BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Andreas Tolias**

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

POSITION TITLE: **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 Date MM/YYYY	FIELD OF STUDY
Cambridge University, United Kingdom	B.A., M.A.	1990-1993	Natural Sciences
Massachusetts Institute of Technology, Cambridge, MA	Ph.D.	1994-2000	Neuroscience
Max-Planck-Institute Biological Cybernetics, Tuebingen, Germany	Postdoctoral	2000-2006	Neuroscience

A. Personal Statement

Dr. Tolias studies the structure and functional organization of cortical circuits. Research in his lab combines electrophysiological (whole-cell and multi-electrode extracellular), two-photon imaging, molecular, behavioral and computational methods including deep learning. He was trained as an electrophysiologist and computational neuroscientist. His goal is to decipher algorithms of visual perception and cognition. He has trained numerous graduate and postdoctoral fellows who are now tenure track faculty and enjoys mentoring immensely.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024-Present Professor, Department of Ophthalmology, Stanford University, Stanford, CA
2018-2024 Professor of Neuroscience, Department of Neuroscience, Baylor College of Medicine, Houston, TX
2017-Present Brown Foundation Endowed Chair of Neuroscience
2016-Present Founder and Director, Center for Neuroscience and Artificial Intelligence
2013-Present Associate Professor, Department of Electrical and Computational Engineering, Rice University, Houston, TX
2013-2018 Associate Professor, Department of Neuroscience, Baylor College of Medicine, Houston, TX
2008-2011 Assistant Professor, Michael E. DeBakey VA Medical Center, Houston, TX
2006-2013 Adjunct Assistant Professor, Department of Computational and Applied Mathematics, Rice University, Houston, TX
2006-2013 Assistant Professor, Department of Neuroscience, Baylor College of Medicine, Houston, TX
2000-2006 Postdoctoral Fellow, Max-Planck Institute for Biological Cybernetics, Tuebingen, Germany
1995-1999 Teaching Assistant, MIT, Department of Brain and Cognitive Sciences, Cambridge, MA
1994 Teaching Assistant, Harvard University, Applied Mathematics, Cambridge, MA
1993-1994 Research Fellow, Harvard University, Division of Applied Sciences (PI: Kronauer & Stromeyer), Cambridge, MA
1991-1992 Research Assistant, Harvard University (PI: John D. Dowling), Cambridge, MA

Honors

2017 Brown Foundation Chair of Neuroscience
2016 DeBakey Excellence Award
2016-2018 McKnight Memory and Cognitive Disorders Award
2013-2017 NIH EUREKA Award
2011-2016 NIH Director's Pioneer Award

2010-2013 McKnight Endowment Fund for Neuroscience Scholar Award
2009 Kavli Frontiers of Science Fellow, National Academy of Science, USA
2008-2011 Beckman Foundation Young Investigator Award
2001-2004 NRSA-Postdoctoral Fellowship (National Institutes of Health, USA)
1990-1993 Cambridge Commonwealth Trust Scholar (Cambridge University, UK)
1990-1993 Foreign and Commonwealth Office Scholar (Cambridge University, UK)

C. Contribution to Science

a. Organization and computations of cortical microcircuits: A complete census of the constituent cell types and their wiring diagram in mature neocortex remains elusive. By combining octuple whole-cell recordings with an optimized avidin-biotin-peroxidase staining technique, we are carrying out morphological and electrophysiological census of neuronal cell types in mature neocortex and mapping the connectivity between identified cell types. We discovered several connectivity principles and cell types [1]. To characterize the molecular profiles of cell types we developed *Patch-seq* [2] and used it to comprehensively characterize the cell types of the neocortex [4]. We integrate morphological, electrophysiological and molecular classification schemes into a common framework for defining cell types. Specifically, we developed a protocol for high-throughput electrophysiological and transcriptomic analysis of single neurons that combines whole-cell recordings and single-cell RNA-sequencing, which we called *Patch-seq*. Using this approach, we can characterize the electrophysiological and molecular profiles of neocortical neurons. To characterize the sensory representations of neurons we developed *inception loops* [3], a closed-loop experimental paradigm combining *in vivo* recordings from thousands of neurons with *in silico* nonlinear response modeling. Our end-to-end trained, deep learning-based model predicted thousands of neuronal responses to arbitrary, new natural input with high accuracy, and was used to synthesize optimal stimuli---Most Exciting Inputs (MEIs). For mouse V1, MEIs exhibited complex spatial features that occurred frequently in natural scenes but deviated strikingly from the common notion that Gabor-like stimuli are optimal for V1. When presented back to the same neurons *in vivo*, MEIs drove responses significantly better than control stimuli. Inception loops represent a widely applicable technique for dissecting the neural mechanisms of sensation.

1. Jiang X., Shen S., Cadwell C.R., Berens P., Sinz F., Ecker A.S., **Tolias A.S.** (2015). Principles of Connectivity among Morphologically Defined Cell Types in Adult Neocortex. ***Science.*** Vol. 350. no. 6264 DOI: 10.1126

2. Cadwell CR, Palasantza A, Jiang X, Berens P, Deng Q, Yilmaz M, Reimer J, Shen S, Bethge M, Tolias KF, Sandberg R & **Tolias AS** (2016). Morphological, electrophysiological and transcriptomic profiling of single neurons using Patch-seq. ***Nature Biotechnology****,* 34(2), 199-203. doi: 10.1038/nbt.3445. Epub 2015 Dec 21.

3. Walker EY, Sinz FH, Froudarakis E, Fahey PG, Muhammad T, Ecker AS, Cobos E, Reimer J, Pitkow X, **Tolias AS.** (2019) Inception loops discover what excites neurons most using deep predictive models. ***Nature Neuroscience*** Dec;22(12):2060-2065. doi: 10.1038/s41593-019-0517-x. Epub 2019 Nov 4.PMID: 31686023

4. Scala F, Kobak D, Bernabucci M, Bernaerts Y, Cadwell CR, Castro JR, Hartmanis L, Jiang X, Laturnus S, Miranda E, Mulherkar S, Tan ZH, Yao Z, Zeng H, Sandberg R, Berens P, **Tolias AS** (2020) Phenotypic variation of transcriptomic cell types in mouse motor cortex. ***Nature*** 2020 Nov 12. doi: 10.1038/s41586-020-2907-3.

b. Population coding in the neocortex and brain states: Information in the brain is encoded and processed at the population level. While research over the last 100 years has revealed principles of information coding at the single cell level, we are just beginning to understand such principles at the neuronal ensemble level on which research in my lab is focused. For example, responses of cortical neurons to the same stimulus are variable. This variability, which can be correlated among nearby neurons (noise correlations), was thought to reflect noise arising from stochastic features of neural architecture. Contrary to widespread belief, we found that noise correlations of local groups of neurons are often near zero, challenging the view that noise correlations arise from stochastic features of neural architecture [1,2]. Instead, we conjectured that noise correlations, when elevated, reflect meaningful yet complicated signals. We propose that by combining multi-electrode recording

methods with latent space state models [2] will enable us to read out internal signals on a trial-by-trial basis, and thus greatly advance our understanding of the computations underlying decision making and cognition. Simultaneously, in order to gain a more detailed mechanistic understanding of the influence of internally generated brain signals and information processing, we also study the mouse cortex. We have identified specific types of interneurons that are differentially activated during brain state transitions [3] that could provide a mechanism of how internal signals structure population activity in the neocortex. Our most recent results establish for the first time role of population-encoded likelihood functions in mediating behavior and provided a neural underpinning for Bayesian models of perception.

1. Ecker AS, Berens P, Keliris G, Bethge M, Logothetis NK, **Tolias AS**. (2010). Decorrelated neuronal firing in cortical microcircuits. ***Science*****.** 327(5965):584-587.
2. Reimer J, Froudarakis E, Cadwell CR, Yatsenko D, Denfield GH, **Tolias AS**. (2014). Pupil fluctuations track fast switching of cortical states during quiet wakefulness. ***Neuron*****.** 84(2):355-362. PMCID: PMC4323337.
3. Walker E.Y. Cotton RJ, Ma WJ, **Tolias AS** (2020). A neural basis of probabilistic computation in visual cortex ***Nature Neuroscience*** Jan;23(1):122-129. doi: 10.1038/s41593-019-0554-5. Epub 2019 Dec 23.PMID: 31873286
4. Franke K, Willeke KF, Ponder K, Galdamez M, Zhou N, Muhammad T, Patel S, Froudarakis E, Reimer J, Sinz FH**, Tolias AS** (2022). State-dependent pupil dilation rapidly shifts visual feature selectivity ***Nature*** https://doi.org/10.1038/s41586-022-05270-3.

c. Neural coding under ethologically relevant conditions: Information processing in the brain is believed to have adapted to the organism's ethological conditions, and we have thus studied the properties of neural circuits under such conditions. We demonstrated the dynamical nature of neural activity under natural conditions and found that the responses of neurons during eye movements are inconsistent with the idea that sensory and motor information are processed separately in the cortex. Specifically, we found that before the initiation of a saccadic eye movement, receptive fields (RF) shrink and shift towards the saccade target [1], and, recently, it has been shown that this RF re-organization around eye movements seems to be ubiquitously present throughout visually driven activity in the cortex. In a second set of experiments, we studied how stimulus history influences the functional organization of the visual cortex. We demonstrated that neurons acquire new functional properties because of stimulus history: non-direction-selective neurons in V4 became tuned to direction of motion after adaptation [2,3]. This dynamic view of cortical function is ethologically relevant because under natural conditions visual input reaches the brain continuously, so processing always depends on stimulation history. We also studied the features of the neural code relevant for encoding natural scene statistics by recording from up to 500 neurons simultaneously in the mouse primary visual cortex. We found that the perceptually relevant features of natural scenes (higher-order correlations) induce a sparser code, with reliable activation of a smaller set of neurons, which can be read out more easily [4]. This finding indicates a long sought functional benefit of sparsification for natural image statistics. Therefore, a sparsifying mechanism may be a general principle governing the structure of population activity throughout cortical microcircuits. I am the first author or primary investigator in these studies.

1. **Tolias AS**, Moore T, Smirnakis SM, Tehovnik EJ, Siapas AG, Schiller PH. (2001). Eye movements modulate visual receptive fields of V4 neurons. ***Neuron*****.** 29(3):757-767.
2. **Tolias AS**, Smirnakis SM, Augath MA, Trinath T, Logothetis NK. (2001). Motion processing in the macaque: revisited with functional magnetic resonance imaging. ***J Neurosci*****.** 21(21):8594-8601.
3. **Tolias AS**, Keliris GA, Smirnakis SM, Logothetis NK. (2005). Neurons in macaque area V4 acquire directional tuning after adaptation to motion stimuli. ***Nat Neurosci*****.** 8(5):591-593.
4. Froudarakis E, Berens P, Ecker AS, Cotton RJ, Sinz FH, Yatsenko D, Saggau P, Bethge M, **Tolias AS**. (2014). Population code in mouse V1 facilitates readout of natural scenes through increased sparseness. ***Nat Neurosci*****.** 17(6):851-857. PMCID: PMC4106281.

d. Development of experimental and statistical tools to study neural computation at the network level: One of my research directions is to develop experimental and statistical analysis tools to study neural circuits. For example, we adapted large-scale chronic tetrode recording for macaque research and developed statistical methods to monitor the activity of the same neurons and their correlations across weeks during learning [1].

However, electrophysiological methods are blind to cell-type identity, and scaling up recording density to track the activity of every neuron in an extended brain region appears infeasible. Functional imaging by two-photon microscopy enables single-cell resolution of large neuron ensembles and provides cell-type specificity of activity via genetically encoded fluorescent reporters. However, traditional *in vivo* two-photon microscopy works by moving mechanical components, which limits temporal resolution due to inertia. Moreover, axial scanning is even more inertia-limited due to the mass of the objective lens (e.g. 10 Hz). Thus, while all the cells in a volume can be characterized independently, these methods are limited for studying their coordinated activity. To overcome these limitations we developed an *in vivo* 3D high-speed, random-access two-photon microscope (3D-RAMP) allowing us to image all cells (~ 500 neurons) in small volumes of the cortex to study how populations encode visual information, including natural scenes, in the mouse visual cortex[3]. This method currently provides the largest number of neurons that can be recorded densely *in vivo* in 3D at such high rates in light scattering tissue. Recording the activity of ever larger and denser neuronal populations in vivo is progressing at a fast pace and will progress even faster with the BRAIN Initiative. However, analysis of these large data sets is challenging. For example, the estimation of correlation matrices from large populations presents a serious numerical challenge. The amount of recorded data grows linearly with population size, whereas the number of estimated coefficients increases quadratically. This mismatch leads to an increase in spurious correlations, overestimation of common activity (i.e. overestimation of the largest eigenvalues) [45], and poorly conditioned partial correlations. As such, concurrent with our innovations in recording methods, my lab focuses on improving our methods of analyzing such data as well [3]. To study inter-neural correlations between functionally connected brain areas we have also developed a technique that uncovers in-vivo functional connectivity maps across the whole brain (combined-fMRI-microstimulation) [4]. Further, my lab is committed to sharing code and data. All the code we develop is publicly available on GitHub. We strongly believe that such efforts greatly enhance both the reproducibility and broaden the impact of our research.

1. **Tolias AS**, Ecker AS, Siapas AG, Hoenselaar A, Keliris GA, Logothetis NK. (2007). Recording chronically from the same neurons in awake, behaving primates. ***J Neurophysiol*.** 98(6):3780-3790.
2. Cotton RJ, Froudarakis E, Storer P, Saggau P, **Tolias AS**. (2013). Three-dimensional mapping of microcircuit correlation structure. ***Front Neural Circuits*.** 7:151. PMCID: PMC3794294.
3. Yatsenko D, Josic K, Ecker AS, Froudarakis E, Cotton RJ, **Tolias AS**. (2015). Improved estimation and interpretation of correlations in neural circuits. ***PLoS Comput Biol*.** 11(3):e1004083. PMCID: PMC4380429.
4. **Tolias AS**, Sultan F, Augath M, Oeltermann A, Tehovnik EJ, Schiller PH, Logothetis NK. (2005). Mapping cortical activity elicited with electrical microstimulation using FMRI in the macaque. ***Neuron*.** 48(6):901-911.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/andreas.tolias.1/bibliography/40355460/public/?sort=date&direction=descending