Towards a better evaluation of optimal antiviral combination therapy in treating influenza infections

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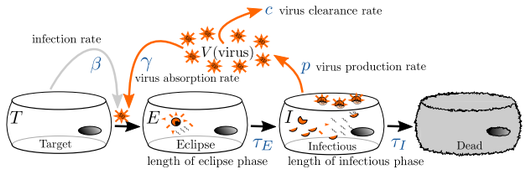
Background

- Since vaccine production takes ∼6 months, antiviral drugs are the first line of defense.
- Two classes of anti-influenza drugs exist, adamantanes (M2 channel inhibitor) such as amantadine, and neuraminidase inhibitors such as oseltamivir.
- Combination therapy can reduce the incidence of drug resistance.

The stochastic model



T → E A target cell enters the eclipse phase (E) with the probability $P = 1 - \exp(-\beta V \Delta t)$

E → I A cell in eclipse phase (E) does not produce virus until it becomes infectious after a time τ_E drawn from a normal distribution.

I → Dead An infectious cell (I) produces virus (V) at a constant rate p for a time τ_I drawn from a normal distribution before it dies (Dead).

V Virus is produced by infectious cells, loses infectivity at a rate c, and is lost due to cell entry at rate $\gamma T V$.

The parameters were determined by fits to in vitro treatment data.

Modelling antiviral efficacy

Antiviral efficacy (ε) is typically represented by

$$\varepsilon = \frac{\varepsilon_{max} D}{D + \mathrm{IC}_{50}}$$

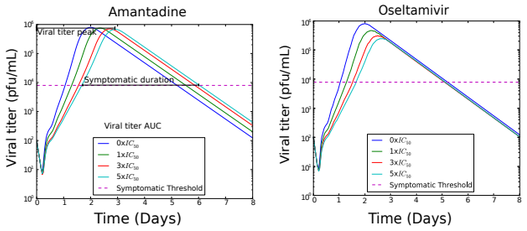
D — drug concentration
ε_{max} — maximum drug efficacy
IC_{50} — drug concentration at which $\varepsilon = \varepsilon_{\max}/2$

Amantadine blocks virion entrance $\beta \to (1-\varepsilon)\beta$

Oseltamivir blocks viral release (= blocks production in model) $p \to (1-\varepsilon)p$

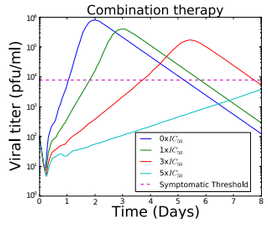
$\varepsilon_{\max}$ is 95% for amantadine, and 76% for oseltamivir.

What does therapy do?



Amantadine shifts the viral titer peak to a later time.

Oseltamivir shifts and decreases the viral titer peak.

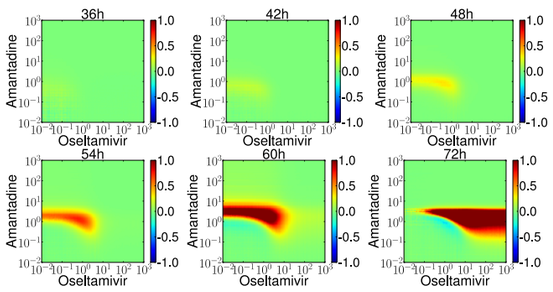


The problems with synergy

When studying combination therapy, synergy is what is typically measured in practice. It is calculated to be:

$$\text{Synergy} \mid \text{Antagony} = W - [M + (1-M)\,N]\,,$$

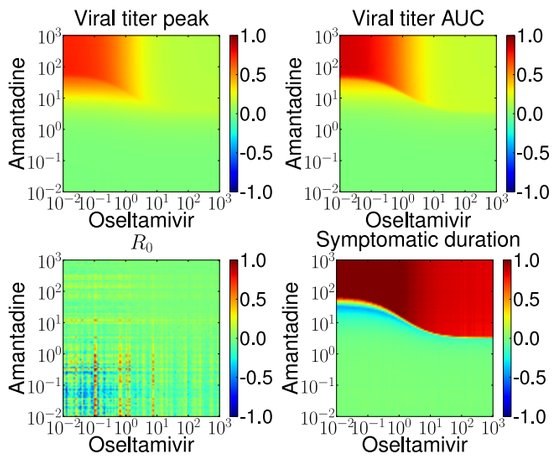
where $W = (1 - V_{\mathrm{treat}}/V_{\mathrm{untreat}})$ is the fractional reduction of viral titer due to the combination, and M and N are the fractional reductions due to monotherapy.



All concentrations are expressed in fold-IC_{50} (*e.g.* 10^2 fold-IC_{50} $= 100 \times \mathrm{IC}_{50}$)

- Optimal synergistic combination depends on time of measurement.
- When concentrations are sufficient to suppress infection ($W = 1 - 0/V_{\mathrm{untreat}} = 1$), synergy cannot be computed.

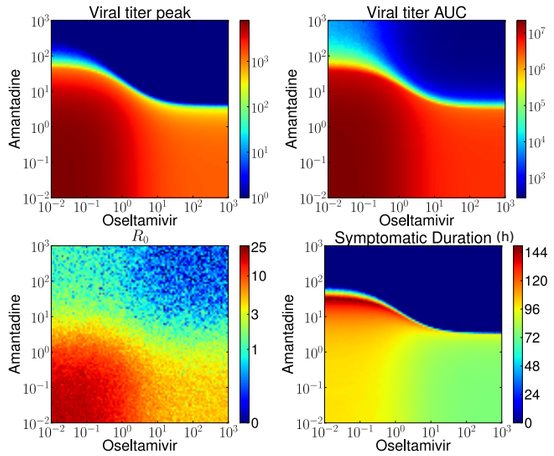
Synergy of severity measures



The basic reproductive number (R_0) is the number of cells a single infected cell will infect over its lifespan.

- Antagony exists in all severity measures (green-blue).
- Low oseltamivir and high amantadine produces the greatest synergistic effect (dark red).
- But what we really want to know is what is the optimal concentration which can suppress the infection...

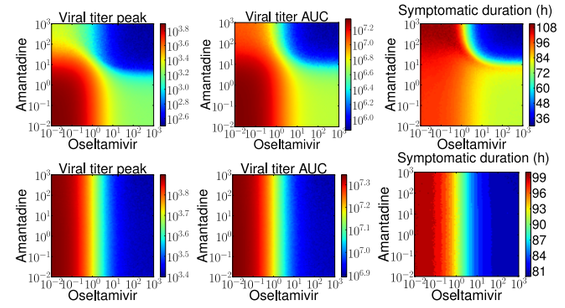
Considering severity measures



When treatment is applied prophylactically (at $t = 0$):

- There is a clear threshold above which the drug combination is sufficient to fully suppress infection (dark blue).
- Optimal drug combinations are found above that threshhold.

What happens if we wait?

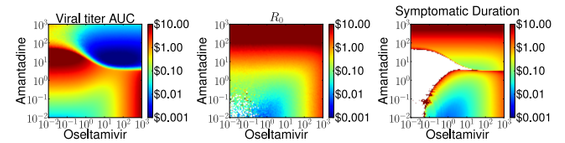


When treatment is initiated at

28 h (top row) the threshold for infection suppression is shifted to higher drug concentrations.

36 h (bottom row) amantadine has no effect since there are no target cells left to infect.

Taking cost into account



Negative cost benefit (bad) = white
Best bang for your buck (best) = blue

We find that some regions of best cost benefit (dark blue) coincide with concentrations which suppress infection.

Conclusion

- Synergy is flawed: it is time-dependent and undefined when antiviral efficacy is sufficient to suppress infection.
- Severity measures allow us to identify a family of drug combinations which suppress the infection → all these concentrations are equally good in this respect.
- From among these combinations, we can now choose optimal candidates based on any additional constraint we choose (e.g., cost).

Where to read more?

- C. Beauchemin, et. al., Modeling amantadine treatment of influenza A virus in vitro. *J. Theor. Biol.*. 254(2):439–451, 2008.
- J. Nguyen et. al., Triple combination of oseltamivir, amantadine and ribavirin displays synergistic activity against multiple influenza virus strains in vitro. *Antimicrob. Agents Chemother.*, 53(10):4115–4126, 2009.