Modelling viral evolution and adaptation: Challenges and rewards

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SUMMARY

• Introduction

On viral diversity and fitness landscapes

• Transition to bipartite viral forms

Population structure, competition and cooperation

• Emergence and fixation of resistant mutants

Mutagens and inhibitors of viral replication
• Genomes
• Forms of transmission
• Infective strategies

VIRUS

Influenza
HIV
Tobacco mosaic virus
T4 bacteriophage
Ebola virus
VIRAL DIVERSITY

A. Neutral mutations
B. Fitness landscape
Genotype-phenotype map
Effect of point mutations

C. Variable environments

D. Complementation
Genome fragmentation

E. Stochastic extinction
Defective interfering particles

F. Lethal mutagenesis
Quasispecies diversity
Interference
Fitness landscapes have very high dimensionality

From Justin Meyer’s webpage, [https://www msu edu/~meyerju3/projects html](https://www.msu.edu/~meyerju3/projects.html)
Example of a large fitness landscape described as a network of genotypes. Lambda’s path from ancestral function (blue) to new function (green).
Deep sequencing and viral fitness landscapes

Global fitness landscape of HIV-1 estimated through computation and deep sequencing


VIRAL DIVERSITY: Multipartite viral forms

C. Variable environments

D. Complementation Genome fragmentation
SEGMENTED GENOMES AND VIRAL REPLICATION

- Full genome (WT)
- Replication errors
- Deletion mutants (segments)
- Mutual complementation
- Multipartite virus: one segment per capsid
FROM COMPETITORS TO COOPERATORS

Isolated replicators
Protists
Solitary individuals

Populations in compartments
Chromosomes
Animals, plants and fungi
Colonies
EXPERIMENTAL PROTOCOL: foot-and-mouth disease virus

Adaptation to culture

Plaque

Plaque-to-plaque passages
After 260 passages two complementary defective genomes appear. They displaced the complete genome cognate virus within a few additional passages.

Two clones of FMDV corresponding to the bipartite genome (C-S8p260, left) and the *wild-type* (C-S8p260d3, right).

Which conditions permit the fixation of multipartite viruses?

**Complementation necessary**
(infection requires high MOI)

**Advantages of a lesser size**
- Faster replication?
- Higher copying fidelity?
- Increased stability of the viral particle
MODEL OF VIRAL COMPLEMENTATION

Infection at a given MOI ($m$)

Replication (depends on intra-cell composition)

Differential degradation ($\sigma$)

New infection

$\rightarrow$ WT (complete genome)

$\rightarrow$ Δ1 (segment 1)

$\rightarrow$ Δ2 (segment 2)
Coexistence

Extinction WT

Multiplicty of infection (m)
DYNAMICAL EQUATIONS

\[ \vec{P} = \begin{pmatrix} P_{\Delta 1} \\ P_{\Delta 2} \\ P_{WT} \end{pmatrix} \]
\[ \|\vec{P}\|_1 = 1 \]

\[ \vec{P}_{n+1} = Z^{-1} D \sum_{a,b,c} \Pr(a,b,c|\vec{P}_n) M_{a,b,c} \begin{pmatrix} a \\ b \\ c \end{pmatrix} \]

\[ M_{a,b,c} \begin{pmatrix} a \\ b \\ c \end{pmatrix} = \begin{pmatrix} \min\{a, b + c\} \\ \min\{b, a + c\} \\ c \end{pmatrix} = \begin{pmatrix} f_{\Delta 1|a,b,c} \\ f_{\Delta 2|a,b,c} \\ \sigma^{-1} f_{WT|a,b,c} \end{pmatrix} \]

\[ \Pr(a,b,c|\vec{P}) = \begin{cases} \delta_{m-(a+b+c)} \frac{m!}{a!b!c!} P_{\Delta 1}^a P_{\Delta 2}^b P_{WT}^c & \text{(multinomial)} \\ e^{-m} \frac{m^{a+b+c}}{a!b!c!} P_{\Delta 1}^a P_{\Delta 2}^b P_{WT}^c & \text{(Poisson)} \end{cases} \]
EVOLUTIONARY OUTCOMES

Extinction WT

Coexistence

$\sigma < \sigma_{crit}$

$\sigma > \sigma_{crit}$
Equivalence of de $\sigma_{\text{crit}}$ with other advantages related to a lesser length:

a) Faster replication

$$\sigma \sim R^{-G}$$

b) Higher copying fidelity

$$\sigma \sim (1 - \rho)^G$$

$$\sigma_{\text{crit}} = \frac{2}{m} \sum_{a,b} \Pr(a, b| \frac{1}{2}, \frac{1}{2}, 0) \min\{a, b\} = \frac{1}{2^m} \left[ 4 \sum_{a < \frac{m}{2}} a \binom{m}{a} + \frac{m}{2} \binom{m}{m/2} \right]$$

MULTIPLE SEGMENTS

Intermediate coexistence regions: can they be observed in nature?

Highly segmented viruses: how have they evolved?
RELATIVE ABUNDANCES OF EACH FRAGMENT

Abundance of the eight segments of Faba bean necrotic stunt virus in two different hosts.


Abundance of the four segments of Alfalfa mosaic virus.

Sicard et al., Nat. Commun. 4, 2248 (2013)
Viruses adapt rapidly to varying environments, including to therapies aimed at controlling their replication and propagation.

Combination therapies have been successful at controlling infections by delaying the appearance of resistant mutants.

Use of dissimilar drugs demands knowledge of the interaction between them.

Experiments with foot-and-mouth disease virus indicate that sequential therapy is more efficient than combination therapy to decrease viral titer.
VIRAL RESPONSE TO DRUGS

Inhibitor

Inhibitor and mutagen

Virus titer (PFU/ml)

Passage number

GU 0 mM
GU 8 mM
GU 10 mM
GU 12 mM
GU 14 mM
GU 16 mM
GU 18 mM
GU 20 mM

+GU (16,18,20 mM)
+R (5 mM)
[+GU (16,18,20 mM)+R]
+GU (16,18,20 mM),+R
Inhibitor of viral replication: Guanidinium hydrochloride (GU)
Mutagen: Ribavirin (R)

Is the sequential treatment always better?
Why and when?

Viable: able to complete the viral replicative cycle

Defective: removed at each passage

Susceptible: inhibitor slows down its replication: $i \cdot m$

Resistant: replication unaffected by inhibitor: $m$

$\mu$, $\omega$ are coupled
DYNAMICAL MODEL for one passage

Can be analytically solved: \( V + v \) gives the titre after one passage

\[
\begin{align*}
v(g + 1) &= i(1 - \mu - w)mv(g) \\
V(g + 1) &= i\mu mv(g) + (1 - w)mV(g)
\end{align*}
\]

Viral parameters: \( m, G, \mu_0, w_0 \)
Therapy parameters: \( w, i \)
COMBINATION: One passage with $i$, $w$

SEQUENTIAL: One passage with $i$, $w_0$, plus a second passage with $i=1$, $w$

$Y_T^C$  

COMPARE!  

$Y_T^S$
VIRAL TITRE OF THE SEQUENTIAL THERAPY
COMPARISON BETWEEN THERAPIES

\[ \text{Min}(Y_T^C, Y_T^S) \]
The combination therapy yields lower titre at low doses of mutagen and/or inhibitor. At high doses, the sequential treatment is preferred.

**THEORETICAL PREDICTION**

The combination therapy yields lower titre at low doses of mutagen and/or inhibitor. At high doses, the sequential treatment is preferred.

These experimental data fix all model parameters but one that has to be determined from viral characteristics: \( m, G. \)
Combination treatment yields lower titer and lower amount of resists.

Sequential treatment yields lower titer and lower amount of resists.

Combined treatment yields lower titer but the sequential treatment is less prone to produce resists.

Deep sequencing of complete viral genomes and complementary techniques work towards characterization of global fitness landscapes.

Quasispecies models should integrate the microscopic and the population level description.

Well designed formal models should establish a feedback with experimental research and improve its predictive power as well as its ability to capture generic mechanisms of viral adaptation.
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