Modelling time-dependent drug concentrations with constant drug concentration in within-host models of influenza

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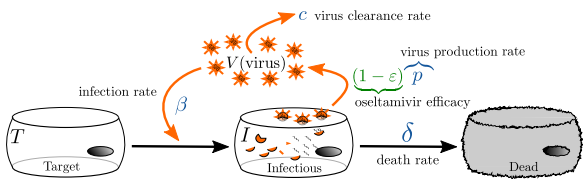
Background

- When studying drug effects in mathematical models of human disease, antiviral concentration is often assumed to be constant for simplicity.
- The drug concentration of oral doses varies with time. Ingestion of a pill causes an increase in drug concentration at the target site followed by decay of the concentration as the drug is metabolized by the body. Thus, the typical drug treatment profile varies with time.
- Pharmacokinetic models can be used to generate realistic time-varying drug concentrations, but can make mathematical analysis difficult when incorporated into viral kinetics models.

Objective

The purpose of this project is to find out if it is possible to simplify the pharmacokinetic model to a constant drug concentration when modelling the effect of oseltamivir on influenza.

Viral Kinetic Model



Viral kinetic model from Baccam et al. (2006).

$$\begin{aligned} \dot{T} &= -\beta TV \\ \dot{I} &= \beta TV - \delta I \\ \dot{V} &= (1-\varepsilon)pI - cV \end{aligned}$$

Parameters of the viral kinetics model were found by fitting the model to data from patients infected with influenza.

$\beta = 1.9 \times 10^{-6}$ [V]$^{-1} \cdot$ h^{-1} $p = 2.3 \times 10^{-3}$ [V] $\cdot$ h^{-1}
$\delta = 0.11$ h^{-1} $c = 0.14$ h^{-1}

Incorporating the Effect of Drug

The following equation

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

converts a time-varying drug concentration, $D(t)$, into a time-varying drug efficacy, $\varepsilon(t)$, for use in the viral kinetic model, where

$\varepsilon_{\max}$ – Maximum drug efficacy
IC_{50} – 50% inhibitory concentration

Pharmacokinetic Model

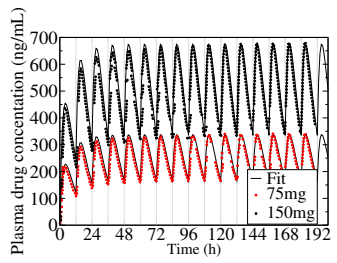
$$D(t) = D_{\text{real}} \left(\frac{[1-e^{-nk\tau}](e^{-kt})}{1-e^{-k\tau}} - \frac{[1-e^{-nk_a\tau}](e^{-k_a t})}{1-e^{-k_a\tau}} \right)$$

$D(t)$ is the time-varying drug concentration used in the viral kinetic model (Dhillon et al., 2006).

τ – Time between doses
k – Decay constant
k_a – Absorption constant
t – Time after n^{th} dose
D_{real} – Oral drug dose
n – Number of doses administered

Oseltamivir Pharmacokinetics

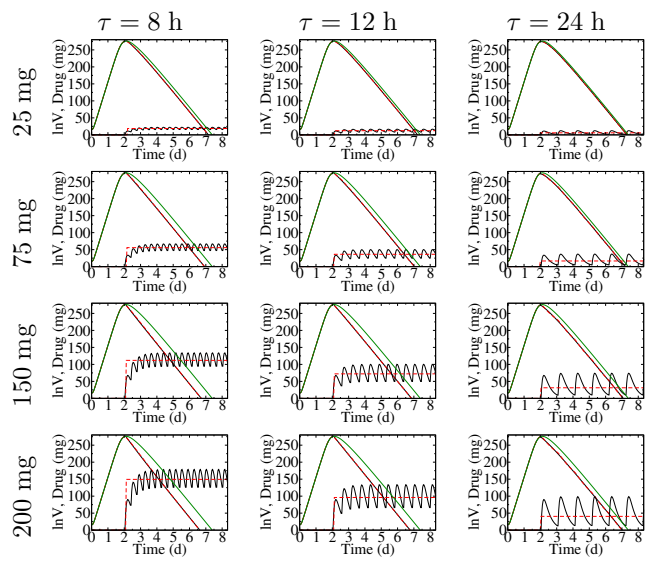
Using least-square fits, pharmacokinetic parameters of oseltamivir are extracted from drug data. Here, oral doses are given twice daily ($\tau = 12$ h).



$k = 0.115$ h^{-1} $k_a = 0.426$ h^{-1}

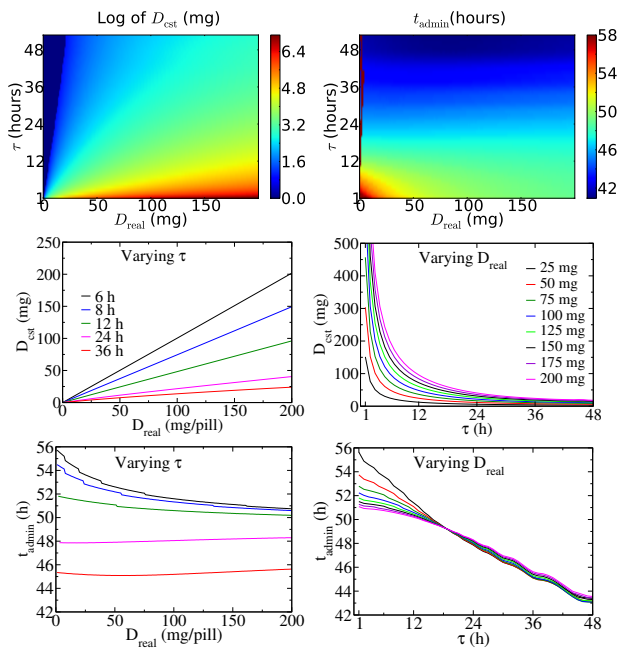
Fitting Procedure

1. Generate viral titer for treatment with a time-varying drug concentration given ingestion of an oral dose D_{real} every τ hours, starting at 48 h post-infection.
2. Use least-square fitting to determine what constant drug dose, D_{cst}, started at time t_{admin}, provides the closest fit to the viral titers obtained under time-varying treatment doses.



Colours as follows: Viral titer in the absence of treatment (—), viral titer and drug concentration for a time-varying (—) and constant drug concentration (- - -). Virus is scaled to make it fit on the graph with drug concentration.

Finding Functional Relationships



A combination of fitting functions to the above graphs and mathematical analysis of the pharmacokinetic model is used to determine equations relating D_{cst} and t_{admin} to D_{real} and τ.

Equations

D_{cst} equation is derived analytically from a first-order Taylor expansion of the pharmacokinetic equation when $t = \tau$.

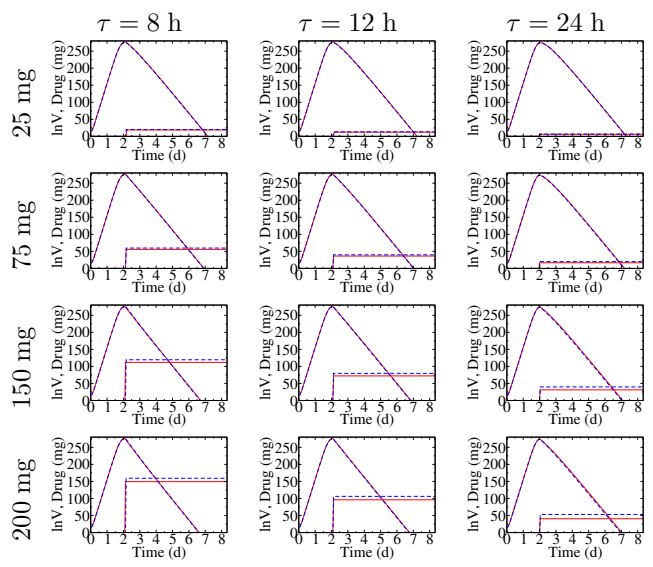
$$D_{\text{cst}} = \frac{D_{\text{real}}}{\tau}\left(\frac{1}{k} - \frac{1}{k_a}\right)$$

t_{admin} was determined from a linear fit to the data and is a work in progress.

$$t_{\text{admin}} = 52.914 \text{ h} - 0.2037\tau$$

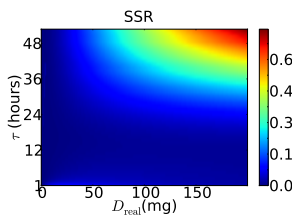
Viral Titers from Equations

Using the equations to find D_{cst} and t_{admin} from D_{real} and τ, we find the viral titers and D_{cst} obtained from these equations (- - -) are a good match to those obtained with the fitted values (—).

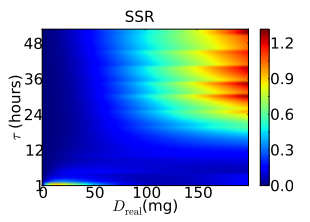


However, there is a slight increase in viral titer SSRs.

SSR of least square fits



SSR of D_{cst} and t_{admin} equations



Conclusions

- We found relationships which allow us to replace a pharmacokinetic model with a constant drug dose.
- While we have mathematically derived an equation for D_{cst}, we have only a heuristic equation for t_{admin}.
- Our D_{cst} equation becomes less accurate when D_{real} and τ are large while the t_{admin} equation is less accurate when τ is small.

Future Work

- Model other drugs for influenza such as amantadine.
- Determine the effect of time of therapy initiation.
- Explore the effects of different viral kinetic models.

References

Baccam, P, C Beauchemin, CA Macken, FG Hayden, and AS Perelson. Kinetics of influenza A virus infection in humans. *J. Virol.*, **80**(15):7590–7599, 2006.

Dhillon, Soraya, and Andrzej Kostrzewski. Clinical Pharmacokinetics. London: Pharmaceutical, 2006.