BIOGRAPHICAL SKETCH

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NAME: Andres Villu Maricq

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POSITION TITLE: Professor of Biology; Director, Center for Cell and Genome Science

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Brown University, Providence, RI	BS	06/1978	Exp Psychology
University of California Berkeley, Graduate Program in Biophysics	PhD	06/1987	Biophysics
University of California San Francisco School of Medicine	MD	06/1990	Medicine

A. Personal Statement

My research explores the molecular machinery that contributes to the information-processing capabilities of the nervous system, with a focus on the regulation and function of synaptic transmission. I use an interdisciplinary approach to address research questions, drawing upon my training and experience in biochemistry, molecular biology, cell biology, electrophysiology, biophysics and genetics. I have decades-long experience in the teaching, training and mentoring of students and postdoctoral fellows. We have focused on the molecular machinery that contributes to the establishment and function of synapses in the model organism *C. elegans*. In studies of glutamatergic synapses, we have identified evolutionarily conserved auxiliary proteins that contribute to the function of AMPA-type ionotropic glutamate receptors (AMPARs), leading to a new concept of an AMPAR signaling complex. We also study the trafficking and transport of AMPARs, and have found that kinesin-1 microtubule-dependent motors and a Ca^{2+}- and calmodulin-dependent kinase (CaMKII) have fundamental roles in the delivery, removal and redistribution of synaptic AMPARs. Additionally, we study the properties of NMDA and kainate receptors and their contribution to synaptic function and the control of behavior. We are now fascinated by the question of how synaptic transmission changes with aging and the synaptopathies might be common to many neurodegenerative disorders. We find that synaptic function and transport of synaptic AMPAR decreases with aging as well as in transgenic models of Alzheimer's disease. In summary, our research is driven by two major goals: first, to obtain a mechanistic, soup-to-nuts understanding of how synapses are built, how synapses contribute to information processing by neural circuits, and ultimately how synapses and neural circuits give rise to complex behaviors, including learning and memory; second, to obtain a molecular-based understanding of how synaptic function changes during aging and in neurodegenerative disorders.

B. Positions and Honors

Positions and Employment

1975-1977 Research Assistant (Dr. Rosemary Sorrentino), Department of Experimental Psychology, Brown University
1977-1978 Honors Research (Dr. Russell Church), Department of Experimental Psychology, Brown University
1978-1990 Combined MD/PhD Program
School of Medicine UCSF/Department of Biophysics UCB
Graduate Research (Dr. Juan Korenbrot, including 1 year transitional postdoc)
1990-1992 Postdoctoral research (Dr. David Julius), University of California, San Francisco

1992-1995 Postdoctoral research (Dr. Cori Bargmann), University of California, San Francisco
1996-2002 Assistant Professor, Department of Biology, University of Utah
1999-2002 Adjunct Assistant Professor, Department of Neurology, University of Utah
2002-2005 Associate Professor, Department of Biology and Adjunct Associate Professor, Department of Neurology, University of Utah
2005-2013 Adjunct Professor, Department of Neurology, University of Utah
2005-present Professor, Department of Biology, University of Utah
2006-present Founding Director, Center for Cell and Genome Science, University of Utah

Other Experience and Professional Memberships

1996-present Member, Society for Neuroscience
1996-present Reviewer: BMC Neuroscience, Cell, Development, Journal of Biological Chemistry, EMBO J., Genetics, J. Neurosci, Learning and Memory, Nature, Nature Neuroscience, Neuron, PloS Biology, Science, TIGS
1998-1999 Consultant, Exelixis Pharmaceuticals
1998-2006 Adhoc Reviewer, NIH Special Emphasis Panel; NIH MDCN1; (Invited Reviewer: NSF)
2002-2005 Reviewer, American Heart Association (Panel 3B)
2005-present Editor, Wormbook: Online Review of *C. elegans* Biology
2007-present Member, College of Science Advisory Committee, University of Utah
2008-2010 Member, NIH Study Section, Synapses, Cytoskeleton and Trafficking Study Section [SYN]
2009/2011 Co-Vice-Chair/ Co-Chair, Gordon Research Conference on Excitatory Synapses and Brain Function
2010-2013 Chair, NIH Study Section, Synapses, Cytoskeleton and Trafficking Study Section [SYN]
2015 Founding Co-Chair, Gordon Research Conference, Modulation of Neural Circuits & Behavior
2016 Advisory Panel for Wellcome Trust Centres, London, England
2016 Co-Director, MBL Summer Neurobiology Course, Woods Hole, MA

Honors

1992-1996 Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) Scientist Development Award
1997-1999 Alfred P. Sloan Research Fellowship
1999-2002 Burroughs Wellcome Fund Young Investigator in Pharmacological Sciences
1999-2004 National Science Foundation Career Development Award
2003-2005 NARSAD Independent Investigator Award
2006-present James E. Talmage Presidential Endowed Chair in Biology, University of Utah
2009-2014 USTAR (Utah Science Technology and Research Initiative), Focus Area Chair, “Nanoscale and Biomedical Photonic Imaging”
2010-2015 NIH Director’s Pioneer Award
2014 University of Utah Distinguished Scholarly and Creative Research Award
2016 NARSAD Distinguished Investigator Award

C. Contributions to Science

My NCBI Bibliography: http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40859993/

The major focus of our research efforts is to obtain a mechanistic understanding of how neural circuits process and store information, thus controlling behavior. Towards this goal, we are developing new strategies and techniques to simultaneously measure behavior (learning), synapse composition, and neuronal activity in a live animal. Neural circuits in simple organisms are more tractable to these studies but, because of evolutionary conservation, the lessons learned will be of immediate relevance to the more complex vertebrate nervous systems. Therefore, we have based our research program on identified circuits in the relatively simple nervous system of the nematode *C. elegans*. Currently, we are focused on four major, interrelated questions about synaptic development, synaptic function and the properties of neural circuits.

C1. Identification and characterization of auxiliary proteins that contribute to synaptic function.

Although nervous systems vary widely in size and number of neurons, synapses themselves are evolutionarily conserved and remarkably similar in all nervous systems. At most synapses, ionotropic glutamate receptors (iGluRs) mediate excitatory synaptic transmission. Remarkably, the strength of this synaptic transmission can change quickly with experience. This synaptic plasticity is believed to underlie one's ability to learn and remember. Important determinants of synaptic plasticity are the number and functional properties of synaptic AMPA-type iGluRs (AMPARs). My laboratory has developed new genetic strategies to uncover the molecular machinery required for synaptic transmission. In a series of studies in the nematode *C. elegans*, we have identified three new classes of auxiliary subunits that contribute to AMPAR function, shown that they have dramatic effects on *in vivo* glutamate-gated currents, and demonstrated that mutations in these genes predictably modify specific behaviors. These discoveries have had a profound impact on the field because they first revealed that iGluRs are not simple stand-alone channels, but rather are part of a complicated signaling machine that is required for synaptic transmission and the plasticity of the nervous system. We are now exploring the function and organization of this signaling complex, as well as searching for auxiliary proteins that might modify NMDA and kainate classes of iGluRs.

Key publications

Wang, R., J.E. Mellem, M. Jensen, P.J. Brockie, C.S. Walker, F.J. Hoerndli, D.M. Madsen and **A.V. Maricq** (2012) The SOL-2/Neto auxiliary protein modulates the function of AMPA-subtype ionotropic glutamate receptors. *Neuron* 75:838-50. (PMCID: PMC3458792)

Wang, R., C.S. Walker, P.J. Brockie, M.M. Francis, J.E. Mellem, D.M. Madsen and **A.V. Maricq** (2008) Evolutionary conserved role for TARPs in the gating of glutamate receptors and tuning of synaptic function. *Neuron* 59:997-1008. (PMCID: PMC2754846)

Walker, C.S., M.M. Francis, P.J. Brockie, D.M. Madsen, Y. Zheng and **A.V. Maricq** (2006) Conserved SOL-1 proteins regulate ionotropic glutamate receptor desensitization. *Proc. Natl. Acad. Sci. (USA)* 103:10787-92. (PMCID: PMC1502309)

Zheng, Y., J.E. Mellem, P.J. Brockie, D.M. Madsen and **A.V. Maricq** (2004) SOL-1 is a CUB-domain protein required for GLR-1 glutamate receptor function in *C. elegans*. *Nature* 427:451-57.

C2. The delivery, removal and redistribution of synaptic AMPA receptors.

Using an *in vivo* approach in *C. elegans*, we recently demonstrated the central importance of UNC-116*,* the homolog of vertebrate kinesin-1 heavy chain (KIF5), for the delivery, and surprisingly, the removal and redistribution of synaptic AMPARs. We show that UNC-116/KIF5 motors provide a rapid-response mechanism for the precise regulation of the number of AMPARs at synapses – a major determinant of synaptic strength. We also found that synaptic transmission can modulate the transport of AMPARs and thus control the number of receptors at synapses and the strength of synaptic transmission. Additionally, we discovered that voltage-gated calcium channels and the Ca^{2+}/calmodulin-dependent kinase CaMKII regulate the delivery and removal of synaptic AMPARs, and participate in synaptic plasticity by regulating the transport of AMPARs. These results should have a profound impact on our understanding of synaptic development and maintenance of synaptic strength, and may have important clinical implications. For instance, disorders such as Alzheimer's disease are distinguished by early defects in synaptic function as well as altered microtubule-dependent transport.

Key publications

Hoerndli, F., R. Wang, J. Mellem, A. Kallarackal, P. Brockie, C. Thacker, D. Madsen and **A.V. Maricq** (2015) Neuronal activity and CaMKII regulate kinesin-mediated transport of synaptic AMPARs. *Neuron* 86:457-74. (PMCID: PMC4409548)

Brockie, P.J., M. Jensen, J.E. Mellem, E. Jensen, T. Yamasaki, R. Wang, D. Maxfield, C. Thacker, F. Hoerndli, P.J. Dunn, S. Tomita, D.M. Madsen and **A.V. Maricq** (2013) Cornichons control ER export of AMPA receptors to regulate synaptic excitability. *Neuron* 80:129-42. (PMCID: PMC3795439)

Hoerndli, F.J., D.A. Maxfield, P.J. Brockie, J.E. Mellem, E. Jensen, R. Wang, D.M. Madsen and **A.V. Maricq** (2013) Kinesin-1 regulates synaptic strength by mediating the delivery, removal and redistribution of AMPA receptors. *Neuron* 80:1421-37. (PMCID: PMC24360545) [Accompanying *Neuron* Preview: Rongo, C. (2013) Going mobile: AMPA receptors move synapse to synapse *in vivo*, 80: 1339-41.]
Video abstract http://www.sciencedirect.com/science/article/pii/S0896627313010027

Mellem, J.E., P.J. Brockie, Y. Zheng, D.M. Madsen and **A.V. Maricq** (2002) Decoding of polymodal sensory

stimuli by postsynaptic glutamate receptors in *C. elegans*. *Neuron* 36:933-44.

C3. Translocation of synaptic receptors.
We also study how synaptic receptors are delivered from subsynaptic stores to the surface of the synapse. In studies of nicotinic receptors, a class of postsynaptic receptors activated by the neurotransmitter acetylcholine, we demonstrated that nicotinic receptors are shuttled between intracellular pools and the synaptic surface. In the process, we discovered an entirely unanticipated and novel signaling pathway that regulates the translocation of these receptors. Thus, we found that Wnt molecules, evolutionarily conserved secreted glycoproteins that are best known for their roles in early development, also have an ongoing role in the adult nervous system to control translocation of the ACR-16/α7 nicotinic receptors and change the strength of synaptic transmission. We discovered that presynaptic neurons release Wnts, which bind to a novel heteromeric postsynaptic receptor that consists of CAM-1, a Ror-family receptor tyrosine kinase (RTK) and LIN-17, a Frizzled receptor. This complex signals through the intracellular intermediate DSH-1 to dynamically regulate ACR-16/α7 translocation and synaptic plasticity. These experiments have shed new light on evolutionarily conserved pathways for the control of receptor translocation and synaptic plasticity, and could lead to new insights into the processes of learning and memory, as well as disorders of nervous system function. Our current efforts are directed towards further elucidating the Wnt-signaling pathway that mediates translocation of synaptic receptors.

Key publications
Jensen, M., F.J. Hoerndli, P.J. Brockie, R. Wang, E. Johnson, D. Maxfield, M.M. Francis, D.M. Madsen and **A.V. Maricq** (2012) Wnt signaling regulates acetylcholine receptor translocation and synaptic plasticity in the adult nervous system. *Cell* 149:173-87. (PMCID: PMC3375111)
Jensen, M., P.J. Brockie and **A.V. Maricq** (2012) Wnt signaling regulates experience-dependent synaptic plasticity in the adult nervous system. *Cell Cycle* 22:2585-86. (PMCID: PMC3409000)
Walker, C.S., P.J. Brockie, D.M. Madsen, M.M. Francis, Y. Zheng, S. Koduri, J.E. Mellem, N. Strutz-Seebohm and **A.V. Maricq** (2006) Reconstitution of invertebrate glutamate receptor function depends on stargazin-like proteins. *Proc. Natl. Acad. Sci. (USA)* 103:10781-86. (PMCID: PMC1502308)
Francis, M.M., S.P. Evans, M. Jensen, D.M. Madsen, J. Mancusco, K. Norman and **A.V. Maricq** (2005) The Ror receptor tyrosine kinase CAM-1 is required for ACR-16 mediated synaptic transmission at the *C. elegans* neuromuscular junction. *Neuron* 46:581-94.

C4. The control of behavior.
We have an ongoing interest in understanding the molecular basis of well-defined, quantifiable behaviors. Early efforts were directed at the control of rhythmic behaviors in *C. elegans*. More recently, we have initiated mechanistic studies of a neural circuit that contributes to navigation along gradients of sensory information. Animals find sparsely distributed resources by navigating along gradients of sensory cues. For example, animals can associate temperature or chemical cues with favorable environmental resources and move towards those cues. The simple neuronal circuits in *C. elegans* have facilitated the identification of circuits that contribute to distinct behaviors. We found that navigation along thermal or chemical gradients depends on a neural circuit centered on the pair of RIA interneurons, which receive glutamatergic synaptic inputs from sensory neurons and interneurons that mediate chemosensation and thermosensation. Both AMPA and kainate classes of ionotropic glutamate receptors are expressed in RIA, and we found that postsynaptic AMPA and kainate receptors differentially mediate error correction when *C. elegans* navigates sensory gradients. Our current efforts are directed towards molecular-based studies of receptor localization and function, and cellular-based studies of information processing by the RIA circuit.

Key publications
Kano, T., P.J. Brockie, T. Sassa, H. Fujimoto, Y. Kawahara, Y. Iino, J.E. Mellem, D.M. Madsen, R. Hosono and **A.V. Maricq** (2008) Memory in *Caenorhabditis elegans* is mediated by NMDA-type ionotropic glutamate receptors. *Curr. Biol.* 18:1010-15. (PMCID: PMC2645413)
Norman, K.R., R.T. Fazzio, J.E. Mellem, M.V. Espelt, K. Strange, M. Beckerle and **A.V. Maricq** (2005) The Rho/Rac-family guanine nucleotide exchange factor VAV-1 regulates rhythmic behaviors in *C. elegans*. *Cell* 123:119-32. [Accompanying *Cell* Preview: Baylis, H.A. (2005) VAV's got rhythm. *Cell* 123:5-7.]
Hills, T., P.J. Brockie and **A.V. Maricq** (2004) Dopamine and glutamate control area-restricted search behavior

in *Caenorhabditis elegans*. *J. Neurosci.* 24:1217-25.
Brockie, P.J., J.E. Mellem, T. Hills, D.M. Madsen and **A.V. Maricq** (2001) The *C. elegans* glutamate receptor subunit NMR-1 is required for slow NMDA-activated currents that regulate reversal frequency during locomotion. *Neuron* 31:617-30.

D. Research Support

Ongoing Research Support

R01 NS094421 (Maricq PI) 9/1/2015 – 8/31/2020
NIH/NINDS
Glutamate-mediated neurotransmission and the control of behavior
The major goal of this project is to elucidate the function of an experimentally accessible neural circuit in a genetically tractable model organism.
Role: PI

R01 NS035812 (Maricq PI) 1996 – 7/31/19
NIH/NINDS
Analysis of Glutamate Receptor Function
The major goal of this project is a genetic and electrophysiological analysis of glutamate receptors and interacting proteins.
Role: PI

Completed Research Support

R01 NS070280 (Maricq PI) 4/1/2010 – 3/31/2015
NIH/NINDS
Development and regulation of cholinergic synapses
The major goal of this project was to gain a mechanistic understanding of synaptic transmission, with a focus on the establishment and regulation of acetylcholine receptors.
Role: PI

DP1 DA0350580 (Maricq PI) 9/30/2010 – 8/31/2016
NIH Director's Pioneer Award
Simultaneous *in vivo* studies of synapses, neurons, and learning and memory
The major goal of this project is the development of new techniques to measure changes that occur during learning to better understand molecular mechanisms that contribute to learning and memory.
Role: PI