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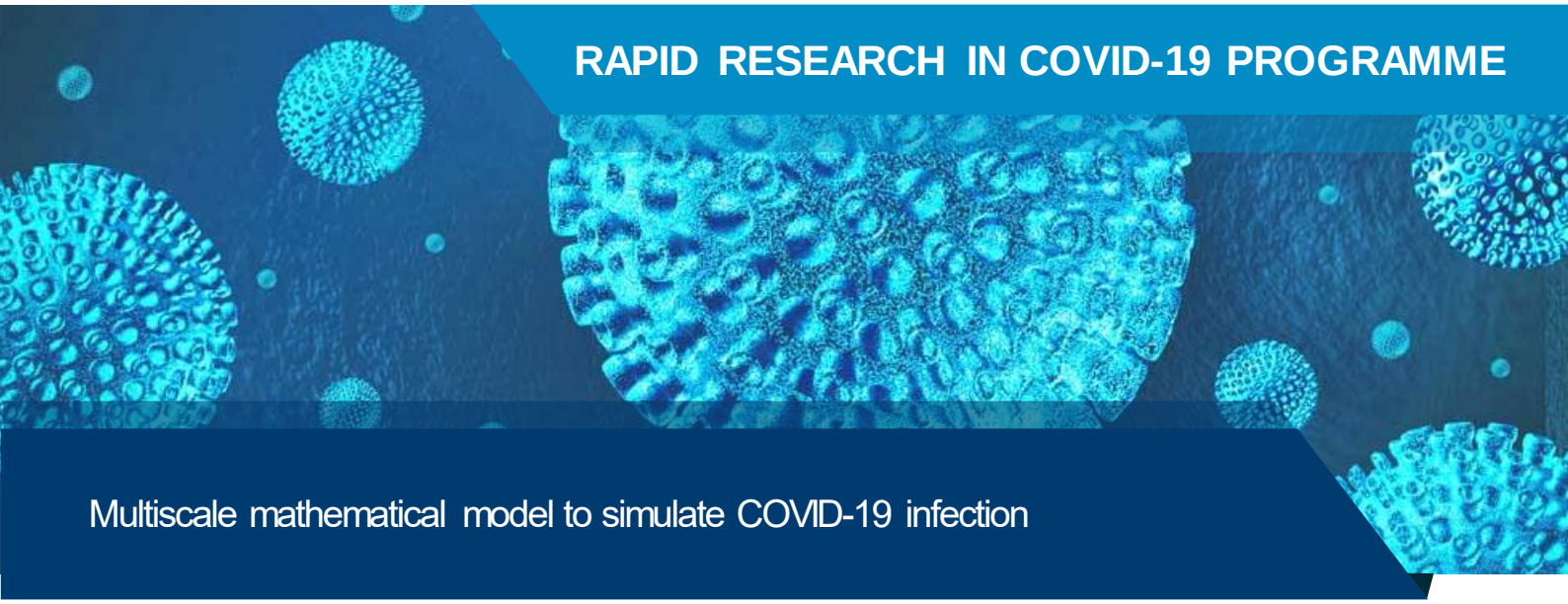
RAPID RESEARCH IN COVID-19 PROGRAMME



Multiscale mathematical model to simulate COVID-19 infection

AIMS

Mathematical models are vital in advising the government on how to deal with pandemics. The majority of models, however, focus on the spread of disease through a population rather than looking at the spread within the body. We aimed to develop a mathematical model that simulates the virus that causes COVID-19 disease in the body, to better understand the disease effects and why severity varies in different patients.

KEY FINDINGS

- Development of a mathematical model to study COVID-19 spread in the body:
  - the model simulates a small section of lung tissue
  - viral particles and immune cells are modelled
  - signaling chemicals, produced by cells following infection, are also modelled
- Preliminary results show the potential of our model to simulate how a patient's immune system responds to COVID-19 infection. We can use this model to study different immune reactions and assess the effects of these different responses. This is helping us to understand why some patients have more severe disease.

WHAT DID THE STUDY INVOLVE?

We developed a mathematical model for the spread of COVID-19 infection within a human body. We worked with specialists studying viruses, as well as those researching the immune system, to make sure that the model contained the latest biological knowledge. We also worked with infectious disease doctors to ensure we were testing relevant clinical scenarios.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

The model simulates a variety of different types of immune cells as well as the virus (Figure 1), where we focus on the start of infection and the body's initial response to it.

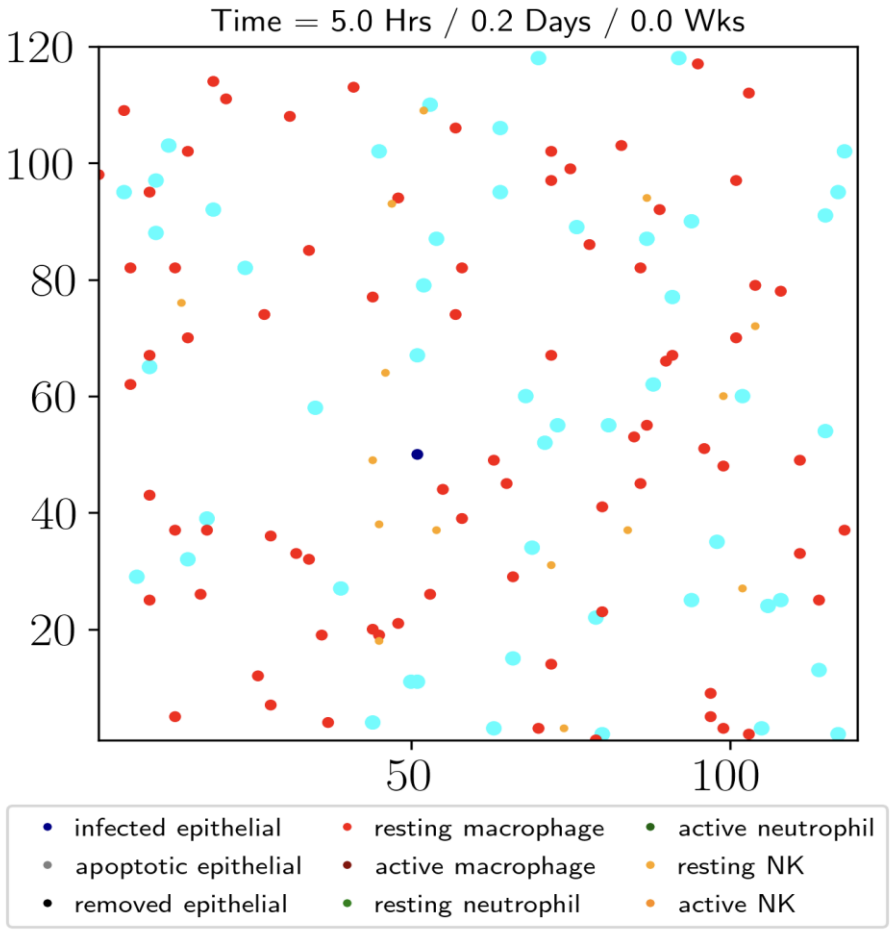


Figure 1: Start of an example simulation. White space indicates healthy cells. Blood vessels (shown as cyan coloured circles) are randomly distributed throughout the grid. Initially, a single cell is infected by a single virus particle. Immune cells are randomly distributed throughout the grid and are colour-coded according to the key provided.

As the infection spreads through the grid, signaling chemicals (cytokines) are released by cells. These cytokines activate further immune response. A plot of an example simulation after a few days of initial infection is show in Figure 2.

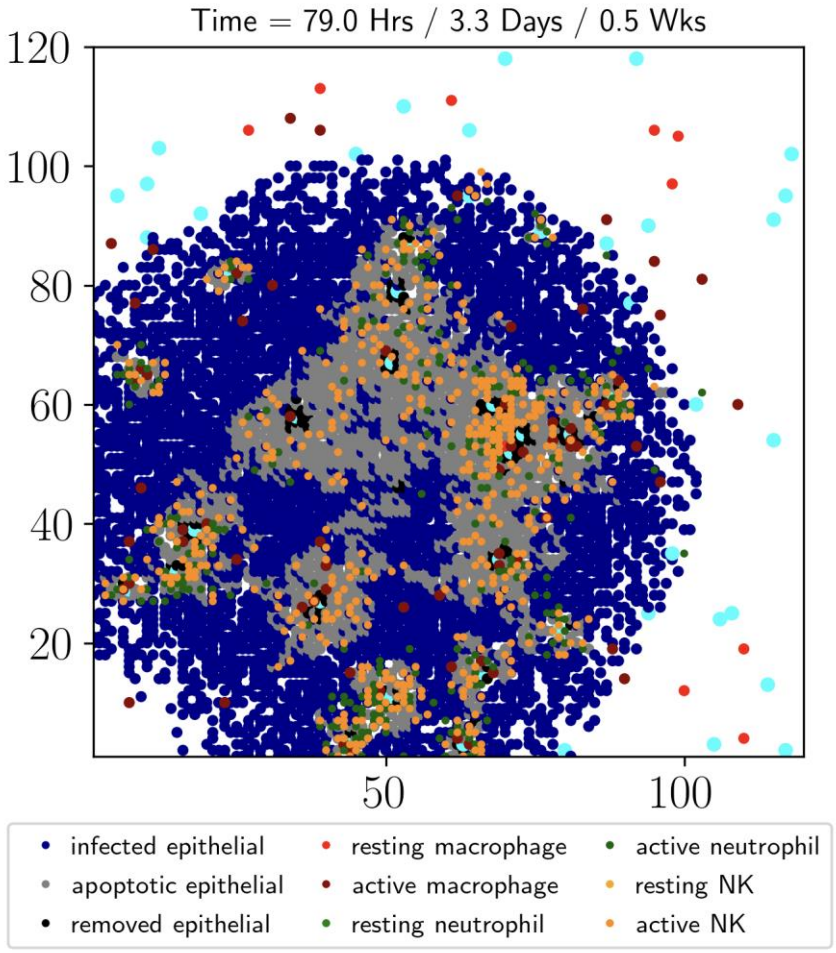


Figure 2: Example simulation after 79 hours, post-infection. Following viral entry, replication and production, the infection spreads from a single infected cell into neighbouring cells. Immune cells respond by secreting cytokines which recruit other immune cells from nearby blood vessels. Natural killer (NK) cells (orange dots) trigger apoptosis in infected cells in an attempt to clear the infection. Macrophages (red dots) and neutrophils (green dots) kill virus also clear away dead cells (grey dots).

Our model is able to consider various immune responses, specifically looking at immune systems which are impaired or respond differently in some way, which are thought to be common in more severe disease. These sorts of investigations are hard to achieve in the laboratory.

The body's response to viral infection is complex, with many biological and immune responses/interactions. Therefore, by necessity, mathematical models involve simplifications. Adding further detail to our model is the subject of future work. Validating each component of the model is also essential. Test simulations have been conducted to achieve this and results have been compared with laboratory results. At the start of the project, most of the laboratory results were limited. However, recently, more detailed data have emerged, and this final stage of validation is therefore also the subject of future work.

Natural killer (NK) cells are a type of immune cell, and their function can be decreased in older patients. We have seen in our simulations that when we decrease the effectiveness of NK cells, a higher virus count is seen and hence more severe disease.

A chemical called Type I interferon (IFN-1) is known to be an important first responder to infection. A delayed IFN-1 response is thought to contribute to the development of severe disease. In our simulations, we are able to replicate these findings, as delaying the IFN-1 response leads to an increase in infected cells counts and viral replication.

WHAT IMPACT COULD THE FINDINGS HAVE?

- Model simulations can help increase understanding of COVID-19 disease. Increased awareness of the mechanisms responsible for severe disease in specific subgroups of patients will help to guide future management and treatment of the infection in these populations.
- Model simulations could be used to help personalise therapy.
- Model results could help to understand differences in transmission and therefore help to inform public policy and control future spread.

HOW WILL THE OUTCOMES BE DISSEMINATED?

We currently have a manuscript in preparation which we plan to submit to Royal Society Open Science in June 2021. We have continued the development of our model, with the aid of internal University funding, and have submitted another grant application to continue this promising work.

We are part of the Royal Society's Rapid Assistance in Modelling the Pandemic (RAMP) initiative and through this also collaborate with several colleagues in the Joint UNIversities Pandemic Epidemiological Research (JUNIPER) consortium. Collaborations with these groups mean that insights from our work will ultimately feed into the Scientific Pandemic Influenza Group on Modelling (SPI-M) and the Scientific Advisory Group for Emergencies (SAGE). Both of these bodies advise the UK government on scientific matters relating to the UK's pandemic response.

CONCLUSION

Working alongside experts studying viruses and the immune system, as well as infectious disease doctors, we have developed a mathematical model for COVID-19 infection. The model is capable of simulating viral spread within a human lung. We are able to simulate people's different immune responses, leading to increased understanding of this disease and why is affects people differently.

Our results have suggested that reducing the effectiveness of specific immune cells, such as natural killer (NK) cells, which may occur naturally as a result of ageing, for example, leads to more severe disease. Additionally, altering the timing and amount of cell signalling molecules that are produced as part of the immune response is helping us to understand more about why certain groups of patients suffer more severe disease.

The work carried out during this project has laid important groundwork for future studies. There is much more we can do, adding complexity to the model and validating our findings against new emerging data, as well as investigating new clinical scenarios that will help to guide future treatment of this disease.

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ADDITIONAL INFORMATION

Project completed on 30/12/2020. Amount awarded: £24,760.