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The novel coronavirus SARS-CoV-2 is the source of a global pandemic and ongoing public health crisis. Mounting evidence points to dysregulated and hyper-reactive inflammatory responses, including hyperinflammation and cytokine storms, as particular presentations in severe COVID-19. Much remains to be uncovered about the mechanisms that lead to disparate outcomes in coronavirus disease 2019. Here, quantitative approaches, especially mechanistic mathematical models, can be leveraged to improve our understanding of the immune response to SARS-CoV-2 infection. We have developed a quantitative framework to interrogate open questions about the innate and adaptive immune reaction in COVID-19. This talk will outline our mechanistic model of SARS-CoV-2 viral and immune response dynamics at both the tissue and systemic levels. A portion of this work is done as part of an international and multidisciplinary coalition working to establish a comprehensive tissue simulator (physicell.org/covid19). Ultimately, by improving our understanding of SARS-CoV-2 infection and immune responses to novel coronavirus, our results help to understand the orchestration of the immune response after infection and to identify mechanisms defining differential clinical manifestations of COVID-19. (Received September 11, 2020)