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Editorial

Mathematical and Computational Biology of Viruses at the Molecular or Cellular Levels

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Description/Preface

Mathematical and computational biology of viruses at the molecular or cellular levels are more difficult to accurately address than at the population level. While it is easier to achieve fairly good forecasts at the population level, as we have witnessed during the past two years via the modeling and predicting of COVID-19 pandemics, the sophistication of molecular and cellular biology processes requires significant challenges to be overcome when mathematics and computations are applied. Nevertheless, it is a growing field experiencing its own success. This Special Issue provides a glimpse into some of the successes and aims to inspire more work within the wide spectrum of viral research at these two distinct levels.

The present volume contains the seven articles that were accepted and published in the Special Issue "Mathematical and Computational Biology of viruses at the Molecular or Cellular Levels" during 2021–2022. The Special Issue covers representative topics related to this theme. The first topic focuses on the molecular level and concentrates on the RNA secondary structure of RNA viruses [1]. It starts with a mathematical analysis of the RNA motifs in viruses, analyzing data from the web resource RNASIV (RNA structure in viruses) [2] in order to categorize the various RNA structures based on their tree-graph properties via an eigenvalue analysis [3], with the second eigenvalue of the Laplacian matrix belonging to the coarse-grained tree-graph of the RNA secondary structure being examined. The same concept is carried out in [4] for an eigenvalue analysis of HDVdb [5], a database of HDV sequences that is divided into various HDV genotypes, in order to predict whether the peculiar RNA-editing mechanism achieved by a conformational switch in RNA that is known to occur in HDV genotype 3 [6] can occur in other genotypes as well. Two publications that appeared independently at around the same time [4,7] addressed this problem. A mathematical analysis by computations performed in [4] succeeded to predict that the RNA editing mechanism by a conformational switch in HDV genotype 3 occurs in HDV genotype 7 as well. Here it is shown more clearly in Figure 1 (a zoom-in of Figure 3(A) in [4]) that the familiar SL1 hairpin from genotype 3 with the GAAC tetraloop is present also in genotype 7, while no systematic way from the computational standpoint was presented in [7] to show the presence of the SL1 hairpin particularly in genotype 7 and not in other genotypes, although the experiment performed in [7] with the added RNA motifs surrounding SL1 in strain dFr7024 (as depicted in Figure 4(D) of [7]) was beneficial. The impact of this finding would be revealed in the future as more data is gathered, but it exemplifies the power of mathematics and computations to predict new findings at the molecular or cellular levels.

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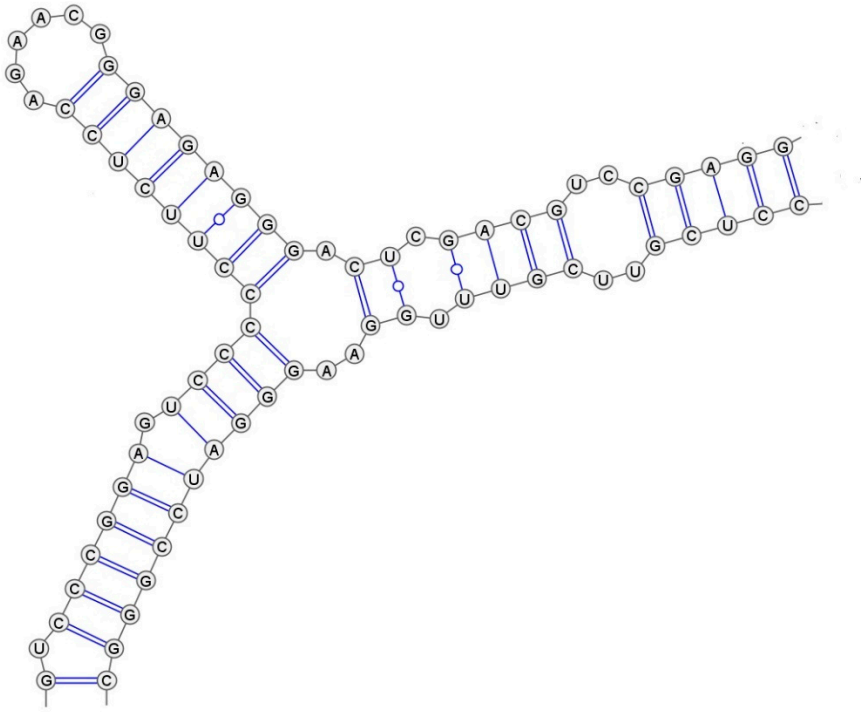

Figure 1. A zoom-in of Figure 3(A) in [4], where the folding prediction by energy minimization using either mfold/UNAFold [8] or Vienna's RNAfold [9] of MG711735 from genotype 7 [5] is performed, with an SL1-like hairpin that contains the sub-sequence "GAAC" as in SL1 from genotype 3. The secondary structure is drawn using VARNA [10].

The HDV paper in [4] already mentions addressing HDV viral kinetics across the different genotypes through the use of a simple differential equation model (transitioning from the molecular to the cellular level), and from here on, the Special Issue is devoted to the cellular level. The next topic is a Markov chain-based stochastic modelling of the HIV-1 life cycle in a CD4 T cell, as put forth in the paper by Sazonov et al. [11]. A new tool to simulate the HIV life cycle in infected cells is provided by a high-resolution mathematical model formulated as a Markov chain jump process. The model is applied to generate the statistical characteristics of the cell infection multiplicity, cooperative nature of viral replication, and variability in viral secretion by phenotypically identical cells. The results of the simulation with the model suggest that the stochastic effects inherent in HIV replication cycle must be considered among the relevant mechanisms contributing to the phenotypic diversity and variability of dynamics of HIV infection. In the next paper by Lederman et al. [12], the topic of unidentifiability in parameter estimation, referring to one's inability to uniquely estimate the model parameters from the available data, is addressed. It is first examined using Lambda–Omega models and is then exemplified on a viral infection kinetic model for HIV. The issue of unidentifiability appears in viral kinetic models, and it is important to understand the type of unidentifiability being faced to provide solutions to it. In this fundamental paper about unidentifiability, as well as in the next one that presents a simple mathematical model for studying HDV and HBV kinetics in a coupled way [13], finite-difference numerical schemes are used to solve the underlying differential equations of the model. Unlike applications such as in, for example, refs. [14,15], where more sophisticated numerical methods are needed to solve the differential equations of the model, in the papers in this Special Issue, the models are simple enough to utilize a standard Runge–Kutta scheme of the fourth order. In the two papers on HDV-HBV interaction [13,16], the devised models were either solved numerically or solved analytically using Wolfram's Research Mathematica through the use of hypergeometric functions to represent the solution, and Berkeley Madonna was used for parameter estimation. The improved kinetic model for HDV-HBV interaction [16] ameliorates the deficiencies of

past models [17,18], and the initial attempt in [13] presented a new concept, but it only considered scarce data from very few patients. Next, in the paper by Grebennikov et al. [19], a calibrated mathematical model of antiviral immune response to SARS-CoV-2 infection is developed, and the new model considers the innate and antigen-specific responses to SARS-CoV-2 infection. Thus far, more than a dozen of mathematical models of SARS-CoV-2 infection have been developed, such as in [20], and the study in [19] is unique in that it highlights the value of mathematical modelling in gaining a mechanistic view of the kinetic regulations of SARS-CoV-2 infections and antiviral immune responses. Finally, it is worthwhile to mention that viral kinetic models can become more complicated in a variety of ways, an example being HCV multiscale models [21–24], presenting new mathematical challenges that could be the topic of a future Special Issue.

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