

Characterizing evolutionary dynamics on a broader scale: a strain-space model for SARS-CoV-2

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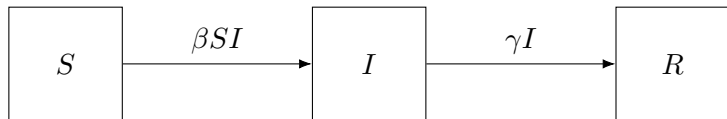
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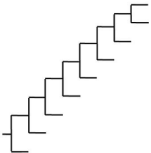
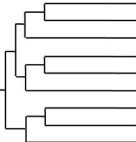
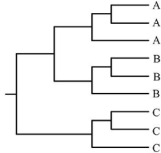
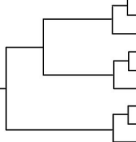
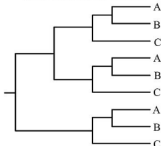
October 17, 2022

Infection spread with compartmental models



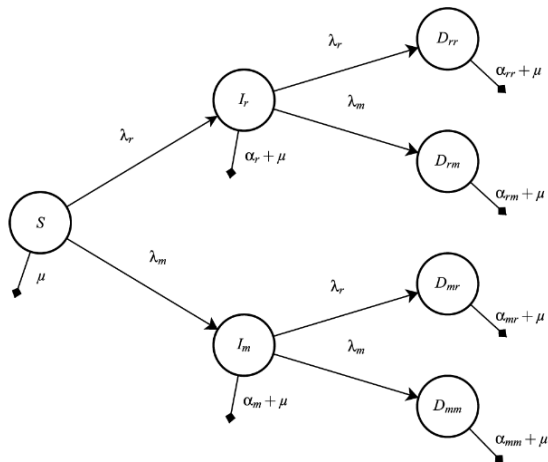
- $S(t)$ - fraction of susceptible hosts at t
- $I(t)$ - fraction of infected hosts at t
- $R(t)$ - fraction of recovered hosts at t
- $1 = S(t) + I(t) + R(t)$ is constant

Broad use of genomic data in dynamical epidemic models has been limited

	Continual Immune Selection	Weak or Absent Immune Selection	
		Tree shape controlled by non-selective population dynamic processes	
		Population size dynamics	Spatial dynamics
Idealized Phylogeny Shapes		Exponential growth 	Strong spatial structure 
		Constant size 	Weak spatial structure 
Examples	Human influenza A virus intra-host HIV	inter-host HIV inter-host HCV	Measles, rabies inter-host HIV
Tree Inferences	Detection of antigenic escape mutations	Estimation of population growth rates	Estimation of population migration rates

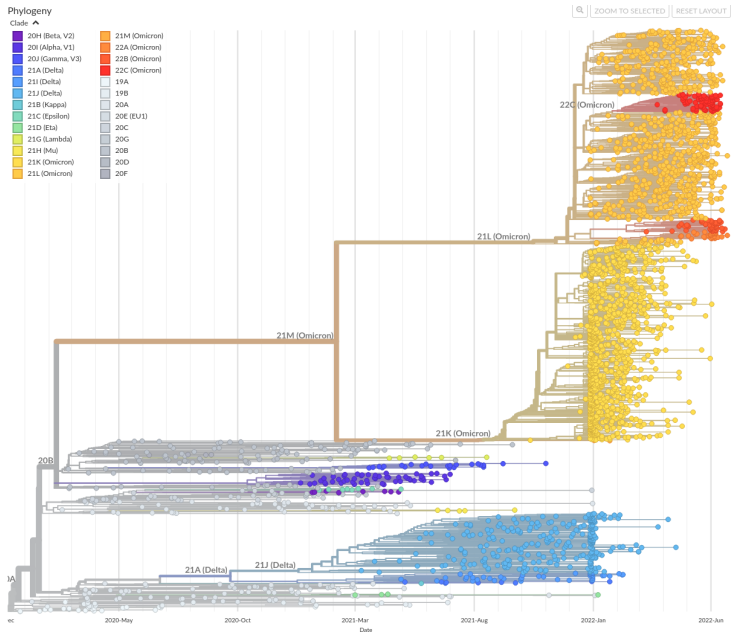
[Grenfell et al., 2004]

Modeling multiple infections is challenging



[Alizon and van Baalen, 2008]

How to incorporate more data?



A useful approximation

RESEARCH ARTICLE | BIOLOGICAL SCIENCES

Dynamics and selection of many-strain pathogens

Julia R. Gog and Bryan T. Grenfell [Authors Info & Affiliations](#)

December 12, 2002 | 99 (26) 17209–17214 | <https://doi.org/10.1073/pnas.252512799>

227 196

Abstract

Strain structure is of fundamental importance in the underlying dynamics of a number of pathogens. However, previous models have been too complex to accommodate many

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Abstract

Derivation of the Model

Application to Antigenic

J. Math. Biol. 44, 169–184 (2002)
Digital Object Identifier (DOI):
10.1007/s002850100120

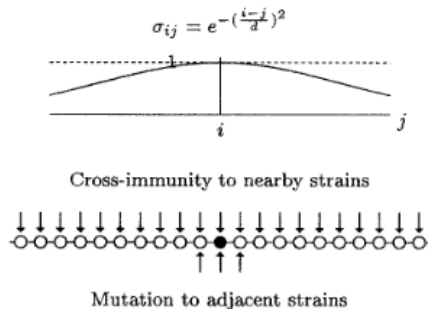
Mathematical Biology

J.R. Gog · J. Swinton

A status-based approach to multiple strain dynamics

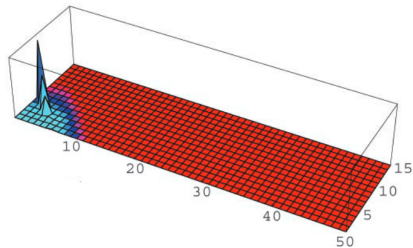
Received: 5 April 2000 / Revised version: 24 July 2001 /
Published online: 8 February 2002 – © Springer-Verlag 2002

Infections provide cross-immunity to nearby strains



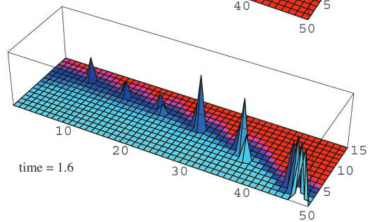
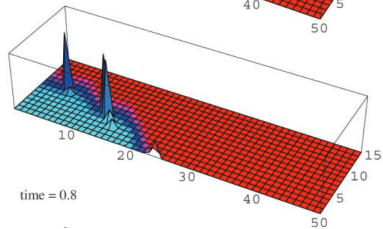
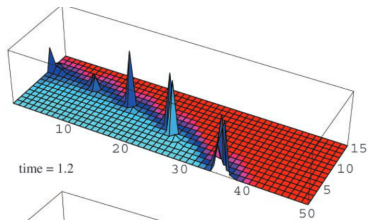
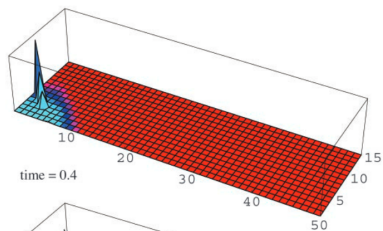
[Gog and Grenfell, 2002]

Extending the strain lattice to 2 dimensions



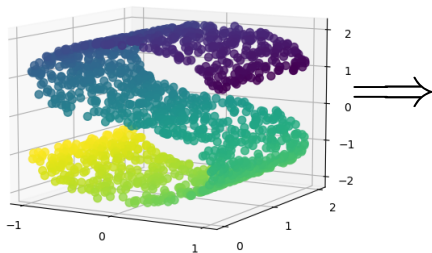
[Gog and Grenfell, 2002]

Extending the strain lattice to 2 dimensions



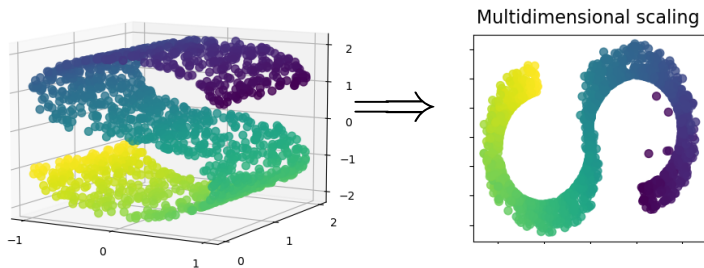
[Gog and Grenfell, 2002]

Projecting points to low dimensions while preserving distances



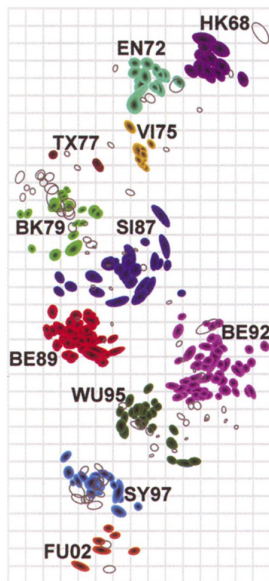
[Pedregosa et al., 2011]

Projecting to low dimensions while preserving distances

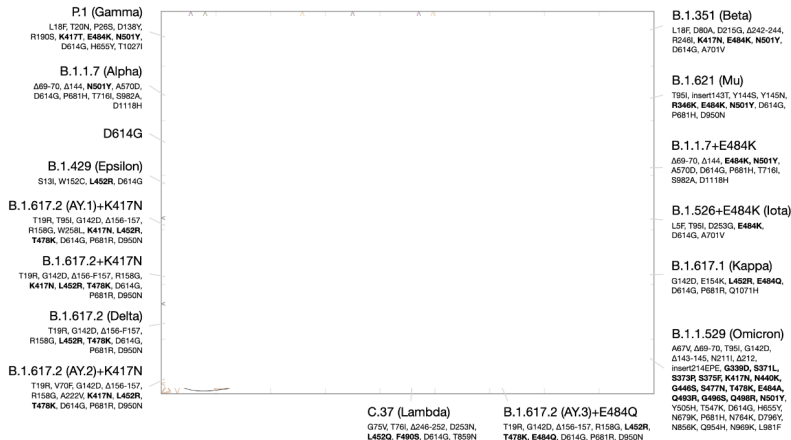


[Pedregosa et al., 2011]

Approximating genomic data in 2 dimesions

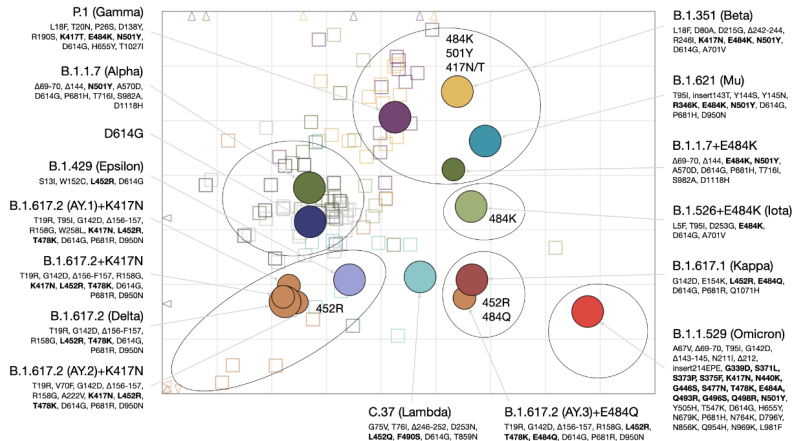


Mapping SARS-CoV-2 in 2D



[Wilks et al., 2022]

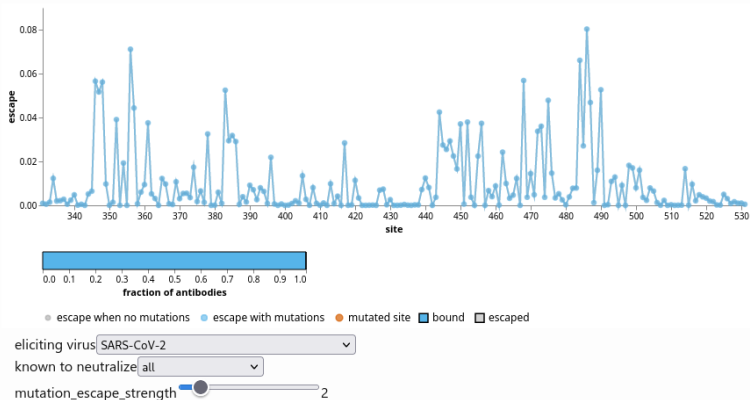
Mapping SARS-CoV-2 in 2D



[Wilks et al., 2022]

Methods of adding more genomes: polyclonal antibody binding studies

Escape calculator for SARS-CoV-2 RBD



[Greaney et al., 2022]

Interpolating more data into antigenic map

For each pair of genomes g_i and g_j ($i \neq j$)

1. Find the closest lineages in existing antigenic map to g_i , and g_j , and corresponding points x_i and x_j
- 2.
- 3.
- 4.

Interpolating more data into antigenic map

For each pair of genomes g_i and g_j ($i \neq j$)

1. Find the closest lineages in existing antigenic map to g_i , and g_j , and corresponding points x_i and x_j
2. Determine difference in polyclonal binding affinity $B(g_i, g_j)$
- 3.
- 4.

Interpolating more data into antigenic map

For each pair of genomes g_i and g_j ($i \neq j$)

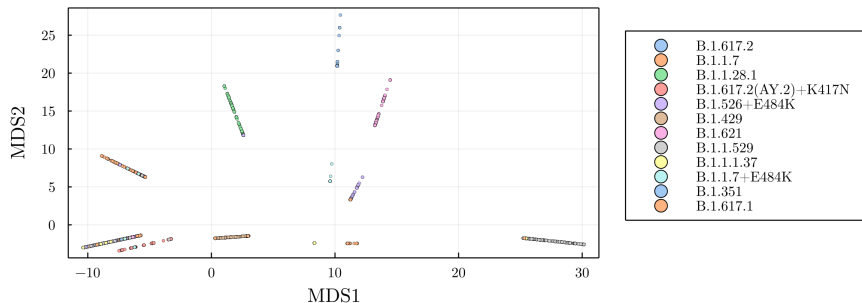
1. Find the closest lineages in existing antigenic map to g_i , and g_j , and corresponding points x_i and x_j
2. Determine difference in polyclonal binding affinity $B(g_i, g_j)$
3. Distance between g_i and g_j is $\|x_i - x_j\| + B(g_i, g_j)$
- 4.

Interpolating more data into antigenic map

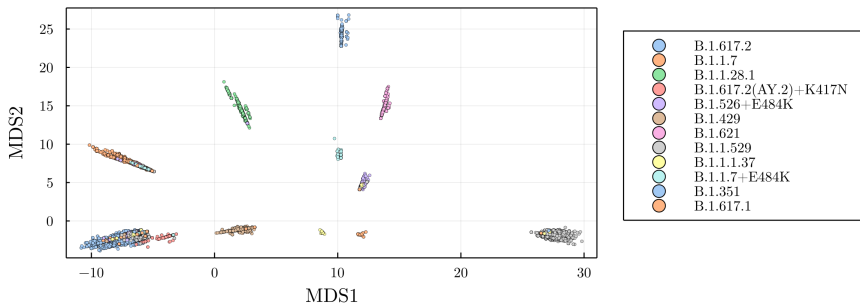
For each pair of genomes g_i and g_j ($i \neq j$)

1. Find the closest lineages in existing antigenic map to g_i , and g_j , and corresponding points x_i and x_j
2. Determine difference in polyclonal binding affinity $B(g_i, g_j)$
3. Distance between g_i and g_j is $\|x_i - x_j\| + B(g_i, g_j)$
4. Use these distances as inputs to multidimensional scaling

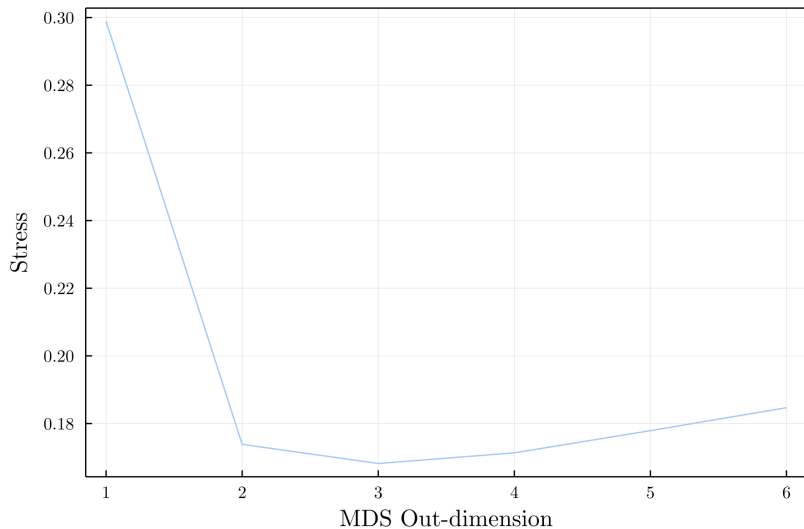
Antibody Binding map



Homoplasic mutations map



Evaluating the MDS approximation



Model parameters/variables

Symbol	Description
N	Size of variant grid
K	Total population
S_{ij}	Population susceptible to variant $(i, j) \in [0, N]^2$
I_{ij}	Population infected by variant $(i, j) \in [0, N]^2$
R_{ij}	Recovered from variant $(i, j) \in [0, N]^2$
V_{ij}	Immune by vaccination to variant $(i, j) \in [0, N]^2$
σ_{ijkl}	Probability that exposure to variant (i, j) causes immunity to variant (k, l)
β_{ij}	Transmission rate of variant (i, j)
$v_{ij}(t)$	vaccination rate at time t against variant (i, j)
$s(t)$	stringency at t
ξ	Recovery rate of all strains
γ	Rate of immunity loss of all strains

Table of symbols for Model 2

Model Equations

$$\frac{S_{ij}}{dt} = - \sum_{kl} s(t) \beta_{kl} \sigma_{ijkl} S_{ij} I_{kl} + \gamma(R_{ij} + V_{i,j}) - v_{ij}(t)S \quad (1)$$

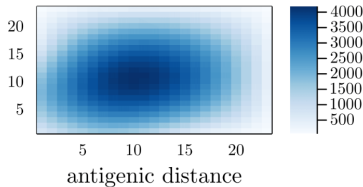
$$\frac{I_{ij}(t)}{dt} = s(t) \beta_{ij} S_{ij} I_{ij} - \xi I_{ij} + M (-4I_{ij} + I_{i-1,j} + I_{i+1,j} + I_{i,j-1} + I_{i,j+1}) \quad (2)$$

$$\frac{R_{ij}(t)}{dt} = \sum_{kl \neq ij} s(t) \beta_{kl} \sigma_{ijkl} S_{ij} I_{kl} + \xi I_{ij} - \gamma R_{ij} + v_{ij}(t)S \quad (3)$$

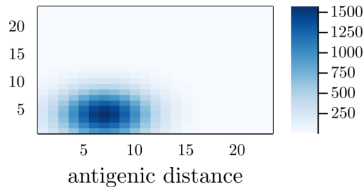
$$\frac{V_{ij}(t)}{dt} = v_{ij}(t)S - \gamma V_{ij} \quad (4)$$

Model Dynamics

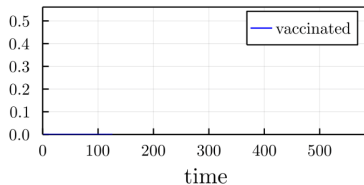
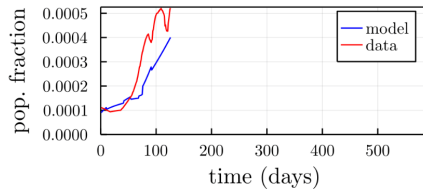
I



V



Incident (daily) cases



Further work

- More detailed methods for interpolation of additional genome data
- Differentiate between antigenic and genomic space
 - non-local diffusion
- Model fitting
- Applications
 - ▶ Simple inference on antigenic space
 - ▶ VoC-aware NPI usage and vaccination



Alizon, S. and van Baalen, M. (2008).

Multiple infections, immune dynamics, and the evolution of virulence.

The American Naturalist, 172(4):E150–E168.



Gog, J. R. and Grenfell, B. T. (2002).

Dynamics and selection of many-strain pathogens.

Proceedings of the National Academy of Sciences, 99(26):17209–17214.



Greaney, A. J., Starr, T. N., and Bloom, J. D. (2022).

An antibody-escape estimator for mutations to the sars-cov-2 receptor-binding domain.

Virus evolution, 8(1):veac021.



Grenfell, B. T., Pybus, O. G., Gog, J. R., Wood, J. L.,
Daly, J. M., Mumford, J. A., and Holmes, E. C. (2004).
Unifying the epidemiological and evolutionary dynamics of
pathogens.
science, 303(5656):327–332.



Lapedes, A. and Farber, R. (2001).
The Geometry of Shape Space: Application to Influenza.
Journal of Theoretical Biology, 212(1):57–69.



Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V.,
Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss,
R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau,
D., Brucher, M., Perrot, M., and Duchesnay, E. (2011).
Scikit-learn: Machine learning in Python.
Journal of Machine Learning Research, 12:2825–2830.



Smith, D. J., Lapedes, A. S., de Jong, J. C., Bestebroer, T. M., Rimmelzwaan, G. F., Osterhaus, A. D. M. E., and Fouchier, R. A. M. (2004).

Mapping the Antigenic and Genetic Evolution of Influenza Virus.

Science, 305(5682):371–376.



Wilks, S. H., Mühlemann, B., Shen, X., Türeli, S., LeGresley, E. B., Netzl, A., Caniza, M. A., Chacaltana-Huarcaya, J. N., Daniell, X., Datto, M. B., Denny, T. N., Drosten, C., Fouchier, R. A. M., Garcia, P. J., Halfmann, P. J., Jassem, A., Jones, T. C., Kawaoka, Y., Krammer, F., McDanal, C., Pajon, R., Simon, V., Stockwell, M., Tang, H., van Bakel, H., Webby, R., Montefiori, D. C., and Smith, D. J. (2022).

Mapping SARS-CoV-2 antigenic relationships and serological responses.

Preprint, *Immunology*.

Mutation homoplasy

