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

KEITH D. POORE, HANA M. DOBROVOLNY, AND CATHERINE A.A. BEAUCHEMIN
Department of Physics, Ryerson University, Toronto, ON

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 \( P = 1 - \exp(-\beta \tau) \)

E → Dead An infectious cell (I) produces virus (V) at a constant rate \( \beta \) and is lost due to cell entry at rate \( \gamma T \).

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

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 by:

\[ \text{Synergy} = \frac{W - (M + (1 - M)N)}{M} \]

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

Modelling antiviral efficacy

Antiviral efficacy \( e \) is typically represented by

\[ e = \frac{e_{\text{max}} D}{D + IC_{50}} \]

- \( D \) — drug concentration
- \( e_{\text{max}} \) — maximum drug efficacy
- \( IC_{50} \) — drug concentration at which \( e = e_{\text{max}}/2 \)

Amantadine blocks virus entry \( \beta \to (1-e)\beta \)

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

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

Synergy of 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 threshold.

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.

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?