Sample Phymbie LaTeX Poster using pdflatex

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Abstract

Influenza A has become a growing concern for health authorities worldwide both in its seasonal and pandemic forms. The annual cost of influenza illness and the threat of an imminent pandemic make it necessary to revisit the treatment options currently available. Here, we show that using a controlled experimental system, the hollow fiber infection model (HFIM), it is possible to develop rigorous mathematical models of the course of influenza A infection and the effect of drug pressure. The current work reports on our preliminary experiments examining the effects of amantadine on flu A.

Background

- Until recently, adamantane drugs were the primary prophylaxis and treatment method used to prevent and control influenza infection.
- Resistance to adamantanes emerges rapidly during treatment. Resistant variants show no evidence of fitness impairment and are readily transmissible (Deyde et al., 2007).
- There is now wide-spread resistance among circulating influenza strains worldwide with 90.5% and 15.5% resistance prevalence among H3N2 and H1N1 strains, respectively (Deyde et al., 2007).

Long-term objective

- To develop comprehensive models of influenza infection, its response to drugs, and emergence of drug resistance in multiple systems (tissue culture, animals, humans).

Approach

- Develop simple yet accurate mathematical models to fully capture influenza dynamics in vitro in the presence of drug.

The mathematical models

Simple model

$$\frac{dT}{dt} = -(1-\epsilon)\beta VT$$
$$\frac{dI}{dt} = (1-\epsilon)\beta VT - \delta I$$
$$\frac{dV}{dt} = pI - cV - \gamma TV$$

Eclipse model

$$\frac{dT}{dt} = -(1-\epsilon)\beta VT$$
$$\frac{dE}{dt} = (1-\epsilon)\beta VT - kE$$
$$\frac{dI}{dt} = kE - \delta I$$
$$\frac{dV}{dt} = pI - cV - \gamma TV$$

Delay model

$$\frac{dT}{dt} = -(1-\epsilon)\beta VT$$
$$\frac{dI}{dt} = (1-\epsilon)\beta V(t-\tau)T(t-\tau) - \delta I$$
$$\frac{dV}{dt} = pI - cV - \gamma TV$$

where the free virions (V) are absorbed by target cells (T) which can then become infected (I). The effect of amantadine, $(1-\epsilon)$, is such that it will reduce the rate at which virus (V) successfully infect target cells (T).

Drug is modeled by:

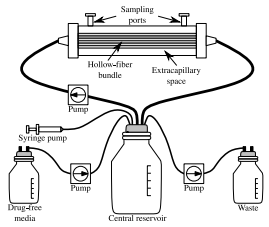
$$\epsilon(t) = \frac{\epsilon_{\max} D(t)}{D(t) + \mathrm{IC}_{50}}$$

where $D(t)$ is the amantadine concentration and $\epsilon_{\max}$ is its maximum effect.

The basic reproductive number is given by

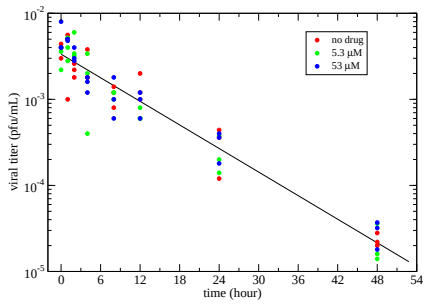
$$R_0 = \underbrace{\frac{p}{\delta}}_{\text{virion/cell}} \cdot \underbrace{\frac{\beta T_0}{c + \gamma T_0}}_{\text{infection rate}}$$

The HFIM experimental model



- HFIM loaded with 10^8 MDCK cells in growth medium + 100 cells pre-infected with A/Albany/1/98 (H3N2) and kept at cst amantadine concentration.
- At t = 22 h, 28 h, 46 h, 72 h, 96 h, and 144 h, 3 mL of the 15 mL of the HFIM are harvested for analysis.

Clearance in the HFIM



Using the model

$$\frac{dV}{dt} = -cV$$

which integrates to

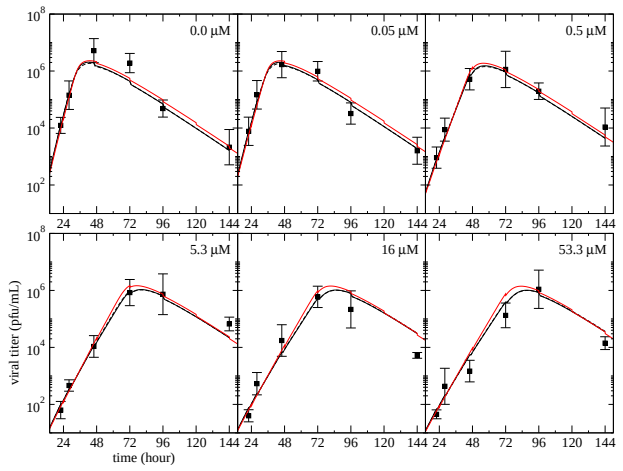
$$V(t) = V(0)\,e^{-ct}$$

or

$$\ln(V) = \ln(V) - ct$$

- Deposited virus + drug → plaque assays at various time to obtain rate of loss of infectivity.
- Linear least square fit: $c = 0.105 \pm 0.003\ \mathrm{h}^{-1}$: half-life of 6.6 ± 0.2 h for influenza virions in HF.

Fitting models to experiments



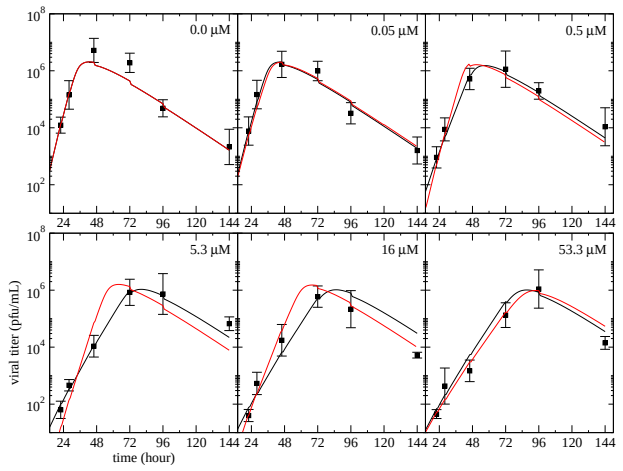
Fit of the simple (–), eclipse (- -), and delay (–) models against the experimental viral titer.

A first stab at drug resistance

We investigated the effect of fixing $\epsilon_{\max} = 95\%$ with

$$\mathrm{IC}_{50} = \begin{cases} 0.40\ \mu\mathrm{M} & t \le \tau_\mu \\ 33\ \mu\mathrm{M} & t > \tau_\mu \end{cases}$$

Drug concentration (µM)	τ_μ (h)
0.0	144
0.05	120
0.5	13
5.3	15
16	9.2
53.3	0



Viral titer when drug resistance is ignored (—) or included in an implicit way (—).

Parameter estimates from the fits

Param.	Simple model	Eclipse model	Delay model
$1/k$ or τ (h)	—	3.2	0.22
$1/\delta$ (h)	13	13	13
p/δ	1.7	1.6	1.7
β/γ	6.9	29	8.8
R_0	11	36	13
IC_{50} (µM)	0.40	0.30	0.38
$\epsilon_{\max}$	0.56	0.74	0.60
SSR	3.6	3.7	3.6
AIC_C	-65	-61	-61

Parameter consistencies

		HFIM vs human primary infection		
System	Model	eclipse phase	infect. cell lifespan	R_0
Human	simple	—	6.0 h	11
	eclipse	6.0 h	4.6 h	22
HFIM	simple	—	13 h	11
	eclipse	3.2 h	13 h	36
	delay	0.22	13 h	13

- Basic reproductive numbers, R_0, found for the HFIM data compared well with those found for an in vivo human infection (Baccam et al., 2006).
- The longer infected cell lifespan and shorter eclipse phase found for the HFIM may reflect active killing of infected cells by the immune system in vivo or differences between MDCK and human lung epithelial cells.
- IC_{50} ~0.3–0.4 µM for amantadine in good agreement with 0.56 µM found for in vitro A/Panama/2007/99 (H3N2) infection of MDCK cells (Ilyushina et al., 2006).

Parameter inconsistencies

- The models predict an infected cell will produce $p/\delta \sim 1.7$ infectious virion over its lifespan.
- Even though cells would be producing ~ 1.7 virion, the basic reproductive number, R_0, suggest they would infect ~ 11–36 cells over their infected lifespan.
- $\beta > \gamma$ suggesting that less than one virion is lost for each cell becoming infected.

Conclusion

- The controlled experimental system allows the use of simple yet accurate mathematical models to quantify the dynamics of the experiments.
- The parameter values found were consistent with those available for a human influenza infection.
- The results indicated that experimental manipulations accounted for a loss of ~ 90% of infectious virions: a fact that was verified experimentally.
- We showed that the rapid emergence of drug resistance over the course of a single treatment can account for the low efficacy (~ 56–74%) found for amantadine.
- This work constitutes a first step in developing a combination of experimental and theoretical tools to quantitate drug effects and the emergence of drug resistance over the course of an influenza infection.

Where to read more?

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