Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Systems Biology

Quantitatively mapping immune control during influenza

Jordan J. A. Weaver and Amber M. Smith

Abstract

Host immune responses play a pivotal role in defending against influenza viruses. The activation of various immune components, such as interferon, macrophages, and $CD8^+$ T cells, works to limit viral spread while maintaining lung integrity. Recent mathematical modeling studies have investigated these responses, describing their regulation, efficacy, and movement within the lung. Here, we discuss these studies and their emphasis on identifying nonlinearities and multifaceted roles of different cell phenotypes that could be responsible for spatially heterogeneous infection patterns.

Addresses

Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Corresponding author: Smith, Amber M. (amber.smith@uthsc.edu)

Current Opinion in Systems Biology 2024, **38**:100516

This review comes from a themed issue on **Mathematical Modelling (2023)**

Edited by **Jana Wolf** and **Kevin Thurley**

For complete overview of the section, please refer the article collection - Mathematical Modelling (2023)

Available online 20 March 2024

https://doi.org/10.1016/j.coisb.2024.100516

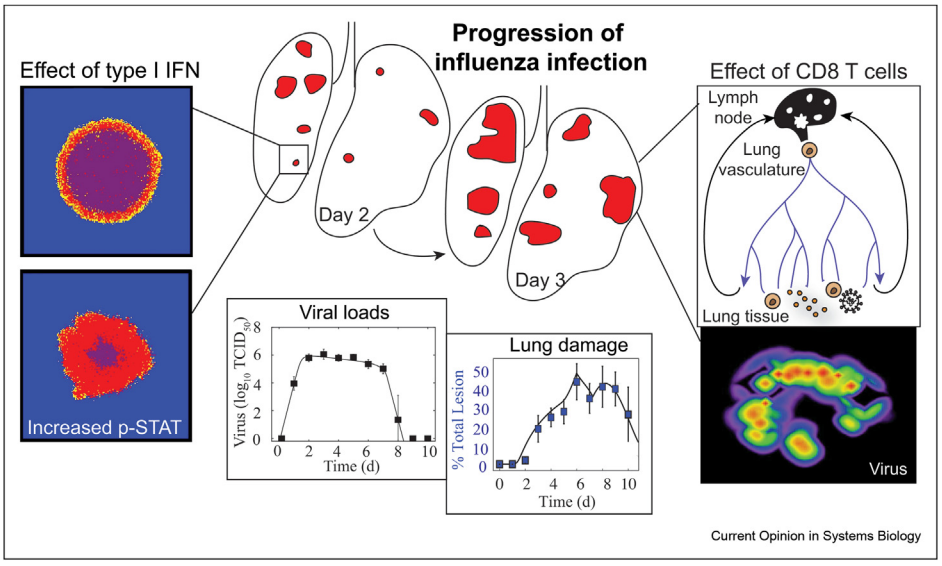
Introduction

Influenza viruses pose a significant threat to human health, causing 250,000 to 500,000 deaths annually worldwide [1]. Universal vaccines have been projected to prevent $1–3.5 billion in influenza-related healthcare costs annually in the United States [2]. Outcomes of influenza are variable, where infections in the lower airways tend to be more severe. Host immune responses are designed to restrict viral spread while preserving lung function and structure. However, these defenses can become overexuberant and dysregulated, especially during highly pathogenic influenza or bacterial coinfection, or disrupted when other viruses invade. Dissecting the complexity of host immunity and the myriad ways in which it interacts with influenza viruses is difficult, but mechanistic mathematical models have become an invaluable tool.

By abstracting biological processes into equations and parameters, models of influenza have predicted dynamics and outcomes under a variety of conditions and informed future experimentation (reviewed in Refs. [3–5]). Relatively simple mathematical models with 3–4 equations effectively depict the dynamics of influenza viral loads, but small changes in viral loads can result in significant changes to immunity and outcome [6]. In general, upon establishing a foothold in the lung, the virus deposits in multiple areas of the airways and begins replicating. Histomorphometry images from influenza infection in mice revealed the evolution of viral lesions in the lung, starting as small lesions that gradually enlarge until $CD8^+$ T cells initiate the clearance of infected cells (Figure 1) [6]. This results in irregular tissue damage patterns and accentuates a disparity between viral loads, which reach their peak at 2 d post-infection (pi), and infected areas, which reach their peak at 6 d pi. Although the spread of influenza *in vitro* and *in vivo* has been probed using various modeling frameworks ([7–14] and reviewed in Ref. [15]), these spatiotemporal dynamics can be captured without resorting to explicit spatial models. Combining the cumulative area under the curve of the model-predicted infected cell dynamics and relative $CD8^+$ T cell dynamics was shown to represent the growth of the total area of infection within the lung (Figure 1) [6,16]. The whole lung histomorphometry data verified that little cell death occurred before $CD8^+$ T cell arrival yet viral loads did not continue to increase. The divergence between the viral load dynamics and the expanding area of infection is curious and likely a consequence of the preliminary influence of innate responses like type I interferons (IFN-α,β) and macrophages, which act to curb viral replication and spread. Consequently, recent studies have developed more intricate models to explore these responses, shedding light on their role in controlling influenza and immunopathology (reviewed in Ref. [17] and herein).

Here, we focus on recent advances in modeling immune responses to influenza that impact virus spread and clearance, namely IFN-α,β, macrophages, and $CD8^+$ T cells. We review ordinary differential equation (ODE) modeling of macrophage and $CD8^+$ T cell responses. These studies highlighted the significance of nonlinear elements within the models and their relation to cytokine regulation and spatial movement of immune cells.

Figure 1



Modeling influenza spread in the lung. Schematic of the progression of influenza spread in the lung at 2 and 3 d post-infection (adapted from histomorphometry images from Myers et al. [6]). The corresponding viral loads together with the ODE model fit and the corresponding dynamics of lung damage together with the model prediction (Left) Results of a spatial model of viral spread showing the effect of IFN-β production from infected cells without and with increased phosphorylation of STAT [7] (Right) Schematic of a spatial model of T cell migration and efficacy (adapted from Levin et al. [9]). Corresponding model results showing viral containment and irregularity of virus spread, where red indicates higher density of virus. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

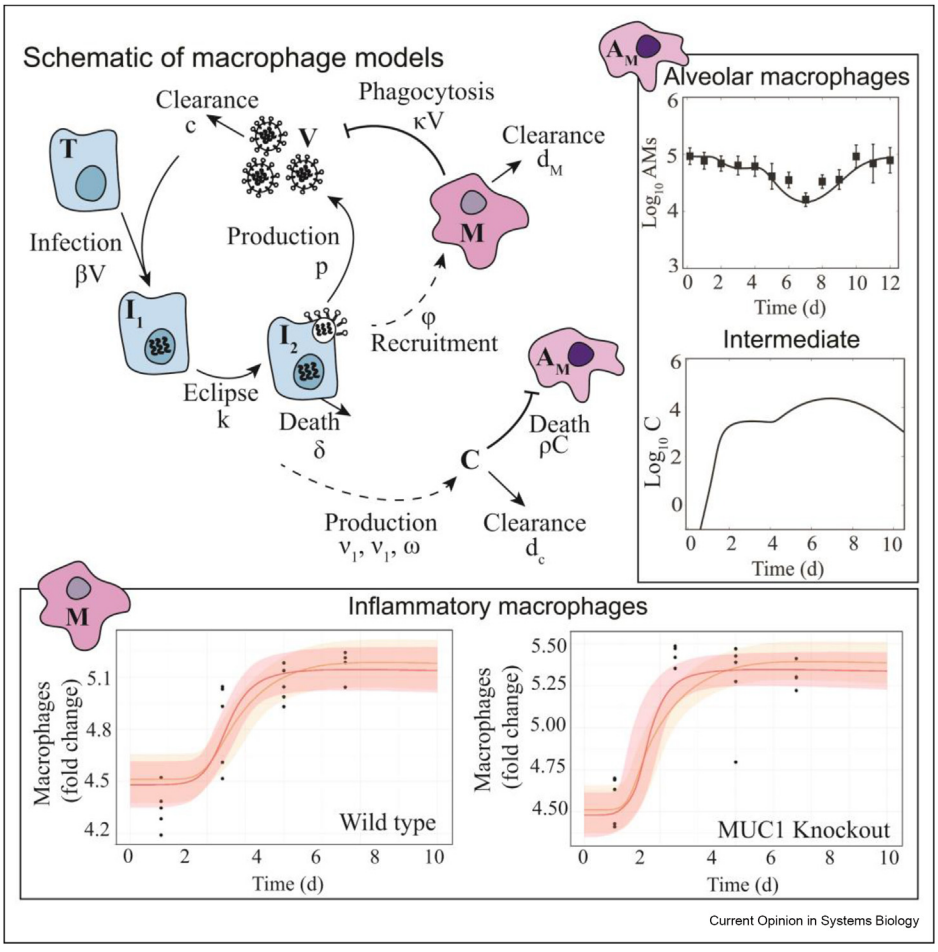
They have also underscored the importance of iterative examination with experimental designs based on *in silico* predictions to confirm model findings and provide additional biological context. We also review the recent increase in the use of spatially explicit infrastructures, such as agent-based models (ABMs), to investigate viral control by IFN-α,β and $CD8^+$ T cells. These studies showed that spatially variable infection patterns could be replicated, although it is unclear whether this is important as viral and immune dynamics have little variation despite infected lesions being of different numbers, sizes, and locations within the murine lung [6,16].

Quantifying macrophage-mediated viral clearance and immunopathology

Alveolar macrophages (AMs) are pivotal to the frontline cellular defense mechanism against influenza and secondary bacterial infections (reviewed in Refs. [3,18]). Our preceding studies demonstrated a significant depletion of AMs during IAV progression, consequently elevating time-dependent susceptibility to secondary bacterial infections (reviewed in Refs. [3,18]). Their loss suggests a minimal role in viral clearance, but they may modulate tissue inflammation [19]. Until recently, influenza models lacked a dedicated equation to explicate these cellular dynamics. To propose an accurate equation suggestive of potential mechanisms underpinning this depletion, the integration of an intermediary equation was necessitated [16]. The equation for this unknown population required multiple production terms, leading to peaks at 3–4 and 6–7 d post-infection (pi) that corresponded to the two phases of AM loss (Figure 2). The multiple production terms hint at the potential for contributions from different immune sources and/or nonlinearities in the rate of production of the intermediate. These dynamics could mirror the behavior of IFN-γ, a proposed contributor to alveolar macrophage depletion [20], and/or represent multiple time-dependent mechanisms. Additional experiments and models should help better define these dynamics and evaluate IFN-γ-mediated effects in increasing lung injury and regulating CCR2+ macrophages [21].

Macrophages recruited to the site of infection have varied phenotypes with diverse roles during influenza infection, including virus phagocytosis, antigen presentation, cytokine production, and tissue repair. However, their presence can lead to heightened inflammation. Although temporal inflammation scores can be approximated with a simple model using infected cells as a proxy [6], there are more potentially complicated dynamics given log–linear correlations with an inflammatory macrophage phenotype in addition to neutrophils [6,16]. The development of models describing influenza virus-induced macrophage activation is underway [22–27]. One study assessed the effects of MUC1 (Figure 2) [22], which is a cell surface mucin that acts as

Figure 2



Modeling macrophage responses during influenza. Schematic of ODE models of influenza infection (adapted from models in Smith et al. [16] and Li et al. [22]). The corresponding model results for alveolar macrophages and the intermediate (C) responsible for their depletion (top right; adapted from Smith et al. [16]) and for inflammatory macrophages with and without deletion of MUC1 (bottom; adapted from Li et al. [22]).

a physical barrier to infection and regulates inflammation (reviewed in Ref. [28]). In mice, deletion of MUC1 in macrophages reduced their phagocytosing abilities. This was associated with earlier viral peaks and elevated inflammatory responses, exemplifying the multifaceted role of MUC1. The model estimated a ∼40−45% reduction in the rates of viral infectivity and macrophage recruitment when MUC1 was present [22]. However, these changes did not significantly affect viral loads or clearance times. Interestingly, several modeling studies have found that virus phagocytosis by macrophages is relatively insensitive [6,29,30], demonstrating that terms for this process are statistically indistinguishable from constant clearance terms [27]. This occurs despite the clear occurrence of macrophage-mediated phagocytosis *in vivo*. This divergence calls for the exploration of a broader range of experimental scenarios with varied levels of macrophages and corresponding measurements of inflammation temporally defined.

Illustrating spatiotemporal viral control

Patterns of influenza infection in the lung suggest the growth of individually seeded sites with the intersection of multiple viral lesions and indicate the potential to modify immune control in a spatial domain. *In vitro*, increases in virus-infected cells tend to emanate from a central point, radiating outwards. Several models have captured these dynamics, where the pattern can be represented in partial differential equation or agent-based models as a growing circle on a continuous cellular sheet (Figure 1) ([7−14] and reviewed in Ref. [15]), where the plaque radius grows linearly as the virus diffuses while the affected surface area increases quadratically. When assuming virus movement is through diffusion and advection, as in mucociliary transport, the speed of virus spread can increase [11]. However, adding heightened rates of IFN-α,β production or the absence of NS1 viral antagonism to these models could replicate their effect in limiting viral

expansion (Figure 1) and explain some strain-specific dynamics [7,9,11,24].

Although simple spatial models of virus spread paint a picture of nearly circular viral plaques, *in vivo* infections show irregularly shaped areas of infected tissue and more complex host responses. Coupling the effects of paracrine and autocrine IFN-α,β signaling and increasing the rate of STAT phosphorylation within an ABM showed the potential for irregular growth patterns to emerge (Figure 1) [7]. Effects of mucociliary transport and/or bacteria in directing viral movement and clearance might also pave the way for greater viral travel [11] or infections in different areas of the lung [16]. Furthermore, lung topography with features like alveoli and bronchial branching can also pose a physical barrier, challenging the simplistic assumption of a uniform cellular sheet within ABMs and potentially creating heterogeneity in viral lesions and immune efficacy. More elaborate 3D models of viral infections in the lung are being crafted with early results showing that the initial number of foci scales with viral load peaks [31], suggestive of a dose effect. However, simplifying this structure to connected monolayers of infection with $CD8^+$ T cell migration highlighted the potential for heterogeneous viral lesions and constraints on T cell search patterns in situations where virus spread outpaces chemokine diffusion (Figure 1) [9]. Clustering of the cells was observed in the simulation, which can slow clearance and create nonlinear dynamics in the efficacy of infected cell removal.

This nonlinearity is consistent with ODE models of $CD8^+$ T cell control, where density-dependent rates of infected cell clearance align best with data for multiple $CD8^+$ T cell phenotypes and during experimental depletion of these cells [6]. Collectively, these studies suggest a functional speed limit with higher numbers of $CD8^+$ T cells being insufficient to expedite recovery. How this could be influenced by the lesion size and shape, especially as infected areas merge, remains uncertain. However, as spatial infrastructures evolve, the use of data from imaging techniques tracking the location, speed, and movement of virus and immune cells will be valuable in model parameterizations and explorations.

Concluding remarks

Detailing influenza virus interplay with host immunity, the nuanced roles of immune responses, and the subsequent implications for disease progression within the lung is important. Synergizing experimental and clinical insights with multiple mathematical modeling styles bridges these gaps and offers a clearer window into the mechanistic underpinnings of influenza as an inflammatory disease (reviewed in Refs. [3–5] and herein). The studies mentioned here depict regulatory nonlinearities in various immune responses, which can complicate the interpretation of experimental and clinical data. Understanding these dynamics is particularly important because influenza infections in humans are highly heterogeneous with variable levels of immune cells, cytokines, and disease. This is likely due to a multitude of factors, including infection history, genetics, sex, and underlying comorbidities, and accurately interpreting differences in host immunity is critical.

As the studies described here illustrate, discriminating between mechanisms of early viral control by macrophages is difficult. These challenges are in part due to the difficulty of finding a statistically superior model structure when the dynamics of recruited macrophages only exhibit an exponential increase followed by saturation (Figure 2). Because many models can reproduce these dynamics and only a simple model would be statistically justifiable, careful calibration to multiple and diverse sets of experimental data is required. However, the use of experimentally manipulated data should be done cautiously as this can alter more than the intended population, thereby eliciting changes in model parameters [6]. Detailing phenotypic changes through surface markers and cytokine expression may also help develop models that study macrophage responses. These should also help improve the predictability of inflammation dynamics, which align with disease severity [6].

Efforts in forecasting disease severity through mathematical links with viral, immune, and histopathology kinetics have commenced and have emphasized unexplained nonlinearities using hyperbolic and Hill functions [6,16,32–34]. This could indicate the cooperativity of multiple mechanisms, and questions about how different cell types and cytokines are contributing to these connections remain to be explored in detail. Disrupting disease profiles with bacterial pathogens or experimental manipulation has proven a valuable approach for obtaining a more comprehensive understanding of immune control during influenza and improving model accuracy (reviewed in Ref. [4]). How other respiratory viruses interfere with influenza infection to improve or exacerbate disease is being modeled with potential implications for modifications to immune mechanisms [35]. Their impact on contiguous viral lesion formation and impacts of coinfected cells is well suited for implementation within ABMs.

While spatially implicit strategies remain invaluable to linking cell phenotype to function, exploiting spatial architectures like those discussed here could also help explain viral migration and spatially variable rates in immune efficacy in the upper and lower airways [36]. A better understanding of factors leading to more severe infections is warranted, and employing diverse and complimentary mathematical approaches will undoubtedly shed light on the pathophysiological interactions that define disease trajectory and severity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was supported by NIH grants no. AI170115 and AI139088.

References

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

1. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, *et al.*: **Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project**. *J Glob Health* 2019 Dec, **9**, 020421.

2. Sah P, Alfaro-Murillo JA, Fitzpatrick MC, Neuzil KM, Meyers LA, Singer BH, *et al.*: **Future epidemiological and economic impacts of universal influenza vaccines**. *Proc Natl Acad Sci USA* 2019 Oct 8, **116**:20786–20792.

3. Smith AM: **Host-pathogen kinetics during influenza infection and coinfection: insights from predictive modeling**. *Immunol Rev* 2018 Sep, **285**:97–112.

4. Smith AM: **Validated models of immune response to virus infection**. *Curr Opin Struct Biol* 2018 Dec, **12**:46–52.

5. Handel A, Liao LE, Beauchemin CAA: **Progress and trends in mathematical modelling of influenza A virus infections**. *Curr Opin Struct Biol* 2018 Dec, **12**:30–36.

6. • Myers MA, Smith AP, Lane LC, Moquin DJ, Aogo R, Woolard S, *et al.*: **Dynamically linking influenza virus infection kinetics, lung injury, inflammation, and disease severity**. *Elife* 2021 Jul 20, **10**, e68864.

Using an iterative mathematical-experimental approach, the authors demonstrate nonlinear CD8 T cell-mediated clearance and temporal dynamics of viral spread and inflammation in the lung.

7. • Aponte-Serrano JO, Weaver JJA, Sego TJ, Glazier JA, Shoemaker JE: **Multicellular spatial model of RNA virus replication and interferon responses reveals factors controlling plaque growth dynamics**. In *PLOS comput biol.* Edited by Kosakovsky Pond SL; 2021 Oct 25, e1008874. 17(10.

Using a multiscale model of influenza virus spread and autocrine and paracrine interferon signaling, the authors show viral plaque regulation with increased phosphorylation of STAT

8. Sego TJ, Aponte-Serrano JO, Ferrari Gianlupi J, Heaps SR, Breithaupt K, Brusch L, *et al.*: **A modular framework for multiscale, multicellular, spatiotemporal modeling of acute primary viral infection and immune response in epithelial tissues and its application to drug therapy timing and effectiveness**Peirce SM. *PLoS Comput Biol* 2020 Dec 21, **16**, e1008451.

9. • Levin D, Forrest S, Banerjee S, Clay C, Cannon J, Moses M, *et al.*: **A spatial model of the efficiency of T cell search in the influenza-infected lung**. *J Theor Biol* 2016 Jun 7, **398**:52–63.

The authors develop a spatial model of T cell search in the lung during influenza, where branching of the vasculature is included. The model suggests T cells cluster in areas of high chemokine concentration and that this can be strain-dependent.

10. Whitman J, Dhanji A, Hayot F, Sealfon SC, Jayaprakash C: **Spatio-temporal dynamics of Host-Virus competition: a model study of influenza A**. *J Theor Biol* 2020 Jan, **484**, 110026.

11. Quirouette C, Younis NP, Reddy MB, Beauchemin CAA: **A mathematical model describing the localization and spread of influenza A virus infection within the human respiratory tract**Antia R. *PLoS Comput Biol* 2020 Apr 13, **16**, e1007705.

12. Olmos Liceaga D, Nunes SF, Saenz RA: **Ex vivo experiments shed light on the innate immune response from influenza virus**. *Bull Math Biol* 2023 Nov, **85**:115.

13. Haghnegahdar A, Zhao J, Feng Y: **Lung aerosol dynamics of airborne influenza A virus-laden droplets and the resultant immune system responses: an in silico study**. *J Aerosol Sci* 2019 Aug, **134**:34–55.

14. Michael Lavigne G, Russell H, Sherry B, Ke R: **Autocrine and paracrine interferon signalling as 'ring vaccination' and 'contact tracing' strategies to suppress virus infection in a host**. *Proc R Soc B Biol Sci* 2021 Feb 24, **288**, 20203002. 1945.

15. Gallagher M, Brooke C, Ke R, Koelle K: **Causes and consequences of spatial within-host viral spread**. *Viruses* 2018 Nov 13, **10**:627.

16. Smith AP, Lane LC, Ramirez Zuniga I, Moquin DM, Vogel P, Smith AM: **Increased virus dissemination leads to enhanced lung injury but not inflammation during influenza-associated secondary bacterial infection**. *FEMS Microbes.* 2022 Aug 17, **3**, xtac022.

17. Minucci SB, Heise RL, Reynolds AM: **Review of mathematical modeling of the inflammatory response in lung infections and injuries**. *Front Appl Math Stat* 2020 Aug 26, **6**:36.

18. Smith AM, McCullers J: **Secondary bacterial infections in influenza virus infection pathogenesis**. In *Influenza pathogenesis and control - volume I [internet]*. Edited by Compans RW, Oldstone MBA, Cham: Springer International Publishing; 2014 [cited 2015 Sep 6]:327–356. Available from: http://link.springer.com/10.1007/82_2014_394.

19. Westphalen K, Gusarova GA, Islam MN, Subramanian M, Cohen TS, Prince AS, *et al.*: **Sessile alveolar macrophages communicate with alveolar epithelium to modulate immunity**. *Nature* 2014 Feb, **506**:503–506.

20. Bansal S, Yajjala VK, Bauer C, Sun K: **Influenza-induced interferon-γ promotes alveolar macrophage depletion during secondary pneumococcal infection**. *J Immunol* 2018 May 1, **200**(Supplement). 108.5-108.5.

21. Schmit T, Guo K, Tripathi JK, Wang Z, McGregor B, Klomp M, *et al.*: **Interferon-γ promotes monocyte-mediated lung injury during influenza infection**. *Cell Rep* 2022 Mar, **38**, 110456.

22. • Li K, Cao P, McCaw JM: **Modelling the effect of MUC1 on influenza virus infection kinetics and macrophage dynamics**. *Viruses* 2021 May 7, **13**:850.

Using a model of macrophage dynamics during influenza, the authors show that MUC1 reduced infectivity and macrophage recruitment by 40–45%.

23. Li K, McCaw JM, Cao P: **Modelling within-host macrophage dynamics in influenza virus infection**. *J Theor Biol* 2021 Jan, **508**, 110492.

24. Li K, McCaw JM, Cao P: **Enhanced viral infectivity and reduced interferon production are associated with high pathogenicity for influenza viruses**Antia R. *PLoS Comput Biol* 2023 Feb 9, **19**, e1010886.

25. Torres M, Wang J, Yannie PJ, Ghosh S, Segal RA, Reynolds AM: **Identifying important parameters in the inflammatory process with a mathematical model of immune cell influx and macrophage polarization**. In Adler FR. *PLOS comput biol*, vol. 15; 2019 Jul 31, e1007172. 7.

26. Lee J, Adler FR, Kim PS: **A mathematical model for the macrophage response to respiratory viral infection in normal and asthmatic conditions**. *Bull Math Biol* 2017 Sep, **79**:1979–1998.

27. Ackerman EE, Weaver JJA, Shoemaker JE: **Mathematical modeling finds disparate interferon production rates drive strain-specific immunodynamics during deadly influenza infection**. *Viruses* 2022 Apr 27, **14**:906.

28. Dhar P, McAuley J: **The role of the cell surface mucin MUC1 as a barrier to infection and regulator of inflammation**. *Front Cell Infect Microbiol* 2019 Apr 24, **9**:117.

29. Smith AM, Adler FR, Perelson AS: **An accurate two-phase approximate solution to an acute viral infection model**. *J Math Biol* 2010 May, **60**:711–726.

30. Smith AP, Moquin DJ, Bernhauerova V, Smith AM: **Influenza virus infection model with density dependence supports biphasic viral decay**. *Front Microbiol* 2018, **9**(1554), https://doi.org/10.3389/fmicb.2018.01554.

31. Moses ME, Hofmeyr S, Cannon JL, Andrews A, Gridley R, Hinga M, *et al.*: **Spatially distributed infection increases viral load in a computational model of SARS-CoV-2 lung infection**Smith AM. *PLoS Comput Biol* 2021 Dec 23, **17**, e1009735.

32. Manchanda H, Seidel N, Krumbholz A, Sauerbrei A, Schmidtke M, Guthke R: **Within-host influenza dynamics: a small-scale mathematical modeling approach**. *Biosystems* 2014 Apr, **118**:51–59.

33. Mochan E, Sego TJ, Ermentrout B: **Age-related changes to the immune system exacerbate the inflammatory response to pandemic H1N1 infection**. *Bull Math Biol* 2022 Aug, **84**:88.

34. Handel A, Li Y, McKay B, Pawelek KA, Zarnitsyna V, Antia R: **Exploring the impact of inoculum dose on host immunity and morbidity to inform model-based vaccine design**Davenport MP. *PLoS Comput Biol* 2018 Oct 1, **14**, e1006505.

35. Pinky L, DeAguero JR, Remien CH, Smith AM: **How interactions during viral–viral coinfection can shape infection kinetics**. *Viruses* 2023 May 31, **15**:1303.

36. Pinky L, Burke CW, Russell CJ, Smith AM: **Quantifying dose-, strain-, and tissue-specific kinetics of parainfluenza virus infection**Faeder JR. *PLoS Comput Biol* 2021 Aug 12, **17**, e1009299.