Research Statement

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1 Overview

My research is in *mathematical biology*, which, in my understanding, is a mathematical field, where the research problems (mathematical) are prompted by various questions with biological motivation and/or background. Broadly speaking, I usually work with various dynamical system, both deterministic and stochastic, and therefore rely heavily on the theory of dynamical systems, stochastic processes, ordinary and partial differential equation, numerical analysis, and computer simulations.

Mathematical biology is a very broad field, and it can be classified further by the specific area of biology involved, or by specific mathematical tools used, or by the degree of *exactness* the abstract mathematical models approximate the reality. From a technical point of view, direct computation of the exact model of any phenomenon is practically impossible, and this implies that correctly reduced, albeit seemingly oversimplified, approximate models allow to address "right questions." In my work I am mostly interested in analysis of such kind of approximate models, which, albeit far from being an exact description of reality, still relevant to the original biological system. Here is a citation by James Murray (from his first volume of Mathematical Biology), one of the classics of modern mathematical biology:

> "There has been a considerable amount of study of systems where the community matrix has diagonal symmetry or antisymmetry or has other rather special properties, where general results can be given about the eigenvalues and hence the stability of the steady states. This has had very limited practical value since models of real situations do not have such simple properties. The stochastic element in assessing parameters mitigates against even approximations by such models. However, just as the classical Lotka–Volterra system is not relevant to the real world, these special models have often made people ask the right questions. Even so, a preoccupation with such models or their generalizations must be avoided if the basic aim is to understand the real world."

This citation succinctly justifies and highlights my interest in "these special models."

In this document I present in a nontechnical way a number of the most interesting, from my point of view, results that my co-authors and I obtained about some of "the special models" I worked with. Additional results, proofs, and general statements of the theorems can be found in the cited papers.

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2 Recent (and ongoing) projects

2.1 Heterogeneous populations and epidemics

Everyone is different. This simple fact should be included in our mathematical models to approximate the reality. There are various ways to include this inherent heterogeneity, the key and natural fact is that any attempt to formulate a more detailed mathematical model that includes a heterogeneous structure of a population usually yields a more complicated mathematical object to analyze. And yet in some cases quite full mathematical analysis is feasible, as I showed in a series of papers in which I analyzed a heterogeneous SIR model.

The tools that I use originated in late 80's and early 90's of the last century in the works of my collaborator Dr. Karev (e.g., [15]), who discovered that if we put some constraints on the form of analytical expressions for the birth and death rates of our mathematical models then there is an efficient way to reduce the dimensionality of the model and hence to analyze it. In 2004 in my first solo publication [22] I generalized this approach to the systems of equations (which, I must mention, was quite an obvious generalization) and applied this technique to analyze a distributed Lotka–Volterra model. Dr. Karev, Dr. Berezovskaya, Dr. Koonin and I collaborated on several projects, related to the theory of heterogeneous populations, that utilize the same original idea to formulate mathematical models. We studied the effect of cell heterogeneity on cancer cell dynamics [18], dynamics of rotifer populations under toxicant exposure [16], and analysis of replicator equations [17]. In 2008–2012 I published three papers [21, 23, 24] that for the first time used the same approach to analyze a heterogeneous SIR epidemic model, which is a very natural object for this framework.

Assume that the individuals of our population are different in their susceptibility to a particular disease. Then we can describe the epidemic spread in the population with the following system:

$$\partial_t s(t,\omega) = -\omega s(t,\omega) I(t), \quad \dot{I}(t) = \int_\Omega \omega s(t,\omega) I(t)\,\mathrm{d}\omega - \gamma I(t), \tag{2.1}$$

where ω is the distributed (discretely or continuously) parameter, Ω the set of admissible values of ω, $s(t,\omega)$ is the density of the susceptibles with parameter ω at time t. We need also the initial conditions

$$s(0,\omega) = s_0(\omega), \quad I(0) = I_0. \tag{2.2}$$

As formulated, problem (2.1)–(2.2) is an infinite dimensional dynamical system, and still its full analysis is possible. In particular, I proved in [23, 24]

Theorem 2.1. *Problem* (2.1)–(2.2) *is equivalent to a two-dimensional system of ODE*

$$\dot{S} = -h(S)I, \quad \dot{I} = h(S)I - \gamma I, \tag{2.3}$$

where the explicit form of nonlinear function h is given in [23] and is fully determined by the initial moment generating function for $s_0(\omega)$.

Having at my disposal Theorem 2.1, I proved in [23] that the final epidemic size can be found as a solution of a very compact equation, namely,

Theorem 2.2. *Consider model* (2.1)–(2.3). *Let M_0 be the moment generating function of the initial distribution of susceptibility. Then the final epidemic size $S_\infty = \lim_{t\to\infty} \int_\Omega s(t,\omega)\,\mathrm{d}\omega$ can be found as the root to*

$$S_\infty = S_0 M_0\left(\frac{S_\infty - N}{\gamma}\right). \tag{2.4}$$

Finally, I would like to mention one more result from [21, 23].

Theorem 2.3. *Consider model* (2.1)–(2.2) *and assume that initially the susceptibility to a disease is gamma distributed. Then system* (2.3) *takes the so-called power law form*

$$\dot{S} = -\beta S^p I, \quad \dot{S} = \beta S^p I - \gamma I, \tag{2.5}$$

where $\beta > 0$ *and* $p > 1$ *are determined by the initial conditions and parameters of the gamma-distribution.*

These three theorems (significantly more general statements can be found in the cited papers) illustrate nicely the general ideology of the theory of heterogeneous populations as I use it in my modeling projects. Using this theory I am able to achieve transparent analytical results that allow further insights into the disease dynamics (allow answering "the right questions" in the spirit of the citation above). For example, equation (2.4) was very carefully scrutinized in [19] with significant implications for vaccination strategies; system (2.5) provides a solution to a long standing problem of mechanical derivation of the power law transmission function in mathematical epidemiology; and system (2.3) contributes to the general idea that ODE models can and should be considered as a "correct" averaging through heterogeneous populations (see, e.g., [11, 13] for a discussion). My paper [23] was included in the F1000 database, in which senior scientists and leading experts in all areas of biology and medicine recommend the most important articles, rating them and providing short explanations for their selections.

I would like to note that models of the form (2.1)–(2.2) were studied in the literature for a while, however, the methods that had been employed for their analysis (general manipulation of the obtained equations, qualitative analysis of aggregate variables, moment closure approximations, etc) usually did not result in simple quantitative expressions similar to (2.3), (2.4), or (2.5). I was able to achieve a decisive progress through uniting the description of the epidemic process in the form (2.1)–(2.2) and the analytical power of the theory of heterogeneous populations.

Currently my graduate student and I have several ongoing projects that expand the results mentioned above. In particular, we are looking at the problems with several distributed and correlated parameters, at the systems with non-exponentially distributed infectious periods, and also consider the statistical problem of system's identification.

2.2 Replicator equation: Spatial structure

The so-called replicator equation arises in several evolutionary contexts (e.g., [30]) and takes the form

$$\dot{p}_i = p_i((\boldsymbol{A}\boldsymbol{p})_i - \boldsymbol{p}\cdot\boldsymbol{A}\boldsymbol{p}), \quad i = 1, \ldots, k, \tag{2.6}$$

where $\boldsymbol{p}$ is the vector of frequencies whose asymptotic behavior depending on the matrix $\boldsymbol{A}$ and initial conditions we need to determine. This is a classical object nowadays (e.g., [14]), however, using the methods of the theory of heterogeneous populations discussed in the previous section and the Newton polygon algorithm, developed by Dr. Berezovskaya, for studying the flow of a planar polynomial dynamical system in a neighborhood of a singular equilibrium, Dr. Karev, Dr. Berezovskaya and I were able to obtain several new results about solutions to the replicator equation [17]. Currently, together with Dr. Bratus and Dr. Semenov we study how the solutions of the replicator equation can be inferred from the geometric properties of the surface defined by the mean population fitness $\boldsymbol{p}\cdot\boldsymbol{A}\boldsymbol{p}$ [4].

A significant portion of my research was devoted to the specific question how to add a spatial structure to the replicator equation (2.6). The usual way of turning the dynamical system $\dot{\boldsymbol{n}} = \boldsymbol{f}(\boldsymbol{n})$ into the reaction–diffusion system is by adding the Laplace operator: $\partial_t \boldsymbol{n} = \boldsymbol{f}(\boldsymbol{n}) + \boldsymbol{D}\Delta\boldsymbol{n}$. Since the solutions to the replicator equation belong to the simplex S_n (i.e., $\boldsymbol{p} > 0$, $\|\boldsymbol{p}\|_1 = 1$), the same must be true for the distributed replicator equation, and this can be achieved in this simple way by adding the Laplace operator only if all the diffusion coefficients are the same. In case they are different something new is required. There exist several different approaches to study the replicator equation with explicit space. For example, Vickers and co-authors used the principle of local population regulation, such that the fitness values are adjusted such that the total local population size stays constant (e.g., [35, 36]). Another approach is by Cressman (e.g., [10]), in which he considered what can be called an open replicator system.

Dr. Bratus, Dr. Posvyanskii and I in a series of recent publications [5, 7, 6, 9, 28, 8] used the principle of global regulation to consider as a counterpart of (2.6) the following *spatial replicator equation*:

$$\partial_t p_i = p_i\Big((\boldsymbol{A}\boldsymbol{p})_i - f_0^{sp}(t)\Big) + d_i\Delta p_i, \quad d_i > 0, \quad i = 1, \dots, k, \tag{2.7}$$

where

$$f_0^{sp}(t) = \int_\Omega (\boldsymbol{p}\cdot\boldsymbol{A}\boldsymbol{p})\,\mathrm{d}\boldsymbol{x}, \quad \boldsymbol{x}\in\Omega.$$

For (2.7) we always have $\sum_i \int_\Omega p_i(\boldsymbol{x}, t)\,\mathrm{d}\boldsymbol{x} = 1$, and hence the solutions belong for all time moments to the integral simplex.

The key original question was to determine what new appears in (2.7) compare to the non-distributed case (2.6). In particular, we proved in [7] that it is possible to have spatially non-homogeneous equilibrium solutions. The methods we use are the standard methods of PDE analysis, which rely on the representation of the solutions as Fourier series through the eigenfunctions of Laplace operator, constructing Lyapunov functionals, and using various inequalities in corresponding metric spaces.

Theorem 2.4. *For system* (2.7) *to possess spatially inhomogeneous equlibrium solutions it is necessary that* (2.6) *has an equilibrium* $\hat{\boldsymbol{p}} \in \operatorname{int} S_n$ *and that the diffusion coefficients are sufficiently small.*

We also considered a special case of the autocatalytic system in [6], for which we proved

Theorem 2.5. *Consider system* (2.7) *with* $\Omega = [0, 1]$ *and* $\boldsymbol{A} = \operatorname{diag}(a_1, \dots, a_k)$. *Then there exists a spatially non-uniform solution to* (2.7) *if*

$$\sum_i \frac{d_i}{a_i} < \frac{1}{\pi^2}\,.$$

Summarizing a number of other results presented in [7, 6] we came to the informal conclusion that despite appearance of spatially non-homogeneous equilibrium solutions to (2.7) the behavior of the spatially distributed replicator equation (2.7) is qualitatively similar to to the solutions of the mean field model (2.6) in the sense that the interacting populations survive or go extinct in both models for that same parameter $\boldsymbol{A}$ irrespective of the diffusion coefficients d_i. On the other hand, it is well known that the spatial structure often mediates the coexistence of different populations in a community and therefore we were forced to modify our model to discover this effect.

The analogy with the diffusion equation in a porous medium motivated us to introduce the following model [9]:

$$\partial_t p_i = p_i\Big((\boldsymbol{A}\boldsymbol{p}) - f_1^{sp}(t) + d_i\Delta p_i\Big), \quad f_1^{sp}(t) = \int_\Omega (\boldsymbol{p}\cdot\boldsymbol{A}\boldsymbol{p} + \sum_i d_i p_i \Delta p_i)\,\mathrm{d}\boldsymbol{x}, \tag{2.8}$$

which we called the *replicator equation with the global regulation of the second kind*. Problem (2.8) is a very interesting (and much less studied than the semilinear reaction–diffusion systems) mathematical object with a lot of open mathematical questions. In [8, 9] we proved that for sufficiently large diffusion parameters d_i (note that the diffusion coefficients now depend on the concentrations) the behavior of solution of (2.8) is qualitatively similar to solution of (2.6) (which means exactly that in a well-stirred reactor the mean filed approximation is sufficient).

More importantly, we showed numerically in [9] and proved in [8] that for sufficiently small d_i the replicator equation of the second kind mediates coexistence of interacting populations. The key role in this is played by very special solutions that are non-zero only in some part of Ω. The proofs are quite subtle and technical and prompt for generalizations.

2.3 Eigenvalues of Eigen's quasispecies model

Eigen's quasispecies model has a unique position in mathematical biology, because not only it brings together mathematics and biology, but also attracts attention of theoretical physicists since it has been known for quite a while that this model is equivalent to the famous Ising model in statistical physics. Literally, hundreds of people contributed to the analysis of this model. Mathematically the analysis of this model boils down to determining the dominant eigenvalue and the corresponding positive eigenvector (that was called the quasispecies by Manfred Eigen, [12]). To be specific, I formulate two most used versions of this model. First, for the classical quasispecies model we need to compute the dominant eigenvalue and the corresponding eigenvector of the eigenvalue problem

$$\boldsymbol{Q}\boldsymbol{W}\boldsymbol{p} = \lambda\boldsymbol{p}, \tag{2.9}$$

where $\boldsymbol{W} = \mathrm{diag}(w_0, \dots, w_{l-1})$ is a diagonal matrix, and $\boldsymbol{Q}$ is a doubly stochastic matrix with the entries

$$q_{ij} = q^{N-H_{ij}}(1-q)^{H_{ij}}, \quad q \in [0,1],$$

where q is the probability of the error-free replication, N is the length of sequences, and H_{ij} is the Hamming distance between sequences i and j.

Second, the so called Crow–Kimura model, which has quite similar properties, for which we consider

$$(\boldsymbol{M} + \boldsymbol{\mathcal{M}})\boldsymbol{p} = \lambda\boldsymbol{p}, \tag{2.10}$$

where $\boldsymbol{M}$ is a diagonal matrix, $\boldsymbol{\mathcal{M}}$ is the mutation matrix, which depends on one parameter μ, which is the mutation rate.

The motivating question for me to start studying problems (2.9) and (2.10) was the fact that while biologists use freely the two most important concepts of the quasispecies theory (the notions of the quasispecies and the error threshold), mathematically we are still lacking efficient ways to calculate λ and $\boldsymbol{p}$ in many important cases. Dr. Bratus, Dr. Semenov and I published a series of papers [3, 31, 32, 33], in which we obtained a number of new results for both (2.9) and (2.10). I am very

proud that I was able to interest my coauthors in this problem by giving several initial talks during the years 2010–2011 in Moscow, Russia. I would like also to mention that I also benefited a lot from multiple conversations on this topic with Dr. Karev, Dr. Saakian, Dr. Wolf, and my postdoc mentor Dr. Koonin.

The original idea was quite naive, but it did lead to a significant progress. Matrices $\boldsymbol{Q}$ and $\boldsymbol{\mathcal{M}}$ have a very special structure and it is quite straightforward to show that they are diagonalizable and find a basis consisting of their eigenvectors. These computations can be done explicitly, because these matrices depend only on one parameter. We rewrote problems (2.9) (in [3]) and (2.10) (in [31]) in these eigenbases. This led, for instance, to a parametric solution for the vector $\boldsymbol{p}$ (see Section 5 in [3]) and to the speed of convergence of the eigenvector $\boldsymbol{p}$ to the limiting uniform distribution when $\mu \to \infty$. Let me mention one more specific result from [3], which was new; even more importantly, this result could not be derived with the existing approaches (notably, the maximum principle for the Crow–Kimura model).

Proposition 2.6 (Proposition 6.1 in[3])**.** *Assume that* $\boldsymbol{M} = \mathrm{diag}(0, 0, \ldots, 0, N, 0, \ldots, 0)$. *Then the following holds:*

$$\lim_{N\to\infty} \frac{\lambda(\mu)}{N} = \sqrt{\mu^2 + 1} - \mu. \tag{2.11}$$

The fitness landscape $\boldsymbol{M}$ here is of the form of the classical single peaked landscape, the main difference is that the fitness N corresponds to all the sequences that have the same number of 0 and 1 sites. A very important conclusion is that in this case there exists no error threshold because the dependence on μ is analytical for any $\mu > 0$.

In [31] Semenov, Bratus and I calculated, among other things, the exact expressions for $\lambda(q)$ and its first and second derivatives for the values of $q = 0, 1/2, 1$. Probably one of the most intriguing results in this paper is the one which we did not prove. Specifically,

Conjecture 2.7. *Consider problem* (2.9)*. Then the error threshold, if it exists, occurs at the critical mutation probability*

$$\hat{q} = \sqrt[N]{\frac{\lambda(1/2)}{\lambda(1)}} = \frac{1}{2}\sqrt[N]{\frac{\sum w_i}{\max\{w_i\}}}.$$

While the approach in [3] is elementary, the actual computations and estimates are often quite subtle and tedious. Dr. Semenov and I, while working on these computations, noticed that there is a much simpler heuristic approach to (2.10). Under some natural assumptions (Section 2 of [32]) we showed that problem (2.10) in the limit N of the sequence length can be rewritten as

$$\boldsymbol{m} \circ P(s) + \mu \mathcal{S}\, P(s) = \lambda P(s), \tag{2.12}$$

where $\boldsymbol{m} = (m_0, \ldots, m_N)$ is the fitness landscape, $P(s)$ is the unknown probability generating function for the eigenvector $\boldsymbol{p}$, $\mathcal{S}$ is a differential operator, $\mathcal{S}\, P(s) = (1-s^2)P'(s) - (1-s)P(s)$ and $\boldsymbol{m} \circ P(s) = \sum m_i p_i s^i$. Equation (2.11) allows an elementary approach to finding the leading eigenvalue and eigenvector of (2.10) for many interesting cases. For example, assuming that $\boldsymbol{m} = (N, 0, \ldots, 0)$ is the classical single peaked fitness landscape yields immediately

Proposition 2.8 (Example 3.1 in [32])**.** *Consider* (2.10) *for the single peaked landscape* $\boldsymbol{M} = (N, 0, \ldots, 0)$. *Then*

$$\lim_{N\to\infty} \frac{\lambda(\mu)}{N} = 1 - \mu, \quad \mu < 1,$$

and

$$\lim_{N\to\infty} p_i(\mu) = (1-\mu)\mu^i.$$

We still do not have a rigorous proof that our limiting procedure will always yield the correct results, however, a number of examples in [32] show that it is quite probable to be true (for two examples we actually have a proof, for the rest of them we presented numerical evidence).

In our most recent published paper [33] on the Eigen model Semenov and I returned back to the classical Eigen problem (2.9) and used geometric methods to analyze it. We introduced two major novel contributions. First, we considered the full permutation non-invariant model (vast majority of the existing approaches study the model where the fitness of a sequence is determined the number of zero and ones in it, and not by their order; we partially dropped this assumption). We introduced what we called the two-valued fitness landscape, for which the matrix $\boldsymbol{W}$ is given by $w_i = w + s$ if $i \in A$, and $w_i = w$ if $i \notin A$. We proved

Theorem 2.9 (Section 4 in [33])**.** *Consider the metric space $X = \{0,1\}^N$ of all the possible sequences of length N with the Hamming distance. Let G be a group acting on X by isometries and let A be a G-orbit. Then the algebraic equation for the leading eigenvalue λ has degree at most $N+1$ and can be written down in an explicit form (eq. (20) in [33]).*

This theorem, being probably a little more abstract than most biologically oriented studies of the Eigen model, shows that the underlying structure of the mutational landscape in the form of a hypercube actually is very important in our understanding of possible solutions. Namely, if the structure of the matrix $\boldsymbol{W}$ is somehow related to the group of isometries of the hypercube then some definite progress can be achieved in calculating λ and $\boldsymbol{p}$. Additionally, the language of the group theory gives us an opportunity to look at the phenomena, including the notorious error threshold, associated with the quasispecies model from a more general and abstract point of view.

Our second major contribution in [33] is an abstract generalization of the classical Eigen model to the general case of isometry groups acting on finite metric spaces. For instance, we considered in details in [33] what would happen if the classical hypercube of the Eigen model is replaced with a much more geometrically simple N dimensional simplex (when the distance of any vertex to any other is equal to one). We proved that in this case the leading eigenvalue solves an algebraic equation of degree 2. A quite abstract and far reaching generalization is presented in just finished project [34].

Concluding this section I would like also to mention that Dr. Bratus, Dr. Hu, graduate student Safro and I used the approach of global regulation that I discussed in Section 2.2, to analyze a spatial quasispecies model in [2]. We found that taking into account the process of the global regulation does not lead to drastic qualitative changes in the behavior of solutions, and asymptotically solutions tend to the same equilibrium quasispecies vector $\boldsymbol{p}$.

3 Other topics

The topics that I mentioned in Section 2 occupied my research for the most of last decade. For all of them I have ongoing research projects. Here I would like to mention briefly several other research projects, most of which were accomplished during my postdoc years 2004-2009 at NIH.

In [26] Dr. Karev, Dr. Koonin and I reconsidered and generalized stochastic model, initially suggested in [1], to model the horizontal gene transfer. We introduced into the model the processes of

"immigration," i.e., the process of interpopulation gene transfer and showed, contrary to the original conclusion in [1], that horizontally transferred genes can be maintained in a significant part of the population even if being neutral or slightly deleterious.

In [18, 25] Dr. Berezovskaya, Dr. Karev, Dr. Koonin and I generalized the model suggested in [37] to study the interactions of oncolytic viruses and cancer cells. Mathematically, we considered the so-called ratio dependent functional response that leads to a singular equilibrium at the origin. We proved that such, quite natural, modification leads to the regimes of cancer cell extinction within the framework of deterministic model. In [18] we also showed, mostly using numerical experiments, that tumor cell heterogeneity can lead to various nonlinear effects, including quasi-random behavior.

In [20, 27, 29] Dr. Wolf, Dr. Koonin and I comprehensively reviewed and studied the problem of the origin of the standard genetic code. This project was quite different from other ones I took part in, since it mostly relied on evolutionary simulations (and included more statistical analysis than any other of the projects I participated in). In particular, we showed that the standard code appears to be the result of partial optimization of a random code for robustness to errors of translation. In [27] we put forward and supported the hypothesis that the original two-letter genetic code possessed an extremely high degree of robustness to errors of translations.

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