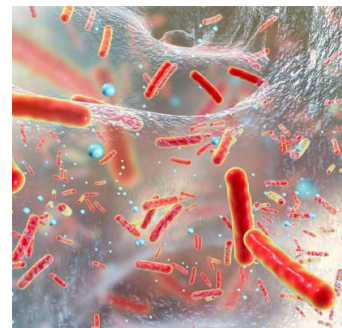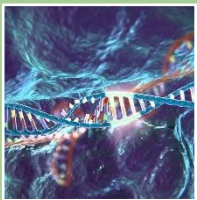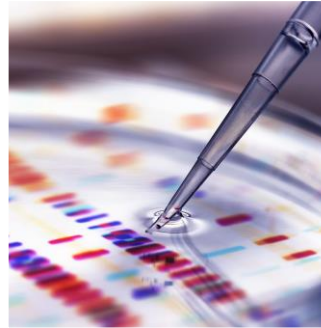# 2nd Friendly Workshop on Mathematical Biology

Enes Seyfullah Kotil

Theoretical Biology Laboratory

November 3, 2022

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Chair

Assist. Prof. Dr. Enes Seyfullah Kotil

Organizing Committee

Ramin Nashebi

Scientific Committee

Prof. Dr. Murat Sarı
Assist. Prof. Dr. Enes Seyfullah Kotil
Assist. Prof. Dr. Hüseyin Tunç

Workshop Schedule

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11:00-11:30	Evaluation of Alzheimer's Disease in the Perspective of Cerebrospinal Fluid Biomarkers
11:30-12:00	Identifying Evolutionary Rescuer Essential Genes by CRISPRi-Seq
12:00-12:30	Modelling the Impact of Persisters in the Evolution of Antibiotic Resistance
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Development of the evolutionary escape model to identify drugs that delay resistance

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Abstract: Antimicrobial resistance is an inevitable situation. Many approaches can be used to defeat resistance. One of these approaches is that considers the heterogeneity of the bacterial population. Resistance can be overcome if bacteria that show resistance in the bacterial population can be predicted before drug use. Here, we provided a technique with an applied experimental and computational approach to predict bacterial evolution against the drugs. For this purpose, we produced the dataset that includes known compounds enriched with twenty-one novel compounds that we identified for this work. We applied two methods to measure bacterial resistance against these drugs. In our first method, we have measured the concentration that kills the single-step mutant, known as a mutant prevention concentration (MPC). Our second method involved evolution experiments performed for five days with serial passages at pre-determined drug concentrations. The change in growth rate during the experiments was taken as the output. The data obtained from these two methods we developed our predictive model, the evolutoinary escape model (ESM). According to the model's prediction, drugs that develop low resistance were tested *in vitro*. Among the molecules tested *in vitro*, it was determined that KL-4 had superior properties in delaying the development of resistance. Estimating drug escape routes may be a promising method to delay resistance. Overall, our approach can foresee antibiotic resistance and contribute to drug design that delays resistance.

Keywords: antibiotic resistance, evolution, growth rate, mutant prevention concentration

Evaluation of Alzheimer's Disease in the Perspective of Cerebrospinal Fluid Biomarkers

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Abstract: Alzheimer's disease, which is accepted as the most common form of dementia worldwide, has left its mark on the 21st century with its social and economic difficulties and its thought to have aspects that are still unknown in medical terms. It is neuropathologically characterized by neurofibrillary tangles, amyloid plaques and histopathological changes. Aβ (1-42), phosphorylated tau (p-tau18) in threonine-181, and total tau (t-tau) are considered essential biomarkers for the diagnosis of Alzheimer's disease. In this study, it is aimed to analyze the complexity of Alzheimer's disease and its relationship with various neurodegenerative processes, with the guidance of three cerebrospinal fluid biomarkers, using unsupervised machine learning methods.

Keywords: Alzheimer disease, Unsupervised learning, Cerebrospinal fluid

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Identifying Evolutionary Rescuer Essential Genes by CRISPRi-Seq

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Abstract: Once bacteria are forced to grow under in challenging conditions, such as in the presence of stressors or inhibitors, the genotype most suited to the current environment multiplies rapidly in the population. Over time, it has become most of the existing population. Thus, bacterial evolution occurs because of natural selection. In fact, bacterial communities have a variety of suitable solutions that drive evolution. The key concern with these solutions is the bacterial resistance to antibiotics, which is a worrisome global problem. A question that is not emphasized enough in antibiotic resistance is, which essential genes in evolving bacteria are more critical to their new state? If this question can be explained in terms of all genes in various conditions, essential genes can be identified, and their relevance with resistance clarified. Based on these concepts, we conducted research that could identify and screen for essential genes that became more important after evolution in bacteria by performing a genome wide CRISPRi screen. We referred these genes as evolutionary essential genes. For this purpose, we transformed a genome-wide library of CRISPRi plasmids into the *E.coli* strain exposed to adaptive laboratory experiments in the presence of five different antibiotics. We performed knock-down screening by inducing single guide RNA expression plasmid in all wild-type and evolved cell lines carrying the CRISPRi library. Then we analyzed sgRNA presences and counts by Next Generation Sequencing. As a result of comparison and normalization of all data, we revealed which genes became more important after evolution due to their rescuer role. We found that 134 essential genes were common in all experimental conditions. Highlighting and classifying these rescuer genes and their related features, could be promising in discovering potent novel therapies against antibiotic resistance.

Keywords: *antibiotic resistance, bacterial evolution, CRISPRi, essential genes, drug candidates.*

Modelling the Impact of Persisters in the Evolution of Antibiotic Resistance

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Abstract: Persister cells play a crucial role in evolution of antibiotic resistance by constituting an evolutionary reservoir of valid cells. This phenotypically heterogeneous subpopulation of bacteria survives under lethal antibiotic treatment and regrowth after cessation of treatment without being resistant. It has been found that persisters facilitated the evolution of antibiotic resistance by extending the window of opportunity for rare mutants and preventing loss of resistant mutants during antibiotic exposure. However, this experimental finding is poorly understood theoretically. Here, a mathematical model has been developed to establish a theoretical framework for this experimental result and provide further knowledge about the dynamic of persister cells and their contribution in the evolution of antibiotic resistance. Furthermore, it has also been aimed to clarify the importance of SOS response and persister switching in this evolutionary trend.

Keywords: Persisters, Antibiotic tolerance, SOS response, Persister switching, Antibiotic resistance, Mathematical modelling.

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Extreme learning machine approach for solving ordinary differential equations arising in biology

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Abstract: Mathematical models are widely used to understand the dynamics of various biological processes. Modelling of such processes generally yields nonlinear system of differential equations (ODE) that can only be solved with some numerical techniques. Here we propose an extreme learning machine (ELM) approach for solving such ODEs to find out continuous approximate solutions. The ELM approach is shown to have considerable advantageous over the existing neural net-work based approximate methods and numerical initial value problem solvers. Two test problems representing between host and within host viral dynamics are considered to measure the efficiency of the current approach.

Keywords: Machine learning, Artificial neural network, Mathematical biology, Viral dynamics, Ordinary differential equations

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Evolution of HIV in the Presence of Antiretroviral Therapy

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Abstract: The Human Immunodeficiency Virus (HIV) is a chronic infectious disease that causes Acquired Immunodeficiency Syndrome (AIDS). Although there is no definitive treatment, it can be controlled by using antiretroviral drugs. However, many patients fail in treatment with the emergence of drug-resistant virus. The aim of this study is to observe the evolution of HIV in the presence of antiretroviral drugs. In addition, the effect of timing and the adherence level to the treatment regimen on the progression to AIDS are investigated. Here, a mathematical model is proposed that varies depending on the pharmacokinetic parameters of the drugs. The most observed mutations in NRTI treatment are selected from the literature and the model used is extended to the N-strain.

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Isolation and Biotechnological Evaluation of Specific Lactic Acid Bacteria Strains From the Poultry Gastrointestinal System

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Abstract: The microbiota plays a vital role in maintaning gut health and influences the overall performance of chickens. In-feed supplementations of prebiotics and probiotics strengthen the gut microbiota for improved host performance and colonization resistance to gut pathogens such as Salmonella, Campylobacter and Lysteria. The mechanism of action of probiotics come through the production of organic acids, activation of the host immune system and production of antimicrobial substances (bacteriocins, lactic acid, hydrogen peroxide.). The use of lactic acid bacteria (LAB) and probiotic cultures in the breeding of animals such as poultry and swine are quite common. It is known that those strains can produce bacteriocins when grown in pure culture. However, the production of bacteriocin using co-culture of microorganisms has not been much studied so far. This study aims to develop the innovations in this area by the investigating bacteriocin-producing Enterococcus faecium, Ligilactobacillus salivarius and Limosilactobacillus reuteri bacterial strains isolated from chicken intestine. The bacteria analysis will performe using selective media for Limosilactobacillus reuteri followe by confirmation using the specific detection of reuterin produced by Limosilactobacillus reuteri. Additionally, the co-cultivation of Ligilactobacillus salivarius, Limosilactobacillus reuteri and Enterococcus faecium was also will investigate. The antimicrobial activity of the produced bacteriocins will evaluate against Salmonella enterica, Salmonella enterica serovar typhimurium, Escherichia coli using agar difusion method. Finally, the probiotic effects of chicken feed supplemented with Enterococcus faecium, Limosilactobacillus reuteri and Liglactobacillus salivarius on chickens will be investigated.

Key words: probiotics, chicken gut microbiota, feed supplements, lactic acid bacteria, bacteriocins

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Evolutionary Dynamics and the Effects of Non-pharmaceutical Interventions on the Viruses

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Abstract: Changes take place in genotype and phenotype characteristics of mutated parasites/viruses such as contagiousness, virulence, and duration of infection. From past to present, host-parasite relationships and the evolution of virulence have been the subject of various studies. Outbreaks maximize fitness as virulence and contagion evolves. Classical theory predicts that virulence should reduce optimal fitness. However, virulence evolution may be affected by non-pharmaceutical interventions (NPI). Our primary aim in this study is to investigate whether non-pharmaceutical interventions can provide a meaningful benefit to reduce virulence. The study also consists of an evaluation of the modeling techniques used.

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