Impact of Interferon on the Antiviral Effects of Defective Interfering Particles

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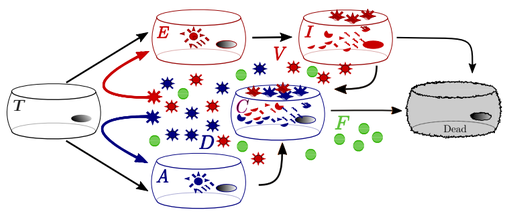
Background

- Defective interfering particles (DIPs) are virions missing the viral genome that allows them to replicate on their own.
- They require co-infection with a standard virion to enable replication, interfering with the production of standard virus in the process.
- DIPs may also stimulate an interferon (IFN) response that further suppresses standard virus replication.
- The aim is to evaluate the impact of DIPs and IFN on viral replication.
- We used Python programming to simulate a modified version of the Kirk and Bangam DIP mathematical model incorporating IFN.

DIP model incorporating IFN



$$
\begin{aligned}
\frac{dT}{dt} &= -\frac{\beta}{1+\epsilon_1 F}(V+D)T \\
\frac{dE}{dt} &= \frac{\beta}{1+\epsilon_1 F}VT - \frac{\beta}{1+\epsilon_1 F}DE - kE \\
\frac{dI}{dt} &= kE - \delta I \\
\frac{dV}{dt} &= \frac{p}{1+\epsilon_2 F}I + \frac{\rho}{1+\epsilon_2 F}C - cV \\
\frac{dA}{dt} &= \frac{\beta}{1+\epsilon_1 F}DT - \frac{\beta}{1+\epsilon_1 F}VA \\
\frac{dC}{dt} &= \frac{\beta}{1+\epsilon_1 F}VA + \frac{\beta}{1+\epsilon_1 F}DE - \delta C \\
\frac{dD}{dt} &= \frac{r}{1+\epsilon_2 F}C - cD \\
\frac{dF}{dt} &= \alpha D - \nu F.
\end{aligned}
$$

- Target cells, T, can be infected by DIPS, D, or standard virus V.
- Cells infected by virus enter an eclipse phase, E, before becoming fully infectious, I.
- Cells infected by DIPS, A, do not produce DIPS unless they are coinfected, C, with standard virus.
- IFN, F, can reduce the infection rate or reduce the viral production rate.

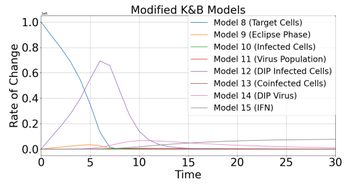
Definitions of model parameters

Model parameters are taken from Kirkwood and Bangham, *Proc. Natl. Acad. Sci. USA* (1994).

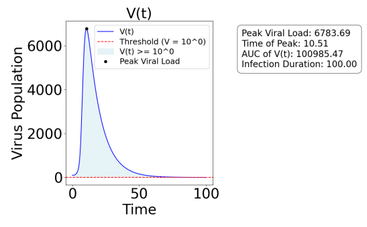
Parameter	Definition	SARS-CoV-2	Units
T_0	initial target cells	1×10^6	cells
V_0	initial viral titer	1×10^4	PFU/mL
D_0	initial DIPs	1×10^6	PFU/mL
β	viral infection rate	1×10^{-6}	$(\text{PFU/mL})^{-1}\cdot\text{h}^{-1}$
k	transition rate from E to I	0.033	h^{-1}
δ	death rate of infectious cells	50	h^{-1}
p	viral production rate	0.5	$(\text{PFU/mL})\cdot\text{h}^{-1}$
c	viral clearance rate	0.1	h^{-1}
r	DIP production rate	5	$(\text{PFU/mL})\cdot\text{h}^{-1}$
α	IFN production rate	0.1	h^{-1}
ν	IFN clearance rate	0.01	h^{-1}
ϵ_i	Strength of IFN response	1	–

Methods

1. We graph the full model system in order to see rates and their relationships with each other.



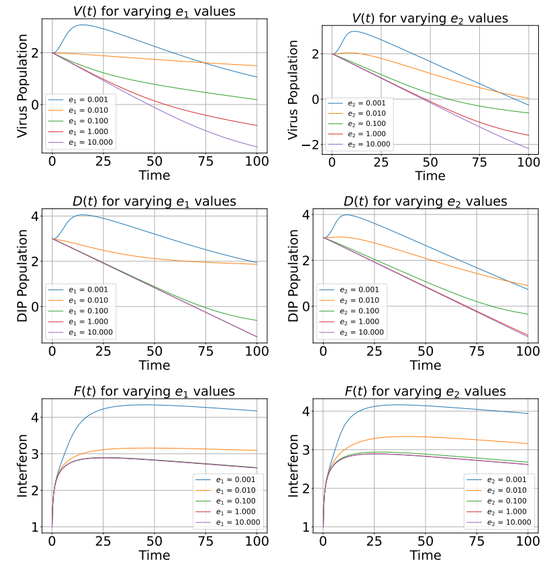
2. We measure features of the viral titer curve, for $V(t)$, specifically peak viral load, time of peak viral load, infection duration, and area under the viral curve.



3. We examine a range of parameter values for r, ϵ_1, and ϵ_2 to assess the effects of DIPs and IFN independently and together.
4. We create heat maps of viral titer features as functions of DIP production rates and IFN response strength in order to discern their impact on infection intensity.

Graphical analysis

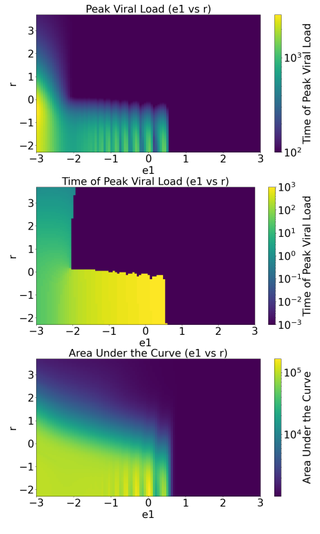
IFN has a number of antiviral effects. We separately examine the effect of IFN reducing the viral infection rate or reducing the viral production rate.



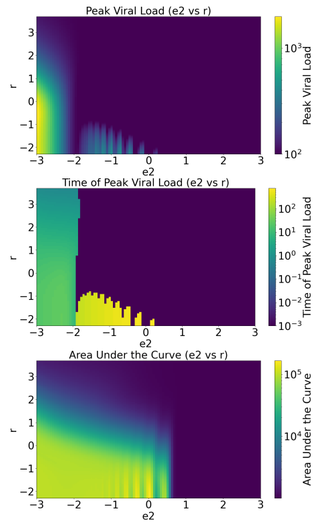
IFN acting on β results in slightly higher DIP production and longer lasting infections than IFN acting on p.

Interferon acting on β

To better explore the interplay of DIP production and IFN effects, we varied both ε_i and r over a wide range.



Interferon acting on p



We again see some differences in infection outcomes depending on the mechanism of action of IFN, although generally high DIP production and a strong IFN effect suppresses standard virus production.

Conclusions

- Increased effect of IFN led to inhibition of the infection.
- Increased DIP production rate led to a reduction in infection intensity.
- There were some differences in how the two mechanisms of IFN viral suppression affect the infection dynamics.
- There appear to be synergistic interactions between DIPs and IFN.

Future directions

- Quantitatively compare the effect of IFN reducing infection rate and IFN reducing production rate.
- Examine a stochastic version of the model to better capture dynamics when the number of virus and DIPS is small.
- Introduce DIPS with a delay to better simulate using DIPs as treatment.
- Incorporate other immune responses such as antibodies or cytotoxic T cells.