Research Summary

Over the last five years the work in my research group has primarily focused on two main themes: the properties and the role of astrocytes in the nervous system, and the odor coding in the olfactory system. Both of these themes have come to the forefront of the neuroscience research as a result of new types of data becoming available. It was natural for my group to become involved with this work from the computational side, due to my previous expertise in sensory systems, in stochastic and dynamical system properties of neurons and neural networks. In both of these primary research directions in the last five years I was able to develop new collaborations, train graduate and undergraduate students, publish in prime scientific journals, present at conferences and workshops, and obtain grant funding. Both directions include some projects that are true to biological detail and are tightly related to data, and some projects that are more theoretical, designed to elucidate principles of neural function. Below you will find more details about each project, including summaries of published or completed papers, description of ongoing funded efforts, and details of student involvement in each of the two research directions.

For more updates on the projects, and the status of preprints, please refer to my website www.math.utah.edu/~borisyuk under “Research”.

I. Astrocytes.

Astrocytes are the major glial cell type in the mammalian brain, as numerous as neurons. Recent studies have revealed that astrocytes play many key roles in the functioning of the central nervous system (CNS). Experiments reveal that astrocytes wrap around many individual synapses, are involved in the uptake of neurotransmitters, gliotransmission (release of neuroactive compounds such as glutamate, ATP), K+ buffering, and regulating the blood-brain-barrier. Through such functions, astrocytes are able to modulate neuronal activity at the level of a single synapse as well as in large neural networks, but their exact role, mechanisms of actions, and properties are not well understood and are one of the most quickly developing areas of neuroscience research.

While astrocytes are not as electrically active as neurons, many of their functions may be mediated via calcium transients. Despite significant research efforts, there is little consensus on the role of astrocyte calcium signaling in the brain. Until recently, there were no experimental techniques that could track changes in Ca2+ concentration with sufficient spatial and temporal resolution to accurately assess astrocyte function. Concomitant with this lack of experimental data, the modeling of astrocytic Ca2+ transients has been lagging behind similar work in neurons.

Moreover, neural network models almost never take astrocytes into considerations. To remedy the situation the field needs ways to include “effective” astrocytes into the networks, which will faithfully reflect the modulation of neuronal activity by astrocytes, without additional complexity of simulating detailed astrocyte models alongside the neural network. This is the goal of my just-funded NSF grant. It will build in the work already done and on the results of the ongoing projects described below.
1.1. Calcium Activity in Astrocytes


In a joint work with experimentalists in John White’s lab (Boston University) we created a detailed biologically-realistic model of an astrocyte functional subcompartment, and investigated how the evoked calcium transients are produced in astrocytes, and how the experimentally-observed variability of calcium responses is achieved (Handy et al., 2017; Taheri et al., 2017). In contrast to many earlier astrocyte models, we used the newly-available data from brain slices (and not cultured astrocytes that can be quite different), we included the calcium exchange between astrocyte and the extracellular space, and used models for individual channels and pumps that were as specific to astrocytes as possible.

Our astrocyte calcium model was able to reproduce the variability and match many characteristics of the recorded cortical astrocyte calcium responses. Furthermore, we elucidated the underlying bifurcation structure of our mathematical model, and as a result we categorized all experimental and model-generated astrocyte Ca2+responses into four general types based on their temporal characteristics. We varied key channel parameters, mimicking various biologically relevant conditions, such as pharmacological blocking of individual currents. We tracked resulting changes in the underlying bifurcation structure as the Hopf bifurcations delimiting the oscillatory range shifted or were destroyed, making specific experimentally-testable predictions. We found that response-type frequencies do indeed change in the predicted manner in the few relevant experiments that so far have been performed, but they also vary between sub-compartments of astrocyte (soma, large and small processes), possibly reflecting the functional changes between astrocyte subcompartments.

We also found that store-operated calcium channels, plasma membrane bound channels with little activity during calcium transients, have a surprisingly strong effect on calcium response characteristics, underscoring the importance of considering these channels in both experiments and mathematical settings. For example, we predicted that upon partial blocking of SOC channels the oscillatory responses will become more common, but upon complete blocking of these channels, the multi-peak response will be fully eliminated.

Next, we used our understanding of the parameter space to create a database that can be used by experimentalists to help determine the underlying, experimentally inaccessible calcium-handling mechanisms in their cells. This database, as well as all of the corresponding codes for these papers, has been uploaded to ModelDB (Model no. 189344). We used the database to match our collaborators’ experimental data from different astrocyte compartments. By comparing the locations of the data matches in the database, we predicted that a dynamics of a signaling molecule, IP3, involved in calcium release, is progressively slowed as one moves away from the soma, and that specific pumps (PMCA and SERCA) are, respectively, down- and up-regulated in the processes compared to the soma. Similarly, data from different conditions, such as healthy and diseased astrocytes can be compared, as the data become available.
1.2. **Diffusion with recharging traps at the boundary**


In new collaboration with my colleague mathematician Dr. Sean Lawley (Math, Utah) we have recently considered a new type of stochastic process we termed DiRT (diffusion with recharging traps) that can describe many diverse biological systems characterized by randomly moving particles that can be captured by traps in their environment. Examples include neurotransmitters diffusing in the synaptic cleft before binding to receptors and prey roaming an environment before capture by ambush predators. In most cases, the traps cannot capture particles continuously. Rather, each trap must wait a transitory “recharge” time after capturing a particle before additional captures. This recharge time is often overlooked. In the case of instant recharge, the average number of particles captured before they escape grows linearly in the total number of particles. In stark contrast, we proved (Handy et al., 2018), through a series of lemmas and theorems, that the average number of captured particles grows at most logarithmically in the total particle number. This is a fundamental effect of recharge, as it holds under very general assumptions on particle motion and spatial domain. Furthermore, we characterized the parameter regime in which a given recharge time dramatically affects a system, allowing researchers to easily verify if they need to account for recharge in their specific system.

We have also shown (Handy et al., 2019) that the coefficient of variation of the number of captured particles for the process with recharge is always higher than the coefficient of variation of the instantaneous process, meaning that it has increased variability. We have also found that the recharge rate determines the mean and variance of the clearance time, defined as the time it takes for all particles to leave the domain. The clearance time is also affected by the size of the domain, but is quite insensitive to the number of receptors. Additionally, we extended the model to partially absorbing traps (a particle that comes in contact with a capture region has some probability of not being captured) by including an appropriate Robin boundary condition, and find that the domain size and number of traps, respectively, control the duration and amplitude of the trap activation.

Importantly, while insight into this problem can be gained with direct Monte Carlo simulations of the DiRT process, such simulations are computationally expensive for a large number of particles. Further, due to the correlations that arise between particles, this spatial and stochastic process is challenging to investigate analytically. Thus, we developed new tools by approximating this stochastic process with a continuous-time Markov process on a discrete state space, along with its corresponding mean field approximation and reduction in the limit that captures occur instantly.

As consequences for the astrocyte project, first, we obtained estimates for the amount of neurotransmitter absorbed from the cleft by the astrocyte, depending on astrocyte proximity, and second, estimates of the number of neurotransmitter molecules reaching the postsynaptic receptors. Thus, we have now characterized the effect of the astrocyte proximity on synaptic efficacy and on the activation level of astrocyte itself.
1.3. **Ongoing Project: Effects of Synaptic Ensheathment in Neuronal Networks**

- NSF DMS (#1853673, PI: Borisyuk, 2019-2022)

This project, recently funded by NSF DMS (#1853673) will use mathematical methods to study the role of synapse wrapping (ensheathment) by astrocytes, with the aim of creating framework for efficient and accurate astrocyte representation in neuronal networks. Astrocytes extend multiple “arms”, called processes, and are involved in many important brain functions. Often astrocytes wrap their processes around synapses – the points of contact between neurons. The number of wrapped synapses and the tightness of wrapping varies between brain areas, and changes during some diseases such as epilepsy. The role of such differences is not yet understood, and will be investigated in this project. The problem is challenging, because it is intrinsically multi-scale: the astrocyte wrapping acts at the microscopic scale of individual synapses and molecules, but it affects neuronal networks involving thousands of neurons. In this project, the effects of wrapping will first be studied at the individual synapse level by developing relevant mathematical theory and detailed models true to biology. Next, from these results, the essential features of connections altered by wrapping will be extracted and included in neuronal network models. The effective network-level representation of astrocyte ensheathment will be minimal, for ease of implementation in a variety of future networks and minimization of computing costs, and yet, because it is derived from detailed models, will preserve the essential biologically-relevant microscopic-scale features. The resulting hybrid networks will allow to emulate and observe the effect of ensheathment conditions corresponding to different brain areas and disease states.

More specifically, computational and mathematical analysis will be used to study the role of synaptic ensheathment at different spatial and temporal scales. First, the influence of the degree of synaptic ensheathment on the synaptic function will be investigated at the fine spatial scale and short time scale of molecules and receptors. Namely, it will be studied how ensheathment affects the (random) number of molecules reaching the post-synaptic and astrocytic receptors as a function of time, the resulting astrocyte calcium response, and excitability of the postsynaptic cell. This will involve extending mathematical theory of diffusion with switching boundaries to spatially-extended initial conditions, and extending a method to quantify roles of individual parameters in controlling the system behavior. These detailed biologically-realistic studies will inform how synaptic and post-synaptic properties are parametrized by the level of ensheathment. Next, in an excitatory-inhibitory network, each synapse will be endowed with its own ensheathment parameter, and the resulting firing rate and synchronization properties will be determined based on the distribution of the ensheathment parameters. This will be done both in simulations and by extending network activity coherence measures to include synaptic ensheathment.

Synaptic ensheathment is ubiquitous in the brain, but it is not ordinarily included in models as a property of network structure. Thus, this study explores a novel aspect of a more general problem of network structure-function relationship, central in modern neuroscience. Expected findings from this work will also contribute to understanding the complex interactions between the two major brain cell types.

Below we describe the ongoing early work on various components of this project, and preliminary results.
1.3a. From astrocyte receptors to calcium response (ongoing)

Our recent model of astrocyte calcium transients (Handy et al., 2017; Taheri et al., 2017) use time course of a signal molecule IP$_3$ as the input. To connect our results on dependence of astrocyte receptors activation on ensheathment – to the calcium response, we need an additional link connecting a time course of astrocyte receptors activation to a time course of IP$_3$. A summer REU student Yousef Alamri is working on developing such a link.

We are developing a detailed model of the G-protein-coupled receptors, constrained by the astrocyte experimental data, and including homologous and heterologous receptor desensitization. We have confirmed that such extended model still produces previously described diversity of Ca responses to single stimulus pulses, and that their properties are aligned with experimentally recorded ones, and is robust to parameter changes.

Next we will make predictions for the responses to trains of stimulus pulses at different frequencies, bath applications of stimuli and bath washout. Finally, we will vary parameters corresponding to different states and sub-compartments of the astrocyte, and use receptor activation profiles corresponding to different ensheathment levels, and build a detailed description of the post-synaptic neuronal excitability dependance on the ensheathment.

1.3b. From astrocyte calcium to neuron excitability (ongoing)

In our previous work (Handy et al. 2017, Taheri et al. 2017), we created a detailed model of evoked calcium transients in astrocytes. Using this as a starting point, we are building an extended model in which we also include key potassium and sodium fluxes, and examining the level of calcium activity needed to have a significant impact on extracellular concentrations, and hence, the excitability of nearby neurons. While proposed experimentally, a detailed model including all three of these ions has not been created. Extending from our previous work, we consider a multi-compartment (extracellular space, astrocyte cytosol, and astrocyte ER) model of the tripartite synapse. While space is not included explicitly, the role of synaptic ensheathment can be investigated through the relative volumes of each compartment.

We created a partial version of this model proposed here with a help of a summer REU student Daniel Griffin. He started with our model from Handy et al. (2017), and extended it to include sodium-calcium exchangers, sodium-potassium pumps, and leaky sodium and potassium channels. This initial attempt at extending the model did not focus on building these new components from astrocyte literature, but instead, we chose them from existing models, regardless of cell type, and investigated whether our hypothesized pathway is capable of creating meaningful change in the firing of neurons. Additional effort was put into choosing a model for the sodium-calcium exchanger to fit with evidence from the astrocyte literature that it can also run in reverse. With the new additions we successfully tuned parameters of the model in such a way that our original calcium mode results remained entirely intact.

Further, we tested whether this pathway was strong enough to affect the firing of neurons. We created an artificial spike in extracellular potassium, and ran the model with and without a simultaneous calcium transient in the astrocyte. In the baseline condition (no potassium spike, no astrocyte activity) the step-current input to the neuron was not strong enough to make it fire. With the increased potassium and no astrocyte response the neuron did fire a spike, but with the simultaneous calcium activity in the astrocyte,
the potassium concentration was compensated, and the neuron returned to its original response. These preliminary results confirm astrocytes’ ability to modulate spiking.

1.3c. Towards effective neuron-astrocyte networks (ongoing)

In previous work (Handy et al. 2018, Handy et al. 2019) we found that the level of astrocyte ensheathment can influence the duration and strength of receptor activation on the postsynaptic terminal. Astrocyte ensheathment will also have other effects, such as the effect on postsynaptic excitability described above, but only the effect on synaptic conductance is included in this first pass on the astrocyte-neuron network. We created exponential integrate-and-fire networks with either random connectivity, or two-layer spatial connectivity, tuned to different modes of activity. Then we allow a fraction of synapses to be “ensheathed” to a different degree by making them weaker and faster, as suggested by our detailed synaptic ensheathement studies. In all cases that we have considered so far, increased ensheathment lead to increase in tendency to synchronous behavior. While more work needs to done to understand and refine these results, they lead us to believe that increased ensheathment in brain networks, as observed, for example, during epilepsy, might be contributing to (rather than protecting against) increased probability of seizures, suggesting astrocyte ensheathment as possible therapy target.

1.4. Students involved

All components of astrocyte projects have involved and will involve graduate students mentored by me, and undergraduate students, also mentored by me, often with help from graduate students.

Graduate:


Undergraduate:

Daniel Griffin (now a PhD student at Michigan State) did a project with us in the Summer of 2016 as an undergrad in Utah State University. He worked on extending our existing model of astrocytes, allowing to collect preliminary data included in the funded NSF grant proposal.

Alexandria Cervantes had just finished her freshman year at the California State University, Monterey Bay, when she visited in the summer of 2016 through Graduate Preparation Institute at the U. Alexandria wrote software for running simulations that paralleled the experiments that my collaborators were doing at the time. Alexandria is now finishing, and will continue towards graduate degree in math education.

Emma Fine in 2017-18 ran simulations on the astrocyte model to explore parameter regimes that we hadn’t looked at before. This work is now being continued by Yousef Alamri (Summer 2019) to include model of G-protein coupled receptors on astrocyte membrane.
2. **Olfactory coding**

Compared to other sensory systems, much less is known about olfactory coding. This is due partially to the difficulty, until recently, of making efficient recordings even at the early stages of the olfactory system, and partly due to the more complex and less ordered nature of the olfactory stimulus space, compared, say, to the auditory or visual. We consider the problem of modeling the olfactory system and the olfactory coding from multiple angles, at different levels of processing and spatial scales, and in different species.

2.1. **Intraglomerular Circuits**


Olfaction in mammals is a dynamic process driven by the inhalation of air through the nasal cavity. Inhalation determines the temporal structure of sensory neuron responses and shapes the neural dynamics underlying central olfactory processing. Inhalation-linked bursts of activity among olfactory bulb (OB) output neurons [mitral/tufted cells (MCs)] are temporally transformed relative to those of sensory neurons. In collaboration with Matt Wachowiak’s lab (U of Utah) we investigated how OB circuits shape inhalation-driven dynamics in MCs using a modeling approach that was highly constrained by experimental results. First, we constructed models of canonical OB circuits that included mono- and disynaptic feedforward excitation, recurrent inhibition and feedforward inhibition of the MC. We then used experimental data to drive inputs to the models and to tune parameters; inputs were derived from sensory neuron responses during natural odorant sampling (sniffing) in awake rats, and model output was compared with recordings of MC responses to odorants sampled with the same sniff waveforms. This approach allowed us to identify OB circuit features underlying the temporal transformation of sensory inputs into inhalation-linked patterns of MC spike output.

We found that realistic input-output transformations can be achieved independently by multiple circuits, including feedforward inhibition with slow onset and decay kinetics and parallel feedforward MC excitation mediated by external tufted cells. We also found that recurrent and feedforward inhibition had differential impacts on MC firing rates and on inhalation-linked response dynamics. These results highlight the importance of investigating neural circuits in a naturalistic context and provide a framework for further explorations of signal processing by OB networks.

2.2. **Detailed Model of External Tufted Cell in the Olfactory Bulb**


One of the cell types in the olfactory bulb that was predicted from our earlier work (Carey et al. 2015) to play a crucial role in shaping the temporal dynamics of the OB output was bursting external tufted (ET) cell. Little work had been done to model the dynamics of the ET cell or include it in network models of the olfactory bulb. Carey et al. (2015) did include an ET cell model, however its burst-generating mechanism was not analyzed, some of the key known physiological mechanisms were not included, and its behavior in isolation was not compared to existing in vitro recordings. We set out to remedy the situation, and introduced a novel detailed conductance-based model of the bursting activity in external tufted (ET) cells.
of the olfactory bulb. The ionic currents included in the model were chosen to be specific to ET cells, and their kinetic and other parameters were based on experimental recordings. We validated the model by showing that its bursting characteristics under various conditions (e.g. blocking various currents) are consistent with experimental observations.

Further, we identified the bifurcation structure and dynamics that underlies bursting behavior. This analysis allowed us to make predictions of the response of the cell to current pulses at different burst phases. We found that depolarizing (but not hyperpolarizing) inputs received during the interburst interval can advance burst timing, creating the substrate for synchronization by excitatory connections. It has been hypothesized that such synchronization among the ET cells within one glomerulus might help coordinate the glomerular output.

Next we investigated model parameter sensitivity and identified parameters that play the most prominent role in controlling each burst characteristic, such as the burst frequency and duration. Finally, the response of the cell to periodic inputs was examined, reflecting the sniffing-modulated input that these cells receive in vivo. We found that individual cells can be better entrained by inputs with higher, rather than lower, frequencies than the intrinsic bursting frequency of the cell. Nevertheless, a heterogeneous population of ET cells (as may be found in a glomerulus) is able to produce reliable periodic population responses even at lower input frequencies.

2.3. **Network Model of Lateral Inhibition in Mouse Olfactory Bulb**

- **Zavitz D., Youngstrom I.A., Borisuyk A., Wachowiak M. Selectivity of lateral inhibition in the olfactory bulb. To be submitted soon**

The olfactory bulb (OB) is the first step in the processing of the olfactory information and is comprised of glomeruli, the functional units of the OB that receive convergent excitatory input from olfactory sensory neurons (OSN). Glomeruli have complex internal circuitry as well as inhibitory circuitry between glomeruli mediated by short axon cells in the glomerular layer, in addition to other interneuron populations. Previous work both experimental and theoretical have investigated which computations these inhibitory interglomerular networks perform and what structure they may have. Some publications, both experimental and theoretical, argued that suppressive odor responses are broad, while others found evidence that they are sparse and selective. We set out to address this controversy.

The approach that we chose, once again in collaboration with Wachowiak lab, was to construct a general interglomerular network model in which local intraglomerular circuitry is simplified, and the main emphasis is on the internode wiring. We postulated wiring rules for individual short axon cells based on previously published statistics of single cell anatomical reconstructions. However, this does not constrain the relationship between different cells in the same glomerulus, and, ultimately, how many target nodes a given glomerulus connects to. This means that in this biologically-constrained model we can introduce a single parameter that explicitly governs the selectivity of the interglomerular inhibitory connections, and study in this data-constrained model how the connection selectivity affects odor processing.

The resulting “packet” networks have connectivity structure unlike other commonly used network types: at high selectivity they have a small characteristic pathlength compared to random networks (like the small-world and scale-free), but unlike scale-free networks packet networks do not have "hubs" (nodes with very
high degree), and unlike small world networks their clustering coefficient is low. We performed detailed numerical and analytical study of connectivity in this novel network type.

Further, we endow the nodes of the network with a firing rate activity model, and using experimentally measured OSN responses to odors as input, we calculate the networks’ odor responses at different values of selectivity parameter. We describe how various commonly measured features of odor responses (e.g. lifetime sparseness or the ratio of active to suppressed glomeruli) are affected by network selectivity, and compare the outcomes to what is observed experimentally.

We find that many previously-reported features of odor response can be reproduced by either sparsely or densely connected networks and cannot be used as evidence for inhibition density. In particular, the “contrast enhancement” in a sense of decreasing similarity between similar odors can be achieved without preferential connections between functionally similar glomeruli, and without relying on spatial patterning of the cell responses. We propose that both selectively connected and relatively densely connected networks can efficiently decorrelate odor representations, and it is the mean strength of interglomerular inhibition that primary determines transformation of odor representations by the OB.

To distinguish between selective and non-selective networks a different type of experiment needs to be performed. We suggest using experiments that exploit differences in network connectivity properties directly. One such experiment that may distinguish between selective and unselective networks would be to optogenetically stimulate a single glomerulus and count the glomeruli that are suppressed. Selective networks’ connections are strong enough that a significant number of glomeruli should be suppressed. However, because the glomeruli in non-selective networks distribute their connections so widely, few if any of the connections are strong enough to produce a suppressive response. These experiments are being performed in the collaborators’ lab.

2.4. **Ongoing project: Circuit Function in the Mammalian Olfactory Bulb**

- NIH. 1R01NS109979-01 (PI: Wachowiak, Role: Co-Investigator. 2018-2023). Using functionally-defined glomeruli to probe circuit function in the mammalian olfactory bulb

The overall goal of this new project is to use a combination of experimental and computational techniques to better understand how odor coding ‘space’ is mapped across glomeruli of the olfactory bulb (OB), how OB circuits perform fundamental operations on sensory input and to generate an improved model for exploring how OB circuits transform odor representations.

While much of this project is devoted to experimental work, there are two specific computational aims.

The first computational aim is to establish a diagnostic odorant panel that is optimized for probing odor representations across the dorsal OB. In the related experimental work the data is being collected for simultaneous responses of many dorsal OB glomeruli to large panels of low-concentration odors. Some of the odors reliably activate only a single glomerulus, and are thus powerful for uniquely identifying that glomerulus. Our goal is to identify the panel of odors that covers a maximal number of glomeruli with as little overlap and as few odors as possible, and preferentially includes sparsely represented odors (optimally, the single-gglomerulus ones). Ideally, the panel would also include structurally diverse odors of high potency and be consistent across datasets/animals. We have now built a computational algorithm for choosing a panel for the given individual dataset optimizing an appropriate cost function. We have verified with a few representative sets of data that the resulting odor panel is robust with the respect to panel-choice strategy.
An undergraduate student Audrey Brown is now applying the algorithm across datasets. It is likely that we will not find a unique globally optimal panel, but preliminary results show that the multiple “near-optimal” panels are likely to overlap in many odors, possibly leading to a “core” odor set. Once found, the diagnostic panel of odorants will provide a valuable tool for the community for easy identification of many unique glomeruli and their further characteristics.

Second computational goal is to build on the modeling frameworks that we have already developed. We will incorporate new data emerging from this project on the organization of the olfactory input, circuit element response properties, and output characteristics to generate a predictive model that includes both inter- and intra-glomerular connectivity, that is deeply rooted in experimental data, comprehensive enough to capture key behaviors of the OB network, yet flexible and computationally manageable in order to support its use as a tool to guide further experiments.

We will be building on our previous work: a detailed model of feedforward inhibitory and excitatory circuits within a single glomerulus (Carey et al. 2015, see above), and an elucidated relationship between interglomerular connectivity and odor representations (Zavitz et al. above, manuscript in preparation).

We will use the integrated network model to begin exploring emergent features of OB network function. For example, we will ask how the full network model alters patterns of OSN inputs across glomeruli using the input matrices imaged from our diagnostic panel, comparing recorded input patterns and predicted output patterns within the same multidimensional coding space. We expect these analyses to lead to new insights into how the OB network transforms odor representations and to generate predictions that can be tested with further circuit manipulations.

2.5. Ongoing project: Antennal-Lobe-to-Mushroom Body connectivity in fruit fly

- Amematsro E, Zavitz D., Borisuyk A., Caron S. The role of bias and structure in the antennal lobe connection to Kenyon cells. Manuscript in preparation

Antennal lobe (AL) in insects is an analog of the mammalian olfactory bulb in that it is organized in glomeruli, and it receives input directly from olfactory receptors. The outputs from the AL project to several higher brain area, including the mushroom body (possibly the site for the associative memory), where the output from just a few dozen glomeruli diverges to about 2,000 Kenyon cells (KCs). Our collaborator Sophie Caron (U of Utah) has collected detailed statistics on the wiring between the AL and the Kenyon cells in the fruit fly Drosophila melanogaster, such as the number of connections sent out by many of the glomeruli, and the number of connections that the KCs receive. But there are many unresolved questions. In particular it has been suggested that the wiring between AL and KCs is random, unstructured, and that some specific glomeruli send many more or many fewer connections to the KCs than average (bias in connectivity). What would be the functional role of the lack of structure and biases in wiring?

We set out to investigate this question by creating a minimal model of the fly olfactory processing, from receptors to the KCs, then assuming one of the AL-to-KCs wiring schemes (bias/no-bias and structure/no-structure), using database of receptor responses to a panel of odors as inputs, and analyzing the outputs. We find that both the bias, and, to a larger degree, structure reduce the coding capacity of the Kenyon cell outputs. We employed 3 different measures of the coding capacity/dimension of the coding space, and the result is consistent. So, possibly the random connectivity allows to maximize the number of individual odors that can be represented.
We are now investigating representation of binary mixtures, and finding that the monoglomerular odors that activate over- or under-represented glomeruli have mixture representations that are much less consistent than mixtures of multiglomerular odors. So, the investigation of the role of bias is ongoing.

2.6. **Students involved**

All components of olfactory projects have involved and will involve graduate students mentored by me, and undergraduate students, mentored by me, often with help from graduate students.

**Graduate:**


**Undergraduate:**

Biology undergraduate student Audrey Brown did a freshman-year project with me in Spring 2018. She then continued working to write and test custom software for analyzing olfactory data. I guided Audrey to learn quite a bit of neuroscience, programming, and data science.

Since the Fall of 2018 we are also been working with Elom Amematsro in Sophie Caron’s lab (Biology) to help him build a computational model for the fly early olfactory system. Elom is now running simulations, which we expect to turn into a manuscript in the next few weeks.