BIOGRAPHICAL SKETCH

NAME: Hancock, William Olaf

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

POSITION TITLE: Professor, Chair of the Intercollege Graduate Program in Bioengineering

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Duke University, Durham, NC	B.S.E.	05/1988	Biomedical and Electrical Engineering
University of Washington, Seattle, WA	Ph.D.	08/1994	Bioengineering
University of Washington, Seattle, WA	Postdoctoral	11/1999	Physiology and Biophysics

A. Personal Statement

My doctoral work in bioengineering with Lee Huntsman and Al Gordon used mechanical experiments and computational modeling to understand the kinetics of calcium activation of cardiac muscle, and my postdoctoral work in biophysics with Joe Howard focused on the role of inter-head coordination in kinesin mechanochemistry. Since 2000, my lab at Penn State has been carrying out fundamental and applied studies of kinesin motor proteins and microtubules. A principal focus is studying the fundamental mechanism of kinesin-2 motors, along with the roles of motor transport and microtubule dynamics in neurons and in dividing cells. We employ single-molecule fluorescence assays, stopped-flow and steady-state biochemical assays, and computational modeling to infer the rates of key mechanochemical transitions in the kinesin hydrolysis cycle. We also carry out in vitro reconstitution experiments to bridge our knowledge at the single-molecule level to understanding complex intracellular behavior such as bidirectional transport in neurons and the regulation of microtubule organization in the mitotic spindle. We have had a productive collaboration with the Steve Block lab at Stanford to study the mechanical behavior of kinesin-2, and we have recently begun a collaboration with Steve Rosenfeld's lab at the Cleveland Clinic to investigate the role of kinesin-5 in regulating microtubule dynamics. We have been using single-molecule TIRF to study the properties of kinesin for 10 years, but in an effort to push toward higher temporal resolution we have recently adopted gold nanoparticle labeling in combination with Dark-field TIRF and Interferometric Scattering (iSCAT) microscopy for high resolution motor tracking. This new thrust has involved a new and productive collaboration with Philipp Kukura at Oxford, who is a pioneer in the iSCAT technique.

In other work in my lab, we are investigating the role of kinesins and +-tip tracking proteins in organizing the neural cytoskeleton and we are carrying out experiments and modeling to uncover the multimotor dynamics between kinesin and dynein that underlie bidirectional transport in cells. We also develop microengineering tools for both new approaches for studying fundamental questions in cell biology as well as for creating microscale "lab-on-a-chip" devices that integrate microtubules and motor proteins. Work in my lab is inherently interdisciplinary and I have strong collaborations with colleagues in cell biology (Melissa Rolls), electrical engineering (Tom Jackson), physics (Erkan Tuzel, WPI) and statistics (John Fricks). Likewise, graduate students in my lab come from both the bioengineering program and the biological sciences umbrella program at Penn State. I have been funded by NIH, NSF, the American Heart Association, DARPA, and the Whitaker foundation; additionally I have participated in the NSF-funded Center for Nanoscale Science MRSEC at Penn State. I have taught courses in Cellular and Molecular Bioengineering at both the undergraduate and graduate levels for the last 14 years, I am an advisor for undergraduate honors students in biomedical engineering, and I am currently the Chair of the Intercollege Graduate Degree Program in Bioengineering at Penn State. Key recent papers:

1. An EB1-kinesin complex is sufficient to steer microtubule growth in vitro. Chen, Y., Rolls, M.M., Hancock, W.O. 2014. Current Biology. 24(3):316-21.
2. Bidirectional cargo transport: moving beyond tug of war. Hancock W.O. 2014. *Nat Rev Mol Cell Biol.* 15(9):615-28. PMID: 25118718
3. Kinetics of nucleotide-dependent structural transitions in the kinesin-1 hydrolysis cycle. 2015. Mickolajczyk, K. J., N. C. Deffenbaugh, J. Ortega Arroyo, J. Andrecka, P. Kukura, and W. O. Hancock. *Proc. Natl. Acad. Sci.*, 112:E7186-7193. PMID: 26676576

4. Andreasson, J.O., Shastry, S., Hancock, W.O. and Block, S.M. 2015. The mechanochemical cycle of mammalian kinesin-2 KIF3A/B under load. *Current Biology* 25(9):1166-1179. PMID: 25866395.

B. Positions and Honors

Positions and Employment

2000-2006	Assistant Professor, Department of Bioengineering, The Pennsylvania State University
2006-2012	Associate Professor, Department of Bioengineering/Biomedical Engineering, The Pennsylvania State University
2012-	Professor, Department of Biomedical Engineering, The Pennsylvania State University
2014-	Chair, Intercollege Graduate Degree Program in Bioengineering, The Pennsylvania State University

Other Experience and Professional Memberships

1993-	Member, Biophysical Society
2000-	Member, ASCB
2001-	Member, Biomedical Engineering Society
2001-2003, 2009	NSF site visit panel, Cornell Nanobiotechnology Center
2002-2007	Motors Thrust Leader, Penn State Center for Nanoscale Science NSF MRSEC
2004	NSF Review Panel, Nanoscale Science and Engineering Centers
2005-2009	American Heart Association Review Panel, Region 1, Basic Cell Biology
2007	NSF/NIH Review Panel, Mathematical Biology
2008-	Editorial Board and Special Issue Editor, Cellular and Molecular Bioengineering
2009	NSF Review Panel, Engineering Frontiers in Research and Innovation
2009	NIH Special Emphasis Panel, Neurodevelopment and Cellular Neurobiology
2009	NIH Challenge Grants Reviewer
2009	NIH Nanoscience and Nanotechnology in Biology and Medicine, Ad Hoc Reviewer
2010	NIH Special Emphasis Panel NIGMS
2011, 2013	NIH Macromolecular Structure/Function B (MSFB) Study Section
2013-	Publication Subcommittee, Biophysical Journal

Honors

2014	Fellow, American Institute for Medical and Biological Engineering
2014	First place, Cell Slam, American Society for Cell Biology Annual Meeting 2014, Philadelphia, PA

C. Contribution to Science

1) My postdoctoral work on kinesin-1 investigated the role of the two heads in kinesin processivity. By constructing a one-head kinesin heterodimer and analyzing its motility and biochemical properties, we showed that kinesin processivity results from coordinated behavior of the two motor domains. Specifically, one headed kinesin detaches slowly from microtubules, demonstrating that inter-head tension accelerates detachment of the trailing head during the portion of the hydrolysis cycle when both motor domains are attached to the microtubule. This phenomenon was later termed “rear-head gating” because the activity of the rear head is gated to maintain the hydrolysis cycle of the two heads out of phase.

a. Processivity of the motor protein kinesin requires two heads. W.O. Hancock and J. Howard. 1998. J Cell Biol. 140:1395-405. PMID: 9508772
b. Kinesin's processivity results from mechanical and chemical coordination between the ATP hydrolysis cycles of the two motor domains, W.O. Hancock and J. Howard. 1999. Proc Natl Acad Sci. 96:13147-52. PMID: 10557288
c. Kinesin's tail domain is an inhibitory regulator of the motor domain. D.L. Coy, W.O. Hancock, M. Wagenbach, and J. Howard. 1999. Nature Cell Biol. 1:288-92. PMID: 10559941

2) Upon starting my lab at Penn State, I developed a number of connections with the materials community, including the Center for Nanoscale Science MRSEC. The goal of the work was to integrate microfabrication and functionalized nanoparticles with biological motors for both applications such as molecular sorters and

sensors, as well as developing new platforms for investigating fundamental biological questions. This work culminated in developing an approach using dieletrophoresis to create an "artificial mitotic spindle" of aligned microtubules that can be used as a tool for "bottom up" investigations of the mitotic spindle.

a. Lithographically patterned channels spatially segregate kinesin motor activity and effectively guide microtubule movements. S.G. Moorjani, L. Jia, T.N. Jackson and W.O. Hancock. 2003. NanoLetters 3:633-637.
b. Millimeter scale alignment of magnetic nanoparticle functionalized microtubules in magnetic fields. M. Platt, G. Muthukrishnan, W.O. Hancock, and M.E. Williams. 2005. Journal of the American Chemical Society, 127(45):15686-15687. PMID: 16277494
c. Microtubule alignment and manipulation using AC electrokinetics. M. Uppalapati, Y. M. Huang, T.N. Jackson and W.O. Hancock. 2008. Small 4(9): 1371-81. PMID: 18720434
d. "Artificial Mitotic Spindle" generated by dielectrophoresis and protein micropatterning supports bidirectional transport of kinesin-coated beads. M. Uppalapati, Y.-M. Huang, V. Aravamuthan, T.N. Jackson and W.O. Hancock. 2011. Integrative Biology 3:57-64. PMID: 21031221

3) My lab is focused on understanding the mechanochemical mechanism of the kinesin-2 motor KIF3A/B, which is involved in axonal and intraflagellar transport, among other roles. We discovered that its reduced processivity is due to its longer neck linker, a sequence that connects each head to the coiled-coil stalk domain. Using single-molecule investigations, molecular dynamics, and biochemical studies, we showed that the neck linker plays a key role in transmitting mechanical tension between the two heads. Furthermore, we found that the response of kinesin-2 to obstacles such as microtubule associated proteins (MAPs) on the microtubule surface differs from that of kinesin-1 and results from the longer neck linker of kinesin-2, which gives it more conformational flexibility in stepping.

a. The Processivity of Kinesin-2 Motors Suggests Diminished Front-Head Gating. G. Muthukrishnan, Y. Zhang, S. Shastry and W.O. Hancock. 2009. Current Biology 19(5):442-7. PMID: 19278641
b. Neck linker length determines the degree of processivity in Kinesin-1 and Kinesin-2 motors. S. Shastry and W.O. Hancock. 2010. Current Biology 20: 939-943. PMID: 20471270
c. Kinesin's neck-linker domain determines its ability to navigate obstacles on the microtubule surface. G.J. Hoeprich, A.R. Thompson, D.P. McVicker, W.O. Hancock and C.L. Berger. (2014) Biophysical Journal. 106(8): 1691-700. PMID: 24739168.
d. The mechanochemical cycle of mammalian kinesin-2 KIF3A/B under load. Andreasson, J.O., S. Shastry, W.O. Hancock, and S.M. Block. (2015) Current Biology. 25(9):1166-1179. PMID: 25866395

4) One definition of biomedical engineering research is "the application of engineering tools to fundamental problems in medicine and the life sciences". Accordingly, analytical and computational modeling of biological systems at the molecular and subcellular level is an important component of my research. Indeed, much of the experimental work in my lab is intertwined with modeling efforts and carried out in an iterative cycle of modeling and experiment. Our recent work employed Brownian dynamics simulations and matrix computational approaches to understand the diffusing and binding of the tethered head of kinesin during walking. With our new capabilities in nm and msec-scale tracking of kinesin heads during stepping, this modeling framework will be directly applicable to the work proposed here. We have also used simulations of multi-motor assays to understand coupling between motors and emergent behaviors when many motors are working together, as is usually the case in cells. These modeling tools will be employed in the proposed work both to understand nanoscale dynamics of stepping heads and the complex motor-motor coupling in multi-motor assays.

a. Monte Carlo analysis of neck linker extension in kinesin molecular motors. M.L Kutys, J. Fricks and W.O. Hancock. 2010. PLoS Computational Biology 6(11): e1000980. PMID: 21079666
b. Kinesins with Extended Neck Linkers: A Chemomechanical Model for Variable-Length Stepping. J. Hughes, W.O. Hancock, J. Fricks. 2012. Bulletin of Mathematical Biology. 74(5):1066-97.
c. Estimating Velocity for Processive Motor Proteins with Random Detachment. Hughes, J., Shastry, S., Hancock, W.O., Fricks, J. 2013. Journal of Agricultural, Biological, and Environmental Statistics. 18(2):204-217.
d. Transport by Populations of Fast and Slow Kinesins Uncovers Novel Family-Dependent Motor Characteristics Important for In Vivo Function. G. Arpag, S. Shastry, W.O. Hancock and E. Tuzel. 2014. Biophysical Journal. 107(8):1896-904. PMID: 25418170.

5) In ongoing work, we have used in vitro reconstitutions to understand the interplay of kinesin motors, the plus-tip tracking protein EB1, and dynamic microtubules in maintaining proper microtubule polarity in neurons. Proper neuronal function requires stereotyped orientations of microtubules such that different cargo are transported to axons and dendrites. Using live imaging in fly larvae, Melissa Rolls identified a complex of kinesin-2 and EB1 that is hypothesized to guild growing microtubules along existing microtubules to reinforce uniform microtubule polarity. We reconstructed this system under the microscope and confirmed that the binding kinetics and mechanical properties of these players are sufficient to produce microtubule bending and alignment. This work defines a new paradigm for the role of EB1 and kinesin motors in organizing the microtubule cytoskeleton in neurons and potentially many cell types.

a. An EB1-kinesin complex is sufficient to steer microtubule growth in vitro. Chen, Y., Rolls, M.M., Hancock, W.O. 2014. Current Biology. 24(3):316-21.
b. Kinesin-2 and Apc function at dendritic branch points to resolve microtubule collisions. A.C. Weiner, M.C. Lanz, D.J. Goetschius, W.O. Hancock and M.M. Rolls. Cytoskeleton. Jan 19. doi: 10.1002/cm.21270. PMID: 26785384.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=hancock-wo

D. Research Support

Ongoing Research Support

2R01GM076476 Hancock (PI) 07/01/2016-06/30/2020
Molecular Mechanism of Kinesin Motility
Goal is to understand chemomechanical mechanism of Kinesin-1,-2,-3 and -5 classes of molecular motors.
Role: PI

NSF-DMS/NIGMS J. Fricks (PI) 07/01/2016-06/30/2020
Collaborative Research: Bridging Understanding of Motor-Cargo Transport from Artificial to Cellular Systems
Goal is to model microtubule-based cargo transport at the nanoscale of individual motors, at the mesoscale of motor-cargo complexes, and the microscale of cargo moving through complex microtubule architectures. Collaboration with John Fricks (PSU Statistics, PI), Peter Kramer (RPI, CoPI), Scott McKinley (Tulane, CoPI) and W.O. Hancock (PSU, BME, CoPI).
Role: Co-PI

R01GM121679 Hancock (PI) 01/01/2017-12/31/2021
Multimotor Mechanisms in Microtubule-based Transport
Goal is to understand coordination of kinesin and dynein motors in intracellular transport.
Role: PI