Gradual antigenic drift explains complex reccurent pattern of human influenza A

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Abstract

To what extent epidemic peaks amplitude variability can be due due non-linear dynamics alone ?

To test between a continuous antigenic drift scenario and a punctuated evolutionary one, we have developed a simple model, the perturbated SIRS model.

Results : discrete evolution (burst of positive selection) are not correlated with peak variability.

calculer la correlation entre la date du peak et la date de la mutation a grand effet tracer ce coeff en fonction de l'intensité du forcage saisonier et de la variance de la loi normale

construire un test statistique pour voir si l'effet est significatif.

idée en vrac mais bien !!!: il nous faut determiner l'amplitude de l'immune escape. une facon de calibrer: regarder la perturbation d'un modele SIRS voir a partir de quelle niveau on genere des peaks plus grand...

on peut faire le calcul avec comme ordre de grandeur la valeur de l'equilibre endemique calculer l'ecart entre le peak et l'equilibre endemique

Keywords:
influenza, punctuated immune escape, status based model, history based model, reduced susceptibility, reduced infectivity

1 Intrinsic period of oscillation in a SIRS model

Assuming a constant hosts population size, the $SIRS$ model is:

$$\frac{dS}{dt} = -\beta SI + g(1 - S - I) \quad (1)$$

$$\frac{dI}{dt} = \beta SI - \nu I \quad (2)$$

$$(3)$$

The $SIRS$ model can be simplified, resulting in a reduction in the number of parameters. Measuring time in units of duration of infection, $t' = t\nu$, we get the non dimensional system:

$$\begin{aligned}
\frac{dS}{dt'} &= -R_0 SI + e(1 - S - I) \\
\frac{dI}{dt'} &= R_0 SI - I
\end{aligned}$$

With $R_0 = \frac{\beta}{\nu}$ and $e = \frac{g}{\nu}$.
The model has two possible steady states

- Disease-free equilibrium: $S = 1$, $I = 0$
- Endemic equilibrium: $S = \frac{1}{R_0}$, $I = \frac{e - e/R_0}{1+e}$.

The stability of the endemic equilibrium is determined by the eigenvalues of the Jacobian matrix:

$$J = \begin{pmatrix} -R_0 I - e & -R_0 S - e \\ R_0 I & R_0 S - 1 \end{pmatrix}$$

Evaluated at the endemic equilibrium it results in:

$$\begin{pmatrix} \frac{e(1-R_0)}{1+e} & -1 - e \\ \frac{e(R_0-1}{1+e} & 0 \end{pmatrix}$$

The eigenvalues are solution of

$$\begin{aligned}
\det J - \lambda I_2 = 0 \\
\lambda^2 - \frac{e(1 - R_0)}{1 + e}\lambda + e(R_0 - 1) = 0
\end{aligned}$$

A straightforward calculation shows that the discriminant is negative and the eigenvalues thus complex:

$$\lambda_i = \frac{\frac{e(1-R_0)}{1+e} \pm i\sqrt{4e(R_0 - 1) - \frac{e^2(R_0-1)^2}{(1+e)^2}}}{2}$$

The period of the dampened oscillations is given by

$$\begin{aligned}
T &= 2\pi\frac{1}{\Im\lambda} \\
&= 2\pi\sqrt{\frac{4}{4e(R_0 - 1) - \frac{e^2(R_0-1)^2}{(1+e)^2}}}
\end{aligned}$$

In the natural timescale, the period is divided by ν As $e \to 0$, the period can be simplified in :

$$T = 2\pi\sqrt{\frac{DL}{R_0 - 1}}$$

expressed in natural timescale with $D = 1/\nu$ and $L = 1/g$.

2 seasonal forcing

2.1 Floquet

We now consider the following non autonomous system:

$$\frac{dS}{dt} = -\beta(t)SI + g(1 - S - I)$$
$$\frac{dI}{dt} = \beta(t)SI - \nu I$$

with $\beta(t) = \beta_0(1 + e\cos(2\pi t))$.

For positive initial conditions and some parameters values, the seasonally forced $SIRS$ model admits a stable periodic solution of period T. We will label limit cycle solutions by $\bar{\mathbf{x}}(t) = (\bar{S}(t), \bar{I}(t))$ in the following calculations and have $\bar{\mathbf{x}}(t+T) = \bar{\mathbf{x}}(t)$ for all times, t. The curve, $\bar{\mathbf{x}}(t)$, cannot be calculated in closed form. However good estimates can be obtained via numerical integration of Eq. (1).

In order to study stability, we now consider a dynamical path beginning close to, but not on, the limit cycle, $\bar{\mathbf{x}}(t)$. If the limit cycle solution is stable then the difference between this path and the geometric curve of the limit cycle will decay as time progresses. Similarly to the expansion about a fixed point, we can write this difference as $\epsilon\xi(t) = \mathbf{x}(t) - \bar{\mathbf{x}}(t)$ where, again, ϵ expresses our anticipation that the deviation from the limit cycle is small. Expanding in powers of ϵ and letting $\epsilon \to 0$, one then finds that the time evolution of $\xi(t)$ takes on the linear form, $\frac{d\xi}{dt} = \mathbf{A}(t)\xi$, where the matrix $\mathbf{A}(t)$ is the Jacobian matrix evaluated at the limit cycle. Therefore, due to the periodic nature of $\bar{\mathbf{x}}(t)$, all elements of $\mathbf{A}(t)$ are periodic.

An analytical tool to characterize the stability or otherwise of limit cycle solutions is Floquet theory, the mathematical theory of linear differential equations with periodic coefficients. Since, we have $\mathbf{A}(t+T) = \mathbf{A}(t)$, Floquet theory is applicable. In our case, T is the period of the mean-field limit cycle under consideration. The general solution of

$$\frac{d\xi}{dt} = \mathbf{A}(t)\xi$$

takes the form:

$$\xi(t) = \sum_{i=1}^{n} c_i e^{\mu_i t}\mathbf{p}_i(t)$$

μ_i are complex numbers called characteristic or Floquet exponents. Floquet exponents can be calculated numerically by solving the matrix differential equation

$$\frac{d\mathbf{X}}{dt} = \mathbf{A}(t)\mathbf{X}$$

over one period (from $t = 0$ to $t = T$) with the identity matrix as an initial condition ($\mathbf{X}(0) = \mathbf{I}$) The matrix $\mathbf{X}(T)$ is known as a fundamental matrix. Floquet multipliers, ρ_i are the egeinvalues of $\mathbf{X}(T)$. ρ_i are also the eigenvalues of the (linear) Poincaré map $x(t) \to x(t+T)$ From ρ_i, Floquet exponents, μ_i are calculated as $\mu_i = \frac{\ln(\rho_i)}{T}$

In term of Floquet multipliers, the general solution is

$$\xi(t) = \sum_{i=1}^{n} c_i e^{\frac{\ln(\rho_i)}{T}t}\mathbf{p}_i(t)$$

expressing $\rho_i = |\rho_i| e^{i\arg(\rho_i)}$ we have:

$$\xi(t) = \sum_{i=1}^{n} c_i e^{(\frac{\ln(|\rho_i|)}{T} + i\frac{\arg(\rho_i)}{T})t} \mathbf{p}_i(t)$$

that gives the damping rate and oscillation period

if $\Re(\rho_i) > 0$ $\arg(\rho_i) = \arctan(\frac{\Im(\rho_i)}{\Re(\rho_i)})$ else $\arg(\rho_i) = \pi - \arctan(\frac{\Im(\rho_i)}{\Re(\rho_i)})$

2.2 larger perturbation

2.3 Invasion orbit