Modeling of Viral Coinfection in Human Respiratory Tract Using Stochastic Method

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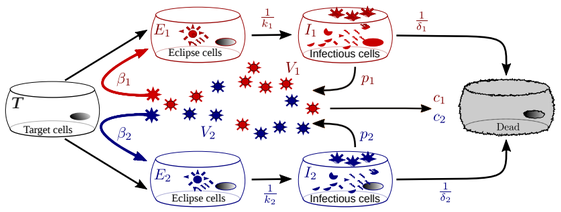
SciCom Let's Talk Science

- Molecular diagnostic techniques have revealed that approximately 43% of the patients hospitalized with influenza-like illness are infected by more than one viral pathogen at the same time and have distinct disease outcomes compared to single viral infections.
- It is not clear how the two different viruses interact within the respiratory tract of the infected person and modify disease severity.
- Mathematical models can be used to help us understand the dynamics of such infections within the person.
- The aim of this research is to develop a kinetic model of viral coinfection and use the model as a tool to help public health researchers better understand the disease progression, outcomes and controls for the coinfected patients.

Coinfection model



Our previous work with deterministic models of coinfection shows that

- Viruses interact though resource competition.
- The virus with a higher growth rate consumes more target cells and produces higher peak viral load.
- Duration of coinfection can be long enough (more than 14 days) if viruses are able to infect the same cells and have access to renewable supply of cells.
- Using ODEs our models of viral coinfections reproduce the average behavior of the disease.
- In reality, viral infections are discrete and stochastic.

Objectives

- Stochastic simulations of single virus infections have shown that there is an extinction probability that depends on the size of the initial viral inoculum and parameters that describe virus-cell interactions.
- The coexistence of viruses predicted by the ODEs might be difficult to observe in reality.
- In this work, we develop the stochastic counterpart of the ODEs, a continuous-time Markov chain (CTMC) model in order to analytically derive the extinction probabilities and to determine which virus dominates the infection and duration of coinfection.
- We examine whether stochastic effects early in the infection can allow slower growing viruses to consume more target cells, contrary to the predictions of ODEs.
- Trajectories for the CTMC model are simulated using Gillespie's tau-leap algorithm.

Stochastic coinfection model

The transition probabilities for the corresponding CTMC model are enlisted below.

Transitions	Propensity
$T \to T-1, E_1 \to E_1+1$	$\beta_1 T V_1$
$T \to T-1, E_2 \to E_2+1$	$\beta_2 T V_2$
$E_1 \to E_1-1, I_1 \to I_1+1$	$k_1 E_1$
$E_2 \to E_2-1, I_2 \to I_2+1$	$k_2 E_2$
$I_1 \to I_1-1$	$\delta_1 I_1$
$I_2 \to I_2-1$	$\delta_2 I_2$
$V_1 \to V_1+1$	$p_1 I_1$
$V_2 \to V_2+1$	$p_2 I_2$
$V_1 \to V_1-1$	$c_1 V_1$
$V_2 \to V_2-1$	$c_2 V_2$

Probability of stochastic extinction

The CTMC model approximated by multi-type branching process under appropriate conditions enabled to derive the probability that the infection does not become established which is known as extinction probability, $\xi(\rho_{V_1}\rho_{E_1}\rho_{I_1}\rho_{V_2}\rho_{E_2}\rho_{I_2})$.

$$\rho_{V_1} = min\{\frac{c_1(p_1+\delta_1)}{p_1(c_1+\beta_1 T)}, 1\}$$

$$\rho_{E_1} = \rho_{I_1} = min\{\frac{\delta_1(c_1+\beta_1 T)}{\beta_1 T(p_1+\delta_1)}, 1\}$$

$$\rho_{V_2} = min\{\frac{c_2(p_2+\delta_2)}{p_2(c_2+\beta_2 T)}, 1\}$$

$$\rho_{E_2} = \rho_{I_2} = min\{\frac{\delta_2(c_2+\beta_2 T)}{\beta_2 T(p_2+\delta_2)}, 1\}$$

- There is a non zero value for extinction probability that depends on the parameters that describe the virus-cell interactions.
- Probability of disease outbreak is $(1-\xi)=1-\frac{1}{\mathcal{R}_{01}}\frac{1}{\mathcal{R}_{02}}$.

Parameter values

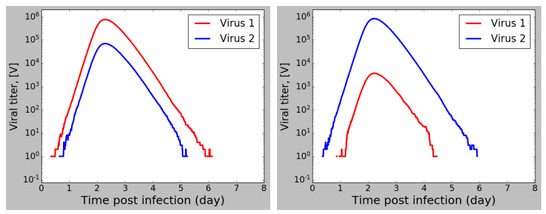
Parameter	Value	Units
β	3.2×10^{-5}	cell^{-1} [V]$^{-1}$ d^{-1}
k	4.6	d^{-1}
δ	5.2	d^{-1}
p	4.6×10^{-2}	[V] d^{-1}
c	5.2	d^{-1}
T_0	4.0×10^{8}	cell
V_0	7.5×10^{-2}	[V]

Growth rate, $\lambda =$
$\sqrt[3]{-\frac{q}{2}+\sqrt{\frac{q^2}{4}+\frac{u^3}{27}}}+\sqrt[3]{-\frac{q}{2}-\sqrt{\frac{q^2}{4}+\frac{u^3}{27}}}-\frac{B}{3}$
$u = C-\frac{B^2}{3}$, $q = D+\frac{2B^3-9BC}{27}$
$B = k+\delta+c$, $C = k\delta+kc+c\delta$,
$D = -kc\delta(R_0-1)$

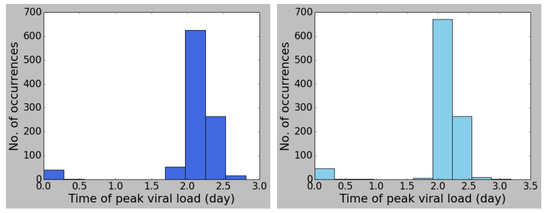
Same growth rate

We set the initial conditions and transition rates for virus 1 and virus 2 equal to each other.

Two stochastic trajectories of viral load curve:

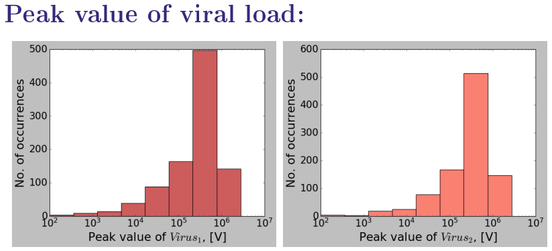


Time of peak viral load:



Mean of time of peak virus 1: 2.09 days
Standard deviation: 0.45 days
Mean of time of peak virus 2: 2.06 days
Standard deviation: 0.47 days

Peak value of viral load:

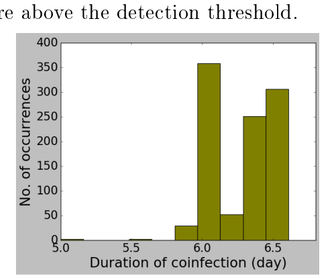


Mean of peak virus 1: 4.01×10^5 [V]
Standard deviation: 2.92×10^5 [V]
Mean of peak virus 2: 4.12×10^5 [V]
Standard deviation: 2.93×10^5 [V]

Peak of virus 1 appears 509 times over virus 2 from 1000 stochastic realizations.

Duration of coinfection

Coinfection duration is defined as the time during which both infections are above the detection threshold.

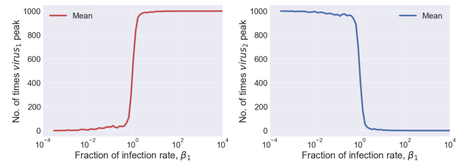


Mean of coinfection duration: 6.37 days
Standard deviation: 0.17 days

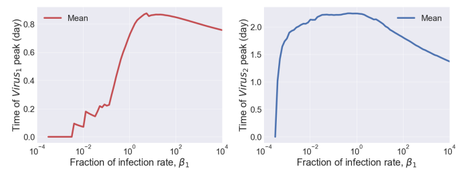
Different growth rates

We vary the growth rate of the first virus by varying the infection rate, β_1.

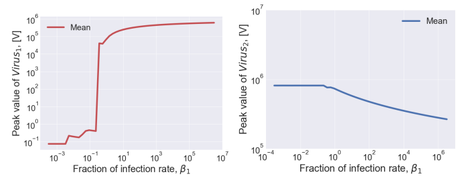
No. of times Virus 1 and Virus 2 peak:



Time of peak of Virus 1 and Virus 2:

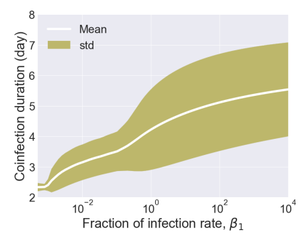


Peak of Virus 1 and Virus 2:



- ODEs predict that if the growth rate of one virus is higher than the other it will *always* have a higher peak viral load.
- If growth rates are similar, the virus with the higher growth rate will not always have a higher peak viral load.
- Unlike the prediction of ODEs, now there is the possibility that slower growing virus might dominate infection dynamics.

Duration of coinfection



- Viruses do not coexist for more than ~ 6 days.
- Virus with higher extinction coefficient dies earlier than the other virus leading to competitive exclusion and opposing the coexistence cases predicted by the deterministic model.

Conclusion

Stochasticity allows for a weaker virus to out-compete a stronger virus, but only if the difference between the two is not very big.

Future direction

Include associated generation of immune components in the model.