Response to the Editor and Reviewers

**Manuscript ID:** 221728399 (Journal of Biological Dynamics)

**Title:** An eclipse-phase lag drives oscillations in a viral infection model with a general growth function

**Authors:** Menghan Chen, Lin Wang and James Watmough (corresponding author).

**E-mail:** James Watmough <watmough@unb.ca>

**Dear Editor:**

We would like to thank you for your time and efforts in reviewing and handing our manuscript. According to the reviewers’ comments, we have carefully revised our manuscript to meet with the journal standards. We believe that the quality of our paper has been improved and hope that the revised manuscript is suitable for publication.

Thank you very much for your consideration. I look forward to hearing from you soon.

Yours sincerely,

Corresponding author: James Watmough

**Response to Reviewers**

**Dear Reviewers,**

We are grateful for your in-depth reviews and valuable suggestions for us to improve our paper. Following your suggestions, we have carefully revised our paper and addressed all of your concerns. Here we will response to your comments point by point.

Yours sincerely,

Corresponding author: James Watmough

**Responds to the reviewers’ comments:**

Reviewer 1

This work concerns the impact of eclipse phase to the process of viral infection. The

authors used the within host model derived by Jenner et al, and made generalization. Formal mathematical analysis has been conducted with numerical simulations. The

study was in general well designed and most of the analysis is correct. One of my major concerns is the novelty of the study. The authors claimed, in section of introduction (last line in Page 3), the novelty of the paper includes “consider the possibility of the survival of infected cells from t-\tau to t”. This is incorrect. There are numerous papers have considered this important factor, which is obviously important in the early stage of viral infection. I am also not quite sure about the second novelty the authors claimed, but perhaps the authors should list some references regarding dynamical systems and the analysis for within host ODE/DDE models and then clearly state the limitations of previous papers. I do not agree with the third novelty, as the important role of eclipse phase in the viral infection process has been clearly emphasized and discussed in many previous papers. Please consider to cite some relevant papers by Alan Perelson, Linda Allen, Alun Lloyd, Jane Heffernan, Catherine Beauchemin and others. Here are some minor suggestions:

**Response**

We reworked the model to include latent infected cells as a new variable (L). Although Jenner et al. and other scholars also focused on the eclipse phase, it was not explicitly stated, meaning that their model assumes that eclipse-phase cells do not appear in the density-dependent cell growth term. We have made additions based on this.

In addition, we reworked our innovative work in the penultimate paragraph of the introduction.

1. The abstract is kind of difficult to read, please consider to rephrase this part. For

example: what is “the period between activation and infectivity”? I don’t think

this is an appropriate name. What is “these process”? Please clearly state what

the important parameters are, in the sentence of “..the role of eclipse time delay

and important parameters…”. Please rephrase the sentence “… but can also

destabilize and stabilize…”.

**Response**

We have restated the abstract section.

1. Line 6 Page 1, please rephrase “it is precisely because…”

**Response**

We have modified this in the first paragraph of the introduction and marked it in red.

3. Please also consider to re-write the second paragraph of introduction, there is

lack of logic.

**Response**

The second paragraph of the introduction has been revised and the logic reworked.

4. For both model 1 and model 2, I have difficulty in understanding the biological

meaning of the transition rate d\_D.

**Response**

My understanding of d\_D is that apoptotic cells can be engulfed by phagocyte cells. However, phagocytic cells are not considered in the model, so the biological process follows the self-clearance of apoptotic cells.

5. Page 15, I am curious about whether there are other forms of function f(S,I,D),

other than the one proposed by Jenner.

**Response**

The f (S, I, D) function also includes the following forms.

,，

We have also added in the main manuscript.

1. First paragraph of section 4.1 seems a repetition.

**Response**

We have removed the beginning of section 4.1. We have only described the main content to be studied in this section.

1. Please mention the connections between Table 1 and Table 2.

**Response**

In Section 4.1, we give the connection between Table 1 and Table 2. and show for which simulations the data 1 and data 2's are used respectively.

8. Are parameter values in Table 2 realistic? Whether the authors have justified their choices of parameter values?

**Response**

Some are deterministic parameters derived from experimental findings. Others are certain ranges of parameters derived from experimental findings, within which deterministic parameters are selected based on certain theoretical studies.

1. The conclusion and outlook part is relatively weak. The area of within host modeling is very important and there are so many open problems, I think this part needs more effort.

**Response**

The conclusion and outlook sections have all been restated.

Reviewer 2

The current manuscript investigates the dynamics of a viral infection model where eclipse-phase delay is included. The analytical techniques involved are linear stability analysis, Lyapunov functional approach and bifurcation theory. Local/global stability, as well as bifurcations are observed in various parameter regions. In summary, theoretical results seem correct. However, the manuscript should be substantially reorganized, in particular, the arguments in proof, including those in L210-250. Furthermore, a thorough check of the whole manuscript should be performed, to correct following items and other similar points:

**Response**

In lines 210-250, we readjusted the order of theoretical analysis. We first verify Beretta and Kuang 's five conditions. The distribution of roots of equation (31) under different conditions of lemma 3.3 and 3.4 is discussed again.

1. \item Line 72: ``Section 3.1" should be ``Subsection 3.1"; ``Section 3.2" should be ``Subsection 3.2"; ``Section 3.3" should be ``Subsection 3.3"

**Response**

``Section 3.1/3.2/3.3" has been changed to``Subsection 3.1/3.2/3.3"in our paper.

1. \item Line 80: What is function $h$?

**Response**

$h$ is a function that has the same assumption as f. Hence, h (x, w, y, z) <h (x). The function g (x) =s (\ Smax-x), ensure that all h (x) < g (x). Based on this inequality, the equation (4) is obtained to prove the boundedness of the solution.

1. \item What is $\Gamma$ in Line 86

**Response**

$ \ Gamma $ is the positive invariant set obtained by the second part of the proposition 2.2 proof. That is, if the trajectory starting from an initial point in $ \ Gamma $ remains permanently in $ \ Gamma $, then $ \ Gamma $ is an invariant set.

1. \item L99: ``," should be ``."

**Response**

We check all punctuation issues in the Proposition 2.2.

\item L393: ``CoViD-19"

**Response**

1. We have replaced all ``CoViD-19' in our paper with ``Covid-19".

Reviewer 3's remarks follow.

Comments on TJBD-2022-0098 eclipse-phase dynamics cause oscillations

1. The abstract and title do not make clear what quantity is oscillating: number of infected individuals in a population, viral load within a single patient, etc. Add a few words to the start of the abstract, and consider tweaking the title, to make clear at the outset that the oscillations involve within-host dynamics.

**Response**

At the beginning of the abstract, we revised that oscillation refers to the viral load within the single infected patient and revised the title.

(2) The model (2) is not quite a generalization of (1) because cells in the eclipse (latent) phase disappear entirely from the system temporarily--they leave S at time t-tau and only reappear (in I, minus attrition) at time t. If dead cells reduce susceptible cell reproduction, shouldn't latent-phase cells be accounted for in some way also? At present, during eclipse phase they do not affect reproduction or any other process in the model, but physically they are still taking up space.

**Response**

We reconsidered the model and included the latent infected cells as a new variable. The specific model is shown in the manuscript, models 2a-2e. The schematic diagram is shown in Figure 1.

(3) In hypothesis H\_1, do you want f to be monotone decreasing (or at least nonincreasing) in I and D? Your condition f(S,I,D)<f(S,0,0) merely ensures that reproduction is less with infected and dead cells than without, but does not preclude a decrease (as I or D increases) followed by an increase, etc.

**Response**

On page 2, H1, we have made a change to this issue and marked it in blue.

1. Typo on line 329 where one sentence breaks off into a new sentence which doesn't parse. Also all authors are duplicated in [1] in the bibliography.

**Response**

We revised the sentence in line 329 and the error in bibliography [1].

1. Use paragraph breaks (and perhaps some editing) in the (long) first paragraph of the Discussion section to separate the summary of results from the conclusions to be drawn.

**Response**

The discussion section is divided into two paragraphs. The first paragraph is the mathematical result obtained, and the second paragraph is the biological conclusion obtained.