

# RI: Small: Synthetic Connectomics

## 1 Introduction

**Goal:** The goal of this project is to develop techniques and algorithms for an automated analysis of neural circuits (the "connectome": see below for definition) of synthetically evolved neural controllers for complex sensorimotor tasks.

**Background:** Connectomics is the study of the connectome, a complete wiring diagram of the brain (Seung 2012; Sporns 2012; Sporns et al. 2005). In the past few years, connectomics has emerged as a key methodology in neuroscience, serving as a main motivation for large collaborative projects on the brain, both in the United States (the BRAIN Initiative [Insel et al. 2013] and the Human Connectome Project [Van Essen et al. 2012]) and in Europe (the Human Brain Project [Markram 2012]). Currently, the only available connectome is that of the nematode *C. elegans* (302 neurons and complete connectivity known [White et al. 1986a]). Due to such a lack of connectome data, research efforts have been focused more on data acquisition (e.g., imaging) than on analysis (see Section 2 for details).

**Gap:** The current connectome data are largely incomplete, hindering the development of robust analysis techniques. The wiring diagram of the brain alone cannot fully represent function, thus a large amount of unknowns (polarity, synaptic strength, and delay) has to be filled in (plus neural activity: Koene 2012). Furthermore, even if a complete connectome data set is available today, scientists would be unable to make sense of it due to the extreme scale and complexity (e.g., there are 75 million neurons in the mouse brain [Williams 2000]). In sum, there is a gap in (1) connectome data (along with full physiological properties) and (2) methods for analyzing the connectome.

**Insight:** The main insight of this project is to circumvent the lack of connectome data by synthetically evolving neural circuits in fully controlled sensorimotor task environments, based on which robust analysis techniques and algorithms can be developed.

**Objectives:** The main objectives of this project are (1) to evolve synthetic neural circuits as controllers in complex sensorimotor tasks (to circumvent the incomplete data issue), and (2) to develop techniques and algorithms to analyze the synthetic connectome (to address the issue of lack in analysis tools).

**Approach:** (1) For the evolution of synthetic neural circuits, an algorithm that allows topological augmentation (Stanley and Miikkulainen 2002) will be used, thus enabling the emergence of an arbitrary neural circuit topology fit to the task. (2) For the analysis, the following methods will be explored: (a) behavior categorization (see e.g. Jenkins and Mataric 2002; Kuehne et al. 2014), (b) internal dynamics characterization (Choe et al. 2012; Kwon and Choe 2008, 2009), (c) systematic lesion studies to infer causal structures (cf. Friston; Pearl 2009; 2001), (d) individual vs. social context comparison, (e) circuit module identification through phylogenetic profiling (cf. Secretan et al. 2011), and (f) task-circuit mapping through black box transfer learning.

**Intellectual merit:** Please refer to the project summary and the research plan (Section 4).

**Broader impacts:** Please refer to the project summary and Section 5.

## 2 Background

In this section, we will review the current state of connectomics, including data acquisition (Section 2.1) and analysis techniques (Section 2.2). We will also discuss evolution of synthetic neural

circuits (Section 2.3) and their analysis (Section 2.4).

## 2.1 Connectomics: Data acquisition

Connectomics aims to obtain the connectome from the whole brain and analyze it in full detail at subcellular resolution. However, because of technological limitations, current efforts are focused on either small volumes (on the order of 100  $\mu\text{m}$ ) of nm-resolution samples or large volumes (whole brain) at hundreds of  $\mu\text{m}$  resolution.

Currently, the only full connectome that is available is that of the nematode *C. elegans*. All 302 neurons, their connections, and other somatic cells have been mapped out fully (White et al. 1986b). Various connectivity analysis (e.g., Kaiser and Hilgetag 2006; Watts and Strogatz 1998) and open-source simulation efforts (OpenWorm) are based on the *C. elegans* connectome data. The *Drosophila melanogaster* (fruit fly) connectome has also been extensively mapped, especially for the medulla in the optic lobe. However, due to the complexity of the *Drosophila* brain ( $\sim 90,000$  cells in its brain, of which  $\sim 90\%$  are neurons) compared to that of the *C. elegans*, the full connectome has not been mapped.

Cellular-level connectome (nm resolution) of larger animals seems to be beyond the horizon at the moment, although technologies for obtaining such data are actively being developed. For an overview of such methods, see Choe (2014), especially those employing electron microscopy, e.g., serial block-face electron microscopy (Denk and Horstmann 2004) and automated tape-collecting ultramicrotome (Hayworth et al. 2006). These techniques have been used to map small volumes of neural circuitry ( $\sim 100^3 \mu\text{m}^3$ ) at nm resolution (on the order of 10 nm), for example the mouse retina (Helmstaedter et al. 2013) or the rabbit retina (Anderson et al. 2011). At a similar scale, Bock et al. (2011) combined functional imaging (two-photon calcium imaging) and serial transmission electron microscopy to image 450  $\mu\text{m}$  wide and 350  $\mu\text{m}$  deep volume from the mouse visual cortex (this data set is available through the Open Connectome Project). In a similar vein, Mishchenko et al. (2010) studied the ultrastructure of rat hippocampal neuropil from serial sectioning transmission electron microscopy images (45–50 nm thick sections, 2.2 nm in-plane resolution).

At the  $\mu\text{m}$  scale, light microscopy techniques are being developed for connectomics, with the aim of obtaining local circuits based on histological stains (e.g., Knife-Edge Scanning Microscopy and related techniques: Chung et al. 2011; Li et al. 2010; Mayerich et al. 2008) and long-range projections based on tracer injections (Hintiryan et al. 2012; Mitra 2012). The typical volume that can be imaged with these methods is  $\sim 1 \text{ cm}^3$  at the resolution of  $\sim 1 \mu\text{m}$ . See Choe (2014) and Kleinfeld et al. (2011) for related approaches such as array tomography, serial two-photon tomography, and all-optical histology. Optical sectioning techniques such as scanned light-sheet microscopy (Keller et al. 2008) are also promising, especially when combined with tissue clearing methods like CLARITY (Chung and Diesseroth 2013). Fluorescence probes are routinely used to label distinct neuronal types or molecular signatures such as presynaptic vs. postsynaptic densities for the detection of synaptic connections. Most of the above techniques have been applied to mouse brain imaging (see Choe et al. 2014 for publicly available data).

In all cases above, the available data are only partial and in many cases geometric reconstructions are incomplete, thus analysis based on the data are scarce.

## 2.2 Connectomics: Analysis

As mentioned earlier, current connectomics is more focused on data acquisition than analysis. This is partly due to the lack of complete connectome data. Currently, most analysis methods

depend on graph-theory-based techniques or neuronal morphology based inference.

With a connectivity matrix (regardless of it being complete or incomplete), we can use standard graph theoretic measures such as in-degree, out-degree, clustering index, etc. (Barabasi 2002; Sporns 2002; Sporns and Tononi 2002) and also look for motifs, stereotypical subgraphs that are found to be overexpressed in the network (Watts and Strogatz 1998). These techniques have been used on the *C. elegans* connectome (White et al. 1986a), macaque visual cortical area connectivity (Kötter 2004), and diffusion MRI data of the human brain (Hagmann et al. 2007; van den Heuvel and Sporns 2011). (See Kaiser (2011) for a tutorial on graph-based connectomics analysis.) The outcome of such an analysis is broad-stroke characterizations of basic principles, such as small-world, scale-free, or rich-club (highly connected nodes connect heavily among themselves) properties and differences in those across different conditions and populations. Analysis based on optimization principles (wiring length, path length [number of hops], or energy minimization) have also led to some major insights (Chklovskii et al. 2002; Kaiser and Hilgetag 2006).

Limited efforts have been reported in the literature based on detailed 3D reconstruction of local circuits (on the scale of 100  $\mu\text{m}$ , at a resolution of  $\sim 10 \text{ nm}$ ) and in some cases correlated with activity recordings. Bock et al. (2011) used calcium imaging to map the neural activity, and fluorescence and electron microscopy to map the ultrastructure of the mouse visual cortex. They were able to correlate the orientation tuning of neurons with specific excitatory connection patterns and broader inhibitory connection patterns, confirming an earlier hypothesis regarding these connectivity patterns based on functional recordings. On the other hand, Helmstaedter et al. (2013) were able to infer new, functionally distinct class of retinal cell types in the mouse retina. Such inference was based on dendritic morphology and local circuit connectivity, leading to functional characterization (local motion and direction sensitivity).

As we can see from the above, analysis in connectomics is only in its infancy, far from being able to infer function of the whole system based on connectivity.

### 2.3 Synthetic evolution of neural circuits

Early efforts in neuroevolution were limited to adjusting the connection weight, while leaving the neural circuit topology fixed (Montana and Davis 1989; Whitley et al. 1993; Wieland 1990). In these approaches, each genotype was mapped to a full neural network. However, these approaches were not flexible enough and could not handle increasing level of task complexity. More recent approaches were based on single neuron-level evolution (Agogino et al. 2005; Gomez and Miikkulainen 1997; Moriarty and Miikkulainen 1997; Potter and Jong 2000), however, the evolved neurons had to be assembled into a network, which typically had a fixed topology.

In this project, we need a method that allows the network topology to evolve, thus the methods above are not suitable. There are several approaches that allow network topology evolution (Fullmer and Miikkulainen 1992; Yao 1999), however, these were based on weight-topology co-optimization, thus, they were not flexible enough.

For our project, we will use a neuroevolution technique called the Neuroevolution of Augmenting Topologies, or NEAT (Stanley and Miikkulainen 2002). Unlike most other neuroevolution techniques, NEAT allows the neural circuit to evolve to have an arbitrary connection topology. In NEAT, the chromosome encodes neurons and their connections separately, as well as the connection weights. Neurons and connections can be added or removed to change the network topology, thus the chromosome has a variable length. Mating of chromosomes with different network topology is achieved through the use of a quantity called “innovation number”, unique to each gene,

that indicates the evolutionary origin of that particular gene. Innovation numbers allow only compatible genes to mate (i.e., genes that have the same ancestral origin). See Figure 1 below for the genotype to phenotype mapping, and crossover of topologically different networks. Mutation is not shown in the figure but its implementation is straight-forward (insert or delete connections or neurons). Another unique mechanism of NEAT is “speciation” that helps freshly changed topology to be preserved despite the initial plunge in fitness. The rest of the algorithm is similar to other neuroevolution or evolutionary algorithms: instantiate phenotype from genotype → test in the task environment → calculate fitness → selection and reproduction.

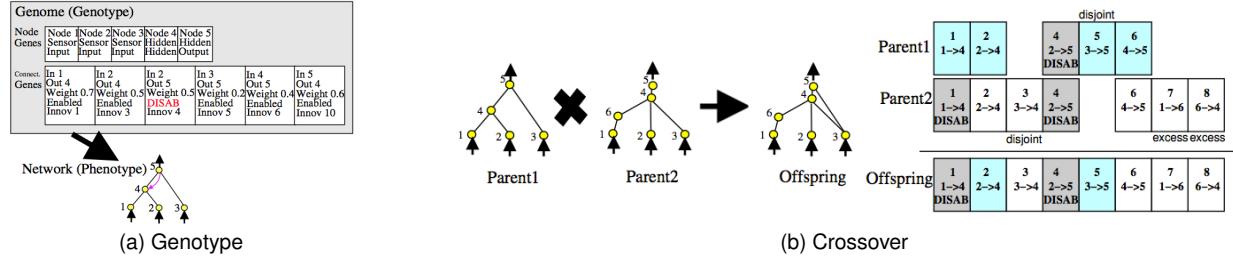


Figure 1: **Neuroevolution of Augmenting Topologies (NEAT).** (a) The genotype-to-phenotype mapping in NEAT is shown. Each node and each connection has a gene. Each connection gene has an enable/disable flag and a unique identifier, the *innovation number*. (b) Crossover of two parents with different topology is shown. The genes of the two parents are aligned so that the innovation numbers match up. Adapted from Stanley and Miikkulainen (2002).

## 2.4 Synthetic neural circuits: Analysis

Although there is a significant body of work on neuroevolution, there is surprisingly little work on the analysis of the resulting neural circuits. This is perhaps due to the task-oriented nature of neuroevolution research, where the research efforts are focused on effective evolution rules to achieve high performance or to obtain certain kinds of circuits (e.g., modular circuits).

There are only a small number of exceptions to the above (for a review, see Ruppin 2002). Beer et al. (1999) studied evolved central pattern generator (CPG) circuits in the context of insect locomotion. In the work, Beer et al. were able to correlate general motion components to specific circuit properties. However, the CPG circuits they considered had a maximum size of only 5 nodes (fully connected). Floreano and Mondada (1996), on the other hand, performed receptive field analysis of the hidden unit weights in evolved neural networks. The analysis was limited due to the standard, fully connected multilayer architecture of the neural network. Finally, Seth (2005) used a lesion technique to infer causal connectivity in evolved neural circuits. As shown by Pearl (2001), lesions can be effective means to infer causality in a graph. However, in Seth’s work, the sensorimotor controller neural network had a direct mapping from sensory to motor neurons, thus the topology was simple, and inferred function was very high level, e.g., predicting the overall behavioral fitness based on lesioned neural networks.

In sum, methods for analyzing synthetically evolved neural circuits are very limited at the time, mirroring the lack of such methods in connectomics. Furthermore, evolved networks of only very simple topology (fully connected, or multi-layer) were considered in existing works.

## 2.5 Summary

The current state of connectomics is incomplete in terms of data, while synthetically evolved neural circuits can help address the gap in the meanwhile. Both fields of connectomics and neuroevolu-

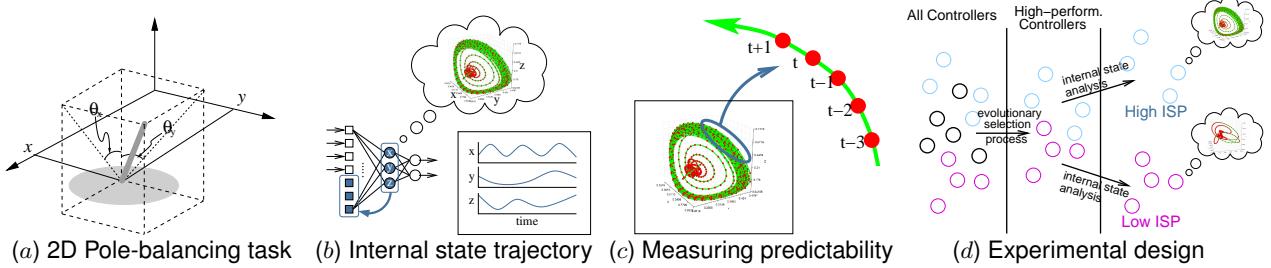
tion currently lack principled means to analyze the neural circuits, natural or synthetic.

### 3 Prior Work

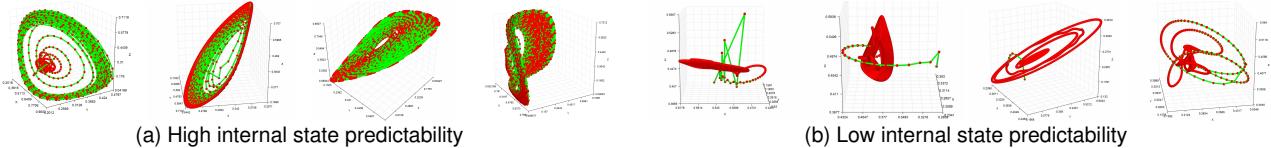
#### 3.1 Analysis of internal dynamics of evolved neural circuits

What kind of general principle can we derive from the study of neural dynamics of evolved neural circuits? In our previous work, we investigated predictive properties in the internal dynamics (hidden unit activation over time) in evolved recurrent neural network controllers (Choe et al. 2012; Kwon and Choe 2008, 2009).

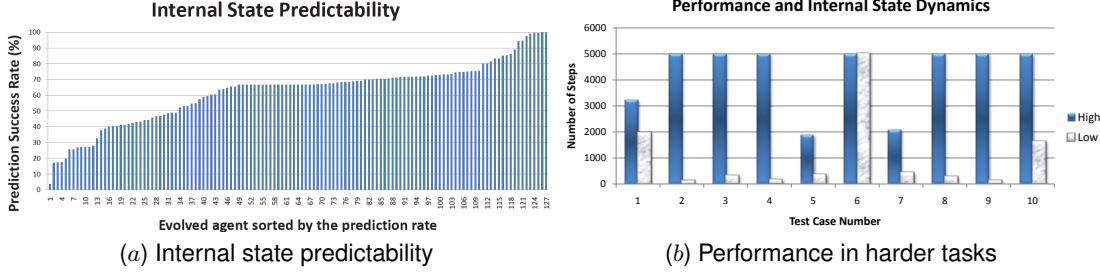
Figure 2 shows a general overview of the task and analysis framework. First, we evolved recurrent neural networks to control a cart in a 2D pole balancing task (Figure 2a). Once high-performance individuals emerged, we analyzed their internal state dynamics (Figure 2b,c,d). Predictability of the internal state trajectory (activity of 3 hidden neurons over time) was measured by training a supervised learning algorithm (backpropagation) and observing the training error, where the inputs to the predictor network were past activity values and the target output was the current activity value (Figure 2c). We found that there is a varying degree of predictability to these internal state trajectories (Figure 3 and 4a). All these individuals, regardless of the predictability of their internal states, have the same performance (meet a fixed performance criterion) since that is how they were selected (Figure 2d). However, once the task environment changes slightly, those with high predictability were able to maintain their performance while those with low predictability showed degraded performance (Figure 4b). These results suggest that dynamic properties of the internal state can hold important clues to the adaptive success of evolved neural controllers.



**Figure 2: Predictability of internal state trajectory in a pole-balancing controller network.** (a) 2D pole balancing task. (b) A recurrent neural network controller for (a), illustration of its hidden-unit activations (internal state) over time (lower right, three neurons x, y, and z), and a 3D plot of the internal state trajectory. The connection weights are adapted using genetic search. (c) Measuring predictability of internal state trajectory. Given a few past data points as input ( $t - 3$  to  $t$ ), how well can the next data point ( $t + 1$ ) on the trajectory be predicted? (d) Experimental design showing population (left), selection (middle), and post-selection analysis (right). Individuals that pass the selection stage have equal task performance, but analysis of their internal state can show different characteristics: Some with highly predictable internal state trajectory, and others much less (ISP = Internal State Predictability). Adapted from Choe et al. (2012).



**Figure 3: Internal State (Hidden Unit) Trajectories.** Examples are shown for highly predictable (top row) and hard to predict (bottom row) internal state trajectories. The three axes correspond to the three hidden units' activity level. The highly predictable group shows smooth and periodic orbits, whereas the hard to predict group shows sudden turns and tangled trajectories. Adapted from Kwon and Choe (2008).

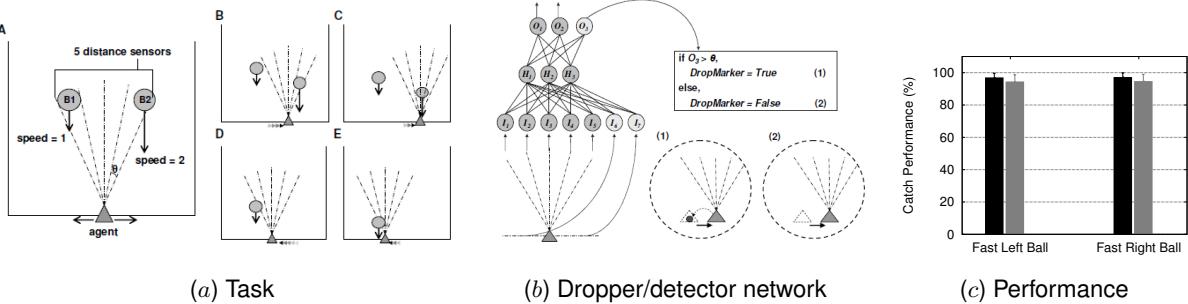


**Figure 4: Internal State Predictability and Task Performance.** Results from the analysis of internal state predictability and subsequent performance in harder task environments are shown. (a) The internal state predictability measured with a supervised learner is shown for 130 highly successful pole balancers (all of the controllers were able to balance the pole for 5,000 or more steps). There is a large variability in predictability. (b) Comparison of the top 10 (blue bar) and bottom 10 (white bar) controllers in (a) are shown. In this comparison, the pole balancing task was made harder by increasing the initial tilt angle of the pole. We can see that the controllers with high internal state predictability mostly retain their performance, while those with low predictability lose most of their performance. Adapted from Kwon and Choe (2008).

### 3.2 Evolution of primitive tool use: Utilizing external markers

To understand how synthetically evolved neural circuit controllers function, we need to examine the whole context, i.e., the agent-environment and sensorimotor coupling of the agent. Our prior work on evolved neural controllers in simple sensorimotor tasks such as ball catching (Chung and Choe 2009) and foraging (Chung and Choe 2011) demonstrates this point.

We tested whether evolved feedforward neural networks can exhibit memory related behavior, if the ability to drop and detect external environmental markers are allowed. Feedforward neural networks are reactive, thus their output only depends on the immediate input, not past input. For example, the ball catching task (Figure 5a) or the foraging task (Figure 6a) requires memory: catch first ball and return to second ball that is out of sensor range (Figure 5a); or get food from first target within the sensor range, return to nest, and get food from the second target that was seen earlier when at the first target (Figure 6a). The agent was allowed to drop and detect markers in the environment (Figure 5b and 6c). Feedforward networks cannot solve these problems.

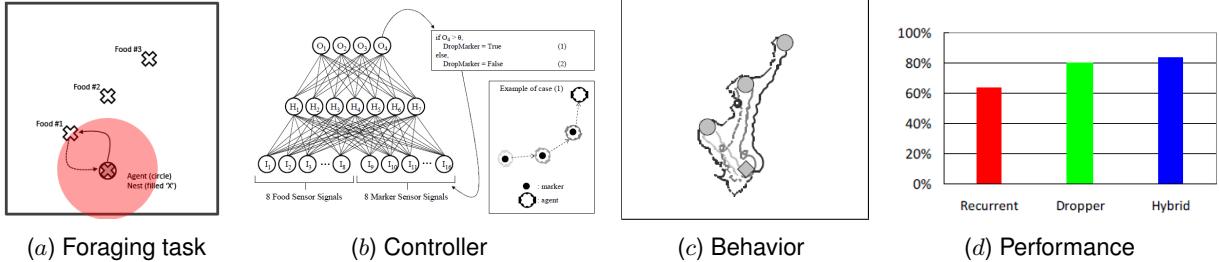


**Figure 5: Dropper/detector network's performance in ball catching.** (a) The ball catching task is illustrated. (b) The dropper/detector network is shown (it is basically feedforward). Genetic search is conducted on the connection weights. (c) Performance comparison between dropper/detector network (gray) and a recurrent network (black) is shown. See text for details. Adapted from Chung et al. (2009).

Although the evolved neural circuits are feedforward networks, with the addition of the external marker dropper/detector, we have been able to evolve agents that can exhibit memory behavior (Figure 5c and 6d). The performance was comparable to networks with built-in dynamic memory (recurrent networks) without the dropper/detector. Interestingly, behavioral patterns of drop-

per/detector networks also showed more economy (Figure 6c; recurrent network data not shown).

These results show the importance of taking into consideration environmental factors and how the agent can affect them through sensorimotor interaction.



**Figure 6: 2D foraging task and dropper/detector network.** (a) 2D foraging task is shown. The x mark at the bottom is the nest, and the top three are food sources. The foraging agent, shown as a circle, is overlaid on top of the nest. The sensor range is shown in red. (b) The controller network for the foraging agent is shown. The network is again a feedforward network, with additional sensors for marker detection and an added output for marker dropping. (c) Sample trajectory of a dropper/detector network. (d) Performance comparison is shown for three types of networks, recurrent network (red), dropper/detector network (green), and hybrid (recurrent network with dropper/detector, blue). Adapted from Chung and Choe (2011).

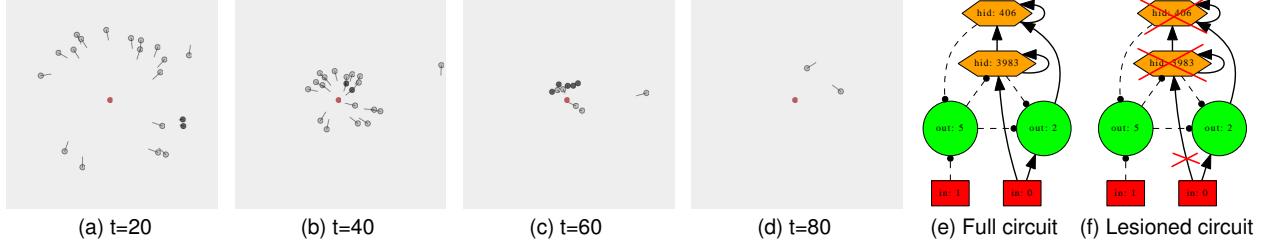
### 3.3 Results from prior NSF support

The PI has been supported by NSF as follows. (a) Award number: #1208174, Amount: \$200,868, Period: 9/1/2012–8/31/2014. (b) Title: Open Web Atlas for High-Resolution 3D Mouse Brain Data. (c) Summary: Intellectual merit: The grant resulted in innovative brain imaging and neuroinformatics frameworks, and an open online mouse brain atlas. The framework included a novel distance-attenuation technique for in-browser 3D visualization, and the use of OpenLayers mapping API for a fully multiscale navigation environment. Furthermore, interoperability with other brain atlases (such as the Allen Brain Atlas) has been incorporated. Finally, an interactive data volume viewer using WebGL was developed for free viewing of regions of interest. Broader impacts: We launched <http://kesm.org> to deliver our submicrometer-resolution mouse brain atlases ( $\sim 4.5$  TB) and published associated code on SourceForge (project: kesmba). We also ran exhibits at conferences (2012, 2013, and 2014), and organized a tutorial (2013). We also participated in Texas A&M University’s *Aggieland Saturday* event and the national *Discover Engineering* event. Three Ph.D. and four M.S. and two REU students were trained. (d) Publications: The project (and related NSF projects) resulted in three journal papers (Choe et al. 2011b; Chung et al. 2011; Mayerich et al. 2011b), seven conference papers (Choe et al. 2011a; Kwon et al. 2011; Mayerich et al. 2011a; Sung et al. 2013; Yang and Choe 2010, 2011a,b), two Ph.D. dissertations (Sung 2013; Yang 2011), six M.S. theses (Choi 2013; Kim 2011; Lal Das 2014; Shah 2014; Yang 2014; Zhang 2014) (e) Data and code are available from <http://kesm.org> and SourceForge (kesmba).

## 4 Research Plan

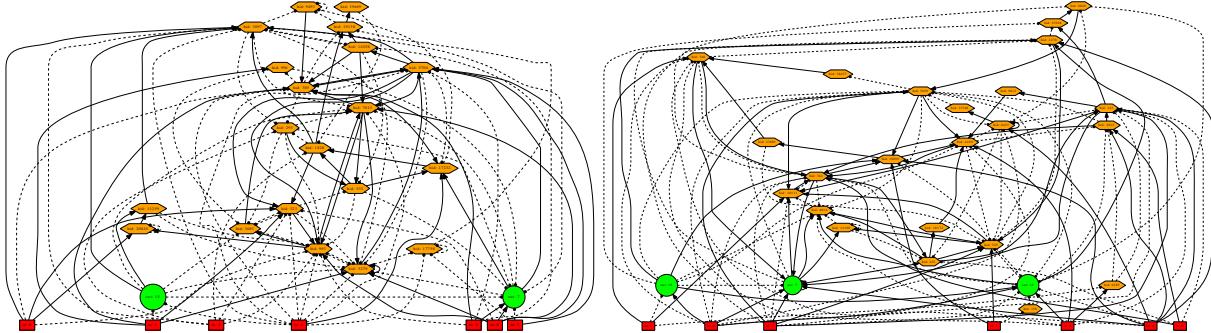
### 4.1 Task 1: Synthetic Evolution of Neural Circuits

To construct complex synthetic neural circuits that can exhibit complex behavior, we will use the NEAT algorithm (Section 2.3). NEAT enables complexification of behavior based on complexification of neural circuit topology (Stanley and Miikkulainen 2002), thus it is a good match with our aim of generating complex synthetic neural circuits.



**Figure 7: Crowded Navigation.** Navigation task in a crowded environment is shown. (a)–(d) Behavior of identical agents, trying to reach the goal in the middle. Severe crowding can be observed in step (b). (e) Simple evolved circuit (Red rectangle = input unit, green circle = output unit, orange hexagon = hidden unit, solid arrow = excitatory connection, dashed disc = inhibitory connection). (f) Lesioned circuit. Unpublished results.

We conducted preliminary simulations to test NEAT in increasingly complex and diverse task environments. Figure 7 shows a navigation task in a crowded environment. Some circuits from an early generation is also shown. Figure 8 shows more advanced circuits from later generations (these agents had more sensors than those in Figure 7). We also experimented with a more complex task of reaching a target using a tool (stick). Figure 10 shows the task and some evolved behavior.



**Figure 8: Evolved Controllers for Crowded Navigation.** More complex evolved circuits. See Figure 7 for plotting conventions. These controllers may have additional sensors such as proximity sensors (more input units) or actuators such as repellant generators (more output units). Unpublished results.

**Plan:** We will evolve neural circuits in multiple tasks that require a varying degree of perceptual, cognitive, and motor capability. We will systematically generate these tasks in a parameterized manner, along a small number of task dimensions: (1) simple vs. complex environment, (2) memory needed vs. memory not needed, (3) single vs. multiple objectives, (4) environment altering vs. not, (5) supervised learning vs. reinforcement learning, (6) single agent vs. multi agent environment.

**Research issues:** As we can see in Figure 8, the resulting circuits can be quite complex, sometimes reaching a size of hundred or more neurons. To make our analysis feasible, we will try two approaches: (1) put a conservative limit on how fast the circuits can grow, and (2) employ modular learning (Valsalam et al. 2012) in agents that have a modular morphology (also see Sims 1994).

## 4.2 Task 2a: Behavior Categorization

It would be very difficult to analyze evolved neural circuits based on holistic behavior of the agent. Also, behavior can vary greatly depending on the task and agent's sensorimotor system. For

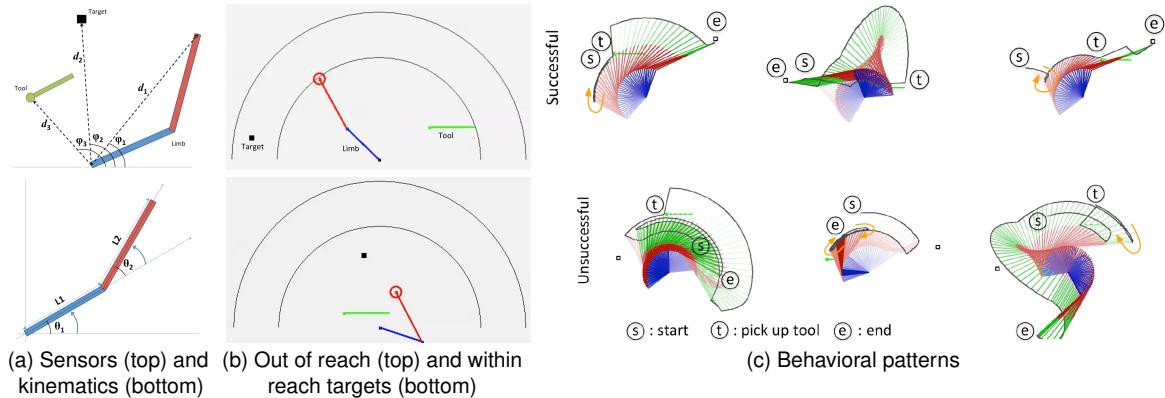
example, navigation (Figure 7), pole balancing (Figure 2, Figure 9), and jointed limb control (Figure 10) can exhibit very different kinds of behavior.

Each behavioral trajectory (regardless of the task) typically consists of multiple different segments. In navigation, moving straight, reversing, turning around, momentary stopping, etc. are good examples of such a segment (a component action or motor primitive). For target reaching with a limbed arm, moving toward target, flexing, unflexing, turn, grab tool, etc. could be natural component action. Different sub-circuits or patterns of activity may be related to these component actions, thus identifying these actions can significantly aid in the analysis.

**Plan:** We will take two main approaches to carry out behavior categorization. (1) Clustering: We will collect behavioral data into a multivariate vector and run cluster analysis based on multi-scale sliding windows. The resulting clusters can be used as initial behavioral categories. (2) Microstimulation: We will also conduct systematic microstimulation of the hidden neurons to elicit short yet coherent behavioral patterns. All hidden neurons will be stimulated in isolation for a varying length of time. This is inspired by the work of Graziano (2009), where he showed that short simulation of motor neurons in the macaque monkey lead to muscle twitches but prolonged duration of stimulation gives rise to complex behavioral patterns such as reaching or jumping.



**Figure 9: 2D Pole Balancing Behavior.** Cart position is plotted for successful (first four, red) and unsuccessful (last four, orange) trials in a 2D pole balancing task. Adapted from Kwon and Choe (2008).



**Figure 10: Tool Pick-Up and Reaching Task.** A more complex task is shown: picking up a tool (or not) and reaching a target using a jointed limb. (a) The sensors (limb angle, target [black box] and stick's [green] angle and distance) and kinematics are shown. (b) Top: target (black box) is beyond the arm's reach. Bottom: target is within the arm's reach. (c) Various evolved reaching behavior (time-lapsed: dark = close to present, light = farther into the past). Target (box) appears in random locations, and limb configuration is also random in the beginning. The agent may or may not pick up the tool. Major events are marked (s), (t), and (e). End-effector trajectories are shown as gray curves. Unpublished results.

**Research issues:** There are various parameters that may have to be tuned for the clustering step: Number of clusters, window size, etc. We will mix manual observation and systematic parameter sweep to overcome this issue. We will also employ minimum description length-based approaches for behavior segmentation (cf. Hewlett and Cohen 2011). As for the microstimulation experiment, it is unclear whether stimulating a single neuron can result in expressed behavior. We will co-stimulate tightly coupled neurons (e.g., clusters of neurons identified in Section 4.3 right below) in

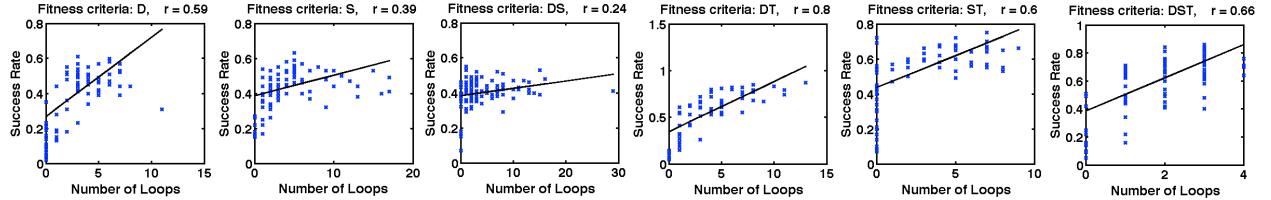
case we cannot elicit coherent behavior.

**Evaluation:** The research team will manually rank the quality of behavioral categorization resulting from the above approach. On the order of 100 categories will be ranked as bad (=0), neutral (=5), or good (=10), and the average score will be calculated.

### 4.3 Task 2b: Internal Dynamics Characterization

Measuring the internal state activity and analyzing the dynamic trajectories will be of key importance to this project. (See Figure 3 for example trajectories.) The internal dynamics is initiated by input stimulus and partly modulated by the agents' own actions. Thus, analysis of internal dynamics must be investigated in the behavioral context. We will collect neuronal activation time series while the agent is behaving in the environment, so that behavior and internal activity can be co-registered.

**Plan:** Analysis of the internal dynamics will be in many ways similar to that of the motor behavior (Section 4.2): (1) clustering, (2) segmentation, (3) phase-plane analysis (including detection of phase transitions), and (4) stimulus-induced activity measurement to characterize receptive fields. Furthermore, (5) we will extract time series data that correspond to component actions identified in Section 4.2 and analyze their properties. (6) We will also check the correlation between the number of cycles in the neural circuit (the connectivity graph), as these recurrent loops contribute to memory and give rise to periodic dynamics (Figure 11). Finally, (7) we will conduct selected microstimulations and observe their effects. For the analysis, we will use mutual information (Sporns and Tononi 2002), predictability (Choe et al. 2012; Kwon and Choe 2008), synchronization (Choe and Miikkulainen 2004), and other quantitative measures. The techniques we develop for this task will serve as a basis for subsequent tasks (Section 4.4 to 4.6).



**Figure 11: Number of Cycles in the Connectivity Graph vs. Performance.** The correlation between number of cycles (loops) in the neural circuit graph vs. fitness is shown for different fitness criteria used (D: distance to target; S: # steps taken; T: # times tool picked up; DS, ST, DST: combined fitness [by multiplication]). The task was the reaching task in Figure 10. More cycles generally led to higher fitness. Unpublished results.

**Research issues:** The example shown in Figure 3 is for a convenient case where there are only 3 hidden neurons, so visualization is trivial. However, in a general case, the internal state has a much higher dimension. Our planned clustering can help, but we will also use dimensionality reduction techniques, both linear (PCA) and nonlinear (ISOMAP, LLE, etc.) to tackle this issue. In terms of counting the loops, we may have to normalize the count by the overall size of the graph (number of nodes), since more advanced circuits appear later in the generation and they tend to be large in size and thus potentially contain more loops. Finally, since connections can have either a positive sign (excitatory) or a negative sign (inhibitory), the analysis can become non-trivial. Almost all graph-based approaches assume that connections are excitatory. With inhibitory connections, disinhibition and other unintuitive effects can emerge (see e.g., Choe 2004). We expect this difficulty can be overcome to some degree by considering groups of neurons as a unit

(see Section 4.6 for module identification) and minimizing inhibitory interaction across groups.

**Evaluation:** A similar approach as Section 4.2 will be used for the validation of our method.

#### 4.4 Task 2c: Systematic Lesion Studies

When analyzing a neural circuit, inferring the causal ordering of neural activation can help. For example, which upstream neuron's firing causes some other downstream neuron's firing? Such causal relations can be inferred effectively using lesions (or *surgery*, as called by Pearl 2001).

**Plan:** Based on preliminary analysis (other sections), we will choose certain connections or nodes to remove (see Research Issues right below for details). Next, we will form a hypothesis of how the lesion will affect the behavior and the internal dynamics. Finally, after the lesion, we will observe changes in the behavior (Section 4.2) and the internal dynamics (Section 4.3), and compare to our predictions. Component actions identified in Section 4.2 will allow us to take a modular approach when choosing the locus of lesion. How to choose the right locus and size of the lesion will be a major consideration. The effect of lesion closer to the sensory neurons or the motor neurons would be easier to analyze, so we will start with those neurons. Next, we will use the internal dynamics clustering results from Section 4.3 to identify groups of neurons to be lesioned and observe the effect. Finally, we will start with a given component action identified in Section 4.2 and search for lesion sites that selectively disable that specific component action (this can be done by searching the path that links appropriate sensors to their actuators: cf. Izquierdo and Beer 2013, where a similar approach was taken to analyze the *C. elegans* klinotaxis circuit).

**Research issues:** It is possible that lesioning can break parts of the on-going dynamics in the neural circuit. For example, Seth (2005) argued that causal analysis should be done without lesioning to preserve the native dynamics. In his work, vector autoregressive modeling was combined with the Granger causality measure to conduct causal analysis. We will adopt this approach in case we find that lesioning disrupts normal dynamics of the neural circuit.

**Evaluation:** We will use the set of component actions in Section 4.2 to measure and validate the effects of lesion. We will also be able to validate causal modeling approaches for functional connectivity inference (Friston 2009; Lee 2011) since we have full connectivity and activity data.

#### 4.5 Task 2d: Individual vs. Social Context Comparison

It is important to consider the social context when analyzing the neural circuits. This applies to all tasks discussed above: behavior, internal dynamics, and lesion studies. For example, consider the lesion study. When the input representation and output representation are a good match, lesion studies can sometimes turn up paradoxical results depending on single or multi agent configuration. For example, consider the neural circuit in Figure 7e. It was evolved in the crowded navigation task (Figure 7). We removed connections and nodes one by one, finally reaching Figure 7f, where all hidden neurons are removed. Strangely, this stripped circuit still performed well. On further investigation, we found that this made sense, since one input is a fixed value and this one was linked positively to the thrust output (move forward), and the other input, the angle to the goal sensor, was linked negatively to the orientation output (turn heading). However, it turns out that this kind of success is only possible when the agent is taken out of the crowded navigation context. If the stripped agent is put in a crowded context, it could not perform well due to deadlock-like situations, and without any memory it was unable to realize that there is any problem.

**Plan:** For the different tasks and different kinds of analyses (other sections above), we will repeat the experiments and compare the results during (1) individual behavior and (2) group behavior.

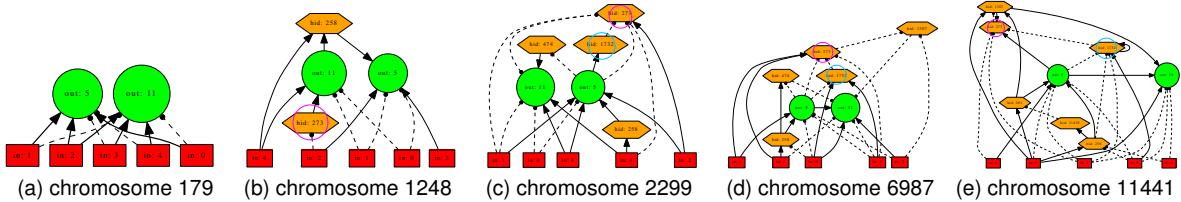
Comparing all different combinations of tasks vs. analysis techniques may be too much work. We will begin with analysis techniques that are expected to show a more obvious difference in the individual vs. social context, e.g., the lesion analysis (Section 4.4).

**Research issues:** Depending on the task, the degree of social interaction can vary greatly. For example, the interactions can become quite complex in a competitive coevolution environments (Stanley and Miikkulainen 2004). We will limit our experiments to simple social interactions such as collision avoidance, etc.

**Evaluation:** Task performance and behavioral observation (e.g., are all component actions observed) under the two conditions (individual vs. social) will be used for the evaluation.

## 4.6 Task 2e: Circuit Module Identification Through Phylogenetic Profiling

One important merit of synthetically evolved neural circuits is that we have full access to the phylogenetic history of any given neural circuit. Furthermore, due to the innovation number feature in NEAT, we can also keep track of individual neuron and connection's ancestry. For example, see Figure 12, where descendants of a simple initial circuit (a) is shown. As marked in the figure (hid:273), we can see which neuron originated when and how their participation in a growing circuit changes over time. Furthermore, certain groups of neurons maintain their close coupling as the generation moves on (hid:273 and hid:1732). We can exploit this property to make the neural circuit analysis much easier, starting with a minimal circuit that has an identified function, and gradually adding to the complexity. Also, we can identify modules based on their evolutionary ancestry. This kind of analysis is not possible in natural connectomics (although a similar approach may be possible by looking into developmental stages of brain formation).



**Figure 12: Phylogenetic Progression.** Evolved neural circuits sorted by their ancestral order is shown (toward left: ancestors, toward right: descendants). The task was simple navigation. Plotting conventions are the same as Figure 7. Certain hidden neurons (hid:258 [not marked] and hid:273 [circled in magenta]) appear quite early (in b) and persist till the end (in e). Later on, hid:273 pairs up with hid:1732 (circled in cyan) and this pair persists toward the end. Unpublished results.

**Plan:** Circuit modules are duals of functional units. The purpose of searching for modules is to learn what functional units exist. On the other hand, when we already have some functional units in mind (such as attention, memory, sequence learning, binding, normalization, decision making, etc. [see Marcus et al. 2014]), then we can search specifically for circuit modules that serve those functions. So, here we have a chicken-or-egg problem. However, we can turn this to our advantage. We can direct our search for modules in both directions: (1) given a sub-circuit, look for component actions they are related to, and (2) given a component action, look for sub-circuits that affect it. The identified modules will be passed through a series of lesion experiments (Section 4.4) to see if the lesions lead to selective disablement of component actions identified in Section 4.2. We will also check if modules persist over generations.

**Research issues:** In NEAT, the sign (polarity) of the connection, not just the weight, can change as part of the mutation process. This is not biologically plausible and can make phylogenetic

analysis difficult since totally opposite function can emerge as a result of a single mutation. For the various tasks of the agents, we will first test if turning off connection sign mutation seriously affects NEAT performance. Once it is confirmed we will disable connection sign mutation.

**Evaluation:** We will identify modules based on clustering and other methods described in the sections above for validation. Identified modules from a series of neural circuits with the same ancestral origin will be compared. We will also evolve circuits using a modular neuroevolution techniques (Valsalam et al. 2012) where the modules are clearly predefined (e.g., for a modular morphology), and use our approach to identify modules. Finally, we will validate the module’s function against physical laws derived from behavior (using Schmidt and Lipson 2009).

## 4.7 Task 2f: Task-Circuit Mapping Through Black Box Transfer Learning

Our final approach is to use machine learning to map neural circuits to specific tasks, treating the neural circuit as a black box. This is a more holistic approach when a complete circuit is used, but it can also be used to test sub-circuit function. The basic idea is to sandwich an arbitrary synthetic neural circuit  $N$  with machine learning algorithms at the input ( $ML_A$ ) and the output side ( $ML_B$ ), as shown in Figure 13. Then we subject the combined system to different categories of real and parametrically generated tasks (various supervised, unsupervised, and reinforcement learning tasks;  $task_1, task_2, \dots, task_n$ ). Our assumption is that the hybrid system will achieve the highest performance when the task and circuit matches. In the figure, (1)  $task_2$  is fed into the hybrid ML-neural circuit system, and the hybrid system is activated. (2) Outcome from the hybrid system is returned to the task specification and the performance measured, which in turn (3) provides feedback signal to the machine learning algorithms. If the neural circuit implements a function closest to  $task_i$ , the performance on  $task_i$  will be the highest, compared to other tasks. Our preliminary results on supervised learning tasks (neural network trained with  $task_i$ , tested with  $task_j$ , where  $i$ =row and  $j$ =column index) show that this approach can indeed be effective (Figure 13b), where the diagonal entries (meaning task matches the circuit) have the highest value (max value normalized to 1.0).

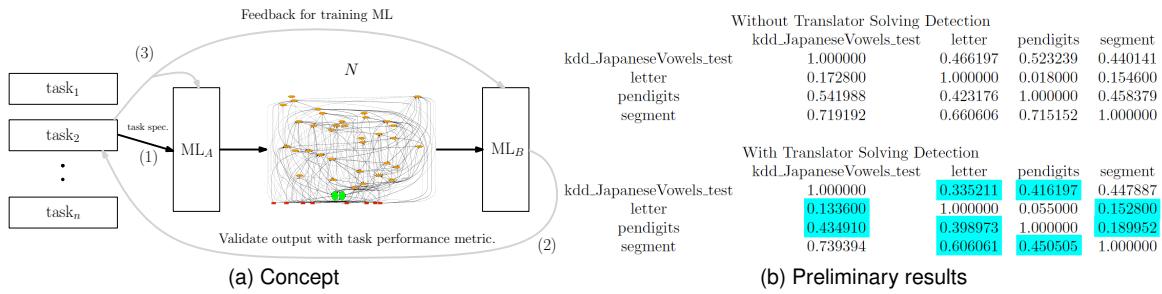


Figure 13: **Blackbox Transfer Learning to Infer Neural Circuit Function.** (a) Given a set of tasks and an unknown circuit ( $N$ ), can we train input and output translators ( $ML_A$  and  $ML_B$ , respectively) so that the circuit  $N$  can perform well in each task? The main hypothesis is that the task that matches the circuit would result in the highest performance. A key to this approach is to prevent the translators themselves from solving the task, while using the neural circuit as some sort of a noisy communication channel. (b) Preliminary results, without (top) and with (bottom) preventive measures against translators themselves solving the task (solving detection). See text for details. Unpublished results.

**Plan:** We will conduct experiments outlined above (and Figure 13). The choice of algorithm for the ML boxes is open ended, however, we will first experiment with NEAT as it starts out as a fully connected one-layer feedforward neural network, thus is largely assumption free. One main concern is that the machine learning algorithms ( $ML_A$  and  $ML_B$ ) themselves are powerful

enough to solve the problem by themselves, just using the neural circuit  $N$  as an information conduit. Three methods will be used to circumvent this problem: (1) Check if  $ML_X$  is doing the real work, by treating  $ML_X$  as the neural circuit  $N$  itself and repeating the experiment with brand new  $ML_A/ML_B$  wrappers. (2) Using different categories of machine learning tasks (e.g., supervised, unsupervised, and reinforcement learning) serves as a natural deterrent for this kind of behavior. For example, a circuit evolved on a supervised learning task will not be suitable for a reinforcement learning task. (3) Use mutual information measurement to ensure that the output of the  $ML_A$  and  $ML_B$  boxes does not contain information encoding solutions of the task. Figure 13b shows pilot results of this information theory-based approach, where results using this mechanism (matrix in the bottom: “With translator solving detection”) show lower score (highlighted in cyan) for task-circuit mismatch (off-diagonal entries), compared to the case without the mechanism (matrix on top: “Without translator solving detection”).

**Research issues:** One immediate issue is the mismatch in dimensionality of the input and output of the task environment and the neural circuit. This can be easily fixed by adjusting the NEAT network size in the ML boxes. We will also consider using dimensionality reduction techniques to match the dimensions. Another issue is that given an unknown neural circuit, it is difficult to know a priori what sorts of tasks should be given. We will combine lesion studies (Section 4.4) with extracted component actions (Section 4.2) to pair up subset of the neural circuit with smaller unit tasks. This approach will also make the analysis scalable, by inferring the function of the neural circuit, module by module.

**Evaluation:** Evaluation will be done through a systematic pairing of neural circuit vs. task, and the results collected as in Figure 13b. We will also compare the “with” and “without solving detection” conditions to prevent the ML boxes solving the tasks themselves, bypassing the neural circuits.

## 4.8 Summary of Research Plan

In summary, we will construct and validate a synthetic neural circuit analysis pipeline (Figure 14). This project goes beyond structural connectomics (Sporns 2012; Sporns et al. 2005) or brain activity mapping (Alivisatos et al. 2012; Koene 2012) by encompassing both. Furthermore, the project incorporates the behavioral and environmental aspect of the agent into the analysis, enabling a full, systematic investigation of neural circuit function. The focus of this project is on synthetic neural circuits, but the methods we develop here will be equally applicable to real connectome data, and more importantly it will *inform connectomics what kind of data it will need to reach its ultimate goal*. As a proof-of-concept, we will apply our methods to existing *C. elegans* data (White et al. 1986b) and compare to published analysis results such as those by Izquierdo and Beer (2013).

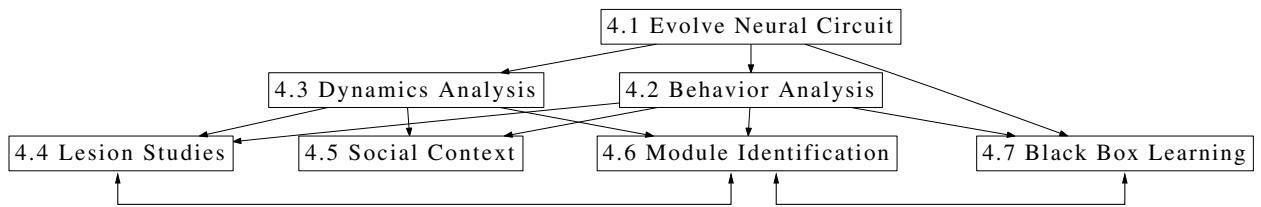


Figure 14: **Analysis Pipeline.** The relationship between various tasks are shown. Also see Table 1.

## 5 Broader Impacts of the Proposed Work

Broader impacts of this project will be reinforced through concrete activities described below.

**5.1 Interactive web-portal for the exploration of the synthetic connectome:** This research project will generate a variety of simple to complex neural controllers and simulations in sensorimotor control tasks. These neural circuits and behavioral simulations will be curated and integrated into an online portal where the general public can interact, experiment, and analyze the neural circuits and simulations. The research team will publicize the resource through YouTube videos and social media.

**5.2 Synthetic connectomics challenge:** A “synthetic connectomics challenge” will be organized at major conferences such as Neural Information Processing Systems and International Joint Conference on Neural Networks. The challenge will include pre-analyzed circuits (resulting from our project) and novel circuits that have not been analyzed by us.

**5.3 Education:** Graduate students will be trained as part of this project (direct funding via this grant). Undergraduate students will be trained using the REU supplement mechanism (support for year 1 [summer 2016] requested in the budget) and the college-level undergraduate summer research program at Texas A&M University College of Engineering. Research results will be incorporated into graduate and undergraduate level courses: Introduction to Artificial Intelligence (undergrad and graduate), Machine Learning (graduate), Neural Networks (graduate), and Cortical Networks (graduate).

**5.4 Dissemination:** All source code and data will be released to the public using GNU Public License and Open Data Commons Attribution License. See the Data Management Plan in the supplementary documents section for details.

**5.5 Summary of Broader Impacts:** The interactive portal will allow the general public to engage in the project in a playful and entertaining manner, all the while being educated. The synthetic connectomics challenge will start a whole new field, and the collective findings will help propel natural connectomics research. Graduate and undergraduate students trained in this project are expected to become outstanding multidisciplinary researchers. Code and data dissemination will enable other research groups to easily extend upon this research.

## 6 Management Plan

The time line for each task in the research plan and the broader impact plan is shown below, semester by semester, starting with Fall 2015. The PI and two graduate students will be the core personnel for this project. For each semester, roughly 3 to 4 tasks are scheduled, which will be distributed evenly among the research team. The research team will hold a weekly meeting resembling a SCRUM (Cohn 2010) meeting to make continual progress. Broader impact activities such as REU training and dissemination are included in all 3 years.

Table 1: Tasks and Timeline

Task	Y1	Y2	Y3
Task 1 (§4.1) Evolve synthetic neural circuits			
Task 2a (§4.2) Behavior categorization			
Task 2b (§4.3) Internal dynamics characterization			
Task 2c (§4.4) Systematic lesion studies			
Task 2d (§4.5) Individual vs. social context comparison			
Task 2e (§4.6) Circuit module identification through phylogenetic profiling			
Task 2f (§4.7) Task-circuit mapping through black box transfer learning			
Broader impact (§5)	—	—	—

## REFERENCES CITED

- Agogino, A., Tumer, K., and Miikkulainen, R. (2005). Efficient credit assignment through evaluation function decomposition. In *Proceedings of the 7th annual conference on Genetic and evolutionary computation*, 1309–1316. ACM.
- Alivisatos, A. P., Chun, M., Church, G. M., Greenspan, R. J., Roukes, M. L., and Yuste, R. (2012). The brain activity map project and the challenge of functional connectomics. *Neuron*, 74(6):970–974.
- Anderson, J. R., Jones, B. W., Watt, C. B., Shaw, M. V., Yang, J.-H., DeMill, D., Lauritzen, J. S., Lin, Y., Rapp, K. D., Mastronarde, D., Koshevoy, P., , Grimm, B., Tasdizen, T., , Whitaker, R., , and Marc, R. E. (2011). Exploring the retinal connectome. *Molecular Vision*, 17:355–379.
- Barabasi, A.-L. (2002). *Linked: The New Science of Networks*. Cambridge, MA: Perseus Publishing.
- Beer, R. D., Chiel, H. J., and Gallagher, J. C. (1999). Evolution and analysis of model cpgs for walking: II. general principles and individual variability. *Journal of computational neuroscience*, 7(2):119–147.
- Bock, D. D., Kerlin, A. M., Andermann, M. L., Hood, G., Wetzel, A. W., Yurgenson, S., Soucy, E. R., Kim, H. S., and Reid, R. C. (2011). Network anatomy and in vivo physiology of visual cortical neurons. *Nature*, 471:177–182.
- Chklovskii, D., Schikorski, T., and Stevens, C. (2002). Wiring optimization in cortical circuits. *Neuron*, 34:341–347.
- Choe, Y. (2004). The role of temporal parameters in a thalamocortical model of analogy. *IEEE Transactions on Neural Networks*, 15:1071–1082.
- Choe, Y. (2014). Physical sectioning microscopy. In Jaeger, D., and Jung, R., editors, *Encyclopedia of Computational Neuroscience*. Berlin: Springer. First edition. In press.
- Choe, Y., Kwon, J., and Chung, J. R. (2012). Time, consciousness, and mind uploading. *International Journal on Machine Consciousness*, 4:257–274.
- Choe, Y., Kwon, J., Mayerich, D., and Abbott, L. C. (2014). Connectome, mouse. In Jaeger, D., and Jung, R., editors, *Encyclopedia of Computational Neuroscience*. Berlin: Springer. First edition. In press.
- Choe, Y., Mayerich, D., Kwon, J., Miller, D. E., Chung, J. R., Sung, C., Keyser, J., and Abbott, L. C. (2011a). Knife-edge scanning microscopy for connectomics research. In *Proceedings of the International Joint Conference on Neural Networks*, 2258–2265. Piscataway, NJ: IEEE Press.
- Choe, Y., Mayerich, D., Kwon, J., Miller, D. E., Sung, C., Chung, J. R., Huffman, T., Keyser, J., and Abbott, L. C. (2011b). Specimen preparation, imaging, and analysis protocols for knife-edge scanning microscopy. *Journal of Visualized Experiments*, 58:e3248. doi: 10.3791/3248.
- Choe, Y., and Miikkulainen, R. (2004). Contour integration and segmentation in a self-organizing map of spiking neurons. *Biological Cybernetics*, 90:75–88.

Choi, J. (2013). *Knife-Edge Scanning Microscope Mouse Brain Atlas in Vector Graphics for Enhanced Performance*. Master's thesis, Department of Computer Science and Engineering, Texas A&M University.

Chung, J. R., and Choe, Y. (2009). Emergence of memory-like behavior in reactive agents using external markers. In *Proceedings of the 21st International Conference on Tools with Artificial Intelligence, 2009. ICTAI '09*, 404–408.

Chung, J. R., and Choe, Y. (2011). Emergence of memory in reactive agents equipped with environmental markers. *IEEE Transactions on Autonomous Mental Development*, 3:257–271.

Chung, J. R., Kwon, J., and Choe, Y. (2009). Evolution of recollection and prediction in neural networks. In *Proceedings of the International Joint Conference on Neural Networks*, 571–577. Piscataway, NJ: IEEE Press.

Chung, J. R., Sung, C., Mayerich, D., Kwon, J., Miller, D. E., Huffman, T., Abbott, L. C., Keyser, J., and Choe, Y. (2011). Multiscale exploration of mouse brain microstructures using the knife-edge scanning microscope brain atlas. *Frontiers in Neuroinformatics*, 5:29.

Chung, K., and Diesseroth, K. (2013). CLARITY for mapping the nervous system. *Nature Methods*, 10:508–513.

Cohn, M. (2010). *Succeeding with agile: software development using Scrum*. Pearson Education.

Denk, W., and Horstmann, H. (2004). Serial block-face scanning electron microscopy to reconstruct three-dimensional tissue nanostructure. *PLoS Biology*, 19:e329.

Floreano, D., and Mondada, F. (1996). Evolution of homing navigation in a real mobile robot. *Systems, Man, and Cybernetics, Part B: Cybernetics, IEEE Transactions on*, 26(3):396–407.

Friston, K. (2009). Causal modelling and brain connectivity in functional magnetic resonance imaging. *PLoS Biology*, 7:e1000033.

Fullmer, B., and Miikkulainen, R. (1992). Using marker-based genetic encoding of neural networks to evolve finite-state behaviour. In Varela, F. J., and Bourgine, P., editors, *Toward a Practice of Autonomous Systems: Proceedings of the First European Conference on Artificial Life*, 255–262. Cambridge, MA: MIT Press.

Gomez, F., and Miikkulainen, R. (1997). Incremental evolution of complex general behavior. *Adaptive Behavior*, 5(3-4):317–342.

Graziano, M. (2009). *The Intelligent Movement Machine: An Ethological Perspective on the Primate Motor System*.

Hagmann, P., Kurant, M., Gigandet, X., Thiran, P., Wedeen, V. J., Meuli, R., and Thiran, J.-P. (2007). Mapping human whole-brain structural networks with diffusion MRI. *PLoS ONE*, 2:e597.

Hayworth, K. J., Kasthuri, N., Schalek, R., and Lichtman, J. W. (2006). Automating the collection of ultrathin sections for large volume TEM reconstructions. *Microscopy and Microanalysis*, 12(Suppl. S02):86–87.

- Helmstaedter, M., Briggman, K. L., Turaga, S. C., Jain, V., Seung, H. S., and Denk, W. (2013). Connectomic reconstruction of the inner plexiform layer in the mouse retina. *Nature*, 500:168–174.
- Hewlett, D., and Cohen, P. (2011). Fully unsupervised word segmentation with bve and mdl. In *Proceedings of the 49th Annual Meeting of the Association for Computational Linguistics: Human Language Technologies: short papers-Volume 2*, 540–545. Association for Computational Linguistics.
- Hintiryan, H., Gou, L., Zingg, B., Yamashita, S., Lyden, H. M., Song, M. Y., Grewal, A. K., Zhang, X., Toga, A. W., and Dong, H.-W. (2012). Comprehensive connectivity of the mouse main olfactory bulb: Analysis and online digital atlas. *Frontiers in Neuroanatomy*, 6(30).
- Insel, T. R., Landis, S. C., and Collins, F. S. (2013). The nih brain initiative. *Science*, 340(6133):687–688.
- Izquierdo, E. J., and Beer, R. D. (2013). Connecting a connectome to behavior: an ensemble of neuroanatomical models of *c. elegans* klinotaxis. *PLoS computational biology*, 9(2):e1002890.
- Jenkins, O. C., and Mataric, M. J. (2002). Deriving action and behavior primitives from human motion data. In *Intelligent Robots and Systems, 2002. IEEE/RSJ International Conference on*, vol. 3, 2551–2556. IEEE.
- Kaiser, M. (2011). A tutorial in connectome analysis: Topological and spatial features of brain networks. *NeuroImage*, 57:892–907.
- Kaiser, M., and Hilgetag, C. C. (2006). Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLoS Computational Biology*, 2:805–815.
- Keller, P. J., Schmidt, A. D., Wittbrodt, J., , and Stelzer, E. H. K. (2008). Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy. *Science*, 322:1065–1069.
- Kim, D. (2011). *Automatic Seedpoint Selection and Tracing of Microstructures in the Knife-Edge Scanning Microscope Mouse Brain Data Set*. Master's thesis, Department of Computer Science, Texas A&M University, College Station, Texas.
- Kleinfeld, D., Bharioke, A., Blinder, P., Bock, D. D., Briggman, K. L., Chklovskii, D. B., Denk, W., Helmstaedter, M., Kaufhold, J. P., Lee, W.-C. A., Meyer, H. S., Micheva, K. D., Oberlaender, M., Prohaska, S., Reid, R. C., Smith, S. J., Takemura, S., Tsai, P. S., , and Sakmann, B. (2011). Large-scale automated histology in the pursuit of connectomes. *Journal of Neuroscience*, 31:16125–16138.
- Koene, R. A. (2012). Experimental research in whole brain emulation: the need for innovative in vivo measurement techniques. *International Journal of Machine Consciousness*, 4(01):35–65.
- Kötter, R. (2004). Online retrieval, processing, and visualization of primate connectivity data from the cocomac database. *Neuroinformatics*, 2(2):127–144.

- Kuehne, H., Fraunhofer, F., Arslan, A., and Serre, T. (2014). The language of actions: Recovering the syntax and semantics of goal-directed human activities. In *2014 IEEE Conference on Computer Vision and Pattern Recognition*, 780–787. IEEE.
- Kwon, J., and Choe, Y. (2008). Internal state predictability as an evolutionary precursor of self-awareness and agency. In *Proceedings of the Seventh International Conference on Development and Learning*, 109–114. IEEE.
- Kwon, J., and Choe, Y. (2009). Facilitating neural dynamics for delay compensation: A road to predictive neural dynamics?. *Neural Networks*, 22:267–276.
- Kwon, J., Mayerich, D., and Choe, Y. (2011). Automated cropping and artifact removal for knife-edge scanning microscopy. In *Proceedings of the IEEE International Symposium on Biomedical Imaging*, 1366–1369.
- Lal Das, S. (2014). *Cell Detection in Knife-Edge Scanning Microscopy Images of Nissl-stained Mouse and Rat Brain Samples using Random Forests*. Master's thesis, Department of Computer Science and Engineering, Texas A&M University.
- Lee, J. H. (2011). Tracing activity across the whole brain neural network with optogenetic functional magnetic resonance imaging. *Frontiers in neuroinformatics*, 5.
- Li, A., Gong, H., Zhang, B., Wang, Q., Wan, C., Wu, J., Liu, Q., Zeng, S., and Luo, Q. (2010). Micro-optical sectioning tomography to obtain a high-resolution atlas of the mouse brain. *Science*, 330:1404–1408.
- Marcus, G., Marblestone, A., and Dean, T. (2014). The atoms of neural computation. *Science*, 346(6209):551–552.
- Markram, H. (2012). The human brain project. *Scientific American*, 306(6):50–55.
- Mayerich, D., Abbott, L. C., and McCormick, B. H. (2008). Knife-edge scanning microscopy for imaging and reconstruction of three-dimensional anatomical structures of the mouse brain. *Journal of Microscopy*, 231:134–143.
- Mayerich, D., Kwon, J., Panchal, A., Keyser, J., and Choe, Y. (2011a). Fast cell detection in high-throughput imagery using gpu-accelerated machine learning. In *Proceedings of the IEEE International Symposium on Biomedical Imaging*, 719–723.
- Mayerich, D., Kwon, J., Sung, C., Abbott, L. C., Keyser, J., and Choe, Y. (2011b). Fast macro-scale transmission imaging of microvascular networks using KESM. *Biomedical Optics Express*, 2:2888–2896.
- Mishchenko, Y., Hu, T., Spacek, J., Mendenhall, J., Harris, K. M., and Chklovskii, D. B. (2010). Ultrastructural analysis of hippocampal neuropil from the connectomics perspective. *Neuron*, 67:1009–1020.
- Mitra, P. P. (2012). Technical white paper: Mouse brain architecture project. Technical report, Cold Spring Harbor Laboratory. <http://brainarchitecture.org>.
- Montana, D. J., and Davis, L. (1989). Training feedforward neural networks using genetic algorithms. In *Proceedings of the 11th International Joint Conference on Artificial Intelligence*, 762–767. San Francisco, CA: Morgan Kaufmann.

- Moriarty, D. E., and Miikkulainen, R. (1997). Forming neural networks through efficient and adaptive co-evolution. *Evolutionary Computation*, 5:373–399.
- Pearl, J. (2001). Reasoning with cause and effect. *AI Magazine*, 23:95–111.
- Potter, M. A., and Jong, K. A. D. (2000). Cooperative coevolution: An architecture for evolving coadapted subcomponents. *Evolutionary Computation*, 8:1–29.
- Ruppin, E. (2002). Evolutionary autonomous agents: A neuroscience perspective. *Nature Reviews Neuroscience*.
- Schmidt, M., and Lipson, H. (2009). Distilling free-form natural laws from experimental data. *science*, 324(5923):81–85.
- Secretan, J., Beato, N., D'Ambrosio, D. B., Rodriguez, A., Campbell, A., Folsom-Kovarik, J. T., and Stanley, K. O. (2011). Picbreeder: A case study in collaborative evolutionary exploration of design space. *Evolutionary Computation*, 19(3):373–403.
- Seth, A. K. (2005). Causal connectivity of evolved neural networks during behavior. *Network: Computation in Neural Systems*, 16(1):35–54.
- Seung, H. S. (2012). *Connectome: How the Brain's Wiring Makes Us Who We Are*. Boston, MA: Houghton Mifflin Harcourt.
- Shah, R. S. (2014). *Reducing Chatter in Knife-Edge Scanning Microscopy*. Master's thesis, Department of Computer Science and Engineering, Texas A&M University.
- Sims, K. (1994). Evolving 3D morphology and behavior by competition. In Brooks, R. A., and Maes, P., editors, *Proceedings of the Fourth International Workshop on the Synthesis and Simulation of Living Systems (Artificial Life IV)*, 28–39. Cambridge, MA: MIT Press.
- Sporns, O. (2002). Graph theory methods for the analysis of neural connectivity patterns. In Kötter, R., editor, *Neuroscience Databases: A Practical Guide*. Boston, MA: Kluwer Publishers.
- Sporns, O. (2012). *Discovering the Human Connectome*. Cambridge, MA: MIT Press.
- Sporns, O., and Tononi, G. (2002). Classes of network connectivity and dynamics. *Complexity*, 7:28–38.
- Sporns, O., Tononi, G., and Kötter, R. (2005). The human connectome: A structural description of the human brain. *PLoS Computational Biology*, 1:e42.
- Stanley, K. O., and Miikkulainen, R. (2002). Evolving neural networks through augmenting topologies. *Evolutionary Computation*, 10:99–127.
- Stanley, K. O., and Miikkulainen, R. (2004). Competitive coevolution through evolutionary complexification. *Journal of Artificial Intelligence Research*, 21:63–100.
- Sung, C. (2013). *Exploration, Registration, and Analysis of High-Throughput 3D Microscopy Data from the Knife-Edge Scanning Microscope*. PhD thesis, Department of Computer Science and Engineering, Texas A&M University.

- Sung, C., Woo, J., Goodman, M., Huffman, T., and Choe, Y. (2013). Scalable, incremental learning with MapReduce parallelization for cell detection in high-resolution 3D microscopy data. In *Proceedings of the International Joint Conference on Neural Networks*, 434–440.
- Valsalam, V. K., Hiller, J., MacCurdy, R., Lipson, H., and Miikkulainen, R. (2012). Constructing controllers for physical multilegged robots using the enso neuroevolution approach. *Evolutionary Intelligence*, 5(1):45–56.
- van den Heuvel, M. P., and Sporns, O. (2011). Rich-club organization of the human connectome. *The Journal of neuroscience*, 31(44):15775–15786.
- Van Essen, D., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S., Penna, S. D., Feinberg, D., Glasser, M., Harel, N., Heath, A., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., Oostenveld, R., Petersen, S., Prior, F., Schlaggar, B., Smith, S., Snyder, A., Xu, J., and Yacoub, E. (2012). The human connectome project: A data acquisition perspective. *NeuroImage*, 62(4):2222 – 2231.
- Watts, D. J., and Strogatz, S. H. (1998). Collective dynamics of small-world networks. *Nature*, 393:440–442.
- White, J. G., Southgate, E., Thomson, J. N., and Brenner, S. (1986a). The structure of the nervous system of the nematode *caenorhabditis elegans*. *Philosophical Transactions of the Royal Society of London B*, 314:1–340.
- White, J. G., Southgate, E., Thomson, J. N., and Brenner, S. (1986b). The structure of the nervous system of the nematode *caenorhabditis elegans*. *Philosophical Transactions of the Royal Society of London B*, 314:1–340.
- Whitley, D., Dominic, S., Das, R., and Anderson, C. W. (1993). Genetic reinforcement learning for neurocontrol problems. *Machine Learning*, 13:259–284.
- Wieland, A. P. (1990). Evolving controls for unstable systems. In Touretzky, D. S., Elman, J. L., Sejnowski, T. J., and Hinton, G. E., editors, *Connectionist Models: Proceedings of the 1990 Summer School*, 91–102. San Francisco, CA: Morgan Kaufmann.
- Williams, R. W. (2000). Mapping genes that modulate mouse brain development: a quantitative genetic approach. In Goffinet, A. F., and Rakic, P., editors, *Mouse Brain Development*, 2149. New York: Springer.
- Yang, H.-F. (2011). *Reconstruction of 3D Neuronal Structures from Densely Packed Electron Microscopy Data Stacks*. PhD thesis, Department of Computer Science and Engineering, Texas A&M University.
- Yang, H.-F., and Choe, Y. (2010). Electron microscopy image segmentation with estimated symmetric three-dimensional shape prior. In *Proceedings of the 6th International Symposium on Visual Computing*.
- Yang, H.-F., and Choe, Y. (2011a). Ground truth estimation by maximizing topological agreements in electron microscopy data. In *Proceedings of the 7th International Symposium on Visual Computing (LNCS 6938)*, 371–380.

- Yang, H.-F., and Choe, Y. (2011b). An interactive editing framework for electron microscopy image segmentation. In *Proceedings of the 7th International Symposium on Visual Computing (LNCS 6938)*, 400–409.
- Yang, W. (2014). *Automated neurovascular tracing and analysis of the Knife-Edge Scanning Microscope India ink data set*. Master's thesis, Department of Computer Science and Engineering, Texas A&M University.
- Yao, X. (1999). Evolving artificial neural networks. *Proceedings of the IEEE*, 87(9):1423–1447.
- Zhang, W. (2014). *Real-time Image Error Detection in Knife-Edge Scanning Microscope*. Master's thesis, Department of Computer Science and Engineering, Texas A&M University.