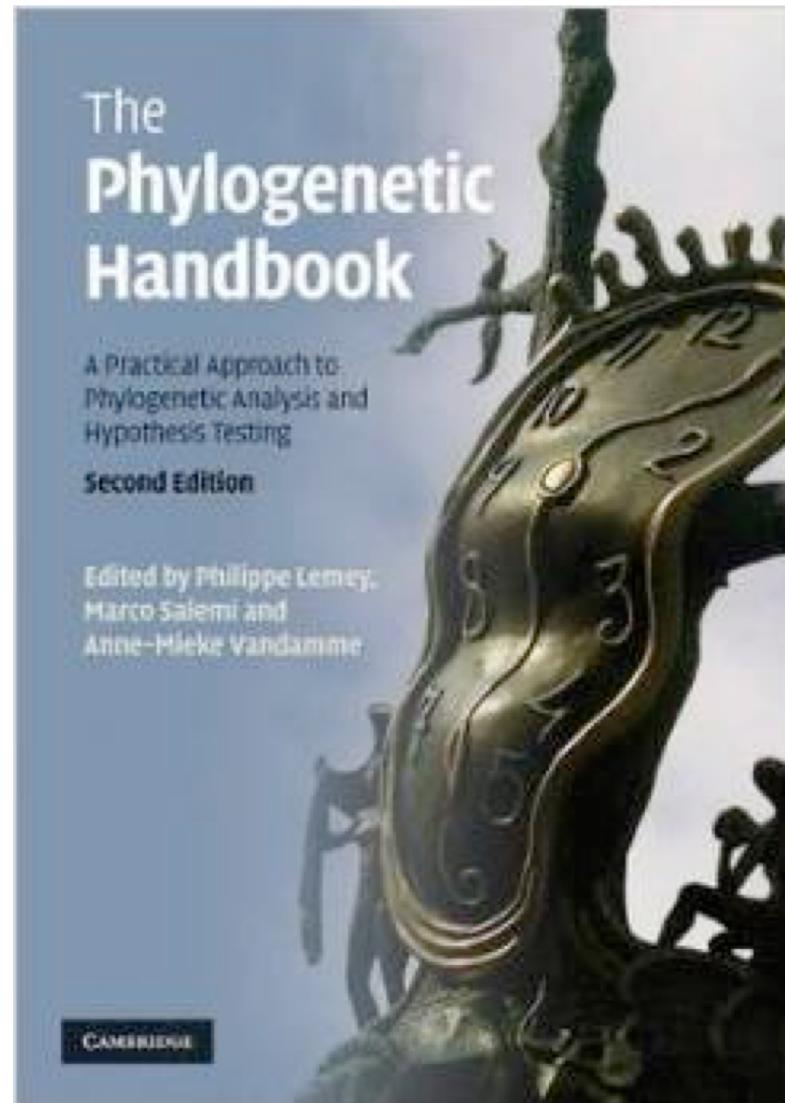
More complex substitution models exist



Transition / transversion ratio can be a long way from 1:1

Phylogenetic models

For further reading

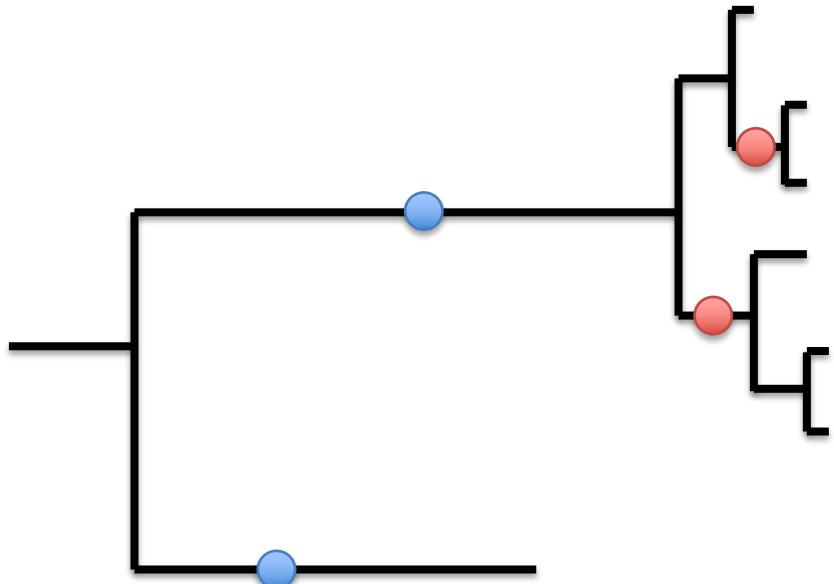


Inference of selection in a phylogeny

dN/dS

Assumption that synonymous mutations are neutral.

Compare non-synonymous and synonymous mutation rates



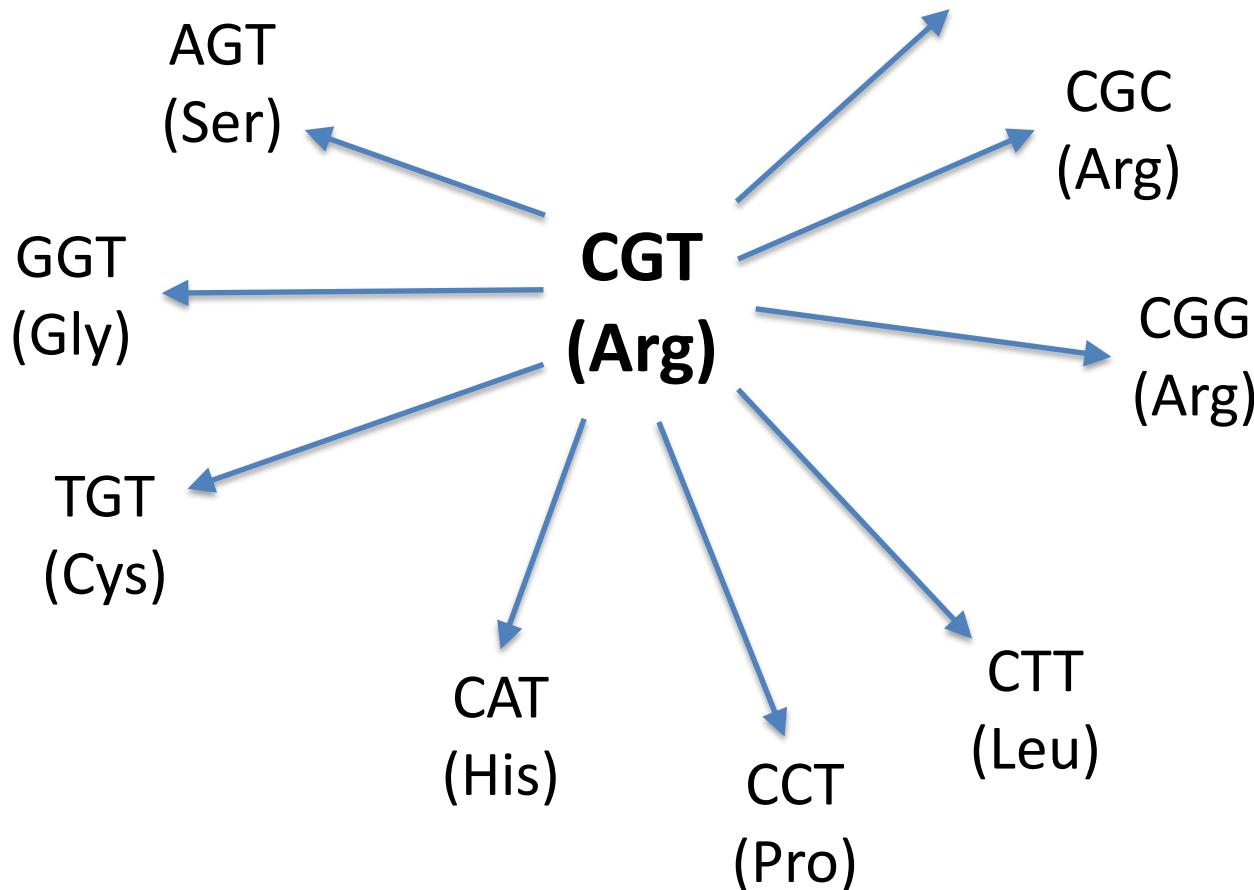
Tree gives numbers of synonymous
and non-synonymous substitutions

Calculate opportunity for
synonymous and non-synonymous
mutations

Rate = #substitutions / opportunity

Inference of selection in a phylogeny

Mutation opportunity :
3 / 9 synonymous



Modelling selection in a phylogeny

dN/dS

Interpretation

$dN/dS < 1$: Indicates purifying selection outweighs positive selection
Selection to keep the current set of amino acids
e.g. Functionally-important amino acids

$dN/dS > 1$: Indicates positive selection outweighs purifying selection
Selection to replace amino acids
e.g. Time-dependent fitness

Can also identify variation in dN/dS in a subsection of sites within a sequence

Reality check : dN/dS is very rarely >1 . Problem here is that this is an average measurement of selection at a locus, across all substitutions

Influenza virus

Influenza virus

Pandemic influenza:

Arises from a novel viral strain: Little pre-existing immunity in the human population.

Previous events in 1918 (1977), 1957, 1968, 2009

1918 pandemic

Thought to be avian in origin

50-100 million deaths

(3-6% global population)

2009 ‘swine flu’

Origin in pigs

300-500 thousand deaths



Influenza virus

Seasonal influenza:

Continued lifespan of a pandemic strain

Infects 10-15% of the global population each year, causing 300-500 000 deaths

Strains currently circulating:

A/H1N1 strain : Arose from the 2009 pandemic.

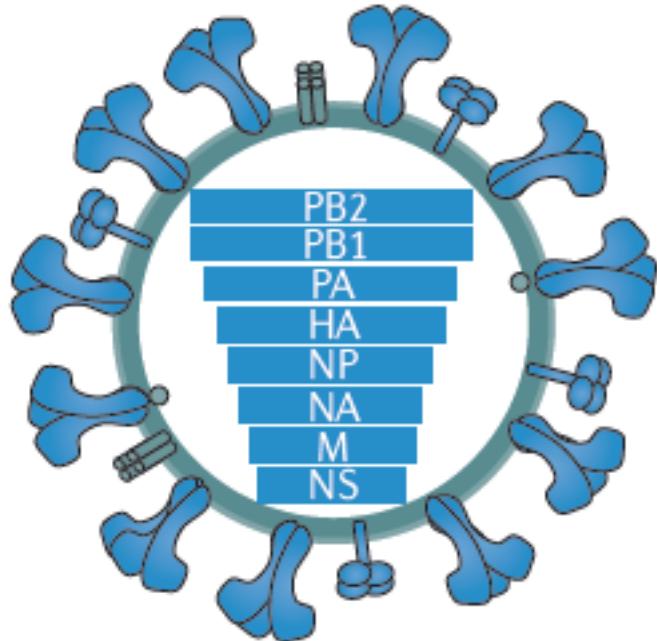
A/H3N2 strain : Arose from the 1968 pandemic.

Influenza B : Less common, generally milder.

Influenza virus

Viral genetics

Genes packaged within viral capsid



HA : Binds to host cell surface

NA : Promotes release from host cell surface

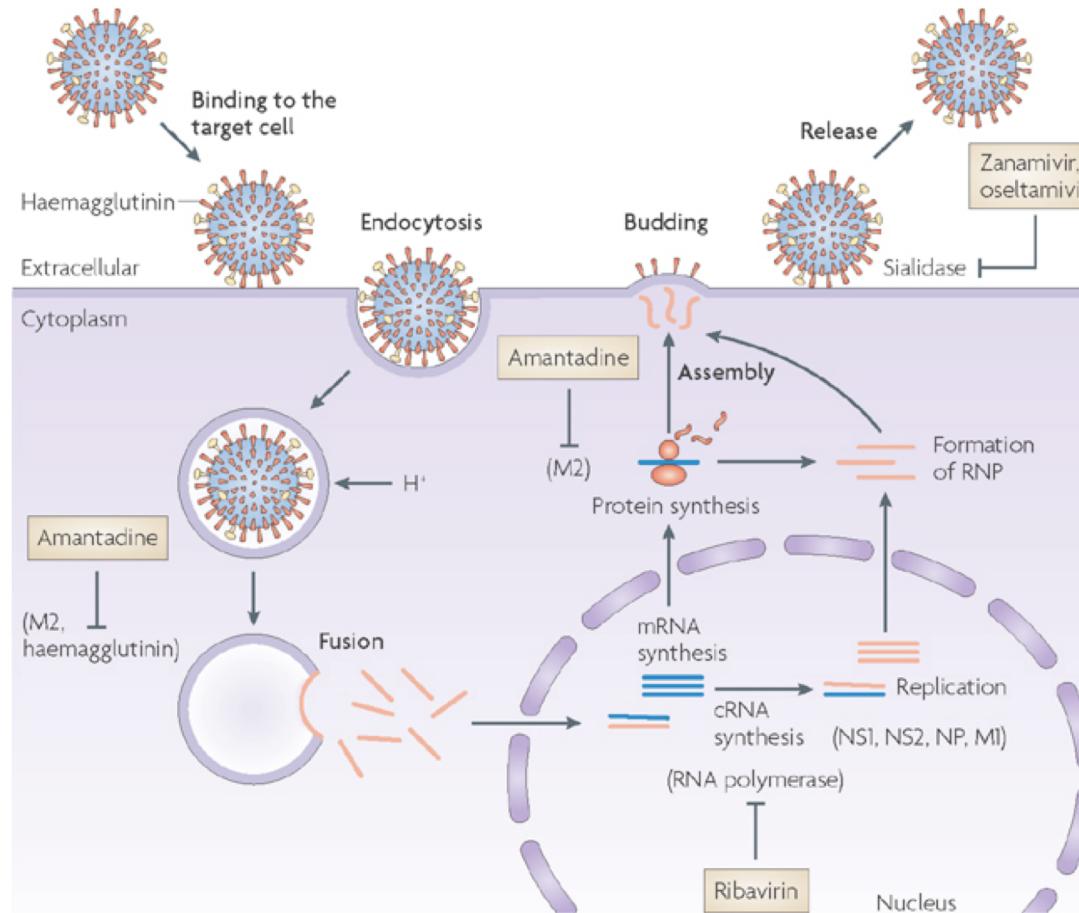
M: Part of capsid structure. Ion channel M2 allows H⁺ ions into capsid: uncoating of capsid

PB1, PB2, PA, NP : Involved in viral replication

PB1-F2, NS1 : Disrupt host immune system: interferon antagonists

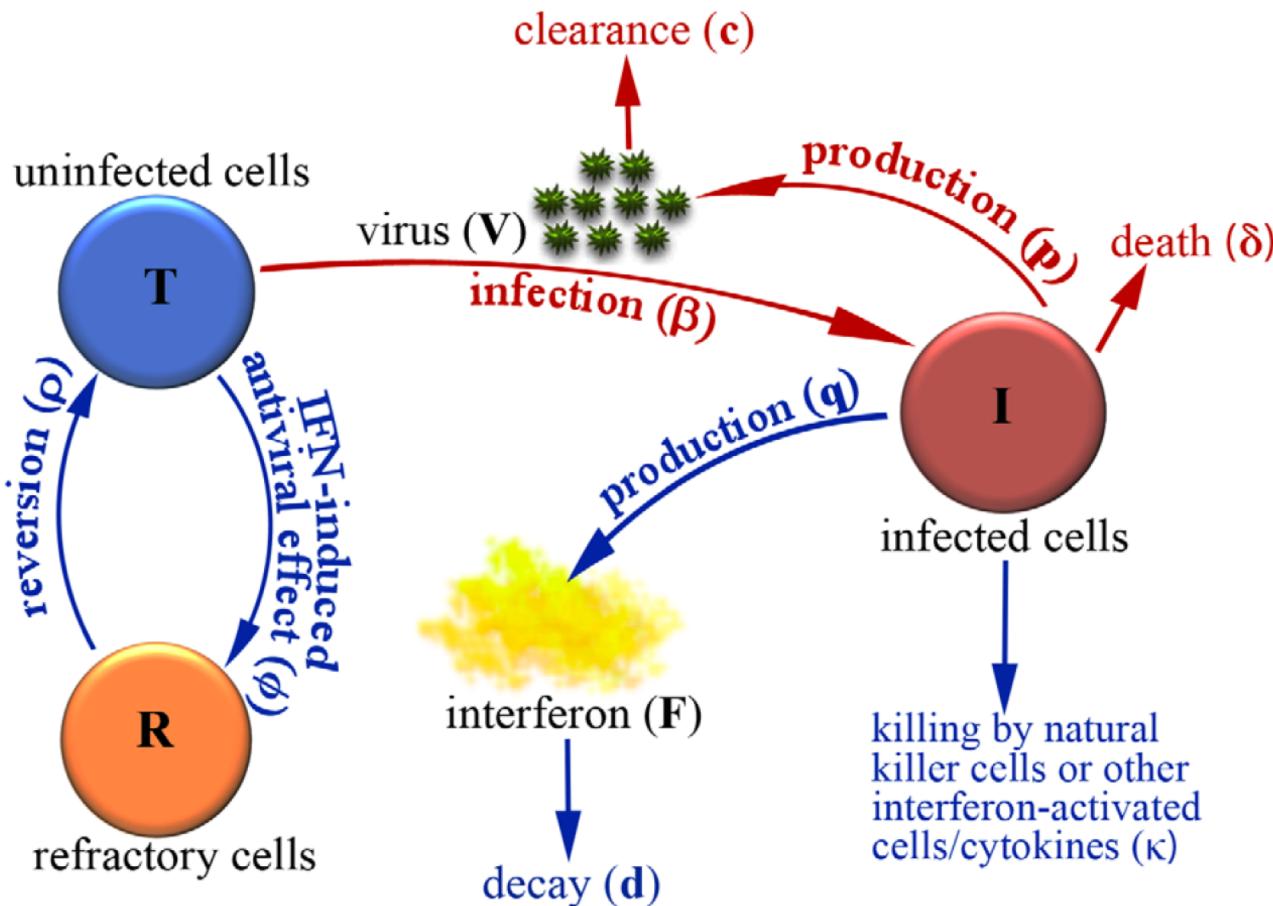
What happens when you get influenza?

Life cycle of a virus



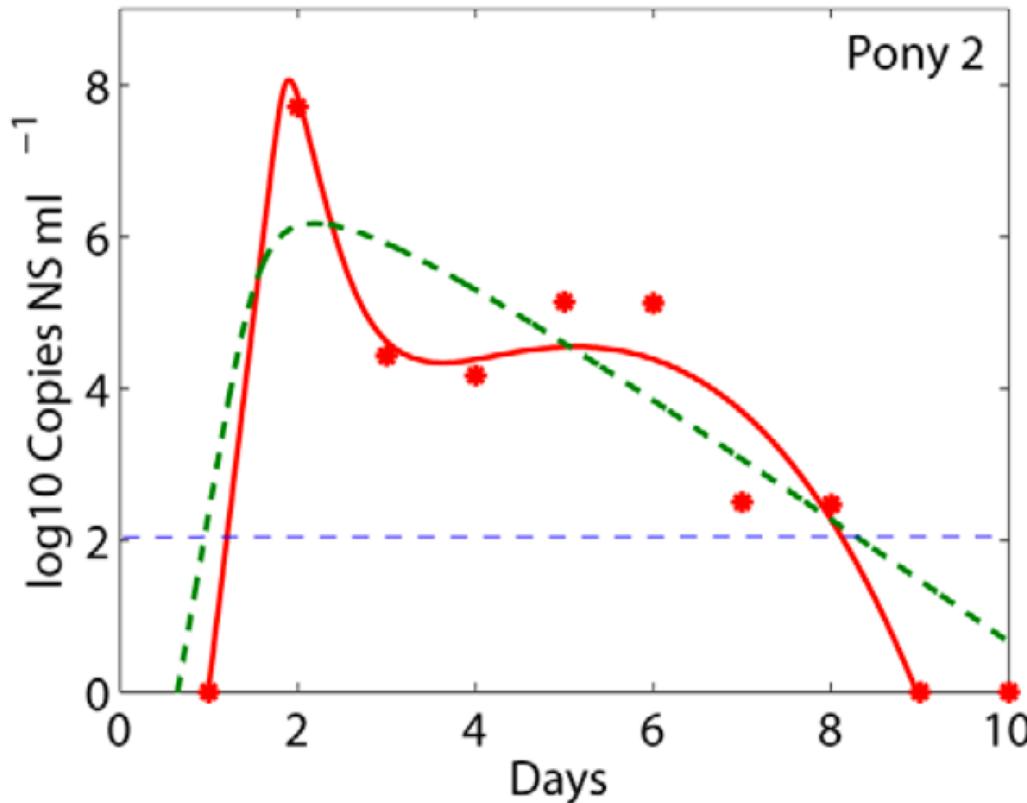
What happens when you get influenza?

Mathematical model of infection



What happens when you get influenza?

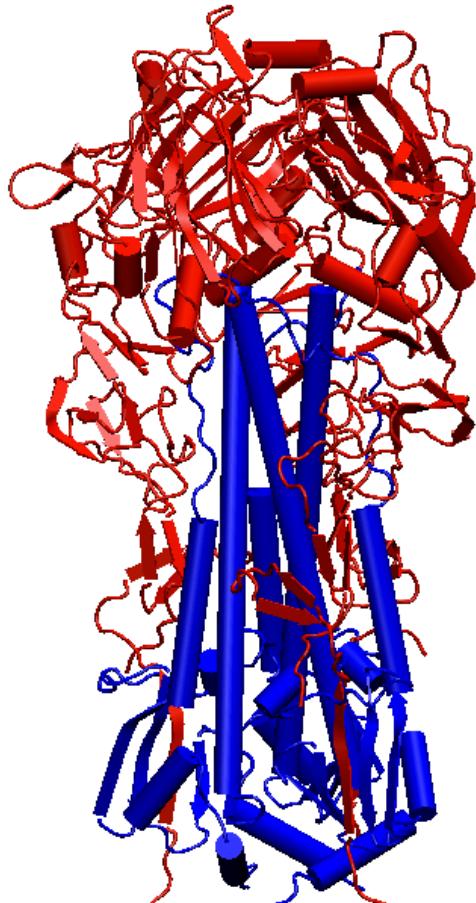
Mathematical model of infection



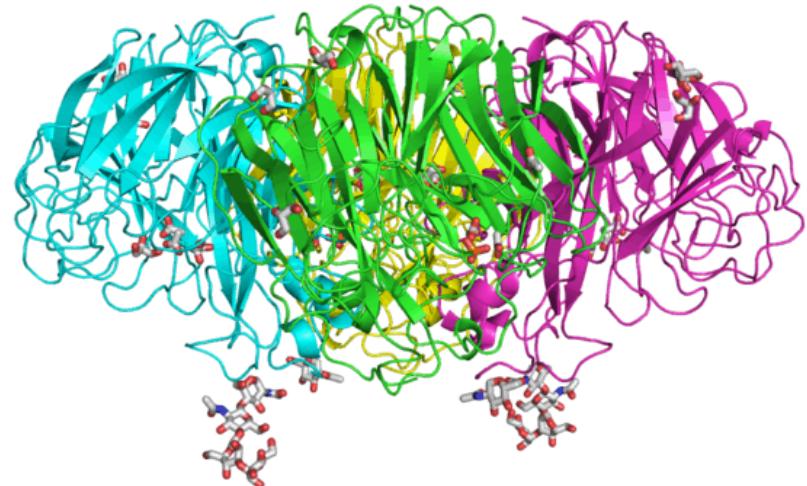
Strain-specific adaptive immune response kicks in after a few days

What happens when you get influenza?

Adaptive response targets viral surface proteins



Haemagglutinin (HA)



Neuraminidase (NA)

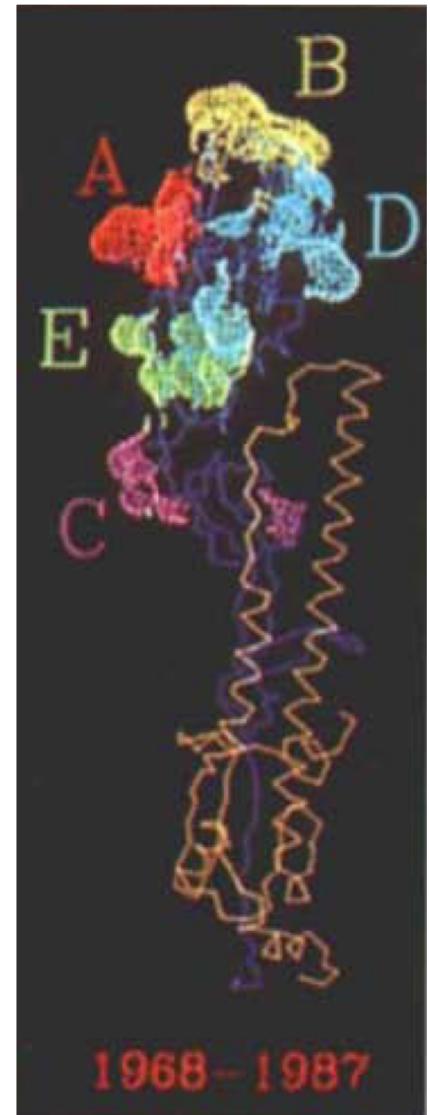
Influenza and human immunity

Adaptive immunity

Recognition of specific regions of the virus

Antibodies bind the antigenic regions of the HA protein.

Following infection, the immune system retains a memory of the virus. This produces a strain-specific immunity against influenza



Influenza and human immunity

Vaccination against influenza

Vaccine primes the immune system

Effectiveness of the vaccine depends upon how closely it resembles the actual strain

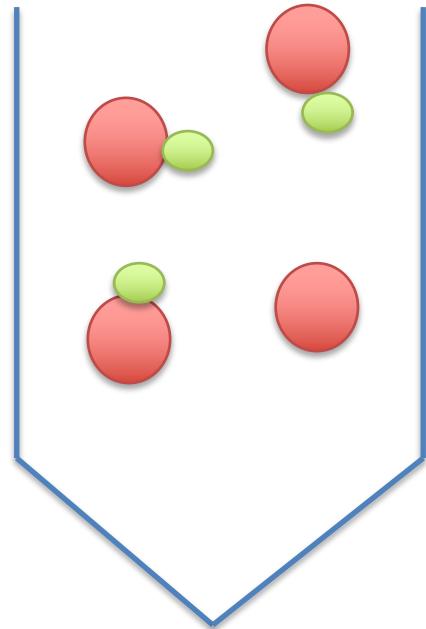
The degree of resemblance can be measured using a biological assay



Influenza and human immunity

Haemagglutination assay: Measure amount of virus

Influenza virus binds red blood cells. Measure number of unbound cells



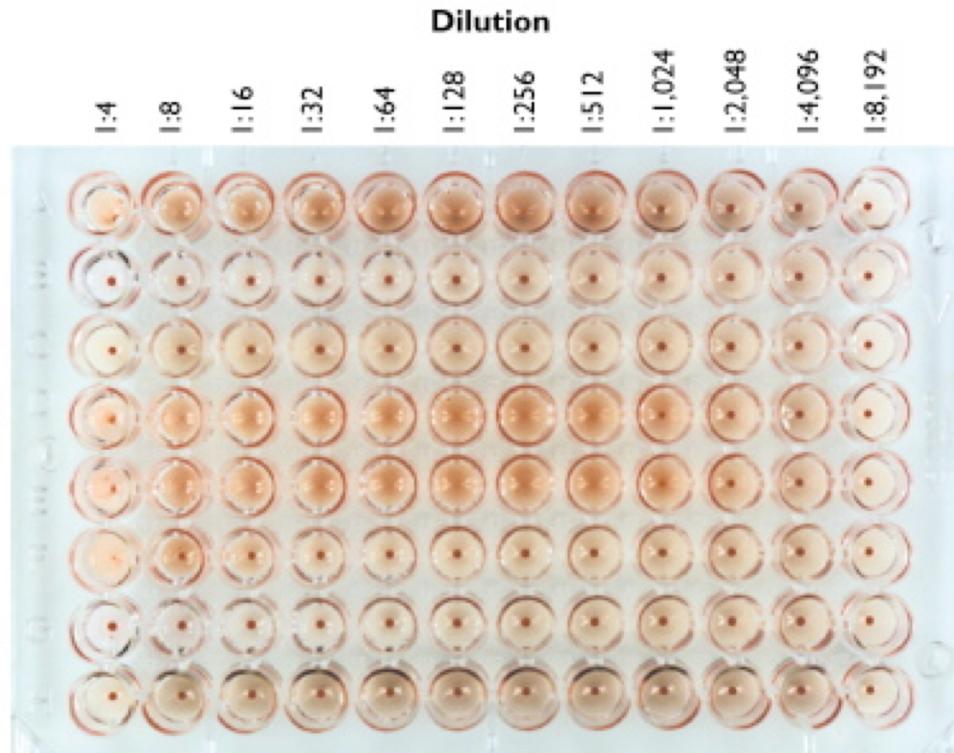
Cells at bottom of well indicate that not all were bound by the virus

Antibodies in the sample prevent binding

Influenza and human immunity

Haemagglutination assay

Influenza virus binds red blood cells. Measure number of unbound cells.



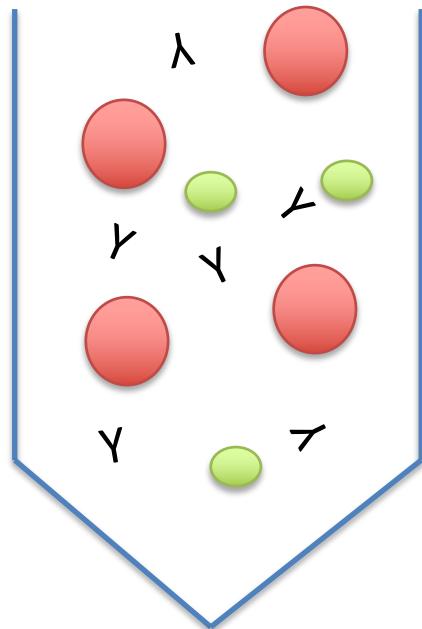
Row B: No binding : No detectable virus

Row D: Binding up to 512-fold dilution of viral protein: lots of virus

Influenza and human immunity

Haemagglutination inhibition assay: Effect of antibodies

Influenza virus binds red blood cells. Measure number of unbound cells



Cells at bottom of well indicate that not all were bound by the virus

Antibodies in the sample prevent binding

Influenza and human immunity

Haemagglutin inhibition assay

Tabulate the extent of protection:

Viruses	Isolation Date	Haemagglutination inhibition titre ¹													
		Post infection ferret sera										AUS	AUS	CDC	JAP
		A/NC 20/99	A/Eg 96/02	A/Neth 128/04	A/Theis 24/05	A/HK 2637/04	A/Eg 39/05	A/Vic 500/06	A/Mal 100/06	A/Taiw 42/05	A/Tok 6708/05				
A/New Caledonia/20/99	9.6.99	Ex	320	320	640	320	1280	1280	640	640	80	40			
A/Egypt/96/02 (H1N2)	25.1.02	Ex	320	640	640	320	640	640	320	320	40	<			
A/Netherlands/128/04	14.9.04	MDCK1 \4	160	320	1280	640	1280	640	640	640	160	40			
A/Thessaloniki/24/05	3.2.05	E2 \3	160	320	1280	640	1280	640	640	640	160	40			
A/Hong Kong/2637/2004	24.6.04	MDCK2 \4	80	160	320	160	320	640	160	320	40	<			
A/Egypt/39/2005	25.11.05	E1 \4	320	320	640	320	1280	1280	640	640	80	40			
A/Victoria/500/2006	19.4.06	E3 \1	160	160	1280	640	640	640	1280	1280	320	40			
A/Malaysia/100/2006	unknown	E3 \1	160	160	1280	640	1280	640	640	1280	160	40			
A/Taiwan/42/2005	28.1.06	C4 \1	<	<	<	<	160	80	40	40	640	80			
A/Tokyo/6708/2005	9.9.06	E1/1 \1	80	40	80	80	320	640	80	160	1280	640			

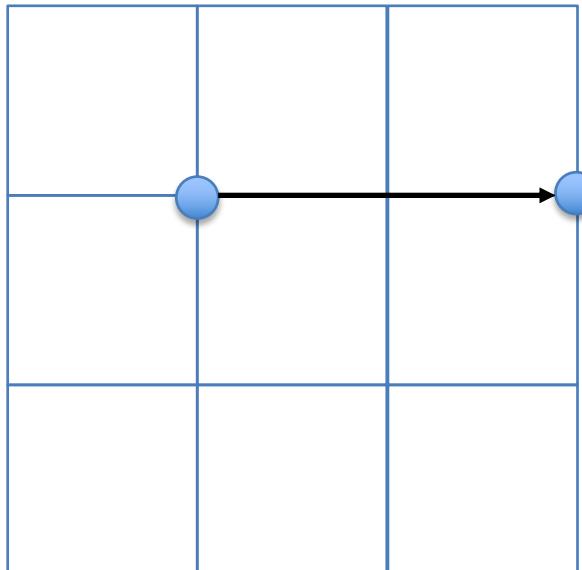
Used to choose vaccine strains for each flu season

Influenza and human immunity

Viral strain mapping

Concentrations describe an ‘antigenic distance’ between viruses:
One unit equals a halving of protection

Measure many strain-strain distances



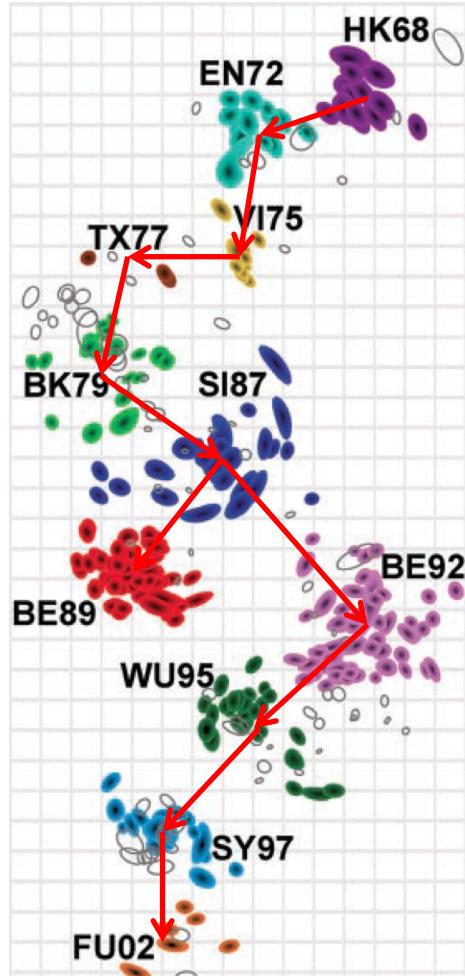
Project distances onto a two-dimensional surface

$$D = \begin{pmatrix} d_{11} & d_{12} & \dots & d_{1n} \\ d_{21} & \ddots & & d_{2n} \\ \vdots & & \ddots & \vdots \\ d_{n1} & d_{n2} & \dots & d_{nn} \end{pmatrix} \quad D_{\mathcal{R}^2} = \begin{pmatrix} d'_{11} & d'_{12} & \dots & d'_{1n} \\ d'_{21} & \ddots & & d'_{2n} \\ \vdots & & \ddots & \vdots \\ d'_{n1} & d'_{n2} & \dots & d'_{nn} \end{pmatrix}$$

Minimise the difference between the 2-dimensional, and n-dimensional distances

Influenza and human immunity

Viral strain mapping

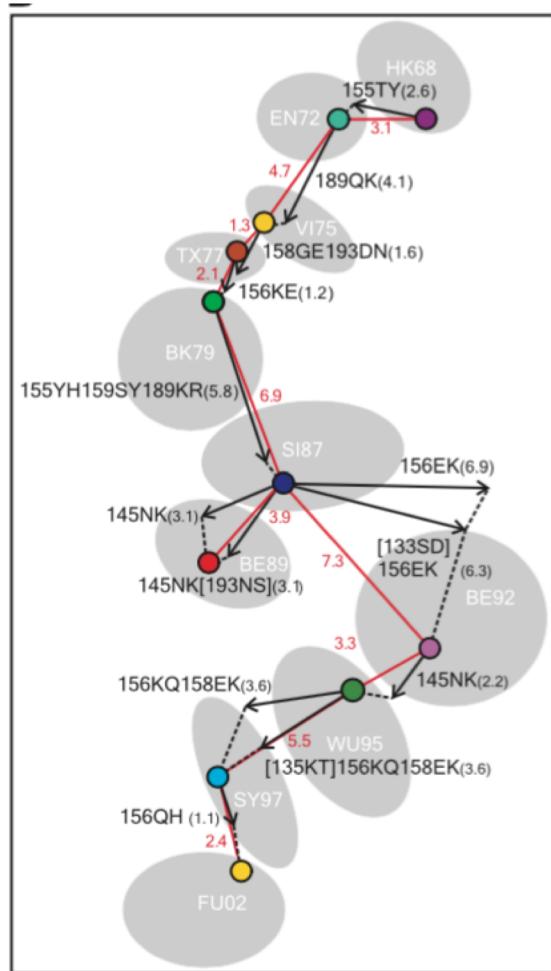


Observe “antigenic clusters”

Discrete jumps occur in the antigenic properties of the virus

Influenza and human immunity

Small numbers of changes underlie antigenic change



Only a few changes are required to
for a transition between clusters

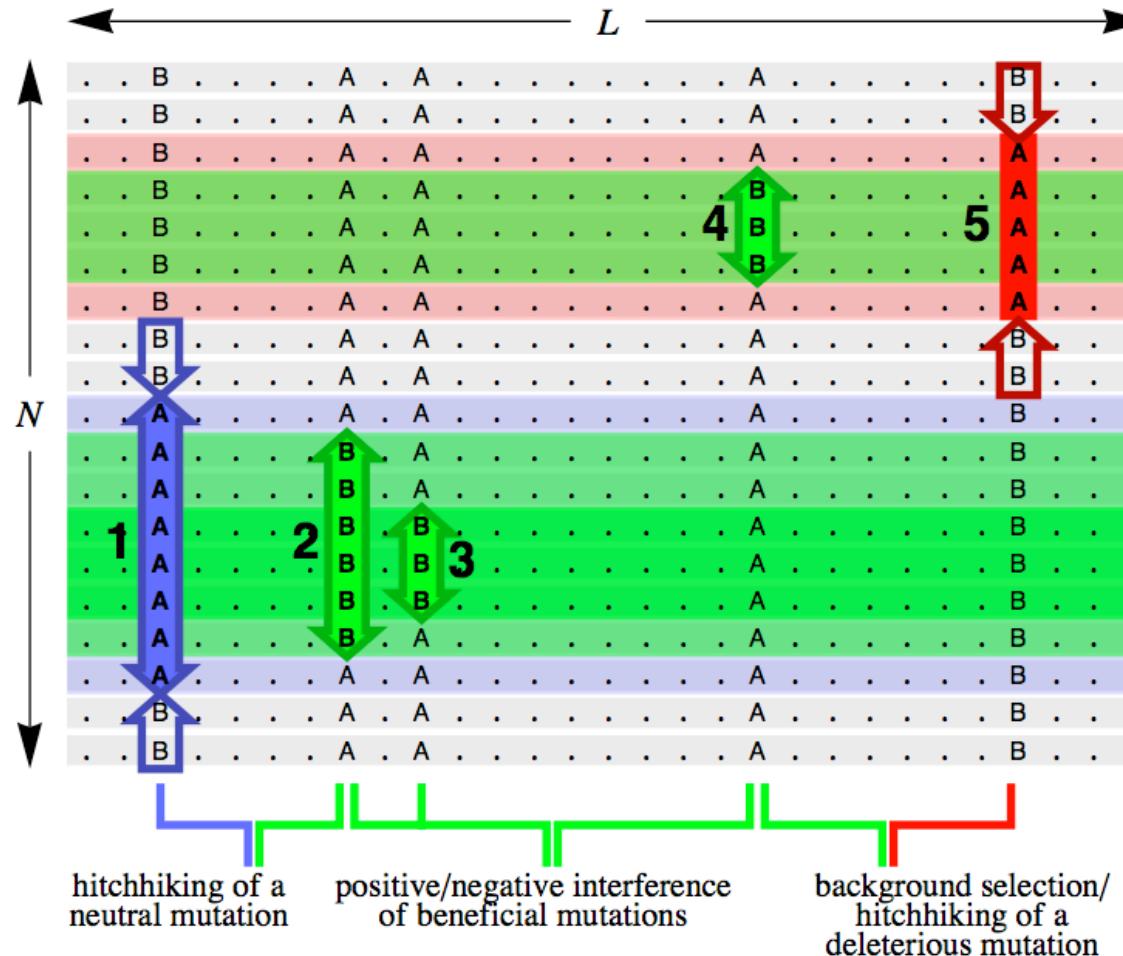
Why are more mutations observed?

Why don't substitutions happen
more quickly?

Does this make influenza evolution
predictable?

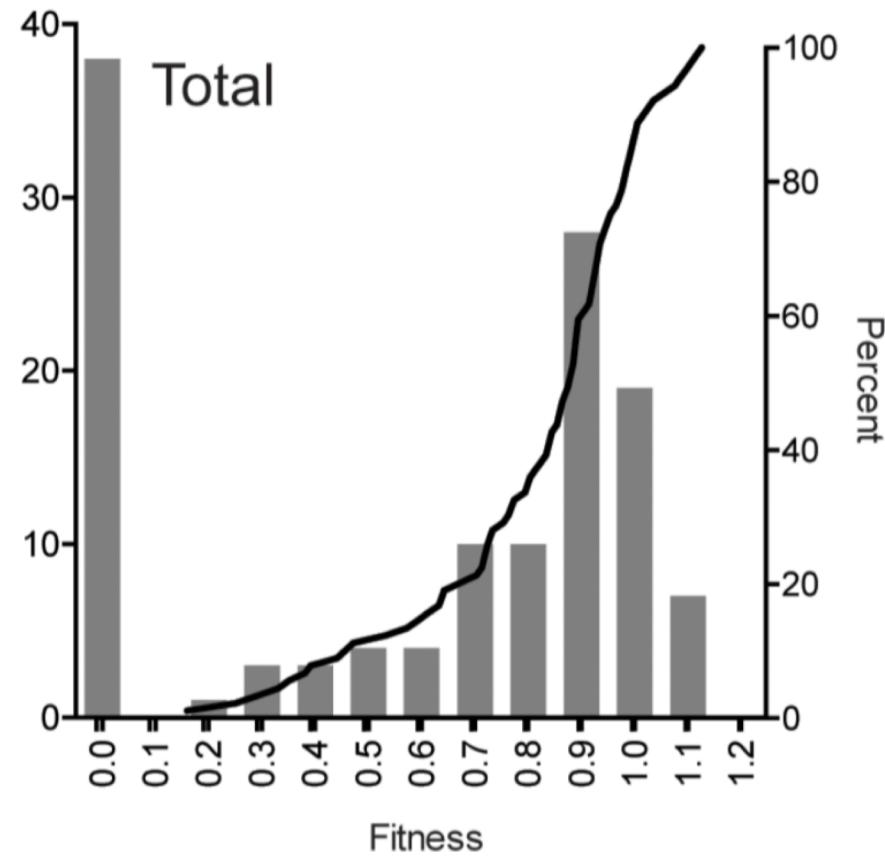
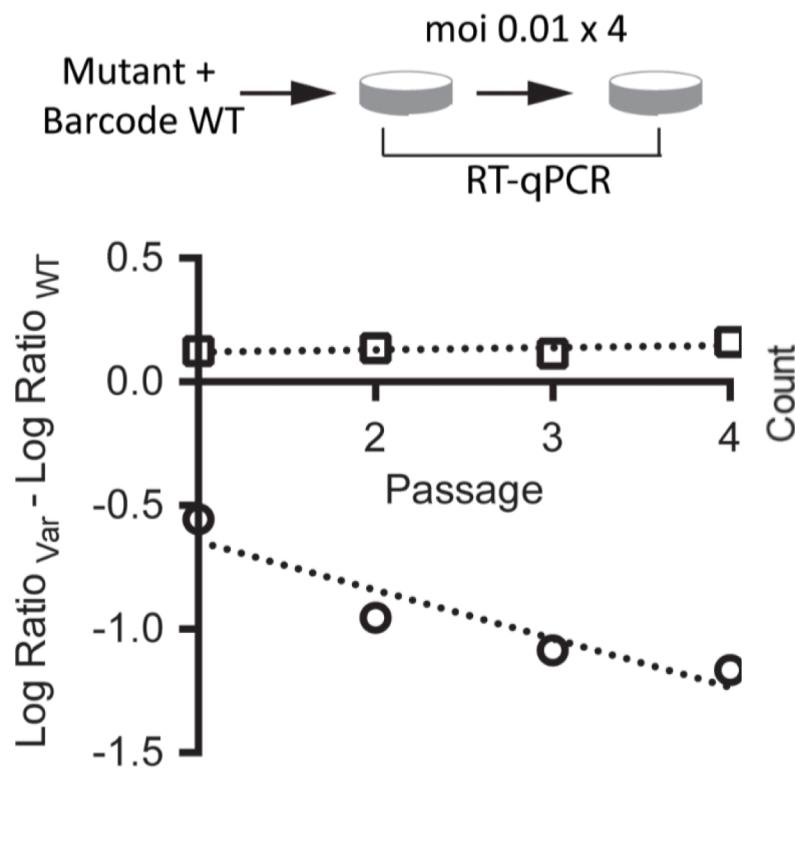
Selection across multiple loci

Variants don't occur in isolation, but on a context of sequences



Mutational load

Experimental data: Most fitness effects are deleterious



Mutational load

Viruses have high mutation rate and large populations

$$N\mu \gg 1$$

At least one mutation at every site will occur every generation

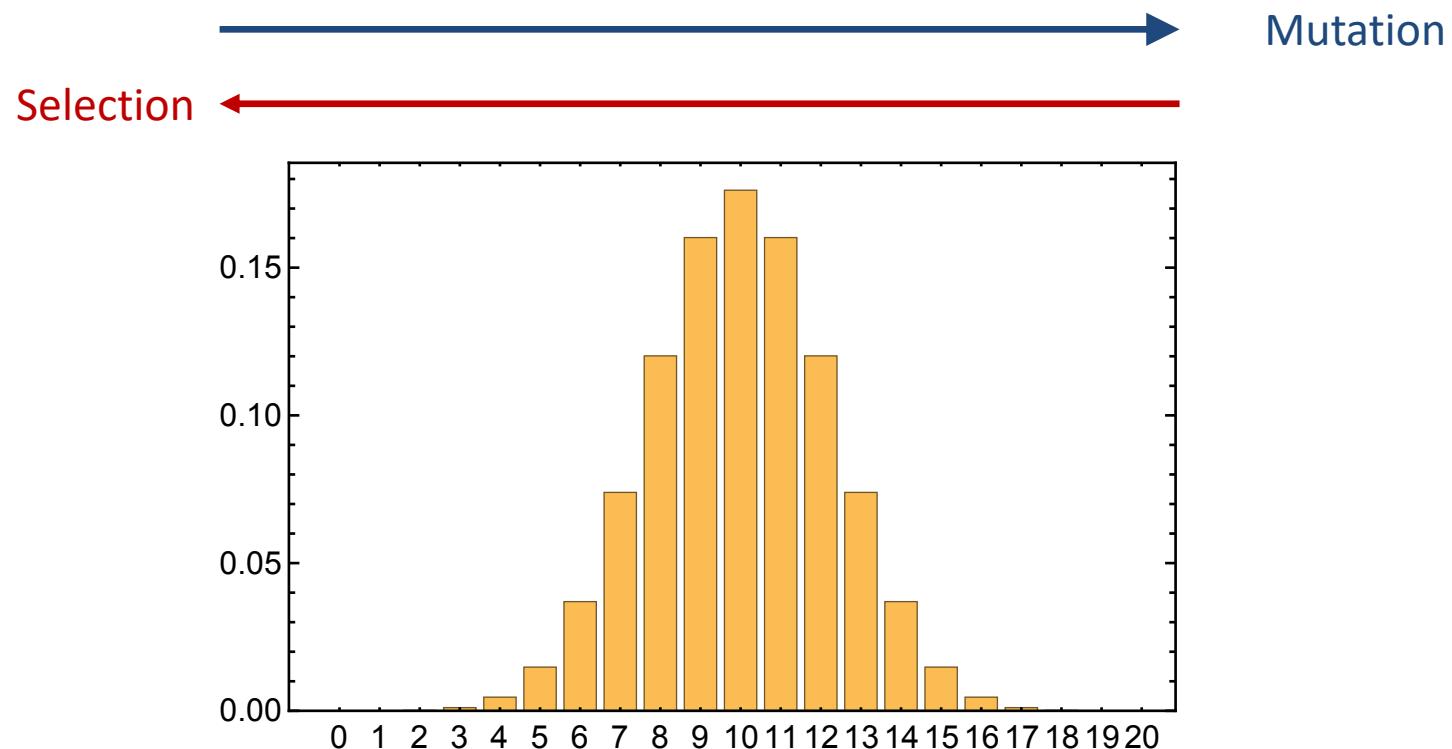
Therefore, nearly all sites in the genome will be polymorphic

Mutational load

Mutation-selection balance:

Variants are created by mutation and removed by selection

On average, viruses carry some number of deleterious variants



Diversion : HIV mutation + selection rates

Mutation-selection balance in HIV:

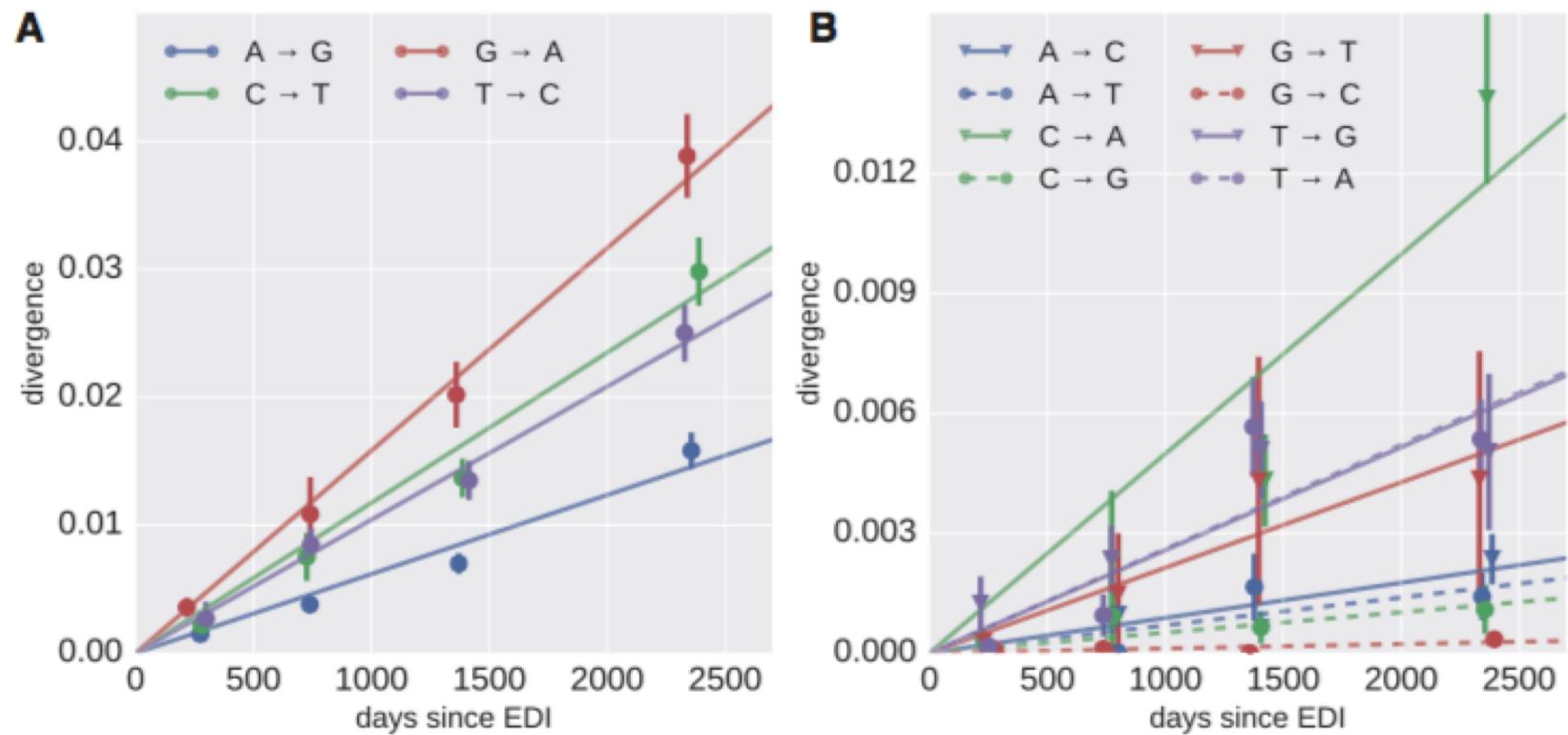
Mean allele frequencies:

Neutral case: $\langle q \rangle = \mu t$

With fitness cost s : $\langle q \rangle = \frac{\mu}{s} (1 - e^{-st})$

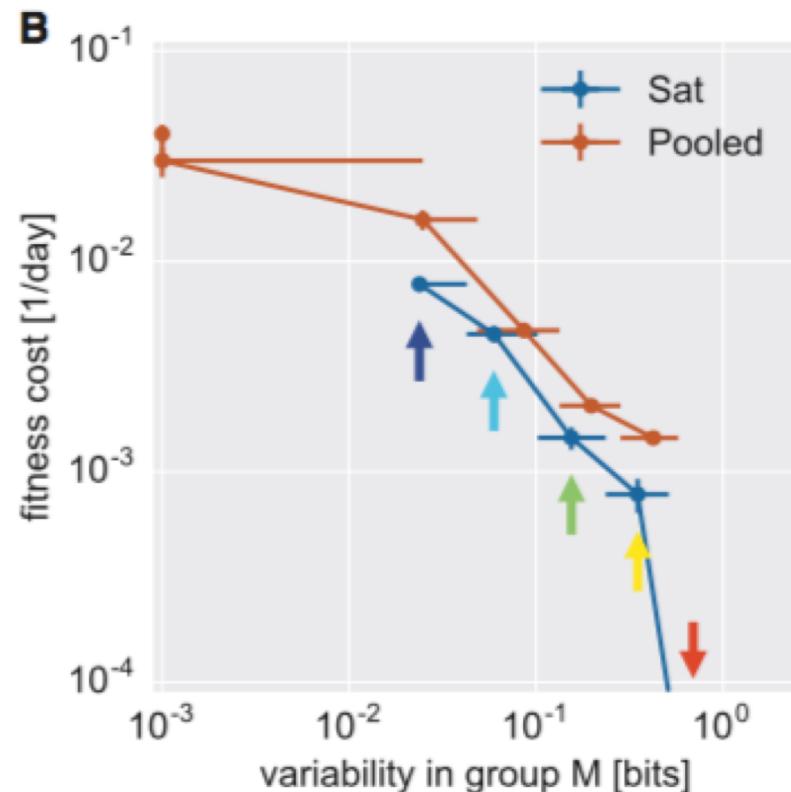
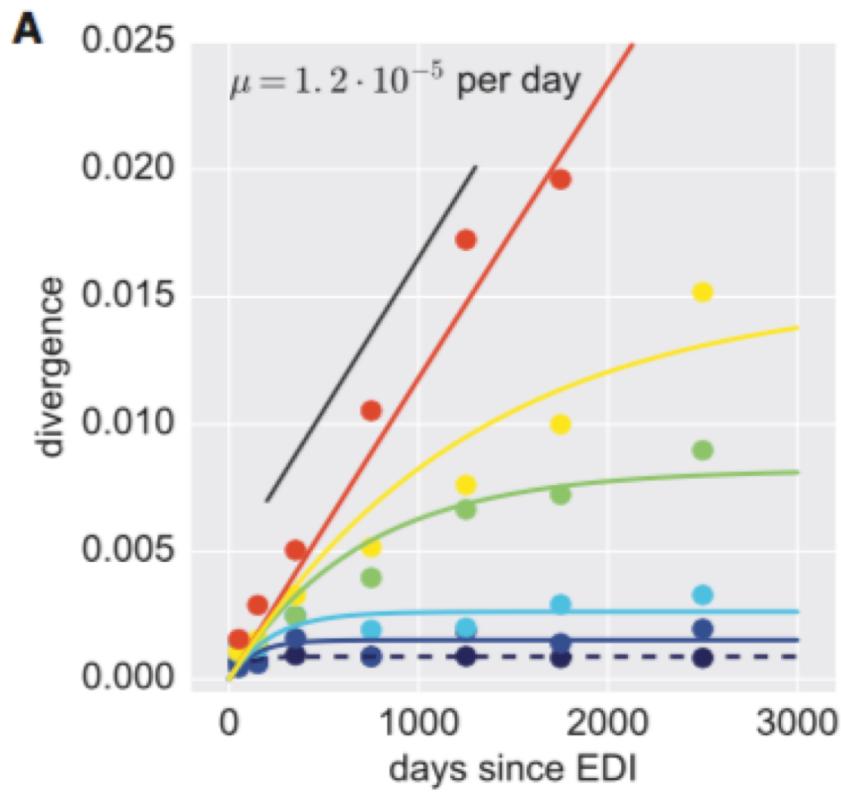
Diversion : HIV mutation + selection rates

Mutation rates in within-host HIV



Diversion : HIV mutation + selection rates

Selection in within-host HIV: Categories of mutations

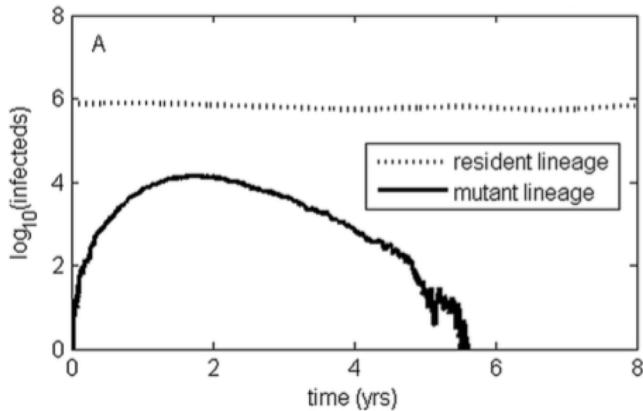


Mutational load

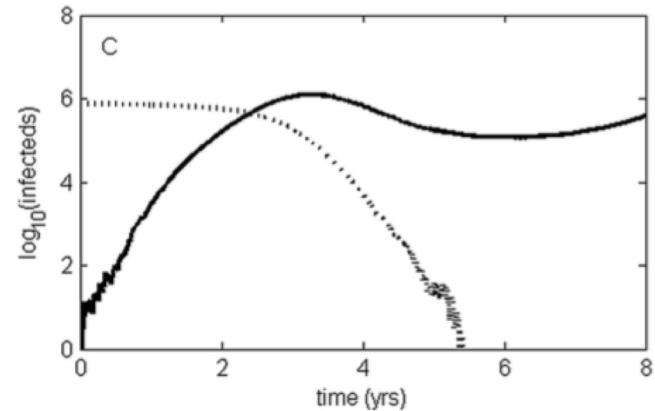
Fate of beneficial mutations

Good background

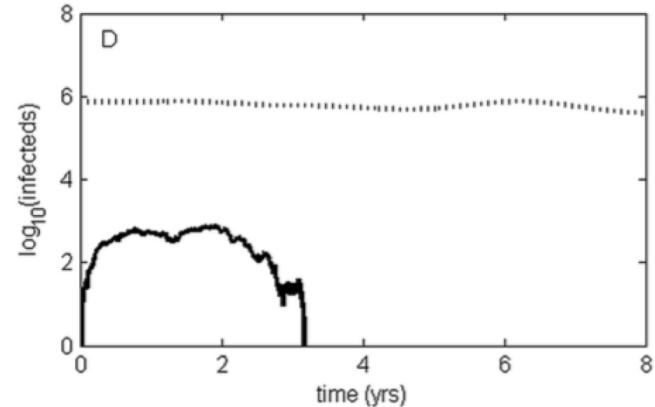
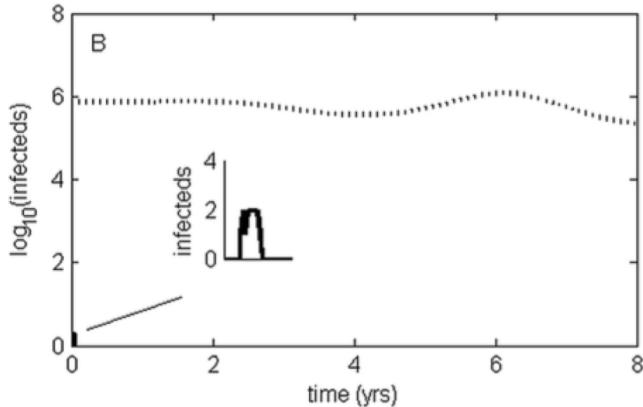
Weak mutation



Strong mutation

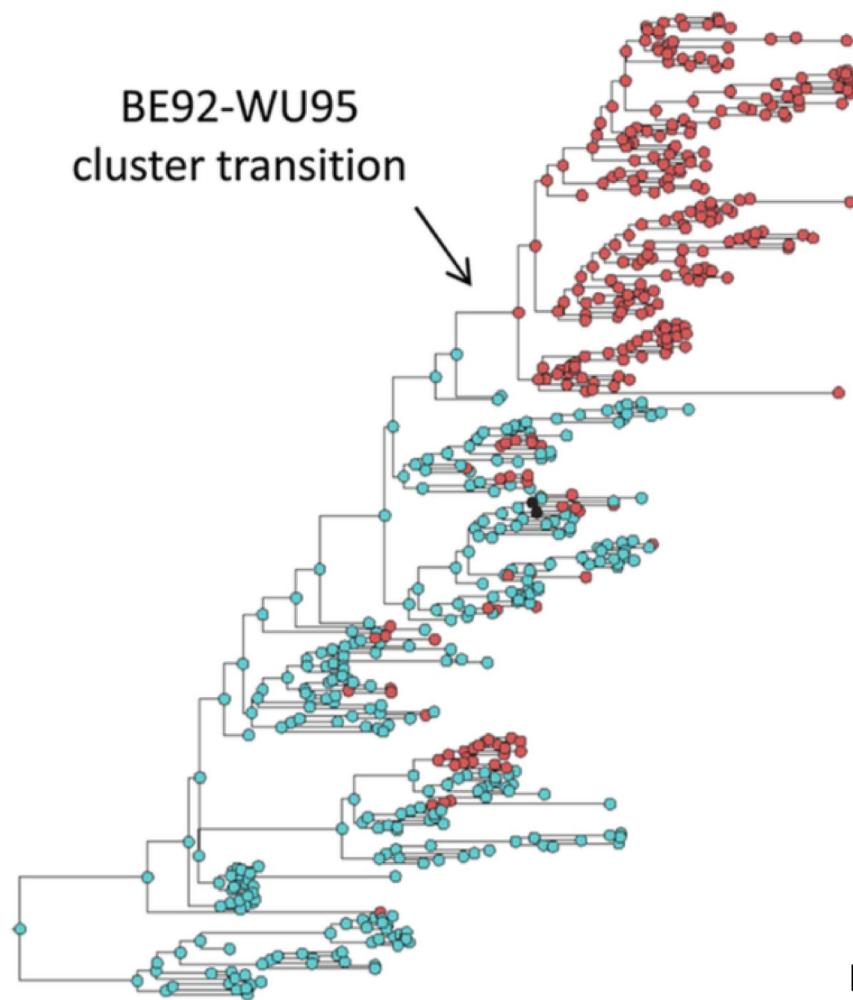


Poor background



Mutational load

Example: N145K mutation

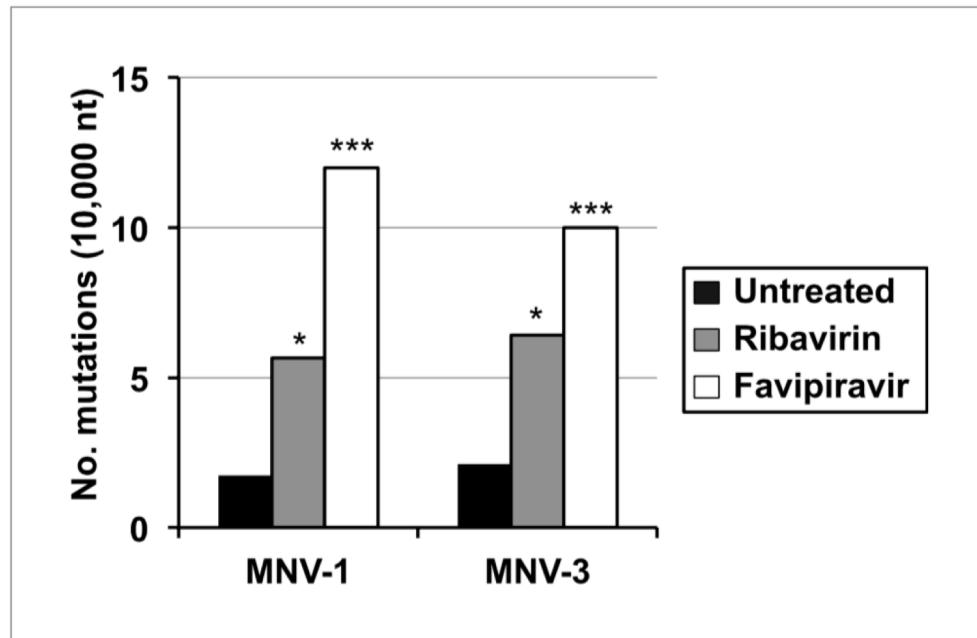


Mutational load in antiviral therapy

Antiviral drugs target polymerase. Affect viral replication

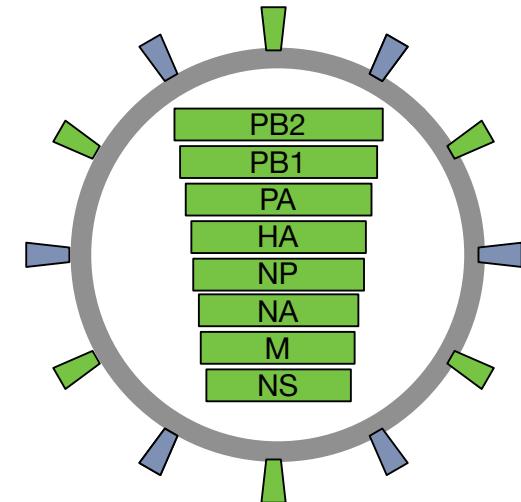
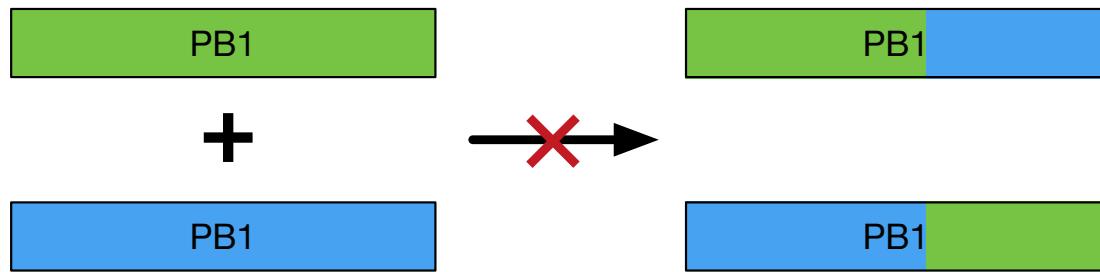
Amantadine: Block proton channel

Favipiravir: Increase viral mutation rate

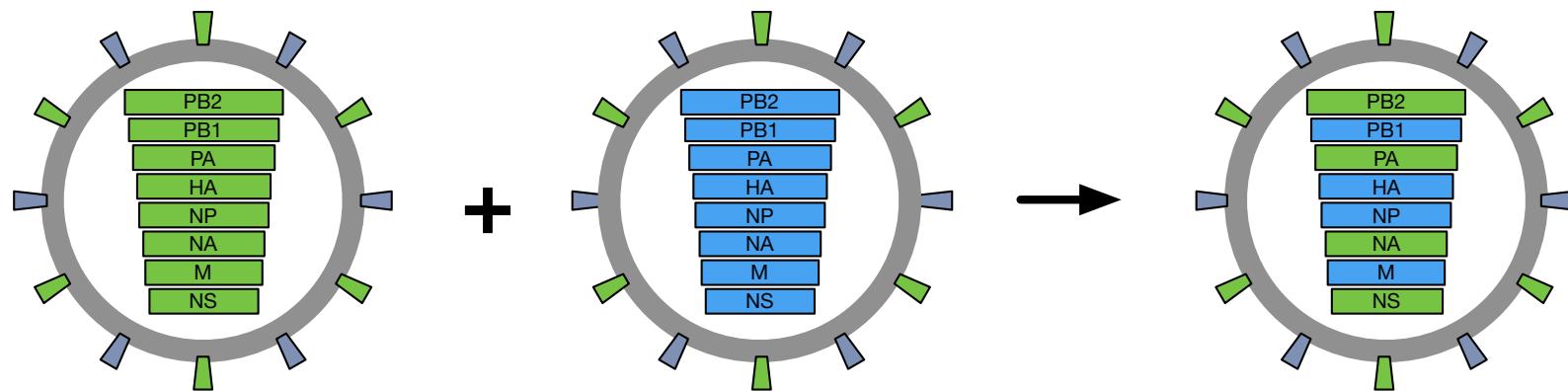


Adaptive immune response

Strain-specific



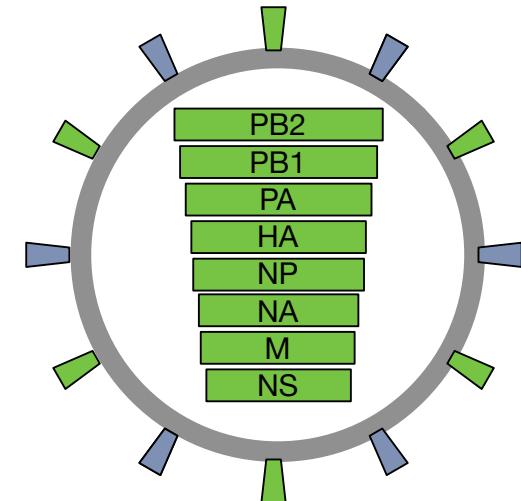
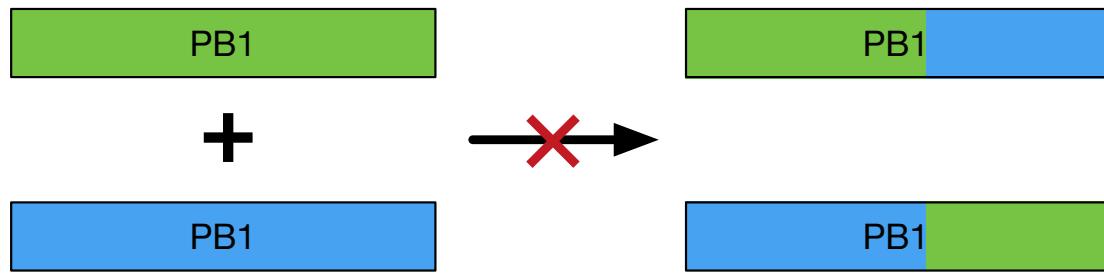
Rapid reassortment between segments



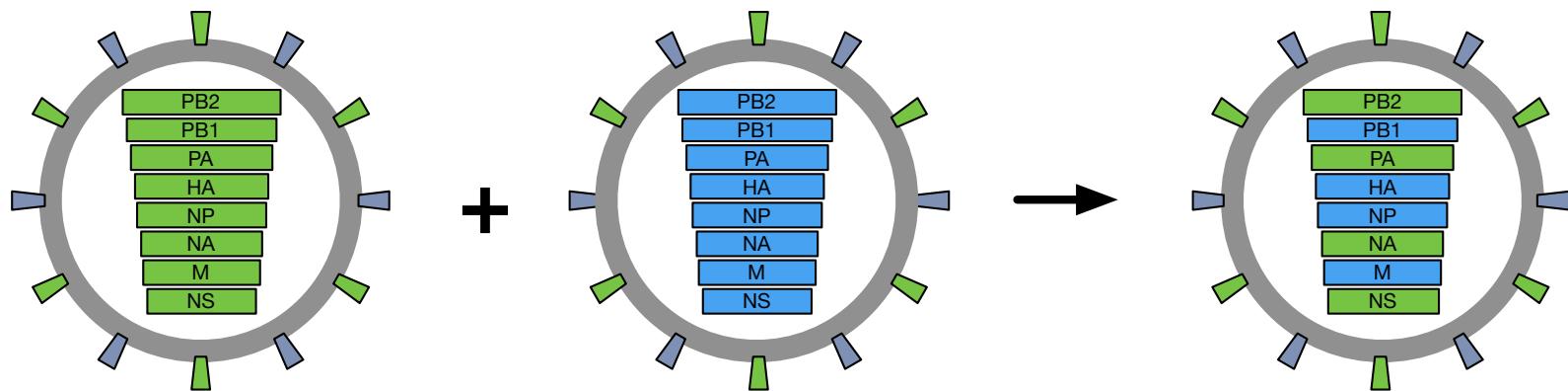
High mutation rate: Between 10^{-5} and 10^{-4} per base per generation

Influenza dynamics

Lack of recombination within segments



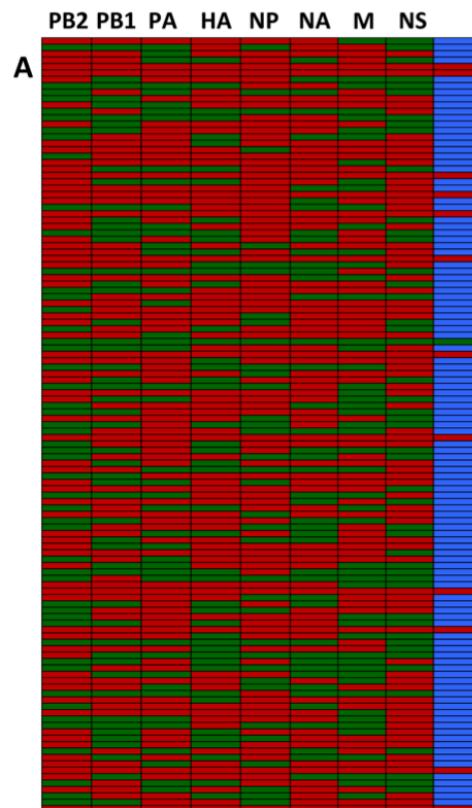
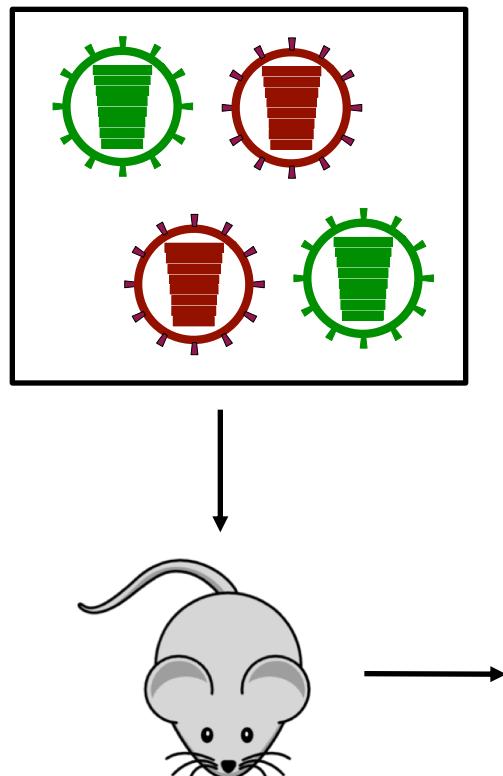
Rapid reassortment between segments



High mutation rate: Between 10^{-5} and 10^{-4} per base per generation

Evaluating reassortment

Evidence for rapid reassortment from animal experiments



Large input dose

More reassortment
observed at higher dose

N.B. May be different
in human infection

Mutational load

Mutation-selection balance:

Variants are created by mutation and removed by selection

On average, viruses carry some number of deleterious variants

Rate of mutation is proportional to genome length:

Selection for a shorter genome

Mutational load

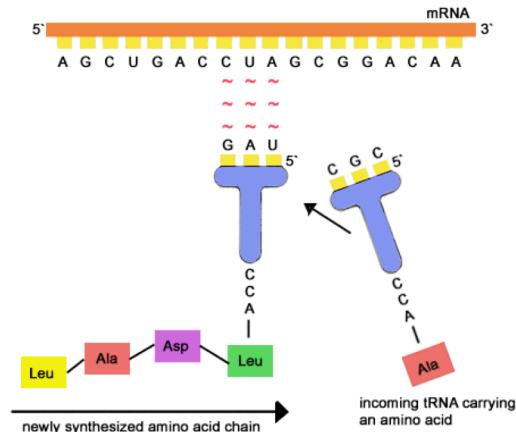
Overlapping reading frames: PB1 segment

RNA: ... CCU UAC AGC CAU GGG ACA GGA ACA GGA UAC ACC ...
 P P Y S H G T G T Y T ...

... CCU UAC AGC **CAU** **G**GG ACA GGA ACA GGA UAC ACC ...
P P Y S H G T G T Y T ...

... C CUU ACA GCC **AUG** GGA CAG GAA CAG GAU ACA CC...
M G Q E Q D T P

Two proteins, PB1 and PB1-F2, produced from the same genetic sequence

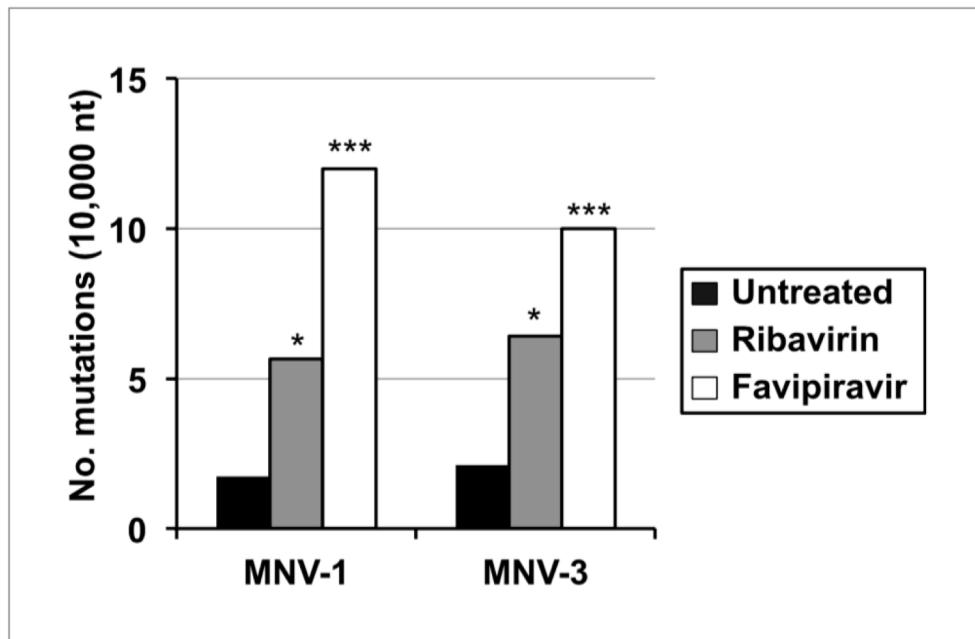


Mutational load

Influenza drugs

Amantadine: Block proton channel

Favipiravir: Increase viral mutation rate

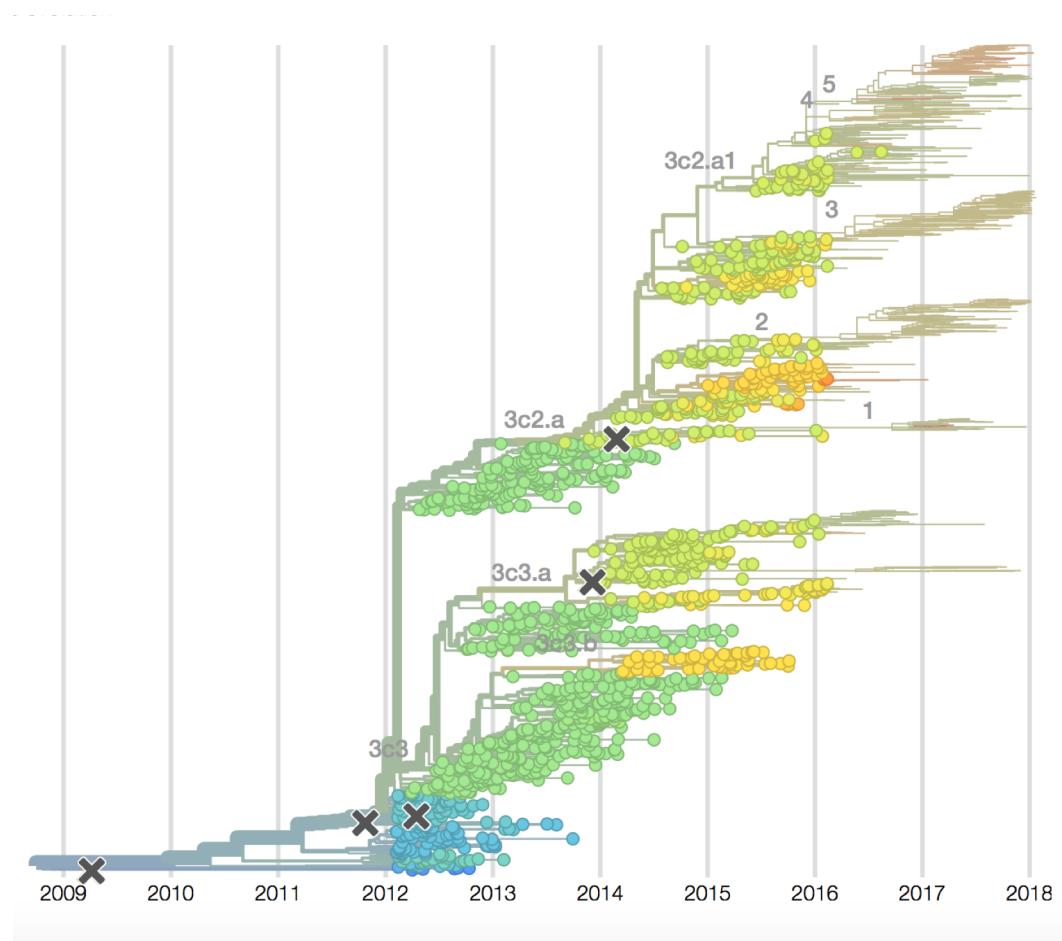


Global influenza evolution



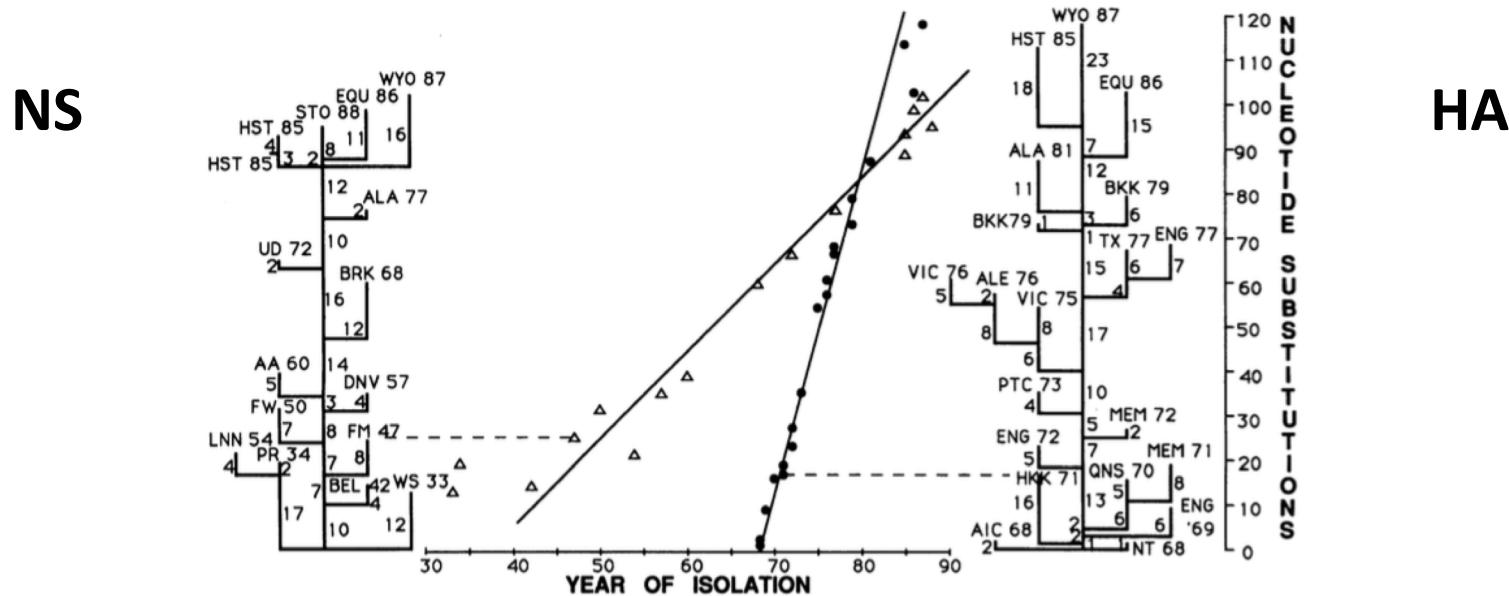
Why does influenza evolve so fast?

Rapid observable evolution : (www.nextflu.org)



Phylogenetic studies of influenza

Identification of Darwinian selection



1. Shape of the tree suggests continual replacement of the strain
- 2: HA evolves faster than NS
- 3: Changes in HA are often at proposed antigenic sites.

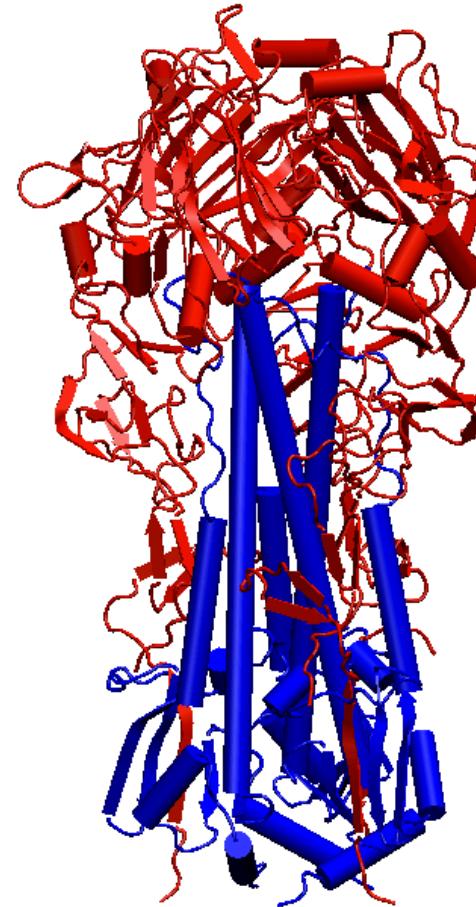
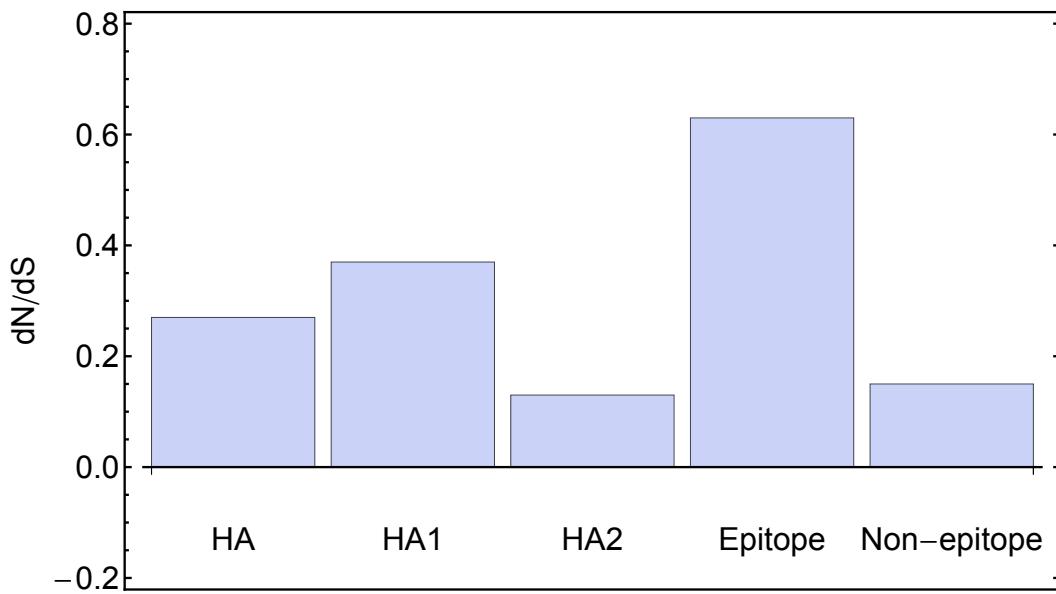
Selection in the influenza virus

Measurement via dN/dS

HA1 : Red

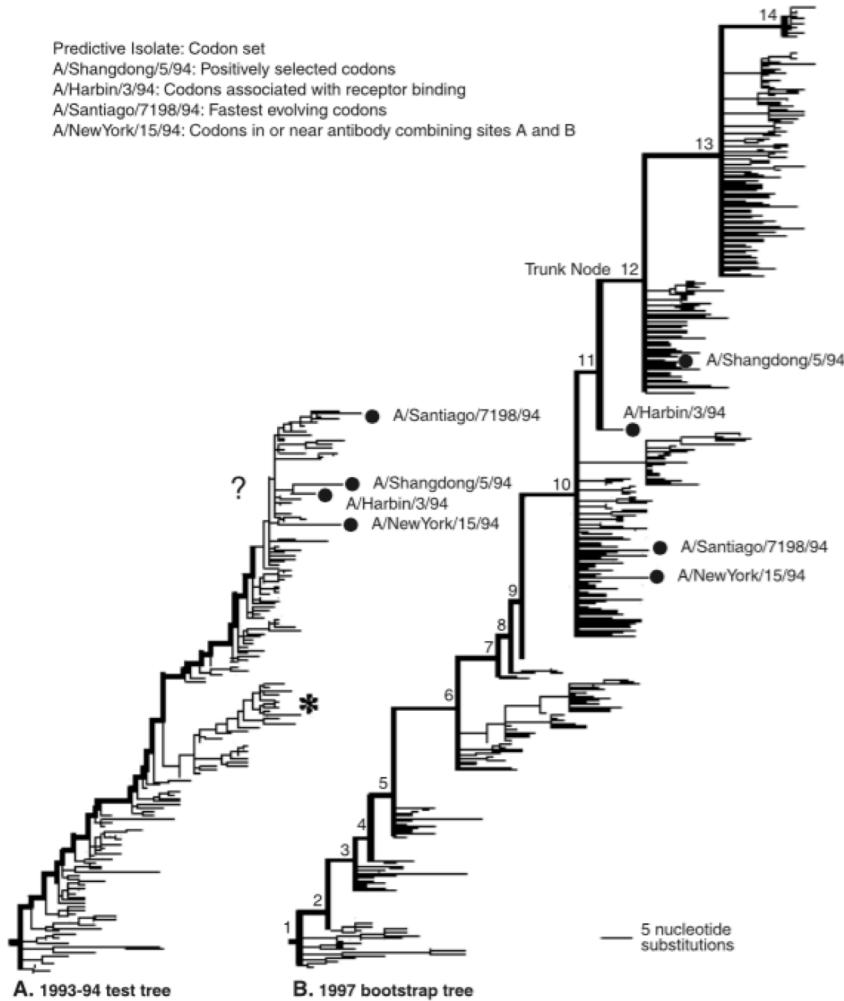
HA2: Blue

Epitope region known to interact with human immune system



Basic prediction method

Sites with the most non-synonymous substitutions



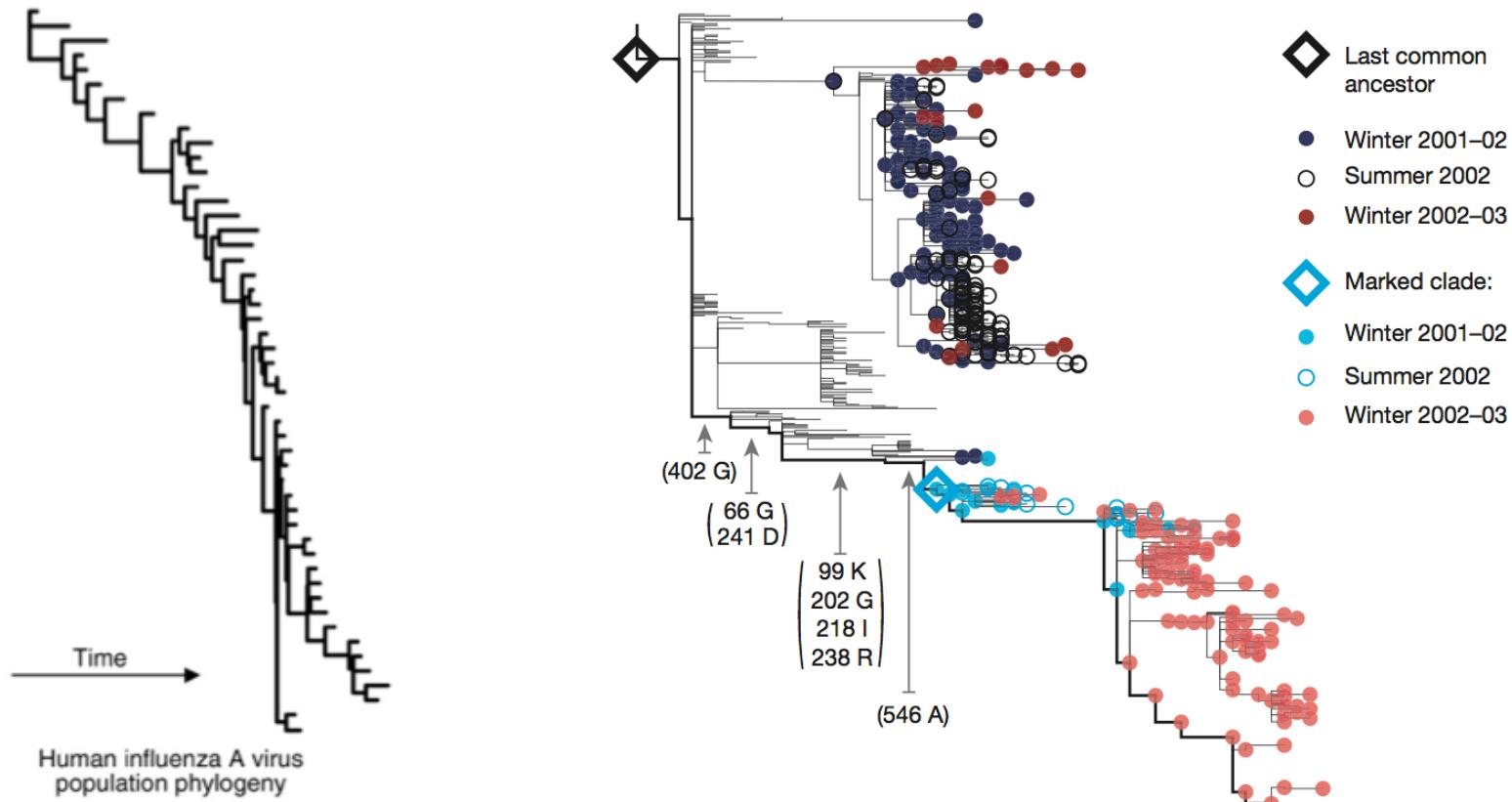
18 sites in the HA genome have the most fixation events

Idea: Find the sequence with the most fixations in these sites

Good model for retrospective prediction

More advanced prediction method

Competition between clades



Can influenza evolution be predicted?

Calculate clade fitness to predict change in frequency

$$X_\nu(t) = \sum_i x_i$$

Clade frequency: Sum of frequencies of strains in a clade

$$\hat{X}_\nu(t+1) = \sum_i x_i \exp(f_i)$$

Predicted clade frequency: proportional to exponential growth by fitness

Mean calculated over multiple phylogenetic trees

Note: Correct inference of fitness implies predictive knowledge of short-term evolution

Can influenza evolution be predicted?

Require a strain-specific fitness function:

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

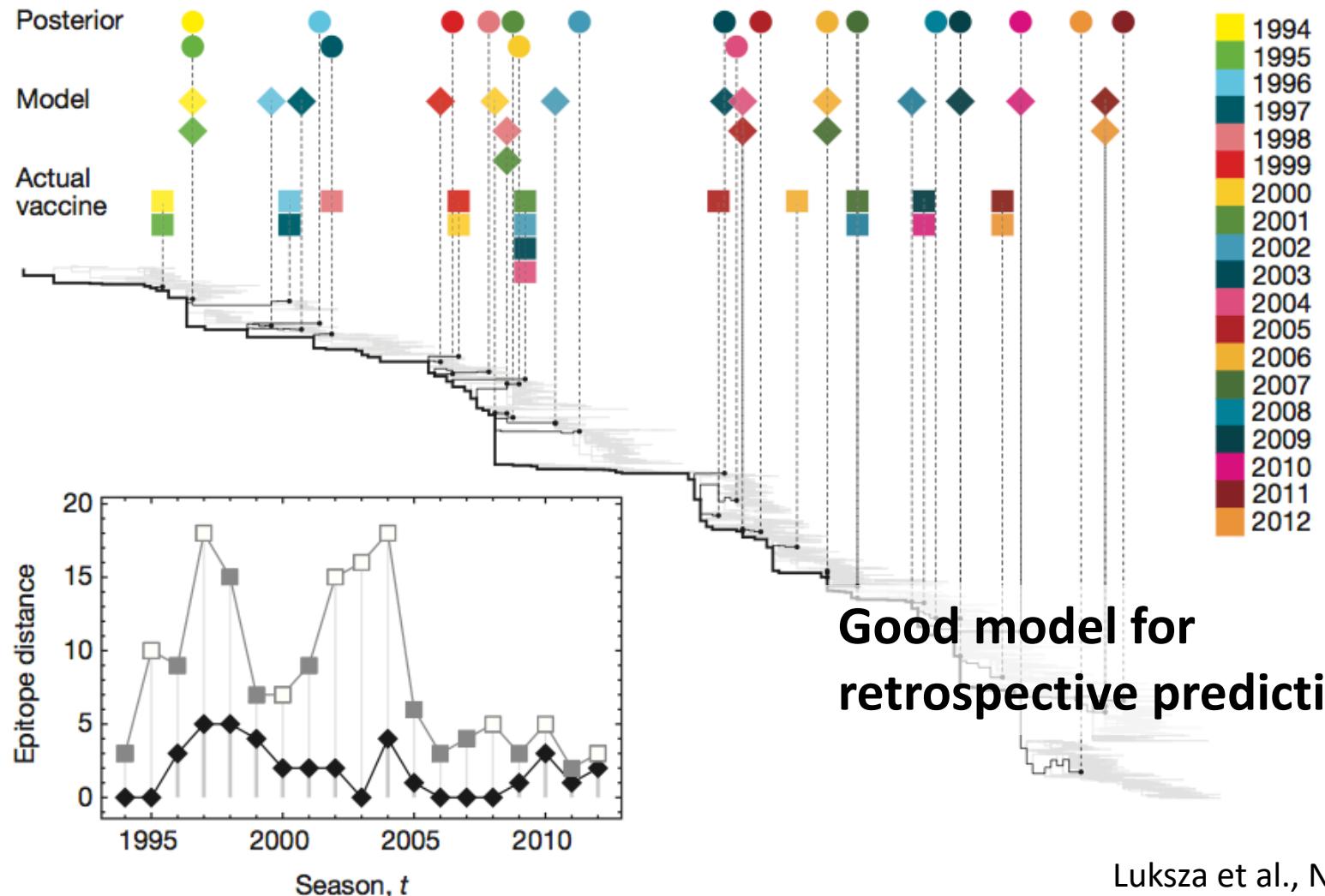
f_0 Base fitness: normalisation

$\mathcal{L}(\mathbf{a}_i)$ Cost of non-synonymous non-epitope mutations

$\mathcal{C}(\mathbf{a}_i, \mathbf{a}_j)$ Cross-immunity: Based upon past existence of strain
Non-synonymous epitope mutations increase distance
and decrease cost of cross-immunity

Can influenza evolution be predicted?

Predicted versus actual vaccine strain



Can influenza evolution be predicted?

General problems:

Comparison with real vaccine strain unfair:

Don't have the 2012 data in 2012...

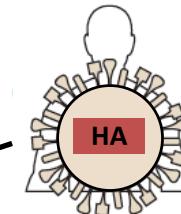
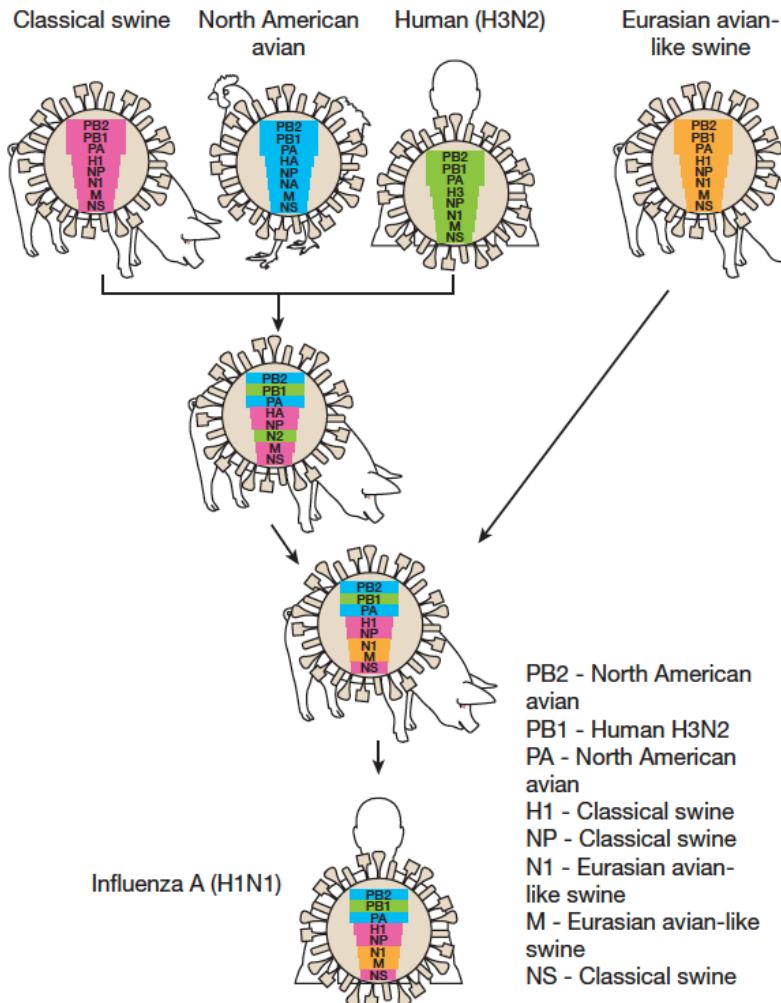
Methods better at retrospective prediction than at predicting the future.

Influenza prediction versus Google DeepMind

Can we predict the next
influenza pandemic?

Reassortment?

Origin of the 2009 pandemic

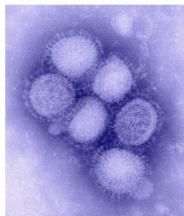
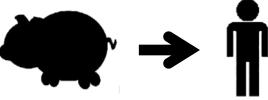
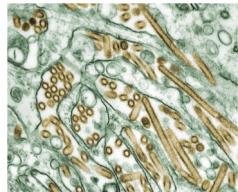


Genes came from multiple species

Multiple reassortant events over time

HA gene of classical swine flu had its origin in the 1918 pandemic:
more elderly people had greater immunity

Or just mutation/selection?

Strain	Transmission	Mortality
H1N1	  → 	500,000 infections (UK 2009) Death rate: 1 in 4000
H5N1	  → 	700 infections (World 2003-14) Death rate: 1 in 2
H7N9	  → 	775 infections (World 2013-16) Death rate: 1 in 2.5

Key differential: Mode of transmission

Experimental evolution

Take a highly pathogenic, non-transmissible virus...

Ferrets infected with mutant form of the virus kept in cages a short distance apart

Select for more transmissible viruses across multiple generations

With five mutations, the virus became airborne-transmissible: suggests that a pandemic may be fairly likely



Response to the experiments

Senior author Ron Fouchier, "is so prepared for a media storm that he has hired an advisor to help him work on a communication strategy"

"Probably one of the most dangerous viruses you can make"

Ron Fouchier

"Terror fear as scientists DELIBERATELY create 'Armageddon' bird flu virus in lab", *Daily Mail*

"I can't think of another pathogenic organism that is as scary as this one",

Paul Keim, chairman of the U.S National Science Advisory Board for Biosecurity

Moratorium on experiments, and on funding for experiments

Can we do anything about it?

Preventing a pandemic is difficult...

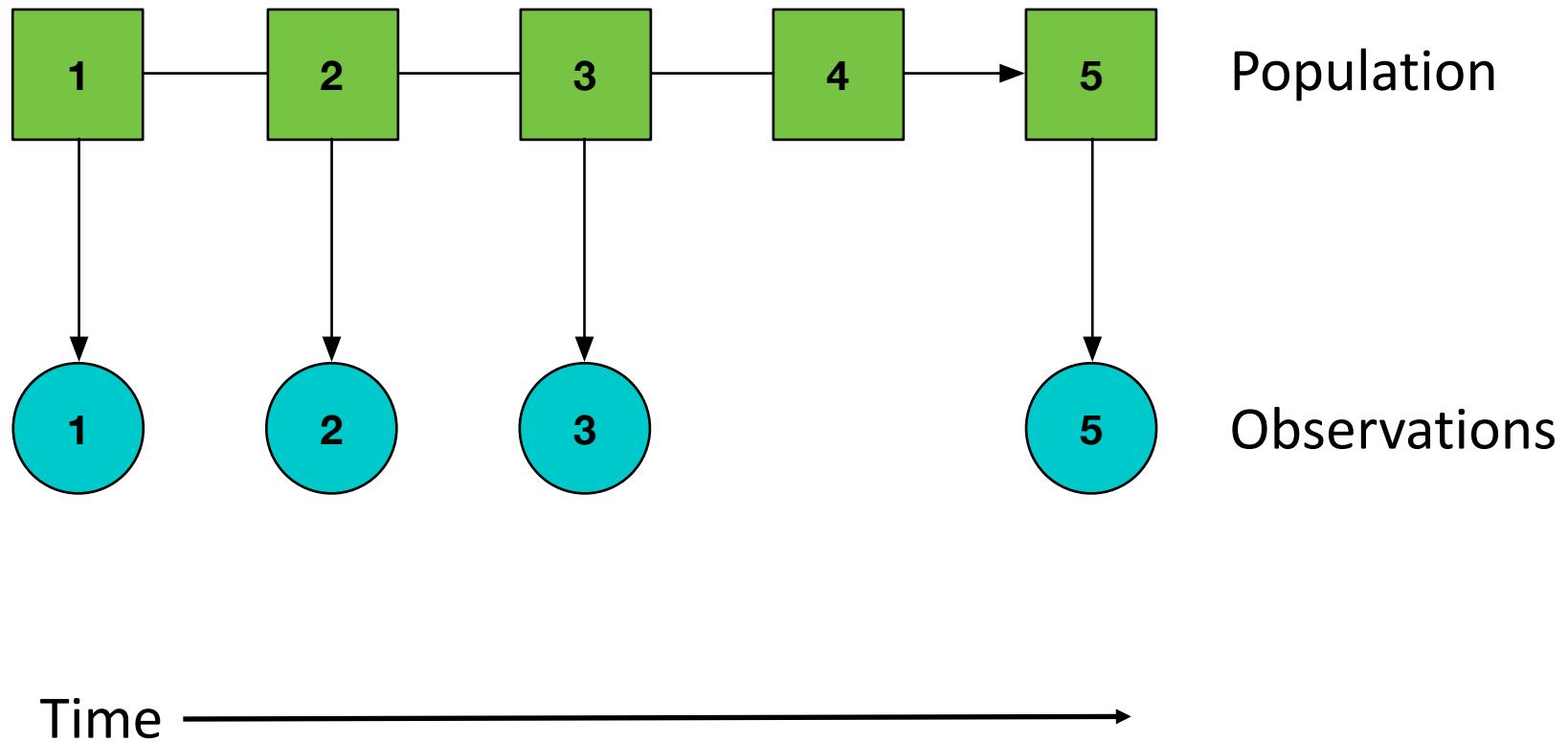
Strategies for containing an emerging influenza pandemic in Southeast Asia

Neil M. Ferguson^{1,2}, Derek A.T. Cummings³, Simon Cauchemez⁴, Christophe Fraser¹, Steven Riley⁵, Aronrag Meeyai¹, Sopon Iamsirithaworn⁶ & Donald S. Burke³

Strategies for mitigating an influenza pandemic

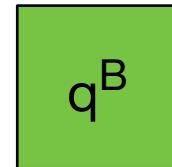
Neil M. Ferguson¹, Derek A. T. Cummings², Christophe Fraser¹, James C. Cajka³, Philip C. Cooley³ & Donald S. Burke²

Modelling influenza evolution

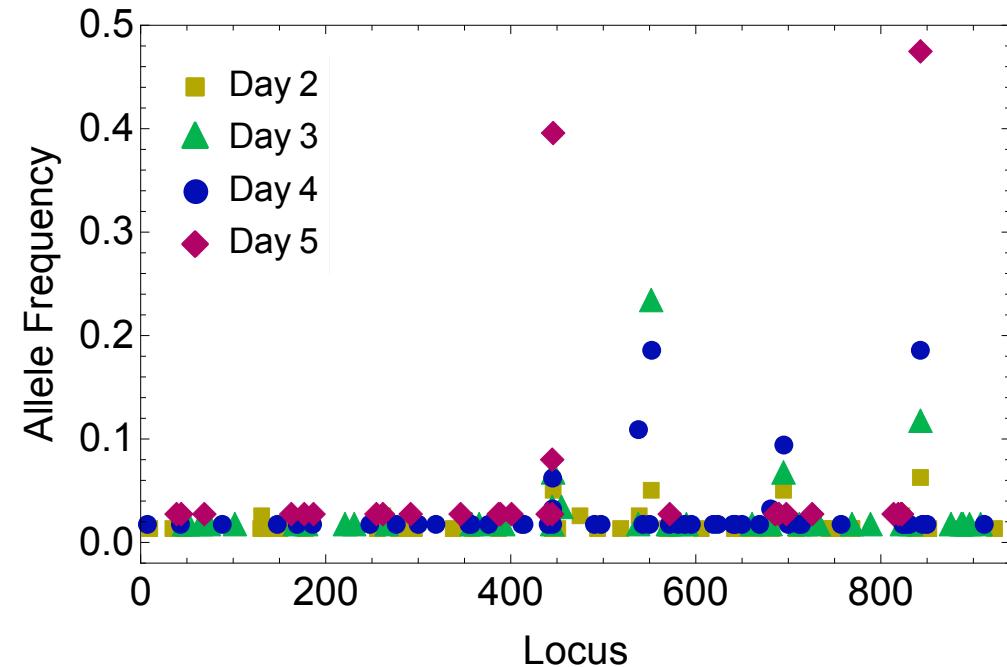
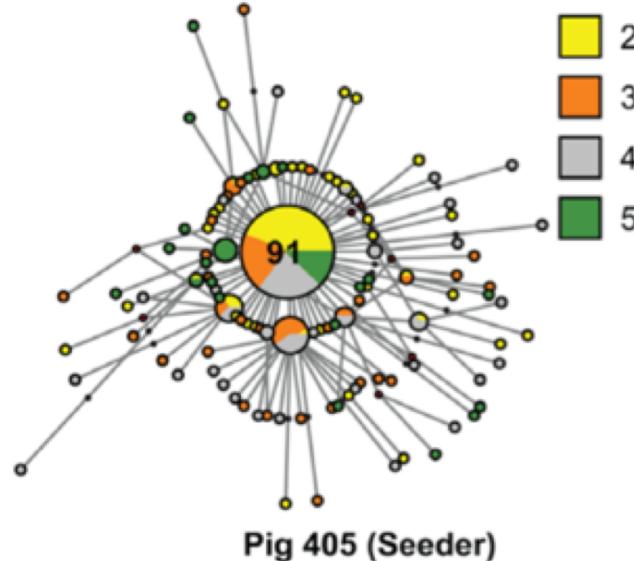


What do we mean by a population?

Population contains viruses



Genome space is large (c. 10^{8000} possible sequences)



Few variants exist at substantial frequencies

What do we mean by a population?

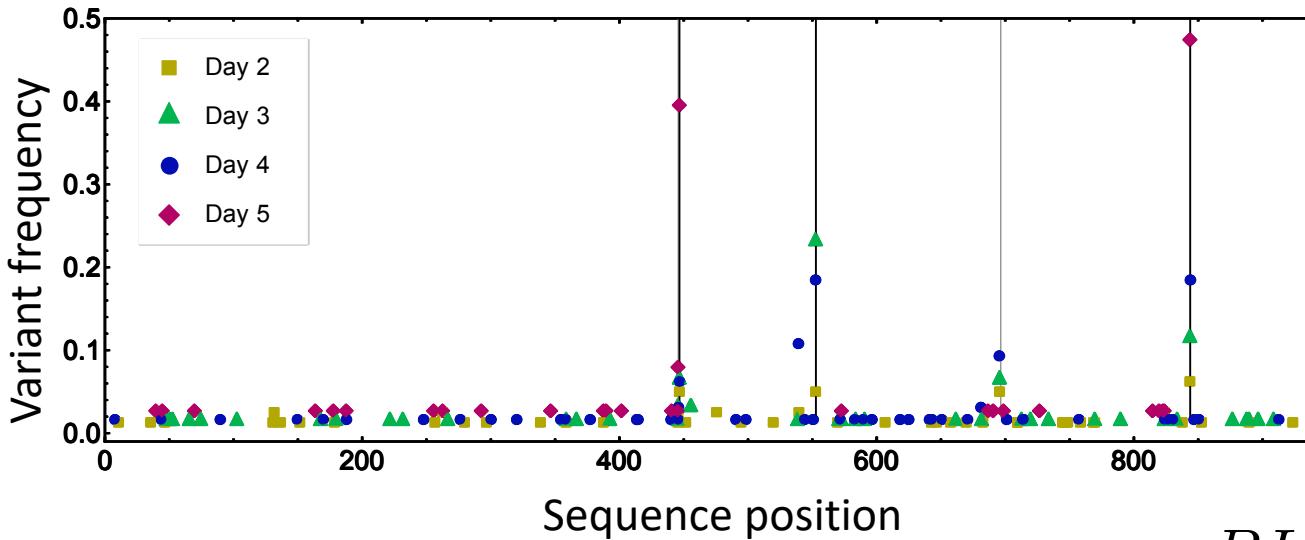
Define haplotypes at a reduced set of positions

q^B

ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGC~~G~~TCAAGG
ACGGCTT**A**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCT**G**TTCACTTACAGTGC~~G~~TCAAGG
ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCT**G**TTCACTTACAGTGC~~G~~TCAAGG
ACGGCTT**A**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCT**G**TTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCTTTCACTTACAGTGGGTCAAGG
ACGGCTT**C**GAGCTCGATCAGCT**G**TTCACTTACAGTGGGTCAAGG

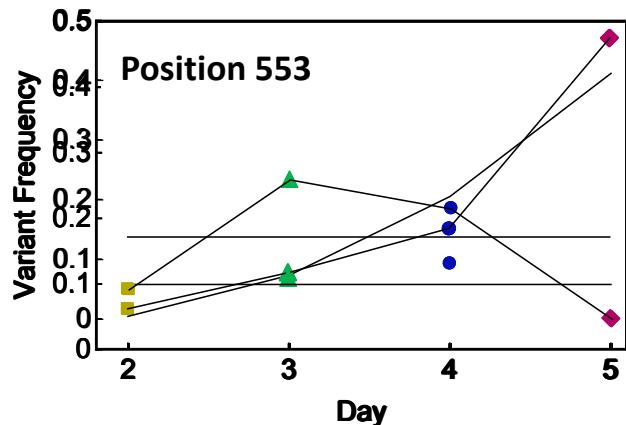
Representative haplotypes

Genetic variants in a single animal



Statistical model

$$BIC = -2L + k \log n$$



447

844

853

Constant selection

Variable selection

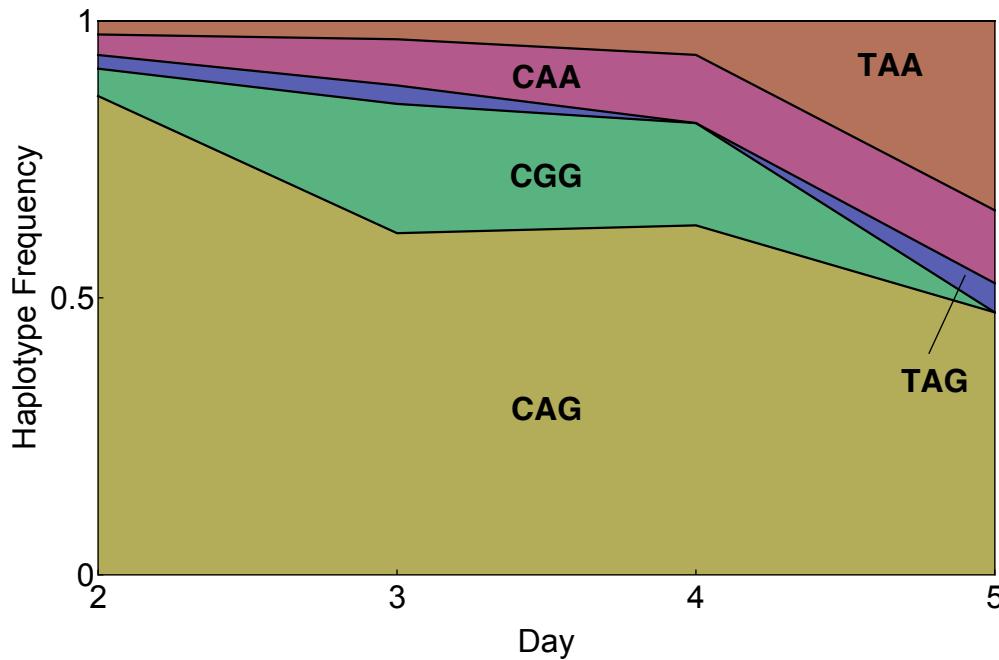
Non-constant selection

parameters

observations

Representative haplotypes

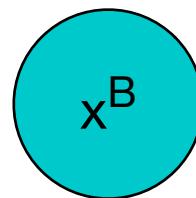
Representative haplotypes give intuitive insight into the data



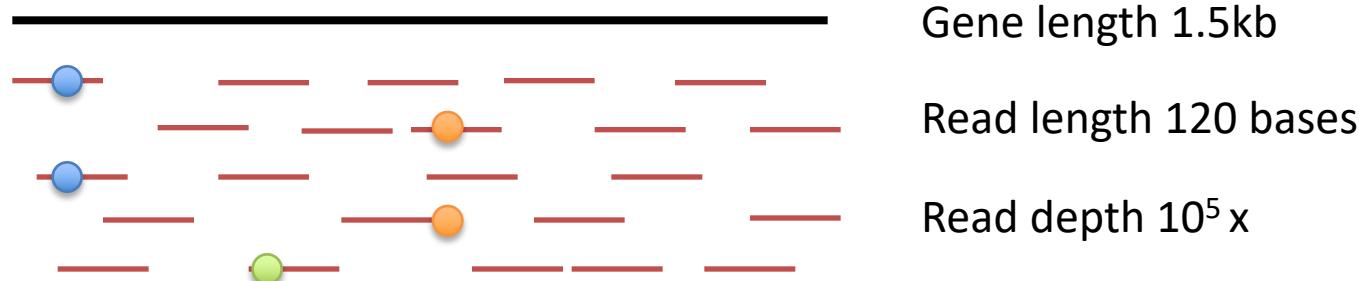
Haplotype Key		
Locus		
447	553	844
T	A	A
C	A	A
T	A	G
C	G	G
C	A	G

What do we mean by observations?

Capillary sequence data

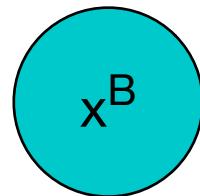


Next-generation sequence data



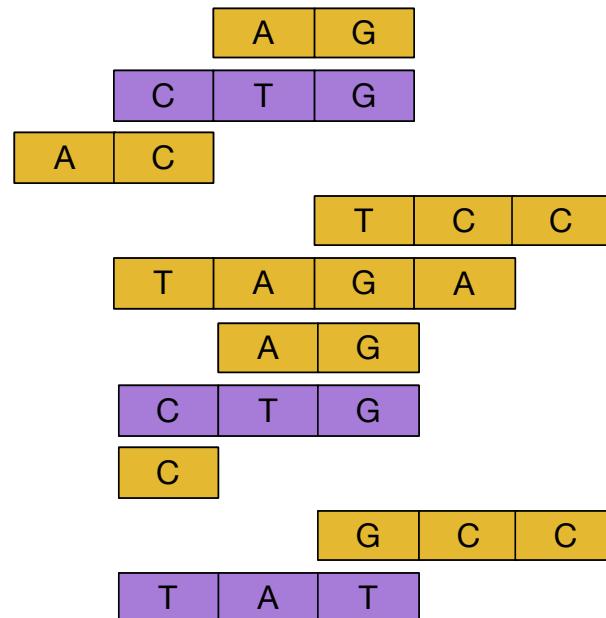
What do we mean by observations?

Observations via short reads



Categorise by variants described

Loci	4	83	177	203	375	600	...
------	---	----	-----	-----	-----	-----	-----

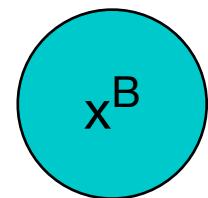


Counts of partial haplotypes

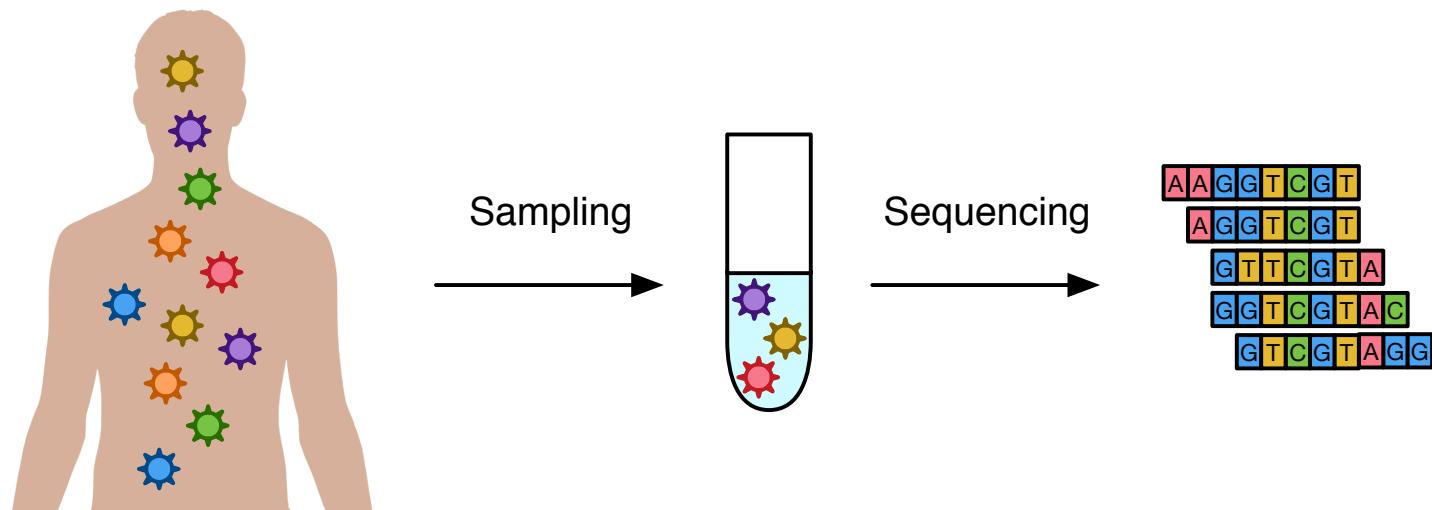
C T G	235
C A T	72
T A T	8

What do we mean by observations?

Noise in sequence data

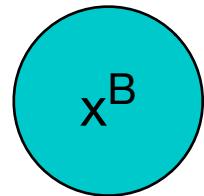


Incomplete sampling, inaccurate sequencing

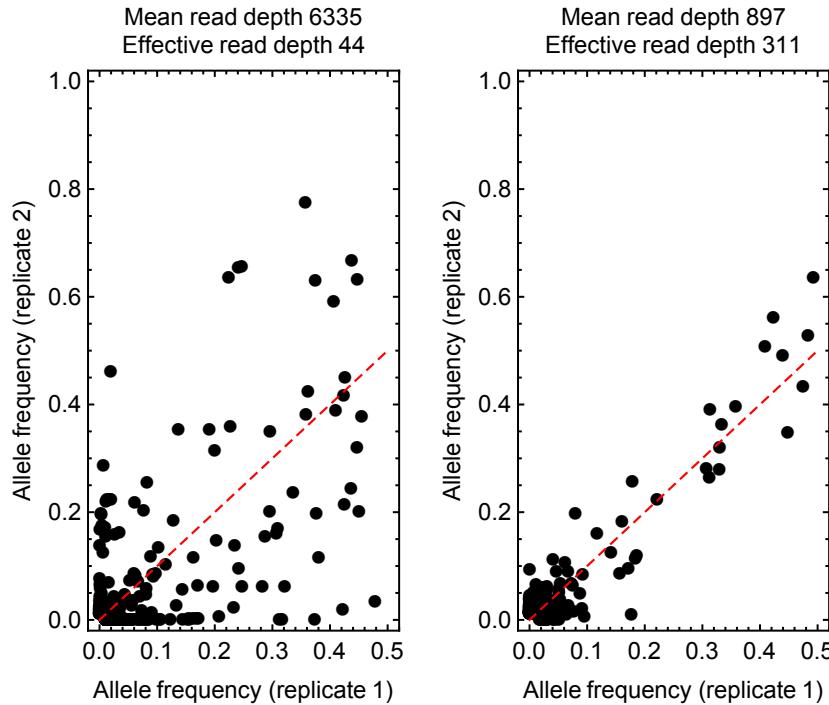


What do we mean by observations?

Noise in sequence data



Estimate the extent of variance from replicate data



Multinomial data frequencies p_i

Dirichlet multinomial model $\alpha_i = C p_i$

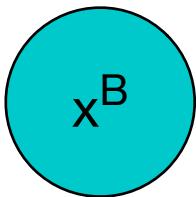
Effective depth of sampling

$$n_i^e = \frac{n_i(1+C)}{n_i + C}$$

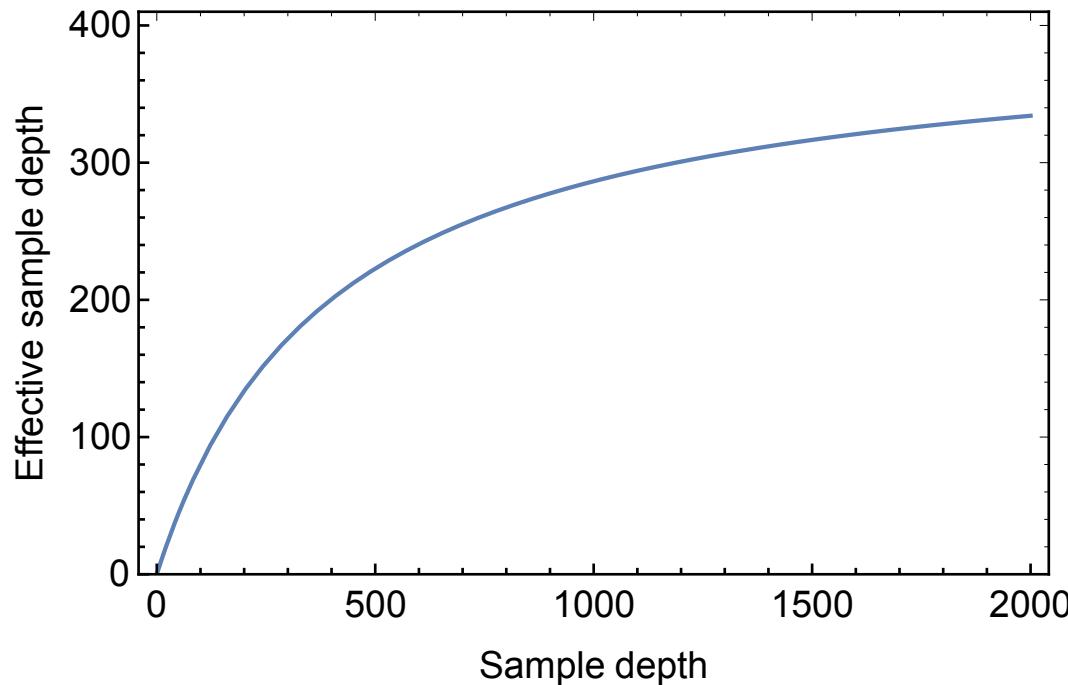
For read depth n_i

What do we mean by observations?

Noise in sequence data



Example: effective depth of sampling: $C = 400$



What do we mean by observations?

Reconstruct potential full haplotypes from partial haplotypes

Short read data

A	C	G	-	-
---	---	---	---	---

-	T	G	G	-
---	---	---	---	---

-	C	G	C	-
---	---	---	---	---

-	-	-	C	A
---	---	---	---	---

T	C	-	-	-
---	---	---	---	---

-	-	-	C	T
---	---	---	---	---

-	-	-	G	T
---	---	---	---	---

-	-	A	-	-
---	---	---	---	---

A	C	A	-	-
---	---	---	---	---

-	C	G	C	-
---	---	---	---	---



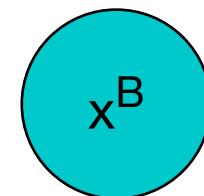
Haplotypes

A	C	G	C	T
---	---	---	---	---

T	C	G	C	T
---	---	---	---	---

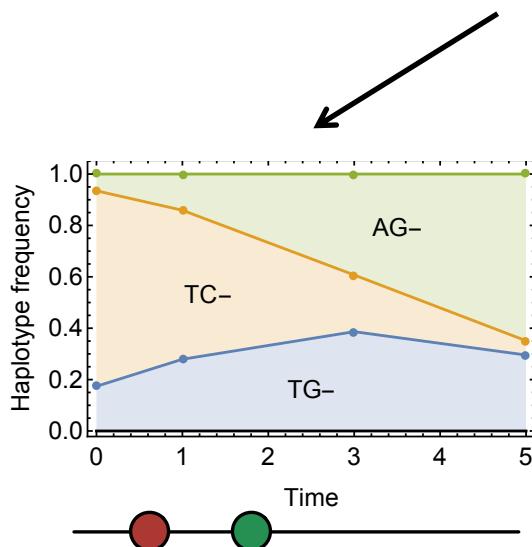
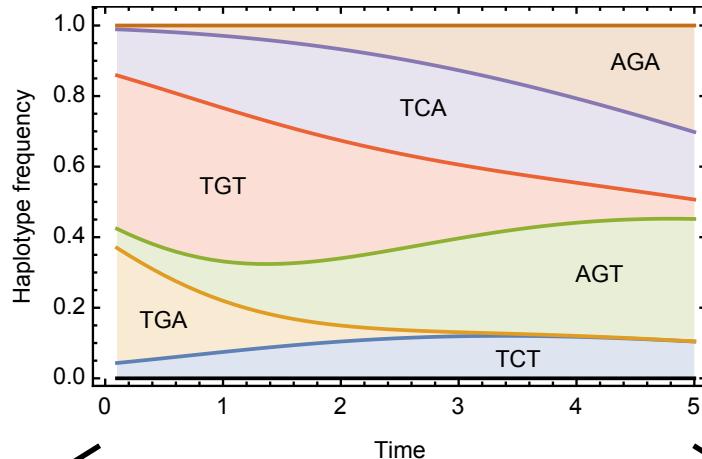
A	T	G	G	T
---	---	---	---	---

A	C	A	C	A
---	---	---	---	---

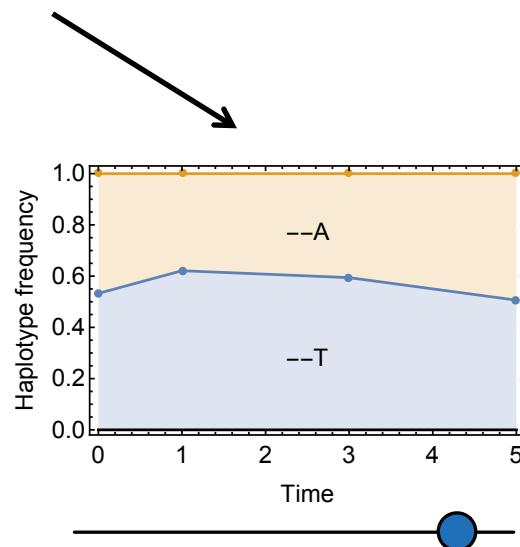


Overall model

Fit a full sequence model to the partial sequence data

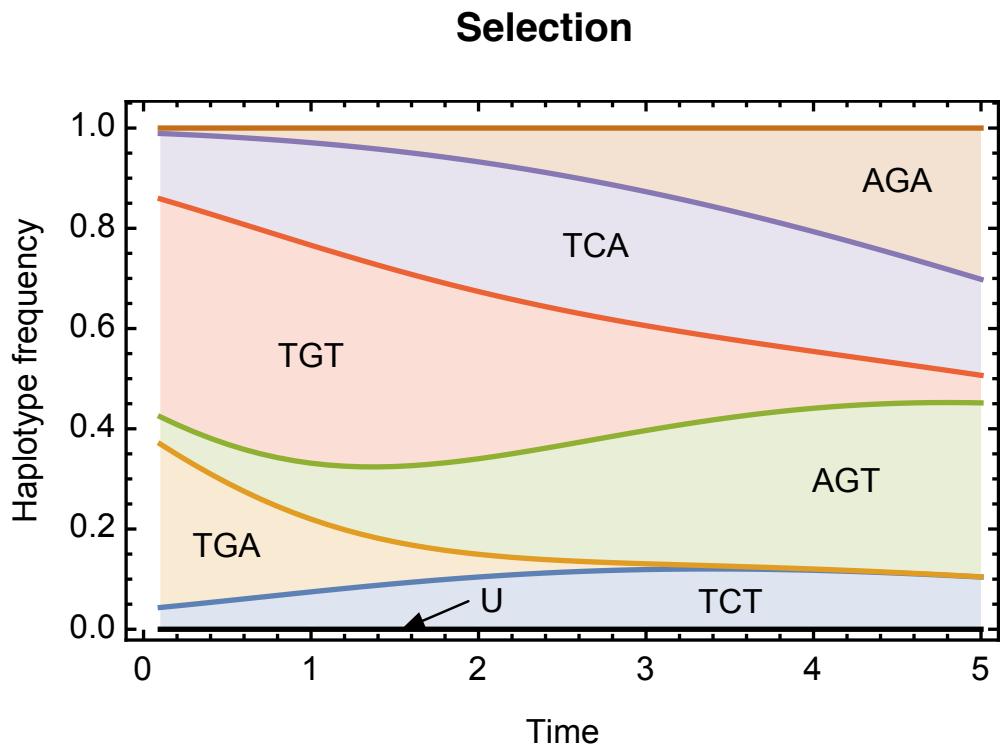
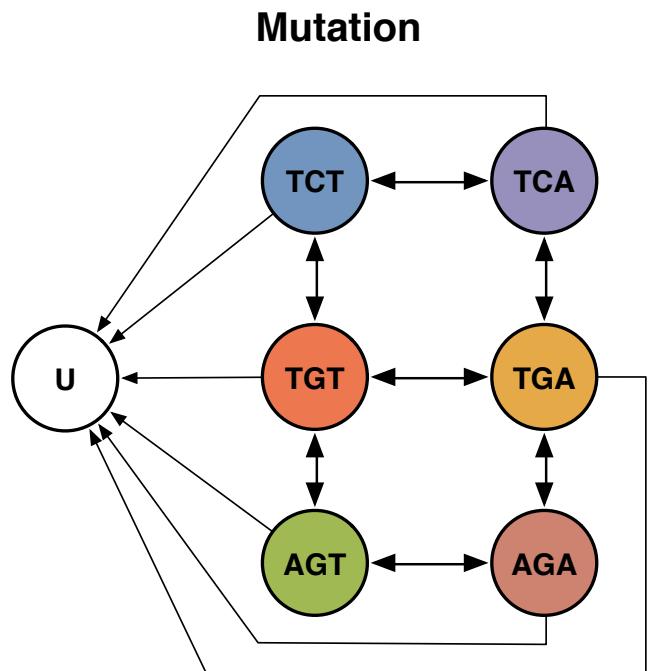


Observations



Constructing the model

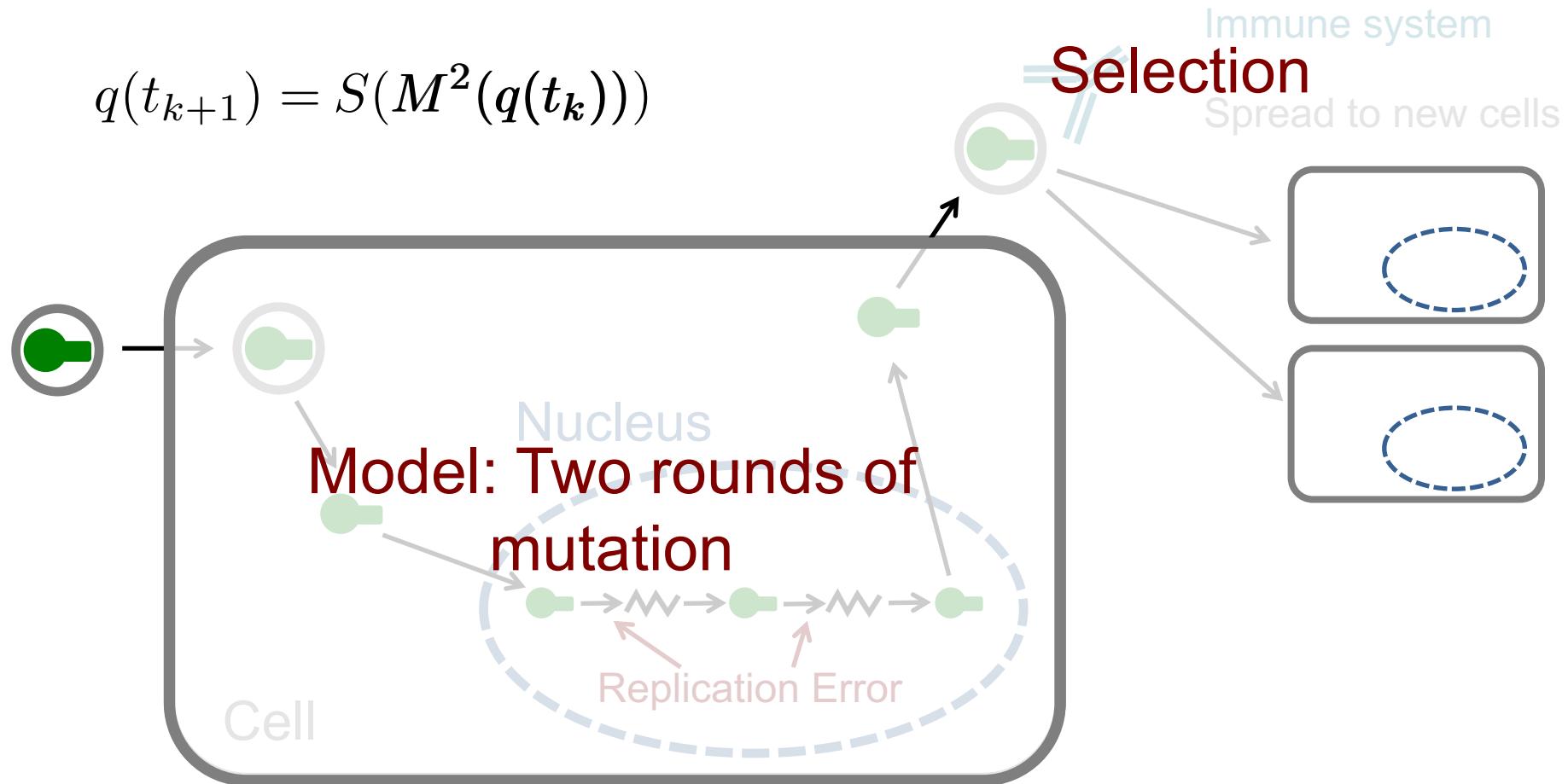
Effects of selection and mutation



Model of viral evolution

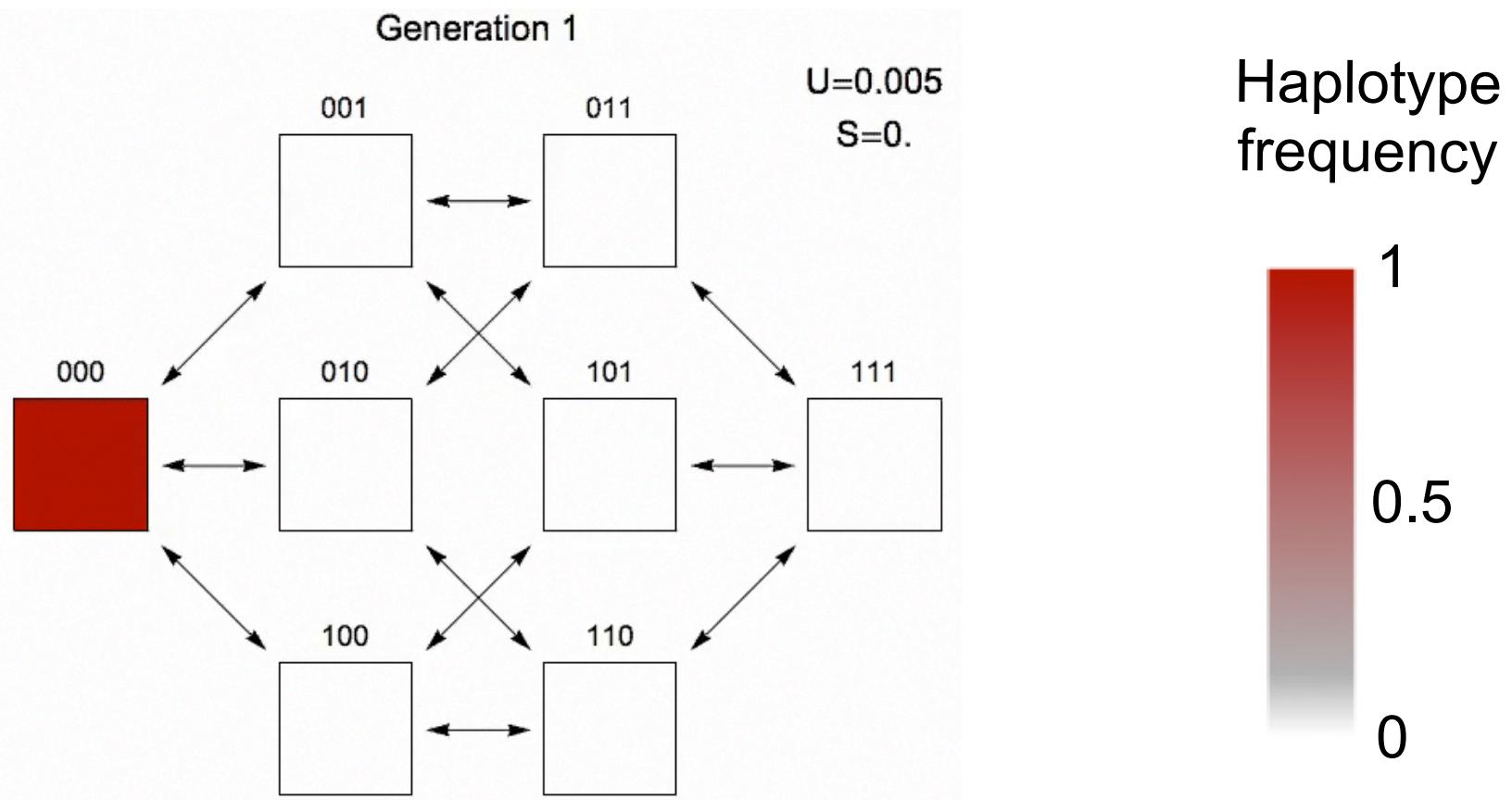
Selection and mutation occur within cells

$$q(t_{k+1}) = S(M^2(q(t_k)))$$



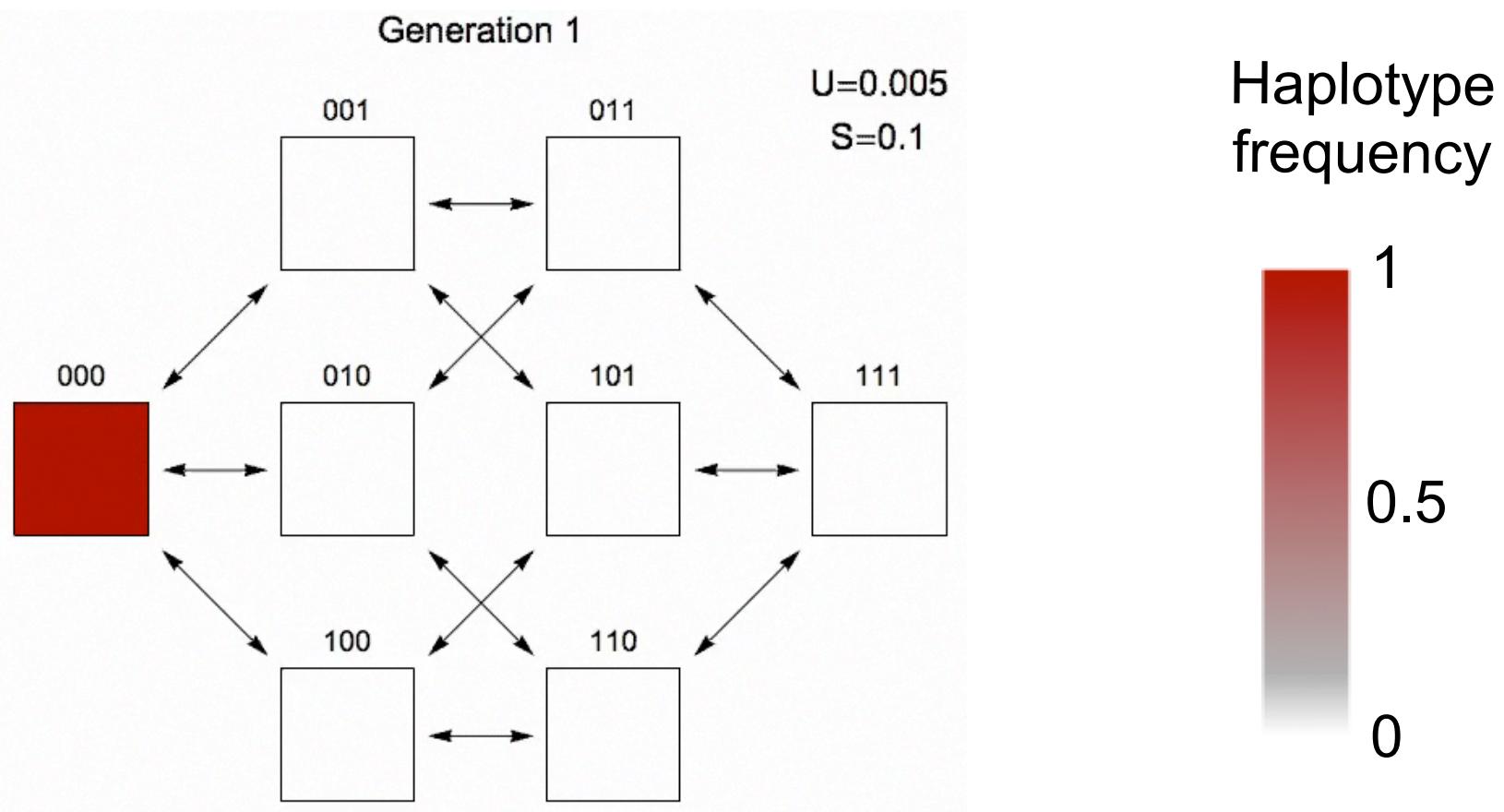
Model of viral evolution

Mutation + selection model: three loci, two alleles



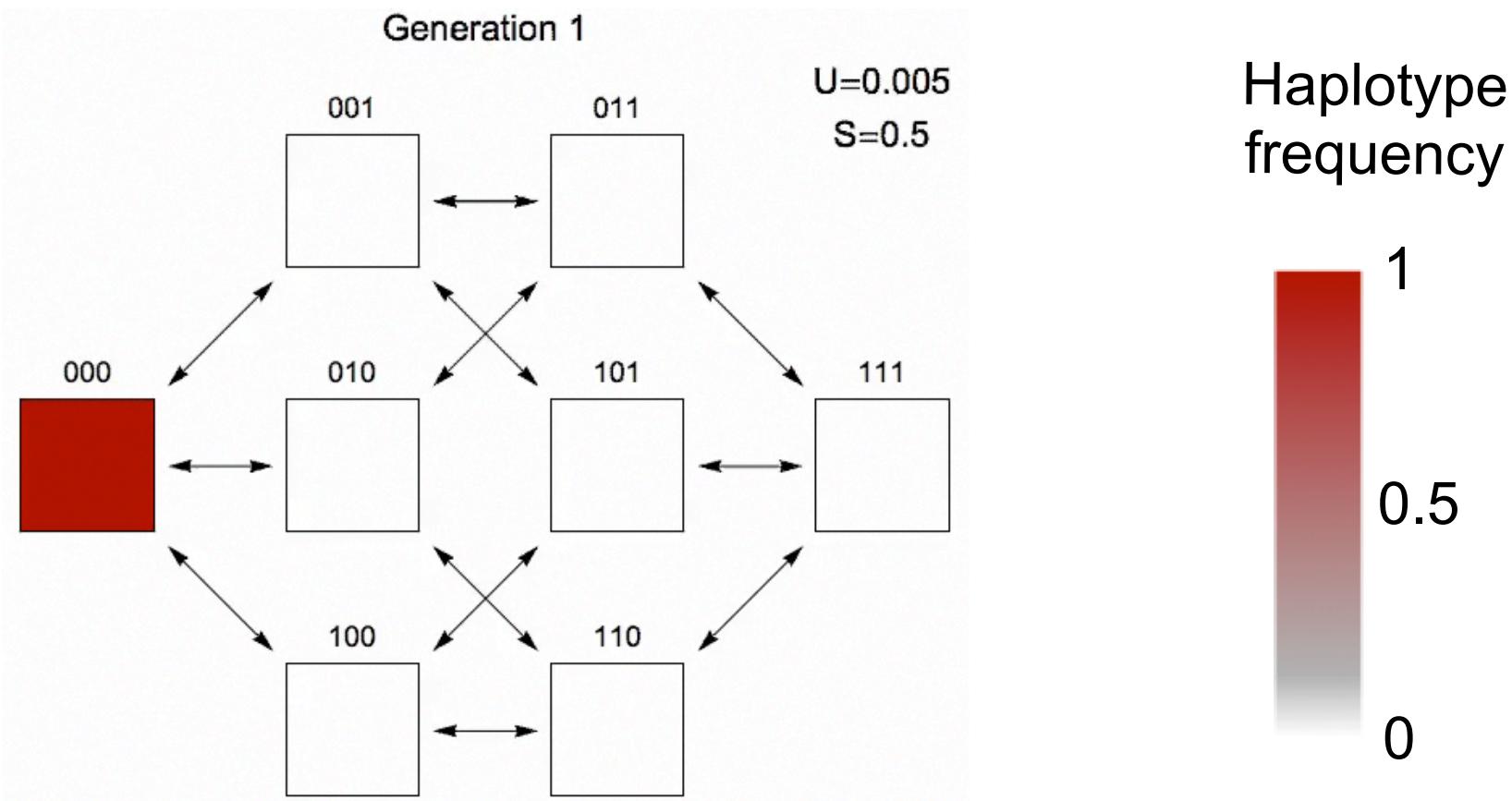
Model of viral evolution

Mutation + selection model: three loci, two alleles



Model of viral evolution

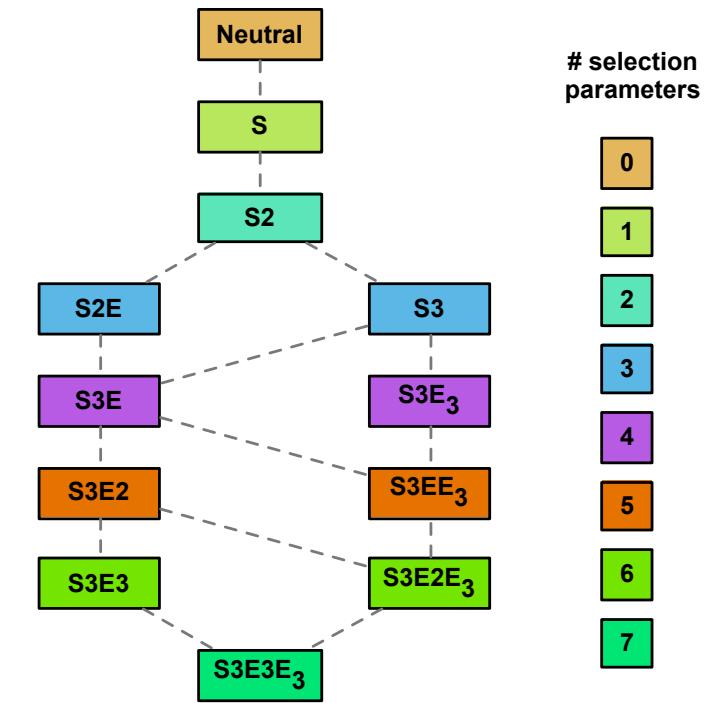
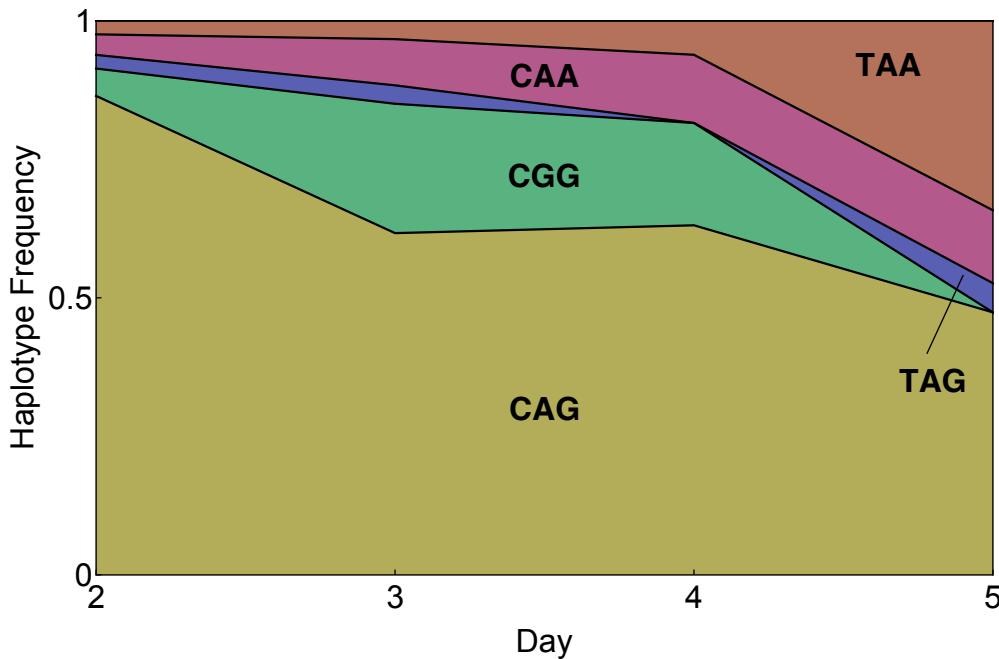
Mutation + selection model: three loci, two alleles



Multi-locus model of evolution

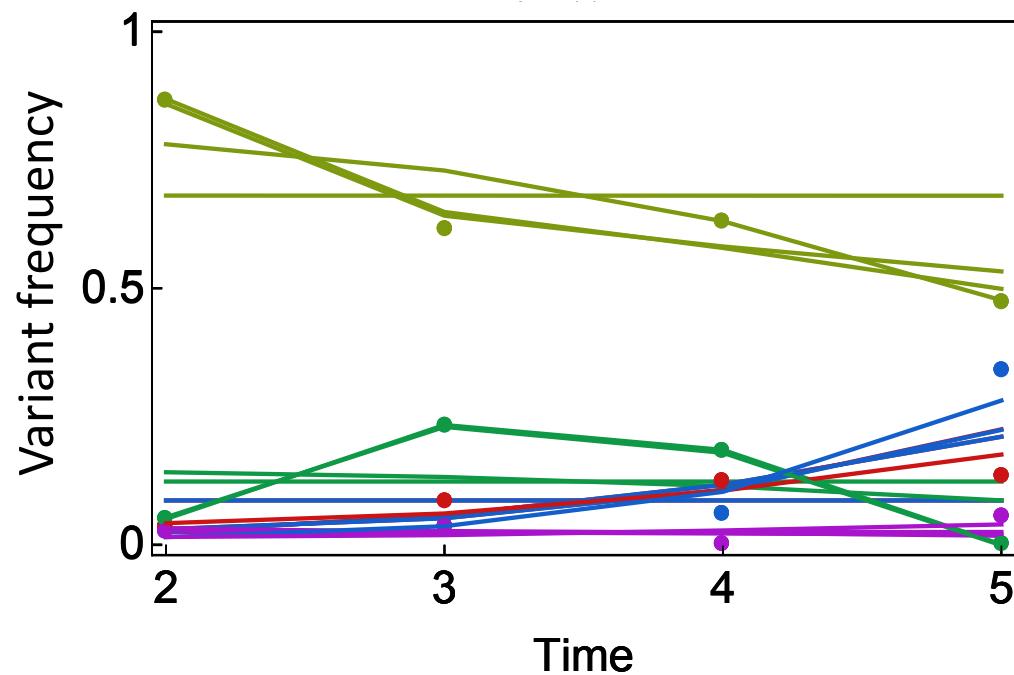
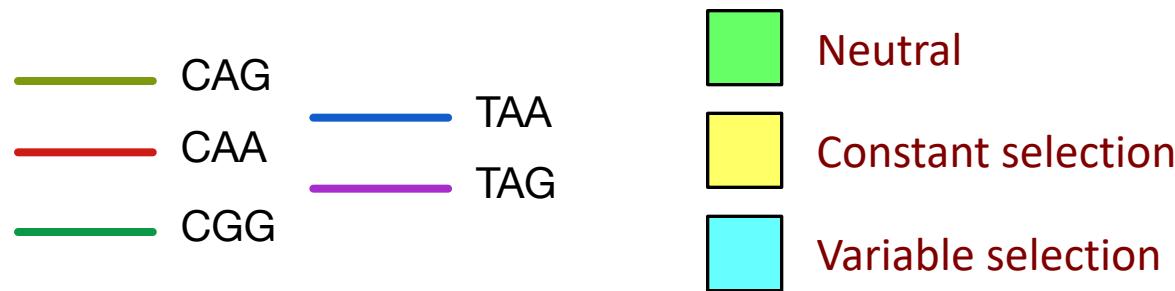
Collect multi-locus sequence data - haplotypes

Hierarchical network of models of selection



Hierarchical fitness model

Multi-locus model of evolution



Model 1 (26/101) (BIC)

447 553 844

Analysis of swine data

Evidence for selection at two loci

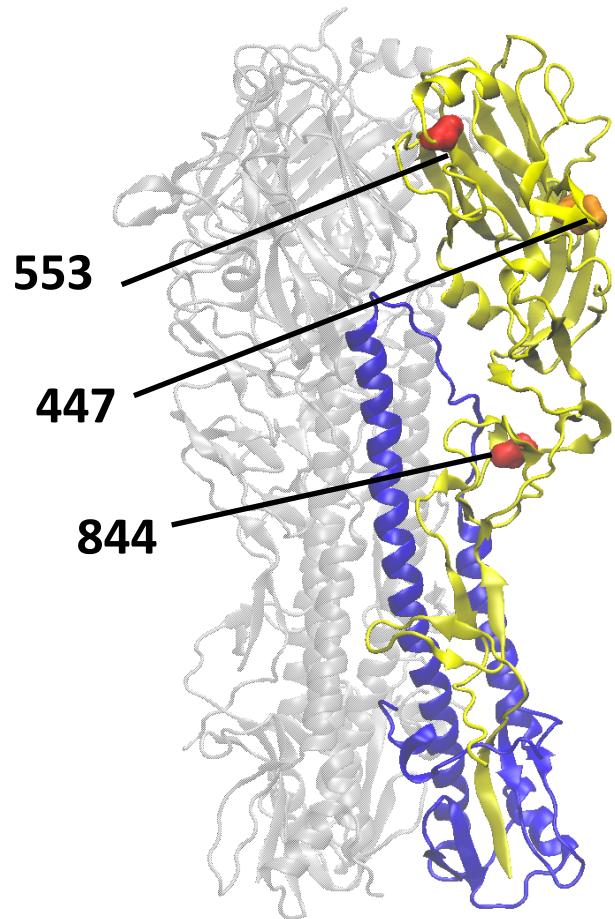
Positive selection for substitution G844A

Variable selection for A553G

(+ve to -ve)

NS change at epitope site:

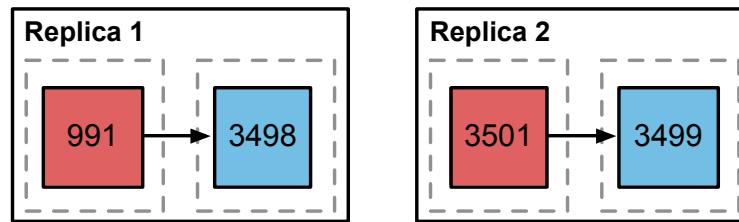
Adaptive immune response?



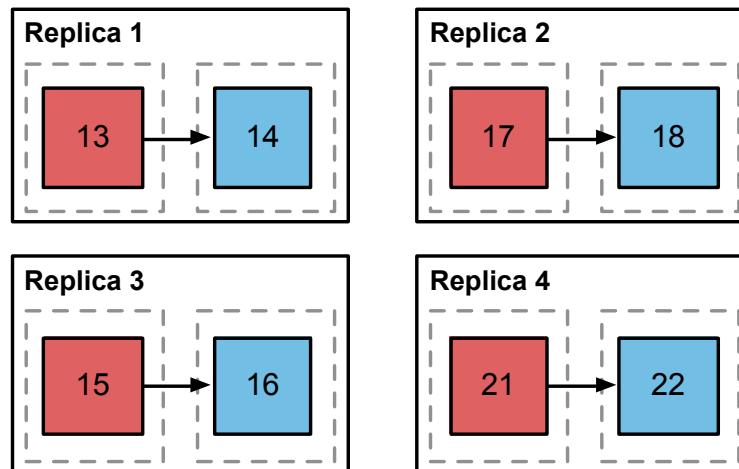
Analysis of A/H5N1 ferret data

Sequence data from Wilker et al, Nature Communications 2013

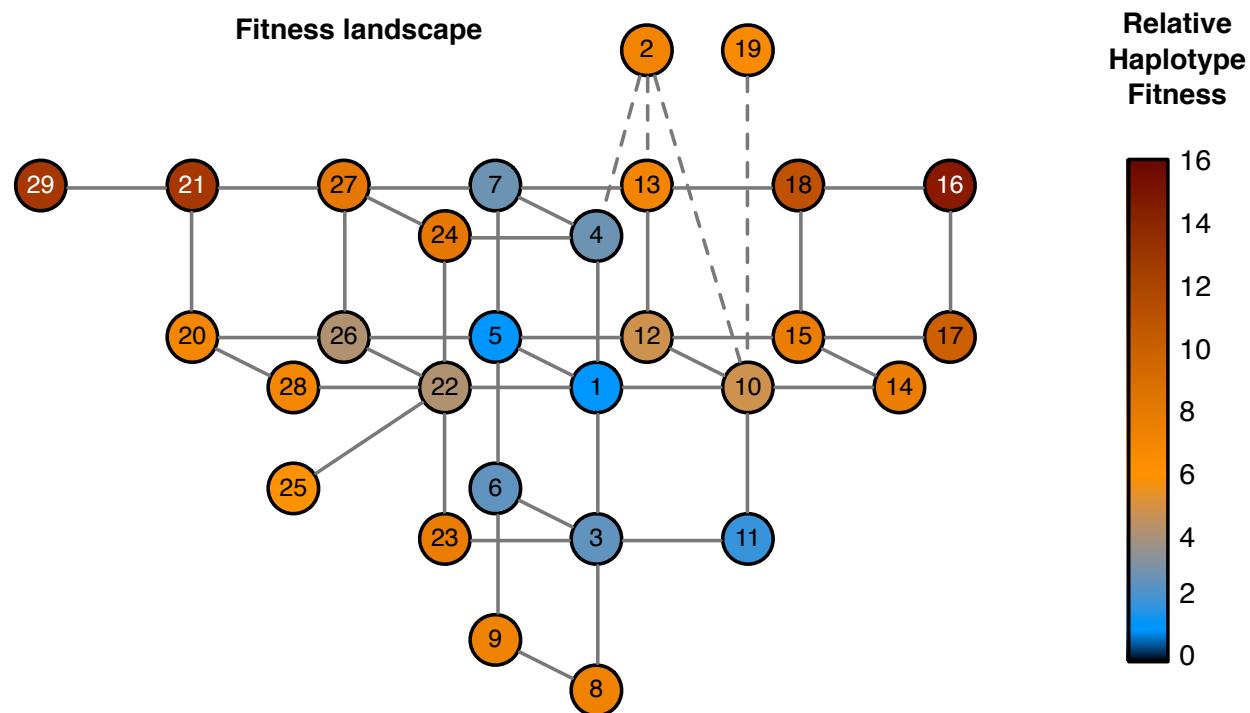
Experiment 1: VN1203-HA(3)-CA04



Experiment 2: VN1203-HA(4)-CA04

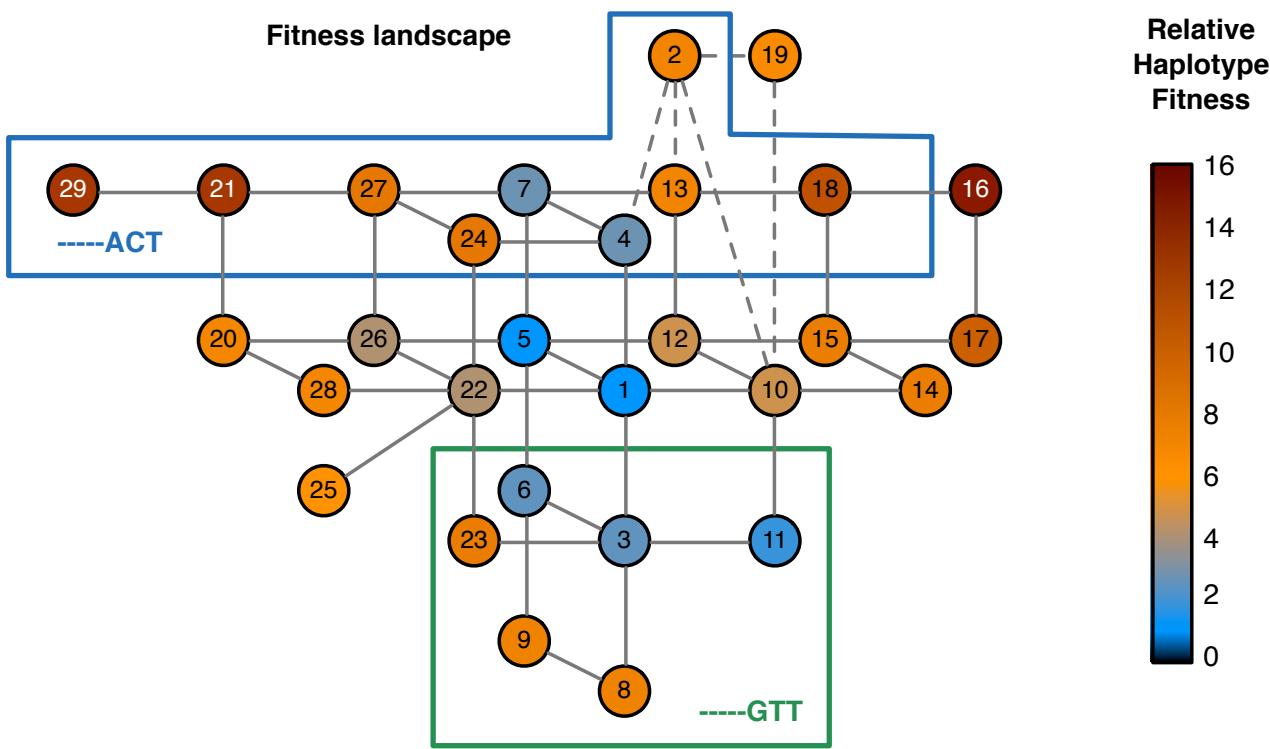


Ex 1: Inferred fitness landscape

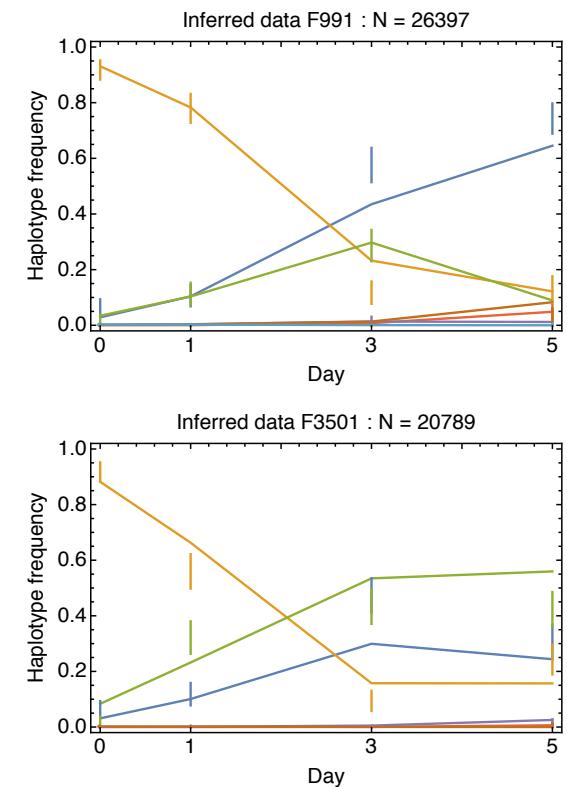


1	A G A G G G C T	9	A G A A T G T T	16	G G A A T A C C	23	A T A G G G T T
2	G G C G G A C T	10	G G A G G G C T	17	G G A A T G C C	24	A T A G G A C T
3	A G A G G G T T	11	G G A G G G T T	18	G G A A T A C T	25	A T A G G G C C
4	A G A G G A C T	12	G G A G T G C T	19	G G C G G G C C	26	A T A G T G C T
5	A G A G T G C T	13	G G A G T A C T	20	A T A A T G C T	27	A T A G T A C T
6	A G A G T G T T	14	G G A A G G C T	21	A T A A T A C T	28	A T A A G G C T
7	A G A G T A C T	15	G G A A T G C T	22	A T A G G G C T	29	A T C A T A C T
8	A G A A G G T T						

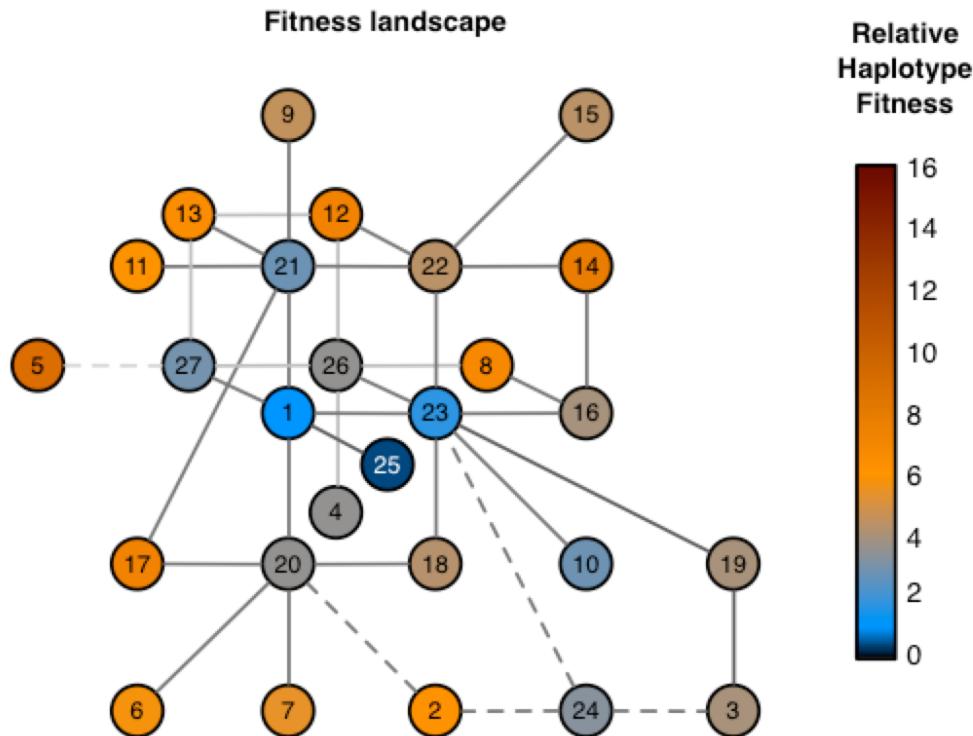
Multiple pathways to adaptation



1 A G A G G G G C T	9 A G A A T G T T	16 G G A A T A C C	23 A T A G G G T T
2 G G C G G G A C T	10 G G A G G G G C T	17 G G A A T G C C	24 A T A G G A C T
3 A G A G G G T T	11 G G A G G G G T T	18 G G A A T A C T	25 A T A G G G C C
4 A G A G G G A C T	12 G G A G T G C T	19 G G C G G G G C C	26 A T A G T G C T
5 A G A G T G C T	13 G G A G T A C T	20 A T A A T G C T	27 A T A G T A C T
6 A G A G T G T T	14 G G A A G G C T	21 A T A A T A C T	28 A T A A G G C T
7 A G A G T A C T	15 G G A A T G C T	22 A T A G G G C T	29 A T C A T A C T
8 A G A A G G T T			



Ex 2: More pathways to adaptation



Inferred parameters (with epistasis)		
	Ex. 1	Ex. 2
G496T	0.72	1.07
G738A	0.99	0.93
G496T+G738A	1.63	1.65

1	GGAGAGTGACGG	10	GAAGAGTTACAG
2	GGAGAAATGGCGG	11	TAAGCGTGGCAG
3	GAAGCGTGACGG	12	TAAGAGAGACAG
4	GAATAGAGACAG	13	TAAGAGAGGCAG
5	GGAGCGAGGCAG	14	TACGAGTGACAG
6	GAAGAAATGGAAG	15	TAATACTGACAG
7	GAAGAAATTGCAG	16	GACGAGTGACAG
8	GACGAGAGACAG	17	TAAGAAATGGCAG
9	TAAGAGTGGAAAG	18	GAAGAAATGACAG

19	GAAGCGTGACAG
20	GAAGAAATGGCAG
21	GAAGAGTGACAG
22	TAAGAGTGACAG
23	TAAGAGTGACAG
24	GGAGAGTGACGG
25	GAAGAGTGGCAA
26	TACGAGAGACAG
27	GAAGAGAGGGCAG

Explanation

Evolution driven by low-frequency standing variation

In an unfit virus there are very many beneficial mutations

Competition between those which already exist and those which need to be created by mutation

Question: Which ones do we need to look out for?

“It is very hard to predict, especially the future”, *Niels Bohr*

Influenza - future research

Combining population genetic theory with data

Can genome sequencing be used in a clinical context?