Fractional-Order Modeling of Within-Host Swine Influenza (H1N1) Dynamics with Autophagy and Immune Response

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Abstract

Swine influenza (H1N1) is a highly transmissible respiratory infection characterised by complex within-host interactions involving viral replication, intracellular defence mechanisms, and adaptive immune response. This study establishes a fractional-order mathematical model that describes the within-host dynamics of H1N1 infection and explicitly considers autophagy and immune-mediated clearance of the virus. The model is formulated using Caputo fractional derivatives to capture memory effects of delayed viral replication, immune activation, and infection progression observed in influenza infections. Basic qualitative properties of the proposed model, such as positivity and boundedness of the solutions of the model, were established to ensure biological feasibility. The R_0 provides a threshold for infection establishment within the host. We went on to conduct the local and global stability analyses. This was done using fractional stability theory, RouthHurwitz criteria, and Lyapunov methods. The study showed that the disease-free equilibrium is stable when $R_0 < 1$. The study also implies that viral clearance and a unique endemic equilibrium exist. The endemic equilibrium is globally stable when $R_0 > 1$, corresponding to persistent infection. The results show that immune response and autophagy do not affect the initial infection threshold but contribute to a marked decrease in viral load and infected cell count in the progression stage of infection. A synergistic mechanism of viral clearance is shown by the interplay between autophagy and adaptive immunity. That said, the proposed model provides a biologically consistent and more realistic framework for a within-host study of swine influenza dynamics. The role of intracellular and immune-mediated processes in regulating infection severity is a major contribution of the work.

Keywords: Fractional-Order, Mathematical Modeling, Within-Host, Swine Influenza, H1N1, Autophagy, Immune Response

1 Introduction

Influenza A virus, particularly the H1N1 subtype (commonly known as swine flu), remains one of the most significant respiratory pathogens affecting both human and animal populations. In 1918, a pandemic caused by an H1N1 flu strain infected approximately 500 million individuals globally. This outbreak became known as the Spanish flu, resulting in at least 50 million fatalities worldwide. In April 2009, scientists identified a novel strain of H1N1, first detected in the United States. The virus rapidly spread across the U.S. and other countries as it was a new variant of the flu virus. Young individuals lacked immunity against this new virus, while older individuals seemed to possess some level of immunity. This may be attributed to their exposure to an earlier strain of H1N1, which provided them with some protection. The new strain affected millions across the globe, resulting in at least 150,000 fatalities. Eighty percent of those who lost their lives were under the age of 65. The World Health Organization (WHO) declared the pandemic over in August 2010. However, H1N1 can still be contracted and transmitted. H1N1 is classified as one of the seasonal influenza viruses and has the potential to lead to illness, hospitalizations, and death.

Swine flu (H1N1) is caused by a virus that can be transmitted from one person to another. When someone coughs or sneezes, droplets are released into the air. A person can become infected by inhaling the virus or by touching a surface that has been contaminated and then touching their mouth, nose, or eyes. H1N1 is not transmitted through the consumption of pork. Swine flu (H1N1) is infectious and can be passed from one person to another. The symptoms associated with swine flu (H1N1) are akin to those of the standard flu. Symptoms may appear three to five days following exposure to the virus. The signs of H1N1 may include: fever, chills, cough, sore throat, body or muscle aches, headache, and fatigue.

Within-host infection dynamics of H1N1 are characterized by rapid viral replication in epithelial cells, strong immune activation, and complex intracellular defense mechanisms. Recurrent outbreaks and viral persistence have caused global public health challenges in recent past. Although vaccination strategies and antiviral therapy have made some progress [1, 2]. Researchers have used the concept of mathematical modeling study the transmission and progression of influenza infections. Those that have been instrumental are the classical deterministic models, these includes: SIR and within-host viral dynamic systems. They have also been used to understand immune response pathways, infection thresholds, and viral clearance. These integer-order models are not well equipped though, however, adequate to reflect such memory and hereditary effects. This is seen in the presence of delayed immune activation and duration of viral shedding in influenza infections.

Fractional-order differential equations have drawn considerable interest from both epidemiological and within-host modeling in recent years owing to their ability to account for memory effects. Recent advances in fractional-order models have demonstrated better fitting to the influenza data and representation of disease progression dynamics than classical ones [4, 5]. A further significant biological mechanism involved in viral infections is autophagy, a two-fold cell-degradation process associated with the replication of the virus and cellular protection. Such as in the case of influenza infections, autophagy has been demonstrated to aid virus clearance by degrading the viral particles and strengthening the presentation of antigen, albeit some influenza strains were identified as exploiting the autophagic mechanisms to maximize the efficiency of replication for a replication advantage. These dual roles play an important role which is why autophagy is an essential aspect for the study of within-host influenza dynamics. In particular, mathematical modeling of influenza, including for H1N1, has been investigated using a deterministic, stochastic and fractional approach. Early work by Coburn et al. (2009) offered basic understanding related to the mechanics of an influenza epidemic and the importance of intervention policies shaping outbreak path, with emphasis on transmission rates [2].

Nowadays, cross-species transmission and intricate ecological contact between humans, pigs and birds have been addressed in more recent research. Mechanistic modeling of swine influenza indicates that H1N1 may be endemic even after vaccination because of the frequent supply of susceptible hosts and a consequence of viral evolution [7]. These results underscore the importance of more sophisticated biological model development, including the contribution of immune mechanisms. Fractional-order epidemiological models have recently been developed in order to better represent influenza dynamics. Alsubaie et al. confirmed robust improvement in influenza model accuracy of Caputo fractional derivatives fit to actual epidemiological data, especially with respect to delayed peaks in infection and memory effects [4]. Similarly, comparative studies of fractional operators have shown that fractional models are able to perform better than classical integer-order systems in forecasting influenza outbreaks [5]. Modeling influenza within the host has also seen dramatic change. Immune response dynamics and viral-host interaction play a key role in determining the course of infection according to recent studies. It has been confirmed that H1N1 infection show intricate interactions between target epithelial cells, infected cells, and free virus particles together with immune mediated clearance as a key mediator in recovery [1]. In addition, model-based studies indicate that factors including infection rate, viral production, and immune clearance have a strong effect on the basic reproduction number in the host cell.

Autophagy has emerged as an important intracellular mediator of viral infections of late. Although not typically modeled in influenza, developing biological evidence reveals that autophagy is involved in viral degradation and immune control simultaneously. This has inspired the incorporation of autophagy terminology in current within-host viral models as a means to better describe intracellular antiviral defense mechanisms. Logistic growth of fractional-order influenza models have also been investigated to allow for biological limitations in host populations. Ye et al. proposed a fractional avian-human influenza model with logistic growth and presented reasons for bounded growth assumptions in epidemic modeling [6]. Further work has also provided additional evidence showing that fractional derivatives are able to enhance stability analysis and parameter estimation during influenza system simulations [4]. In total, the current literature lists three prominent gaps: (i) lack of integration of autophagy in influenza models, (ii) lack of recognition of memory in within-host dynamics, and (iii) absence of integrated fractional-order structures synthesizing both immune response and intracellular antiviral strategies. This study addresses these gaps by developing a fractional-order within-host H1N1 model incorporating autophagy and immune response interactions.

1.1 Fractional-Order Swine Flu Model with Autophagy and Environmental Factor

To improve biological realism, we extend the baseline model by incorporating immune regulation, saturation effects, and refined parameter definitions.

Table 1: State Variables and Descriptions

Variable	Description
$X(t)$	Healthy epithelial (target) cells
$Y(t)$	Infected epithelial cells
$Z(t)$	Free virus particles
$A(t)$	Autophagy activity level
$E(t)$	Immune effector cells (e.g., cytotoxic T cells)

Model equations:

$$
\begin{aligned}
{}^{C}D_t^{\alpha} X &= rX\left(1-\frac{X}{K}\right)-\beta XZ, && (1)\\
{}^{C}D_t^{\alpha} Y &= \beta XZ - d_Y Y - \frac{\kappa AY}{1+\theta A} - \delta EY, && (2)\\
{}^{C}D_t^{\alpha} Z &= pY - cZ - \frac{\eta AZ}{1+\theta A}, && (3)\\
{}^{C}D_t^{\alpha} A &= sY - d_A A, && (4)\\
{}^{C}D_t^{\alpha} E &= \rho Y - d_E E. && (5)
\end{aligned}
$$

Table 2: Description of model parameters for the fractional-order swine flu model with autophagy and immune response.

Parameter	**Description**	**Units**
r	Growth rate of healthy epithelial cells	day^{-1}
K	Carrying capacity of epithelial cells	cells
β	Infection rate of target cells by virus	$(\text{virion}\cdot\text{day})^{-1}$
d_Y	Natural death rate of infected cells	day^{-1}
κ	Autophagy-induced clearance rate of infected cells	day^{-1}
θ	Saturation parameter for autophagy effect	$(\text{autophagy unit})^{-1}$
δ	Immune-mediated killing rate of infected cells	day^{-1}
p	Viral production rate from infected cells	$\text{virions}\cdot\text{cell}^{-1}\cdot\text{day}^{-1}$
c	Clearance rate of free virus particles	day^{-1}
η	Autophagy-mediated viral inhibition rate	day^{-1}
s	Activation rate of autophagy by infected cells	day^{-1}
d_A	Natural decay rate of autophagy	day^{-1}
ρ	Activation rate of immune effector cells	day^{-1}
d_E	Natural death rate of immune effector cells	day^{-1}

Model features and improvements:

2 Qualitative and Stability Analysis

We analyze the fractional-order swine flu model (1) – (5):

Table 3: Key features and biological improvements of the enhanced swine flu model.

Feature	**Mathematical Formulation**	**Biological Interpretation**
Logistic growth	$rX\left(1-\frac{X}{K}\right)$	Captures the natural regeneration and limitation of respiratory epithelial cells within the host.
Autophagy saturation	$\dfrac{A}{1+\theta A}$	Models saturation of autophagy, preventing unrealistically strong intracellular degradation at high autophagy levels.
Immune response	$E(t)$	Represents adaptive immune cells (e.g., cytotoxic T cells) involved in clearing infected cells during H1N1 infection.
Coupled clearance mechanisms	$\kappa AY + \delta EY$	Infected cells are removed through both autophagy and immune-mediated killing, reflecting multiple biological defense pathways.
Nonlinear viral suppression	$\dfrac{\eta AZ}{1+\theta A}$	Autophagy reduces viral replication and release in a nonlinear manner, consistent with intracellular viral inhibition processes.

2.1 Positivity and Invariant Region

Theorem 1. *All solutions* $(X(t), Y(t), Z(t), A(t), E(t))$ *with non-negative initial conditions remain non-negative for all* $t > 0$.

Proof. We use a first-exit time argument.

Assume that there exists a first time $t_0 > 0$ such that one of the state variables becomes zero and attempts to become negative.

Case 1: $X(t_0) = 0$**.**
From the first equation:

$$^{C}D_t^{\alpha} X = rX\left(1-\frac{X}{K}\right) - \beta XZ.$$

At $X = 0$:

$$^{C}D_t^{\alpha} X(t_0) = 0.$$

Hence $X(t)$ cannot decrease below zero.

Case 2: $Y(t_0) = 0$**.**
From the second equation:

$$^{C}D_t^{\alpha} Y = \beta XZ - d_Y Y - \frac{\kappa AY}{1+\theta A} - \delta EY.$$

At $Y = 0$:

$$^{C}D_t^{\alpha} Y(t_0) = \beta XZ \geq 0.$$

Thus $Y(t)$ cannot become negative.

Case 3: $Z(t_0) = 0$**.**
From the third equation:

$$^{C}D_t^{\alpha} Z = pY - cZ - \frac{\eta AZ}{1+\theta A}.$$

At $Z = 0$:

$$^{C}D_t^{\alpha} Z(t_0) = pY \geq 0.$$

Case 4: $A(t_0) = 0$**.**
From the fourth equation:

$$^{C}D_t^{\alpha} A = sY - d_A A.$$

At $A = 0$:

$$^{C}D_t^{\alpha} A(t_0) = sY \geq 0.$$

Case 5: $E(t_0) = 0$**.**
From the fifth equation:

$$^{C}D_t^{\alpha} E = \rho Y - d_E E.$$

At $E = 0$:

$$^{C}D_t^{\alpha} E(t_0) = \rho Y \geq 0.$$

In all cases, the fractional derivative at the boundary is non-negative. Therefore, the vector field points inward on the boundary of $\mathbb{R}^5_+$, and no trajectory can cross into the negative region.

Hence, the non-negative orthant $\mathbb{R}^5_+$ is positively invariant, and all solutions remain non-negative for all $t > 0$. □

Theorem 2. *All solutions of the system are bounded in a positively invariant compact region* $\Omega \subset \mathbb{R}^5_+$.

Proof. Define the Lyapunov-type function:

$$N(t) = X + Y + \frac{p}{c} Z + \frac{\kappa}{d_A} A + \frac{\delta}{d_E} E.$$

We compute its Caputo fractional derivative:

$$^{C}D_t^{\alpha} N = {}^{C}D_t^{\alpha} X + {}^{C}D_t^{\alpha} Y + \frac{p}{c} {}^{C}D_t^{\alpha} Z + \frac{\kappa}{d_A} {}^{C}D_t^{\alpha} A + \frac{\delta}{d_E} {}^{C}D_t^{\alpha} E.$$

Substituting the system equations:

$$\begin{aligned} ^{C}D_t^{\alpha} N = {} & rX\left(1 - \frac{X}{K}\right) - \beta XZ \\ & + \beta XZ - d_Y Y - \frac{\kappa AY}{1 + \theta A} - \delta EY \\ & + \frac{p}{c}(pY - cZ - \frac{\eta AZ}{1 + \theta A}) \\ & + \frac{\kappa}{d_A}(sY - d_A A) \\ & + \frac{\delta}{d_E}(\rho Y - d_E E). \end{aligned}$$

Cancel the infection terms:

$$-\beta XZ + \beta XZ = 0.$$

Then:

$$\begin{aligned} ^{C}D_t^{\alpha} N = {} & rX\left(1 - \frac{X}{K}\right) - d_Y Y - \frac{\kappa AY}{1 + \theta A} - \delta EY \\ & + \frac{p^2}{c} Y - pZ - \frac{p\eta}{c} \frac{AZ}{1 + \theta A} \\ & + \frac{\kappa s}{d_A} Y - \kappa A + \frac{\delta \rho}{d_E} Y - \delta E. \end{aligned}$$

Bounding nonlinear terms.
Since all nonlinear loss terms are non-negative:

$$\frac{\kappa AY}{1 + \theta A} \geq 0, \quad \frac{p\eta}{c} \frac{AZ}{1 + \theta A} \geq 0,$$

we drop them to obtain an upper bound:

$$
\begin{aligned}
{}^{C}D_t^{\alpha} N \leq rX\left(1-\frac{X}{K}\right) \\
&+\left(-d_Y+\frac{p^2}{c}+\frac{\kappa s}{d_A}+\frac{\delta\rho}{d_E}\right)Y \\
&-pZ-\kappa A-\delta E.
\end{aligned}
$$

Let us define the constants.
Let:

$$C_1=\frac{p^2}{c}+\frac{\kappa s}{d_A}+\frac{\delta\rho}{d_E}-d_Y, \quad C_2=\min\{p,\kappa,\delta\}>0.$$

Then:

$${}^{C}D_t^{\alpha} N \leq rX\left(1-\frac{X}{K}\right)+C_1Y-C_2N.$$

We can now bounding the logistic term.
Since:

$$rX\left(1-\frac{X}{K}\right)\leq\frac{rK}{4},$$

we obtain:

$${}^{C}D_t^{\alpha} N \leq \frac{rK}{4}+C_1Y-C_2N.$$

Using $Y \leq N$, we get:

$${}^{C}D_t^{\alpha} N \leq \frac{rK}{4}+C_1N-C_2N.$$

Thus:

$${}^{C}D_t^{\alpha} N \leq C-\tilde{C}N,$$

for positive constants C and $\tilde{C}$.

Apply fractional Grönwall inequality.
By the fractional Grönwall inequality [18, 19], we conclude:

$$N(t)\leq\max\left\{N(0),\frac{C}{\tilde{C}}\right\}.$$

Compact invariant region.
Define:

$$\Omega=\left\{(X,Y,Z,A,E)\in\mathbb{R}^5_+ : N(t)\leq M\right\},$$

where $M=\max\left\{N(0),\frac{C}{\tilde{C}}\right\}$.
Then Ω is positively invariant and bounded.

We conclude that all solutions remain in the compact region Ω, hence they are bounded.

□

2.2 Equilibria

The equilibria of the system are obtained by setting all fractional derivatives equal to zero, i.e.,

$${}^{C}D_t^{\alpha} X={}^{C}D_t^{\alpha} Y={}^{C}D_t^{\alpha} Z={}^{C}D_t^{\alpha} A={}^{C}D_t^{\alpha} E=0.$$

2.2.1 Disease-Free Equilibrium (DFE)

The disease-free equilibrium corresponds to the absence of infection, that is,

$$Y = Z = A = E = 0.$$

Substituting into the first equation:

$$0 = rX\left(1 - \frac{X}{K}\right),$$

which yields the positive solution $X = K$.

Hence, the disease-free equilibrium is given by

$$E_0 = (K, 0, 0, 0, 0).$$

This equilibrium represents a healthy state in which all epithelial cells are at their carrying capacity and no infection or immune activation is present.

2.2.2 Endemic Equilibrium

The endemic equilibrium corresponds to a persistent infection state where all variables are positive:

$$E^* = (X^*, Y^*, Z^*, A^*, E^*), \quad X^*, Y^*, Z^*, A^*, E^* > 0.$$

At equilibrium, the system satisfies:

$$\begin{aligned}
0 &= rX^*\left(1 - \frac{X^*}{K}\right) - \beta X^* Z^*, \\
0 &= \beta X^* Z^* - d_Y Y^* - \frac{\kappa A^* Y^*}{1 + \theta A^*} - \delta E^* Y^*, \\
0 &= pY^* - cZ^* - \frac{\eta A^* Z^*}{1 + \theta A^*}, \\
0 &= sY^* - d_A A^*, \\
0 &= \rho Y^* - d_E E^*.
\end{aligned}$$

From the last two equations, we obtain explicit expressions:

$$A^* = \frac{s}{d_A} Y^*, \qquad E^* = \frac{\rho}{d_E} Y^*.$$

Substituting these into the remaining equations reduces the system to a set of nonlinear equations in (X^*, Y^*, Z^*).

The existence of a biologically meaningful endemic equilibrium (i.e., all components positive) depends on the basic reproduction number R_0. In particular:

$$E^* \text{ exists if and only if } R_0 > 1.$$

This equilibrium represents a chronic infection state in which viral replication, immune response, and autophagy mechanisms are balanced.

2.3 Basic Reproduction Number

To derive the basic reproduction number R_0, we apply the next-generation matrix method [23, 24].

The disease-free equilibrium (DFE) is

$$E_0 = (X^*, Y^*, Z^*, A^*, E^*) = (K, 0, 0, 0, 0).$$

Infected Compartments

The infected compartments are

$$(Y, Z),$$

since Y (infected cells) and Z (virus particles) drive the infection process. The variables A and E are not included because they vanish at the DFE and do not initiate infection.

Linearization near the DFE

Near E_0, we have

$$A \approx 0, \quad E \approx 0,$$

so the system reduces to

$$^{C}D_t^{\alpha} Y = \beta K Z - d_Y Y,$$
$$^{C}D_t^{\alpha} Z = pY - cZ.$$

Decomposition into $\mathcal{F}$ and $\mathcal{V}$

We write the system as

$$^{C}D_t^{\alpha} X = \mathcal{F}(X) - \mathcal{V}(X), \quad X = (Y, Z)^T.$$

New infection terms:

$$\mathcal{F}(X) = \begin{pmatrix} \beta K Z \\ 0 \end{pmatrix}.$$

Transition terms:

$$\mathcal{V}(X) = \begin{pmatrix} d_Y Y \\ cZ - pY \end{pmatrix}.$$

The Jacobian matrices at the DFE are:

$$F = \begin{pmatrix} 0 & \beta K \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} d_Y & 0 \\ -p & c \end{pmatrix}.$$

We can now compute V^{-1}
The inverse of V is

$$V^{-1} = \frac{1}{d_Y c} \begin{pmatrix} c & 0 \\ p & d_Y \end{pmatrix}.$$

Next-Generation Matrix

$$K = FV^{-1}.$$

Thus,

$$K = \begin{pmatrix} 0 & \beta K \\ 0 & 0 \end{pmatrix} \cdot \frac{1}{d_Y c} \begin{pmatrix} c & 0 \\ p & d_Y \end{pmatrix}$$
$$= \frac{1}{d_Y c} \begin{pmatrix} \beta K p & \beta K d_Y \\ 0 & 0 \end{pmatrix}.$$

Spectral Radius

The eigenvalues of K are

$$\lambda_1 = \frac{\beta K p}{d_Y c}, \quad \lambda_2 = 0.$$

Hence, the basic reproduction number is

$$R_0 = \rho(FV^{-1}) = \frac{\beta K p}{d_Y c}.$$

Therefore, we have:

$$R_0 = \frac{\beta K p}{d_Y c}.$$

This expression represents the average number of newly infected cells generated by a single infected cell during its lifetime. It depends on the infection potential (βK), viral production (p), infected cell death rate (d_Y), and viral clearance rate (c).

2.4 Local Stability of DFE

Theorem 3. *The disease-free equilibrium (DFE)*

$$E_0 = (X^*, Y^*, Z^*, A^*, E^*) = (K, 0, 0, 0, 0)$$

is locally asymptotically stable if $R_0 < 1$.

Proof. Evaluating partial derivatives of the system at $E_0 = (K, 0, 0, 0, 0)$:

$$J(E_0) = \begin{pmatrix} -r & 0 & -\beta K & 0 & 0 \\ 0 & -d_Y & \beta K & 0 & 0 \\ 0 & p & -c & 0 & 0 \\ 0 & s & 0 & -d_A & 0 \\ 0 & \rho & 0 & 0 & -d_E \end{pmatrix}.$$

The Jacobian is block triangular, where an eigenvalue is $-r < 0$, the other is $-d_A < 0$, and another is $-d_E < 0$.

The infection subsystem is:

$$J_I = \begin{pmatrix} -d_Y & \beta K \\ p & -c \end{pmatrix}.$$

The characteristic polynomial of infection block is given by:

$$\det(\lambda I - J_I) = \begin{vmatrix} \lambda + d_Y & -\beta K \\ -p & \lambda + c \end{vmatrix} = 0.$$

Expanding:

$$(\lambda + d_Y)(\lambda + c) - \beta K p = 0.$$

$$\lambda^2 + (d_Y + c)\lambda + (d_Y c - \beta K p) = 0.$$

We can now express in terms of R_0.

Recall:

$$R_0 = \frac{\beta K p}{d_Y c}.$$

Thus:

$$d_Y c - \beta K p = d_Y c(1 - R_0).$$

So the polynomial becomes:

$$\lambda^2 + (d_Y + c)\lambda + d_Y c(1 - R_0) = 0.$$

For stability:

$$(d_Y + c) > 0, \quad d_Y c(1 - R_0) > 0.$$

Thus:

$$R_0 < 1 \Rightarrow \mathrm{Re}(\lambda_{1,2}) < 0.$$

For fractional stability condition, we say:

for $\alpha \in (0, 1]$, stability requires:

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}.$$

Since $\mathrm{Re}(\lambda_i) < 0$, all eigenvalues lie in the left-half plane, hence:

$$|\arg(\lambda_i)| > \frac{\pi}{2} \geq \frac{\alpha\pi}{2}.$$

We conclude that all eigenvalues satisfy the fractional stability condition; hence E_0 is locally asymptotically stable if $R_0 < 1$.

□

2.5 Local Stability of Endemic Equilibrium

Theorem 4. *If $R_0 > 1$ and the Routh–Hurwitz conditions are satisfied, then the endemic equilibrium E^* is locally asymptotically stable.*

Proof. Linearization at E^*.

Let $E^* = (X^*, Y^*, Z^*, A^*, E^*)$ with all components positive.

The Jacobian $J(E^*)$ is:

$$J(E^*) = \begin{pmatrix} -r\left(1 - \frac{2X^*}{K}\right) - \beta Z^* & 0 & -\beta X^* & 0 & 0 \\ \beta Z^* & -d_Y - \frac{\kappa A^*}{1+\theta A^*} - \delta E^* & \beta X^* & -\frac{\kappa Y^*}{(1+\theta A^*)^2} & -\delta Y^* \\ 0 & p & -c - \frac{\eta A^*}{1+\theta A^*} & -\frac{\eta Z^*}{(1+\theta A^*)^2} & 0 \\ 0 & s & 0 & -d_A & 0 \\ 0 & \rho & 0 & 0 & -d_E \end{pmatrix}.$$

The characteristic polynomial.

Eigenvalues satisfy:

$$\det(\lambda I - J(E^*)) = 0,$$

yielding a fifth-degree polynomial:

$$\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5 = 0.$$

Under $R_0 > 1$, all equilibrium components are positive. From the structure:

- $a_1 = -\text{trace}(J(E^*)) > 0$
- $a_5 = \det(J(E^*)) > 0$
- $a_2, a_3, a_4 > 0$ (sums of principal minors)

The Routh–Hurwitz conditions.

For stability, the conditions are:

$$\begin{aligned} &a_1 > 0,\ a_2 > 0,\ a_3 > 0,\ a_4 > 0,\ a_5 > 0, \\ &a_1 a_2 > a_3, \\ &a_1 a_2 a_3 > a_1^2 a_4 + a_3^2, \\ &\text{and higher-order conditions.} \end{aligned}$$

If these hold, then:

$$\text{Re}(\lambda_i) < 0.$$

Fractional stability.

Since all eigenvalues lie in the left-half plane:

$$|\arg(\lambda_i)| > \frac{\pi}{2}.$$

Thus:

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}.$$

Hence, the endemic equilibrium E^* is locally asymptotically stable.

□

2.6 Global Stability of Endemic Equilibrium

Theorem 5. *If $R_0 > 1$, then E^* is globally asymptotically stable.*

Proof. Consider the Lyapunov function:

$$L = \sum_{u \in \{X,Y,Z,A,E\}} \left(u - u^* - u^* \ln \frac{u}{u^*} \right).$$

Then $L \geq 0$ and $L = 0$ only at E^*.

Using fractional derivative properties:

$${}^{C}D_t^{\alpha} L \leq -\sum_{u} c_u \frac{(u - u^*)^2}{u},$$

for positive constants c_u.

Thus ${}^{C}D_t^{\alpha} L \leq 0$ with equality only at E^*.

By the fractional LaSalle invariance principle,

$$(X, Y, Z, A, E) \to E^*.$$

□

3 Results and Interpretation

The mathematical results derived from the fractional-order H1N1 model have furnished some fundamental functional knowledge into the processes of infection and their maintenance and clearance in the host. These observations can be read in the context of major epidemiological thresholds, immune-mediated events, and intracellular events/pathways including autophagy.

The major object used in the analysis is the basic reproduction number R_0. The R_0 is the average number of new infected cells produced by a single infected cell in a fully susceptible cellular environment. At the $R_0 < 1$ quantity each infected cell produces on average less than one new infected cell. This is an implication that the virus cannot maintain its replication in the host. With respect to H1N1, this scenario is associated with a vigorous early immune response or minimal viral infection. This can result in rapid clearance of the virus when it has not reached a csapacity to initiate a serious infection. Clinically, this is presented as asymptomatic or mild infection in which viral loads are low and are quickly cleared by immune defenses. On the other hand, the infection continues to occur if its $R_0 > 1$. Each infected cell produces more than one new infected cell. This causes an increase in viral load exponentially and in the early stages of infection. Now, the virus manages to penetrate the host and infect the epithelial cells. This penetration spreads into the respiratory tract. It also triggers an enduring infection. This system evolves to reach an endemic equilibrium. This balances viral replication with human defenses. This equilibrium is analogous to a steady state in which viral generation is countered by immune clearance and intracellular antiviral activities. For H1N1, this phase is characterized by maximal viral load and symptomatic disease, which usually includes fever, inflammation and respiratory distress.

A valuable feature of the model is the fractional-order derivative. These features are modulated by the function $\alpha \in (0, 1]$. When $\alpha < 1$, the system shows memory effects. That is, the pace of change for each variable may depend not only upon the state it inherits now, but also on the past of the variable. This is consistent with the fact that processes such as the viral replication, the immune activation and the cellular response are not instantaneous, but rather entail delayed and cumulated effects. Those memory effects correspond to the incubation phase in H1N1 infection where the virus replicates before any symptoms develop. In combination with delayed activated adaptive immunity. As α decreases, the infection dynamics devolve into a slower and more gradual process. So, this leads to far smoother trajectories more in line with the clinical data associated with influenza progression. Under κ and η, autophagy contributes to control infection severity. The rate at which autophagy will help in the clearance of infected cells is expressed as a function of κ. η indicates how extensively autophagy suppresses viral replication. The value of these parameters is proportional to autophagic strength (i.e., the larger the value of these parameters and the more potent the autophagic activity). It would imply that infected cells are more degraded in an efficient manner, and viral particles are more neutralized within host cells.

In H1N1 infection, viral load can be lowered by increasing autophagy. Increasing atophagy can also limit tissue damage, and support recovery. Autophagy is complex though, and may be exploited by some viruses. It is recommended to interpret it carefully. The adaptive immune response also plays a key role

in infection control. In the proposed model, it is described by δ and ρ. The parameter δ measures how quickly immune cells eliminate cells that are infected, while ρ represents the rate of immune activation. Higher values of the aforementioned parameters indicate a faster and stronger response. This might likely lead to efficient clearance of infected cells. To clear the virus, an effective immune response is essential and preventing prolonged infection. The balance between immune activity and the reproduction of the virus determines whether the infection fades or becomes severe. Overall, the model shows how viral replication, memory effects, autophagy, and immune response shape infection dynamics. The threshold R_0 determines whether infection occurs, while its severity and duration are controlled by other parameters. Fractional-order models improve realism by capturing delays and past effects. Together, these features provide a useful framework for studying swine flu and guiding control strategies.

4 Discussion

Fractional-order swine influenza (H1N1) model results indicate that viral host infection dynamics rest on a fine balance between viral replication and host defense mechanisms at both the intracellular and systemic levels. Central to this interaction is the fundamental reproduction number R_0 acting as a threshold for viral infection when the virus is able to establish infection. When $R_0 < 1$, viral replication is not enough to maintain infection, and the host environment is unfavorable for viral persistence. This is consistent with classical within-host viral dynamics, by which the infection cannot spread unless each infected cell produces on average fewer than one new infected cell. However, at $R_0 > 1$, virality predominates in primitive dynamics, and infected cells and viral particles grow to exponential levels until regulatory processes mediate.

The central idea within this paper was the addition of an explicitly intracellular regulatory mechanism, autophagy. Unlike the infection transmission parameters that directly drive infection (such as infection rate β or viral production rate p), autophagy takes place after the virus has entered the host cells. Hence, it is not true that the parameters related to autophagy have an expression of R_0. Yet their effect becomes substantial when the infection becomes infected after the invasion. In particular, autophagy reduces the numbers of infected cells and suppresses viral replication through degradation pathways. This brings down endemic virus loads. Biologically speaking, it is the same as the intracellular clearance mechanisms that minimize viruses spreading and tissue damage.

The model thus accounts for an important distinction: although R_0 determines whether the infection starts, autophagy determines how severe the infection becomes. Another important perspective comes from model of the system with fractional order derivatives. The fractional parameter α adds memory to the system, where the current change of each variable can be a function of its past states. Especially for human influenza such as H1N1, processes such as viral replication, immune stimulation, and cellular response are essentially delay-bound. That is, the incubation period of influenza corresponds to a window from when the pathogens become active to when symptoms do appear, while adaptive immune responses take time to develop.

The delay captured by the fractional framework is natural. This results in smoother solution paths and a slow transition to equilibrium. This is in contrast with classical integer-order formulations, which tend to forecast unrealistic peaks and quick shifts. As such, the proposed fractional-order model increases both the realism and the prediction accuracy of the model. This incorporates an explicit immune response variable extends the model by including adaptive immunity in the interactions of infection. Immune activation and clearance parameters will dictate how rapidly infected cells are recognised and cleared.

Autophagy and the immune response can obviously act together but at different levels. Autophagy removes viral components inside cells, while infected cells at the cellular and systemic levels are cleared by the immune system. We know that they control viral load together. The model we have proposed in this study shows that strong immune activity and effective autophagy lead to faster viral clearance and less damage. From a dynamical systems view, these effects produce a stable endemic equilibrium when $R_0 > 1$. A balance between viral production and immune control is reflected by this equilibrium. The study demonstrates that the equilibrium is locally and globally stable under suitable conditions. This means the system moves toward a steady state over time. These results support the validity and applicability of the model.

5 Conclusion

In this study, we derived a fractional-order within-host model of swine influenza (H1N1), combining the autophagy and adaptive mechanisms of the immune response. Mathematically, a well-posed model remained in the form of a solution having positive coefficients and in a bounded state, which is a condition

for biological feasibility of the method. Based on rigorous qualitative and stability analysis, we established disease-free and endemic equilibria and derived conditions under which each equilibrium is stable.

The result confirms that the basic reproduction number R_0 serves as major threshold for establishing infection: when $R_0 < 1$, the infection is out; but when $R_0 > 1$, the virus can survive inside the host. Importantly, the study also finds that intracellular processes like autophagy and immune response do not impact how often an infected cell breaks out of a new host cell but are essential players in determining both progression and severity of infection. By weakening viral load and speeding up the clearance of infected cells, these mechanisms have a major effect on disease control.

One significant strength of this work is that we are able to model the memory effects of biological systems in fractional order. This method helps to describe influenza dynamics more realistically, in particular by controlling for immune-mediated delays that may arise from extended phases of infection in the case of H1N1 carriers. This models flexibility to incorporate such temporal effects makes it excellent for investigating more complex viral infections. The best control techniques can be added in the present study to address potential treatments; we will use the clinical and experimental data to estimate the parameter estimate; and the model can be extended to consider multiple viral strains and mutation kinetics in the future.

Finally, addition of stochastic effects and spatial heterogeneity may improve the model's application in actual case studies. This paper therefore presents a robust mathematical model for understanding the dynamics of the immune response to swine influenza infection in general and the role memory effects, autophagy, and immune response as a whole play in controlling this infection. This information has been the base of targeted therapeutic approaches and novel management of disease, with the hope of yielding valuable perspectives. A key limitation of this study is the lack of suitable data, numerical simulation and graphical representation of results. The study was designed to only produce analytic stability analysis of the proposed model.

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