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ABSTRACTS

Nargiz Huseynova, Malahat Orucova Studing of the Exact Inverse Problem in Relative Potential and it is Solution	93
Simon Serovajsky, Daniyar Nurseitov, Syrym Kasenov, Rinat Islamov, Alexandr Ilin Control of the sequential treatment process of many antibiotics	95
Evgeny Ivanko Optimization heuristic for identification keys	97
Vladimir Jaćimović, Milica Kankaraš Influence of stochastic noise on bifurcations of stationary states in systems of ordinary differential equations	99
Milojica Jaćimović, Nevena Mijajlović Methods of Linearization for Solving Quasi-variational Inequalities	100
Vyacheslav V. Kalashnikov, Vladimir A. Bulavsky, Nataliya I. Kalashnykova Consistent Conjectures Are Nash Optimal Strategies in the Upper Level Game	101
Sergey Kalenkov, Georgy Kalenkov, Alexander Shtanko Hyper-spectral Fourier-holography of microobjects	103
Igor Kaporin Optimization of the aggregation cancellation fast matrix multiplication scheme	105
Alexander Kel'manov Some Euclidean discrete optimization problems and efficient algorithms with performance guarantees for their solutions .	106
Alexander Kel'manov, Sergey Khamidullin An efficient approximation algorithm for a sequence bi-partitioning problem	107
Alexander Kel'manov, Vladimir Khandeev An exact pseudopolynomial algorithm for a bi-partitioning problem	108
Ruben V. Khachaturov Lattice of Cubes, its basic properties and application in combinatorial optimization	110
Mikhail Khachay, Ekaterina Neznakhina k-Minimum Hamiltonian Cycles Problem. Complexity and Approximability	112
Elena Khoroshilova Terminal Control: Linear-Quadratic Case	114
Konstantin Kobylkin Covering algorithm for the simplest polyhedral separability problem	116

Control of the sequential treatment process of many antibiotics

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It is known that the effectiveness of the antibiotic treatment is reduced eventually. So the antibiotic should be replaced. We consider a mathematic model and control problem of the sequential treatment process of many antibiotics. Suppose due to mutations appear bacteria resistant to the action of this antibiotic. This bacteria class becomes the dominant if the organism is not cure. So the given antibiotic has already non-effective. The treatment continues with using another drug. If we abstain for some time from the treatment, then the sensitivity of bacteria to the initial antibiotic is gradually recovering because the general bacteria population is more viable than mutants.

Let us consider n different antibiotics. The system is described by functions $x_i, i = 0, \dots, n$. It characterizes the evolution of the bacteria number of i -th class, which are resistant to i -th antibiotic, where zero antibiotic is the absence of any drug. These bacteria are sensitive to all antibiotics. The treatment process is divided by sequential stages. It is possible that there exist stages without any drug. There are the stages with zero antibiotic. The considered system is described by the system of nonlinear differential equations

$$\dot{x}_i = \sum_{j=0}^n a_i^j x_j - b_i x_i \sum_{j=0}^n x_j - f_i^{u_k}(x_i), \quad i = 0, \dots, n, \quad t \in (t_k, t_{k+1})$$

at the k -th stage of the process, where t_k is the begin of k -th stage of the treatment, and u_k is a number of the used antibiotic.

We suppose the birth of mutants, which are resistant to each antibiotic, from each bacteria class. Therefore the first term at the right side of the equations (1) describes the augmentation of the number of i -th bacteria class by the natural birth rate and the mutations of other bacteria classes. The positive value a_i^j characterizes the birth rate of i -th bacteria class from j -th bacteria class. Besides the environment is bounded. So the real augmentation of bacteria number is decreased. This phenomenon is described by the second terms at the

right side of the equations (1). The positive number b_i characterizes the degree of the influence environment boundedness to the augmentation of number for i -th bacteria class. The third summands at the right side of the equations (1) that is the functions f_i^j describe the influence of j -th antibiotic to i -th bacteria class. It depends from the number of the considered bacteria class.

The parameters of the system satisfy some constraints. At first the natural augmentation of bacteria number is appreciably exceeded its augmentation by mutations. So the general bacteria population is more viable than mutants. The linear terms at the right side of the equations (1) correspond to the model of Malthus. It guarantees the exponential augmentation of bacteria population. The quadratic terms are typical for Verhulst's model. It realizes going to the stationary state of the system. This is the maximum of bacteria number, which can exist at this environment. Therefore the influence of the antibiotic has the degree of the augmentation more than two. So we use the formula $f_i^j(x) = c_i^j x^{\theta_i^j}$, where the parameter $\theta_i^j > 2$ describes the influence of the j -th antibiotic to the i -th bacteria class. The constants c_i^j satisfy the conditions $c_i^0 = 0$, $c_i^i = 0$ for all $i = 0, \dots, n$. Other parameters c_i^j are equal to $s_j d_i^j$, where s_j is the concentration of j -th antibiotic, and d_i^j is a positive number.

There is the general bacteria class only at the initial stage of the process, i.e. $x_0(t_0) = x_{00}$, $x_i(t_0) = 0$, $i = 1, \dots, n$. The infection of the organism is considered at the initial stage. So the antibiotic is not applied so far, i.e. $u_0 = 0$. Besides we change the drug at the each stage, i.e. $u_k \neq u_{k+1}$. The organism is reputed cured if the total bacteria number at a time T is not greater than maximal admissible value x_* .

We have the problem of choosing the optimal strategy of the treatment. It consists in the selection of the starting time of the stage of the treatment, the numbers of the antibiotics, and its concentration for each stage. We take into consideration that the large value of the antibiotic concentration invokes the intoxication of the organism. We use the experimental data of Scientific Center for Anti-infectious Drugs (Almaty).