Research Statement

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My graduate study originally focused on low-dimensional topology and knot theory. Supervised by topologist Xiao-Song Lin, I obtained some results about invariants of 3-manifolds and knots derived from Hopf algebras and representations of braid groups. However, it was at that time that I decided to use mathematical knowledge to solve biological problems. On my road to applied mathematics, particularly, mathematical modeling of biology medicine, I had made an extensive exploration. And my research turned out to cover a diversity of areas. In order to study coalescent theory in molecular evolutionary biology, I studied stochastic processes, and did some work on Markov processes and coalescent theory. My Ph.D thesis was on a new type of algebra, evolution algebra, which I defined inspired by genetics. After graduation, I conducted a postdoctoral fellowship supported by the National Science Foundation (NSF) at the Mathematical Biosciences Institute (MBI). At the MBI, in collaboration with applied mathematician Avner Friedman and physician E. Antonio Chiocca, I started to use partial differential equations to model brain tumor growth and virotherapy. Since then, understanding the mechanisms of establishment and destruction of cancers has become one of my major professional interests, and it initiated my studies including dynamics of infectious diseases and stem cell modeling. Upon finishing the three-year postdoctoral research, I moved to the Department of Mathematics in the College of William and Mary (WM). At WM, I established a stem cell research project with biologists Ting Xie at the Stowers Institute for Medical Research and Angelique Bordey at Yale University and applied mathematician Philip Maini in the Centre for Mathematical Biology (CMB) at the University of Oxford; I expanded my research group through a joint graduate education project with my collaborator in the Department of Mathematics and Statistics at the Old Dominion University (ODU); I also formed a undergraduate interdisciplinary teaching group with three biology faculty members on WM campus. About eleven years ago, I realized guiding and working with graduate students is a very important part of academic life, and then I decided to move to a research department where I can have my own graduate students. In 2014, I moved to the Department of Mathematical Sciences at New Mexico State University (NMSU). At NMSU, I have developed projects with Physician Eric Holland in the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, established my research group which has graduate students, visiting scholars, and undergraduate research students, and have been holding the weekly Math Biol Seminar which is open to the whole university since 2016. Recently, Physician Eric Bartee from the Medical School at University of New Mexico (UNM) contacted me to initiate projects on oncolytic crash and potassium function in viral therapy. The last January, I started a project on optimization of CAR T cell therapy with Physician Cameron Turtle in Fred Hutch now in University of Sydney.

Since 2004, I have published one research monograph in the series of Lecture Notes in Mathematics of Springer, 53 research papers, edited one journal issue, and 10 manuscripts under review or in progress, 1 book project in preparation, and 6 preprints. Some of my work are widely cited worldwide and some has become a sub-field of mathematics. Currently I have seven research projects, (**1**) collective dynamics of solid tumors and their microenvironment: collaborating with Eric Holland in Fred Hutch and Philip Maini at the CMB Oxford, one sub-project was funded by the National Institute of Health (NIH), we are currently working on two sub-projects: OPN functions and abscopal effects; (**2**) Brain tumor growth with therapies and virotherapy: collaborating with E. Antonio Chiocca at the Harvard Medical School and Avner Friedman at OSU, one sub-project was funded by NSF, we are currently working on the project of oncolytic crash initiated by Eric Bartee at the Medical School UNM since July 2021; (**3**) potassium in tumor growth and viral infection: this is a new project also initiated by Eric Bartee at UNM since September 2020, we finished one sub-project; (**4**) optimization of CAR T cell therapy: in January 2022, I started to develop this project with Cameron Turtle and work on a grant proposal; (**5**) stem cell biology: collaborating

with Ting Xie at Stowers Institute, Angelique Bordey at Yale, Philip Maini at the CMB Oxford, and Jie Zheng in Shanghai Tech University; (**6**) disease ecology: collaborating with Jingan Cui in Beijing University of Architecture and Civil Engineering, a part of which was supported by National Nature Science Foundation of China; (**7**) developing analysis methods for the qualitative study of Ito stochastic differential equations.

In fall 2018, I was leading a 10 million dollar proposal to establish "Southwest Institute for Mathematical Biology"which was submitted to NSF-Simons Foundations with three institutions: NMSU, University of Texas at El Paso, and New Mexico Institute of Mining and Technology. Although it was not funded, we developed some research and education projects among 11 faculty members in the southwest area. In August 2020, we submitted a three million dollar proposal Modeling "Public Health Disinformation Evolution and Intervention Impacts in a Mid-Size Southwestern City"to DOD with colleagues from Computer Science, Sociology, and Mathematical Sciences departments in NMSU, where we were able to apply mathematical analysis to discrete space although it was not funded. I was awarded the "Outstanding Faculty Award in Creative Activity/Scholarship"of the College of Arts and Sciences in NMSU 2017. In what follows I will briefly summarize my accomplishments in two groups, current research and past research.

1.1 Brain tumor growth with therapies and virotherapy

When I was a postdoctoral fellow at MBI, I started to model brain tumor growth and oncolytic viral therapy with Avner Friedman and E. Antonio Chiocca. Recently, medical professor Eric Bartee contacted me to study the oncolytic crash phenomenon observed in his experiments. With collaborators and students, I have published 20 articles [17-23, 25-26, 29-30, 32, 38-41, 46, 51, 54-55], and one manuscript [59] in preparation ([x] indicating papers listed in my CV, and they are available on my homepage https://web.nmsu.edu/ jtian/). *Some of our work have been widely cited* by both medical researchers and mathematicians from many institutions such as Northwestern University, Harvard University, New York University, Cornell University, Vrije Universiteit Amsterdam, University of Cambridge, Cancer Research UK Clinical Center, etc.

Glioma is the most serious of malignant brain tumors. In order to improve the efficacy of therapies, it is important to understand tumor progression. We first studied glioma progression under virotherapy. Virotherapy is a promising treatment. However, most experiments of virotherapy conducted on mice show a lack of efficacy in eradicating tumors. This failure has mostly been attributed to interference by the immune system. An immunosuppressive agent cyclophosphamide (CPA) can reduce the percentage of immune cells. To determine how different

protocols of CPA treatment and the burst size of the virus affect tumor growth, we introduced a mathematical model in collaboration with physician Chiocca's group. Mathematically, our model is a free boundary problem with five nonlinear partial differential equations. A detailed numerical analysis of this type of problem was done in [20]. Biologically, we showed that the diameter of the glioma will decrease to 1 mm if the burst size of the virus is three times the size seen in experiments, and that the effect of repeated CPA treatment is to maintain a low density of uninfected cells in the tumor, thus reducing the probability of migration of tumor cells to other locations in the brain. These predictions were further confirmed by new experiments further conducted by Chiocca's group. The research was published in the journal **Cancer Research** [19]. We have also finished a study of an ODE version of this model with emphasizing periodic behaviors of solutions [25].

To have a clear dynamical picture of tumor virotherapy, I did a mathematical analysis of the basic common model for virotherapy in [26]. The analysis shows the replicability of oncolytic virus is a critical parameter. However, the timing of the intracellular process of viral infection plays an important role as shown in some experiments. We have to incorporate this process in the mathematical model as the lytic cycle parameter. In [29], we found such a rich dynamical behaviors involved in virotherapy. The lytic cycle can induce backward Hopf bifurcations, and we extended these studies in [32] and [41]. We obtained a functional relation between viral burst size and lytic cycle. Because two different immune systems, innate and adaptive, have different effects in virotherapy, we proposed PDE systems to study them in [38-39], and obtained some balance conditions. Combining timing and spatial distributions, we recently formulated a model of functional PDEs for oncolytic virotherapy which incorporates virus diffusivity, tumor cell diffusion, and the viral lytic cycle. Our analysis shows that the model has similar qualitative behaviors as ODE models but the conditions have medical implications [40]. The complexity of oncolytic virotherapy arises from many factors. In a recent study, we incorporate environmental noise and stochastic effects into our basic deterministic model and propose a stochastic model for viral therapy in terms of Ito SDEs [51]. We show that there are three ergodic invariant probability measures which correspond to equilibrium states of the deterministic model, and the extra possibility to eradicate tumors due to strong variance of tumor growth rate and medium viral burst size. To obtain deep insights to both innate and adaptive immune systems with noise effects, we proposed a 4-dimensional Ito SDE model and obtained very interesting new phenomena, namely, stochastic Hopf bifurcations without parameters [54-55] which is the first time this has been observed in Ito stochastic differential equations.

Traditional treatments of tumor are resection, then radiotherapy and chemotherapy. In order to find an optimal combination of these treatments for patients who have glioma, we developed a mathematical model for glioma prognosis, which incorporates radiotherapy and chemotherapy (treatments of temozolomide) after resection (published in **Journal of Neuro-Oncology** [21]). This is a free boundary problem with three nonlinear partial differential equations. With my undergraduate research student Dian Yang, we have done some mathematical analysis on this model in [30]. With two undergraduate students Kendall Stone and Tomas Wallin, we finished a study of the ODE version of this model. We found a weak solution for different treatments, and made some suggestions for treatments based on our study [23]. Recently, we proposed and analyzed a functional reaction-diffusion system for tumor radiotherapy [46].

The effect of medical treatments of tumors only lasts for a period of finite time. Thus, when dynamical systems that describe the tumor dynamics are disturbed by therapies, these perturbations are actually finite-time perturbations. In paper [22], we did a general study of finite-time perturbations of dynamical systems. Under certain conditions, we showed that finite-time perturbed dynamical systems are asymptotically equivalent to unperturbed dynamical systems. This means the tumor eventually comes back and grows if the treatment cannot cure it within a period of finite time.

Recently, Eric Bartee's lab showed that the induction of anti-tumor immune responses during

myxoma virus therapy for skin cancer melanomas is dependent on the initial dose of virus used in the treatment and that this dependence is mediated by some event that occurred early after treatment. Their subsequent studies show that immediately after treatment (16-24 hours) tumors display large numbers of discrete viral infections. However, rapidly thereafter (48-72 hours) a large majority of these infections are lost (the ones which remain do expand out). We have termed this phenomenon oncolytic crash. We hypothesize that the dose dependence of oncolytic therapy is due to the fact that the vast majority of viral infections are rapidly lost after treatment which forces to use a huge amount of virus initially to establish a very few actually progressive infections. To understand oncolytic crash, we are trying to build this hypothesis into a two-stage model where the first stage has 6 variables and the second has 8 variables, a two-stage free boundary problem. We are working on this project currently [63].

The recognition of data patterns of gene expression relating to tumorgenesis is very important. Working with other colleagues, we used computational statistics to study these patterns in [17-18].

1.2 Collective dynamics of solid tumors and their microenvironment

Tumor initiation and growth have strong interactions with the microenvironment. Several years ago, I started to work with Holland's lab in Fred Hutch on tumor modeling in a variety of environmental factors. We published 7 articles [42-43],[45], [48-49], and [52-53], submitted 1 paper [56], and have 2 manuscripts [61-62] in preparation.

Tumor-infiltrated immune cells compose a significant component of many cancers. They have been observed to have contradictory impacts on tumor growth. Although the primary reasons for these observations remain elusive, it is important to understand how immune cells infiltrating into tumors is regulated. Based on our experimental results, we proposed a model of PDE free boundary type where immune cells migrate into the tumor. Combining experiments with computations, we concluded that the chemoattractant gradient field produced by tumor cells may facilitate immune cell migration to the tumor site, the chemoattractant production rate may be utilized to classify wtIDH1 and muIDH1 tumors, and the dynamics of immune cells infiltrating into tumors is largely determined by tumor cell chemoattractant production rate and chemotactic coefficient. Our major results were published in **Neoplasia** [43], and our numerical analysis of the model was published in [42]. To gain deep understanding of tumor cell chemoattractant production rate and chemotactic coefficient, we varied these two parameters with noises and proposed a system of Ito stochastic differential equations (SDEs). This analysis confirms our numerical studies [52]. Immune cell migration to tumor site was modeled as chemotaxis. To learn such mechanics, we conducted a study about stochastic PDE system of chemotaxis in [48]. Ostepontin (OPN) has been a topic in Holland's lab, and we are currently numerically studying a free boundary problem with 6 PDEs describing OPN dynamics [62].

Glioblastomas are highly malignant brain tumors. Knowledge of growth rates and growth patterns is useful for understanding tumor biology and planning treatment logistics. Based on untreated human glioblastoma data collected in Norway, we first fitted the average growth to a Gompertz curve, then found a best fitted white noise term for the growth rate variance. Combining these two fits, we obtained a new type of Gompertz diffusion dynamics, which is a stochastic differential equation. Newly collected untreated human glioblastoma data in US re-verified our model. Instead of growth curves predicted by deterministic models, our SDE model predicts a band with a center curve as the tumor size average and its width as the tumor size variance over time. Given the glioblastoma size in a patient, our model can predict the patient survival time with a prescribed probability. The survival time is approximately a normal random variable with simple formulas for its mean and variance in terms of tumor size. Our model can be applied to studies of tumor treatments. As a demonstration, we numerically investigated different protocols of surgical resection using our model and provide possible theoretical strategies. Our work was published in **Scientific Reports** [49]. We also conducted detailed analysis of this SDE [53]. Tumor shape has

great impact on its growth dynamics. We study this aspect in [45], and incorporate clinical data in [61].

Cervical cancer is the second most common form of cancer worldwide. Human papilloma virus (HPV) can be sexually transmitted. Genital HPV is the major etiologic factor in cervical cancer. But most women infected with HPV, even those infected with the types that are most closely associated with cervical dysplasia, will not develop invasive cervical cancer. Unlike normal cells, HPV-infected cells undergo differentiation and remain active in the cell cycle. The presence and persistence of viral DNA in lesion sites is a necessary condition to establish an epidemiologically evident tumor. Malignant progression is slow; it may take decades to develop a visible cancer. To understand how HPV infection leads to cervical cancers under environmental factors, we proposed a system of Ito stochastic differential equations based on a deterministic model in [56].

1.3 Disease ecology and infectious diseases

Mathematical ecology is a classical field. However, there are still many new problems that require further study. Disease ecology merges key ideas from ecology, medicine, genetics, immunology and epidemiology to explore interactions that lead to the occurrence and evolution of disease within entire ecosystems. It is of global importance. In this aspect, I have published 8 papers, [24], [27], [33], [35-37], [44], and [50], and 1 manuscript submitted [57].

Cholera is an ancient disease that continues to cause epidemics and pandemics despite ongoing efforts to limit its spread. The present pandemic started in Indonesia in 1961. It spread into Europe, South Pacific and Japan in the late 1970s. In the 1990s, the cholera spread in South America. Recently, there have been many outbreaks round the world. To understand the dynamics of cholera, we conducted global stability analysis for several existing deterministic cholera epidemic models. These models, incorporating both human population and pathogen V. cholerae concentration, constitute high dimensional nonlinear autonomous systems. We employed three different techniques, monotone dynamical systems, geometric approach, and Lyapunov functions, to investigate the endemic global stability for several biologically important models in [27]. With a graduate student, we have proposed some control strategies in cholera modeling in [33]. Inspired by some models for cholera dynamics with time periodic parameters, I studied such non-autonomous systems, and found several new results on classical Floquet theory in [35]. For example, for the stability of periodic solutions to autonomous differential equations and non-autonomous periodic systems, we gave some results for the Poincaré map and the linearizations around periodic solutions, and some results on Floquet exponents of delay linear periodic systems. Based on our deterministic models, we propose a stochastic model for cholera epidemics incorporating environmental fluctuations, which is a nonlinear system of Ito SDEs [49]. We defined the **basic stochastic reproduction value** R_s, which determines the dynamical patterns of the stochastic model. When $R_s < 1$ with probability 1, the cholera infection will be extinct within finite periods of time almost surely. When $R_s > 1$ with probability 1, the cholera infection will persist most of the time, and there exists a unique stationary ergodic distribution to which all solutions of the stochastic model will approach almost surely as noise intensities are bounded. When the basic reproduction number R_0 for the corresponding deterministic model is greater than 1, and the noise intensities are large enough such that $R_s < 1$ with probability 1, the cholera infection is suppressed by environmental noise.

The pandemic of avian influenza seems possible almost in every winter. The scientific community is focusing on experimental research of all kinds of different candidates of avian influenza viruses. H5N2 is one such candidate. Based on observations and experimental data, we put forward two deterministic models (each with thirteen nonlinear ordinary and partial differential equations) to study the evolution and dynamics of H5N2. The models incorporate mutation from low pathogenic avian influenza viruses to high pathogenic counterparts, and also incorporate the spreading into human population. We tried to answer several questions posed by a experimental

group in the Netherlands. They are different from traditional SIR or SI models. We did numerical study of the PDE version of our model in [24] and [36]. We also conducted studies on a minimal model of plankton systems with a new feature of spatial diffusion and maturation delay in [37]. Recently, we conducted a general study about how asymptomatic transmission shifts epidemic dynamics [44].

1.4 Modeling of stem cell regulation

Understanding of stem cell regulation is fundamentally important for medical uses of stem cells and tumor initiation. To study regulation of stem cells via physical interaction, I collaborated with Ting Xie at Stowers Institute for Medical Research. Particularly, we focused on the mechanism of Drosophila female germline stem cells competing for niche space and how one cell is physically pushed out of the niche, which will then have a high possibility of becoming a cancer stem cell. We published a preliminary study in [28]. To study the regulation of stem cells via signaling molecules, we collaborate with Angelique Bordey at Yale School of Medicine. Particularly, we focus on the signaling molecules GABA, glutamate, and Shh in the niche subventricular zone of human neural stem cells, which has important features related to cancer stem cell initiation. Working with Philip Maini, we are finalizing a manuscript [64]. We recently started to a study of neurons transportation in subventricular zone, which may need our studies in [31] and [34].

My honors student Brian Waldman at WM did some numerical research on periodic behavior of intestinal stem cells by using delay differential equations in his honors thesis.

1.5 Function of potassium in viral infection and virotherapy

We started this project in September 2020. Critical ions used by the body to maintain cellular membrane potential. Extracellular potassium K^+ levels are extremely low while intracellular K^+ levels are extremely high. In Bartee's lab at Medical School UNM, they use myxoma virus to infect normal rabbit skin. The virus kills the cells in the middle of the lesion. This killing releases the intracellular K^+ thus increasing the extracellular K^+. The increased extracellular K^+ has the chance to negatively impact viral replication. This is an important question in oncolytic viral therapy. However, there is little research on potassium functions in viral infection. We use mathematical modeling to figure out if there are theoretical conditions for the death of cells and the clearing of K^+ under which extracellular K^+ would build up to a level high enough to inhibit myxoma virus replication. I build a mixed PDE-ODE system for this problem. We conducted experiments with rabbit, and in the same time, we conducted detailed numerical studies of the mathematical model to verify with experimental results. In August 2022, we submitted our first manuscript [47], which is now published the **Journal of Virology**. We plan to continue this study to find if there is a threshold value for potassium functionality.

1.6 Optimization of CAR T cell therapy

Chimeric antigen receptor (CAR) T cell therapy has been in development for more than two decades. Recent US FDA approval of BCMA-targeting and CD19-targeting CAR-T cell therapies for certain relapse/refractory hematologic malignancies have energized the field. Many other CAR-T cells targeting various antigens are in clinical trials to treat various human diseases such as cancer, infectious diseases, autoimmune diseases, cardiac diseases etc. However, not all clinical trials have achieved expected results. The challenge is to identify mechanisms which determine CAR-T cell expansion and persistence, the durability of antitumor response produced by CAR-T cells, and toxicities caused by the treatment. Current research has accumulated a large amount of discrete experimental and clinical data on each step of CAR T cell therapy, and each data set may reveal some aspect of one step of CAR T cell therapy. But, it is difficult to recognize mechanisms behind these discrete data for the whole treatment process and challenge to predict outcomes of

CAR T cell therapy based on these discrete bits of knowledge, let alone to achieve optimal benefits for patients. These steps are distinct in time and spatial scales, and importantly, are dynamic in time and space. Therefore, it is clear that the discrete experimental and clinical trial data call for a collective study on dynamics of CAR T cell therapy in order to optimize it. Collaborating with Frederick Locke at Moffitt, we plan to use a combination of mathematical modeling and medical experiments and clinical trials to study the collective dynamics of CAR T cell therapy in order to attain optimal protocols for treatment. Our plan consists of five stages: the first three stages are to construct mathematical models for three basic processes of CD19 CAR T cell therapy for local optimization - ex vivo CAR T cell expansion, interaction of CAR T cells, cancer cells, and endogenous immune cells, and inflammatory process induced by CAR T cells, the fourth stage is to integrate these three processes into a theoretical framework combining pharmacokinetics of lymphodepleting chemotherapy and consolidative therapy for global optimization, and the last stage is to extend this framework to CAR T cell therapy targeting other cancer antigens. To start, we are working on identification of patient variabilities with different noises using stochastic differential equations [58], and prepare a grant proposal.

1.7 Stochastic differential equations

The subject of SDEs is interesting in theory and applications. The basic theory was established in the 1950s, and the theory is still in development. For systems of ODEs, there are well-developed tools to analyse their local and global behaviors of the solutions. There are concepts, for example, maximal interval of existence of solutions, equilibrium points, stability of solutions, and there are theorems, for example, Hartman-Grobman Theorem, center manifold theorem. For SDEs, there are concepts and theorems which are corresponding to those in ODEs. For instance, ergodic invariant measures correspond to equilibrium points. However, it is difficult to prove existence of ergodic invariant measures for a given SDE system in some domains, in general. Systematic methods for analysis of SDEs are still lack although some partial results and tools have been developed. For example, for Kolmogorov type of SDE systems with non-degenerated noise, there are some results about existence of ergodic invariant measures under certain conditions. In our research on Ito stochastic differential equations, we have constructed stochastic Liapunov functions to prove existence of ergodic invariant measures, and boundary analysis for some SDE systems with certain boundaries; for noise degenerated problems, we use the Hörmander Theorem to study hypoellipticity and transition probability density functions, and apply some knowledge from control theory and support theorem (Stroock-Varadhan support theorem) to study the supports of invariant measures. We plan to develop systematic methods to qualitatively analyse SDEs, which we hope it will become a tool box for researchers to use in their study of stochastic models. In a four dimensional SDE system, we discovered Hopf bifurcation without parameters which is the first time to obtain in Ito SDEs, for which we termed as stochastic Hopf bifurcation without parameters [54-55]. For one dimensional SDEs, we obtained a complete classification and easy-check criterions for long-term behaviors of the solutions [60]. I have a book project about SDEs and applications with AMS.

From application perspective, stochastic differential equations not only offer a broad spectrum for interpretations, but also provide a way to construct more realistic models for the real-world. Deterministic ODE models may model the averages of variables (for example, populations), while SDE models may model each variable (for example, individuals). For stable stochastic dynamics, there is an ergodic invariant measure. In theory, we can have the distribution function, the expectation and variance for interpretation of the results. If the ergodic invariant measure is not explicitly obtained, we can run numerical simulations with the same initial condition for any numbers of times to get an approximation of the distribution, expectation, and variance. Even for transient stochastic dynamics, we can define relevant stopping times. Then, we can perform numerical simulation with the same initial condition for any numbers of times, and

obtain approximations of probability distributions for the stopping times. That will provide the information for interpretation of the results. We did some in silicon clinical trials using this scheme and tried to understand patient variability [56].

2.1 Research in low-dimensional topology and knot theory

During the first several years of my graduate study, my focus had been directed towards low-dimensional topology and knot theory. In order to understand the quantum invariants of links and 3-manifolds defined without representations of quantum groups, I gave a method to construct them, and made a detailed comparison of all methods of defining invariants without representations. We concluded that, essentially without representations of quantum groups, there is only one family of invariants that can be constructed. I published three papers on those results [8-10].

Since Reshetikhin and Turaev constructed invariants of links and 3-manifolds and established the equivalence of tensor categories and 3-dimensional topological quantum field theories, the representation theory of Hopf algebras, particularly, quantum groups, has become an important tool in the study of low-dimensional topology. However, the necessity of representation theory can be obliterated, since, in a sense, the objects and their representations are equivalent. Actually, there is some work already done in this direction. Hennings was the first to use quasitriangular ribbon Hopf algebras and their right integrals to directly construct invariants for colored framed links and 3-manifolds. Then, Kauffman and Ohtsuki modified Henning's method and defined so-called universal invariants of framed links and 3-manifolds. In my study, we first explored if there is any alternative approach to construct invariants without representations. To do this, fixing a ribbon Hopf algebra, we defined an algebraic tensor product space and a formal tensor space, whose elements may be regarded as homogeneous tangle diagrams. Then we constructed a map from the algebraic tensor product space to the formal tensor space under certain conditions. This map gives a regular isotopic universal invariant of homogeneous tangles. By a linear map on the algebra, we defined a topological invariant of the 3-manifold obtained by surgery along the framed link. Thus we found another way to construct invariants of links and 3-manifolds without representations. These results was published in [8]. Secondly, we carried out a comprehensive comparison among all the work that had been done in this direction. An interesting result I obtained is that there is an accompany algebra for every unimodular quasitriangular ribbon Hopf algebra which is also the same type algebra. This intrinsic property of Hopf algebras helps to reveal relations among invariants defined by Hennings, Kauffman and Radford, Ohtsuki and us. That is, these four approaches and their results are equivalent, if the difference by a constant or accompany is ignored. Our conclusion is that there is only one family of invariants of links and 3-manifolds that can be constructed without representations of quantum groups [9].

One problem remained — what is the difference between invariants derived with and without braid group representations? To figure out this difference, we turned to the fundamental algebraic structure behind 3-manifold theory: braid groups. The smooth manifold of the representation variety $R = R(F_n, G)$, where G is a semisimple compact Lie group, can be obtained by taking braid group B_n as a subgroup of $Aut(F_n)$. This manifold gives a representation of $Aut(F_n)$, or B_n on the diffeomorphism group of R, which is a linear representation of B_n on Lie algebra of R along a fixed path. By taking Lie group $SU(2, C)$, the Burau representation is obtained on the complex part of the Lie algebra. After taking a product manifold of the representation space, $SU(2, C)^n$, we got a new family of representations of braid groups on the tangent bundle of this product manifold which is a generalized Long's structure [10]. An interesting case is in my preprint [6].

It is interesting to find relations between braid groups and evolution algebras. My honors student Carolyn Troha at WM did some exploration about the relations in her honors thesis.

2.2 Algebraic structures from genetics

This research was motivated by a study of algebras in genetics including Claude E. Shannon's Ph.D thesis and coalescent theory. It occurred to me that a coalgebraic structure of genetic inheritance exists when we look at Mendelian genetics reversely from progeny to parents. For non-Mendelian genetics, we defined a new type of algebra, evolution algebra. It was published as a research monograph in the series of Lecture Notes in Mathematics of Springer [1], and other related publications are [2-6]. I also have an invited expository article on evolution algebra [7]. These algebras have raised interests among pure and applied mathematicians. Particularly, ***evolution algebra has become a sub-field in mathematics***. There were international workshops and winter schools held on evolution algebras in Europe and America (for example, some links listed on https://web.nmsu.edu/ jtian/e-algebra/e-alg-index.htm); many research papers were produced to study evolution algebras (there are more than 250 papers in MathSciNet), several Ph.D theses and honors theses studied evolution algebras; my monograph was adopted as research text in some colleges and universities, for example, in Reed College and UC Irvine; some paper even starts to study the history of evolution algebra.

The importance of these algebraic structures is twofold. From the biological viewpoint, genetic coalgebra models genetic processes back in time, which is helpful in building phylogenetic trees for a given population. Evolution algebra models non-Mendelian inheritance process in time, for example, organelle inheritance, which can produce a long-term distribution of a given non-Mendelian heredity process. These algebras reveal new mathematical structures in genetics. From the mathematical viewpoint, genetic coalgebra is an example of coalgebra from natural science, while evolution algebras are non-associative and non-power-associative Banach algebras from natural science. What makes the theory of evolution algebras different from the classical theory of algebras is that in evolution algebras, there are two different types of generators: algebraically persistent generators and algebraically transient generators, and evolution algebras possess an evolution operator which reveals the dynamical information of evolution algebras. These notions of mixture of algebra and analysis make evolution algebras a sub-field of mathematics with its own value. In addition, evolution algebras have connections with several sub-fields in mathematics, for example, graph theory, group theory, Markov chains, dynamical systems, knot theory, 3-manifolds, and the study of the Riemann-zeta function (the Ihara-Selberg zeta function), and could be a unified tool for studies in these fields.

Coalgebraic structure of genetic inheritance: The coalgebraic structure of genetics, which we called genetic coalgebras, exists when we consider multiplication in the direction from progeny to parents. The coalgebraic structure is not the dual coalgebraic structure and can be used in the construction of phylogenetic trees. Mathematically, to construct phylogenetic trees means to solve equations of principal or plenary powers $x^{[n]} = a$ or $x^{(n)} = b$. This is generally impossible in algebras. However in coalgebras, we can solve them in the sense of tracing back for their ancestors. In paper [2], we developed a theoretical framework of coalgebraic structure of genetics. From the view of genetics, we introduced a series of fundamental algebraic concepts and examined their properties which are of genetic significance.

Evolution algebra: In my book *Evolution Algebras and Their Applications*, we introduced a new type of algebra, evolution algebras. Evolution algebras were motivated by evolution laws of genetics. We view alleles (or organelles) as generators of algebras, and define the multiplication of two "alleles" G_i and G_j by $G_i \cdot G_j = 0$ if $i \neq j$. However, $G_i \cdot G_i$ is viewed as "self-reproduction", so that $G_i \cdot G_i = \sum_j p_{ij} G_j$, where the summation is taken over all generators G_js. Then, the reproduction process in genetics is represented by multiplication in algebras. Evolution algebras are commutative, but not necessary associative. When the p_{ij}s are Markovian transition probabilities, the properties of algebras can be associated with properties of Markov chains. Markov chains allow us to develop algebras at deeper hierarchical levels than standard algebras. Introducing several new algebraic concepts, algebraic persistency, algebraic transiency, algebraic periodicity, we establish hierarchical structures for evolution algebras in Chapter 3. The analysis developed

in this book, particularly in Chapter 4, enables us to take a new perspective into Markov process theory and to derive new algebraic properties on Markov chains at the same time. We see that any general Markov chain has a dynamical hierarchy and the probabilistic flow is moving with invariance on this hierarchy, and that all Markov chains can be classified by the skeleton-shape classification of their evolution algebras. When we apply the algebras back to non-Mendelian genetics, such as organelle heredity, we can not only explain a puzzling feature of establishment of homoplasmy from heteroplasmic cell populations and the coexistence of mitochondrial triplasmy, but also predict mechanisms to establish the homoplasmy of cell populations. Actually, these mechanisms are hypothetical in current mitochondrial disease research. Evolution algebras have many connections with other fields of mathematics, such as graph theory, group theory, knot theory, and Ihara-Selberg zeta functions. Evolution algebras provide a theoretical framework to unify many phenomena. We put these related ideas in Chapter 6 as further research topics.

2.3 Colored coalescent theory and stochastic processes

Evolution algebra can be thought of as an algebraic view of coalescent theory as I defined. When I started to study biology, I contacted biologist Michael T. Clegg in UC Riverside and he introduced coalescent theory to me. We have published 5 papers [12-16].

Coalescent theory is a basic theoretical framework for molecular population genetics. Mathematically, coalescent theory studies stochastic processes leading to the most recent common ancestor (MRCA) from a sample under various model conditions. If one views more commonly studied branching processes as stochastic models of generating random trees from their roots, coalescent processes can be viewed as inverse processes, which recover random trees from their leaves. In order to answer a question about migration in human evolution history asked by Michael Clegg, we introduced a **colored coalescent** model to incorporate geographic factors. Moving backward along colored genealogical trees, the color of vertices may change only when two vertices coalesce. The rule that governs the change of color involves a parameter. We found the explicit formulas of expectation and the cumulative distribution function of the coalescent time to MRCA with different colors. For example, when $x = \frac{1}{2}$ for a sample of n colored individuals, the expected time to reach a black MRCA or a white MRCA is $3 - \frac{2}{n}$ respectively. On the other hand, the expected time for the colored coalescent process to reach a MRCA, either black or white, is $2 - \frac{2}{n}$, which is the same as that in the standard Kingman coalescent process. We also studied colored coalescent processes with color mutation processes, which are independent Poisson processes running on random genealogical trees. These results appeared in [12] and [14].

Inspired by coalescent theory, we introduced a stochastic model called "multi-person simple random walks"or **coalescent random walks** on a graph G. There is a finite number of persons distributed randomly at the vertices of G. In each step of the Markov chain, we randomly pick up a person and move it to a random adjacent vertex. To study this model, we introduced two new concepts: tensor powers of graphs and **tensor products of Markov processes**. In this context, a coalescent random walk becomes a simple random walk on a tensor power of G. We gave estimates of the expected number of steps for these persons to meet all together at a specific vertex. This work was published in [15].

In order to understand time scaling in coalescent theory, we introduced the notion of **frequency** for graphs and Markov processes. This serves as a scaling factor between any Markov time of a continuous time Markov process and that of its jump chain. However, for a Markov process with huge states, the computation of any quantities, even for its jump chain, is still difficult. For a lumpable process, in order to recover certain quantities from the jump chain of the lumped process, it needs a type of **commutativity** among four processes: Markov process X, its lumped process $\bar{X}$, the jump chain of X, and the jump chain of $\bar{X}$. We gave a necessary and sufficient condition for commutativity, and conditions to recover some of the basic quantities of the original process from the jump chain of the lumped Markov process. These results appeared in [13] and [16].