MARMARA ÜNİVERSİTESİ YAYINEVİ

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Assoc. Prof. Dr. Bülent Yılmaz
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# Preface

The goal of the "International Conference on Applied Mathematics, Modeling and Life Sciences" is to bring together leading and young scientists from around the world working in problems related to the title of the Conference. Indeed, the topics of the Conference are at the very heart of the understanding of many important problems arising in the natural sciences.

This conference will undoubtedly stimulate and create additional interest in applied mathematics, modeling and life science problems not only among experts from Universities in Istanbul, but also among researchers including young researchers such as PhD students and Postdocs from Turkey and elsewhere.

This conference financially supported by Marmara University Scientifical Research Project Unit (BAPKO) by the project number FEN-L -110618-0339. Organizers thanks to Marmara University Scientifical Research Project Unit (BAPKO).

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# Abstracts

## Global existence and exponential stability for a nonlinear Timoshenko system with delay

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In this paper, we consider a Timoshenko system in bounded domain with a delay term in the nonlinear internal feedback and prove the global existence of its solutions in Sobolev spaces by means of the energy method combined with the Faedo-Galerkin procedure.

under a condition between the weight of the delay term in the feedback and the weight of the term without delay. Furthermore, we establish a decay rate estimate for the energy by introducing suitable Lyapunov functionals.

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# Some properties of the index of hom-Lie algebras

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The notion of hom-Lie algebras was introduced by Hartwig, Larsson, and Silvestrov in [7]. A hom-Lie algebra is a triple $(\mathfrak{g}, [-,-], \alpha)$, where $\alpha$ is a linear self-map, in which the skewsymmetric bracket satisfies an $\alpha-$twisted variant of the Jacobi identity, called the Hom-Jacobi identity. When is the identity map, the Hom-Jacobi identity reduces to the usual Jacobi identity, and $\mathfrak{g}$ is a Lie algebra. In [1] Makhlouf and Silvertrov introduced the notion of hom-associative algebra $(\mathcal{A}, \mu, \alpha)$ in which $\alpha$ is a linear self-map of the vector space $\mathcal{A}$ and the bilineary operation satisfies an $\alpha-$twisted version of associativity. associative algebras are a special cases of hom-associative algebras in which $\alpha$ is the identity map. The dual notion of hom-coalgebra was considered in [3].

The first main purpose of this paper is to introduse the notation of the index of hom-Lie algebras in the case of coadjoint and for an arbitrary representation. To give also the index of semidirect products of hom-Lie algebras. And finally we give the index of a hom-Lie algebra by extension.

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# Whitham modulation theory for the cylindrical Gardner equation

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In this work, we apply the Whitham modulation theory to the cylindrical Gardner (cG) equation. The Gardner equation has the form

$$u_t + 6uu_x - 6\alpha u^2 u_x + \epsilon^2 u_{xxx} = 0,$$

where $u = u(x,t)$, $\alpha = \pm 1$, $0 < \epsilon << 1$. This equation is a mathematical model for weak nonlinear dispersive waves in large amplitude internal water waves. The cG equation is the cylindrical version of the Gardner equation which is obtained by employing a parabolic similarity reduction to the (2+1) dimensional Gardner-Kadomtsev-Petviashvili equation.

We obtain the conservation laws associated with Whitham theory for the cG equation by using a perturbation method. Then, these conservation laws are used to derive a system of three quasilinear first order partial differential equations. This system is called Whitham modulation system and describes the modulations of the travelling wave solutions of the cG equation. By introducing appropriate Riemann type variables, the corresponding modulation equations are transformed into simpler form. This simpler form is important to understand the dispersive shock wave phenomena in the cG equation.

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# Integration of humanized S. cerevisiae transcriptomic data with genome scale metabolic model: biomarker and drug target prediction for Alzheimer's disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common cause of dementia and death, characterized by deposits of amyloid-$\beta$ (A$\beta$) peptides. Hence, a detailed investigation is needed for understanding the metabolism of AD to aid in the development of new therapeutic approaches. The aim of this study is the investigation of novel biomarker and drug target candidates for the diagnosis and treatment of AD. For this purpose, transcriptomic data which was collected from humanized S. cerevisiae that expressed amyloid peptides (A$\beta$42) was integrated into a genome scale metabolic model of yeast by using E-flux approach. After the integration, simulation was carried out and flux distributions of both control and disease cases were compared in terms of growth rate and ethanol production rate. Results showed that while growth rate was decreased, ethanol production was increased. Based on flux distribution, we also defined highly affected reactions and biomarker candidates. Energy, lipid, amino acid metabolisms and transport reaction of some metabolites such as oxygen, glycose were found to be altered in AD. Ethanol and NH3 metabolites were predicted to be highly secreted, and, hence, defined as potential biomarkers. Drug target identification was performed by single gene deletion analysis. Results showed that defined drug targets were mostly related with energy metabolism process.

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# Development of a web–based tool for network analysis of protein structures

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The visualization of protein networks on 3D conformations of biomolecules is essential since network investigation is common in identifying the function and dynamics of biological macromolecules.

Networks have recently become more important in order to investigate the structural analysis of proteins. Therefore, the need for useful network visualization and analysis tools that can work together with modern data analysis environments (such as the web) are getting increasingly popular each day. Common web applications for network analysis provide narrow functionality, mostly limited to network visualization and basic analysis options. The main objective of this study is to develop a web tool to visualize and analyze the protein structure networks where the edge weights are defined by custom network metrics.

First step in network construction is to get the protein structure data. This newly developed tool supports the output of a model structure obtained from any molecular modelling program in PDB format, or the files supplied from the Protein Data Bank [4]. To analyse the 3D topology of protein structure, nodes are added with their 3D coordinates of the representative atoms in each network type using the information in the PDB file. This tool supports single chain as well as multimeric proteins and protein complexes. Depending on the type of analysis to be performed, the user can select chain(s), network type, threshold for network construction and residue separation along the backbone chain.

Shortest path between selected two nodes can be calculated based upon the optional algorithms such as Dijsktra [2], Floyd–Warshall [3], Bellman–Ford [4]. After the shortest paths are evaluated, they are visualized both on the interaction energy network graph and 3–dimensional structure of the protein.

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# Estimation of economic growth with grey translog production function

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In this paper, we investigate the effect on economic growth (GDP) of economic input factors by using CES and Translog production functions. Used method is applied for China's economy. In the model, we used capital, labor and energy as influential input factors. Energy is driving force of the economic growth of countries. CES function is estimated by using Kmenta approach. In estimation of Translog production function, the ridge regression method is used to estimate the historical data.The dynamic estimation results of output elasticity and the substitution elasticity are estimated. For predict of economic growth in the future, input factors belong to Translog production model is estimated by using Time -Varying Grey Prediction Model. Findings show that Translog model have better results than CES model. Output elasticities of all factors are positive. Size order of output elasticities of factors is labor, capital and energy. This situation represent the China's economy is labor and capital intensive.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



## Some results on difference eigenvalue problems

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In this study, a second order difference problem with potential function $q(n)$ is given. Sum representations of solutions are found. Also, we acquire asymptotic formulas for eigenfunctions and behaviors of eigenfunctions for the problems are investigated and simulated by graphics and tables.

In this work, we use generally these references [1-4].

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# Application of biosorption on two natural organic wastes; palm leaves and abundant dates for the removal of methylene blue from aqueous solution : kinetic study and modeling

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Dyes are widely used in printing, food and cosmetic industries, but especially in the textile industry due to their chemical stability and the ease of their synthesis as well as their variety of colors. However, these refractory dyes are at the origin of the pollution when they are evacuated to the environment. There is a wide variety of wastewater treatment processes ; physico-chemical treatments (adsorption, coagulation / flocculation, precipitation, advanced oxidation techniques .....), these treatments are commonly used for industrial effluents. In this study, palm leaves and abundant dates were evaluated for their ability to remove methylene blue (MB) from aqueous solution. Sorption Kinetic experiments were studied at various initial dye concentrations and sorbent dosages. The equilibrum sorption data of MB by wastes was fitted to the Langmuir and Freundlich isotherm models using non-linear regression technique. The results indicate that both of Langmuir and Freundlich equations provide good correlation of the experimental data. Biosorption kinetics obtained at different initial concentrations were analysed using pseudo-first-order, pseudo-second-order and pseudo-nth order equations. The results indicate the potential of palm leaves and abundant dates as biosorbents for the removal of basic dye from aqueous soulution.

**Key words:** Biosorption, Methylene blue, Langmuir isotherm, Freundlich isotherm, modeling.

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# A ground state solution for a nonhomogeneous Kirchhoff type problem

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Abstract: In this work, we investigate the existence of a positive ground state solution for anonlocal problem of Kirchhoff type with Dirichlet's conditions in a bounded domain with smooth boundary in $\mathbb{R}^3$ . The approach is essentially based on variational methods; we use the Nehari decomposition and the Ekeland variational principle to obtain this solution.

Namely we considere the following problem:

$$(\mathcal{P}_\lambda)\begin{cases} -(a\int_\Omega |\nabla u|^2 dx + b)\Delta u = |u|^4 u + \lambda f & \text{in } \Omega \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

where $\Omega$ is a regular bounded domain in $\mathbb{R}^3$, $a, b$ are positive constants and $f$ belongs to $H^{-1}$ ($H^{-1}$ is the dual of $H_0^1(\Omega)$) .

**Theorem 1** *Let $a > 0$, $b > 0$, then there exists $\lambda_* > 0$ such that the problem $(\mathcal{P}_\lambda)$ admits a positive ground state solution for all $0 < \lambda < \lambda_*$.*

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# On a non-stationary, non-Newtonian lubrication problem with Tresca fluid-solid law

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In this paper, we consider the non linear problem in a dynamic regime in a three dimensional thin domain $\Omega_\epsilon$ with boundary $\gamma_\epsilon$. This boundary of the domain isn assumed to be composed of three portions. In the first step, we derive a variational formulation of the mechanical problem and prove the existence and uniqueness of the weak solution.

Let $\omega$ be a fixed bounded domain of $\mathbb{R}^3$ of equation $x_3 = 0$. We suppose that $\omega$ has a lipschitz continuous boundary and is the bottom of the fluid. The upper surface $\gamma_\epsilon^1$ is defined by $x_3 = \epsilon h(x')$, $x' = (x_1, x_2)$.

We introduce a small parameter $\epsilon$ that will tend to zero, and $h$ a smooth bounded equation function such that

$$0 \leqslant h_\star \leqslant h(x') \leqslant h^\star$$

with Tresca boundary conditions. The fluid is acted upon by given body forces of density $f_\epsilon$.

In the first step, we derive a variational formulation of the mechanical problem and prove the existence and uniqueness of the weak solution. We then study the asymptotic behaviour in the one dimension case when the parameter of the domain tends to zero. In which case, a specific Reynolds equation associated with variational inequalities is obtained and uniqueness is proved

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# Periodic solution of a class of differential equation via averaging theory

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In this work we shall study the class of Duffing differential equations of the form

$$x'' + cx' + f(t)x^2 + g(t)x^4 = h(t) \tag{1}$$

where $c$ is a real parameter, $f(t)$, $g(t)$ and $h(t)$ are continuous $T$–periodic functions.

Instead of working with the Duffing differential equation (1) we shall work with the equivalent differential system

$$\begin{aligned} x' &= y, \\ y' &= -cy - f(t)x^2 - g(t)x^4 + h(t). \end{aligned} \tag{2}$$

We define the polynomial

$$\begin{aligned} p(x_0) = & -\left(\int_0^T e^{-ct}\int_0^t e^{cs}g(s)\,ds\,dt - \frac{e^{-cT}}{c}\int_0^T e^{cs}g(s)\,ds\right)x_0^4 \\ & -\left(\int_0^T e^{-ct}\int_0^t e^{cs}f(s)\,ds\,dt - \frac{e^{-cT}}{c}\int_0^T e^{cs}f(s)\,ds\right)x_0^2 \\ & +\frac{e^{-cT}}{c}\int_0^T e^{cs}h(s)\,ds + \int_0^T e^{-ct}\int_0^t e^{cs}h(s)\,ds\,dt. \end{aligned}$$

Our first result on the periodic solutions of the differential system (2) is the following.

**Theorem 2** *For every simple real root of the polynomial $p(x_0)$ the differential system (2) has a periodic solution $(x(t), y(t))$ such that $(x(0), y(0)) = (x_0, 0)$.*

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# Investigation of catalytic loop motions and global dynamics of caspase-7 structures

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Proteins are highly fluctuating biological macromolecules changing conformations by local and global motions under different conditions. These motions are very crucial and most of the time they are associated with functions of the proteins. Despite the tertiary structure of proteins notably influence the loop motions hindering an establishment of a common guideline, the contribution of the softest modes to the rearrangement of the loop positions are undeniable. Also, an enzyme's conformational dynamics can be altered by binding a ligand leading to an allosteric change on its activity. In caspases, which are highly regulated and involved in apoptosis, binding of a small molecule to the dimeric interface away from the binding site induces a conformation that resembles the pro-caspase form of the molecule by shifting loop positions and further explained by a mutation study [1] [2].

The structural fluctuations enabling distinct conformational samplings for a protein is the key mechanism for understanding the function of that molecule. Alterations observed in these fluctuation mechanisms caused due to mutations can enhance the knowledge of protein dynamics phenomena. Computational methods, such as molecular dynamics can be used as complementary tools for experiments.. Here in this study, large effects caused by small changes in the structure is illustrated one more time via shifts in long-range conformational dynamics within caspase-7. For this purpose, we have conducted MD simulations to gain insights on the effect of single mutations in global structure dynamics and catalytic activity. Molecular dynamics (MD) simulations were performed for wildtype and mutant structures (C290N, R187M, Y223A, G188L and G188P) using NAMD[3] software and CHARMM27 force field for 500 ns (250ns x 2 duplicates) and CHARMM32 for the allosterically inhibited structure (DICA- bound caspase-7). The results show the dramatic change in global dynamics compared to wildtype structure when the active residue (G188P and G188L) is mutated or an inhibitor is bound to the allosteric site.

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# Computational approaches to the investigation of Peptide-MHC complex stability

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Major histocompatibility complex (MHC) molecules are heterodimeric cell surface glycoproteins playing a novel role in the regulation of the adaptive immune response by binding antigenic peptides and presenting them at the cell surface for T cell recognition [1]. In humans, MHC molecules are called as Human Leukocyte Antigens (HLA). HLA-A2 is the most common HLA-A allele in different ethnic populations. Among the HLA-A2 allelic variants, HLA-A*02:01 is the most frequent one and it is commonly used to study HLA-A2-restricted cytotoxic T lymphocyte (CTL) responses [2]. In recent years, studies have focused on designing peptide based vaccines, hence the factors affecting the peptide immunogenicity has become a popular subject for detailed studies. Several studies proposed that stability is significant parameter for peptide immunogenicity [3]. Therefore, in order to investigate the stability of peptide-MHC complexes, we have employed various computational techniques. Firstly, molecular docking studies were performed for 12 peptide-HLA-A*02:01 complexes by DockTope web server. Then, 100 ns parallel molecular dynamics simulations were carried out on the docked structures using GROMACS software with the OPLS-AA/L all-atom force field at 310 K. In the final step, pairwise amino acid non-bonded interaction energies were calculated via gRINN tool. Our study revealed the critical residues which play a role in the observed differences in the stability in these 12 peptide- HLA-A*02:01 complexes.

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## Molecular applications of graph indices

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Graphs are used to model many real life situations. In the last few decades, modelling molecules via replacing the atoms by the vertices and bonds by the edges became very popular due to their applications in chemistry, physics, pharmacology, etc. Applying some mathematical formula to the corresponding graph model instead of costly laboratory experiments helps one to save time and money.

In this work, we give some graph theoretical indices which helps us to find physical and chemical properties. By means of these formulae, we can compare molecules and/or their isomers to obtain the most advantegeous formulae for the claimed property.

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## Comparative analysis of K. pneumoniae genome-scale metabolic networks

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Infectious diseases are serious global public health threats despite novel developments in healthcare technologies. Extensive use of antibiotics to cure infections has caused emergence of highly resistant strains. *Klebsiella pneumoniae*, a member of *Enterobacteriaceae* family, is a causative agent of life-threatening nosocomial infections. However, conventional infection-prevention and treatment efforts are not sufficient to preclude the infections by resistant *Klebsiella* strains.

Genome-scale metabolic network models (GEMs) are promising platforms to identify novel metabolic genes because their inhibitions trigger lower frequency of resistance mutations. In this study, a GEM of *K. pneumoniae* strain MGH 78578 (iYL1228) (1) and a GEM of the highly virulent strain KPPR1 (iKp1289) (2) were used comparatively to investigate the essential genes and metabolites. Using gene- and metabolite-centric approaches, essential enzymes were determined as putative drug targets in different host mimicking conditions. Some filtering strategies were perfomed in order to determine more efficient targets with a minimal side effect in human.

The integrated approach including constraint-based analysis of the GEMs combined with the bioinformatic filtering process resulted in more than 30 essential non-human homologous genes for each growth simulation. A total of 31 non-homologous genes were found as druggable. 5 out of these genes were identified to be virulence-related genes in both strains, and these genes are capable of broad spectrum antibacterial targets. The metabolite-centric approach has also revealed several common potential drug targets in these strains. Therefore, analysis of the metabolic networks has demonstrated that both *K. pneumoniae* strains share a similar metabolic profile and the putative targets suggested in this study may have a therapeutic potential to cope with both strains.

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## Combining PSO and VNS metaheuristics to solve multiple biological sequence alignment problem

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In this research work, we aim to present an intelligent hybrid algorithm called PSO-VNS to solve the multiple sequence alignment (MSA) problem, which is recognized as one of the most important problems in Bioinformatics field. The proposed approach combines particle swam optimization (PSO) metaheuristic and variable neighborhood search (VNS) technique. The main idea of this hybridization scheme is to apply the PSO algorithm to discover the search space globally, but it is easily trapping into local optimum and it suffers from the premature convergence problem. To overcome these limits, VNS is incorporated as local improvement approach in order to guide the search process over other attractive regions to improve solution quality. Numerical results on BaliBASE benchmark have shown the capability of the proposed method to achieve good quality solutions comparing to those obtained by some literature works.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Genome-scale brain metabolic networks as scaffolds for mapping disease-related alterations

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Integrative systems-wide analysis of data and networks at genome-scale enables a holistic understanding of the functionality and working principles of the cell. Metabolic networks are among major cellular network types since it is the metabolism that runs the cellular factory. Therefore, reconstruction of brain-specific metabolic networks is crucial to map the effect of brain-related diseases such as neurodegenerative diseases and brain tumors on cell metabolism. In this talk, I will focus on our efforts on reconstructing brain-specific metabolic networks that take into account neuron-astrocyte specificity and the interactions between these two essential cell types. Then, I will present the use of the reconstructed networks as scaffolds to map transcriptome data for neurodegenerative diseases using a graph-based approach termed reporter pathways. I will also present our work on constraint-based modelling of brain metabolic networks for the analysis of brain tumors. A key point in modelling some neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease is to take into account the aggregation of disease specific proteins in the cell. I will conclude with our ongoing research on Parkinson's Disease where we map transcriptome data on the reconstructed brain-specific metabolic networks to demonstrate the effect of alpha-synuclein aggregation on brain metabolism.

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# Geometry of second order degenerate Lagrangian theories

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In this study we present the Hamiltonian formulations of the dynamical systems generated by the second order Pais-Uhlenbeck, Sarıoğlu-Tekin and Clèment Lagrangians.

Pais-Uhlenbeck Lagrangian is non-degenerate in the sense of Ostrogradsky whereas Sarıoğlu-Tekin and Clèment Lagrangians are degenerate. For the degenerate or/and constraint systems, the Legendre transformation is not possible in a straight forward way. For the degenerate systems, one additionally needs to employ, for example, the Dirac-Bergmann algorithm in order to arrive at the Hamiltonian picture.

We shall follow several alternative methods while arriving at the Hamiltonian representations of Pais-Uhlenbeck, Sarıoğlu-Tekin and Clèment dynamics. At first, we first shall identify the configuration spaces, the tangent and the cotangent bundles. We shall first use Jacobi-Ostrogradsky momenta to define the primary sets of constraints. Accordingly, the total Hamiltonian will be written. The Dirac-Bergmann algorithm will be run in order to identify the final constraint submanifold. In each step of the algorithm, we shall revise the total Hamiltonian by adding the secondary constraints. Once the final constraint set is determined, it is immediate to write the Hamilton's equations governing the dynamics. This is the first and most common way. An alternative way arriving at the Hamilton's equations is to construct the Dirac bracket. To do this, we shall first classify the constraints, determining the final constraint submanifold, into two classes, namely the first and the second. Then, using this classification, we shall define the Dirac brackets associated with the physical systems.

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# Optimality conditions for second order differential inclusions with viable constraint

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In the present paper we derive the optimality conditions for the Mayer problem of second order discrete and differential inclusions with viable constraint. Optimization problems for second order differential inclusions with viable constraints have wide area in application. However optimization problems of second-order differential inclusions with viable constraints considered in this paper have not been examined yet. Applying necessary and sufficient conditions to problems with geometric constraints, optimality conditions for second order discrete inclusions are formulated. Using Locally Adjoint Mapping we derive necessary and sufficient conditions for the optimality of the discrete approximation problem. Using first and second order difference operators and an auxiliary multifunction, we approximate the convex problem by the discrete approximation problem. Passing to the limit, sufficient conditions to the optimal problem are established. We derive optimality conditions for Mayer problem for the second order differential inclusions

(1) minimize $\varphi(x(t), x'(t))$
(2) $x''(t) \in F(x(t), x'(t)), a.e.t \in [0, 1]$
(3) $x(t) \in M, a.e.t \in [0, 1]$,
(4) $x(0) \in A, x'(0) \in B$ .

A feasible trajectory $x(\cdot)$ in the problem is taken to be an absolutely continuous function on time interval $[0, 1]$ together with the first order derivatives.

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## Consensus formation in a social group with a leader

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Opinion dynamics of a group of individuals is the change in the members' opinions through mutual interaction with each other. The related literature contains works in which the dynamics is modeled as a continuous system, of which behavioral patterns are analyzed in regard to the parameters contained in the system. These models are constructed by the assumption that the individuals are independent. Besides, the decisions of the individuals are only affected by two forces: self-bias force and group influence force. In this work we consider a nonlinear dynamical system which models the evolution of the decision of a group under the existence of a leader, which we formulate as

$$\frac{dx_i}{dt} = -\gamma_i(x_i - \mu_i) + \sum_{j=1}^{N} \kappa_{ij} h(x_j - x_i) + C_i(x_0 - x_i),$$

Bifurcation analysis of this system is performed to obtain stability results on the system.

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# Nonlinear dark solitary SH waves in a hyperbolically heterogeneous layer

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This work investigates the propagation of non-linear shear horizontal (SH) waves in a layer of finite depth overlying a rigid substratum. We assume that the layer consists of heterogeneous, isotropic, and incompressible hyper-elastic materials. If the materials are homogeneous, isotropic, and compressible, see the work [1]. By using the method of multiple scales [2], we show that the self-modulation of non-linear SH waves is governed by the non-linear Schrödinger (NLS) equation. Using known properties of solutions of NLS equation, we find that dark solitary SH waves can exist depending on the non-linear constitution of the layer. Consequently, not only the effect of the heterogeneity but also the effect of the non-linearity on the deformation field is discussed for these waves.

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# Lyapunov-type inequalities for higher-order forced dynamic equations with mixed non-linearities on time scales

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In this paper, by using Green function method, we establish new Hartman and Lyapunov inequalities for even-order forced dynamic equations on time scales $\mathbb{T}$:

$$x^{\Delta^{2n}}(t) + (-1)^{n-1} \sum_{i=1}^{m} q_i(t)|x^{\sigma}(t)|^{\alpha_i - 1} x^{\sigma}(t) = g(t),$$

satisfying the Lidstone boundary conditions

$$x^{\Delta^{2i}}(t_1) = x^{\Delta^{2i}}(t_2) = 0; \qquad 0 \le i \le n-1, \qquad t_1, t_2 \in [t_0, \infty)_{\mathbb{T}},$$

where $n, m \in \mathbb{N}$ and the non-linearities satisfy

$$0 < \alpha_1 < \cdots < \alpha_j < 1 < \alpha_{j+1} < \cdots < \alpha_m < 2.$$

No sign restrictions are imposed on the potentials $q_i$, $i = 1, 2, \ldots, m$ and the forcing term $g$. The inequalities obtained generalize and compliment the existing results in the literature.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Nontarget binding of canabinoids in central nervous system: molecular docking with monoamine oxidases

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Cannabinoids are structurally diverse compounds that bind to and modulate the activity of cannabinoids receptors [1]. Despite current interest in medical cannabis as a treatment for epilepsy and other seizure disorders, they are known to have various adverse effects, especially the synthetic cannabinoids. We presume that some of these adverse effects can be originated from their nontarget binding to central nervous system (CNS) biomacromolecules. The aim of this study is to investigate the binding affinities of several cannabinoids to monoamine oxidases (MAO) which are the important enzymes catalyzing the degradation of neurotransmitters such as serotonin, dopamine, adrenaline, etc. For this purpose, binding affinities of 6 representative cannabinoid ligands to MAO-A and MAO-B enzymes were predicted with molecular docking calculations. Conformational scans of cannabinoid compounds were made by the PM6 method and the structures were optimized using Spartan 16. The crystal structure of the MAO-A (pdb code: 2Z5X) and MAO-B (pdb code:2XFN) were cleaned and prepared for doking with AutodockTools. AutodockVina was used to calculate binding energies. Enzymes - ligand Interactions and binding poses were examined with Discovery Studio program. The calculated binding energies ranged from -6 to -10 kcal/mol confirming the good affinity of the studied cannabinoids to MAO. They showed stronger binding affinity to MAO-A than MAO-B. The highest binding affinity belogs to the cannabicyclohexanol ligand. Our results show that, apart from their natural receptors, such compounds can be potential inhibitors of CNS enzymes such as MAO.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# A bi-projection scheme for the numerical simulations of two-phase incompressible viscoplastic flows

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Viscoplastic materials are common in many industrial processes, as in food industry with dairy products, chocolate confection, pulp suspensions, in the petroleum industry with drilling mud, cement, waxy crude oil, and in various geophysical phenomena such flows of slurries, debris and lava. In many cases, mixtures of fluids with different properties occur as sliding of mud in water, dam break of granular matter in air or water. In food industry, the cleaning of a viscoplastic material from conduits is achieved through the displacement induced by water steam or air. Also in the process of oil recovery, a flow of gas, steam or even water is used to push and transport heavy and highly viscous fluids.

A numerical scheme for solving incompressible Bingham flows with variable density, plastic viscosity and yield stress recently proposed and analyzed in [2] will be presented. The mathematical and computational difficulties due to the non-differentiable definition of the stress tensor in the plug regions, *i.e.* where the strain-rate tensor vanishes, is overcome by using a projection formulation (see [1]). This projection definition of the plastic tensor is coupled with a fractional time-stepping scheme designed for Newtonian incompressible flows with variable density. The plastic tensor is treated implicitly in the first sub-step of the fractional time-stepping scheme and a fixed-point iterative procedure is used for its computation. A pseudo-time relaxation term is added into the Bingham projection whose effect is to ensure a geometric convergence of the fixed-point algorithm. This is a key feature of the bi-projection scheme which provides a fast and accurate computation of the plastic tensor. The use of the discrete divergence-free velocity to convect the density in the mass conservation equation allows us to derive lower and upper bounds for the discrete density. First, the main results concerning stability and error estimates will be briefly summarized. Then, numerical results will be presented and discussed. An application to the numerical simulations of dam breaks of dense granular material will be shown.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Spatially explicity modelling of inverse colony formation in cellulolytic biofilms

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Cellulosic ethanol is a liquid transportation fuel that is derived from non-edible and renewable plants materials, such as corn stover, switchgrass or woody biomass. In consolidated bioprocessing, hydrolysis and fermentation of the sugars in the solid lignocellulosic substrates are performed by cellulolytic bacteria that adhere to cellulose fibres and form microbial layers. In this talk we present a mathematical model for the formation of such cellulolytic biofilms. It is a highly nonlinear degenerate coupled PDE-ODE system for the colonising bacteria and for the immobilised carbon source. In computer simulations we show that the model is able to reproduce the characteristic spatio-temporal features of such biofilms. The computer simulations also give strong evidence for the existence of travelling waves which correspond to observation that were reported in the experimental literature. The mathematical proof of the existence of these travelling waves is posed as an open question.

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# In silico modelling on fish toxicity of Pharmaceuticals

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The environmental risks of continuously consumed pharmaceuticals and chemicals as well as their effects to the non-target organisms in the marine environment are becoming an important concern worldwide. The physicochemical, biological, toxicological, and eco-toxicological data of these chemicals and drugs are needed for the environmental risk assessment. To fill the wide data gap, mathematical modeling techniques such as Quantitative Structure Toxicity Relationships (QSTR) are valuable tools for toxicity prediction of the untested compounds, owing to their advantage in reducing experimental costs and time. Another important problem is the complexity of the toxicity initiating mechanisms and adverse outcome pathways. Acetylcholinesterase enzyme (AChE) is a toxicity biomarker of contaminants such as insecticides, metals, synthetic detergents, etc. [1]. Molecular docking calculations on AChE can give structural insight into toxicological information about ligand-target interactions.

The aim of this study was to generate mathematical QSTR fish toxicity models to predict the fish toxicity of untested chemicals and the binding mechanism to fish AChE via molecular docking. We revisited fish toxicity data (fish lethality data, $LC_{50}$) of 79 pharmaceutical ingredients [2] and generated several MLR QSTR models whose reliability were checked by the internal and external validation criteria regarding the OECD principles. Descriptors were calculated using Dragon, Spartan and ADMET software and QSARINS was used for model development. The applicability domains of the models were defined by using leverage approach. We predicted the toxicities of 121 chemicals with no reported experimental fish lethality ($LC_{50}$) data in the literature. Docking calculations with Autodock Vina revealed that lipophilic and hydrogen bonding interactions are important for binding of several toxic chemicals to fish AChE (pdb code: 1GPK).

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# On time-dependent Hamiltonian realizations of planar and nonplanar systems

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We shall elucidate the key role played by the cosymplectic geometry in the theory of time dependent Hamiltonian systems in $2D$. In accordance with this, we shall exhibit the cosymplectic and conformal characters of some biological systems including the host-parasite model. While arriving at the Hamiltonian generators of the systems, the method of Jacobi's last multiplier will be employed.

In the second part, a generalization of the cosymplectic structures to time-dependent $3D$ Nambu–Poisson Hamiltonian systems will be achieved. To this end, we shall write the Nambu-Hamilton formalism in a covariant formulation. This will help us Jacobi's last multiplier diagnosis of $3D$ systems. Particularly, we shall exhibit a general algorithm valid for obtaining the Jacobi's last multiplier for $3D$ Nambu-Hamiltonian systems. Further, the covariant representation also enables us to introduce, what we call, conformal Nambu-Hamiltonian systems. We shall illustrate our pure geometric constructions on various different formulations of the chaotic Qi system.

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# Age-dependent transmission dynamics of hepatitis B in Turkey

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Hepatitis B virus causes an infectious disease hepatitis B which results in human morbidity and mortality through the consequences of chronic infection [1]. WHO (World Health Organisation) reported that approximately 257 million people were living with chronic hepatitis B infection all over the world in 2015 and they declared that Turkey is an intermediate endemicity stage. There are two main serologic markers to detect hepatitis B virus: HBsAg and HBeAg. Resistance of the surface antigen HBsAg in the serum of infected individuals more than six months converts the acute phase of the disease to the chronic phase [2]. The lack of both antigens and the existence of the antibody 'antiHBs' carry a patient to the compartment of recovered and immunised individuals [5]. In this paper, we propose a mathematical model for understanding the transmission dynamics of Hepatitis B in Turkey. The suggested model is based on the classical approach for epidemiological modeling that is known as SIR (Sussuptible-Infectious-Recovered) model [3, 4]. We analyse the model for hepatitis B virus transmission and discuss the affect of external factors like age and demography on the transmission rate. We study the existence and stability of the disease-free and endemic steady state solutions of the model and determine the basic reproduction number. Since the epidemiological models are strictly related with population characteristics, we test our model with a real data set from Turkey. We estimate the associated parameters and generate appropriate simulations.

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# On discontinous Dirac operator with Herglotz-Nevanlinna function in boundary conditions and transmission conditions

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In this presentation, we consider the problem $L$ of the form

$$l(y) := By' + Q(x)y = \lambda\rho(x)\, y, x \in [a,\omega_1)\bigcup(\omega_1,\omega_2)\bigcup(\omega_2,b]$$
$$U(y) := y_2(a) + f_1(\lambda)y_1(a) = 0$$
$$V(y) := y_2(b) + f_2(\lambda)y_1(b) = 0$$
$$\begin{cases} y_1(\omega_i+0) = \alpha_i y_1(\omega_i-0) \\ y_2(\omega_i+0) = \alpha_i^{-1} y_2(\omega_i-0) + h_i(\lambda)\, y_1(\omega_i-0) \end{cases}$$

where $B = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}$, $y(x) = \begin{pmatrix} y_1(x) \\ y_2(x) \end{pmatrix}$ $Q(x) = \begin{pmatrix} p(x) & q(x) \\ q(x) & -p(x) \end{pmatrix}$, $p(x)$, $q(x)$ are real valued functions in $L_2[a,b]$, $\rho(x) = \begin{cases} \rho_1, & a \le x < w_1 \\ \rho_2, & w_1 < x < w_2 \\ \rho_3, & w_2 < x \le b \end{cases}$ and $\rho_1, \rho_2, \rho_3$ are positive real numbers, $\lambda$ is a spectral parameter, $f_i(\lambda) = a_i\lambda + b_i - \sum_{k=1}^{N_i} \frac{f_{ik}}{\lambda - g_{ik}}$, $i = 1,2$,$h_i(\lambda) = m_i\lambda + n_i - \sum_{r=1}^{L_i} \frac{U_r^{(i)}}{\lambda - t_r^{(i)}}$, $i = 1,2$,$\omega_i \in (a,b)$ , $\alpha_i$,$a_i$, $b_i$, $m_i, n_i, f_{ik}$,$g_{ik}$,$U_r^{(i)}$ and $t_r^{(i)}$ are real numbers, $\alpha_i > 0$, $a_1 < 0$, $a_2 > 0 m_i > 0$, $U_r^{(i)} > 0$ and $f_{1k} < 0$, $f_{2k} > 0$. Direct and inverse problems are studied for the problem $L$ which is discontinous Dirac operator with Herglotz-Nevanlinna function in boundary conditions and transmission conditions. This type of spectral problems which have Herglotz-Nevanlinna function in boundary conditions were investigated and this kind of problems also arise in various studied of mathematics in [1-2]. In this study, first, the space that corresponds to problem is introduced. After, the inner product on this space is defined and the operator model that corresponds to the given problem is constructed on this space. Then the integral equations and asymptotics of eigenfunctions of the problem are obtained. The characteristic function and also weight numbers are defined. After the Weyl solution and the Weyl function of the problem are formed. Finally, some uniqueness theorems are proved by using Weyl function and some spectral data.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Comparative analysis of human cancers through molecular signatures

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Cancer is one of the most significant diseases causing that lots of people suffer and lose their lives. Identifying efficacious biomarkers and therapeutic targets for accurate diagnosis, prognosis, and treatment is important for both prevention of tumor development and enhancement of efficient treatment strategies in human cancers. Through integration of genome-scale biomolecular networks with functional genomics data, the molecular mechanisms underlying diseases can be unveiled, which helps us to identify biomarkers and drug targets as well as the disease-specific molecular signatures in cancers, in a systematic way. To this end, 39 transcriptome datasets including 1732 expression profiles (normal vs. tumor) for 13 different cancer types were obtained from NCBI Gene Expression Omnibus (GEO). Integration of these high-throughput data from different omic levels with genome-scale human biomolecular networks, i.e., protein-protein interaction, metabolic (HMR 2.0), and transcriptional regulatory networks, provided (i) the identification of reporter molecules associated with various cancer types at RNA (mRNA and miRNA), protein (receptor, signaling mediator, transcription factor, and enzyme), and metabolite levels, (ii) the construction of disease-specific sub-networks, (iii) the elucidation of biological processes, signaling and metabolic pathways associated with cancers, and (iv) the comparative analysis of molecular mechanisms behind the cancers studied. The information provided by this study might be used to create a comprehensive molecular map indicating similarity and dissimilarity among different cancer types, to study the disease trajectories, to design disease-specific systems biomarkers for early diagnosis, to identify novel drug targets, and to develop or improve the treatment strategies in human cancers. This study was supported under TUBITAK/MAG/116M014 project.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Machine learning algorithm to predict the adverse effects of antidepressants

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**Objective** Drug adverse effects (AEs) are one of the main health threats worldwide, and an important obstacle in drug development. Therefore, early and accurate prediction of AEs by computer-aided methods is extremely important for reducing health risks, as well as costs and time during drug development because clinical trials are expensive and time-consuming.
**Methods** We proposed a machine learning model for AE prediction by integrating the known AEs of a drug with the drug's chemical structure properties. A total of 338 chemical properties were used. The model was built to predict 329 known AEs of 27 approved antidepressant drugs, and three machine learning algorithms for this task were compared.
**Results** This evaluation, based on a ten-fold cross-validation, showed that the multilayer perceptron algorithm surpassed the others. AEs which have F-measure value zero and below 50% accuracy were considered as unsuccessful. Depending on these evaluation criteria, 242 out of 329 AEs were successfully predicted. Also, the model successfully predicted the AEs associated with withdrawal of indalpine, pheniprazine, medifoxamine, zimelidine and amineptine.
**Conclusion** The results suggest that chemical properties of drugs have significant role for adverse drug reaction prediction. Also, addition of biological properties, including protein targets, enzymes and transporters may significantly improve the AE prediction performance.

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# Null forms and integration factors of an Easter Island population model

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A mathematical model that represents the dynamics of growth and sudden decrease in the population Easter Island was introduced by Basener and Ross (2005). Later on its Lie symmetries were investigated and its integrability was demonstrated that with by quadrature if the involved parameters verify certain relationships by Nucci and Sanchini (2015). This study focuses on the null forms and integration factors of this model by utilizing extended Prelle-Singer method which has some interconnections between Lie and $\lambda$-symmetries. The extended Prelle-Singer method that has effective properties to determine first integral, Lagrangian and Hamiltonian forms of any second or third order ordinary differential equation. Furthermore $\lambda$-symmetry is a reasonable method to reduce degree and first integrals of the differential equations and it has significant relationship between Lie symmetries that enable to find $\lambda$-symmetries of governing equation via simple algorithm. The main goal of this work, using the direct mathematical connection between $\lambda$-symmetries and null forms, Prelle-Singer method is implemented to Easter Island population model and based on this application some results are presented.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Improved Laguerre matrix method for solving some nonlinear functional partial differential equations

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In this study, a modified matrix-collocation method based on Laguerre polynomials to find the approximate solutions of the mentioned nonlinear functional differential equations under the initial or boundary conditions is proposed. These type equations are used as mathematical models in many problems in fields of engineering, mathematics, physics, chemistry, population dynamics, control theory and biology. There exists main challenges for solving the mentioned problems due to large range of variables, nonlinearity and multi-dimensionality, so on; thereby, the numerical methods have been developed by many authors. To show the effectiveness of this approach, some examples along with error estimations are illustrated by tables and figures; the consistency of the technique is analyzed.

**Keywords:** Nonlinear functional partial differential equations, Laguerre polynomials, Matrix and collocation methods, Error estimations.

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# Image processing by using High Dimensional Model Representation (HDMR) with pre-processed data through wavelets

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High Dimensional Model Representation (HDMR) being a well known decomposition method for multivariate functions it can be used in image reconstruction. But in order to be able to proceed with HDMR the data matrix in question is to be completed in an efficient manner. Thus the main objective is first to complete a matrix with missing data and then to construct a mathematical model based on this new approximation. Starting with the univariate case for data imputation without losing from the generality it will be generalized to multivariable one. A major assumption to be made is that a part of a data vector is missing without any prior knowledge about its structure. The main purpose here is to guess a sparse frame that can represent complete data vector $f$. In the present article the data imputation taken into consideration is intended to be done in a wavelet basis. Numerical implementati will be given and the generalization to multivariate case will be discussed.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Coarse-grained approaches to analyze ribosomal complexes dynamics: ENM and RedMD

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The ribosome is a molecular machine that synthesizes all cellular proteins using mRNA carrying the genetic code, across all kingdoms of life. Ribosomes are composed of two subunits, small and large, in both prokaryotes and eukaryotes. The small subunit is responsible for decoding of the mRNA in decoding center (DC) and the large subunit catalyzing peptide bond formation in peptidyl transferase center (PTC). Protein synthesis includes 4 major steps; initiation, elongation, termination and ribosomal recycling. Elongation step is highly similar while the initiation process is significantly different between prokaryotes and eukaryotes [1]. With the help of improved structural analysis methods, performing molecular dynamics (MD) simulations and applying elastic network model (ENM) to the both prokaryotic and eukaryotic ribosomal structures provide us to look from an enhanced perspective to ribosomal translational mechanism [2, 3]. In this study, collective and functional dynamics of bacterial and human ribosomal complexes were explored with ENM [2] using an in-house code and MD simulations using RedMD [4]. In RedMD both harmonic/anharmonic motions were considered to capture 100 ns long dynamical behavior. In ENM only harmonic interactions were taken into account while larger time scales were examined. Root mean square deviation, root mean square fluctuation and principle component analysis calculations were carried out to compare and combine the results to get insights on dynamical behaviors of ribosomal complexes. For both bacterial and human ribosomal complexes, we observe the universal "ratchetlike motion" and a swivel movement of 30S/40S head and beak regions in the direction of E-tRNA. We also note that L1 stalk undergoes high fluctuations showing its critical role on helping the exit of E-tRNA from the complex. MD analyses indicate that local fluctuations for bacterial and human ribosomes differ in some critical regions, such as uL4, one of the tunnel wall proteins known to be important for macrolide discrimination.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Einstein's general theory of relativity explained geometrically

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Einstein's General Theory of Relativity is the best available theory of universal gravitation. It was given in 1915-1916 by Albert Einstein and is heavily based on (Riemannian) differential geometry. Thus it involves a $4-$dimensional manifold admitting a metric $g$ of Lorentz signature $(-,+,+,+)$. The metric $g$ and its consequences (its Levi-Civita connection and associated curvature tensor) play the role of gravitational field. In the earlier (Newtonian) theory the Universe was considered to be controlled by Euclidean geometry and the gravitation field arose because of the effects of forces on particles. Free particles followed straight lines. In Einstein's theory, free particles, acted upon only by gravitational fields, follow geodesics determined by the metric (more precisely, its connection). The central question then becomes this; given the distribution of matter and energy how do we find the metric. For this, Einstein's equations are employed which equate a geometrical quantity formed from $g$ to a mathematically similar quantity formed from the matter and energy distribution (the sources of the gravitational field). These equations are second order partial differential equations and are rather difficult to solve. But many solutions are known. Some consequences predicted by the theory are a theory of cosmology, black holes, the bending of light, the problem regarding the perihelion procession of Mercury, gravitational waves and many others. All of these have been successfully confirmed.

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# Time-dependent perfusion coefficient determination in a 2D bioheat transfer problem

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We have considered the initial boundary value problems for 2D heat equation with different boundary conditions which are observed in a bio-heat transfer process describing the relation between the tissue temperature and the arterial blood perfusion. Our emphasis is on the inverse problem of finding the time-dependent perfusion coefficient of the heat equation from integral overdetermination data. The mathematical model of this problem coincide the bio-heat transfer model of a rectangular perfused tissue with the thickness is $L$ and length is 1, which is showed by upper skin at $y = L$, a wall between the tissue and an adjoint large blood vessel at $y = 0$ under the convective condition at $x = 1$ and the same temperature at $x = 0$ and $x = 1$ (Ionkin-type boundary conditions) in a 2D bioheat transfer problem. The similar model which is considered a rectangular perfused tissue with length and thickness equal to some value $L$ and 1, respectively, including (some) given temperature on the upper skin $y = 1$, adiabatic conditions at $x = 0$ and $x = L$, and convective heat transfer between the tissue and an adjoint large blood vessel at $y = 0$ as a space-dependent bioheat transfer problem presented in [1, 2].

Since the basis property of the root functions of the auxiliary spectral problem is satisfactorily studied in [3], the Fourier series analysis of the direct and inverse initial boundary value problems (IBVPs) are suitable for two dimensional heat equation with the special type of boundary conditions (Ionkin-type boundary conditions). However, such a method cannot be applied to IBVPs for the heat equation with more general non-local boundary conditions because of the impossibility of performing the spectral analysis of auxiliary spectral problem.

(This is a joint work with S. Erkovan)

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# Global stabilization of solutions of damped nonlinear wave equations by finite dimensional feedback controllers

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The talk is devoted to the problem of global stabilization of solutions of the initial boundary value problems for the 3D strongly damped nonlinear wave equation and the Korteweg de Vries-Burgers equation. A common feature of these equations is that the semigroups generated by initial boundary value problems for these equations are asymptotically compact semigroups which have finite-dimensional global attractors in corresponding phase spaces. We show that any arbitrary given solution of the initial boundary value problem for each of these equations can be stabilized by using a feedback controller depending only on finitely many large spatial-scale parameters, such as the low Fourier modes or other finite rank spatial interpolant operators.

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# Lumping protein complexes to reduce protein-protein interaction networks

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Thousands of human proteins assemble thousands of functional protein complexes. Conformational variations of these quaternary protein structures, protein isoforms and post-translational modifications make the picture even more complicated [1]. Especially in network biology applications, most of the time it is impossible to handle whole protein-protein-interaction map at once. There are various approaches for network reduction for computational efficiency to overcome this obstacle [2]. Nevertheless protein complexes can be very useful as data reduction guide. Here in this study we used protein complexes as a base for network-reduction by proposing a node-lumping procedure. The comprehensive resource of mammalian protein complexes (CORUM) was used to extract protein complex interactions [3]. In order to cope with the problems caused by temporal protein complexes additional biological data were used. Gene co-expression data and known protein isoforms were used as guides in this purpose. Modular analysis of the resulting context specific network and examination of highly connected nodes were conducted. The results indicated that the procedure is fruitful in pathway elucidation.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Inverse problem for polynomial pencil with seperable boundary condition

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Consider the following differential equation on the interval $0 \leq x \leq \pi$

$$-y'' + \sum_{m=0}^{n-1} \lambda^m q_m(x) y = \lambda^{2n} y, \tag{3}$$

where $\lambda$ is a real parameter and $q_k(x) \in C^1[0,\pi]$, $k = \overline{0, n-1}$ are complex valued functions on $[0,\pi]$. Denote by $y(x,\lambda)$ solution of above equation with boundary conditions

$$\begin{aligned} y(0) &= 0 \\ y'(\pi) + Hy(\pi) &= 0 \end{aligned} \tag{4}$$

for real $H$ number.

In the present paper, we concern with inverse nodal problem for polynomial pencil of Sturm-Liouville operator which is different from classic Sturm-Liouville operator, [1, 2, 3]. By using Prüfer substitution, we give a reconstruction formula for $q_k(x)$, $k = \overline{0, n-1}$ by nodal data.

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# Optimal control of a giving up smoking model with age-structured in smoking classes

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In the present study, we consider a giving up smoking model with age-structured both in occasional smokers and smoker's compartments. We use education campaign as a control variable in potential smokers which will decrease attitude towards smoking of the potential smokers. In order to decrease the number of smokers, nicotine replacement therapy were used as a control variable in smoker's class. These two control variables were taken into account and optimal system is derived using Pontryagin maximum principle type results. Finally, we present some simulations which support our theoretical findings and show the effectiveness of the model.

**Key Theorems:**

There exist optimal control variables $u_1^*,\ u_2^* \in U$ such that $J(u_1^*, u_2^*) = \min_{u_1,u_2 \in U}\ J(u_1, u_2)$ subject to the proposed control system.

The desired optimal values of the control variables are

$$u_1^* = \min\left\{c, \max\left\{0, \frac{\Big(\lambda_1(t) - \lambda_4(t)\Big)P(t)}{B_1}\right\}\right\}, \tag{5}$$

$$u_2^* = \min\left\{l, \max\left\{0, \frac{\int_0^\infty s(t,a)\Big(\lambda_3(t,a) - \lambda_4(t)\Big)}{B_2}\right\}\right\}, \tag{6}$$

corresponding to state and adjoint variables.

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# Herpesviral infection mechanisms through analysis of virus-human protein-protein interactions

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Human Herpesvirus 1 (Herpes simplex virus 1 (HSV-1)) and Human Herpesvirus 4 (Epstein Barr virus (EBV)) are members of Herpesviridae family which are double-stranded DNA viruses. HSV-1 causes lifelong infection and it is largely responsible for oral sores and it can be related to some cancers. EBV plays important roles in infectious mononucleosis and it is in the origin and progression of human carcinomas. A comprehensive understanding of these viral infection mechanisms and generating common or specific treatment methods are possible through a better understanding of the pathogen–host interactions (PHIs). Therefore, aim of this study is to understand HSV-1 - human and EBV - human protein-protein interaction networks, through a comparative analysis of targeted human proteins by these viruses.

PHI data for HSV-1 and EBV were retrieved from PHISTO (www.phisto.rg). Virus-targeted human proteins were obtained from the PHI data and were analyzed thoroughly. GO enrichment, pathway enrichment and gene set enrichment analyses were performed to understand their functional properties.

We found that the targeted human proteins by both viruses are associated with common processes such as cell cycle, transcription and translation, although some specific proteins of EBV target human proteins which are related to specific processes such as telomere maintenance, negative regulation of apoptotic process and osteoblast differentiation. Identification of commonly targeted human proteins by both virus strains may be useful for understanding of general mechanism during cancer or other lethal diseases. Moreover, investigation of specifically targeted human proteins by viruses may provide information about their specific mechanisms during life cycle.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Predicting new drug binding sites on the bacterial ribosome using residue network analysis and elastic network model

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As bacteria gain resistance to conventional drugs, there is an urgent need to explore new therapeutics or repurpose old drugs before simple infection diseases become untreatable. At this point, investigating allosteric communication pathways of the ribosomal complex becomes very important to reveal allosteric sites that can be considered for drug design/repurposing. Here, we present a computationally efficient and force field-free method to explore potential allosteric signaling paths on the supramolecule ribosome [1]. Ribosomal complexes at four different translation states are described as a weighted residue networks composed of nodes and edges. Nodes placed at alpha carbon and phosphor atoms are linked by edges whose length depend on local atom-atom interactions within 4.5 Å. Then, we calculate k-shortest pathways between two functional sites in constant communication: the decoding center and peptidyl transferase center. We determine optimal and sub-optimal short pathways composed of highly conserved residues and known antibiotic binding sites. Elastic network model using normal mode analysis further indicates that residues forming these pathways have the ability for fast communication during functional motions of the complex. This in turn would help the propagation of a perturbation in long-ranges, required for allostery. Finally, we perform centrality analysis of the network to determine critical residues frequently visited by shortest pathways throughout the network. We note that residues with high betwenness values belonging to top 5% quantile inherently form pathways linking distant functional sites of the complex. More importantly, these pathways pin numerous allosteric sites previously suggested by experimental studies. Our calculations on four different translation states highlight inter-subunit bridges B3, B5, B7 and B8 as potential druggable sites.

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## Integrating phylogeny-based tabu search in multiple sequence alignement

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Nowadays, Multiple Sequence Alignment (MSA) is a central problem in computational biology for discovering functional, structural, and evolutionary information of biological sequences. However, MSA problem is becoming more and more difficult when handling sequences having low similarities. Therefore, recent MSA approaches do not always provide consistent solutions. Tabu Search is a very useful and widely applied meta-heuristic approach in solving real world optimization problems from many domains. For the alignment of multiple sequences, which is a NP-hard problem, we apply a tabu search algorithm improved by several neighborhood generation techniques using phylogeny concepts guide trees. The algorithm is tested with the BAliBASE benchmarking database, and experiments showed encouraging results compared to the recents algorithms.

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# Existence-uniqueness and permanence of the HSP 70 synthesis model

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HSP70 synthesis is an important process for living organisms. Basically, the physiologic loop of this protein in the body can be explained as follows: The transcripton factor called heat shock factor (HSF) mediates the regularization of the transcriptional level of HSPs. HSF can be found in both the cytoplasm and the nucleous in an eukaryotic cell in an inactive form or in a form with no DNA binding until the cell is under the normal conditions. The denaturation of some proteins are started when the stressful conditions are occured. The releasing of HSF molecules after the phosphorylation assemble into trimers and accumulation within the nucleus is induced by the binding of the HSP70 molecules with the denaturated proteins or substrate [1]. The active form of HSF is formed with the phosphorylated trimers. The transcription is initiated when this active form makes bound with a specific DNA recognition sequence called Heat Shock Element (HSE). Therefore, as the level of misfolded proteins increases, the stress dependent activation of HSF increases. The heat shock transcriptional response decreases upon prolonged exposure of cells at medium heat shock ($42^oC$) or upon return to its physiological temperature ($37^oC$). HSP70-dependent conversion of the active HSF trimers to non-active monomers accompanies this decrease and their spatial distribution within a cell turns to normal. Another important aspect of these proteins is their important role for the tumour invasion which makes the model for the synthesis of these proteins of significant importance.

In this study, the mathematical modeling of the HSP70 synthesis [2] is modified to include the effect of the temperature increase on the substrate. The corresponding model is then shown to have a unique solution with the permanence properties. Finally, the model is solved numerically by finite difference method which is the combination of forward and backward Euler methods. The results of the numerical simulations confirm the expected behaviour of the synthesis.

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# Impulsive fractional eigenvalue problem via Coulomb potential

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In this study, we introduce fractional Sturm-Liouville problem having Coloumb potential under impulsive condition:

$$-D^{\alpha}_{\pi,-}p(t)\ {}^{C}D^{\alpha}_{0,+}y(t)+\left(\frac{A}{t}+q(t)\right)y(t)=0, \tag{1}$$

$$\Delta y|_{t=t_k}=I_k(y(t_k)),\ \ \Delta y'|_{t=t_k}=I^*_k(y(t_k)),\ t_k\in(0,\pi),\ k=1,2,..,n, \tag{2}$$

$$y'(0)+y(0)=0,\ \ y'(\pi)-Hy(\pi)=0, \tag{3}$$

where $D^{a}_{\pi,-}$ is the Riemann-Liouville derivative [1], ${}^{C}D^{a}_{0,+}$ is the Caputo derivative [1], $I^{1-\alpha}_{a,+}$, $I^{1-\alpha}_{b,-}$ is the Riemann-Liouville integral [1], $p,q$ is real-valued continuous function in interval $[0,\pi]$, $A,H$ are finite numbers, $\frac{y(x)}{x}\in C[0,\pi]$, $I_k,I^*_k:R\longrightarrow R$ and $\alpha_1,\alpha_2,\beta_1,\beta_2\in R$ and $\alpha_1\alpha_2+\alpha_1\beta_2+\alpha_2\beta_1\neq 0$, $0=t_0<t_1<...<t_n<t_{n+1}=\pi$, $\Delta y_{t=t_k}=y\left(t_k^{+}\right)-y\left(t_k^{-}\right)$, $y\left(t_k^{+}\right)=\lim\limits_{h\longrightarrow 0^{+}}y(t_k+h)$ and $y\left(t_k^{-}\right)=\lim\limits_{h\longrightarrow 0^{-}}y(t_k+h)$ represent the right and left limits of $y(t)$ at $t=t_k$, $k=1,2,..,n$, $\Delta y'|_{t=t_k}$ has a similar meaning for $y'(t)$. Firstly, we obtain integral representation for solution of farctional Sturm-Liouville problem having Coloumb potential under impulsive condition. Secondly by using Schaefer fixed point theorem, the existence of solutions is obtained.

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# On generalized and fractional derivatives and their applications to classical mechanics

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A generalized differential operator on the real line is defined by means of a limiting process. When an additional fractional parameter is introduced, this process leads to a locally defined fractional derivative. The study of such generalized derivatives includes, as a special case, basic results involving the classical derivative and current research (Katugampola (2014) and Khalil (2014)) involving fractional differential operators. All our operators satisfy properties such as the sum, product/quotient rules, and the chain rule. As an application we show that the phase plane orbits of solutions defined by physical laws modeled by second order autonomous systems are generically independent of the choice of the generalized derivative used to define them and subject only to a nonlinear time shift. (See J. Phys. A: Math. Theor. 51 (2018) 365204 (18 pp) for further details.)

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# Iterative methods for Forward and Inverse Bioelelectric Field Problems

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Fundamental problems in electrophysiology can be studied by computationally modeling and simulating the associated microscopic and macroscopic bioelectric fields.

The motivating applications represent a class of bioelectric field problems that arise in electrocardiography (ECG) [4] and electroencephalography (EEG)[3].

The localization of electromagnetic field generators in the brain from surface measurements EEG is a major problem in neurological pathologies such as epilepsy and in human cognitive neurosciences. This problem is known as the inverse problem in EEG.

ECG investigates the relationship between the electrical activity of the heart and its induced voltages measured on the torso surface. This relationship can be characterized mathematically as an inverse problem where the goal is to to recover noninvasively regional information about intracardiac electrical events from electrical measurements on the body surface.

We need a fast, realistic and reliable method to solve the forward and inverse problems for calculating the electric potential in the human torso/head from the knowledge of the electromagnetic field generators. These calculation requires an anatomically realistic model (geometry and conductivities) of the different media constituting the torso/head.

The approach proposed here is not to resort to an optimization problem, as is the case generally in solving inverse problems[1, 2], but to a Steklov-Poincare' formulation, inspired by Domain decomposition techniques for the numerical solution of partial differential equations in nontrivial domains.

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## Aggregation and integration in systems biology models

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A key feature in Systems Biology approach in Life Science Problems is to conceive the system as a whole and to make the harmony of constituents at the forefront, as opposed to the classical approach that conceives the system as a big-bag-of-ingredients. As such, obtaining system properties emergent from network interactions are desired. To this end, methods for aggregation and integration of data or models not only for single -omic level but also spanning possibly several omic layers are of great value [1].

The problem of integration and aggregation is rather challenging since the nature, scope, type, scale in time and space of models are inherently different. Similarly, source, methods used, platform, noise level of available data is highly diverse. Owing to this broad variety and heterogeneity, such aggregation and integration attempts require a collection of methods and approaches for various situations. A short list of available approaches include, and is not limited to, the use of unified kinetic formats for metabolic reaction systems [2]; (bayesian) rank aggregation methods for aggregation of prioritized gene lists [3]; boolean models for integration of transcriptome to fluxome data or models, as well as the use of general-scope modeling platforms and dedicated markup language [4].

The talk will present a brief overview and underlying principles of such intergration and aggregation methods and will further focus on aggregation of transcriptome data and its integration of fluxome, using example case for weak acid stress on *Saccharomyces cerevisiae* [5].

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Local-in-space blow-up criteria for a class of nonlinear dispersive wave equation

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The subject of my talk is concerned with blow-up phenomena for the nonlinear dispersive wave equation on the real line, $u_t - u_{xxt} + [f(u)]_x - [f(u)]_{xxx} + \left[g(u) + \frac{f''(u)}{2}u_x^2\right]_x = 0$ that includes the Camassa-Holm equation as well as the hyperelastic-rod wave equation ($f(u) = ku^2/2$ and $g(u) = (3-k)u^2/2$ ) as special cases (see [3], [2, 4] [5]). The blow-up problem of the Cauchy problem for this equation is difficult to due to its complicated structure of the equation ([7]). It should be noted that blowup criteria for such type equation systematically involved the computation of some global quantities or other global conditions like antisymmetry assumptions or sign conditions on the associate potential. In this context, a local-in space blow-up criteria which only involves the values of $u_0'(x_0)$ and $u_0(x_0)$ in a single point $x_0$ is a specially interesting ([1]). The main goal is to present some a local-in-space blow-up criterion (i.e., a criterion involving only the properties of the data $u_0$ in a neighborhood of a single point) simplifying and precising earlier blow-up criteria for this equation ([6]).

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# Input-output method on reduction SEIR-SEI model

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Mathematical model become important tool in studying the dynamics of disease transmission. One group of models that has been widely used in epidemiology is the host vector model [1]. Here, we reduction SEIR-SEI model by using quasi steady state approximation become three dimensional system without vector population. we consider the following origin models

$$\begin{aligned}
\dot{S}_h &= \mu_h N_h - \frac{\beta_h I_v S_h}{N_v} - (\mu_h + u)\, S_h \\
\dot{E}_h &= \frac{\beta_h I_v S_h}{N_v} - (\mu_h + \alpha_h)\, E_h \\
\dot{I}_h &= \alpha_h E_h - (\mu_h + \gamma_h)\, I_h \\
\dot{R}_h &= \gamma_h I_h - \mu_h R_h + u S_h \\
\dot{S}_v &= \mu_v N_v - \frac{\beta_v I_h S_v}{N_h} - \mu_v S_v \\
\dot{E}_v &= \frac{\beta_v I_h S_v}{N_h} - (\mu_v + \alpha_v)\, E_h \\
\dot{I}_v &= \alpha_v E_h - \mu_v I_v
\end{aligned} \tag{7}$$

by using quasi steady state approximation and the fact that the size population is constant, system (7) can be reduced become the simpler form below

$$\begin{aligned}
\dot{S}_h &= \mu_h N_h - \frac{\beta_h I n_h \alpha_v \beta_v S_h}{(\mu_v + \alpha_v)\,(\beta_v I n_h + N_h \mu_v)} - (\mu_h + u)\, S_h \\
\dot{E}_h &= \frac{\beta_h I n_h \alpha_v \beta_v S_h}{(\mu_v + \alpha_v)\,(\beta_v I n_h + N_h \mu_v)} - (\mu_h + \alpha_h)\, E_h \\
\dot{I}_h &= \alpha_h E_h - (\mu_h + \gamma_h)\, I_h
\end{aligned} \tag{8}$$

Furthermore, we will analyze the model include equilibrium stability, controllability, observability and design control $u$ using input-output linearization [2].

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Chelyshkov collocation approach for Lotka-Volterra model with time-delay

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In this study, a collocation method is proposed to obtain the approximate solutions of the population models for two interacting species. By using the Chelyshkov polynomials and collocation points, the problem is transformed to a nonlinear system of algebraic equations with the unknown Chelyshkov coefficients. This system is then solved, yielding coefficients of the approximate polynomial solutions. In addition, the technique of residual correction, which aims to increase the accuracy of the approximate solution by estimating its error in the examples.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# The analytical and numerical results for the generalized fractional Benjamin-Bona-Mahony equation

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In this talk, we consider the generalized fractional Benjamin-Bona-Mahony (BBM) equation

$$u_t + u_x + \frac{1}{2}(u^{p+1})_x + \frac{3}{4}D^\alpha u_x + \frac{5}{4}D^\alpha u_t = 0,$$

which is derived by Erbay et.al. in [1]. We obtain the conserved quantities of the generalized fractional BBM equation. Some new analytical results on the solitary waves of the corresponding equation are presented. We propose the Fourier pseudo-spectral method for the generalized fractional BBM equation and some numerical results for the various powers of nonlinearity and fractional dispersion are illustrated in the present study.

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# The effect of substituents on Phthalocyanine-DNA binding: molecular dynamics and docking studies

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Owing to its central role in replication and transcription, DNA has been a major target for antibiotic, anticancer, and antiviral drug. Cationic porphyrins are considered as functional compounds that strongly bind to DNA and photodynamically modify the target site of a DNA molecule by a mechanism similar to that of anti-cancer drugs [1]. On the other hand, despite spectrophotometric studies on the interactions of phthalocyanines (Pcs) with DNA are abundant, molecular modelling studies have not yet been recorded in the literature to our knowledge. The aim of this study is to investigate the interactions between DNA segment (PDB ID: 2DND) and Pcs possessing substituents with different skeletons. We explored chain flexibility by increasing the number of carbon atoms in the substituents.

The Pc structure bearing pyridine-2-yl-ethynyl groups was obtained in silico referring to a recent experimental study [2]. Upon modifications on the substituents, a series of substituted Pc structures were generated by extending the carbon chains systematically. All structures were subjected to conformational analysis and optimized with semi-empirical PM6 method. A 20 ns Molecular Dynamics simulation was carried out on DNA using GROMACS 5.1.2 package with AMBER99 force-field [3]. All structures were docked to the relaxed DNA segment using Autodock Vina and binding modes were investigated. Results revealed that the number of $\pi$-bonds and the length of the chain influence binding due to the change in flexibility.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# A note on self-adjoint fractional difference operators

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In this study, we give self-adjoint fractional difference operators in Riemann-Liouville and Grünwald-Letnikov sense. We investigate self-adjointness of the fractional difference operators and prove some spectral properties.

*i*) Self-adjoint (nabla right and left) Riemann-Liouville (**R-L)** fractional operator,

$$L_1 x(t) = \nabla_a^{\mu} \left(p(t)_b \nabla^{\mu} x(t)\right) + q(t)\, x(t) = \lambda r(t)\, x(t), \ 0 < \mu < 1,$$

*ii*) Self-adjoint (delta left and right) Grünwald-Letnikov (**G-L)** fractional operator,

$$L_2 x(t) = \Delta_{-}^{\mu} \left(p(t)\, \Delta_{+}^{\mu} x(t)\right) + q(t)\, x(t) = \lambda r(t)\, x(t), \ 0 < \mu < 1,$$

In this work, we use generally these references [1-5].

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# Structural studies on protein-protein interactions and intrinsic protein dynamics decipher how oncogenic mutations work on many levels

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Proteins play critical roles in living cells and they are frequently regulated via their interactions, which can activate/inactivate them. Oncogenic mutations are significantly at or adjoining interface regions, and can abolish/enhance the protein-protein interaction, making the protein constitutively active/inactive [1]. Proteins have a highly dynamic nature resulting in a complex interrelation between structural dynamics and binding behavior. To interact with other proteins, various conformational ensembles sampled by a protein perform local and global fluctuations leading to small or large conformational changes related to functional motion [2]. To show how oncogenic mutations at or adjoining interface regions as well as allosteric sites affect the intrinsic dynamics and interactions of a protein, some important case studies will be introduced in this talk. These case studies include functionally important proteins such as Interleukin-1 (IL-1), which is a large cytokine family closely related to innate immunity and inflammation, and Ras-related C3 botulinum toxin substrate 1 (Rac1), which is a small member of Rho GTPase family involved in regulation of many biological processes through acting as a binary switch between active and inactive states. Understanding the oncogenic mutations' mechanism of action and possible effects on the protein may shed light on the relationship between structure, dynamics and function. Overall, this can make a big contribution on the development of novel drugs and therapeutics for diseases causing malfunction of proteins.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Understanding the dynamic nature of proteins using molecular dynamics (MD) simulations

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Proteins are dynamic entities and their dynamic nature is defined by their flexibility. Proteins undergo conformational changes which may involve both local motions of a few residues and global cooperative motions of several residues. The information about the flexibility and dynamics of proteins could partially be inferred through experimental means, yet computational approaches in recent years has complemented experimental studies and contributed to the understanding on how proteins are in action. Molecular Dynamics (MD) simulation is one of the widely used techniques for elucidating the dynamic character of proteins in atomic scale in real time. In our group, we have studied the application of MD simulations for the investigation of dynamics and detection of allostery in different molecules.

Studies on Human Leukocyte Antigens (HLA) aimed to get a deeper understanding of the effect of polymorphism on the mechanism of HLA function by determining the mechanical and energetical signal transduction within the molecule [1]. Further studies on HLA concentrated on the detection of complex stability and peptide binding affinity. Some other studies concentrated on the effect of single mutations in global structure dynamics and catalytic activity on Caspase−7 molecules. Large effects caused by small changes in the structure are illustrated via shifts in long-range conformational dynamics within Caspase−7.

Furthermore, we have developed a stand-alone graphical user interface (GUI) & command-line software tool called gRINN (get Residue Interaction eNergies and Networks) for the calculation of pairwise amino-acid interaction energies using NAMD or GROMACS MD simulation trajectories supplied by the user [2]. This tool aims to ease the interaction energy analysis of MD trajectories for all the users.

Altogether, our studies based on the usage of MD methodologies on different protein structures aim to illustrate the power of computational approaches in solving the biological problems.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Dispersive shock waves in the cylindrical modified Korteweg de-Vries equation

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In this work, dispersive shock waves (DSWs) in the cylindrical modified Korteweg de-Vries (cmKdV) equation is considered using step like initial data. The mKdV equation has the form

$$u_t + 6u^2u_x + \epsilon^2 u_{xxx} = 0$$

where $u = u(x,t)$, $0 < \epsilon \ll 1$. The mKdV equation has derived in many physical areas such as phonons in anharmonic lattices, ion acoustic solitons and Alfv'en waves in collisionless plasmas, etc..

The modified Kadomtsev-Petviashvili equation is reduced to cmKdV equation by employing a parabolic similarity variable transformation. Then, we find the conservation laws related with Whitham theory for the cmKdV equation using the method of multiple scales. We obtain Whitham modulation equations in terms of Riemann type variables (the Whitham system). DSWs obtained from numerical solutions of the corresponding Whitham systems and direct numerical simulations of the cmKdV are compared for step like initial data.

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# Admissible transformations of nonlinear third order evolution equations

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A set of differential equations can be written as a class of a differential equation which involves some free functions or parameters depending on independent, dependent variables and their derivatives. Those equations are called *class* or *family* of equations. Every different choice of the free functions represent different differential equations of the same family which may express the behavior of various materials for the same physical problem. It is highly important investigating the existence of possible maps between different members of various types of a family of equations induced by admissible point transformations. Members of a particular family of differential equations which are mapped onto each other by a set of admissible point transformations are called *equivalent* and the transformations allow such map are called *equivalence transformations*. Solutions, invariants, concervation laws, etc. of one can construct objects, information for another one via equivalence transformations.

The systematic treatment that Lie's infinitesimal invariance approach could be used in order to construct equivalence transformations was first formulated by Ovsiannikov [1], then after improved and used by many researchers. One of the interesting application of the works is to investigate admissible transformations between linear and nonlinear members of the family of equations, so that the solutions of nonlinear equations can be constructed from the linear one. Within this framework, the equivalence transformations for a (2+1) dimensional general nonlinear diffusion equation is examined and their applications are widely done by Özer [2].

In the present study, we examine the complete group of admissible transformations for the family of general third order nonlinear evolution equations and investigate the possible maps between the members. We also discuss the results in applications.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Eigenvalues of a boundary value problem for the Dirac system on a time scale

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Let us consider the Dirac-type dynamic equations system:

$$BY^{\Delta}(t) + \Omega(t,\lambda) Y(t) = \lambda^m Y(t), \tag{9}$$

on a bounded time scale $\mathbb{T}$. Here $Y(t) = \begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix}$ is a vector-valued unknown function, $\lambda$ is a complex spectral parameter, $B = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}$ and $\Omega(t,\lambda) = \sum_{j=0}^{m-1} Q_j(t) \lambda^j$ such that $Q_j(t)$ are matrix-valued continuous functions with dimension 2x2.

In this study, we build a boundary value problem with system (1) and the following boundary conditions

$$a(\lambda) y_1(\alpha) - b(\lambda) y_2(\alpha) = 0$$

$$c(\lambda) y_1(\beta) - d(\lambda) y_2(\beta) = 0$$

where $\alpha = inf\mathbb{T}$, $\beta = sup\mathbb{T}$, $a(\lambda)$, $b(\lambda)$, $c(\lambda)$ and $d(\lambda)$ are real polynomials.

Some properties of solutions of (1) are investigated and a formulation for the number of eigenvalues of the boundary value problem is given.

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## Some new graph energy types

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In the last seven decades, it has become very popular to model molecules by replacing the atoms by the vertices and bonds by the edges due to their applications in several scientific areas such as chemistry, physics, biotechnology, pharmacology, etc. Studying the corresponding graph model instead of studying the corresponding case, e.g. a molecule, by costly laboratory experiments helps one to save time and money.

In this study, we shall make use of the graph matrices to obtain information about the graph modelling a molecule. In literature, the most widely studied graph matrix is the adjacency matrix although there are many more types of matrices corresponding to a graph. Energy of a graph was defined by Hückel as the sum of the absolute values of the eigenvalues of the adjacency matrix during his search to find a method to obtain approximate solutions of Schrödinger equation, which is a second order differential equation which includes the energy of the corresponding system for a class of organic molecules. As we can model all molecules with graphs, we can calculate the energy of a given graph. Here we obtain the exact formulae and recurrence relations for some new graph matrices.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Spatiotemporal modelling of metabolic networks and quorum sensing in biofilms

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Biofilms are complex microbial communities that are attached to surfaces and embedded in polymeric substances. About 80 percent of the bacterial infectious disease are caused by structured biofilm communities. In this study, it is aimed to analyse a biofilm composed of P. Aeruginosa on chronic wounds via mathematical modelling. The environment is modelled as a 2D structure, where nutrients diffuse from the bottom to top, finite differences approach is used. The biofilm is lattice based, grows and spreads from the bottom to three possible directions. The metabolism of the cells is simulated using dynamic flux balance analysis (dFBA), and metabolic switch is based on quorum sensing, in other words, the genes encoding the metabolic enzymes are regulated as a function of PQS protein produced by the biofilm. Time dependent growth of the biofilm is simulated iteratively by updating the environment, biofilm growth and metabolic status of the cells at each time step. The model is developed and simulated in MATLAB /COBRA toolbox. TESCOBA, a user-friendly tool is developed for model construction, simulation and visualisation of the results.

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# The Klein-Gordon equation: existence and nonexistence

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In this talk, we consider the following coupled Klein-Gordon equations

$$\begin{cases} u_{tt} - \triangle u - \triangle u_t + m_1^2 u + |u_t|^{p-1} u_t = f_1(u,v), & (x,t) \in \Omega \times (0,T), \\ v_{tt} - \triangle v - \triangle v_t + m_2^2 v + |v_t|^{q-1} v_t = f_2(u,v), & (x,t) \in \Omega \times (0,T), \\ u(x,0) = u_0(x),\ u_t(x,0) = u_1(x), & x \in \Omega, \\ v(x,0) = v_0(x),\ v_t(x,0) = v_1(x), & x \in \Omega, \\ u(x,t) = v(x,t) = 0, & x \in \partial\Omega, \end{cases} \tag{10}$$

where $\Omega$ is a bounded domain with smooth boundary $\partial\Omega$ in $R^n$ $(n = 1,2,3)$, $m_1,\ m_2 > 0$ and $p, q \geq 1$ are constants.

In this talk, firstly we will prove global existence and the decay of the solution is established by using Nakao's inequality. We also prove the nonexistence of the solution in finite time and lower bounds for the time of blow up of solutions.

We have following several results:

**Theorem 1**. Let the assumptions of Global existence theorem hold.Thus, we have following decay estimates:

$$E(t) \leq \begin{cases} E(0)\, e^{-w_1 [t-1]^+}, & \text{if } p = q = 1, \\ \left( E(0)^{-\alpha} + C_9^{-1} \alpha \, [t-1]^+ \right)^{-\frac{1}{\alpha}}, & \text{if } p, q > 1, \end{cases}$$

where $w_1,\ \alpha$ and $C_9$ are positive constants which will be defined later.

**Theorem 2**. Let the assumptions of Local existence theorem hold. If initial data satisfies

$$E(0) \leq 0, \quad \int_\Omega (u_0 u_1 + v_0 v_1)\, dx \geq 0,$$

then the corresponding solution blows up in finite time. In other words, there exists a positive constant $T^*$ such that $\lim_{t \to T^*} \left( \|u\|^2 + \|v\|^2 \right) = \infty$.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Mathematical model of Aedes vexans mosquitoes life cycle taking into account the seeking phase of hosts

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Mosquitoes can transmit several diseases such as dengue, chikungunya, Zika, malaria and yellow fever. Understanding the life cycle of mosquitoes could help to protect against mosquitoes and reduce the risk of infections. Several mathematical models have shown that the dynamics of mosquito populations often depends on the following parameters: reproduction rate, mortality rate, migration rate, and mobility rate. Half of the world's population is exposed to the biting of mosquitoes. The objective of this work is to build a model that can help to control and fight against mosquito populations. Using ordinary differential equations, we have developed a mathematical model of *Aedes vexans* mosquito life cycle divided into eight compartments taking into account the aquatic phase and terrestrial phase. The computation of $\mathcal{N}$ representing the average number of eggs laid by each female mosquito during its lifetime allows us to evaluate the persistence of mosquito populations in the breeding sites. We have carried out a sensitivity analysis on different mortality rates and different transition rates. The sensitivity analysis showed the impact of input parameters on $\mathcal{N}$. We have generally shown that all mortality rates have a negative impact on the value of $\mathcal{N}$. Transition rates into compartments have a positive impact on the population of mosquitoes. We have also carried out 500 simulation steps when $\mathcal{N} > 1$ and 100 simulations steps when $\mathcal{N} < 1$ to show the evolution of mosquito populations in each compartment. Results showed that when $\mathcal{N} < 1$, we can observe the eradication of mosquito populations in the breeding sites. When $\mathcal{N} > 1$, we can observe the persistence of the mosquito populations in the breeding sites. The obtained results allow us to show that it is possible to control the dynamics of mosquito populations at each phase of its development.

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# Coupling equation-based model (EBM) with agent-based model (ABM) for studying the intra-host phenomena of Rift valley fever.

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In this article, we have developed a hybrid model by coupling a mathematical model called equation-based model (EBM) of the intra-host phase of Rift valley fever (RVF) and an agent-based model (ABM) of interactions between animals, mosquitoes, water pond and climate factors. The mathematical model describes the dynamics of healthy cells, infected cells, virus populations and immune effector cells. The aim of this work is to create a virtual environment where EBM and ABM models interact together in other to follow the evolution of RVF after animal infection. The other objective of this work is to minimize the storage capacity of the data used by all virtual agents in the computer's central memory. We have presented a mathematical analysis of the EBM model. We have computed the basic reproduction number $R_0$ and have computed the equilibrium points and their stability. We have presented the results of the numerical simulations to illustrate and validate the theoretical results. The obtained results have helped to evaluate the rate of infected cells and viruses in the organism of the animal at each step of the evolution of the disease. This coupled model (EBM/ABM) could help to study the intra-host phenomena of the others diseases.

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# Block-pulse functions and operational matrix for the numerical solution of some classes of stochastic linear and nonlinear integral equations

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In this paper, we obtain a new iterative method for solving stochastic nonlinear Volterra-Fredholm integral equations. We know that stochastic Volterra-Fredholm integral equa- tions arise in many problems in mechanics, finance, biology, science medical, social sciences.etc. So it is necessary to study such problems where there is an increasing demand for studying the behavior of a number of sophisticated dynamical systems in physical and medical, as well as in engineering and finance. These systems are often dependent on a noise source, like e.g. a Gaussian white noise, governed by certain probability laws, so that modeling such phenomena naturally requires the use of various stochastic differential equations. Using Block-pulse functions and operational matrix of integration, a nonlinear Volterra Fred- holm integral equation can be reduced to a nonlinear system of algebraic equations, which can be solved by iterative method. We prove that the rate of convergence is O(h). Finally, illustrative examples are included to demonstrate the validity and applicability of the technique.

**Key-Words**: Stochastic Volterra-Fredholm integral equation; Brownian motion; Approximate solution; Best approximation; Block-pulse functions; Collocation method.

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# Thixotripic yield stress behavior as a singular limit of viscoelasticity

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The lecture will review recent work showing how viscoelastic fluids can exhibit thixotropic yield stress behavior if the relaxation time is large. Methods of dynamical systems and matched asymptotic analysis can be used to analyze this limit. It will be shown how two popular models of entangled polymers, the PEC model and the Rolie-Poly model, can be analyzed in this fashion. The analysis shows a "fast" (elastic) regime, a "yielded" (flowing) regime, and a "slow" regime where deformation is minimal but microstructural changes take place.

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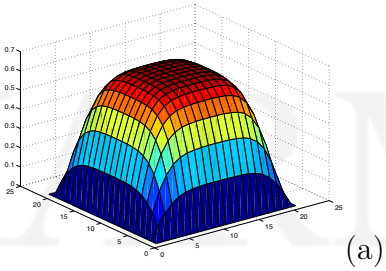


# On the dynamics of a fish & jellyfish ecosystem with spatial species diffusion

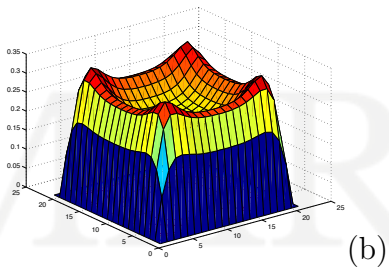
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Dramatic increases in jellyfish populations which lead to the collapse of formerly healthy ecosystems are repeatedly reported from many different sites. Due to their devastating effects on fishery the understanding of the causes for such a blooming is of major ecological as well as economic importance. In previous studies we discussed a unified ordinary differential equation model (ODE model) for fish-jellyfish interactions, and, assuming fish as the dominant predator species, we set-up a combined two species system subject to constant environmental conditions, see [1] and [2]. By totally analytic means we completely classified all biologically relevant equilibria in terms of existence and Lyapunov stability, studied their bifurcation behavior, and gave a description of this system's non-linear global dynamics. Particular interest was paid to connecting orbits that account for a burst of the jellyfish population after a certain sub-critical Andronov-Hopf bifurcation of a mixed species equilibrium.

After a review of these results, we focus on an extension of our model that includes spatial diffusion of the species in one- and two-dimensions. The population regimes near critical points and bifurcation parameters of the ODE model are studied and the analytical results are illustrated by numerical simulations. Although not exploiting the richness of coastal geometries we already see interesting spatial distributions occurring that match observed phenomena of jellyfish bloomings, e.g. the accumulation of jellyfish near shores. The images below give an example of a fish (a) and jellyfish (b) distribution with such a jellyfish accumulation near the shores.



(a)



(b)

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# Modelling the catalytic and inhibition mechanisms of monoamine oxidase: A combined ONIOM and quantum cluster approach

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Two isoforms of monoamine oxidase (MAO-A and MAO-B) are the enzymes catalyzing the degradation of neurotransmitter amines such as serotonin, dopamine, adrenaline etc. Therefore, they are important target enzymes for the treatment of neurodegenerative disorders such as depression, Parkinson and Alzeimer. Understanding the mechanistic details of catalytic reaction provides significant insights into the rational design of noval pharmaceutics with maximized potency. However, modelling the chemical mechanisms of enzymes is still a challenging task.

For this purpose, we applied our own strategy by combining the ONIOM methodology with quantum cluster approach [1–3]. First, we determined the optimum size of the MAO enzyme which is sufficiently large enough to accommodate all important interactions. Active site models with varying sizes of MAO-B were set up according to quantum cluster approach. Comparison of the calculated activation energies for gradually increasing model systems revealed that Cys397 which is covalently bound to FAD should be included in quantum cluster models. Further ONIOM (M06-2X/6-31+G(d,p):PM6) calculations on serotonin and dopamine oxidation by MAO verified that the rate-determining step of the mechanism is a hybrid of hydride and proton transfer. Moreover, MAO catalytic mechanism we proposed provided a crucial step involving a covalent reversible inhibition. This mechanism can be used to modulate the potency and reversibility of novel mechanism-based covalent inhibitors by intelligent modifications in the structure of the inhibitors.

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## Biophysical basis of MHC class I polymorphism

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Highly polymorphic residues in the Human Leukocyte Antigen (HLA) chain of Class I Major Histocompatibility Complex (MHC) determine the chemical specificity of binding pockets [1], peptide contact patterns and stabilities/cell surface expression levels. On the other hand, conserved positions are also buried in the structure and located near peptide binding pockets. In principle, they have the potential to modulate chemical specificity, yet it is not clear why they show persistently low levels of variation.

We studied MHC Class I polymorphism in the context of local residue frustration in the protein structure. Frustration analysis allows the investigation how favorable the contacts of a given residue is in the given protein fold. Minimal frustration indicates that the residue is preferred in the respective location, whereas high frustration indicates the opposite. On a dataset of experimentally determined and homology-modelled MHC structures, we applied frustration analysis using frustratometer2 software [2]. In addition, we analysed residue conservation using the Evolutionary Trace algorithm [3]. In the MHC Class I binding groove, 23 (68%) of the 34 minimally frustrated positions are conserved. 29 out of 36 positions (80%) forming polymorphic peptide binding pockets are "neutral" in terms of frustration. These results indicate that the MHC evolves to maintain a stable fold by conserving the amino acid identity in minimally frustrated positions while allowing for modularity in peptide binding specificity via amino acid changes in neutral binding pocket residues. Moreover, a frustration-based clustering analysis assigns the three HLA gene loci (A, B and C) into separate groups with differences located mainly at positions showing neutral frustration. This result additionally suggests that the known sequence-based groupings between the three loci are reflected in the internal energetics of the MHC as well.

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# Integration of omics data in a network related context to study individualized disease aetiology of Complex Diseases

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Advancements in Omics Technologies enabled analysis of complex disease mechanisms at a cellular level and helped to reveal individualized mechanisms involved in disease aetiology. One way to integrate the omics data is to use pathways that summarizes cellular functions carried out within that pathway.

To this end we developed an analysis platform to analyze disease specific omics data in a pathway related context. Pathways are part of biological interaction networks. We map the disease targeted genes to interaction network then use the network properties to identify disease targeted sub networks ( active sub network search) including most of the disease targeted genes.

In this talk I will go over active sub network search algorithms using network theory concepts then its application to marker pathway identification in complex diseases including cancer and neurological diseases.

I will also summarize how these pathways can be used to identify individualized disease development mechanisms and also how this information can be exploited for finding out personalized treatment options.

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## Optimization problems governed by phase field models

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Optimization problems with interfaces and free boundaries frequently appear in materials science, fluid dynamics, damage problems, topology optimization and biological membranes. The interfacial dynamics is either modeled explicitly by geometric evolution equations or implicitly by using a phase field approach. A phase field model is usually constructed in such a way that in the limit of an infinitesimal interface width (the so-called sharp interface limit) the correct interfacial dynamics is recovered. This approach permits to solve the problem by integrating a set of partial differential equations for the whole system, thus avoiding the explicit treatment of the boundary conditions at the interface. In this talk we concentrate, after displaying the applicability of phase field models by some practical examples, on a multi-material structural topology optimization problem. The optimization problem in the phase field context and its first-order necessary optimality conditions will be derived and numerical simulations will be presented.

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## Random pullback exponential attractors

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Exponential attractors of infinite dimensional dynamical systems are compact, semi-invariant sets of finite fractal dimension that attract all bounded subsets at an exponential rate. They contain the global attractor and are, due to the exponential rate of convergence, generally more stable under perturbations than global attractors.

In the autonomous setting exponential attractors have been studied for several decades and their existence has been shown for a large variety of dissipative equations. More recently, using the pullback approach the theory has been extended to non-autonomous and random problems. We focus on the latter case and present general existence results for random pullback exponential attractors in Banach spaces and derive explicit estimates on their fractal dimension. As an application a stochastic semilinear damped wave equation is considered.

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# History, rare, and multiple events of mechanical unfolding of repeat proteins via AFM

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The mechanics of biological systems is crucial for their function. Individual proteins require flexibility of secondary structures to allow microsecond conformational changes. In the living cell, shape maintenance and structural stability is assured by the mechanics of the cytoskeleton, adhesion complexes and the plasma membrane [1]. Thus, the study of the mechanics of proteins, protein complexes and the membrane is important to understand biological processes. Force spectroscopy (FS) using nanotools, such as magnetic tweezers, optical tweezers and AFM, allows the manipulation of individual proteins and monitoring of the forces required to unfold individual protein domains [2, 3]. Experimentally, a probe functionalized with a biomolecule is moved at a certain velocity and the resulting unfolding forces are recorded. Mechanical unfolding of proteins consisting of repeat domains is an excellent approach to obtain large statistics. However, the probability of unfolding depends on the number of folded domains, which results in changes in the unfolding force. The common use of unspecific attachment approaches to pull the protein of interest holds important limitations to study unfolding history [4]. We implement here a specific binding approach using the ultrastable complex dockerin/cohesin III to assess the unfolding history and to investigate rare and multiple events during the unfolding of repeated domains. We show that this approach is more robust, reproducible and provide larger statistics than conventional unspecific methods. We reveal that unfolding forces increase with the number of unfolded domains and is well described by Monte Carlo simulations.

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# Mathematical assessment of patient-specific brain tumor spread: from microscale to multiscale

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Joint work with: G. Corbin, A. Hunt, and A. Klar (TU Kaiserslautern)
C. Engwer & M. Knappitsch (WWU Münster)
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J. Nieto & J. Soler (Univ. of Granada)

Gliomas are rarely curable brain tumors arising from abnormal glial cells in the brain. In particular, the most agressive type, glioblastoma multiforme, has a poor prognosis with a median survival rate less than one year. Complex therapy approaches including surgical resection of neoplastic tissue, radio- and chemotherapy can still not ensure healing, as an exhaustive removal of the tumor is in general impossible, due to the diffuse infiltration of the cancer cells in the highly anisotropic and patient-specific brain tissue. The correct assessment of tumor margins is therefore crucial for therapy planning enhancement.

We propose and investigate a class of multiscale models for glioma invasion, consisting of kinetic transport equations and accounting for the evolution of cell distribution functions (mesoscale) obtained from descriptions of individual cell motility (microscale), in interplay with subcellular dynamics of receptor binding to the surrounding tissue. We deduce effective macroscale equations characterizing the space-time tumor evolution and carrying information from the lower modeling scales. Thereby particular attention is payed to modeling the effects of the tumor microenvironment on the migratory behavior of glioma cells, including the structure of brain tissue by way of diffusion tensor imaging (DTI) data.

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# Dynamics on matched pairs of Lie groupoids

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The geometrization of the dynamics on Lie groups [6], admits a discrete counterpart which is governed by Lie groupoids, [5, 9]. The (discrete) dynamics, in the framework of Lie groupoids, is encoded by the discrete Euler-Lagrange equations [4], which reduce, under the existence of a symmetry, to the discrete Euler-Poincaré equations [1].

Our motivation is to find a geometric framework in order to couple (match) two mutually interacting discrete systems. To this end, we shall first present the basics on Lie groupoids and Lie algebroids. The discrete dynamics in the framework of Lie groupoids will also be given. The matched pair theory, which is a general recipe for coupling two geometries under interaction, [7, 8, 2, 3], will follow. The talk will be concluded with the presentations of some concrete examples.

This is a joint work with Oğul Esen, and is supported by the TÜBİTAK project 117F426: "Matched pairs of Lagrangian and Hamiltonian Systems".

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# Asymptotics of eigenvalues and eigenfunctions of a differential operator with a constant delayed argument

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In this work, we shall study the eigenvalue problem $S := S(q; a, \lambda, d_i)$ $(i = 1, 2, 3)$ which consists of Sturm-Liouville equation

$$-u''(t) + q(t)u(t-a) = \lambda^2 u(t)$$

on $\Omega = \cup\Omega^{\pm}$ with boundary conditions

$$u(0) = u(L) = 0,$$

and transmission conditions

$$u(c+0) = d_1 u(c-0),$$

$$u'(c+0) = d_2 u'(c-0) + d_3 u(c-0)$$

where $\Omega^- = [0, c)$ and $\Omega^+ = (c, L]$; the real-valued function $q(t)$ is continuous in $\Omega$ and has a finite limit $q(c \pm 0) = \lim_{x \to c \pm 0} q(t)$, $t - a \geq 0$, if $t \in \Omega^-; t - a \geq c$, if $t \in \Omega^+$; $\lambda$ is a real spectral parameter; $a$, $d_i$ $(i = 1, 2, 3)$ are arbitrary real numbers such that $d_1 d_2 \neq 0$. We shall obtain some asymptotic equalities for eigenvaluees and eigenfunctions of the problem $S$.

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# On the stability and transitions of quasi-geostrophic equations

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The dynamical processes involved in the description of geophysical flows in the atmosphere and the ocean are extremely complex. There are a multitude of physical variables, several processes that determine the evolution of these variables and a wide range of spatial and temporal scales. The simplest set of equations that meaningfully describe the large scale flows in the atmosphere or mesoscale flows in the oceans are the so called quasi-geostrophic equation given by

$$\partial_t \Delta\psi + J(\psi, \Delta\psi) + \beta\partial_x\psi = D(\Delta)\psi + F(t, x, y, z).$$

This work is on recent results on the stability and transitions of the exact solutions in various models of barotropic quasi-geostrophic equations.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# A QSAR model for the prediction of inhibitory activity of coumarin derivatives on leukemia cell lines

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Continuously increasing, more than 15 million cancer cases are estimated worldwide. There is a need for the discovery of better chemotherapeutic agents which are both effective and not toxic. Coumarins are one of the natural compounds that show various biological activities with mild side effects. Developing computational models using Quantitative Structure–Activity Relationships (QSARs) has been very useful in drug design. A QSAR model is a correlation between calculated properties of compounds and their experimentally determined biological activities. Considering the cost and the effort to develop a new drug, QSAR approach is a valuable tool in rational drug design. The aim of this study is to develop a linear QSAR model to predict antitumor activities against leukemia (CCRF) cell lines for new series of coumarin hydrazide-hydrazone derivatives. The $IC_{50}$ (uM) values are retrieved from the literature1. In the present study, 21 structures are drawn and their molecular descriptors are calculated from their 2D molecular structures. These descriptors are used in the multiple linear regression model as input variables. The dataset is split into training and test sets for the model validation. Statistically significant descriptors are selected via All Subsets method. A two–descriptor linear model is developed on the training set (Eq.1). Electronegativity is found to be prominent in describing antitumor activity. Subsequently, the developed model is validated on the test set.

$$p(IC_{50}) = 23.37 - 18.87(D150) + 39.19(AATSC3e) \qquad (1)$$

The obtained model is validated internally and externally according to widely accepted metrics such as $R^2$, $RMSE$, $Q^2_{LOO}$, $Y\text{-}scrambling$, $Q^2_{F1}$, $Q^2_{F2}$, $Q^2_{F3}$, and $CCC$.

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# Prostate cancer spesific metabolic model as tool for drug repositioning

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Genome-scale metabolic models (GEMs) provide insights about cancer-specific metabolism and have been used for identifying potential therapeutic agents and drug targets [1]. Drug repositioning is a time and cost effective way of drug discovery that recently applied together with GEMs for cancer treatment [2]. There are also more than 20 repurposed non-cancer drugs to treat PCa, however GEMs applications for drug repositioning are limited for PCa [3]. In this study, we aimed to reconstruct a generic prostate cancer-specific model for exploring not only this cancer's metabolism but also repurposing new therapeutic agents. RNA-Seq data for 495 individuals suffering from PRAD as well as 52 noncancerous prostate samples from The Cancer Genome Atlas database and proteome data from the Human Protein Atlas v18 were retrieved. Besides, all personalized GEMs based on PRAD transcriptomes were acquired from the Human Pathology Atlas to reconstruct a generic model covering all individual variations as well as proteome and transcriptome. tINIT and reporter metabolites algorithm via RAVEN toolbox were used to reconstruct the model and identify reporter metabolites, respectively. Differentially expressed genes in PRAD specific metabolic model were used as metabolic signatures for drug repurposing. Gene expression profiles from CMap2 were analyzed and statistically evaluated. Drug-gene interactions have been predicted based on calculated confidence scores from drug perturbed gene expression profiles. Reaction fluxes have been altered due to fold changes of the gene expressions to mimic drug effect on PCa metabolism and growth inhibiting drugs were reported as candidates for drug repositioning. In silico cell viability test through PRAD specific GEM, four of 11 drugs were highlighted. Anti-bacterial agents, a thiazide diuretic and a NMDA receptor antagonist have been repurposed to treat prostate cancer whereas experimental validations are on progress.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Behavior of some population models through the Monte Carlo method

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All organisms can be classified as a predator or a prey for some other organisms according to their interactions and eating habits. These interactions can be represented by nonlinear differential equations. In this study, a system of these equations have been discussed through the Monte Carlo algorithm and compared with numerical results. A system of equations has been taken to be deterministic equations. This study aims at analyzing how deterministic problems can be considered by using stochastic approaches. For realizing the behavior of the models, the solutions have thus been discussed in detail.

**Keywords:** Monte Carlo Method, Nonlinear Behavior, Nonlinear Differential Equation, Initial Value Problem.

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# On the finite-zone potentials

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I am going to give a talk about the one-dimensional Schrodinger operator $L(q)$ with a complex-valued PT-symmetric periodic potential $q$. First we consider the general spectral property of the spectrum of $L(q)$ and prove that the main part of its spectrum is real and contains the large part of $[0, \infty)$. Using this we find necessary and sufficient condition on the potential for finiteness of the number of the nonreal arcs in the spectrum of $L(q)$. Besides, we find explicit conditions on the potential $q$ for which the number of gaps in the real part of the spectrum of $L(q)$ is finite. Moreover, we find necessary and sufficient conditions for the equality of the spectrum of $L(q)$ to the half line and consider the connections between spectrality of $L(q)$ and the reality of its spectrum for some class of PT-symmetric periodic potentials. Then, we give a complete description of the shape of the spectrum of the Hill operator with optical potential. Finally I find the necessary and sufficient conditions in term of periodic and antiperiodic eigenvalues as well as in term of the Fourier coefficients of the potential for which the number of the gaps in the real part of the spectrum of $L(q)$ with a PT-symmetric periodic complex-valued potential $q$ is finite. Using it I construct the large and easily checkable classes of the finite-zone PT-symmetric periodic potentials. Then, we discuss the diversity of the results for the PT-symmetric finite-zone potentials and the real finite-zone potentials.

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# Application of Adomian Decomposition Method to Predator-Prey Model With Time Delay

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Lotka-Volterra equations (predator - prey models) are defined as a pair of nonlinear ODE;

$$x' = x(a - by) \tag{11}$$
$$y' = y(-c + dx)$$

where $x$ is for the prey population and $y$ is for the predator population and $a$, $b$, $c$, $d > 0$ to make them biologically meaningful. For this system to be applicable to real populations time lag (from the new born to mature of the prey and predator) have been included in these equations.
In this paper we work on following predator-prey model which is a nonlinear delay differential equation (DDE) system;

$$\frac{d}{dt}pred(t) = 10pred(t-\tau)prey(t-\tau) - \frac{1}{2}pred(t) - \frac{1}{10}pred(t)^2 \tag{12}$$

$$\frac{d}{dt}prey(t) = prey(t)\Big(1 - prey(t)\Big) - pred(t)prey(t)$$

with initial functions $pred(t) = 1$ and $prey(t) = 1$ for $t \leq 0$.

Here $\tau$ is the fixed delay parameter.

Nonlinear DDEs are rarely solvable by analytic methods. In this paper we propose a numerical method - Adomian Decomposition Method (ADM) extended with fixed steps iterations - to solve the system shown above. Main problem of ADM in applying to dynamical systems is the short convergence radius of the solution it proposes. In our method we tried to overcome this problem by implementing ADM for the fixed iteration step starting from the initial point of the system. We use the result of the ADM at the end point of the first iteration step as the initial value of the second iteration step and we continue this iterative method for the next intervals. We compare our results with *dsolve* command of Maple and *NDSolve* command of Mathematica.

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# Exact solutions to the nonlocal Boussinesq equation by two different algorithms

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In this work, we study exact solutions of nonlocal Boussinesq equation (nlBq) which appears in many scientific fields. We generate dark solitons, singular solitons, a new family of soliton and combo dark- singular soliton type solutions of the model by the extended Kudryashov's algorithm. Additional solutions such as singular periodic solutions also fall out of this integration scheme. Also, one soliton, two soliton as well as three soliton type solutions are presented by means of the multiple exp-function algorithm. Lastly, Lie symmetry analysis with the new similarity reductions are also examined.

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# Comparison of computational allosteric pathway identification methods

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Allostery is the key regulatory process of which biological molecules can transmit a stimulus from one site to a physically distinct site [[1]]. The stimulus can change the protein behavior of the protein at the active site and can either increase protein's activity (called as positive allostery) or reduce the activity (called as negative allostery) [[2]]. Changes with allosteric stimulus can be tricky since normally protein fluctuate regularly between ensembles of different conformations and allosteric signal can shift this ensemble to make detection of allosteric mechanism more complicated from static snapshots. Molecular dynamics (MD) simulations are valuable tool for the study of allostery computationally because different motions of proteins can be detected in full atomic details. Providing an all-atom detailed of protein behavior in high resolution and introducing controlled perturbations to the biomolecular system are two main reasons of which MD simulations can be useful in the allostery studies WISP is a program which is useful for detection of suboptimal pathways via protein structure network (PSN) using cross correlation matrix. gRINN is a tool which developed for analysis pairwise residue interaction energy data from protein MD simulation trajectories via protein energy network (PEN) using interaction energy matrix and could be an example applications for investigation of allosteric pathway. Therefore, in order to prove that gRINN tool can be used in allosteric identification, we aimed to select allosteric protein with known allosteric pathway and employed both gRINN and WISP tool to confirm the allosteric pathway. For this reason, CBP (CREB binding protein) was selected as a model allosteric protein and representative structure has been downloaded from PDB bank (PDB ID:2LXS). 100 ns parallel molecular dynamics simulations were carried out with NAMD software with CHARMM36 force field at 300 K. In next step, pairwise amino acid non-bonded interaction energies and possible shortest path identification for allostery were employed via gRINN tool. Similarly, possible shortest paths were also identified with WISP tool. Our study showed that possible allosteric paths can be identified via both gRINN and WISP tools.

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## Lump type solutions to a new extended (3+1)-dimensional nonlinear evolution equation

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In this work, we derive a new extended (3+1)-dimensional nonlinear evolution equation (NLEE) considering the prime number $p = 3$ of generalized Hirota bilinear operators. We obtain abundant lump-type solutions by Maple symbolic computations. The required conditions of the analyticity and positivity of the solutions can be easily achieved by taking special choices of the involved parameters. The main ingredients for this scheme is to recover the Hirota bilinear forms and their generalized equivalences. Lastly, the graphical simulations of the exact solutions are depicted.

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# Batch analyis of RNA-Seq data with docker in AWS cloud

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As the cost of sequencing is decreasing the number of next generation sequencing studies is increasing at a rapid pace. Staggering amount of sequencing data accumulated over the years are kept at publicly available databases such as Short Read Archive (SRA) and European Nucleotide Archive (ENA). The truly enormous amount of sequencing data provides opportunity for mining gene expression and genome variant studies.

However, such a mining task not only requires extensive computational resources but also orchestration of analysis steps at a large scale. The latter challenge is due to the fact that the analysis of sequencing data comprises of multiple steps each carried by different software. If the overall goal can be summarized as "setting up multiple computers and distributing the workload and processes", achieving this manually is clearly impractical. However, by the help of various tools and technologies, setting up such an environment is much easier than before. "Setting up computer" part is taken care by containerization technology in which Docker is the leading platform. "Multiple computers" part is taken care by cloud services where CPU, RAM and harddisk space can be used with hourly fee. In this talk, Amazon AWS EC2 will be demonstrated. Finally, "distributing workload and processes" part can be taken care by bioinformatic pipeline frameworks. In this talk, Nextflow [1] framework will be demonstrated which is able use containers and run in cloud.

Containerization not only eases the pain of software installation and configuration but also supports reproducible research [2]. Combining containerization with cloud computing allows rapid and affordable bioinformatic analysis at scale [3]. Containerization also allows integrative analysis by mixing and matching tools from different fields of bioinformatics. This talk will briefly introduce the aforementioned tools and technologies and then provide an example batch analysis where human RNA-Seq data from multiple sequencing projects were used in order to get with preliminary results related to trans-splicing and non-aligned reads.

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## Simulation of particle translocation through nanopores

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The use of nanopores has become an important technique for detecting specific cells or proteins by reading the ionic current signal. Nanopores are etched on an insulating membrane that bisects two electrolyte-filled reservoirs. When an electrical field is applied, the particles along with ions are actuated toward the pore and eventually while moving through the pore, ionic flow is altered. This change manifests itself in the ionic current signal. This signal provides distinct information about the shape and size of the particle. These signals are classified mainly in three types which are named as conductive, resistive or biphasic. In this process, the electrostatic interactions between the particle and the pore surfaces determine the signal wave shapes. The entire mechanism is not well-understood. Several parameters play roles in the signal generation, which are pore geometry, surface charges, ionic concentration and potential difference [1].

The difficulties encountered in discrimination the nano-sized particles can be overcome by improving the signal sensitivity of nanopores. It is known that the small orifice of conical nanopores increases the particle detection sensitivity due to their asymmetric geometry [2]. Based upon this knowledge, in addition to the conventional conical pore geometry, we present two additional biconical pore configurations to fully explore the effect of pore geometry during the randomly translocated different-sized particles. We compare the sensitivity of nanopores to determine the superior geometry. Steady-state finite-element simulations are carried out for more quantitative analysis by coupling the Poisson, the Nernst-Planck and the Navier-Stokes equations with COMSOL Multiphysics v.4.4 software (COMSOL, Inc.). Each of three pore geometries yield different signal shapes, thus we expect that our results will guide the future experimental work.

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# Mathematical model of the dynamics of blood cell production with mobilisation dependent apoptosis and proliferation regulations.

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In this paper, a mathmatical and numerical analysis of a nonlinear system of two differential equations with delay, describing the dynamics of blood cell production, is investigated. Existence and uniqueness of solutions is proved and first order necessary conditions are derived.

We propose a mathematical model describing the dynamics of a hematopoietic stem cell population with growth factors and mobilisation dependent apoptosis and proliferation regulations. The method of characteristics reduces the age and space-structured model to a system of differential equations with a state-dependent delay.

We are concerned with the following state-constrained problem:

$$(S)\begin{cases} \frac{\partial p(t,x)}{\partial t}+\frac{\partial \gamma(x)p(t,x)}{\partial x}=-[\beta(x)+\mu(x)+\sigma(x)]p(t,x)+4\beta(2x)p(t,2x)+\tau(x)n(t;x), \\ \frac{\partial n(t,x)}{\partial t}=-[\nu(x)+\tau(x)]n(t;x)+\sigma(x)p(t,x) \\ \quad p(t,\frac{x_0}{2})=0 \quad t\geq 0 \\ \quad p(0,x)=\phi(x);\phi\in\chi \\ \quad n(0;x)=\psi(x);\psi\in\chi \end{cases}$$

We denote by $n(t,x)$ and $p(t;x)$ the quiescent and proliferating cell populations at time $t$ and size $x$ with $\frac{x_0}{2}\leq x\leq x_1$.
$\gamma,\beta,\mu,\nu$ and $\eta$ are some parameters.

*AMS 2010 subject classification : 34D20, 34K99, 92C37*
**Keywords** :Existence and uniqueness, hematopoietic stem cells, delay differential equations, characteristic equation.

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MARMARA ÜNİVERSİTESİ YAYINEVİ



# Explosive solutions for a Timoshenko equations with damping term

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We study the following Timoshenko equation

$$\begin{cases} u_{tt}+\triangle^2 u-M\left(\|\nabla u\|^2\right)\triangle u+u_t=|u|^{q-1}u, & (x,t)\in\Omega\times(0,T), \\ u(x,0)=u_0(x),\ u_t(x,0)=u_1(x), & x\in\Omega, \\ u(x,t)=\frac{\partial}{\partial\nu}u(x,t)=0, & x\in\partial\Omega, \end{cases} \tag{13}$$

where $q\geq 1$ is real numbers, $\nu$ is the outer normal and $M(s)=1+s^{\gamma},\ \gamma\geq 1$.

In this talk, we prove the nonexistence of the solution. Our main result:

**Theorem**. Assume $\frac{q-1}{4}\geq\delta\geq\frac{\gamma}{2},\ \gamma\geq 0$ and one of the following statements are satisfied

(i) $E(0)<0$ and $\int_\Omega u_0u_1dx>0$,

(ii) $E(0)=0$ and $\int_\Omega u_0u_1dx>0$,

(iii) $0<E(0)<\frac{\left(a'(t_0)-\|u_0\|^2\right)^2}{8\left[a(t_0)+(T_1-t_0)\|u_0\|^2\right]}$ .

Then the solution $u$ blow up in finite time $T^*$.

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## An application of triangular fuzzy numbers on EEG

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EEG assessment are made by taking into account some specific patterns, wave amplitude and wave frequency. EEG activity will be described as alpha, beta, theta and delta waves as shown in Table I.

EEG exhibit graphical image of brain waves and is managed by veterinarians, medical personnels and scientists. The amplitudes and frequencies of EEG signals are used to predetermine the conditions in human or animal body. Interpretation and giving comments on the EEG waves will be take long time and a large amount of error can be arise in the diagnosis process. Additionally, some significant data will escape the attention.

In this work, delta waves have been transformed into triangular fuzzy sets in order to overcome the above-mentioned deficiencies and find values closer to the truth. In this way, it will be possible to obtain more real and easily interpretable data in the diagnosis and treatment of diseases which are related to sleep disorders and related diseases. Besides, various interpretations were made for diagnosis and treatment of sleep disorders by obtaining entropy and similarity analysis data from the obtained findings. In addition, by using the entropy analysis of delta waves, the relationship between epileptic patients and healthy individuals has been discussed.

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# A degenerate haptotaxis system arising in the modelling of cancer invasion

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Cancer cell migration is an essential stage in the development and expansion of tumours and their metastases. Once a tumour develops in some part of the body, it can grow and make its way through the surrounding tissue in order to reach the blood vessels. After transportation across the blood system and subsequent extravasation, further tumours thus emerge. This process is known as metastasis. Migrating through the extracellular matrix (ECM), the cells need to adhere to it for support and information exchange with their surroundings. Mathematical models of cancer invasion and their subsequent analysis and simulation can contribute to better understanding the involved biological phenomena and enable predictions about the development and the extent of a tumour. Therefore, they can suggest approaches to therapy improvements.

This talk is devoted to a class of strongly coupled PDE-ODE systems with tissue-dependent degenerate diffusion and haptotaxis that can serve as a model prototype for cancer cell invasion through the ECM. The talk covers both the modellings aspects and a discussion of the analytical challenges for this kind of non-standard degenerate systems for which the global existence of weak solutions was established. Moreover, some numerical simulations will be presented which illustrate a possible model behaviour in a two-dimensional setting. The numerical results recover qualitatively the infiltrative patterns observed histologically. They further allow to establish a qualitative relationship between the structure of the tissue and the expansion of the tumor, thus paying heed to its heterogeneity.

This is talk is based on joint work [1, 2] with Christina Surulescu, Alexander Hunt, and Aydar Uatay.

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