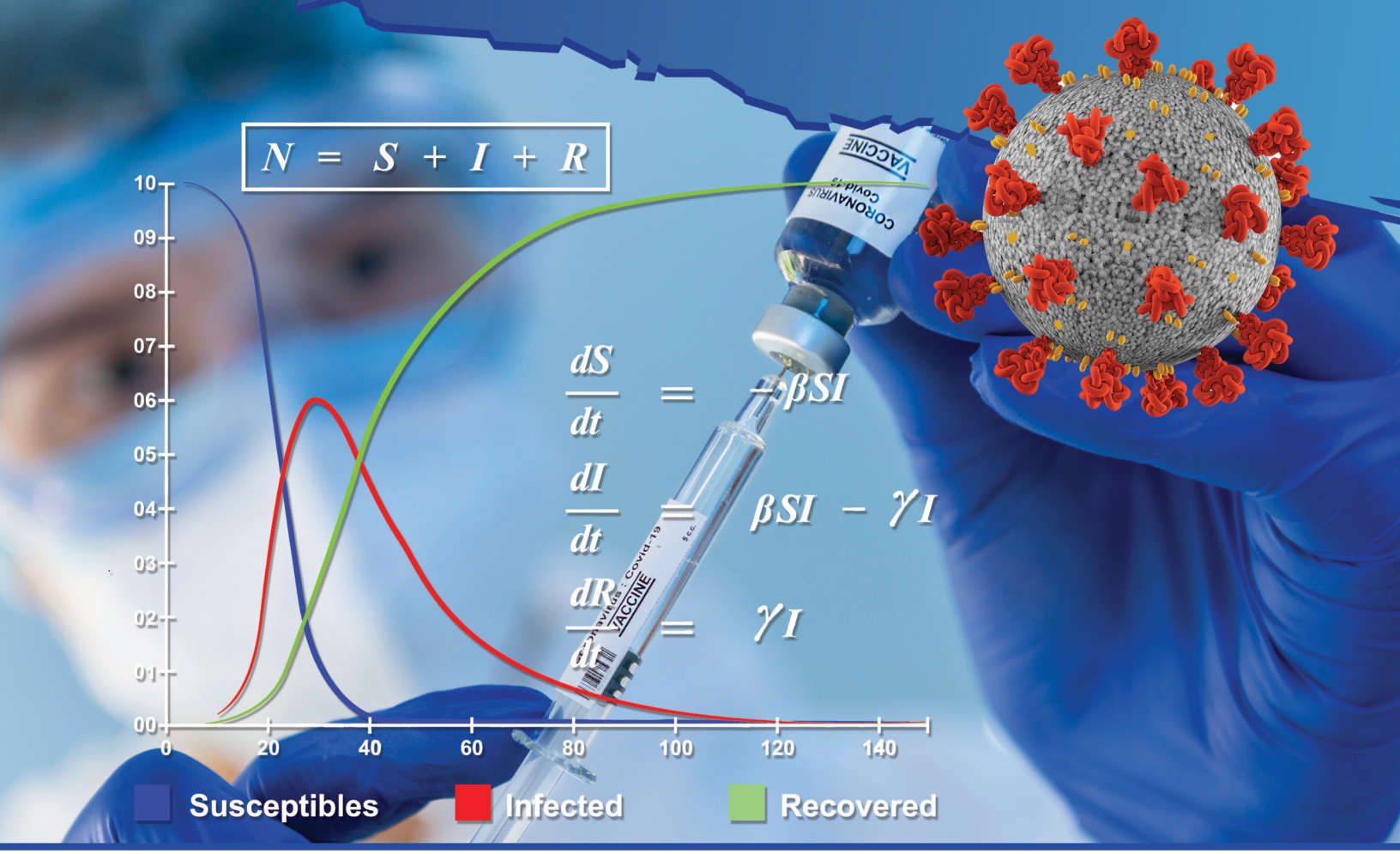
MOVING FROM COVID-19

MATHEMATICAL MODELS TO VACCINE DESIGN: THEORY, PRACTICE AND EXPERIENCES



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Mathematical Models to Vaccine Design: Theory, Practice and Experiences

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Moving from COVID-19 Mathematical Models to Vaccine Design: Theory, Practice and Experiences

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FOREWORD I

Living and coping with COVID 19, the second pandemic of the millennia after the 2009 influenza pandemic, has posed unprecedented challenges. The world has dealt with pandemics before. Human history has been shaped by diseases that present themselves as epidemic, endemic or pandemic diseases. We have registered pandemics since well before the Christian era, and surely, although no registries are available, they have always accompanied humankind. Some remarkable pandemics, that changed the course of history were the Black Plague in the 14th century that killed a great proportion of the European population, and the Spanish Influenza, that occurred little more than a century ago in 1918-19, and killed well over 40 million people, although some scholars say the number of deaths might have reached more the 100 million.

Circumstances have changed and the world is quite different from what it used to be just a few decades ago. Knowledge, technology and communications have developed in an unprecedented speed in human history in the last century and especially in the last four decades. While these are great achievements, they also pose new challenges. Lifestyles have changed and the world faces global threats such as climate change, overpopulation, undernourishment, non-communicable diseases, the emergence of new potentially pandemic infectious diseases such as COVID-19, and many others that have pushed together the global community in efforts to deal with them in a coordinated fashion. Common targets such as the Sustainable Development Goals prove that leaders all over the world are concerned about the future of human kind, although not all to the same extent.

These efforts, however, have been insufficient, and COVID-19 has shown that much more than meetings, nice documents and good intentions are needed to face current challenges. ConfrontingCOVID-19 has risen several questions that need yet to be answered by scientists as well as politicians. For instance, what was the origin of SARS-CoV-2; how can we deal with health inequities such as differential access to vaccines, or why many governments and country leaders disregarded the World Health organization's recommendations.

In this very complicated scenario, any attempt to better understand and cope with COVID-19are welcome. This book will surely provide vast and comprehensive knowledge about the pandemic and its development, and the best ways to confront it.

Editor and author, Andrés Fraguela Collar, has brought together several contributors, from different Mexican institutions as well as from highly renowned institutions from other countries in a great effort to try to understand COVID-19.

In chapter 1, readers will find a very thorough and challenging description of the mathematical modelling of pandemics in general and of COVID-19, in particular.

Chapter 2 will guide them through key issues about the epidemiology of infectious diseases. They will get a comprehensiveview from chapter 3 about what was known at the time the book was written about how SARS-CoV-2 does its damage, how we, human beings, experience the disease and where were the possible treatment options at that moment.

Chapter 4 is devoted to mathematical modelling of epidemics. Chapter 5 will offer readers avery interesting discussion about the importance of data analysis, and the challenges faced when dealing with something new like COVID-19.

Chapter 6 deals with the epidemic progression of the diseases in a non-homogeneous population. Those who love Mathematics will enjoy this chapter.

Chapter 7 leads the reader through the very important subject of social inequities and their role in the propagation of infectious diseases.

Chapter 8 will update the reader on the statistical approach to understand the severity and fatality of COVID-19.

Chapter 9 is devoted to the Cuban experience, on immunotherapy and the role played by mathematical models of disease progression at the individual level.

Chapter 10 and last explains in a very comprehensive manner many aspects of vaccine development and the challenges it poses.

Throughout the book, the reader will find many graphs, tables and formulas, and a very extensive bibliography in each chapter.This book is an example of a multidisciplinary endeavor. It is no easy reading for those who do not have statistical or mathematical background, but anyhow it will be highly enjoyable for any reader and particularly for those familiar with mathematical concepts and methods.

COVID-19 is evolving in many senses, and it is a challenge to health systems, and at the individual level, to both clinicians and researchers. Modelling it has proved to be a very difficult task and as we learn more about it, we discover that there are yet many things to unveil. With this disease, human kind is walking in unchartered territory.

I recommend the reader to follow on new every day developments, to stick to basic publichealth messages which have proven to be the best defense against the disease and to have in mind that this will not be the last pandemic we will face. There is a very high probability of a new pandemic in the future, although we do not know when or how it will occur. As someone said “the clock is ticking, but we do not know what time it shows...”

Enjoy this book, as it contributes to better understand COVID-19.

Pablo Kuri-Morales
Independent Health Consultant

FOREWORD II

Mathematical modeling of infectious diseases has a long history of being used as a tool to study the mechanisms by which a disease can spread within communities, to predict the direction of an outbreak in a population and to evaluate the effectiveness of therapeutic interventions (*e.g.*, vaccination programs) to control an epidemic. These mathematical models derive from basic theories, the collection of statistical data or both, and they help to define parameters for a variety of infectious diseases, and to estimate the effects of the different interventions.

The appearance of a new human viral infection which causes the disease known as COVID-19, constitutes both a challenge and a test to the usefulness and relevance of mathematical modeling. This coronavirus known as SARS-CoV-2 emerged suddenly in South Asia and rapidly disseminated around the globe. It represents a significant concern because, very few times before, the population of the whole world had to face a disease of such pandemic proportions, that has exposed the lack of preparedness of the health care systems to handle thousands of patients and the limited therapeutic interventions to counteract such disease. Fortunately, rapid action in the development of effective vaccines worldwide and the accelerated emergency approval of these therapeutics has let different countries to combat this disease, increasing survival and reducing the death toll.

Current and emerging problems during the pandemic, and the effectiveness of the vaccine platforms developed to cope with it, will define the future of outbreak control. For example, it is unknown whether this novel coronavirus will establish itself in an endemic form or will it eventually die out. Furthermore, the appearance of variants (also known as mutations in the viral genome of SARS-CoV-2) that increase the capacity of the virus to cause disease (*e.g.*, transmissibility), might increase the capacity of the virus to overcome vaccine protection. Therefore, continuous monitoring of the pandemic is required, not only to evaluate vaccine distribution and coverage, but also to follow up individuals who were infected by SARS-CoV-2, since they could be carriers viral variants that might disseminate through the population.

Mathematical modelling can help decide which interventions to avoid and which to test, or can predict epidemic or pandemic patterns, as well as help understanding the impact of vaccination programs. In this book entitled: “Moving from COVID-19 Mathematical Models to Vaccine Design: Theory, Practice and Experiences”, the authors provide a perspective on how to attack a present

problem in public health with mathematical tools, that can guide the decision making related to COVID-19 epidemiology and vaccine production and distribution. But why is this book different from others already published on mathematical modelling? First, the authors of this book are from different countries that are significantly affected by the disease. Second, the book presents a balance set of basic and applied chapters describing topics from disease progression and prevention to those models that could be used in different scenarios. The aim of the book is to present the COVID-19 pandemic as a complex public health problem, that requires the participation of multidisciplinary and interdisciplinary groups of experts to tackle the problems associated with the disease, and demonstrate the role mathematical and computational modeling had during the course and evolution of the pandemic.

The book is divided into 10 chapters. Chapters 1, 4 and 6 introduce mathematical and computational models that can be used to study the COVID-19 pandemic and understand the epidemiology of the disease. Chapters 2 and 3 describe the epidemiology and present the clinical manifestations associated with the disease. Chapter 5 discusses the importance of data science as a tool for COVID-19 informatics. Chapter 7 presents an important aspect of the pandemic that has to do with the impact in populations that lack proper health services or present pre-existing health conditions. Chapter 8 is an overview of the statistical methods that can be used to understand COVID-19 morbidity and mortality. Chapter 9 discusses the impact mathematical modeling and statistics can have in the treatment of COVID-19 patients. Finally, chapter 10 is an overview of all the experimental vaccines available to combat the COVID-19 pandemic. I hope this book becomes a referent for current and future generations of investigators interested in mathematical modeling and infectious diseases, and provides additional tools to understand the current pandemic.

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PREFACE I

The pandemic of COVID-19, caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2), has shaken up our societies, with an intensity and effects not suffered by humanity for a long time. To date, there have been registered millions of deaths associated to COVID-19, and hundreds of millions of confirmed cases all around the world. Moreover, this pandemic has triggered not only a deep and global health crisis, but also an economic and social (without mentioning psychological, educational, *etc*.) crisis like never seen before.

In order to endure and overcome this major tribulation, the different human communities, guided by their respective administrations and governments, have been put to the test in multiple and severe ways, under the direct effects of the disease, and the performance of several therapeutical and non-pharmaceutical interventions and mitigation measures. Among others, we could mention: the severity of symptoms and disease evolution in serious and critical cases (including assisted ventilation), and the long-term effects; the lack of effective treatments, specially in the first stages; unstoppable death tolls and incidence rates, with increasing numbers of hospitalizations that press and even saturate the health care national systems; hygiene or sanitary measures (frequent hand washing, not touching the face, the generalized use of disinfection products, the use of masks, gloves, and glasses, *etc*.); the use of detection tests (as PCR); quarantines, home isolation and confinements; the implementation of severe social distancing and isolation measures (indeed curfews in some cases); mobility, travel, circulation and gathering restrictions, and closure of borders; reduction or suspension of nonessential activities, with loss of millions of jobs and increasing unemployment rates; total or partial closure of colleges and universities and the unequal and frequently improvised performance of on-line education; campaigns for tracing possible cases; vaccination programs; the psychological effects on mental health in the community; *etc*.

Hence, this picture entailed the scientific community to face to an unprecedented challenge, in order to appropriately assess and advise health authorities and decision-makers. Such a kind of complex phenomena appeals to multidisciplinary and interdisciplinary groups of experts to take their part in order to reach a comprehensive approach, able to deal with the many relevant and multifactorial aspects of COVID-19, as illness and as pandemic. Of course, topics as the epidemiological and clinical aspects of the disease are central, but not the unique ones. Other matters require to be understood, as the SARS-CoV-2 virology, or the COVID-19 pathophysiology and immunology; the study of temporal evolution of

infected individuals and their contagiousness; the lack of preparedness of the health care systems and the rapid reaction in Medicine research, including the development and access to vaccines; the population heterogeneity and the effects of mobility and human behavior in the spread of the disease; the role of health and social inequities; *etc*.

In this context, the appearance of scientific works, which organize and summarize a great part of the scientific job carried out, is of great value. In particular, if the subject is approached from a comprehensive and multidisciplinary perspective, considering the individual and collective levels, and their temporal and spatial evolution, the biological, socioeconomic, technological aspects, *etc*., and its consequences for the societies in which it occurs, as the current work does. In addition, the case of this scientific work is especially interesting, since it highlights the role that Mathematical and Computational Modeling can play together with other related areas such as Data Science and Statistics, when dealing with this type of multidisciplinary phenomenon, for which is an excellent reference for researchers and decision makers on how to deal with this type of problem.

Based on all that has been said above, I hope that this book will help researchers and decision makers to better understand and evaluate the situations that can arise in the context of a complex problem such as that caused by the COVID-19 pandemic and the way to face it.

Victoriano Gabriel Covarrubias Salvatori
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PREFACE II

This book is a multidisciplinary work, dedicated to the current problems around the COVID-19 pandemic and which has been carried out by a group of specialists from various scientific institutions in Mexico, United Kingdom, Spain, France, Russia, Cuba, Belgium and India.

Although the book does not exhaust the subject, it is however the result of the authors' effort to convey, to a certain extent, a comprehensive approach. Therefore, although not all possible points of view and relevant matters are addressed, which make up the multidisciplinary dimension of the research that has been carried out around the COVID-19 pandemic and its associated virus SARS-CoV-2 with its variants of concern, those that have proven to be essential and accessible to the authors' competence and resources have been included.

The first chapter aims to give a comprehensive view of results from different scientific perspectives that have been useful for building and studying epidemiological mathematical models for COVID-19. The conclusions and predictions provided by these results, have been the source of key recommendations to decision-making in several countries.

In later chapters, the problem is approached from the epidemiological and from the clinical point of view which together encompass its individual and societal dimensions. As in all health problems both points of view are essential although their methods and analytical tools are different. However, both approaches complement each other to provide the understanding of the measures that contribute to solving problems and their negative effects, which is indispensable for a global approach to the problem. Mathematical modeling, to different degrees and at different times, is present in both approaches.

The epidemiology of COVID-19 requires analyzing and dealing with large volumes of data, through mathematical and statistical models, which allow studying the problem of transmission as a complex problem, by means of theoretical and computational resources. All these conceptual and operational tools are present in the book under a general and global approach.

The exclusive epidemiological perspective, is however insufficient. Clinical aspects such as: pathophysiology, clinical manifestations, pharmacological

treatment of COVID-19, among others, are also essential for understanding and coping with this disease. Chapters 2 and 3 attempt to provide a panoramic view of the epidemiological and clinical components of this multifaceted problem.

Chapters 4 and 5 attempt to advance in the direction of the modeling of epidemics and pandemics, by presenting and discussing techniques and procedures for analyzing and modeling data analysis, thus providing the conceptual and practical bases to solve or minimize the undesirable effects of the pandemic.

Chapters 4 and 6 introduce the reader to the modeling of epidemics through the use of mathematical models. Different perspectives and uses of the models are presented. Chapter 6 in particular is devoted to the study of the effect of population heterogeneity in the process of spread of COVID-19, which is essential for the study of the pandemic, and surprisingly relegated in the available literature, as compared with other topics. “Data Science” is addressed in chapter 5, and shows the process of transforming data into information, using standard procedures with a rich recent development. Data Science is an indispensable tool for a full understanding of the ways in which COVID-19 manifests itself, and the different interpretations.

Population heterogeneity is revealed not only by territorial distribution and demographic factors associated with different social groups, but also by existing social inequalities and biological factors that characterize the response of different individuals to COVID-19 such as age, sex, pre-existing comorbidities, *etc*. Chapters 7 and 8 are devoted to the study of these two interesting topics.

The scientific and methodological approach associated with the study of the presence of “social inequalities” in the evolution of the pandemic, provides essential methods to assess the influence of context in morbidity and mortality associated with COVID-19. Chapter 7 addresses this problem from a conceptual, methodological and practical point of view, showing examples of specific cases.

Chapters 8 and 9 combine quantitative measurement and a qualitative approach to assess and understand the severity, fatality, and impact (both short and long term) of a pandemic with explicit application to COVID-19.

In particular, for a better understanding of the impact of immunotherapy protocols with their modeling aspects, the Cuban protocol, implemented during the pandemic, is shown and developed as an example, of the role and application of mathematical and statistical models.

Chapter 10 addresses a fundamental strategy for the control and elimination of the pandemic, namely the production and application of vaccines. Two key problems are included:

- The conception, production and laboratory evaluation, through clinical trials in its various phases, including the extent and duration of immunity and protection, all encompassed by the clinical aspects of the problem.

- The massive application of strategies to control the disease, to anticipate new mutations and variants, and to build risk perception among the general population. This chapter shows the progress attained on an essential issue with a prospective view to curb and ultimately eradicate the pandemic.

At the end of the book we have included an appendix with a series of graphs, duly selected, that show relevant data on how the COVID-19 pandemic has evolved in different regions and countries of the world. Concretely, this group of charts show the time series of the rolling 7-day average of number of daily new confirmed COVID-19 cases and deaths in the countries with the largest number of accumulated confirmed cases of COVID-19 in the world, and some specific regions (the whole World, the European Union, and the continents of Asia, Europe, North America, South America, and Africa). These plots constitute a simplified snapshot of the pandemic, that would be useful to quickly summarize the whole picture.

The topics covered in the book will undoubtedly be useful for specialists from different areas who have been involved, either in scientific research or daily work, with the COVID-19 pandemic. Doctors from different specialties, epidemiologists, chemists, biologists, pharmacologists, immunologists, microbiologists, mathematicians, computer scientists, sociologists and specialists in data analysis, among others will be clear beneficiaries of the messages conveyed by the book.

It will also be useful to any reader who, without being a specialist in any of these areas, wants to have an overview of the extensive work that has been carried out, during the little more than a year and a half that has elapsed since the beginning of the pandemic today. The book provides a very complete picture of the meaning scope of multidisciplinary scientific work aimed at a common goal.

I must express deserved recognition and gratitude to all who, in one way or another, have made possible the final result of this multidisciplinary work, on a subject that is of fundamental importance for all humanity.

In the first place, our gratitude to all the authors, many of whom were immersed in their professional daily work of caring for COVID-19 patients in intensive care rooms in hospitals or in laboratories dedicated to the creation of vaccines and immunotherapeutic treatments, while they wrote their chapters.

We also want to thank the Council of Science and Technology of the State of Puebla (CONCYTEP) in Mexico and, in particular, the Head of the Council, Dr. Victoriano Gabriel Covarrubias Salvatori, who, on behalf of the State Government, provided his support for the fulfillment of this work.

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