BIOGRAPHICAL SKETCH

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NAME: Frederick Sachs

POSITION TITLE :Distinguished SUNY Professor of Physiology/Biophysics

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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
University of Rochester, Rochester, NY	BA	1962	Physics
Upstate Medical Center, Syracuse, NY	PhD	1971	Physiology

Personal Statement

We discovered mechanosensitive ion channels (MSCs) with a grant from the *Institute of Serendipity* in 1983. This led to our studies of patch and cell cortex anatomy and mechanics. Along the way we found a specific peptide inhibitor for MSCs in a tarantula venom (GsMTx4), cloned it, characterized it, solved the 3D structure and learned to chemically synthesize so it can now be made in GMP quantities for clinical applications. We synthesized the D enantiomer and showed that it was as efficacious as the L, so that its mode of action did not follow standard lock and key binding site models. We addressed the role of mechanics in diseases such as muscular dystrophy, sickle cell anemia and xerocytosis and cloned the human form of PIEZO1 and have published a lot of its biophysics. Our lab tradition is to share technology and knowledge (my students often hate that I talk about what we are doing before its published). We share software such as QuB software for analysis of ion channel kinetics, our algorithms for wide angle EM tomography, new hardware (such as the high speed pressure clamp), and DNA clones of force probes provided by us directly and through Addgene.

I have always used of mathematical models to summarize our data. I began programming in FORTRAN when I worked for IBM after college. In graduate school I continued programming for electrophysiology and built histological models of heart cells. I developed an early microfabricated linear heart cell preparation. As a postdoc in Biophysics/Biochemistry in Hawaii I built nanosecond flash lamps for fluorescence anisotropy measurements and programmed deconvolution on the IBM360. As a Staff Fellow in Biophysics at NIH I worked on water structure in cells using EPR, and developed patch clamp technology and learned noise analysis of channel fluctuations. In the Pharmacology Dept. in Buffalo I developed the first voltage clamp of isolated adult heart cells, built a high speed amplifier for microelectrode voltage clamp, worked on the first patch clamp of tissue cultured cells (collaboration with Erwin Neher), and worked on a variety of other projects. We have an ongoing IND therapy for muscular dystrophy using GsMtx4 and have done a variety of toxicity and pharmacokinetic studies on whole animals. We recently published a high resolution study of traumatic brain injury in an *in vitro* astrocyte model. We have just submitted a paper showing that NMDA channels are mechanically sensitive, like PIEZO channels, in the absence of chemical agonists that is of obvious relevance to traumatic brain injury.

B. Positions and Honors

1986-present Professor of Biophysical Sciences, SUNY at Buffalo.
1984-1986 Associate Professor, Dept. of Biophysical Sciences, SUNY at Buffalo
1980-1984 Assistant Professor, Dept. of Biophysical Sciences, SUNY at Buffalo

1975-1980 Assistant Professor, Dept. Pharmacology & Therapeutics, SUNY at Buffalo
1971-1975 Staff Fellow, Laboratory of Biophysics, NINCDS, Bethesda, MD
1962-1964 Associate Engineer, Douglas Aircraft, Santa Monica, CA

Some AWARDS AND HONORS:

NIH Single Cell Analysis Program, Phase1 award 2015
K.C. Cole Award, Biophysical Society Membrane Subgroup, 2013
Nominated for Nobel Prize in Physics for Mechanical Transduction, 2011
Science and Technology in Society, Invitation only meeting, Kyoto 2004
Biophysical Society Executive Council, 2005-2007
Pioneers of Science, Hauptman-Woodward Institute, 6/1/2006
Inventor of the year, Niagara Frontier Association, 2007, "Mechanically activated channel blocker"
Material Research Society, Invited author and lecturer Nanoscale Electromechanics, 9/2009
WNY Inventor of the Year, 2009
NIH Review Study Section BST-M, 2011

Some Recent Invited Lectures at International Meetings (on mechanical transduction):
Stretch-activated channels and mechanotransduction, Oleron, France, 9/2014
IUPAB, Brisbane, Australia, 8/2014
Mechanotransduction, Gold Coast Queensland, Australia, 8/2014
Second International Symposium on Mechanobiology (ISMB 2014), Okayama, Japan, 5/2014
Sense to Synapse, NYU, 4/2014
Biophysical Society Pennsylvania Network Meeting, Penn State, 10/2013
Mechanoelectric transduction in the heart, Symposium speaker, Oxford University, UK, 9/2013
Keynote speaker, Annual British Heart Foundation (BHF) Centre of Research, London, 2013
Membrane Protein Biophysics Symposium, Univ. Missouri, 3/2013
Mechanoelectric transduction in the heart Symposium speaker, Oxford University, UK, 9/2013
Keynote speaker, Annual British Heart Foundation (BHF) Centre of Research, London, 2013
Force Transduction and Emerging Ion Channels, Berlin, 9/2012
Stretching and Bending Lipid Membranes, Biophysical Society 2012
40 Years of Ion Channels, Santiago, 10/2011
Mechanical transduction in the heart, Oxford UK, 9/2010

C. Contributions to Science

1. **Discovery of mechanosensitive ion channels (MSCs).** While working on the development of the patch clamp in the early 1980s we discovered that suction applied to the patch pipette not only increased the seal resistance, but activated cationic ion channels. Mechanosensitive ion channels had never been recorded before, and we were recording them in skeletal muscle! After lots of controls, we showed that they were in fact mechanosensitive ion channels activated by membrane tension. We had to deal with a lot of negative feedback since no one had ever expected them to be present in non-sensory organs. To understand the mechanics of channel activation we developed tools to study the anatomy of patches using light and HVEM of patches *in situ*. For tomography, we developed new algorithms for tomographic alignment since the patch could be rotated 360^{o}. Our work on these MSCs led to work on bacterial homologs in other labs, and to an X-ray structure, and our eventual cloning of human mechanosensitive channels and demonstrating their connection to xerocytosis and other anemias.

Bae, C., Gnanasambandam, R., Nicolai, C., Sachs, F. and Gottlieb, P. A. (2013). Xerocytosis is caused by mutations that alter the kinetics of the mechanosensitive channel PIEZO1. *Proceedings of the National Academy of Sciences* **110**, E1162-E1168.

Guharay, F. and Sachs, F. (1984). Stretch-activated single ion channel currents in tissue-cultured embryonic chick skeletal muscle. *Journal of Physiology (London)* **352**, 685-701.

Ruknudin, A., Song, M. J. and Sachs, F. (1991). The ultrastructure of patch-clamped membranes: a study using high voltage electron microscopy. *Journal of Cell Biology* **112**, 125-134.

Suchyna, T. M., Markin, V. S. and Sachs, F. (2009). Biophysics and structure of the patch and the gigaseal. *Biophysical Journal* **97**, 738-747.

2. **Discovery of the only known specific inhibitor of mechanosensitive ion channels.** When we discovered MSCs and the physiological role was undefined, we looked for a drug to inhibit them that we could be tested on tissues, but there were none. We embarked on a blind search among arachnid venoms for such a drug, and learned protein chemistry and molecular biology, and developed patch clamp assays to screen the venoms and fractions. We found a tarantula venom with an active component(s) and isolated it and found it to be an ICK peptide we called it GsMtx4. We made it first by molecular biology and then by chemical synthesis that allowed us to create the D enantiomer. We solved the 3D structure by NMR. We showed that the D and L enantiomers were equally efficacious, and hence did not act by traditional lock and key pharmacology. We tested GsMtx4 on mechanical stress induced atrial fibrillation in rabbit heart and showed that we could reversibly inhibit the arrhythmia. We looked at other diseases that affect cell mechanics and we tested dystrophic muscle and found that the stretch-induced Ca^{+2} uptake characterizing the disease came through GsMtx4 sensitive ion channels. We also showed that GsMtx4 potently stimulates neurite growth and inhibits the mutant PIEZO1 channels that are associated with xerocytosis. GsMtx4 is currently designated an orphan drug for muscular dystrophy.

Bode, F., Sachs, F. and Franz, M. R. (2001). Tarantula Peptide Inhibits Atrial Fibrillation During Stretch. *Nature* **409**, 35-36.

Ostrow, K. L., Mammoser, A., Suchyna, T., Sachs, F., Oswald, R., Kubo, S., Chino, N. and Gottlieb, P. A. (2003). cDNA sequence and in vitro folding of GsMTx4, a specific peptide inhibitor of mechanosensitive channels. *Toxicon* **42**, 263-274.

Suchyna, T. M., Johnson, J. H., Hamer, K., Leykam, J. F., Gage, D. A., Clemo, H. F., Baumgarten, C. M. and Sachs, F. (2001). Identification of a peptide toxin from Grammostola spatulata spider venom that blocks cation-selective stretch-activated channels. *Journal of General Physiology* **117**, 371-371.

Suchyna, T. M., Tape, S. E., Koeppe, R. E., Andersen, O. S., Sachs, F. and Gottlieb, P. A. (2004). Bilayer-dependent inhibition of mechanosensitive channels by neuroactive peptide enantiomers. *Nature* **430**, 235-240.

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3. **Development of optical probes to measure forces in specific proteins of living cells.** Our studies of patch mechanics showed that stresses were not confined to the bilayer but also distributed among cytoskeletal components. To learn the stress in those components, we invented genetically coded optical force probes and created chimeras of structural proteins such as actin, actinin, spectrin, filamin, collagen, and laminA. These were transfected into cells and the outputs observed in real time. We calibrated the *strain sensitivity* using biaxial strain of probes attached to rubber sheets, and the *force sensitivity* using DNA springs and showed sensitivity to forces <10pN. We proved that the probes only responded to tension and not to any changes in cell biochemistry induced by mechanical stress. We showed that all structural proteins we tested were under resting tension and that was subject to change using reversible physiological stimuli. We made transgenic animals and cell lines showing that the probes were nontoxic and usable in intact animals. Many of our clones are available from Addgene. Some key findings include:

- *There are major gradients of stress in specific proteins within individual cells.*
- *Cytoskeletal reagents such as colchicine and cytochalasins affect stress in other proteins and thus cannot be treated as specific reagents.*
- *Anisotonic stresses are distributed throughout the cytoplasm and not confined to the cortex.*
- *Increased mechanical stress in actin is associated with stem-like transformation of cell lines.*

Guo, J., Wang, Y., Sachs, F. and Meng, F. (2014). Actin stress in cell reprogramming. *Proceedings of the National Academy of Sciences* **111**, E5252-E5261.

Meng, F. and Sachs, F. (2011). An orientation-based FRET sensor for real-time imaging of cellular forces *Journal of Cell Science* **125**, 743-750.

Meng, F., Suchyna, T. M., Lazakovitch, E., Gronostajski, R. M. and Sachs, F. (2011). Real Time FRET Based Detection of Mechanical Stress in Cytoskeletal and Extracellular Matrix Proteins. *Cellular and Molecular Bioengineering* **4**, 148-159.

Meng, F., Suchyna, T. M. and Sachs, F. (2008). A fluorescence energy transfer-based mechanical stress sensor for specific proteins in situ. *Febs Journal* **275**, 3072-3087.

4. **The use of AFM to study cell mechanics.** To learn more about how cell mechanics affected MSCs, we began using the AFM as a mechanical stimulator and recorder. We built AFMs that allowed us to voltage clamp cells and do AFM on the same cell, and learned nanofabrication to make better cantilevers for work in water. One key finding was that when nucleated cells are swollen hypotonically, they do not become stiff as expected for cells limited only by the cortex. We showed that the cytoskeleton behaved like a sponge. This work contradicted many years of dogma on cell volume regulation that attributed all osmotic stresses to the cortex. We examined how voltage is coupled to membrane mechanics using voltage clamp and AFM. As predicted, membranes move with voltage independent of ion fluxes. We showed the S4 domain of *Shaker* channels moved very little normal to the membrane during gating (<0.1nm), but the membrane moved a lot when the channels opened.

Beyder, A. and Sachs, F. (2006). Microfabricated torsion levers optimized for low force and high-frequency operation in fluids. *Ultramicroscopy* **106**, 838-846.

Beyder, A. and Sachs, F. (2009). Electromechanical coupling in the membranes of Shaker-transfected HEK cells. *Proceedings of the National Academy of Sciences* **106**, 6626-6631.

Beyder, A. and Sachs, F. (2011). Combined Voltage-Clamp and Atomic Force Microscope for the Study of Membrane Electromechanics. In *Scanning Probe Microscopy of Functional Materials: Nanoscale Imaging and Spectroscopy*, (ed. A. Kalinen), pp. 461-489. Pondicherry - 605008, India: Springer Science+Business Media, LLC.

Spagnoli, C., Beyder, A., Besch, S. and Sachs, F. (2008). Atomic force microscopy analysis of cell volume regulation. *Phys Rev E Stat Nonlin Soft Matter Phys* **78**, 031916.

5. **Development of software to analyze single and multiple channel kinetics.** When we began to record single ion channel currents, analysis of the data became a major problem since there were megabytes and then gigabytes of data. We wrote computer codes to analyze the data and that grew into our solution to the Inverse Markov program called QuB. We taught courses in its use and have maintained on an open/free web site with open source code and which has been downloaded over 2000 times. Since much electrophysiological data is currently gathered as stimulus-driven whole-cell currents, we have added algorithms to analyze that data as well. QuB has also been used for the Markov analysis of single motor proteins, single molecule FRET data, and other data arising from state models.

Qin, F., Auerbach, A. and Sachs, F. (1996). Estimating single-channel kinetic parameters from idealized patch-clamp data containing missed events. *Biophys.J* **70**, 264-280.

Qin, F., Auerbach, A. and Sachs, F. (1997). Maximum likelihood estimation of aggregated Markov processes. *Proc.R.Soc.Lond B Biol.Sci.* **264**, 375-383.

Qin, F., Auerbach, A. and Sachs, F. (2000a). A Direct Optimization Approach to Hidden Markov Modeling for Single Channel Kinetics. *Biophysical Journal* **79**, 1915-1927.

Qin, F., Auerbach, A. and Sachs, F. (2000b). Hidden Markov Modeling for Single Channel Kinetics with Filtering and Correlated Noise. *Biophysical Journal* **79**, 1928-1944.

My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/frederick.sachs.1/bibliography/40670978/public/?sort=date&direction=ascending

Current and Pending Support

Ongoing Research Support

R01HL054887 (NIH) Sachs (PI) 05/01/2013-05/31/2017

“Cell mechanics and Mechanical Transduction by Ion channels"

The goals of this grant are mostly to study PIEZO1 channels and to continue our work on fluorescent stress sensors.

NSF/CMMI-1537239 Sachs (co/PI) 09/01/2015-08/31/2018
Force Transduction mechanisms at adherens junction

This grant aims to explore how forces due to fluid flow are transmitted between the cytoskeleton and E-cadherin that drives remodeling of adherens junctions in epithelial cells.

Completed Research Support within the last 3 years

1R21NS085517-01 Sachs (co/PI) 09/01/2013-08/31/2015
Traumatic brain injury: early mechanosensitive events in astrocytes

The goal of this work was to study the initial events of TBI in a cultured astrocyte model.

DM102091 (USAMRAA) Sachs(PI) 02/25/2011-03/24/2014
The Use of Inhibitors of Mechanosensitive Ion Channels as Local Inhibitors of Peripheral Pain

The goal of this grant was to work on the basic science of pain transduction and the potential clinical role of GsMTx4 as an analgesic.

R01GM084891-01A1 (NIH) Sachs(co/PI) 06/01/2009-03/30/2013
Algorithms for Molecular Kinetics

The goal of this grant was software maintenance on the QUB suite of ion channel analysis code.

The Children’s Guild Sachs(PI) 08/01/2010-08/31/2013
GsMTx4 Peptide as a Potential Therapy for Duchenne Muscular Dystrophy.

This grant funded cytoskeletal stress sensors and the use of GsMTx4 as a therapy for Duchenne dystrophy.