Research Summary

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Overview of Research Interests

Stochastic Processes on Networks with Applications in Biology

- Complexity reduction methods for stochastic network models in neuroscience
- Stochastic dynamics on networks: Neuronal network modeling of sleep-wake regulation
- Contagion dynamics on adaptive networks: Norovirus as a case study

Dynamical Systems Applications in Biology

- Mathematical modeling of retinal degeneration

Stochastic Models in Genetics

- Waiting time distributions: Gene regulation and multi-stage carcinogenesis
- Steady-state fluctuations of a genetic feedback loop: An exact solution

Statistical Methods and Applications

- Methods for estimating power law distributed regions in data
- Methods for analyzing psychomotor vigilance task (PVT) data used in sleep research
- Classifying the contributions of olfactory receptor neuron activity to navigational behavior in *Drosophila* larvae
- Fitting logistic growth curves to multiple isolates of a lethal pathogen of amphibians

Overview of Research Interests

I have a broad background in applied mathematics with specific training and expertise in probability, mathematical modeling, and network theory. My research is in the field of mathematical biology, an interdisciplinary field that lies at the interface of mathematics, statistics, and biology. I develop and analyze mathematical models, combining methods from probability and stochastic processes, network theory, and dynamical systems to shed light on biological issues.

My primary interests are in investigating the roles of stochasticity, network structure, and forces like evolution in shaping the dynamics of biological systems, and studying new mathematical questions that come up in these applications. Therefore, I use stochastic processes extensively in my research, as detailed below. A particular challenge of developing and analyzing stochastic models of biological systems is the need to bridge multiple spatial and temporal scales: from microscopic to macroscopic, from millisecond to millions of years. For example, stochasticity is fundamental to gene expression and ion channel gating in neural activity; it also plays an under-appreciated role in physiological regulation at larger scales, such as the regulation of sleep and wake behavior. This behavior is governed by networks of neurons in the brain with underlying structures that likely influence dynamics, suggesting a prominent role for stochastic processes evolving on networks. To what extent are the dynamics that we observe shaped by the stochastic nature of biochemical reactions, by physiological structure such as neuronal networks, and by the constraints of evolution? In the sections below, I describe three main aspects of my research used to gain insight into both small and large facets of biological regulation: 1) stochastic processes on networks, 2) dynamical systems applications in biology, and 3) stochastic models in genetics. I also describe a related fourth area of my research involving statistical methods and applications.

I really enjoy working with students, and I encourage them to have a say in what they work on to foster their development as independent thinkers and researchers. This is reflected in the diversity of projects described below. My department has two relatively new PhD programs: one in Mathematics (with an Applied Mathematics track) and one in Statistics & Data Science; both programs started in Fall 2017. As a result, most of the research I've done with students at UNR has been with Masters and undergraduate students. I have an incoming PhD student in Applied Mathematics starting in Fall 2021, and she will work on topics in mathematical neuroscience.

Stochastic Processes on Networks with Applications in Biology

The study of networks with stochastic processes evolving on the nodes has become a very active area of research in mathematical biology, with a broad range of scientific applications including neuroscience, epidemiology, ecology, and evolutionary biology. Many biological processes can be thought of as flows on networks, from ion channel dynamics to the flow of biomass through food webs. Network structure plays a key role in these dynamics, and finding reduced descriptions of high dimensional biological networks can help us to understand their function by uncovering their essential regulating components. The projects described below pair biologically-motivated numerical studies with mathematical analysis to answer specific questions about these and similar systems.

Complexity reduction methods for stochastic network models in neuroscience

The inclusion of stochastic effects within dynamical neural models is a topic of growing importance in mathematical neuroscience. A major source of noise in neural systems is the random gating of ion channels, and such systems are typically represented as a Markov process on a graph. The stochasticity of spike generation is well captured by computational models of Markov processes with voltage-dependent transition rates, but at the cost of complex, time-consuming simulations. These and other discrete-state, continuous-time Markov processes occur throughout neuroscience and cell biology representing the random dynamics of processes transitioning among multiple locations or states. Complexity reduction for such models aims to capture the essential dynamics and stochastic properties via a simpler representation, with minimal loss of accuracy. Classical approaches, such as aggregation of nodes and elimination of fast variables, lead to reduced models that are no longer Markovian. The stochastic shielding approximation is a new heuristic approach to efficient, accurate simulation of Markov chain models [23].

In collaboration with P.J. Thomas (Case Western) [11], I conducted a thorough mathematical analysis of the stochastic shielding approximation. The method is based on replacing a high-dimensional stochastic process defined on a graph with a lower-dimensional process on the same graph, rather than replacing a complex network with a simpler one. We show that this form of model reduction can be represented as a mapping from the original process to an approximate process defined on a significantly smaller sample space. Our analysis results in a new, quantitative measure of the importance of individual edges within a Markov process on a graph. Our *edge importance measure* confirms the optimality of the stochastic shielding approximation, and also sheds new light on to the contributions of different ion channel transitions to the variability of neural systems.

In [9], we (with R.F. Galan, EE/CS, Case Western) extended the work above by exploring the robustness of the stochastic shielding phenomenon and the accuracy of the approximation under conditions of timescale separation and sparsity in the stationary distribution, via the edge importance measure described in [11]. We show that typical edge importance hierarchy is robust to the introduction of timescale separation for a class of simple networks, but that it can break down for more complex systems with three or more distinct timescales, such as the nicotinic acetylcholine receptor, a well-studied ion channel that can exhibit bursting behavior. We also establish that the edge importance measure remains a valid tool for analysis for arbitrary networks regardless of multiple timescales. Lastly, I have two projects in early stages that extend these methods and apply them to other systems: calcium release in neural signaling (with P.J. Thomas, Case Western) and flows on river delta networks (with I. Zaliapin, UNR).

Stochastic dynamics on networks: Neuronal network modeling of sleep-wake regulation

Another fundamental question regarding neural systems and other applications involving networks is the extent to which the network architecture may contribute to the dynamics occurring on the network. In collaboration with J. Best (Ohio State) and M.S. Blumberg (Psychological and Brain Sciences, U. Iowa) [14], I explored the relative contributions to network dynamics made by the graph structure and by the nature of the stochastic process occurring on the graph. Using degree distribution as a marker of graph structure, we considered randomly generated graphs on N nodes with varied degree distributions. We considered two different stochastic processes on the graphs: a percolation type process of activity and a neural spiking process. We asked to what extent the graph structure is reflected in the dynamics of the process on the graph. Our findings suggest that memoryless processes, such as percolation-like processes and spiking of integrate-and-fire neurons, are more likely to reflect the degree distribution. We find that processes with memory, such as those

in which nodes change their firing rate in response to inputs, can robustly produce power law and other heavy-tailed distributions of activity regardless of degree distribution. These results are an important step toward advancing our understanding of how neuronal network structure influences the dynamics of sleep-wake regulation in the mammalian brain.

Focusing on the study of two interacting networks, such as the dynamics between sleep-active and wake-active neuronal networks, (in collaboration with F. Olmez, SJTU (China), P. Kramer, RPI, and J. Best, Ohio State) we currently have a model that robustly produces wake bout durations distributed as a power law followed by an exponential tail for the case where both networks have degree distributions with low mean degree [29]. The size of the power law region and the variability of the power law exponent across different realizations of the model depends on the network structure. In addition, the distribution of wake bout durations depends on the age of the mammal so a related question is: what developmental changes are influencing the distribution of wake bouts? We are currently working on this and related questions in [29]. To accurately quantify the power law region output from this model, we had to first develop a new method [5], described in the power law subsection in the "Statistical Methods and Applications" section at the end of this document.

Lastly, I recently wrote a book chapter (peer-reviewed) on network structure and dynamics of biological systems geared toward advanced undergraduate researchers and beginning graduate students (and their advisors) in mathematical and computational biology [6]. My chapter covers some open research topics in network theory applied to biological networks.

Contagion dynamics on adaptive networks: Norovirus as a case study

Stochastic processes on networks can also be used to study infectious disease dynamics. Classical contagion models, such as the Susceptible-Infected-Recovered (SIR) model, and other infectious disease models typically assume a well-mixed contact process. This may be unrealistic for infectious disease spread where the contact structure changes due to individuals' responses to the infectious disease. For instance, individuals showing symptoms might isolate themselves, or individuals that are aware of an ongoing epidemic in the population might reduce or change their contacts. In collaboration with former Honors student Brittany Lemmon (currently a PhD student in Biostatistics at UC Davis) and P. Hurtado (UNR) [25], we investigate contagion dynamics in an adaptive network context, meaning that the contact network changes over time in response to individuals getting sick and changing their behavior. We consider norovirus as a specific example and focus on the spread of disease in a local population, such as a college campus. We generate the contact network, which includes age structure, based on interaction data from the well-known POLYMOD study [24]. We investigate questions related to disease dynamics and applications to public health.

This project started out as Brittany's Honors thesis, and she received a prestigious Honors Undergraduate Research Award (HURA) at UNR in 2019 for this project. She presented her research at the SIAM Conference on Applications of Dynamical Systems (May 2019) and won a Red Sock Outstanding Poster Award; she was the only undergraduate to win this award, quite an accomplishment. I have since extended Brittany's model and results and I presented our work at the Society for Mathematical Biology Annual Meeting (Aug 2020, Virtual poster presentation); I won an SMB Poster Award for this work and this poster is included in my tenure materials. We have a manuscript in preparation [25] that will be submitted this summer.

Summary of relevant publications and work in progress

Prior to joining UNR, I have two publications related to stochastic processes on networks [11, 14]. Since joining UNR, I have two publications [6, 9] in this area, with the former being an invited book

chapter on network structure and dynamics of biological systems. I also have two manuscripts in preparation [25, 29] and three pending grant proposals briefly described below.

Current projects include:

- Modeling sleep-wake regulation in two interacting neuronal networks [29].

- Contagion dynamics on adaptive networks [25].

- Pending grant proposal (submitted May 2021) – NSF Understanding the Rules of Life: Emerging Networks: "Quantifying the phytochemical landscape through Indigenous Knowledge, interaction diversity, genomics, and network dynamics." PI L. Robinson (Biology), **Co-PI D. Schmidt**, Co-PI L. Dyer (Biology), Co-PI C. Jeffrey (Chemistry).

    - **Summary:** We propose to link layers of networks across multiple scales, from global networks focused on producing sustainable energy, to networks of interactions with the Indigenous peoples whose livelihoods and medicinal plant communities are affected by those production networks, to the ecological, phytochemical, and genetic networks that are the basis of medicinal plant communities and other attributes of biodiversity that sustain all of these networks. In particular, we will focus on networks involving plants in the genus Piper (*Piperaceae*, the pepper family) to understand relationships between international commerce, local Indigenous communities, and basic ecological interactions in high diversity ecosystems.

    - **My Role:** As the sole mathematician on the proposal, I will oversee all aspects of network modeling, including building and analyzing an interaction network model parameterized by our data and simulating distinct processes to examine rates of formation of sub-networks (Objective 3). I will also supervise one graduate student. This is a new interdisciplinary collaboration between the biology, chemistry, and math/stat departments at UNR.

- Pending grant proposal (submitted Sept 2020) – NIH: "Wastewater Surveillance Integrated with Human Testing to Develop Predictive COVID-19 Prevalence Model." PI K. Pagilla (Civil/Envt Engr), Co-I H. Ebrahimian (Civil/Envt Engr), **Co-I D. Schmidt**, Co-I P. Hurtado (Math/Stat), Co-I A. Talaei-Khoei (Information Systems), Co-I M. Pandori (Director, NV State Public Health Laboratory).

    - **Summary:** The goal of the proposed research is to conduct integrated modeling of human testing data and wastewater data on SARS-CoV-2 from COVID-19 monitoring using novel methods. We will monitor SARS-CoV-2 presence from de-identified individuals to community level wastewater treatment plants, identify virus transformations through genomic tools, determine virus fate through the sewer system, compare geospatially identified wastewater data with human testing data from the local health district to assess community prevalence of COVID-19, and analyze models using deterministic, stochastic, geospatial, and empirical tools.

- **My Role:** I will oversee the integration of findings from the different modeling activities with the forecasting models, as well as to develop and implement network-based and stochastic models to study COVID-19 disease dynamics in a college campus setting (Aim 3); I proposed Activity 3-5 and will lead those efforts. I will co-supervise a postdoc and a Ph.D. student in Mathematics/Statistics with P. Hurtado. This is a new interdisciplinary collaboration with researchers at UNR and NV State Public Health department.

- Pending grant pre-proposal (submitted Mar 2021) – NSF Research Traineeship: "A multidisciplinary approach to the photon/material/electron proxy at the nanoscale." PI M.A. Alpuche (Chemistry), **Co-PI D. Schmidt**, Co-PI C. Barile (Chemistry), Co-PI M. Tucker (Chemistry), Co-PI S. Odoh (Chemistry). ,

  - This is a new collaboration, fostered by my interactions with recent Ph.D. graduate (Spring 2021) S. Gutierrez-Portocarrero from the Alpuche Lab. I was an active member of his dissertation committee.

Dynamical Systems Applications in Biology

Mathematical modeling of retinal degeneration

In 2019, I started a collaboration with five women at the Institute for Pure and Applied Mathematics (IPAM)'s summer Program for Women in Mathematical Biology to model retinal degeneration. This collaboration is led by E.T. Camacho (ASU) who is an expert in this field, and the rest of us are at various stages in our careers, from postdoc to associate professor. We have one paper published on modeling the dynamics of photoreceptor metabolism in a single cone cell [4], and another paper submitted on the implications of that model's dynamics for various disease states [1], as described in more detail below.

Cell degeneration, including degeneration that results in retinal diseases, is linked to metabolic disturbances. In the retina, photoreceptor degeneration can result from imbalance in lactate production and consumption as well as disturbances to pyruvate and glucose levels. We aim to identify the key mechanisms in metabolism involved in this degeneration. In [4], we use a nonlinear system of ordinary differential equations to model the metabolic pathway of aerobic glycolysis in a single cone photoreceptor. This model allows us to analyze the levels of lactate, glucose, and pyruvate within a single cone cell. We perform numerical simulations, use available metabolic data to estimate parameters and fit the model to this data, and conduct a sensitivity analysis using two different methods (Latin Hypercube Sampling/Partial Rank Correlation Coefficient and Extended Fourier Amplitude Sensitivity Test) to identify pathways that have the largest impact on the system. Using bifurcation techniques, we find that the system has a bistable regime, biologically corresponding to a healthy versus a pathological state. The system exhibits a saddle node bifurcation and hysteresis. This work confirms the necessity of the external glucose concentration to sustain the cell even at low initial internal glucose levels.

In [1], we further analyze the model developed in [4] specifically focusing on pathological mechanisms. Here we apply two time-dependent global sensitivity analysis techniques; we determine a subset of parameters to which the model is most sensitive at specific times. In particular, this reveals the importance of β-oxidation of fatty acids, G3P degradation and utilization of lipids

for photoreceptor outer segment renewal, external glucose supply, and efficiency of the GLUT1 transporter. Bifurcation analyses identify regions for these parameters characterizing healthy versus pathological functioning of the cone. We also investigate the importance of timing of intervention and the ability of the system to change dynamic course by engaging rescue or self-protection mechanisms. This analysis provides insight into disease mechanisms, as well as potential therapeutic targets and optimal treatment windows for metabolic photoreceptor diseases.

We are currently working to extend this single photoreceptor model into a network model of three interacting neural cell types: photoreceptors (rods and cones), retinal pigment epithelium, and Mueller cells. We have funding from the Mathematical Sciences Research Institute (MSRI) to work on this project during Fall 2021. I am the PI on the funded proposal which was originally awarded for Summer 2020 but delayed due to COVID-19. Future work will consider adding stochastic effects into this network model; I will lead that extension of our work as I have the most expertise in stochastic modeling in this collaboration.

Summary of relevant publications and work in progress
I started working on modeling retinal degeneration in 2019 and I have two publications [1, 4]. Current work in progress is to extend our single cell model to a network model involving three cell types; this will be the focus of our MSRI residency, see below.

Current projects include:

- Grant awarded – **PI D. Schmidt**, 5 Co-PIs, 1 Supporting Faculty. Mathematical Sciences Research Institute (MSRI), UC Berkeley, fully funded 2-week residency for 2020 Summer Research in Mathematics Program to work with my retinal degeneration collaborators. Deferred to Fall 2021 due to COVID-19.

Stochastic Models in Genetics

These projects use mathematical models to explore how genes regulate macroscopic behavior and how populations evolve. Waiting for an event or a sequence of events to occur is a fundamental problem in probability theory, commonly modeled by a Poisson process or other type of stochastic process. Understanding the mechanisms involved in gene regulation, the speed at which genetic regulatory changes can occur, and the rate of cancer onset in multi-stage carcinogenesis are all important problems in genetics and evolutionary biology where waiting-time models can have a large impact. A variety of tools from probability theory, such as Markov chains, branching processes, and Wright-Fisher diffusions, can be used to gain insights into these complicated problems in population genetics. I developed and analyzed models of stochastic gene regulation which yield new insights into evolutionary genetics, cancer progression and related diseases. A central difficulty in such problems lies in capturing the essential components of the process in a mathematical model amenable to analysis, computation, and prediction.

Waiting time distributions: Gene regulation and multi-stage carcinogenesis
In [17-19], I used Markov chain models and a variety of probabilistic techniques to understand how population genetic factors influence the evolutionary process of gene regulation by analytically quantifying the distribution of waiting times for the generation of new transcription factor binding sites in different species (in collaboration with R. Durrett, Duke). We generalized these results in

[15] (with J. Schweinsberg, UCSD) by considering the time it takes to acquire a sequence of m such mutations in a population (m-step model), thinking specifically about modeling multi-stage carcinogenesis. The 2-step process applies to gene regulatory sequence evolution, and our findings show that regulatory sequences can evolve at rates faster than divergence times between species. This supports recent empirical studies that new regulatory sequences typically come from small modifications to existing sequences. Results from the general m-step model give estimates for the rate of cancer progression in colon cancer and other diseases resulting from a sequence of mutations occurring in a collection of cells. Our analysis also exposed some flaws in the literature concerning mathematical limits to Darwinian evolution [16, 17].

I am currently working with former Honors student Dana Winterringer (May 2021 graduate) and soon to be MS student (Fall 2021) on a related model of multi-stage carcinogenesis. Her Honors thesis investigates the influence of diet on the waiting time distribution for the first tumor cell to appear in a model of colorectal cancer. This model is a continuous-time Markov chain with two key pathways (chromosomal instability and microsatellite instability pathways) leading to the tumor state. Dietary effects are modeled by time-dependent mutation rate functions that differ in these two pathways and depend on the diet considered. She and I plan to continue this work for her Master's thesis.

Lastly, I wrote a book chapter (peer-reviewed) on stochastic models in biology with a focus on waiting time distributions and genetics applications [3]. This chapter gives an overview of current research in this area and highlights some of my contributions to the field; it is geared toward advanced undergraduates and beginning graduate students in mathematics.

Steady-state fluctuations of a genetic feedback loop: An exact solution

Gene regulatory networks dynamically orchestrate the level of expression for each gene in the genome by controlling how vigorously that gene will be expressed. Gene expression is inherently stochastic due to the small number of regulatory molecules typically present within a cell. Genetic feedback loops in cells break detailed balance and involve bimolecular reactions, and typically, exact solutions revealing the nature of the stochastic fluctuations in such feedback loops are lacking. In collaboration with T.J. Newman (U. Dundee) and R. Grimma (U. Edinburgh) [12], I analyzed a stochastic model of a gene regulatory feedback loop using the chemical master equation for theoretical analysis. The network we consider breaks detailed balance and involves a single bimolecular reaction step. We provide an exact solution of the steady-state master equation for arbitrary values of the parameters, and present simplified solutions for a number of special cases. Our results emphasize the importance of stochastic effects in modeling gene regulation.

Summary of relevant publications and work in progress

Prior to joining UNR, I have six publications on the topic of stochastic models in genetics [12, 15-19]. Since joining UNR, I have an invited book chapter on stochastic models in biology [3] and two ongoing projects with students in this area.

Current projects include:

- Stochastic model of carcinogenesis focusing on the influence of diet on colorectal cancer, with incoming Master's student (former Honors student) Dana Winterringer. Dana received two funding awards for this work in 2020-21: Nevada Undergraduate Research Award and the NSF EPSCoR Undergraduate Research Opportunity Program award.

- Relaxing the constant population size constraint in models of random genetic drift, with undergraduate math/stats student Kevin Bumgartner. Kevin received a Nevada NASA Space Grant Consortium Research in Science & Engineering Hands on Projects (RiSE and HoP) award in 2017 to fund this research. Kevin paused his schooling when the pandemic hit and plans to finish his degree in Fall 2021. We currently have a draft manuscript on this research and hope to submit it for publication later this year.

Statistical Methods and Applications

Although much of my research revolves around developing and analyzing mathematical models of biological systems, my work also includes some statistical applications, data analysis and method development. In collaboration with R. Durrett (Duke) [20], I used likelihood-based methods to investigate the diversification of zinc-finger binding domains in the human genome. With K.J. Suter's group (Biology, UTSA) [13], I used clustering and other methods to compare the activity of gonadotropin releasing-hormone neurons in rats to study the neuronal mechanisms that regulate hormone secretion.

More recently, I have worked on the following four projects: 1) methods for estimating power law distributed regions in data [5, 10, 28, 29], 2) methods for analyzing psychomotor vigilance task data used in sleep research [26, 27], 3) classifying the contributions of olfactory receptor neuron activity to navigational behavior in *Drosophila* larvae, as part of an ongoing collaboration with D. Mathew's group (Biology, UNR) [7], and 4) fitting logistic growth curves to amphibian pathogen data from varied geographical locations [2]. Each of these recent projects is described in more detail in the subsections below.

Methods for estimating power law distributed regions in data

Motivated by our current project on modeling sleep-wake regulation in a network context [29], we first needed to develop new methods [5] to properly analyze sleep and wake bout distributions from the model, as wake bout distributions tend to show power law behavior only over an intermediate range (not a full tail).

In [5], we developed a new method for estimating a power law region, including its lower and upper bounds, of the probability density in a set of data that can be modeled as a continuous random sample. Our method is a variation of the Kolmogorov-Smirnov method. Our main innovation is to stabilize the estimation of the bounds of the power law region by introducing an adaptive penalization term involving the logarithmic length of the interval when minimizing the Kolmogorov-Smirnov distance between the random sample and the power law fit over various candidate intervals. We show through simulation studies that an adaptively penalized Kolmogorov-Smirnov method improves the estimation of the power law interval on random samples from various theoretical probability distributions.

Statistical methods used in mathematical biology also have applications outside of the biological sciences. For example, I worked with former undergraduate Honors student R. Arnold on fitting power law distributions (Zipf's law) to the frequency distribution of words from a very large data set of English texts [10]. Specifically, we looked at differences in the frequency distributions of words from corpora of different contexts (e.g., academic, newspapers, spoken text) and time periods (e.g., 1800s, early 1900s, present) as measured by best fit power law parameters. For very large samples of count data, such as this word frequency data set, it is much more compact to represent a large sample by the counts of unique elements of the sample. Information-wise, this

equivalent form of the sample is known as *absolute frequency data*. I adapted existing methods to account for the use of count data and analyzed the word frequency data. This work has inspired new research questions and two new collaborations with work in progress as described below.

First, in collaboration with former M.S. student A. Robards and P. Hurtado (UNR), [28] is work (based on A. Robards MS thesis) that generalizes the methods in [10] and other related computational methods to take both absolute frequency data and sample data input. These results will allow for more flexible computational methods which will have applications to a variety of fields, including mathematical biology. Second, I recently started a collaboration with M. Forister, (Biology, UNR) and P. Hurtado in which we ask how the choice of probability distribution influences the estimated power law exponent for a given data set. How do the estimates compare when the underlying methods use truncated versus un-truncated forms of these different probability distributions? This work is in early stages.

Methods for analyzing psychomotor vigilance task data used in sleep research

I have found that data analysis collaborations with scientists can lead to new mathematical and statistical questions to investigate, and often also lead to the development of new statistical tools. I am currently developing a general method for analyzing data from a sensory-motor test known as the psychomotor vigilance task (PVT) [26, 27]. The PVT is a test of alertness commonly used in sleep research. This work is in collaboration with M.L. Splaingard (Director of the Sleep Disorders Center at Nationwide Children's Hospital in Columbus, OH), G.A. Smith (Nationwide Children's), J. Best (Ohio State), P. Hurtado (UNR), and my former student J. Armstrong (UNR Math MS graduate) described in more detail below.

Oftentimes data don't conform to the assumptions of standard (linear model based) frameworks. In such cases, a common solution is to either pre-process the data or to develop a more suitable system-specific model, and from it derive the statistical tools necessary to conduct the desired data analysis. In [26], J. Armstrong and I propose a general method to analyze PVT data by describing a maximum likelihood-based estimation procedure and accompanying parameter identifiability diagnostics. This project is ongoing, and extends J. Armstrong's Master's thesis [22]. I am also working on statistical analyses of normative data for PVT testing in children in [27], since most previous work has focused on PVT data from adults.

Classifying the contributions of olfactory receptor neuron activity to navigational behavior in *Drosophila* larvae

The mechanisms by which olfactory information is encoded in the activities of olfactory receptor neurons (ORNs) and translated into navigational behavior remain poorly understood. In collaboration with D. Mathew's Lab at UNR [7], we sought to determine the contributions of *Drosophila melanogaster* larval ORN activity to navigational behavior. Using odorants to activate ORNs and a larval tracking assay to measure the corresponding behavioral response, my former Master's student (J. Armstrong) and I performed a hierarchical clustering analysis on the data and found that larval ORN activators cluster into four groups based on the behavior responses elicited from larvae. These results provide new insights into the functional relationship between ORN activity and behavioral response. Subsequent optogenetic analyses of a subset of ORNs revealed previously undescribed properties of larval ORNs, namely that different temporal patterns of ORN activation elicit different behavioral outputs. This study challenges traditional methods of incorporating ORN activity into computational models built to predict animal behavior.

D. Mathew and I received an internal grant to work on this paper (UNR New Scholarly Endeavor) in 2017. I also had a supporting/collaborator role on Mathew's project within a larger NIH/NIGMS Center for Biomedical Research Excellence (COBRE) grant during 2017-2020.

Fitting logistic growth curves to multiple isolates of a lethal pathogen of amphibians

The work in [2] is the result of a new collaboration that I started in 2020 with J. Voyles's Lab (Biology, UNR), P. Hurtado, and three genetics researchers from UC Berkeley and the U. of Pittsburgh. The Voyles Lab studies emerging infectious diseases, particularly in frogs, such as the amphibian disease known as chytridiomycosis. This disease is caused by a lethal fungal pathogen, *Batrachochytrium dendrobatidis* (Bd), and this is the focus of [2].

This emerging infectious disease has been implicated in a global loss of amphibian diversity. An important research question is to uncover what abiotic factors drive Bd pathogenicity in different environments and whether or not Bd is evolving functional diversity as it spreads globally. In [2], we studied environmental influences on Bd pathogenicity by quantifying responses of Bd phenotypic traits (e.g., viability, growth rates, carrying capacities) over a range of environmental temperatures to generate thermal performance curves. We selected multiple Bd isolates collected across a latitudinal gradient. For the population viability, we found that the isolates had similar thermal optima at 21 ºC, but there was considerable variation among the isolates in maximum viability at that temperature. Our results suggest that temperatures across latitude may explain some of the variation in Bd viability through vertical shifts in maximal performance. However, the same pattern was not evident for other aspects of viability (such as growth rates), underscoring the importance of measuring multiple traits to understand variation in pathogen responses to environmental conditions.

My main role in this project was to quantify growth differences across a range of temperatures by fitting logistic growth curves to Bd viability time series data (normalized optical density measurements) for each isolate-temperature combination. This approach allowed us to estimate the intrinsic growth rates (r) and carrying capacities (K) over the range of temperatures to quantify differences in the thermal performance curves across isolates. Uncertainty quantification (95% confidence intervals) was done using likelihood profiling. P. Hurtado and I wrote all R code to do these analyses, a supplementary document detailing these analyses, as well as relevant portions of the methods, results, and discussion sections in the main text.

Summary of relevant publications and work in progress

Prior to joining UNR, I have two publications concerning statistical applications [13, 20]. Since joining UNR, I have four publications [2, 5, 7, 10], two MS theses advised [21, 22], and several papers in preparation [26-29]. I also have a non-research publication on balancing an academic career in mathematics with motherhood and family life [8].

Current projects include:

- Power law distributions in biology. [28] and [29] both extend the methods developed in [10] as described above.

- Methods for analyzing psychomotor vigilance task (PVT) data used in sleep research [26, 27]; [26] is an extension of J. Armstrong's Master's thesis [22] and [27] is related work.

- Continued collaboration with J. Voyles and P. Hurtado at UNR. We finished our first collaborative paper and plan to work on related model fitting and method development projects using data collected by her lab.

- Statistical analysis of choreographic structure in dance, with Honors math/stats graduate Amanda Fredrickson (Honors thesis) and P. Hurtado. This project involved innovative data collection and analysis; we wrote a collection of R scripts to analyze Laban notated dance scores (obtained from Ohio State University's dance department) and found different non-trivially repetitive patterns in the scores. R package development is in progress.

References

[1]*Graduate student*, [2]*Undergraduate student*, **Equal authorship*

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