**Systems biology modelling and COVID-19 pandemic dynamics**

Denis A. Sarigiannis1,2,3,4, Achilleas Karakoltzidis2,3, Spyros Karakitsios1,2

1 HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Greece

2 EnvE.X Solutions, Thessaloniki, Greece

3 Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Greece

4 Complex Risk and Data Analysis Center, University School of Advanced Study IUSS, Pavia, Italy

The COVID-19 pandemic has instigated the development of advanced modelling tools using a variety of computational approaches to capture the contagion dynamics and support decision making to protect adequately public health. Over time, the prediction of the pandemic became a particularly complex mathematical challenge, because of the multi-faceted factors and biological, environmental and societal processes contributing to its articulation. These processes were, in turn, affected by factors such as (a) non-pharmacological interventions (such as social distancing, extensive testing, self-testing), (b) pharmacological interventions (vaccination and, as of recent, the availability of targeted antiviral medication), (c) the effect of seasonality (d) the different transmissibility, disease severity and reinfection capacity of the various strains. At the same time, multiple factors related to urban dynamics such as mobility patterns and social distancing measures are detrimental for the transmissibility of COVID-19, while PM related air pollution and climatic conditions themselves (impacted by climate change) comprise additional transmissibility modifiers. In this sense, it is of particular interest to evaluate the impact of various mitigation and adaptation options towards climate change mitigation (e.g. promotion of public transport) and adaptation (e.g. use of biomass burning vs air conditioning for space heating), as well as the use of technological advances such as indoor air purifiers impact transmission of COVID-19 in urban environments. Accounting for all of the above and having in mind the decision-making support to the national health system over the COVID-19 pandemic, a multi-modal computational tool (called CORE: COVID Risk Evaluation model) for evaluating the COVID-19 epidemic health risk in Greece, Italy and USA has been developed, able to access the impact of various pharmacological and non-pharmacological interventions. Unlike conventional epidemiological models, the computational paradigm of the CORE platform is dynamic systems biology modelling, supported by artificial intelligence techniques. CORE is built not simply to capture contagion dynamics but rather to allow integrative assessment of the public health risk associated with infectious disease spread and its management. An Agent-Based Modelling (ABM) approach (Sarigiannis et al., 2018; Chapizanis et al., 2021) has been employed to compute the contact matrix among the various population groups, accounting for their sociodemographic profiles (i.e. age, occupation etc) and the impact of targeted social distancing measures.

CORE has resulted in successfully modelling the dispersion and pathology dynamics of the different strains of SARS-CoV-2 that were introduced in the Greek population since the beginning of the pandemic. Of particular interest is the introduction in the model of the 2 new dominant strains, i.e. Omicron (by the end of November 2021) and Omicron-2 (by February 2022). The greatest challenge in the modelling effort was to capture the dynamic equilibrium of the susceptible population. The latter is affected by (a) the extent to which natural immunity to one strain extends to the other circulating strains at any point in time; (b) the differences in the immunity and the efficiency against infection of the people vaccinated with 2 and 3 doses and (c) the gradual loss of immunity with time, either natural and/or acquired through vaccination. This was resolved by describing the full set of dispersion kinetics for each strain (A, Δ, Ο, O-2) for the various disease states independently, interacting at the level of the susceptible equilibrium; different fraction of the ones that had acquired immunity by one strain, were also deducted from the available susceptible population of the other strains. At the same time, inter-strain differences in transmissibility and re-infection capacity explain very well the pandemic evolution in terms of number of daily infections. Similarly, differences in the severity of the disease caused by the A, Δ, Ο, O-2 strains have been accounted for. These differences resulted in successful prediction of the people who were going to require hospitalization in critical condition (intubated in ICU).

In general, over the last quarter, the theory of dynamic equilibrium that has already been formulated by our team has been confirmed. The relaxation of the social distancing measures by mid-February, allowed the most contagious Omicron 2 mutation (Lyngse et al, 2022) to disperse and to result in an additional peak (practically forming a 6th wave), further delaying the rapid de-escalation of the pandemic. However, a very high 6th wave due to Omicron 2 has been avoided by the additional natural immunity obtained (and added to the overall acquired and already existing natural immunity), because of this fluctuation in the spread of the contagion. Additional factor that come into play at this instance include the significant number of re-infections (accounting for almost 10% of the number of daily cases now), as well as the impact of reduced immunity in people who were vaccinated with the 3rd (booster) dose more than 4 months ago.

Our predictions for the next months are optimistic (also supported by the seasonality effect), given the gradual decline of natural and acquired immunity and the high rate of re-infections related to Omicron 2. Yet, to reduce the risk of extensive flare-up of the pandemic and to return and sustain de-escalation, it is important to:

(a) continue at a high rate both the booster vaccination and the rapid completion of school-age vaccination; and

(b) continue to responsibly comply with the measures currently in force until de-escalation of the dispersion below 5000 per day is observed, including the high number of the self-tests.

**References**

SARIGIANNIS, D. A., KARAKITSIOS, S. P., HANDAKAS, E., PAPADAKI, K., CHAPIZANIS, D. & GOTTI, A. 2018. Informatics and Data Analytics to Support Exposome-Based Discovery: Part 1-Assessment of External and Internal Exposure. Applying Big Data Analytics in Bioinformatics and Medicine. IGI Global.

CHAPIZANIS, D., KARAKITSIOS, S., GOTTI, A. & SARIGIANNIS, D. A. 2021. Assessing personal exposure using Agent Based Modelling informed by sensors technology. Environmental Research, 192, 110141.

LYNGSE, F. P., KIRKEBY, C. T., DENWOOD, M., CHRISTIANSEN, L. E., MØLBAK, K., MØLLER, C. H., SKOV, R. L., KRAUSE, T. G., RASMUSSEN, M., SIEBER, R. N., JOHANNESEN, T. B., LILLEBAEK, T., FONAGER, J., FOMSGAARD, A., MØLLER, F. T., STEGGER, M., OVERVAD, M., SPIESS, K. & MORTENSEN, L. H. 2022. Transmission of SARS-CoV-2 Omicron VOC subvariants BA.1 and BA.2: Evidence from Danish Households. medRxiv, 2022.01.28.22270044.