ABSTRACT. Viral dynamics within plant hosts can be important for understanding plant disease prevalence and impacts. However, few mathematical modeling efforts aim to characterize within-plant viral dynamics. In this paper, we derive a simple system of delay differential equations that describes the spread of infection throughout the plant by barley and cereal yellow dwarf viruses via the cell-to-cell mechanism. By incorporating ratio-dependent incidence function and logistic growth of the healthy cells, the model can capture a wide range of biologically relevant phenomena via the disease-free, endemic, mutual extinction steady states, and a stable periodic orbit. We show that when the basic reproduction number is less than 1 ($R_0 < 1$), the disease-free steady state is asymptotically stable. When $R_0 > 1$, the dynamics either converge to the endemic equilibrium or enter a periodic orbit. Using a ratio-dependent transformation, we show that if the infection rate is very high relative to the growth rate of healthy cells, then the system collapses to the mutual extinction steady state. Numerical and bifurcation simulations are provided to demonstrate our theoretical results. Finally, we carry out parameter estimation using experimental data to characterize the effects of varying nutrients on the dynamics of the system. Our parameter estimates suggest that varying the nutrient supply of nitrogen and phosphorous can alter the dynamics of the infection in plants, specifically reducing the rate of viral production and the rate of infection in certain cases.
1. Introduction.

1.1. Background and motivation. Plants comprise the majority of biomass on Earth [5] and many are infected with viruses [11, 39]. Plant-virus interactions – ranging from mutualistic to antagonistic [38] – may influence ecosystem processes [32]. Models of within-host viral dynamics are crucial for “scaling up” host-virus interactions [12] and can help evaluate the contributions of viral replication and host immunity to disease transmission and virulence [2, 19, 27].

The globally-distributed barley and cereal yellow dwarf viruses (B/CYDVs) can infect over 150 grass species, including major crops such as oats, rice, wheat, and barley [15]. Like many other plant viruses, B/CYDVs are transmitted by aphids, which feed on phloem sap – the fluid that transports sugars and other molecules throughout vasculature of plants [15, 35]. Plant viruses have two general pathways to move through plants: cell-to-cell and through the vascular tissue (i.e., xylem and phloem) [42]. Phloem-limited viruses, such as B/CYDVs, can only move between phloem-associated cells and travel in phloem sap [20, 42], making them reliant on phloem-feeding insects [7]. Other viruses can enter plants from outer cells and move between different types of cells [42]. While cell-to-cell transmission is generally less efficient than phloem movement because viruses must cross cell wall plasmodesmata, the phloem contains its own set of challenges for viruses, including plant defense molecules [7]. Direct cell-to-cell transmission and phloem movement of free viruses are both important for understanding within-plant viral dynamics.

Together, viral replication and transmission between cells can describe the population density of viruses within plants [34, 37]. In general, viral infection of a cell only leads to the production of new virus particles after a delay in time [1, 22]. Delayed differential equations can explain empirical patterns of animal [17, 45] and plant [37] viruses. Time delays in animal virus models that assume cell-to-cell virus transmission can induce oscillations that are absent from models that assume cell-to-free virus transmission [14]. Including cell-to-cell virus transmission in a model with a time delay provides additional biological realism that may improve the model fit to plant virus observations demonstrating non-linear dynamics [37].

There have been numerous attempts at modeling within-host viral infections using delayed differential equations in both cases of virus-to-cell and cell-to-cell transmission. However, most of these studies focused on the within-host dynamics of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) [17, 43, 45]. On the other hand, while the dynamics of vector-host for plant virus has been studied using delay differential equations [25], within-host dynamics of plant viruses are much less explored. For this study, we modified the model by Pell et al. [37] to assume cell-to-cell transmission rather than cell-to-free virus transmission. By assuming that transmission is ratio-dependent rather than mass action, we approximate the rigid cell configuration of plants. We carry out the analysis of the cell-to-cell model and compare our results with the often-used mass action model of transmission. The cell-to-cell transmission model is fitted to the data obtained in Kendig et al. [26] for validation and to obtain further biological implications.

Several studies have shown links between varying nutritional supplies of phosphorus, nitrogen, potassium, and micro-nutrients and plant and virus growth and production rates [30, 31]. Kendig et al. [26] measured B/CYDV virus growth over four levels of phosphorus and nitrogen supply, allowing us to examine model performance with multiple time series of virus dynamics under controlled conditions and study how varying nutritional supplies can affect viral dynamics.
In section 2, we introduce the cell-to-cell transmission model along with further motivations. In section 3, we study some preliminary properties of the model. In particular, we show the existence and boundedness of solutions. Section 4 deals with the stability of the disease-free steady state. The permanence of the system is analyzed in section 5. Via a ratio-dependent transformation, we study the mutual extinction steady state in section 6. The numerical and bifurcation study for the endemic equilibrium is carried out in section 7. Next, we carry out data fitting and study the implication of varying nutrients in host-pathogen dynamics of plants in section 8. Finally, we discuss our findings in section 9.

1.2. Data. The data set used for our study comes from the study by Kendig et al. [26]. Individual oat plants (Avena sativa) were inoculated with aphids carrying one species of CYDV, RPV, and the concentration of virions (i.e., virus particles) per plant were measured periodically over 29 days. To test the effect of host nutrition on virus growth, the plants received one of four treatments (experiments) representing a full factorial combination of low and high nitrogen (N) and phosphorus (P): low N and P (“control” or “low experiment”), elevated N (“+N experiment”), elevated P (“+P experiment”), elevated N and P (“+NP experiment”). For more details on the methods, please refer to Kendig et al. [26].

2. Method. If we consider cell-to-cell transmission to be the main mode that virus spreads through plant cells, then upon contact between an infected cell and a healthy cell, there is a probability that the virus is transmitted successfully. One usual way to model such interaction is to use the traditional prey-dependent Lotka-Volterra type predator-prey model with Michaelis-Menten (or Holling type II) functional response, or sometimes just mass actions. However, the prey-dependent predator-prey system is known to exhibit the controversial “paradox of enrichment” [40] and “biological control paradox” [24, 33], which hinders their biological relevance and applicability. Additionally, some have pointed out the ambiguity in the parameters in certain contexts [6, 21]. Furthermore, mutual extinction is not possible. Yet, mutual extinction of predator and prey is observed in nature [18] and while such phenomenon is rare in plant-virus interaction, it is also possible [16]. To address this limitation, Kuang and Beretta [28] provide a detailed qualitative analysis and motivation for the use of ratio-dependent predator-prey system. Since then, this approach has gained traction due to various applications in biological settings. Additionally, the main aim of mathematical modeling is to be able to capture the various dynamical possibilities of a biological system using just enough complexity. This further motivates our approach in this study.

Following the work of Pell et al. [37], we derive a system of delay differential equations assuming cell-to-cell transmission is the main mode of viral spreading. The total infected cells at any time is given by:

\[ I(t) = \int_0^\tau e^{-\delta u} \frac{\beta S(t-u)I(t-u)}{S(t-u)+I(t-u)} du, \]

where \( \delta \) is the natural death rate of infected cells, \( \tau \) is the delay in virus production after a cell is infected, \( \frac{\beta S(t-u)I(t-u)}{S(t-u)+I(t-u)} \) is the rate of infection at \( t-u \), and \( e^{-\delta u} \) is the probability that the infected cell survives from \( t-u \) to \( t \). With a change of variable, this becomes:

\[ I(t) = \int_{t-\tau}^t e^{-\delta(t-s)} \frac{\beta S(s)I(s)}{S(s)+I(s)} ds. \]
By differentiation, we get the governing equation for $I$.

$$I' = \frac{\beta SI}{S + I} - \delta I - e^{-\delta \tau} \frac{\beta S(t-\tau)I(t-\tau)}{S(t-\tau) + I(t-\tau)}.$$  \hspace{1cm} (3)

We assume the dynamics of the healthy phloem cell follows a logistic growth with a natural death rate $m$, where $m < \delta$.

$$S' = r \left(1 - \frac{S + I}{K}\right) S - mS - \frac{\beta SI}{S + I}. \hspace{1cm} (4)$$

By a change of variable $\bar{r} = r - m$ and $\bar{K} = K \frac{\bar{r}}{r}$, we obtain:

$$S' = \bar{r} \left(1 - \frac{S + I}{\bar{K}}\right) S - \frac{\beta SI}{S + I}. \hspace{1cm} (5)$$

Dropping the bar notation, the cell-to-cell model takes the form:

$$S' = r \left(1 - \frac{S + I}{K}\right) S - \frac{\beta SI}{S + I}$$

and

$$I' = \frac{\beta SI}{S + I} - \delta I - e^{-\delta \tau} \frac{\beta S(t-\tau)I(t-\tau)}{S(t-\tau) + I(t-\tau)}.$$  \hspace{1cm} (7)

The initial conditions are: $S(s) = S_0(s) \geq 0$, $I(s) = I_0(s) \geq 0$ and $K \geq S(s) + I(s) > 0$, $I(0) > 0$ for $s \in [-\tau, 0]$.

3. Preliminary: existence, boundedness and steady states. Before we proceed to the analysis of the cell-to-cell model, we note that the basic reproduction number for the cell-to-cell model takes the form:

$$R_0 = \frac{\beta - \delta}{\delta e^{-\delta \tau}}.$$  \hspace{1cm} (8)

First, we show the positive invariance property of the cell-to-cell transmission model.

**Theorem 3.1.** The solution for system Eq. (6)-(7) with the given constraints exists, is unique and remains non-negative and bounded for all $t > 0$.

**Proof.** Note that the system Eq. (6)-(7) is locally Lipschitz at $t = 0$. This means solution of Eq. (6)-(7) exists and is unique on $[0, c]$ for some $c > 0$. To show positivity, we first proceed to show that $S$ and $I$ are bounded by $K$ for all $t > 0$. Since $S(0) = 0$ implies $S(t) \equiv 0$, we will assume $S(0) > 0$. For similar reason, we assume $I(0) > 0$. Observe that for $t \in [0, \tau]$,

$$\frac{d(S + I)}{dt} = r \left(1 - \frac{S + I}{K}\right) S - \beta e^{-\delta \tau} \frac{S(t-\tau)I(t-\tau)}{S(t-\tau) + I(t-\tau)} - \delta I.$$  \hspace{1cm} (9)

Since $I(t) = \int_{t-\tau}^{t} \beta e^{-\delta \tau} \frac{S(s)I(s)}{S(s) + I(s)} ds$, this implies $I(t) > 0$ for $t \in [0, \tau]$. Thus we obtain:

$$\frac{d(S + I)}{dt} \leq -\frac{r}{K} (S + I - K)S.$$  \hspace{1cm} (10)

This implies $\frac{d(S + I - K)}{dt} \leq -\frac{r}{K} (S + I - K)S$. It follows that for $t \in [0, \tau]$,

$$S(t) + I(t) \leq K + [S(0) + I(0) - K] e^{-\frac{r}{K} \int_{0}^{t} S(s) ds} \leq K,$$  \hspace{1cm} (11)

where the last inequality is because we assume $K > S(0) + I(0)$. Note that if we can show $S(t)$ and $V(t)$ stay positive for $t \in [0, \tau]$ and the solution exists for all positive time. Then, it follows that $S(t) + I(t) < K$ for all $t > 0$. Now we proceed to show the positivity of $S$ and $I$. Toward a contradiction, we suppose there exists
a time $t_1 \in (0, c)$ such that $S(t_1) = 0$, $S(t) > 0$ and $I(t) > 0$ for $t < t_1$. Note that if $t_1 > \tau$, then we can consider the interval $[n\tau, t_1]$ where $n$ is the largest integer such that $n\tau < t_1$. By doing interval-wise, we preserve the condition $K > S(t) + I(t)$. Thus, without loss of generality, we assume $t_1 < \tau$. For $t \in [0, t_1]$, we have

$$\frac{dS}{dt} = r \left( 1 - \frac{S + I}{K} \right) S - \frac{\beta SI}{S + I} \geq -\alpha_1 S,$$

where $\alpha_1 = \max_{t \in [0, t_1]} \{\beta I\}$. This implies $S(t) \geq S(0)e^{-\alpha_1 t} > 0$, which is a contradiction.

One more time, we assume there is $t_2 \in (0, c)$ such that $I(t_2) = 0$, $S(t) > 0$, and $I(t) > 0$ for $t < t_2$. Without loss of generality, we take $t_2 < \tau$. Since $I(t) = \int_{t_2}^{t_1} \beta e^{-\delta \tau} \frac{S(s)I(s)}{S(s)+I(s)} ds$, we have that

$$I(t_2) = \int_{t_2-\tau}^{t_2} \beta e^{-\delta \tau} \frac{S(s)I(s)}{S(s)+I(s)} ds > 0,$$

which is a contradiction. By the above consideration, the solution of Eq. (6)-(7) is positively invariant on $t \in [0, c)$.

Finally, to show that the solution exists globally. Suppose there is $t_0 > 0$ such that $W = S + I$ exists on $[0, t_0)$, but $\lim_{t \to t_0^-} W(t) = +\infty$. Observe that

$$\frac{dW}{dt} \leq rS - \delta I + (\delta S - \delta S) \leq (r + \delta)K - \delta W.$$

Thus, $\limsup_{t \to +\infty} W \leq \frac{(r+\delta)K}{\delta}$, which is a contradiction. Thus the solution of Eq. (6)-(7) exists globally, is unique and remains non-negative. \qed

Now, we consider equilibria of the cell-to-cell models.

**Proposition 1.** The cell-to-cell model eq. (6)-(7) has a boundary steady state, $E_0 = (K, 0)$, where the infected population becomes extinct. Furthermore, assume $R_0 > 1$, then the positive steady state $E^* = (S^*, I^*)$ exists and can be expressed explicitly.

$$I^* = \frac{K}{r} \left( 1 - \frac{\delta}{\beta(1-e^{-\delta \tau})} \right) \left( r - \beta + \frac{\delta}{1 - e^{-\delta \tau}} \right)$$

$$S^* = \frac{\delta}{\beta(1-e^{-\delta \tau}) - \beta I^*}.\quad (17)\quad (18)$$

*Proof.* Setting both equations to 0 to obtain:

$$0 = \left[ r \left( 1 - \frac{S + I}{K} \right) - \frac{\beta I}{S + I} \right] S \quad (19)$$

$$0 = \left[ \frac{\beta S}{S + I} - \delta - e^{-\delta \tau} \frac{\beta S}{S + I} \right] I \quad (20)$$

We find that: $E_{(0,0)} = (0, 0)$ is an equilibrium that is undefined and needs to be blown up to study. $E_0 = (K, 0)$ is a boundary steady state. And for the positive steady state, assuming $S > 0$, we have:

$$(1 - e^{-\delta \tau}) \frac{\beta S}{S + I} = \delta.\quad (21)$$
Solving for $S$,
\[ S = \frac{\delta I}{\beta(1-e^{-\delta \tau}) - \delta}. \tag{22} \]
This gives the condition for the existence of positive steady state: $\beta(1-e^{-\delta \tau}) - \delta > 0$, which is equivalent to $R_0 > 1$. We can then solve for the explicit form of the positive steady state.

To look at the stability, consider the characteristic equation of the cell-to-cell model, $h(\lambda) = \det(\lambda I - P - e^{-\lambda \tau}Q)$, where
\[
P = \begin{pmatrix} \frac{\tau(K-2S-I)}{K} & -\frac{\beta I^2}{(S+I)^2} \\ -\frac{\beta S^2}{(S+I)^2} & -\frac{\tau S - \frac{\beta S^2}{(S+I)^2}}{\beta S^2} \end{pmatrix} \tag{23}
\]
and
\[
Q = e^{-\delta \tau} \begin{pmatrix} 0 & -\frac{0}{(S(t-\tau)+I(t-\tau))^2} \\ -\frac{\beta S^2(t-\tau)}{(S(t-\tau)+I(t-\tau))^2} & -\frac{0}{(S(t-\tau)+I(t-\tau))^2} \end{pmatrix}. \tag{24}
\]
Together, they give:
\[
h(\lambda, \tau) = \lambda^2 + \lambda(-P(1,1) - P(2,2)) + (-Q(2,2))\lambda e^{-\lambda \tau} + (P(1,1)P(2,2) - P(1,2)P(2,1)) + (P(1,1)Q(2,2) - P(1,2)Q(2,1)) e^{-\lambda \tau}. \tag{25}
\]

To clarify, the notation $(i, j)$ represents the corresponding $i^{th}$ row and $j^{th}$ column element of the matrix.

4. Disease-free steady state. Then, at $E_0 = (K, 0)$, the characteristic takes the form:
\[
h(\lambda, \tau) = \lambda^2 + \lambda(r - \beta + \delta) + \lambda e^{-\lambda \tau}(\beta e^{-\delta \tau}) + (r \delta - r \beta) + e^{-\lambda \tau}(r \beta e^{-\delta \tau}). \tag{26}
\]
Simplifying gives:
\[
h(\lambda, \tau) = (\lambda + r)(\lambda + (\delta - \beta) + \beta e^{-(\lambda + \delta) \tau}) \tag{27}
\]
This gives $\lambda_1 = -r$ as one of the roots of the characteristic equation. To find the remaining roots, define:
\[
g(\lambda) = \lambda + (\delta - \beta) + \beta e^{-(\lambda + \delta) \tau} \tag{28}
\]
Since $\lambda$ solves $g(\lambda) = 0$, replace $\lambda = x + iy$ where $x, y \in \mathbb{R}$ into $g(\lambda)$ to obtain:
\[
-x + iy = -\beta + \delta + \beta e^{-(x+\delta) \tau}(\cos(y\tau) - i \sin(y\tau)) \tag{29}
\]
Equating the real parts:
\[
-x = (-\beta + \delta) + \beta e^{-(x+\delta) \tau} \cos(y\tau). \tag{30}
\]

**Lemma 4.1.** If $R_0 > 1$, then $E_0$ is unstable.

*Proof.* Assume $R_0 > 1$. Rearranging $x$ to obtain:
\[
x = (\beta - \delta)(1 - \frac{1}{R_0} e^{-x\tau} \cos(y\tau)) > 0. \tag{31}
\]
Since the real part of $\lambda > 0$, $E_0$ is unstable.

**Lemma 4.2.** If $R_0 < 1$, then $g(\lambda) = 0$ cannot have purely imaginary roots.
Proof. If $\lambda = iy$, then expanding $g(iy) = 0$ and equating the real and imaginary parts (respectively) give

$$y + \beta e^{-\delta \tau} \sin(y\tau) = 0,$$

$$-(\beta - \delta) + \beta e^{-\delta \tau} \cos(y\tau) = 0.$$  \hfill (32)

Solving for $y$ in equation 33 and plug it into equation 32, we obtain

$$\frac{1}{\tau} \cos^{-1}(R_0) + \beta e^{-\delta \tau} \sqrt{1 - R_0^2} = 0,$$

which is impossible for positive values of $\tau$ and $\beta e^{-\delta \tau}$, when $R_0 < 1$. $\square$

**Theorem 4.3.** If $R_0 < 1$, then $E_0$ is locally asymptotically stable.

**Proof.** Consider the family of function $g_\epsilon(\lambda) = \lambda - (\beta - \delta) + \beta e^{-\delta \tau} e^{-\lambda \tau}$ with $\epsilon \in [0, 1]$. Since $g_\epsilon(\lambda)$ is analytic, so $g_\epsilon(\lambda) = 0$ has finitely many roots that are uniformly bounded in every half-plane $\Re(\lambda) > \beta, \beta \in \mathbb{R}$. From Lemma 4.2, there is no roots of $g_\epsilon(\lambda) = 0$ on the imaginary axis. Thus, we can take $\psi$ to be a closed contour in $\Re(\lambda) > 0$, which encloses all the roots with $\Re(\lambda) > 0$ for all $\epsilon \in [0, 1]$.

Since $g_\epsilon(\lambda)$ continuously depends on $\epsilon$, for each $\epsilon$, we can define an open neighborhood $U_\gamma$ for some $\gamma > 0$ such that $g_\epsilon \in U_\gamma$ implies $g_\epsilon$ has the same number of zeros as $g_\epsilon$, by Rouché Theorem [4]. Note that $\{U_\gamma\}_{\epsilon \in [0, 1]}$ is an open cover for $[0, 1]$, which is compact, so there is a finite subcover $U_{\epsilon_1}^\gamma, ..., U_{\epsilon_n}^\gamma$ such that $[0, 1] \subseteq \bigcup_{i=1}^n U_{\epsilon_i}^\gamma$. This implies that all $g_\epsilon(\lambda) = 0$ has the same number of roots in $\psi$ for all $\epsilon \in [0, 1]$.

For $\epsilon = 0$, $g_0(\lambda) = 0$ has a unique root $\lambda = (\beta - \delta) - \beta e^{-\delta \tau} < 0$ (Since $R_0 = \frac{\beta - \delta}{\beta e^{-\delta \tau}} < 1$). Hence, $g_1(\lambda) = g(\lambda) = \lambda - (\beta - \delta) + \beta e^{-\delta \tau} e^{-\lambda \tau}$ has no roots with $\Re(\lambda) > 0$. $\square$

It is worth pointing out the relationship of $\beta, \delta$, and $\tau$ when $R_0 \leq 1$.

**Lemma 4.4.** If $R_0 \leq 1$, then $\beta - \delta < \frac{1}{\tau}$.

**Proof.** Let $\kappa = \beta - \delta < \beta$. Then $R_0 \leq 1$ means $\kappa \leq \beta e^{-(\beta - \kappa)\tau}$. This further implies $\tau \leq \frac{\ln(\beta) - \ln(\kappa)}{\beta - \kappa}$. Let $f(\kappa) = \beta - \kappa - \kappa \ln(\beta) + \kappa \ln(\kappa)$. Then $f(\beta) = 0$ and $f_\kappa(\kappa) = -\ln(\beta) + \ln(\kappa) < 0$ since $\kappa < \beta$. This means $f(\kappa) > f(\beta)$, or $\beta - \kappa - \kappa \ln(\beta) + \kappa \ln(\beta) > 0$. Rearranging, we get $\frac{1}{\beta} > \frac{\ln(\beta) - \ln(\kappa)}{\beta - \kappa} > \tau$. Thus, $\kappa < \frac{1}{\beta} \circ \beta - \delta < \frac{1}{\tau}$. $\square$

Lemma 4.4 gives more insights to the biological process. Since $\frac{1}{\beta}$ can be thought of as the rate at which the virus is being produced, we have that if the difference in production rate of infected cells and its death rate is smaller than the rate that the virus is being produced, then the virus cannot persist.

5. **Permanence.** In the following few theorems, we prove the permanence of the cell-to-cell model. Recall that for our system to be permanent, there must exist $0 < m < M$ such that for all solutions of the cell-to-cell model, we have:

$$\min \{\liminf_{t \to \infty} S \liminf_{t \to \infty} f \} \geq m,$$

$$\max \{\limsup_{t \to \infty} S \limsup_{t \to \infty} f \} \leq M.$$  \hfill (35)

**Lemma 5.1.** The cell-to-cell model is eventually bounded above.
**Proof.** First assume $\beta > \delta$, we note that
\[
S' \leq r \left(1 - \frac{S}{K}\right) S.
\]  
(37)

A standard argument leads to
\[
\limsup_{t \to \infty} S(t) \leq K.
\]  
(38)

Thus there is a time $T > 0$ such that for all $t > T$, $x(t) < K$. This means:
\[
I' \leq \beta \frac{K}{K + I} I - \delta I
\]  
(39)

\[
= \frac{I}{K + I} ((\beta - \delta)K - \delta I).
\]  
(40)

This implies that:
\[
\limsup_{t \to \infty} I(t) \leq (\beta - \delta) \frac{K}{\delta} =: \bar{K}.
\]  
(41)

If $\beta \leq \delta$ then the same argument holds. This conclude the proof. \qed

**Remark 1.** Note that $\bar{K} < K$ when $\beta < 2\delta$, which gives us a sharper upper bound for $\limsup I$.

**Lemma 5.2.** If $2 > \beta \left(\frac{1}{r} + \frac{1}{\delta}\right)$, then the cell-to-cell model is eventually bounded away from 0.

**Proof.** First, note that eventually:
\[
S' = r \left(1 - \frac{S + I}{K}\right) S - \beta \frac{I}{S + I} S
\]  
(42)

\[
\geq S \left(r - \beta - \frac{r(S + K)}{K}\right)
\]  
(43)

\[
= S \frac{r}{K} \left[K \left(2 - \beta \left(\frac{1}{r} + \frac{1}{\delta}\right)\right) - S\right].
\]  
(44)

This implies that:
\[
\liminf_{t \to \infty} S(t) \geq K \left(2 - \beta \left(\frac{1}{r} + \frac{1}{\delta}\right)\right) =: \underline{S}.
\]  
(45)

Now note that, for large $t$, $S > S/2$ and
\[
I' = \beta \frac{S I}{S + I} - \delta I - e^{-\delta \tau} \beta \frac{S(t - \tau)I(t - \tau)}{S(t - \tau) + I(t - \tau)}
\]  
(46)

\[
\geq \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} \beta \frac{K\bar{K}}{K + K}.
\]  
(47)

Denote $a := \beta \frac{S/2}{S/2 + K}$ and $b := e^{-\delta \tau} \beta \frac{K\bar{K}}{K + K}$. Then
\[
I' \geq aI - b.
\]  
(48)

This implies:
\[
I(t) \geq \frac{1}{a} \left[ b + (aI(t - \tau) - b)e^{a\tau} \right],
\]  
(49)

which is equivalent to
\[
I(t - \tau) \leq \left( I(t) - \frac{b}{a} \right) e^{-a\tau} + \frac{b}{a}.
\]  
(50)
Finally, consider

$$I' = \beta \frac{SI}{S+I} - \delta I - e^{-\delta \tau} \beta \frac{S(t-\tau)I(t-\tau)}{S(t-\tau) + I(t-\tau)}$$

(51)

$$\geq \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} \beta I(t-\tau).$$

(52)

Using the inequality in equation (50),

$$I' \geq \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} \beta I$$

(53)

$$= \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} e^{-\alpha \tau} \beta I + \frac{b}{a} \beta e^{-\delta \tau} (e^{-\alpha \tau} - 1).$$

(54)

If $a < 0$, then $b \beta e^{-\beta \tau} (e^{-\alpha \tau} - 1) > 0$, which gives:

$$I' \geq \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} \beta I$$

(55)

$$= \beta \frac{S/2}{S/2 + K} I - \delta I - e^{-\delta \tau} e^{-\alpha \tau} \beta I + \frac{b}{a} \beta e^{-\delta \tau} (e^{-\alpha \tau} - 1).$$

(56)

Assume $|a| < \delta$ and $\beta > \delta$, then we obtain:

$$\liminf_{t \to \infty} I \geq \frac{(S/2)(\beta(1 - e^{-\delta \tau}) - \delta)}{\delta + e^{-\delta \tau} e^{-\alpha \tau} \beta} =: I > 0.$$

(59)

This concludes the proof.

The previous two lemmas lead to the following result.

**Theorem 5.3.** The cell-to-cell model is permanent given $\beta > \delta$ and $|a| < |\delta|$ where $a = \beta \frac{(S/2)}{(S/2) + K} - \delta < 0$. Sufficiently,

$$\beta - \frac{(S/2)}{(S/2) + K} < \delta < \beta,$$

(60)

where $K = (\beta - \delta)K/\delta$ and $S = K(2 - \beta(1/r + 1/\delta))$.

If instead of $S \leq (S/2)$, we use $S \leq S$ in our previous comparison, then the condition in the previous result becomes

$$\beta \left(1 + \frac{1 - \beta/\delta}{1 - \beta/r}\right) < \delta < \beta.$$

(61)

Since $\beta > \delta$, we require $\beta < r$ for this condition to satisfy. This leads to the following corollary.

**Corollary 1.** Assume

1. $\beta > \delta$
2. $\beta < r$
3. $2\beta > \frac{1}{\delta} + \frac{1}{r}$.

Then the cell-to-cell model is permanent.
This result makes sense intuitively because for the infected population to stay positive, the infection rate should be larger than the clearance rate of the infected cells (e.g. $\beta > \delta$). And for the healthy cell population to stay positive, the infection rate should be less than the growth rate (e.g. $\beta < r$). The third inequality implies that if the time it takes to get infected is sufficiently longer than the time it takes for replication and infected cell death, then the infection is permanent. In other word, if the time to get infected is too short, then the infection class grows aggressively and kills off the host and and the infection with it. Later, we will show that if $\beta >> r$, then it is likely that an infection will wipe out both populations.

While the system can be permanent, the following theorem shows that when the transmission rate is less than the death rate of the infected population, then the infected population becomes extinct and the disease free equilibrium is globally stable.

**Theorem 5.4.** Suppose $\beta < \delta$, then $(K, 0)$ is globally asymptotically stable. 

**Proof.** Note that if $\beta < \delta$, then

$$I'(t) = \beta I - \delta I - rS x.$$ 

Since $\lim_{t \to \infty} S = K (2 - \beta (\frac{1}{\delta} + \frac{1}{\beta}))$, then for large $t$ and $0 < \epsilon < 1 - \beta (\frac{1}{\delta} + \frac{1}{\beta})$, we obtain the inequality

$$rS(1 + \epsilon) \left( 1 - \frac{S}{K (1 + \epsilon)} \right) \leq S' \leq r \left( 1 - \frac{S}{K} \right) S.$$ 

This implies $\lim_{t \to \infty} S(t) = K$. 

6. Mutual extinction steady state. Since our model does not contain a virus compartment, the phrase “mutual extinction steady state” is referred to the singularity at $(0, 0)$ where both healthy and infected cells become extinct, which also implies the extinction of the virus. Due to the singularity at $(0, 0)$, the scenario when the infection wipes out the population is difficult to analyze. Thus, we remove this singularity by mean of a change of variable - a method that has been used previously [23, 24].

Under the transformation: $s = x, y = I/S$ (or $I = yx$), the original system becomes:

$$x' = rx \left( 1 - \frac{x(1 + y)}{K} \right) - \frac{\beta xy}{1 + y}$$

$$y' = \beta y - \delta y - ry \left( 1 - \frac{x(1 + y)}{K} \right) - e^{-\delta \tau} \frac{1}{x + y}$$

Note that $U_0 = (0, 0)$ is a steady state of the system. The original $E_{0(0)}$ steady state has been blown up to $U_0$ and $U_n = (0, y_n)$, where $y_n = \frac{\beta e^{-\delta \tau}}{\beta - \delta - r} - 1$.

**Proposition 2.** $U_0$ is always unstable.

**Proof.** The characteristic equation at $U_0$ takes the form:

$$h(\lambda, \tau) = \lambda^2 + \lambda (-r - (\beta - \delta - r)) + (e^{-\delta \tau} \beta) e^{-\lambda \tau} + r (\beta - \delta - r) + (-re^{-\delta \tau} \beta) e^{-\lambda \tau}.$$ 

Simplify gives

$$h(\lambda, \tau) = (\lambda - r) \left( \lambda + r - (\beta - \delta) + \delta e^{-(\delta + \lambda) \tau} \right).$$

Note that $\lambda = r > 0$ is a root, thus $U_0$ is always unstable.
To obtain the global region for \((0, 0)\), we proceed to show that under some constraints, \(y \to \infty\) and \(x \to 0\), which concludes the global stability of \((0, 0)\) in the original system.

We first want to obtain the condition for \(U_n = (0, y_n)\), \(y_n > 0\) to not exist. Note that \(y_n = \frac{\beta e^{-\delta \tau}}{\beta - \delta - r} - 1\), since \(y_n \neq 0\), we would want a condition for \(y_n < 0\). The following are equivalent:

\[
y_n < 0 \quad (68)
\]
\[
\frac{\beta e^{-\delta \tau}}{\beta - \delta - r} - 1 < 0 \quad (69)
\]
\[
\frac{\beta e^{-\delta \tau}}{\beta - \delta - r} < 1 \quad (70)
\]
\[
1 - \frac{\beta}{R_0} \frac{\beta - \delta - r}{\beta - \delta} < 1 \quad (71)
\]
\[
R_{\text{crit}} := \frac{\beta - \delta}{\beta - \delta - r} < R_0 \quad (72)
\]

This gives us the condition \(R_0 > R_{\text{crit}} = \frac{\beta - \delta}{\beta - \delta - r}\), which ensures that \(y_n > 0\) does not exist.

Next, we want a condition to ensure that \(U^* = (x^*, y^*)\), \(x^* > 0\), \(y^* > 0\) to not exist. Assume \(x^*, y^* > 0\) and proceed to solve for them give:

\[
y^* = \frac{1}{\delta} (\beta - \delta - \beta e^{-\delta \tau}) \quad (73)
\]
\[
x^* = \frac{K}{1 + y} \left(1 - \frac{\beta}{r} \frac{y}{1 + y} \right) \quad (74)
\]

Since \(\frac{K}{1 + y} > 0\), the condition for \(x^*\) to not exist (e.g. \(x^* < 0\)) is then \(1 - \frac{\beta}{r} \frac{y}{1 + y} < 0\). Rearranging the inequality to obtain:

\[
y^* \left(\frac{\beta}{r} - 1\right) > 1 \quad (75)
\]
\[
y^* > \frac{r}{\beta - r}. \quad (76)
\]

Note that the first inequality gives the first condition \(\beta > r\) and the second inequality is the second condition.

Putting this back to the \(y^*\) to obtain:

\[
R_0 \frac{\beta}{\beta - r} > \frac{\beta - \delta}{\beta - \delta - r}, \quad (77)
\]

which is the second condition for \(U^* = (x^*, y^*)\) to not exist. Note that this condition is covered by the condition of the non-existence of \(U_n = (0, y_n)\). Thus we arrive at the following lemma.

**Lemma 6.1.** If \(\beta > \delta + r\) and \(R_0 > R_{\text{crit}}\), where \(R_{\text{crit}} = \frac{\beta - \delta}{\beta - \delta - r} > 1\), then \(U_0 = (0, 0)\) is the only equilibrium of the transformed system.

This leads to the following lemma.

**Lemma 6.2.** If the conditions in lemma 6.1 holds, then \(y \to \infty\) as \(t \to \infty\). Furthermore, \(x \to 0\) as \(t \to \infty\).
Proof. First, rearrange the equation for $y$:

$$y' = \left(\frac{r}{K}x\right)y^2 + \left(\frac{r}{K}x\right)y + (\beta - \delta - r)y - e^{-\delta \tau} \frac{x\beta}{1 + y\tau}.$$  \hfill (78)

Under the condition of lemma 6.1 (e.g., only $U_0$ exists), the nullcline for $y$ only intersects 0 at exactly $y = 0$ on the non-negative y-axis. This means $y'$ is either entirely positive or entirely negative for $y > 0$. Since $U_0$ is always unstable, the 0 fixed point is always unstable. Additionally, $y'$ cannot approach 0, which would imply the existence of another steady state. Together, they imply $y' > 0$ for all $y > 0$. Hence, $y$ must approach $\infty$ as $t$ approaches $\infty$.

Note that,

$$x' \leq x \left(r - \beta \frac{y}{1 + y}\right).$$  \hfill (79)

As $y \to \infty$, $\frac{y}{1 + y} \to 1$. Additionally, $\beta > r$ under the assumption of lemma 6.1. This means $\lim_{t \to \infty} x' \leq x(r - \beta) < 0$. Thus $x \to 0$ as $t \to \infty$. \hfill $\square$

Together lemmas 6.1 and 6.2 lead to the following theorem.

**Theorem 6.3.** Under the conditions in lemma 6.1, $(0, 0)$ is globally stable.

**Remark 2.** As noted previously, if $\beta >> r$, then $R_{crit} \approx 1$, which implies if an endemic occurs (e.g., $R_0 > 1 \approx R_{crit}$), it is likely to drive both populations to extinction.

7. **Numerical study of the endemic steady state.** Now we consider the interior equilibrium. The characteristic for $E^*$ takes the form:

$$h(\lambda, \tau) = P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda \tau},$$  \hfill (80)

where $P(\lambda, \tau) = \lambda^2 + a(\tau)\lambda + c(\tau)$, $Q(\lambda, \tau) = b(\tau)\lambda + d(\tau)$ and

$$a(\tau) = -\frac{r(K - 2S^* - I^*)}{K} + \beta U_I - \beta U_S + \delta,$$  \hfill (81)

$$b(\tau) = \beta U_Se^{-\delta \tau},$$  \hfill (82)

$$c(\tau) = \left(\frac{r(K - 2S^* - I^*)}{K} - \beta U_I\right)(\beta U_S - \delta) + \left(\frac{r}{K} S^* + \beta U_S\right)\beta U_I,$$  \hfill (83)

$$d(\tau) = e^{-\delta \tau} \left[\left(-\frac{r(K - 2S^* - I^*)}{K} - \beta U_I\right)(\beta U_S) - \left(\frac{r}{K} S^* + \beta U_S\right)(\beta U_I)\right],$$  \hfill (84)

where

$$U_S = \frac{S^*}{(S^* + I^*)^2}, \quad U_I = \frac{I^*}{(S^* + I^*)^2}. \hfill (85)$$

The stability of the endemic equilibrium is difficult to study, instead we aim to apply the criterion in Beretta and Kuang [10]. First, we will verify the following properties.

1. $P(0, \tau) + Q(0, \tau) \neq 0, \forall \tau \in \mathbb{R}_+.$
2. If $\lambda = i\omega, \omega \in \mathbb{R}$, then $P(i\omega, \tau) + Q(i\omega, \tau) \neq 0, \forall \tau \in \mathbb{R}_+.$
3. $\limsup \left\{ \frac{|Q(\lambda, \tau)|}{|\lambda|} : |\lambda| \to \infty, \text{Re} \lambda \geq 0 \right\} < 1, \forall \tau \in \mathbb{R}.$
4. $F(\omega, \tau) := |P(i\omega, \tau)|^2 - |Q(i\omega, \tau)|^2$ for each $\tau$ has at most a finite number of real zeros.
5. Each positive root $\omega(\tau)$ of $F(\omega, \tau) = 0$ is continuous and differentiable in $\tau$ whenever it exists.
First, we note that for \( r = 0.3, K = 10^3, \beta = 0.1, \delta = 0.0001 \) and \( \tau \) around 50,

\[
P(0, \tau) + Q(0, \tau) = c(\tau) + d(\tau)
= \frac{r}{K}(K - 2S^* - I^*) \left[ \beta U_S(1 - e^{-\delta \tau}) - \delta \right]
+ \beta U_I \left[ \frac{r}{K} S^*(1 - e^{-\delta \tau}) + \delta \right]
\approx 1.7593 \times 10^{-5}.
\]

(86)

Thus, the first property is satisfied. And for the second property, we note that

\[
a(\tau) + b(\tau) = -\frac{r}{K}(K - 2S^* - I^*) + \beta(U_I + U_S(e^{-\delta \tau} - 1))
\approx 0.0282,
\]

(87)

\[
-\omega^2 + c(\tau) + d(\tau) = -\omega^2 + \frac{r}{K}(K - 2S^* - I^*) \left[ \beta U_S(1 - e^{-\delta \tau} - \delta) \right]
+ \beta U_I \left[ \frac{r}{K} S^*(1 - e^{-\delta \tau}) + \delta \right]
\approx -0.0053.
\]

(88)

This means the second property is also satisfied for our choices of parameter values.

Since \( \lambda(\tau) = 0 \) is not a characteristic root for some \( \tau > 0 \), we look for the a real and positive \( \omega(\tau) \) such that a pair of simple and conjugate imaginary roots \( \lambda = \pm i \omega(\tau) \) that cross the imaginary axis at some positive \( \tau^* \). Then solving for the roots of \( F(\omega, \tau) = 0 \) gives:

\[
\omega^2_+ = \frac{1}{2}((b^2 + 2c - a^2) + \Delta^{1/2}),
\]

(89)

\[
\omega^2_- = \frac{1}{2}((b^2 + 2c - a^2) - \Delta^{1/2}),
\]

(90)

where \( \Delta = (b^2 + 2c - a^2)^2 - 4(c^2 - d^2) \). Here we carry out extensive simulation by mean of sampling the parameters within a biologically reasonable range. We found that \( \Delta \) is always negative for the cell-to-cell transmission model. Instead, by choosing parameter outside of the biological range, it is possible to obtain positive value for \( \Delta \).

To demonstrate that increasing the delay in our model can be destabilizing for the endemic equilibrium, we use the following parameter values \( r = 0.3, K = 10^3, \beta = 0.1, \delta = 0.0001 \) and \( \tau \) around 50. With these values, \( \Delta \) is small but positive (\( 2.8376 \times 10^{-5} \)) and the other conditions of the theorem are also hold. Then we see that as \( \tau \) increases the endemic equilibrium is destabilized around \( \tau \approx 50.5 \), see Figures 1 and 2.

Additionally, we provide bifurcation plots with respect to the other parameters at similar initial values. Figure 3(a) shows that increasing the infection rate can be destabilizing; however, as \( \beta \) gets larger, both \( S \) and \( I \) oscillate closer to the mutual extinction steady state. Figure 3(b) shows how decreasing the death rate \( \delta \) can destabilize the stability of the endemic steady state. Figure 3(c) demonstrate an interesting phenomenon. As \( \tau \) increases, it can destabilize the endemic equilibrium; however, if \( r \) increases further, it can stabilize it. On the other hand, decreasing \( r \)
Figure 1. Increasing $\tau$ changes the stability of the positive equilibrium, which gives rise to a stable orbit. For this simulation, we use $r = 0.3, K = 10^3, \beta = 0.1, \delta = 0.0001$ and $\tau$ varies from 1 to 80. We plot $\tau$ over a viable region. For smaller value of $\tau$, either the condition for the theorem is not satisfied or the positive steady does not exist. The switching between a stable positive steady state and a stable orbit takes place around $\tau \approx 50.5$.

Figure 2. Corresponding examples for Figure 1. (a) $\tau = 50$, the oscillation is damping toward the positive steady state. (b) $\tau = 51$, the oscillation is stable.

to 0 leads to the mutual extinction equilibrium. Figure 3(d) gives further details for Figure 1 and 2.

8. Model fitting and interpretation. For numerical fitting, Pell et al. [37] previously uses objective $= \sum_{i=1}^{N} (bI(t_i) + V(t_i) - \hat{V}_i)^2$, as the objective to be minimize in the fitting process. Here, the $i^{th}$ virion data point is $\hat{V}_i$, which is approximated
For this simulation, we start with the following values $r = 0.3$, $K = 10^3$, $\beta = 0.1$, $\delta = 0.0001$ and $\tau = 51$. (a) Increasing the infection rate $\beta$ can have a destabilizing effect on the endemic equilibrium; however, as $\beta$ increases, $S$ and $I$ approach closely to 0. (b) Decreasing the death rate $\delta$ can be destabilizing as well. (c) The growth rate $r$ can be both stabilizing or destabilizing as it varies. As $r$ decreases, it can result in mutual extinction. (d) Shows additional details of Figure 1 and 2. Note that varying the carrying capacity $K$ only changes the size but not the stability.

by $bI(t_i) + V(t_i)$ in their model. The parameter $b$ represents the number of viruses released (and travel to adjacent cell). This is because the data represents the total virions, which is the sum of the virions in the infected cells and the free virions. For our model, the main mode of transmission is cell-to-cell, so the amount of virions outside of the cells are assumed to be negligible. Thus, a small modification gives our objective function.

$$\text{objective} = \sum_{i=1}^{N} (bI(t_i) - \hat{V}_i)^2,$$

For the fitting, We fix $S(0) = 74157.7$, $I(0) = 30$ and $\delta = 1/13$ similar to Pell et al. [37]. The parameters being fitted are $r$, $K$, $\beta$, $b$ and the delay $\tau$. In contrast to Pell et al. [37], the parameter $b$ in our fitting comes from the assumption that the transmission mode is mainly cell-to-cell, so the total number of virus is proportional to the total number of infected cells. Hence, $b$ can be thought of as the expected number of virus being produced by an infected cells in its life time, which has similar meaning to the burst-size but with different biological implication. The fitted parameter values and fitted errors are presented in Table 1 and Table 2, respectively. The fitting is presented in Fig. 4.

While the parameter estimations of the four experiments provide insights into the biological process (e.g. the differentiation between cell-to-cell and virus-to-cell transmission), the issue of parameter identification is evident and needs to be
Figure 4. Parameter fitting result for the cell-to-cell transmission model. The description of each experiment is given in subsection 1.2 and additional details can be found in Kendig et al. [26].

| Parameter | Fitted (CTRL) | Fitted (+N) | Fitted (+P) | Fitted (+NP) | Units |
|-----------|---------------|-------------|-------------|--------------|-------|
| $r$       | 0.9000        | 0.9000      | 0.9000      | 0.8860       | day$^{-1}$ |
| $K$       | 515024        | 719563      | 400294      | 400000       | cells  |
| $\beta$   | 0.5387        | 0.4355      | 0.8925      | 0.6710       | cells virion$^{-1}$ day$^{-1}$ |
| $b$       | 65            | 94          | 62          | 80           | virions cell$^{-1}$ day$^{-1}$ |
| $\tau$    | 8.27          | 12.00       | 12.00       | 12.00        | days    |
| $R_0$     | 1.62          | 2.07        | 2.30        | 2.23         | unitless |

Table 1. Estimated parameter for cell-to-cell model. Note that $\delta$ is fixed to be $1/13$ day$^{-1}$. The value of $R_0$ is calculated based on the estimated parameters. The description of each experiment is given in subsection 1.2 and additional details can be found in Kendig et al. [26].

| Experiment | control | +N  | +P  | +NP |
|------------|---------|-----|-----|-----|
| RMSE       | 4.27e+6 | 5.97e+6 | 3.66e+6 | 8.96e+6 |
| MAPE       | 8.03e-1 | 6.35e-1 | 4.10e-1 | 7.14e-1 |

Table 2. Fitting errors for the cell-to-cell transmission model. The description of each experiment is given in subsection 1.2 and additional details can be found in Kendig et al. [26].

examined in detail prior to more conclusive statements with implications for the biological interpretation of our results.

9. Discussion. The application of delay differential equations in within-host viral infection modeling is abundant; however, it is typically used for the case of either HIV or HBV [17, 43, 45]. On the other hand, within-host viral infection in plants receives much less attention from the modeling community [34, 37]. The differences between human and plant viruses offer rich and vastly unexplored dynamics, yet many of the existing techniques can be applied to both. In this paper, we modify an existing model for plant viral infection to incorporate cell-to-cell transmission. B/CYDV and other plant viruses rely on both cell-to-cell transmission and phloem
transport [42]. In the case of cell-to-cell transmission, it can offer greater protections and chances of spreading for the virus [41, 46]. Through analytical and numerical means, we find several interesting properties of the model, which are not usually seen in classical within-host models.

The classical modeling work on within-host viral infection for HBV by Nowak et al. [36] assumes mass action for viral infection, which is still a dominant assumption in mathematical modeling. However, it presents two biological problems. The first problem is that the basic reproduction number is dependent on the homeostasis size of the healthy cells (e.g. healthy liver size in the case of HBV), which has been discussed in [17, 23]. Additionally, this often causes confusion over the interpretation of $\beta$. Secondly, the spatial structure in a plant could mean that the assumption of homogeneous mixing in mass action may not hold [29]. In general, the issue of spatial-structure is difficult to address without relying on partial differential equations. To address this issue, we limit our system to an experimental setting where a small section of the phloem is considered. By doing so, we assume that if enough cells are packed into a finite space, they will approach a static structure and distribute with a uniform density throughout the plant. This allows us to make appropriate use of the ratio-dependent transmission term.

An interesting feature of our simple cell-to-cell model is that it seems to not exhibit an obvious orbit. By taking 10 million samples of parameters by mean of Latin hypercube samplings within biologically reasonable ranges, we find that the condition for a Hopf bifurcation with increasing $\tau$ is not satisfied (e.g. $\Delta < 0$). Furthermore, experimenting with the other parameters shows that while stability of the positive steady state can switch from a nodal sink to a spiral sink, it often does not give rise to a stable orbit. However, by reducing the $\delta$ to an unrealistically small value (e.g. $\delta = 0.0001$), we find a periodic orbit, see Figure 2. This is surprising since Hopf bifurcation can easily be observed in similar virus-to-cell transmission models such as the ode [23] and dde [17] version with ratio-dependent transmission or either the ode [8] or the dde [9] version with mass action. We argue that, the lack of an orbit within a biologically reasonable parameter range, is perhaps sensible. The advantages of cell-to-cell transmission may lead to a more stable mean for the viruses to establish themselves within the host. If this is true, then an oscillation, which implies a back-and-forth exchange between the virus and the host, would not be quite feasible if the mode of transmission is stable. By stable, we mean the cell-to-cell transmission may hinder the back-and-forth exchange between virus and susceptible cells. Furthermore, note that the cells being packed side-by-side (so the spread of infection propagates outward from the site of infection) could contribute to this stable transmission.

In the mass action version of the virus-to-cell infection model (both ode and dde) [8, 9], the mutual extinction equilibrium is always unstable. Additionally, the dde version of virus-to-cell model also has an unstable extinction equilibrium [17]. In contrast, we establish that for our model, when $R_0$ is sufficiently large, the extinction equilibrium is globally asymptotically stable. While mutual extinction is often not observed in virus-plant interaction, it is possible in extreme cases [16]. This means an aggressive infection would wipe out the healthy population. The virus-to-cell mode of transmission relies on a large number of virus particles to infect the cells. However, there are many barriers for the virus to overcome using this method alone. On the other hand, we argue that while the cell-to-cell mode of transmission is the more stable and likely to be slower mode of transmission, the
viruses are better protected, so the infection can be more steadily. This is perhaps a possible explanation of why the cell-to-cell model can have a global asymptotically stable extinction point. We note that this finding is similarly obtained in the ode version of the virus-to-cell model in Hews et al. [23]. They show the existence of a homoclinic bifurcation which leads to the stability of the extinction steady state. On the other hand, we also establish the conditions for both populations to be permanent. This is perhaps an important aspect to be studied for cell-to-cell transmission model. Since the cell-to-cell mode of transmission is supposedly more stable, it would be interesting in future work to directly compare the conditions for permanence in a similar model but with virus-to-cell infection. Our stability results and open questions are summarized in Table 3.

| Conditions | Results or question |
|------------|---------------------|
| 1. $\beta < \delta$ | $(K,0)$ is globally asymptotically stable |
| 2. $\beta > \delta$ and $\frac{\beta - \delta}{\beta e - \delta \tau} < 1$ | $(K,0)$ is locally asymptotically stable |
| 3. $\beta > \delta$ and $\frac{\beta - \delta}{\beta e - \delta \tau} > 1$ | Open question 1: is $E^*$ stable? when does a periodic orbit occurs? |
| 4. $\beta > \delta + r$ and $\frac{\beta - \delta}{\beta e - \delta \tau} < 1$ | $(0,0)$ is globally asymptotically stable |

Table 3. Stability results and open questions in terms of $\beta, \delta, \tau$ and $\delta$ (note: $R_0 = \frac{\beta - \delta}{\beta e - \delta \tau}$).

Our numerical fitting of the model to experimental data shows similar agreement to the virus-to-cell model in Pell et al. [37]. Specifically, while the model can capture general trend of the data, the details of the oscillation were not captured perfectly, see Figure 4. To fully investigate this issue, statistical analysis on the fitting using the complete data set may help determine whether the fitting is within expectation or there are underlying mechanisms that the model does not capture successfully. Furthermore, there is the issue of parameter identifiability, which is often encountered in biological models [44], yet it is outside of the scope of this paper. Additionally, future modeling attempts could try to incorporate both cell-to-cell and virus-to-cell transmission as done in Yang et al. [45], or the stoichiometric model in Pell et al. [37]. Instead, we aim to show that the cell-to-cell model is able to qualitatively describe the data reasonably well. Furthermore, looking at the estimated parameters from four different experiments, we see that the estimated values for $b$ in all four cases of the cell-to-cell model is lower than that of the virus-to-cell model in [37]. This is expected because the mode of transmission is stable, the virus does not need to produce many particles in order to consistently infect other cells. We also note that the values of $\tau$ estimated for the treatments with elevated nutrients are higher than that of the control experiment (or treatment with low nutrients/control case). This indicates that the nutrient addition extends the time it takes for virus to be produced by infected cells (or the rate of virus production is smaller), which implies that nutrient addition is effective in slowing down the production of virus from infected cells. However, as the values of $R_0$ in all cases of elevated nutrient are higher than the low nutrient experiment, it suggests that the low nutrient environment may negatively affect the survival viral transmission.

From our analysis and extensive numerical simulations, we propose the following hypothesis for the properties of the cell-to-cell transmission model with standard incidence.
Conjecture 1. For $\beta > \delta$ and sufficiently small $\delta$, there exists $R^* > R_*$ such that the endemic equilibrium is globally asymptotically stable whenever $R_0 > R^* > 1$. When $R_0 = R^*$, a Hopf bifurcation occurs leading to a stable periodic orbit. However, as $R_0$ crosses over $R^*$, the system collapses to the extinction equilibrium.

From the bifurcation simulation (see Figure 3), the relative size of $r$ and $\beta$ may play an important role in the existence of such $R^*$. Moreover, aside from $K$, changing any of the remaining parameters ($\beta, r, \delta, \tau$) may affect the dynamics of the system. Since we were able to find the existence of a stable orbit only when $\delta \approx 0$, but not when it is sufficiently large, the following approximation of our model is perhaps of interest for further analysis.

\[
S' = r \left(1 - \frac{S+I}{K}\right) S - \frac{\beta SI}{S+I}, \tag{92}
\]

\[
I' = \beta \left(\frac{SI}{S+I} - \frac{S(t-\tau)I(t-\tau)}{S(t-\tau)+I(t-\tau)}\right). \tag{93}
\]

The model represents the case when the infection is mild. The system has a unique positive steady state, where $S^* = I^*$. By mean of simulation, the system exhibit possible oscillation and stable positive steady state. On the other hand, when the infection is highly lethal, we show that the infected population cannot persist (e.g. $\delta > \beta$). The analysis of such model would be a direct extension of previous study of equations of the type $x'(t) = F(t) - F(t-\tau)$ [3].

One important aspect of the virus cell-to-cell transmission that we did not consider is the explicit spatial structure. For instance, while the virus move between cells slowly, they exploit and modify preexisting pathways within the cells for long distance movements [13]. Thus by incorporating a cylindrical spatial structure (to represent the tube-like phloem), the transmission process would be captured more comprehensively.

10. Appendix.

10.1. Mass action model. For comparison purpose, we present the mass action version of the model by Pell et al. [37]. An in-depth analysis of this model is presented in Beretta and Kuang [9].

\[
\frac{dS}{dt} = r \left(1 - \frac{S+I}{K}\right) S - \beta SV \tag{94}
\]

\[
\frac{dI}{dt} = \beta SV - \delta I - \beta S(t-\tau)V(t-\tau) \tag{95}
\]

\[
\frac{dV}{dt} = b\beta S(t-\tau)V(t-\tau) - dV - \beta SV. \tag{96}
\]

We note that the value of parameter $\beta$ in this system is scaled by the constant of $S(s) + I(s)$. The parameter constraints are established similarly: $S(s) = S_0(s) \geq 0, I(s) = I_0(s) \geq 0, V(s) = V_0(s) \geq 0$ and $K \geq S(s) + I(s) > 0, I(0) > 0$ for $s \in [-\tau, 0]$, where $I_0(0) = \int_{-\tau}^{0} \beta S_0(s)V_0(s)ds$.

The parameter estimation (see Table 4) and data fitting comparison (see Figure 5) show similar capability between the two models. However, as noted before, the mass action version lacks certain biological properties that allow it to be applicable in describing the within host dynamics of plant and virus cells.
Parameter Fitted (CTRL) Fitted (+N) Fitted (+P) Fitted (+NP) Units
---
\( r \) 0.0993 0.0100 0.8579 0.1549 day\(^{-1} \)
\( K \) 4.0000e+5 6.0164e+5 4.0038e+5 1.0987e+6 cells
\( \beta \) 2.0273e-6 2.8651e-7 1.9817e-6 1.9188e-6 cells virion\(^{-1} \) day\(^{-1} \)
\( d \) 0.7129 0.1001 0.1001 0.1001 day\(^{-1} \)
b 118.2189 199.9803 60.4637 56.2613 virions cell\(^{-1} \) day\(^{-1} \)
\( \tau \) 9.6880 21.0000 4.9741 7.4480 days

Table 4. Estimated parameter for mass action model. The description of each experiment is given in subsection 1.2 and additional details can be found in Kendig et al. [26].

10.2. Data fitting code. In this section, we provide the parameter estimation code for the cell-to-cell model, which can be adapted easily for similar models. The complete time serial data can be obtained from Kendig et al. [26].

```matlab
function [sol, err, p] = cell_to_cell_plant_virus(data, tdata)
% Created by Tin Phan (2020)
% the function takes in time series data and
% attempt to fit the cell−cell model to the data
% within some given parameter constraints.
% The solutions (sol), Least Squared Error (err),
% and estimated values for parameters (p) are returned.

%global parameter holder
global p1

%initial function (constant history)
history = ones(2,1).*[74157.7; 30];
tspan = tdata;
```
% Bounds for parameter ranges
% r % k % beta
LB(1) = 0.1; LB(2) = 400000; LB(3) = 0.3;
UB(1) = 0.9; UB(2) = 1100000; UB(3) = 0.9;

% b % tau
LB(4) = 40; LB(5) = 5;
UB(4) = 175; UB(5) = 12;

% initial guesses for parameter values
IC(1) = 0.4;
IC(2) = 600000;
IC(3) = 0.4;
IC(4) = 60;
IC(5) = 8.8;

% % % % % % % % % % % % % % % % % % % Parameter Estimation % % % % % % % % % % % % % % % % % % % %
% Find optimized parameters
options1 = optimset ('Algorithm', 'interior-point',
                    'TolX', 1e-10, 'TolFun', 1e-12, 'TolCon', 1e-12,
                    'MaxIter', 40000);
[p1] = fmincon (@objective, IC, [], [], [], LB, UB, [], options1);
% Note: while fmincon uses "fancier" algorithm,
% it does not provide the Jacobian to calculate
% confidence intervals. The function lsqcurvefit
% can be utilized instead if confidence intervals
% are desired. However, for bounded constraints,
% it is not recommended unless the estimated values
% are away from the boundary.

% Solve equation with the
sol = dde23 (@plant_virus_delay, p1(5), history, tspan, ...
            [], p1); err = objective(data, history, tspan, p1);
p = p1;
end

function err = objective(data, history, tspan, p)
% objective takes in the data, initial condition (history),
% time span (tspan), and current parameters (p).
% This function returns the squared errors to be optimized.

global p1 %global parameters
p1 = p;
% Set option to increase precision.
opts = ddeset('RelTol',1e-8,'AbsTol',1e-10);
% Solve the DDE
sol = dde23(@plant_virus_delay, p1(5), history,...
            tspan,opts,p);

% The dde23 does not allow specifying % the (output) time step. Therefore, we need to approximate % the location of the output corresponding to the data.

%variable to keep track of the index
Indexx = zeros(1,length(tspan)-1);
%start from index 2, because no data at t=0.
for ii = 2:1:length(tspan)
    %whenever sol.x (output time) is greater or equal %to the data, we save all of those values.
    aa = sol.x >= tspan(ii);
    %Then we assign the first time that sol.x >= data.
    NNN = find(aa==1);
    %and save the index.
    Indexx(ii-1) = NNN(1);
end

% Recall b*I is the data in the cell-to-cell model.
% We use the Indexx to approximate the position % of I values corresponding to the data.
err = sum((p1(4)*sol.y(2,Indexx) - data).^2);
end

function y = plant_virus_delay(t,x,Z,p)
% This is a standard DDE function in MATLAB.
% The function takes in time (t),
% values of S and I at t (x), values of S % and I at t-tau (Z), and parameters (p).
% The function returns dS and dI.

global p1
p1 = p;

%passing parameters
r = p1(1); k = p1(2); beta = p1(3);
b = p1(4); tau = p1(5);
delta = 1/13;
% y contains dS and dI
```matlab
y = zeros(2,1);
% Take in S and I at t (current time)
S = x(1);
I = x(2);
% Take in S and I at t-\tau
S_lag = Z(1);
I_lag = Z(2);

% Function definition
dS = r*S*(1-(S+I)/k) - beta*S*I/(S+I);
dI = beta*S*(I)/(S+I) - delta*I ... 
- exp(-delta*tau)*beta*S_lag*I_lag/(S_lag+I_lag);

% Return the differential changes in S and I
y = [dS; dI];
end
```

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