A computational control theory approach to the analysis of virus-host interactome in Covid-19

Paola Lecca
Faculty of Computer Science, Free University of Bozen-Bolzano
39100 Bolzano, Italy
Paola.Lecca@unibz.it

ABSTRACT

This study presensts a computational method of optimal control analysis for the virus-host interactome network for the SARS-Cov-2. The network is modeled as a multi-agent system. The controllability properties of the system have been assessed and the control nodes, i.e. those proteins whose state, if suitably altered, could imply a decrease in the virus capacity to infect the cell, have been identifed.

CCS CONCEPTS

• **Applied computing** → **Biological networks**; *Life and medical sciences*; *Computational biology*; **Systems biology**;

KEYWORDS

Multi-agent systems, optimal control, viral protein network, SARS-Cov-2, Covid-19, ORF8a, ORF9b, ORF3a, NSP5.

1 BACKGROUND

Multi-agent systems are used to model a complex system by decomposing it in small entities (agents) and by focusing on the relations between agents and between agents and their environment. Multi-agent system approach is derived from distributed artificial intelligence research [2], but it is currently used to model various systems of interacting individuals/components, such as biological cells, regulatory processes in physiology and genomics, ecological systems, social behaviour etc. Optimal control theory seeks to find control agents that cause a process to satisfy physical constraints and to minimize (o maximize) some performance measure (defined here as cost integrals of dynamical systems differential equations).

2 METHODS

This study uses the recent experimental results collected by W. Liu and H. Li [1], data on the interactomics of SARS-CoV-2 (Severe Acute Respiratory Syndrome-CoronaVirus -2) novel coronavirus (http://korkinlab.org), and data concerning heme synthesis and metabolism (https://humancyc.org) to build a multi-agent dynamical model of protein-protein interactions in the virus-host interactome currently assumed to be responsible for the attack of the virus to the haemoglobin for sequestering the porphirn in the heme protein. The alteration of the hemoglobin configuration is a cause of the severe pulmonary distress in patients suffering from Covid-19. The virus-host interactom network considered in this study includes the SARS-COV-2 interacome, and the human haeme biosynthesis network. This network is represented as a multi-agent system in continuous space and time,. Each protein that is a node in this network is indeed an agent. The state state $x(t)$ of an agent in a k-dimensional continuous state space $\mathbb{R}^k$ evolves over time according to the controlled stochastic differential equation (according to the probabilistic nature of the molecular interactions)

$$\dot{x}(t) = f(x(t), t)dt + u(x(t), t)dt + \sigma\dot{w}(t). \quad (1)$$

The control of the agent is an $\mathbb{R}^k$-valued function u of $x(t)$ and t. $w(t)$ is a Wiener noise process, and σ is the $k \times k$ variance matrix of the noise. Any autonomous dynamics are modelled by f, which is a $\mathbb{R}^k$-valued function of $x(t)$ and t. The behaviour of the agent is valued by a *cost function*. Given the agent's state $x(t) = x$ at the present time t, and a control u, an expected future cost for each agent is calculated. The expected cost at time t minimized over all controls u defines the optimal expected cost (*cost-to-go*). The optimal control problem is solved by finding the optimal expected cost-to-go which satisfy the stochastic Hamilton-Jacobi-Bellman equation.

3 RESULTS AND CONCLUSIONS

The following viral proteins have been identified as controls: ORF9b (implied in the suppression of the innate immunity), ORF8a (involved in viral replication and cell apoptosis), ORF3a (involved in the viral life cycle) and NSP5 (a gene expression regulator). The master role of these proteins is emerging also in many of the current studies (see for example [3]). The fact that in this study, these proteins have been identified as the controls of the equations of the dynamics of the virus-host interaction network, suggests that these proteins could be the targets of drug treatments aimed at blocking the entry of the virus into the cell (ORF8a), preventing the silencing of the host immune system (ORF9b) and viral genome replication. processes (NSP5). A model sensitivity analysis also showed that these are the proteins to which dynamics are most sensitive

Currently, the pandemic is still ongoing and the huge and incessant research activity around the world is producing new data and new knowledge. The contribution of this work, far from wanting to present certain and definitive results, wants to highlight how mathematical models and computational methods can help the research about Covid-19 by turning to the attention of biological research candidate control proteins and virus-host interactions to be subjected to further in-depth experimental investigations.

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