



II ENCUENTRO RSME-UMA

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MÉTODOS Y MODELOS MATEMÁTICOS CON APLICACIONES BIOMÉDICAS

ORGANIZADA POR: MAIRA AGUIAR, DAMIÁN KNOPOFF

HORARIO

- 12/12/2022, 17:30–18:00:** Roberto Barrio (University of Zaragoza, Spain), *Fast-slow and bifurcation analysis of the generation of early after depolarizations in cardiomyocytes.*
- 12/12/2022, 18:00–18:30:** Vanessa Steindorf (BCAM Bilbao, Spain), *Modelling secondary infections with temporary immunity and disease enhancement factor: mechanisms for complex dynamics in simple epidemiological models.*
- 12/12/2022, 18:30–19:00:** Carlo Giambiagi Ferrari (Universidad de Sevilla, Spain), *Kinetic approach of a SIS model coupled with opinion dynamics.*
- 13/12/2022, 15:30–16:00:** Maíra Aguiar (BCAM Bilbao, Spain), *On the origin of complex dynamics in multi-strain dengue models.*
- 13/12/2022, 16:00–16:30:** Akhil Kumar Srivastav (BCAM Bilbao, Spain), *The effects of public health measures on severe dengue cases: an optimal control approach.*
- 13/12/2022, 16:30–17:00:** Vizda Anam (BCAM Bilbao, Spain), *Understanding the immunological responses mediated by antibodies during primary and secondary dengue infections using three within host dengue models.*
- 13/12/2022, 17:30–18:00:** Paula Patrício (Universidade Nova de Lisboa, Portugal), *Measuring the impact of COVID-19 vaccination and immunity waning: a modelling study for Portugal.*
- 13/12/2022, 18:00–18:30:** Fernando Saldaña (BCAM Bilbao, Spain), *Want to prevent epidemics? Stop spillover events.*
- 13/12/2022, 18:30–19:00:** Nico Stollenwerk (BCAM Bilbao, Spain), *COVID-19: Lock-down and lifting to large subcritical fluctuations, vaccination impact and evolution of new variants.*

RESÚMENES

Roberto Barrio (University of Zaragoza, Spain). *Fast-slow and bifurcation analysis of the generation of early afterdepolarizations in cardiomyocytes*

In this talk we analyze the dynamical mechanisms underlying the formation of arrhythmogenic early afterdepolarizations (EADs) in two mathematical models of cardiac cellular electrophysiology: the Sato et al. biophysically detailed model of a rabbit ventricular myocyte of dimension 27 and a reduced version of the Luo-Rudy mammalian myocyte model of dimension 3. Based on a comparison of the two models, with detailed bifurcation analysis using continuation techniques in the simple model and numerical explorations in the complex model, we propose a conjectured scheme. We will show that in the most relevant parametric

region the change, on EADs, is organized by a hysteresis loop and especial orbits, called “canards” in dynamical systems community, that generates two stable orbits, with and without EAD. It is noteworthy how a standard 1-fast—2-slow decomposition fails to properly describe some dynamical properties of the system. Instead, we combine and refine this approach by further separating the 2 slow variables according to their respective time scales. All these phenomena allow us to propose a dynamical systems conjecture of a global scheme of creation of EADs. This theoretical scheme fits well with electrophysiological experimental data on EAD generation and hysteresis phenomena.

This is a joint work with J. Jover-Galtier, M.A. Martínez, L. Pérez, S. Serrano

Vanessa Steindorf (BCAM Bilbao, Spain). *Modelling secondary infections with temporary immunity and disease enhancement factor: mechanisms for complex dynamics in simple epidemiological models*

Since the COVID-19 outbreak, mathematical modeling has gained notoriety for its importance. However, mathematical models describing the spread of diseases have been used for a much longer time as an important tool to guide public health measures in order to control and prevent infections. For that, the consideration of the intrinsic characteristics of each disease and its limitations in the existing modeling frameworks is crucial for the development extended models and interpretation of the new findings.

In this study, a SIR-SIR model-type is investigated aiming to investigate the role of those well-known biological features in the dynamical behavior of simple epidemiological models, taking into account two subsequent infections, no strain structure, and two intrinsic features of dengue fever: cross-immunity protection between infections and an effect known as antibody-dependent enhancement (ADE).

Differently from the simple SIR model that only exhibits a supercritical transcritical bifurcation (in epidemiology, the so-called forward bifurcation), the SIR-SIR model-type proposed here exhibits a rich dynamical behavior, with different bifurcation structures leading to solutions that converge to DFE, or to the unique positive endemic equilibria, or to the stable limit cycles due to the occurrence of Hopf bifurcation and global homoclinic bifurcation. Also, the model exhibits a subcritical transcritical bifurcation (known in epidemiology as a backward bifurcation), displaying bi-stability in a small parameter region. In addition, several bifurcation structures are identified, such as, Bogdanov-Takens, cusp, and Bautin bifurcations, described for the first time in simple models that incorporate intrinsic features of dengue epidemiology.

The findings in this study can be used as additional information for more extensive modeling development given insights on epidemiological scenarios and in accordance with public health measures.

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Carlo Giambiagi Ferrari (Universidad de Sevilla, Spain). *Kinetic approach of a SIS model coupled with opinion dynamics*

We study a SIS model in a heterogenous population where agents are characterized by their level of awareness. We introduce a new agent, which we call the government, that is constantly sending a message to change the population awareness in order to eradicate the disease.

We take three approaches. First a discrete agent based model which we simulate. Then we derive mean-field equations and study the equilibria of the system and finally we present a Boltzmann-type equation for the evolution of the agent’s awareness. We get a coupling of ODEs and a PDE that describes the dynamic.

- Carlo Finished his PhD in February at Universidad de Buenos Aires with Juan Pablo Pinasco working on kinetic modeling and complex systems.
- He is currently at EDAN in Universidad de Sevilla working on biomathematical models.

Maíra Aguiar (BCAM Bilbao, Spain). *On the origin of complex dynamics in multi-strain dengue models*

Dengue fever epidemiological dynamics shows large fluctuations in disease incidence, and several mathematical models describing the transmission of dengue viruses have been proposed to explain the irregular behavior of dengue epidemics. Multi-strain dengue models are often modeled with SIR-type models where the SIR classes are labeled for the hosts that have seen the individual strains. The extended models show complex dynamics and qualitatively a very good result when comparing empirical data and model simulations. However, modeling insights for epidemiological scenarios characterized by chaotic dynamics, such as for dengue fever epidemiology, have been largely unexplored. The problem is mathematically difficult and to make the urgently needed progress in our understanding of such dynamics, concepts from various fields of mathematics as well the availability of good data for model evaluation are needed.

In this talk, I will present a set of models motivated by dengue fever epidemiology and compare different dynamical behaviors originated when increasing complexity into the model framework.

Akhil Kumar Srivastav (BCAM Bilbao, Spain). *The effects of public health measures on severe dengue cases: an optimal control approach*

Caused by four distinct viruses, dengue fever is transmitted through a bite of infected mosquitoes. With more than one-third of the world population at risk of acquiring the disease, dengue fever is a major public health problem. We propose a vector-host mathematical model considering multiple virus strains and the explicit mosquito population dynamics. Optimal control theory is used to assess control strategies for disease spreading. A detailed sensitivity analysis (PRCC Method) is conducted in order to identify the key model parameters having more influence on the transmission of the disease. In order to find the optimal strategies for suitable control interventions able to reduce dengue prevalence, specifically severe disease cases, and its economic burden, we evaluate the optimal control problem by considering vaccination, non-pharmaceutical preventive measures, and reduction of mosquito population as the available public health control measures. The proposed cost functional includes a weighted sum of several efforts (not necessarily quantified as economic costs) for each specific control measure, including the impact of severe dengue cases on the overall disease transmission. The analysis of control system using Pontryagin's Maximum Principle leads to the existence of the optimal control profiles. A comparative study for three different control strategies is conducted with numerical experiments. Our findings ensure that every individual control strategy has its own impact on reducing the cumulative number of dengue infections. The well planned simultaneous use of the available public health interventions measures is highly effective to control the prevalence of severe dengue cases, even when large outbreaks are occurring.

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Vizda Anam (BCAM Bilbao, Spain). *Understanding the immunological responses mediated by antibodies during primary and secondary dengue infections using three within host dengue models*

At present dengue fever is a major public health problem in the tropics and subtropics. Nevertheless, a threat of possible outbreaks in Europe should not be underestimated. It is

caused by four antigenically related but distinct serotypes (DENV-1 to 4), infection by one serotype confers life-long immunity to that serotype and a period of temporary cross-immunity (TCI) to other serotypes. Although most of the cases recover following a self-limiting non-severe clinical course, there are evidences that sequential infection increases the risk of developing severe disease, due to a process described as antibody-dependent enhancement (ADE).

Mathematical modeling is often used for understanding infectious diseases dynamics and to evaluate the introduction of intervention strategies like vector control and vaccination. A careful review of deterministic dengue modeling was recently published [1], where three structural approaches were studied, the vector-host, the host-to-host and the within-host dynamic models. While the first two approaches aim to describe disease transmission at population level, the within-host framework is built to describe viral replication and antibody responses affecting the disease outcome in primary and recurrent infections, see e.g. [2, 3]. We are using patients data to compare virus load and antibodies dynamics from our model. The produced results gives us the understanding of the immunopathogenesis of severe illness during recurring infections. is critical for future research directions to evaluate the impact of dengue vaccines using available data.

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Paula Patrício (Universidade Nova de Lisboa, Portugal). *Measuring the impact of COVID-19 vaccination and immunity waning: a modelling study for Portugal*

Vaccination strategies to control COVID-19 have been ongoing worldwide since the end of 2020. Understanding their possible effect is key to prevent future disease spread. Using a modelling approach, this study intends to measure the impact of the COVID-19 Portuguese vaccination strategy on the effective reproduction number and explore three scenarios for vaccine effectiveness waning. Namely, the no-immunity-loss, 1-year and 3-years of immunity duration scenarios. We adapted an agestructured SEIR deterministic model [?] and used Portuguese hospitalisation data for the model calibration. Results show that, although the Portuguese vaccination plan had a substantial impact in reducing overall transmission, it might not be sufficient to control disease spread. A significant vaccination coverage of those above 5 years old, a vaccine effectiveness against disease of at least 80% and softer non-pharmaceutical interventions (NPIs), such as mask usage and social distancing, would be necessary to control disease spread in the worst scenario considered. The immunity duration

scenario of 1-year displays a resurgence of COVID-19 hospitalisations by the end of 2021, the same is observed in 3-year scenario although with a lower magnitude. The no-immunity-loss scenario presents a low increase in hospitalisations. In both the 1-year and 3-year scenarios, a vaccination boost of those above 65 years old would result in a 53% and 38% peak reduction of non-ICU hospitalisations, respectively. At that point in time, the results suggest that NPIs should not be fully phased-out but instead be combined with a fast booster vaccination strategy to reduce healthcare burden. The results and conclusions of this study were used to support public health policy making in order to avoid COVID-19 related healthcare burden after September 2021 [?].

When compared with what happened in Portugal, our analysis identified two subsequent waves of hospitalisations. These waves were concurrent in time but with different magnitudes than the ones observed. This is probably due to various mechanisms: vaccination conferred protection against severe disease decayed slower with time than we anticipated; and omicron and subsequent variants presented a lower risk of severe disease and immune escape.

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Fernando Saldaña (BCAM Bilbao, Spain). *Want to prevent epidemics? Stop spillover events*

The emergence of infectious diseases with pandemic potential is a major public health threat worldwide. According to the World Health Organization, around 60% of the reported emerging infectious diseases are zoonoses and have been triggered by spillover events. Although the dynamics of spillover events are not yet well understood, mathematical modeling has the potential to characterize the highly complex interactions among pathogens, wildlife, humans, and the environment where they coexist. In this work, we address the challenges in modeling the emergence of novel infectious agents, so far unexplored, gaining insights into the dynamics of spillover events and the final outcome of an eventual disease outbreak in a population. Focused on the introductory phase of a new infectious disease pathogen, we propose a continuous time stochastic modeling framework to describe a cross-species disease transmission by coupling the dynamics of reservoirs and humans. A complete analysis of the system is conducted, and combined with numerical experiments that are performed to illustrate different scenarios of spillover events, providing insights on the emergence of new infectious diseases that eventually cause explosive epidemics. Applied to the recent Monkeypox outbreak in the European region, we have observed that the dynamics correspond to limited transmission chains of secondary infections that do not represent a high public health risk for the general population.

Nico Stollenwerk (BCAM Bilbao, Spain). *COVID-19: Lockdown and lifting to large subcritical fluctuations, vaccination impact and evolution of new variants*

After a short description of the basic models to describe the initial exponential growth phase of COVID-19 into the lockdown phase and then lockdown lifting, which led to large but subcritical fluctuations, with

extended data from the Basque country, we develop these models further into the vaccination phase, where several vaccines with various differing efficacies were applied in the same population. Eventual waning immunity and the appearance of new variants complicated the situation further. We give implications of such waning immunity and variants' replacements for long term dynamics. Special attention will be given to the evolution of new variants in terms of severity versus mild infection, which is easily captured by the modelling framework, developed as early as in the first phases of COVID-19 in 2020. The content of references [1] to [7] will be covered and additional new research results shown.

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