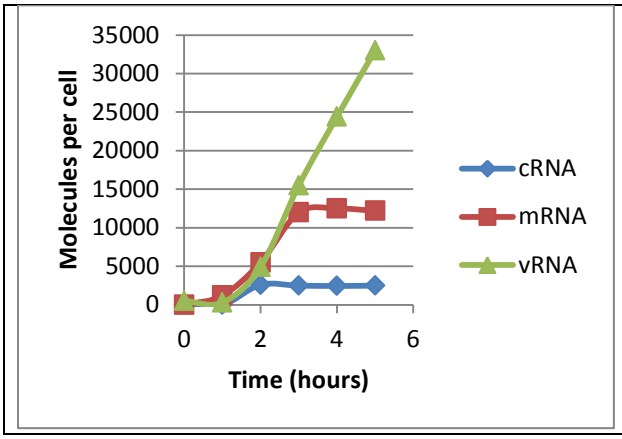
MODELING INFLUENZA REPLICATION

"Influenza A virus is an enveloped negative-strand RNA virus, whose genome comprises eight single-stranded RNA segments. Each RNA segment forms a ribonucleoprotein (RNP) complex with the viral polymerase subunits (PB1, PB2 and PA) and the nucleoprotein (NP). The life cycle of influenza A virus begins with the attachment to cell surface receptors, followed by internalization of virions into cells. After uncoating, viral RNPs (vRNPs) are transported into the nucleus, where genome replication and transcription take place. The viral RNA (vRNA) is then transcribed into mRNA, which is used to produce viral proteins, and replicated via complementary RNA (cRNA). The viral polymerases and NP catalyze both genome replication and transcription. The intracellular kinetics of these three types of RNA (i.e., vRNA, cRNA, and mRNA) differs. In the early phase of infection, viral mRNA is predominantly synthesized to produce viral proteins, whereas in the late phase of infection, mRNA synthesis stops and the replication reaction dominates." (*in* Kawakami et al. *J. Virol Meth.* (2011)). **However, the mechanism by which these differences occur is not well known. In addition, different segments have slightly different replication kinetics. A dynamical model of these events could help shed light into the relevant mechanisms.**

As an example, the replication kinetics of the three types of RNA for the NP segment of influenza are shown below (both in graphical and table form) (from Hatada et al. *J. Biochemistry* 1989).



Time	cRNA	mRNA	vRNA
0	0	0	500
1	0	1200	300
2	2600	5500	4900
3	2500	12000	15500
4	2450	12500	24400
5	2500	12200	33000

One potential (simple) model to describe these kinetics, based on a the biology of infection, is given by

$$\frac{dV}{dt} = \alpha_1 C - (\mu_1 + \theta P)V$$
$$\frac{dV_{out}}{dt} = f\theta V$$
$$\frac{dC}{dt} = rV\left(1 - \frac{C}{C_{\max}}\right) \quad ,$$
$$\frac{dM}{dt} = \alpha_2 V - \mu_2 M$$
$$\frac{dP}{dt} = \sigma M - \mu_3 P$$

where C, M and $V_{out}+V$ represent, respectively, cRNA, mRNA and total vRNA.

The objective of this project is to explore this model to find parameter values that qualitatively reproduce the data presented. Since both mRNA and cRNA seem to attain a (quasi) steady state, the parameters can initially be constrained by finding the steady states of these species in the model (if they exist) and using that information to define some of the parameters. If it is not possible to find a suitable set of parameters, extensions of the model could be considered.