BIOGRAPHICAL SKETCH

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NAME: Grabe, Michael

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

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
Brown University	Sc.B.	05/1996	Mathematics-Physics
University of California, Berkeley	Ph.D.	05/2002	Physics
University of California, San Francisco	Postdoctoral	09/2006	Biophysics

A. Personal Statement

My graduate work in theoretical biophysics and the theory of membranes with Dr. George Oster at U.C. Berkeley gave me a firm grounding in mathematical and computational approaches. With Dr. Oster, I constructed several mathematical models of rotary ATPases. I focused on the mechano-chemistry of the Vacuolar ATPase (V-ATPase) for my graduate dissertation. This enzyme acidifies cellular organelles in addition to the extracellular compartment of bone resorbing osteoclasts. I used the results of our V-ATPase simulations to subsequently construct a general model of organellar acidification. Our model has played a key role in subsequent studies of pH regulation. I followed this work up by using the model to describe pH fluorescence experiments carried out in Dr. Machen and Dr. Moore's labs at U.C. Berkeley. By combining modeling and experiment, we developed the proton pump-leak model of pH regulation, which continues to be one of the dominant views for how pH is set in the secretory pathway.

Next, I carried out my post-doctoral work with Dr. Lily Jan at U.C. San Francisco/Howard Hughes Medical Institute to provide a solid foundation in ion channel physiology. Through a NSF sponsored post-doctoral fellowship, I developed computational methodologies for combining physiological data with existing structural information to advance our knowledge of voltage gating in voltage-gated potassium channels. This work resulted in 7 publications in journals such as Neuron, PNAS, and Nature. I also refined my expertise of using structural models of ion channels to help determine transition rates in kinetic state models. I have continued to use this hybrid modeling approach, in combination with parameter estimation methodologies, to hone kinetic models based on physiological data.

As an independent researcher my lab has focused on the gating and permeation properties of ion channels and transporters at the atomic level. I work closely with experimental labs on several proteins including sodium coupled sugar transporters (SGLTs) (with Drs. Abramson and Wright at UCLA), the ATP channel VDAC (with Dr. Abramson), potassium channels (Dr. Minor at UCSF), and since moving back to UCSF, I collaborate extensively with Dr. Lily Jan attempting to elucidate the function of TMEM16 channels, as outlined in this grant proposal. TMEM16s combine my interests in channels and transporters in 1 protein, as some family members "transport" lipids in an energy-independent manner in addition to conducting ions. ***My lab was the first to show at the atomic level how the fungal TMEM16, nhTMEM16, scrambles phospholipids*** via the hydrophilic groove found at the protein-membrane interface [a]. We also ***hypothesized that the protein significantly deforms the membrane*** to facilitate scrambling based on results from our fast continuum membrane elasticity solver together with our all-atom simulations, and membrane distortions were later confirmed via cryo-EM structures for many family members from several research groups, including the Jan

lab. Together with the Jan lab, ***my lab has employed structure-based methods to probe the functional states of TMEM16A*** [c], which is a calcium activated chloride channel, and most recently, we ***developed a computational tool for quantitatively analyzing TMEM16F-dependent vesicle formation in mammalian cell lines*** [d]. Thus, armed with TMEM16A and F structures, functional assays for testing ion channel function, lipid scrambling and vesiculation, and powerful computational methods for calculating ion/lipid permeation rates and selectivity (see Section C5) as well as membrane bending (see Section C4), we are in an excellent position to answer outstanding questions in the TMEM16 field.

Finally, my lab has a strong mentoring component at the undergraduate, graduate, and post-doctoral levels. The current composition of my lab is four graduate students (iPQB) and 2 post-docs. I graduated 3 graduate students with doctoral degrees and 1 with a master's degree. I have also mentored over 20 undergraduate students in my lab from a number of colleges/universities, and several students have been recognized with national awards (Udall Scholar, Goldwater Scholar, and National Science Foundation Graduate Research Fellowship). The research projects of my more junior students (undergraduates/graduates) are well integrated with the projects of my post-doctoral fellows and staff scientists to allow the more experienced lab members to share their knowledge.

a) Bethel, N.P., and M. Grabe (2016). Atomistic insight into lipid translocation by a TMEM16 scramblase. *PNAS* 113:14049-14054 PMCID: PMC5150362
b) Argudo, D.†, N.P. Bethel†, F.V. Marcoline†, C.W. Wolgemuth, and M. Grabe (2017). New continuum approaches for determining protein induced membrane deformations. *Biophys. J.* **112**:2159-2172 PMCID: PMC5448241
c) Peters C.J., J.M. Gilchrist, J. Tien, N.P. Bethel, L. Qi, T. Chen, L. Wang, Y.N. Jan, M. Grabe, and L.Y. Jan (2018). The Sixth Transmembrane Segment Is a Major Gating Component of the TMEM16A Calcium-Activated Chloride Channel. Neuron 97:1063-1077. PMCID: PMC5860880
d) Han, T., Ye, W., Bethel, N.P., Zubia, M., Kim, A., Li, K.H., Burlingame, A.L., Grabe, M., Jan, Y.N., and Jan, L. Y. (2019). Chemically induced vesiculation as a platform for studying TMEM16F activity. *PNAS* 116:E10740-E10747. PMCID: PMC6347726

B. Positions and Honors

Positions and Employment

1996-2002	Ph.D. Research, Department of Physics, University of California, Berkeley, Prof. George Oster
2002-2006	Postdoctoral Associate, Department of Physiology, Howard Hughes Medical Institute, University of California, San Francisco, Prof. Lily Jan
2006-2012	Assistant Professor, Department of Biological Sciences, University of Pittsburgh
2008-2013	Assistant Professor (secondary appointment), Department of Computational and Systems Biology, University of Pittsburgh School of Medicine
2012-2013	Associate Professor, Department of Biological Sciences, University of Pittsburgh
2012-2013	Visiting Associate Professor, Cardiovascular Research Institute & Department of Pharmaceutical Chemistry, University of California, San Francisco
2013-2018	Associate Professor, Cardiovascular Research Institute & Department of Pharmaceutical Chemistry, University of California, San Francisco
2018-	Professor, Cardiovascular Research Institute & Department of Pharmaceutical Chemistry, University of California, San Francisco

Other Experience and Professional Memberships

1996-	Member, Biophysical Society
2009-2015	Member of the Biophysical Society Membership Committee
2012-	Editor, Journal of Theoretical Biology
2017-	Editor, Biophysical Journal
2017-	Chief Scientific Officer, Berkeley Madonna, Incorporated
2019-	Co-Founder, Equator Therapeutics

Honors

1996	*Magna Cum Laude* with department honors (Brown University)
1997-98	University of California, Berkeley Outstanding Graduate Student Instructor Award

2003-05 NSF Interdisciplinary Informatics Fellowship
2009-11 Alfred P. Sloan Research Fellow in Molecular Biology
2009-14 NSF CAREER Award
2011 Senior Vice Chan Chancellor's Research Seminar, University of Pittsburgh
2012 Shining Star Award for community outreach, Oakland Planning and Development Corporation, Pittsburgh, PA

C. Contribution to Science

1. *Ion regulation of cells and organelles*. As a graduate student with Dr. Oster (UC Berkeley), I constructed several mathematical models of rotary ATPases. I focused on the mechano-chemistry of the Vacuolar ATPase (V-ATPase) for my graduate dissertation. This enzyme acidifies cellular organelles in addition to the extracellular compartment of bone resorbing osteoclasts. I used the results of our V-ATPase simulations to subsequently construct a general model of organellar acidification. More recently, I pushed our model forward to describe pH regulation in lysosomes, the spatial control of ion flow in cardiac cells, isolated vesicles acidified by *single* proton pumps, and osteoclasts that must acidify to break down bone.

a) Grabe, M., H. Wang, and G. Oster (2000). The mechanochemistry of V-ATPase proton pumps. *Biophys. J.* **78(6)**: 2798-2813 PMCID: PMC1300868
b) Hong, TT.†, H. Yang†, SS. Zhang, H.C. Cho, M. Kalashnikova, B. Sun, H. Zhang, A. Bhargava, M. Grabe, J. Olgin, J. Gorelik, E. Marban, L.Y. Jan, and R.M. Shaw (2014). Cardiac spliced BIN1 folds T-tubule membrane, controlling ion flux and limiting arrhythmia. *Nature Medicine* **20**:624-632 PMCID: PMC4048325
c) Veshaguri, S., S.M. Christensen, G.C. Kemmer, M.P. Moller, G. Ghale, C. Lohr, A.L. Christensen, B.H. Justesen, I.L. Jorgensen, J. Schiller, N.S. Hatzakis, M. Grabe, T.G. Pomorski, and D. Stamou (2016). Direct observation of proton pumping by a eukaryotic P-type ATPase. *Science* **351**:1469-1473 PMCID: PMC5023152
d) Marcoline, F.V., Y. Ishida, J.A. Mindell, S. Nayak, and M. Grabe (2016) A mathematical model of osteoclast acidification during bone resorption. *Bone* **93**:167-180 PMCID: PMC5077641

2. Gating of voltage-activated potassium channels. As a post-doctoral fellow with Dr. Lily Jan (UCSF), I developed a computational approach that used high and low-resolution structural information to create a molecular model of the resting state of the voltage-sensing domain of voltage-gated potassium channels. Our model suggested that voltage sensors undergo large conformational changes during activation, which is consistent with biochemical studies and takes a major step toward resolving controversies in this field. We also pushed forward the use of electrostatics calculations to understand the interaction of charged portions of the channel with the membrane potential to quantify the potential's influence on the state of the channel.

a) Lecar, H., H.P. Larsson, and M. Grabe (2003). Electrostatic model of S4 motion in voltage-gated ion channels. *Biophys. J.* **85(5)**: 2854-2864 PMCID: PMC1303566
b) Grabe, M., H. Lecar, Y.N. Jan, and L.Y. Jan (2004). A quantitative assessment of models for voltage-dependent gating of ion channels. *Proc. Natl. Acad. Sci. USA*. **101**:17640-17645 PMCID: PMC539724
c) Lai, H.C., M. Grabe, Y.N. Jan, and L.Y. Jan (2005). The S4 voltage sensor packs against the pore domain in the KAT1 voltage-gated potassium channel. *Neuron* **47**: 395-406 PMID: 16055063
d) Grabe, M.†, H.C. Lai†, M. Jain, Y.N. Jan, and L.Y. Jan (2007). Structure prediction for the down state of a potassium channel voltage sensor. *Nature* **445**:550-553. PMID: 17187053

3. Transport properties of sodium-dependent co-transporters. Through the use of molecular dynamics simulations, my lab confirmed a central tenet of the alternating access mechanism by showing that substrate is loosely bound to the inward-facing state of sodium-dependent transporters. We also have carried out several studies elucidating how water permeates sugar transporters, which is crucial to their role in water in-take in mammals.

a) Watanabe, A.†, S. Choe†, V. Chaptal, J.M. Rosenberg, E.M. Wright, M. Grabe‡, and J. Abramson‡ (2010). The mechanism of sodium and substrate release from the binding pocket of vSGLT. *Nature* **468**:988-991 PMCID: PMC3736980

b) Joh, N.H., T. Wang, M.P. Bhate, R. Acharya, Y. Wu, M. Grabe‡, M. Hong‡, G. Grigoryan‡, and W.F. DeGrado‡ (2014). De novo design of a transmembrane Zn^{2+}-transporting four-helix bundle. *Science* **346**:1520-1524. PMCID: PMC4400864
c) Adelman, J.L.†, C. Ghezzi†, P. Bisignano, D.D. Loo, S. Choe, J. Abramson, J.M. Rosenberg, E. Wright‡, and M. Grabe‡ (2016). Stochastic steps in secondary active sugar transport. *PNAS* **113**: E3960-3966 PMCID: PMC4941443
d) Bisignano, P., C. Ghezzi, H. Jo, N. Polizzi, A. Thorsten, C. Kalyanaraman, R Friemann, MP. Jacobson, E.M. Wright‡, and M. Grabe‡ (2018). Inhibitor binding mode and allosteric regulation of Na^{+}-glucose symporters. *Nature Comm.* **9**: 5245-5255. PMCID: PMC6286348

4. Computational approaches to understanding membrane protein interactions with the membrane. Membrane proteins are characterized by hydrophobic transmembrane (TM) domains; however, many proteins, such as voltage-gated channels, contain charged residues in their TM regions. A central question is how these charged residues are stably accommodated within the hydrophobic core. Classic studies show that there is a 40-60 kcal/mol barrier for charged residues to partition into low-dielectric environments, while the recent 'biological' hydrophobicity scale based on *in vitro* experiments suggests that the barrier is only 2-4 kcal/mol. To address this discrepancy, my group is developing a fast, continuum-based method for calculating the insertion energies and relative stabilities of membrane proteins. Our method utilizes physics based models to describe the protein and its interaction with the membrane. *The distinguishing feature of our model is that continuum elasticity theory is used to allow the membrane to bend in the presence of the protein*, and its potential was highlighted on Faculty of 1000 as "*open[ing] up the exciting possibility of applying continuum theories to describe processes involving very large membrane protein complexes, which is currently out of the reach of microscopic molecular dynamics simulations*" (f1000.com/1108693).

e) Choe, S., K.A. Hecht, and M. Grabe (2008). A continuum method for determining membrane protein insertion energies and the problem of charged residues. *J. Gen. Physiol.* **131**: 563-573 PMCID: PMC2391250
f) Mukherjee, S., H. Zheng, M. Derebe, K.M. Callenberg, C.L. Partch, D. Rollins, D.C. Propheter, J. Rizo, M. Grabe, Q.X. Jiang, and L.V. Hooper (2014). Antibacterial membrane attack by a pore-forming intestinal C-type lectin. *Nature*. **505**:103-107 PMCID: PMC4160023
g) Bethel, N.P., and M. Grabe (2016). Atomistic insight into lipid translocation by a TMEM16 scramblase. *PNAS* 113:14049-14054 PMCID: PMC5150362
h) Argudo, D.†, N.P. Bethel†, F.V. Marcoline†, C.W. Wolgemuth, and M. Grabe (2017). New continuum approaches for determining protein induced membrane deformations. *Biophys. J.* **112**:2159-2172 PMCID: PMC5448241

5. *Slow molecular events at the membrane.* One of the primary goals of my lab is to use computational methods to elucidate slow transitions in membrane proteins such as conformational changes and small molecule and ion permeation. To accomplish these goals, we use conventional molecular dynamics (MD) simulations, and we are also pushing new methodologies such as Weighted Ensemble path sampling and Markov State Models. Recently, we published the first all-atom study of membrane permeation using a Markov State Model formulation.

a) Adelman, J.L., A.L. Dale, M.C. Zwier, D. Bhatt, L.T. Chong, D.M. Zuckerman, and M. Grabe (2011). Simulations of the alternating access mechanism of the sodium symporter Mhp1. *Biophys. J.* **101**:2399-2407 PMCID: PMC3218348
b) Adelman, J.L.‡, and M. Grabe‡ (2013). Simulating rare events using a Weighted Ensemble-based string method. *J. Chem. Phys.* **138**:044105 PMCID: PMC3568092
c) Choudhary, O.P. †, A. Paz†, J.L. Adelman†, J.P. Coulletier†, J. Abramson‡, and M. Grabe‡ (2014). Structure-guided simulations illuminate the mechanism of ATP transport through VDAC1 *Nature Structural Molecular Biology* **21**:621-632 PMCID: PMC4157756
d) Adelman, J.L.‡, and M. Grabe‡ (2015). Simulating current–voltage relationships for a narrow ion channel using the weighted ensemble method. *J. Comp. Theory Chem.* **11(4)**:1907-1918 PMCID: PMC4573566

† - co first-authors; ‡ - co-corresponding authors

Complete List of Published Work in MyBibliography (58 peer-reviewed publications):

http://www.ncbi.nlm.nih.gov/sites/myncbi/1vOSuWF0Ip559/bibliography/46350670/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R0 1GM089740 Grabe (PI) 09/30/11 – 05/31/21
"Computational Studies of Sodium Symporters"
This grant supports our work to understand the transport properties of sugar dependent co-transporters.
Role: PI

R01 GM117593 Zhou (PI) 08/01/15 – 04/30/20
"A Multiscale Model of Protein Mediated Changes in membrane Morphology"
We are developing multi-scale elastic models of the membrane that incorporate an atomistic level understanding of how membrane proteins change bilayer properties. The ultimate goal is to elucidate the mechanism by which the M2 ion channel from influenza casues membrane budding.
Role: Co-I

R01 AG057342 (Kao) 09/30/18 - 05/31/23
"Systematic Profiling of Lysosomes with Age to Improve Proteostasis in Alzheimer's"
The overall objective of this application is to utilize systems biology approaches in C. elegans models of aging and neurodegeneration to understand how age and stress affect lysosomal acidification, constituents and activity.
Role: Co-Investigator

R43 LM013133-01A1 (Nayak) 08/05/19 - 08/04/20
"Quantitative Modeling Software with Applications to Medical Decision Making"
The goal of this proposal is to extend the commercial modeling software Berkeley Madonna to carry out decision analysis.
Role: Co-Investigator

PBBR UCSF No number (Kirichok/Grabe) 12/15/19 – 12/14/20
"The Mechanism of Thermogenic H^+ leak via Mitochondrial ADP/ATP Carrier"
This grant is aimed at understanding how the AAC1 mitochondrial transporter becomes leaky to protons in the presence of endogenous fatty acids and small molecules.
Role: Co-Investigator

Completed Research Support (past three years)

Anton2 PSCA18020P Grabe (PI) 12/01/18 – 11/30/19
Pittsburgh Supercomputing Center
"Mechanistic Insight on Anion Transporters"
This computer grant supports fully atomistic simulations of the DgoT transporter.
Role: PI

R21 NS091941 Rosenberg (PI) 03/01/15 – 02/28/18
"New tools for computing macro and microscopic channel properties from structure"
This grant supports our work to use enhanced sampling to determine long-time scale properties of channels.
Role: Co-I

Anton2 PSCA17061P Grabe (PI) 01/01/18 – 12/31/18
Pittsburgh Supercomputing Center
"Unraveling the mechanism of activation in K2P channels"
This computer grant supports fully atomistic simulations of K^+ channel activation and conduction.
Role: PI