Numerical Modelling of Infection Dynamics in Human Upper Airway

李, 寒羽

氏　　名　：　Li Hanyu

Name

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（上気道におけるウイルス感染ダイナミクスの数値シミュレーション）

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論　文　内　容　の　要　旨

Thesis Summary

Respiratory diseases impact the airways and other structures of the lungs, leading to illness, death, and disability globally. COVID-19, which has garnered significant attention in recent years, serves as a notable example. It is a respiratory disease caused by the SARS-CoV-2 virus, which belongs to the broader family of coronaviruses, also including the viruses responsible for SARS (SARS-CoV) and MERS (MERS-CoV). Symptoms of COVID-19 can range from mild to severe, with some individuals potentially being asymptomatic.

COVID-19 primarily spreads via droplets produced when an infected person coughs or sneezes. Previously reported studies on airborne transmission and infection risk assessment in indoor environments have mainly focused on predicting inhalation exposure concentrations based on indoor airflow analysis. However, a deeper understanding of the pathogenesis and dynamic distribution of respiratory viruses is critical for further prevention and treatment of respiratory diseases. The spread of droplets essentially results from a complex journey of virus-laden droplets transported from the indoor scale into the human body, further expanding from the human scale to the cellular scale. As these broad environmental scales are seamlessly connected via the air, to enhance the accuracy of infection risk assessment predictions, a numerical model capable of estimating virus deposition and replication inside the human body seamlessly is necessary.

In this context, we propose a new numerical framework that combines computational fluid and particle dynamics (CFPD) of the indoor environment with a computational host-cell dynamics (HCD) model simulating the exposure and infection dynamics in human respiratory tract. Here, we study the case of SARS-CoV-2, utilizing CFPD to simulate the steady and unsteady deposition distribution of virus-laden droplets in the upper respiratory tract. It is combined with an HCD model to predict the infection dynamics of SARS-CoV-2 in the nasal cavity-nasopharynx region. This study enhances the HCD model based on the mucociliary clearance movement, carries out optimization of relevant parameters and discusses influential factors, striving to visualize the process of viral infection in the upper respiratory tract. It aims to make a significant contribution to the further prevention and treatment of respiratory diseases.

This thesis consists of six chapters, each of which is briefly summarized below:

Chapter 1 provides a general overview of the thesis, outlines the research objectives, and describes the overall structure of the thesis. To gain a better understanding of the pathogenesis of SARS-CoV-2 and to visualize its infection process in the upper respiratory tract, this chapter includes a literature review that collects clinical and experimental data, presents methods for analyzing particle deposition in the upper respiratory tract, and explains the HCD model that describes the virus dynamics. It also highlights the significance and innovations of this study.

Chapter 2 presents a numerical analysis of the deposition distribution of virus-laden droplets released by coughing in the upper respiratory tract of the susceptible individual. In this study, an important initial condition - the initial viral load - is estimated based on the deposition distribution of infectious droplets in the upper respiratory tract. Therefore, this chapter assumes a scenario of a high risk of respiratory infection and uses two computer-simulated individuals (two computer-simulated persons (CSPs): one infected and one healthy susceptible) to study the risk of exposure to droplet deposition in the upper respiratory tract during coughing and breathing activities. After a comparative analysis of breathing patterns, physical social distance, and particle evaporation conditions, the results from the case where the physical distance is 1m and droplet evaporation is not considered are mainly used as one of the initial conditions for the visualization of virus dynamics in Chapter 4.

Chapter 3 is a first attempt to visualize viral dynamics, offering the combination of CFPD and HCD. It describes how viral dynamics with mucociliary clearance movement are considered in the HCD model and proposes a combination of the HCD model and a 3D shell model with a mucus layer. Based on the simple target cell-limited model, convection-diffusion terms are added using parameters from references in CFD calculations and visual analysis. This chapter updates the HCD model but finds that infection rates and other parameters from the literature do not agree well with clinical data, suggesting that further optimization of initial conditions and parameters is necessary to predict the dynamics of SARS-CoV-2 in the upper respiratory tract. The problems/issues of the CFPD-HCD coupled analysis methods in upper respiratory tract with complex three-dimensional geometry are clearly organized and a solution is proposed.

Chapter 4 deals with parameter optimization of the HCD model to better visualize the SARS-CoV-2 infection dynamics based on the results from Chapter2&3. According to the characteristics of the mucus layer in the upper respiratory tract, this chapter further improves the existing model in Chapter 3 by proposing a multi-compartment model concept to describe the viral dynamics in a simplified single-layer and two-layer mucus. At the same time, it uses SARS-CoV-2 human challenge data from individuals who have not undergone drug treatment and have a clear virus inoculation date as a fitting dataset, with parameter fitting performed by *Monolix*. The results show that the parameters obtained from the two-layer, multi-compartment, low-velocity model, combined with the CFD method, visualize the infection dynamics of SARS-CoV-2 in the nasal-nasopharyngeal region using the 3D shell model, which could help explain some symptoms in the nasal cavity and enable targeted prevention and treatment of COVID-19. Meanwhile, using this method, we also used droplet deposition data from a physical distance of 2m from Chapter 2 for parameter fitting and CFD calculation but found that this method may not be suitable for smaller droplet deposition. Therefore, we should carry out an independent analysis of the influence of the initial droplet distribution on the prediction results.

Chapter 5 is an analysis of the impact of droplet distribution in the nasal-nasopharynx region on virus dynamics prediction. To avoid randomness, this chapter generates an equal number of infectious particles uniformly in the entire geometric model, the vestibular region, and the nasopharynx region as the initial conditions for predicting the infection dynamics of SARS-CoV-2, and then discusses the prerequisites to be considered when using the method in Chapter 4.

Chapter 6 concludes the thesis by providing a summary of each chapter based on the structure of the thesis, and finally outlining the future prospects of this research.