OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: John C. Tuthill

eRA COMMONS USER NAME (credential, e.g., agency login): tuthill

POSITION TITLE: Associate Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Swarthmore College, Swarthmore, PA | B.A. | 05/2006 | biology, anthropology |
| University of Montana, Missoula, MT | - | 04/2007 | genetics |
| Universidad de Buenos Aires, Argentina | - | 11/2007 | neuroscience |
| HHMI/Janelia, Ashburn, VA University of Chicago, Chicago, IL | Ph.D. | 03/2012 | neuroscience |
| Harvard Medical School, Boston, MA | Postdoc | 12/2015 | neuroscience |

 **A. Personal Statement**

I have been engaged in neurobiology research for over 14 years and started my own lab at the University of Washington in 2016. My lab’s research seeks to answer a fundamental question: how does the nervous system use proprioceptive feedback to rapidly and robustly coordinate movements of the body? We study this question in *Drosophila* because of the abundance of genetic tools for identifying neuronal cell-types, and the accessibility of fly sensorimotor circuits for *in vivo* recording and imaging. My lab aims to achieve a comprehensive understanding of how sensorimotor circuits function in a walking fly, including adaptive responses to external stimuli and internal changes, such as injury. We use a variety of techniques — genetics, imaging, electrophysiology, behavior, and computational modeling — to dissect the function of mechanosensory and motor circuits that control fly walking. Our initial studies revealed the basic neural code for leg proprioception in the fly; in other words, how mechanosensory neurons represent the movement and position of the legs. We have also traced these sensory signals into the fly’s ventral nerve cord (VNC), to understand how mechanosensory information is integrated and transformed by central circuits. Finally, we have discovered a gradient of functional, physiological, and anatomical properties among fly leg motor neurons, which resembles the “size principle” in vertebrate motor neurons. In summary, my work has established the *Drosophila* VNC as a model for the comprehensive analysis of sensorimotor neural computations that underlie adaptive behavior, from sensory input to motor output. As part of this fellowship project, I will provide Leila with training in principles of sensorimotor control, *Drosophila* neuroanatomy, and computational methods for data analysis, as well as mentoring to help her achieve her graduate and career goals.

The two papers most relevant to this fellowship proposal are:

1. **Tuthill JC** and Wilson RI. (2016) Parallel transformation of tactile signals in central circuits of *Drosophila*. ***Cell*** 164(5):1046-1059. PMC4879191.
2. Phelps J, Hildebrand DGC, Graham BJ, Kuan AT, Thomas, LA, Nguyen T, Buhmann J, Azevedo AW, Sustar A, Agrawal S, Liu M, Shanny BL, Funke J, **Tuthill JC**, Lee WCA. (2021) Reconstruction of motor control circuits in adult *Drosophila* using automated transmission electron microscopy. ***Cell*** 184(3):759-774. PMC8312698.

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

|  |  |
| --- | --- |
| 2022- | Associate Professor, Dept of Physiology and Biophysics, U of Washington, Seattle, WA |
| 2016-2022 | Assistant Professor, Dept of Physiology and Biophysics, U of Washington, Seattle, WA |
| 2012-2015 | Postdoc Fellow, Wilson Lab, Dept. of Neurobiology, Harvard Medical School, Boston, MA |
| 2008-2012 | Graduate student, Reiser Lab, HHMI-Janelia/U Chicago Joint PhD program, Ashburn, VA |
| 2007 | Research Technician, Tomsic Lab, Instituto de Fisiología, Biología Molecular y Neurociencias, Universidad de Buenos Aires, Buenos Aires, Argentina |
| 2006-2007 | Research Technician, Fishman Lab, Biological Sciences, University of Montana, Missoula, MT |

**Honors**

2020 New York Stem Cell Foundation Neuroscience Investigator Award 2019 Pew Biomedical Scholar Award

2018 McKnight Scholar Award

2017 Allen Institute Next Generation Leadership Council 2017 University of Washington Innovation Award

2017 Searle Scholar Award

2017 Sloan Research Fellowship

2016 Klingenstein-Simons Fellowship

2014 Ruth L. Kirchstein National Research Service Award (NRSA) 2006 Highest Honors in biology and anthropology, Swarthmore College 2005 Bramson prize for best anthropology thesis

2002 Evans Scholarship to attend Swarthmore College

**Other Roles**

2022- Guest Editor, eLife
2022- Ad-hoc member, Sensorimotor Integration Study Section
2019- Editorial Advisory Board, Current Biology

2017-2019 Cycle Co-director, Neural Systems and Behavior Course, MBL

**C. Contributions to Science**

* 1. Neural mechanisms of leg proprioception

In the first studies from my lab, we laid out the basic organization and function of the fly leg proprioceptive system. We used genetic tools to identify leg proprioceptors with distinct anatomical projections into the central nervous system. We then developed a magnetic control system that allowed us to manipulate fly leg joints while we recorded the activity of proprioceptor axons with two-photon calcium imaging. These experiments revealed that leg proprioceptors encode the position and movement of the leg, with distinct, genetically-defined subtypes responding to specific leg positions, directions, and velocities. It also showed that proprioceptive sensors in the fly are highly specialized and functionally analogous to those in vertebrates. In subsequent work, we traced primary sensory signals into downstream circuits of the fly ventral nerve cord, uncovering the anatomy and function of second-order proprioceptive neurons. I have also co-authored two review papers on proprioception with experts in the vertebrate spinal cord and computational modeling.

* + 1. Chen C, Agrawal S, Mark B, Mamiya A, Sustar A, Phelps J, Lee WCA, Dickson B, Card G, **Tuthill JC.** (2021) Functional architecture of neural circuits for leg proprioception in *Drosophila*. ***Current Biology*** 31(23):5163-5175. PMC8665017.
1. Mamiya, A, Gurung, P, Siwanowicz, I, Sustar, A, Chen, C, Phelps, JS, Kuan, AT, Pacureanu, A, Lee, WCA., Mhatre, N, **Tuthill, JC**. (2022). Biomechanical origins of proprioceptive maps in the *Drosophila* leg. ***biorXiv*** 503192 (Preprint). Available from: doi.org/10.1101/069187
2. Agrawal S, Dickinson ES, Sustar A, Gurung P, Shepherd D, Truman J, **Tuthill JC**. (2020) Central processing of leg proprioception in *Drosophila*. ***eLife*** 9:e60299. PMC7752136.
3. Mamiya A, Gurung P, **Tuthill JC**. (2018) Neural coding of leg proprioception in *Drosophila*. ***Neuron*** 100(3):636-650. PMC6481666.

	1. Motor control of walking

When I started my lab, little was known about the neural circuits in *Drosophila* that mediate motor control of the limbs. We first used intersectional genetic techniques to map the hundreds of motor neurons that innervate the fly leg. We then designed hardware and software to track and control fly leg movements in 3D. By combining these tools with electrophysiology and 2-photon imaging, we discovered a gradient of functional, physiological, and anatomical properties among fly leg motor neurons, which resembles the “size principle”, first described in vertebrate motor neurons. Our long-term goal is to understand how sensorimotor circuits function in a walking fly, including adaptive responses to external stimuli and internal changes, such as injury.

* + 1. Azevedo AW, Dickinson ES, Gurung P, Venkatasubramanian L, Mann R, **Tuthill JC**. (2020) A size principle for leg motor control in *Drosophila*. ***eLife*** 3;9:e56754. PMC9329251.
		2. Karashchuk P, Rupp KL, Dickinson ES, Sanders E, Azim E, Brunton BW, **Tuthill JC.** (2021) Anipose: a toolkit for robust markerless 3D pose estimation**. *Cell Reports*** 36(13):109730**.** PMC9329251.
		3. York RA, Brezovec LE, Coughlan J, Herbst S, Krieger A, Lee SY, Pratt B, Smart AD, Song E, Suvorov A, Matute DR, **Tuthill JC**, Clandinin TR. (2022) The evolutionary trajectory of Drosophilid walking. ***Current Biology***32(14):3005-3015. PMC9329251.
	1. Computational neuroanatomy of the *Drosophila* ventral nerve cord

Through collaborations with experts in electron microscopy, x-ray tomography, and image segmentation, we have created important community resources for *Drosophila* neuroanatomy. Specifically, as experts in the anatomy of the fly ventral nerve cord, we have played a key role in analyzing massive microscopy datasets to trace the connectivity of neural circuits.

* + 1. Kuan AT, Maniates-Selvin J, Thomas LA, Nguyen TM, Han J, Chen CL, Azevedo AW, **Tuthill JC**, Funke J, Cloetens P, Pacureanu A, Lee WCA. (2021) Dense neuronal reconstruction through X-ray holographic nano- tomography. ***Nature Neuroscience*** 23: 1637-1640. PMC8354006
		2. Phelps J, Hildebrand DGC, Graham BJ, Kuan AT, Thomas, LA, Nguyen T, Buhmann J, Azevedo AW, Sustar A, Agrawal S, Liu M, Shanny BL, Funke J, **Tuthill JC**, Lee WCA. (2021) Reconstruction of motor control circuits in adult *Drosophila* using automated transmission electron microscopy. ***Cell*** 184(3):759-774. PMC8312698.
		3. Court RC, Armstrong JD, Borner J, Card G, Costa M, Dickinson MH, Duch C, Korff W, Mann R, Merritt D, Murphey R, Namiki S, Seeds A, Shepherd D, Shirangi T, Simpson J, Truman J, **Tuthill JC**, Williams D. (2017) A systematic nomenclature for the *Drosophila* ventral nerve cord**. *Neuron*** 107: 1071-1079. PMC7611823.
	1. Neural mechanisms of tactile sensing

During my post-doc, I pioneered the technique of making *in vivo* electrophysiological recordings from neurons in the *Drosophila* ventral nerve cord (VNC) that are genetically labeled with fluorescent markers. I combined this technique with optogenetic tools to describe the convergence of leg mechanoreceptors in downstream circuits. This study showed that second-order neurons act as parallel information processing channels to encode the position and intensity of peripheral somatosensory stimuli. Because basic mechanisms of somatosensation in flies and mammals are fundamentally similar, these general principles of neural computation are highly relevant to somatosensory processing in other animals. In an invited review article, we summarize general principles of sensorimotor processing in insects, and describe how work in the fly will contribute to future progress.

* + 1. **Tuthill JC** and Wilson RI. (2016) Parallel transformation of tactile signals in central circuits of *Drosophila*.

Cell 164(5):1046-1059. PMC4879191.

* + 1. **Tuthill JC** and Wilson RI. (2016) Mechanosensation and adaptive motor control in insects. Current Biology 26(20):1022-1038. PMC5120761.
	1. Visual motion detection

As a graduate student, I investigated mechanisms of motion detection in the visual system of *Drosophila*. I first studied the algorithmic implementation of motion detection by determining how a visual illusion is perceived by the fly and encoded within visual neurons. I next used advanced genetic tools to understand how genetically- defined cell types contribute to motion detection. In a landmark review article (Huang 2014, *Neuron* 83(6)), this work was cited as an “excellent example” of how to genetically dissect a complex neural circuit. Finally, I showed that behavioral state modifies neural coding at early stages of visual processing by making whole-cell patch-clamp recordings in flying flies. Together, these three papers provided important insight into circuit mechanisms of motion detection, a fundamental neural computation implemented by many species and brain areas.

* + 1. **Tuthill JC**, Chiappe ME, Reiser MB. (2011) Neural correlates of illusory motion perception in *Drosophila*.

PNAS 108(23):9685-90. PMC3111268.

* + 1. **Tuthill JC**, Nern A, Holtz SL, Rubin GM, Reiser MB. (2013) Contributions of the 12 neuron classes in the fly lamina to motion vision. Neuron 79(1):128-40. PMC3806040.
		2. **Tuthill JC**, Nern A, Rubin GM, Reiser MB. (2014) Wide-field feedback neurons dynamically tune early visual processing. Neuron 82(4):887-95. PMID24853944 .

**Complete publication list:** [https://pubmed.ncbi.nlm.nih.gov/?term=tuthill+jc&sort=date](https://pubmed.ncbi.nlm.nih.gov/?term=tuthill%2Bjc&sort=date)