BIOGRAPHICAL SKETCH

DO NOT EXCEED FIVE PAGES.

NAME: Martin Guthold

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

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Ulm	Vordiplom	07/1989	Physics
University of Oregon	PhD	09/1997	Physics & Mol. Biology
University of Oregon	Postdoc	1997	Physics & Mol. Biology
University of North Carolina (Chapel Hill)	Postdoc	2001	Physics & Comp. Sci.

A. Personal Statement

Dr. Guthold's primary appointment is as a professor in the Physics department at Wake Forest University. Dr. Guthold is a member of the Comprehensive Cancer Center. He is the chief scientist of NanoMedica, LLC; a Winston-Salem-based start-up company focused on next-generation sequencing chip-based cancer drug discovery.

Research projects. Dr. Guthold is working on several projects in the general areas of Biophysics and nano- and bio-technology. He makes extensive use of atomic force microscopy-based and optical microscopy-based techniques, in addition to standard molecular biology techniques. In one project, his lab investigates the mechanical and structural properties of fibrin fibers and blood clots, with the overall goal to increase understanding of thrombotic disease. A second project is to investigate the mechanical and morphological properties of cancer cells and normal cells, and understanding how a cell's microenvironment affects these properties. The physical properties of cells complement genetic and biochemical information about the cells and provide a more complete picture about cell behavior. These physical traits may also point the way to new treatment options because of their possible role in the development and spread of cancer, i.e., metastasis. In a third project, Dr. Guthold's team is developing a novel, fast, high-throughput drug discovery technology. The technology utilizes a next-generation sequencing chip and nucleic acid-encoded chemicals. In a fourth project, Dr. Guthold is investigating the mechanical properties of electrospun fibers that may be used in tissue engineering and biomedical applications. Additionally, Dr. Guthold is engaged in AFM imaging projects involving biological samples (e.g., DNA) and organic electronics samples.

Leadership qualifications, relevant administrative, collaborative, mentoring and research experiences. Since joining Wake Forest University in 2001, Dr. Guthold has been supervising 12 Ph.D. students and over 40 undergraduate students. He also has been the principle investigator of multiple-PI grant proposals. In addition to his research, Dr. Guthold directs the graduate program in Physics, which has about 35 Ph.D. students. He has developed classes in professionalism and responsible research conduct, Biophysics (plus lab), and several core Physics classes.

He received the WFU Excellence in Teaching Award (2005) and Excellence in Research Award (2009). In 2011 he was honored with a two-year appointment as a Wake Forest Fellow. In 2016 he received the Outstanding Investigator Award from the International Fibrinogen Research Society.

Dr. Guthold also has numerous collaborations with other researchers. For example, about 15 collaborating groups are using the instruments in his lab. Some current and former collaborators include Bonin, Carroll, Jurchescu, Kim-Shapiro, Macosko, Salsbury (all WFU Physics), Akman, Chen, Gmeiner, Kute, Scarpinato, Torti, Vaughn, Wang (all WFU cancer biology), Profs. Lee, Bierbach, Hantgan, Lord, van Dyke (other departments). International collaborators include Ariens (Great Britain) and Pieters (South Africa). Thus, his

lab provides a rich environment for many interactions with leading research labs, fellow graduate students and post-doctoral researchers.

General lab research areas. Over the last two decades, Dr. Guthold's work has been in the general areas of Biophysics and Nano/biotechnology, resulting in numerous, highly cited publications involving fibrin(ogen), nanofibers, thrombosis & hemostasis, DNA structure, protein/DNA complexes, drug/DNA complexes, AFM-based force measurements and nanomanipulation experiments (e.g. *Science*, *ACS Nano*, *PNAS*, *PLOS Biology*, *EMBO Journal*, *Biomaterials*, *J. Haemostasis and Thrombosis*).

Dr. Guthold is also well versed in nucleic acid-based molecular biology techniques. He was a graduate student and post-doc at the Institute of Molecular Biology (University of Oregon), and throughout his nearly twenty year research career, his work involved biopolymers, such as DNA and protein-DNA complexes and nanofibers. He (or his students) prepared all samples themselves. His research has been funded by the NIH, NSF, American Heart Association, and North Carolina Biotechnology Center (NCBC).

Dr. Guthold's more detailed research expertise in biophysics and nanobiotechnology is listed under section C)

B. Positions and Honors

Positions and Employment

1997	Research Associate, Institute of Molecular Biology, University of Oregon, Eugene, OR
1997-2001	Research Associate, NIH Natl. Center Research Resource, UNC, Chapel Hill, NC
2001	Ajct. Assistant Research Professor, Dept. of Physics, University of North Carolina, Chapel Hill,
2001-2007	Assistant Professor, Dept. of Physics, Wake Forest University, Winston-Salem, NC
2005-	Chief Scientist, NanoMedica, Inc. Newark, NJ
2007-2014	Associate Professor, Dept. of Physics, Wake Forest University, Winston-Salem, NC
2007- 2021	Director, Graduate Program, Dept. of Physics, Wake Forest University, Winston-Salem, NC
2009-	Adjct. Assoc. Professor, Dept. of Cancer Biology, Wake Forest University, Winston-Salem, NC
2014-	Professor, Dept. of Physics, Wake Forest University, Winston-Salem, NC
2021-	Associate Chair, Dept. of Physics, Wake Forest University, Winston-Salem, NC

Other Experience and Professional Memberships

1998-	Member, Biophysical Soc. & Federat. of American Societies for Experimental Biology (FASEB)
2001 -	Member, Comprehensive Cancer Center, Wake Forest University School of Medicine
2004 -	Member, International Fibrinogen Research Society
2006 -	Member, American Physical Society
2003 -	Member of several NSF scientific review panels
2003 -	Member of over 20 NIH scientific review panels (e.g., NCI IMAT (12x), NIH NCRR, P41 (2x), NIH Microscopy & Imaging (3x), NIH Nanotechnology, NIH Hemostasis & Thrombosis), NIH NIBIN, NIH SBIR/STTR)
2018 -	Vice President (and president-elect), International Fibrinogen Research Society

Honors

1990 - 1991	Bafög Scholarship to study overseas, German Government (DM10,000 ~ $5,000)
2005	Reid-Doyle Price for Excellence in Teaching, Wake Forest University ($2,000)
2009	Excellence in Research Award, Wake Forest University ($2,000)
2010	Distinguished Service and Leadership Acknowledgement, Triad Biotech Alliance
2011 - 2013	Wake Forest Fellow ($30,000 lab funds and salary stipend)
2012	Recognition of Scientific Excellence, Seeing at the Nanoscale, 10th Anniv. Celebrat. ($1,000)
2015	Physics Faculty Excellence in Teaching Award, Physics Dept. Wake Forest University ($320)
2016	Outstanding Investigator Award, International Fibrinogen Research Society ($1,000)

C. Contribution to Science

General lab research areas. Dr. Guthold's work has been in five general research areas in biophysics and nanobiotechnology. A list of his publications (>60 peer-reviewed journal publications; >4200 citations; h-factor 30; Google Scholars >6200 citations, h-index 34) can be found here:

http://www.ncbi.nlm.nih.gov/sites/myncbi/martin.guthold.1/bibliograpahy/40523042/public/?sort=date&direction=ascending

1) **Blood clotting, especially the relationship of single fibrin fiber properties, disease and disease intervention.** Blood clots stem the flow of blood, which is essentially a mechanical task. Hence, there has been a longstanding interest in the mechanical properties of clots. The major structural component of a clot are tiny, nanoscopic fibers called fibrin fibers (~ 100 nm diameter). Dr. Guthold's lab has developed a combined atomic force & fluorescence microscope to determine the mechanical and physical properties of biological nanofibers, such as fibrin. Before we started our work in 2006, the mechanical properties of fibrin fibers were unknown. We described their basic properties in an initial publication in *Science*, and have since described extensive and detailed fibrin fiber properties. We are now correlating these properties to diseases and we are investigating novel technologies to dissolve clots. (Overall, over fifteen publications in this area.)

   1. Li, W., Lucioni, T., Li, R., Bonin, K., Cho, S., Guthold, M., "Stretching single fibrin fibers hampers their lysis" *Acta Biomaterialia* (2017) 60, 264-274
   2. A. C. Brown, S. Baker, A. Douglas, M. Keating, M. Alvarez-Elizondo, E. Botvinick, M. Guthold, T. H. Barker "Molecular interference of fibrin's divalent polymerization mechanism enables modulation of multiscale material properties" *Biomaterials* (2015) 49, 27-36
   3. Helms, C. C., Ariëns, R. A. S., de Willige, S. U., Standeven, K.. S., Guthold, M. "α–α Crosslinks Increase Fibrin Fiber Elasticity and Stiffness" *Biophysical Journal* (2012) 102, 168-175
   4. Liu, W., Carlisle, R.C., Sparks, E.A., Guthold, M., "The mechanical properties of single fibrin fibers", J. *Thrombosis and Haemostasis* (2010) 8, 1030-1036.
   5. Liu, W., Jawerth, L. M., Sparks, E. A ., Falvo, M. R., Hantgan, R. R., Superfine, R., Lord, S. T., Guthold, M., (2006) "Fibrin Fibers have Extraordinary Extensibility and Elasticity" *Science* 313, 634

2) **Electrospun nanofibers and their utility in tissue engineering**

Cells are very sensitive to the mechanical properties and the geometry of their substrates. Using the combined atomic force/fluorescence microscopy technique described in 1), Dr. Guthold has determined the mechanical properties and structures of several nanofibers that are used for tissue engineering and other applications. (Overall nine publications in this area)

   1. Baker, S. R., Banerjee, S., Bonin, K., Guthold, M., "Determining the mechanical properties of electrospun poly-epsilon-caprolactone (PCL) nanofibers using AFM and a novel fiber anchoring technique" *Materials Science & Engineering C* (2016) 59, 203-21
   2. Baker, S., Sigley, J., Carlisle, C. R., Stitzel, J., Berry, J., Bonin, K.., Guthold, M. "The Mechanical Properties of Dry, Electrospun Fibrinogen Fibers" *Materials Science and Engineering C* (2012) 32, 215-221.
   3. Carlisle, R.C., Coulais, C., Guthold, M. "The mechanical stress-strain properties of single electrospun collagen type I fibers" *Acta Biomaterialia* (2010) 6, 2997-3003.
   4. Carlisle, R.C., Coulais, C., Namboothiry, M., Carroll, D., Hantgan, R.R., Guthold, M. (2009) "The mechanical properties of individual, electrospun fibrinogen fibers" *Biomaterials* (2009) 30, 1205-1213.

3) **Protein-DNA interactions, cancer drugs and their effect on DNA conformation**

In 1992, as a graduate student, Dr. Guthold was among the first researchers to publish reliable protocols to image DNA and protein-DNA complexes with the atomic force microscope. Ever since, he has used atomic force microscopy and molecular biology techniques to study protein-DNA interaction, DNA conformation, and DNA-drug interactions. He was the first researcher to image dynamic protein-DNA interactions by AFM (1994), he investigated the wrapping of DNA around proteins, and the effect of cancer drugs on DNA conformation. He also used DNA to functionalize carbon nanotubes, so that they could be used in thermal ablation experiments (over 20 peer-reviewed publications in this area).

1. Dutta, S, Rivetti, C, Gassman, NR, Young, CG, Jones, BT, Scarpinato, K, Guthold, M. "Analysis of single, cisplatin-induced DNA bends by atomic force microscopy and simulations" *J. Mol. Recog.* (2018) 31, Art. No. e2731
2. S. Dutta, M. J. Snyder, D. Rosile • K. L. Binz, E. H. Roll, J. Suryadi, U. Bierbach, M. Guthold "PT-ACRAMTU, A Platinum–Acridine Anticancer Agent, Lengthens and Aggregates, but does not Stiffen or Soften DNA", *Cell Biochemistry and Biophysics* (2013), DOI 10.1007/s12013-013-9614-8 (11 pages)

3. Ghosh, S., Dutta, S., Gomes, E., Carroll, D., D'Agostino, Jr., R., Olson, J. Guthold, M., Gmeiner, W. H. "Increased Heating Efficiency and Selective Thermal Ablation of Malignant Tissue with DNA-Encased Multiwalled Carbon Nanotubes", *ACS Nano* (2009) 3, 2667-73.
4. Wong, O.-K., Guthold, M., Erie, D. A., Gelles, J. (2008) "Interconvertable lactose repressor-DNA looped complexes revealed by single-molecule experiments" *PLOS Biology* 6(9):e232, 2028-2042.

4) Physical properties of normal and cancer cells

The behavior of cancer cells is exceedingly complex and influenced by many, interrelated factors. Recent research, indicates that an intricate interplay between genetic mutations and environmental cues, rather than genetic mutations alone, affect cell behavior and fate. A substantial research effort termed 'Physical Sciences Oncology' has been underway in the last several years with the general proposition of looking at cancer with a physicist's eyes. The physical properties of cells are a new layer of cancer cell behavior providing a deeper understanding of cancer. These physical traits may also point the way to new treatment options for cancer. The physical properties of cancer cells are of particular interest because of their possible role in the development and spread of cancer, i.e., metastasis. Dr. Guthold's lab focuses on determining the mechanical properties of normal (non-cancerous) cells, how they compare with cancerous cells, and especially how these properties change as a function of cell micro-environment. (Five publications in this area).

1. Dan Wu, Xinyi Guo, Jing Su, Ruoying Chen, Dmitriy Berenzon, Martin Guthold, Keith Bonin, Weiling Zhao, Xiaobo Zhou "CD138-negative myeloma cells regulate mechanical properties of bone marrow stromal cells through SDF-1/CXCR4/AKT signaling pathway" *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* (2015) 1853 (2) 338-347
2. Xinyi Guo, Keith Bonin, Karin Scarpinato, Martin Guthold, "The effect of neighboring cells on the stiffness of cancerous and non-cancerous human mammary epithelial cells" *New Journal of Physics* (2014) 16, Article Number: 105002, (24 pages)
3. C. D. Markert, X. Guo, A. Skardala, Z. Wanga, S. Bharadwaja, Y. Zhanga, K. Bonin, M. Guthold, "Characterizing the micro-scale elastic modulus of hydrogels for use in regenerative medicine" *Journal of the Mechanical Behavior of Biomedical Materials*, (2013) 27, 115–127
4. S. Dutta, D. A. Horita, R. R. Hantgan, M. Guthold "Probing $a_{IIb}b_3$:Ligand Interactions by Dynamic Force Spectroscopy and Surface Plasmon Resonance", NanoLife (2013), 1340005 (11 pages)

5) Development of a microscopy-based and next generation sequencing-based drug discovery method for aptamers and nucleotide-encoded chemicals.

Dr. Guthold's lab, in collaboration with a team of Wake Forest University Physicists and a company (NanoMedical, LLC) is developing a novel, fast, high-throughput drug discovery technology. The technology utilizes a next-generation sequencing chip and nucleic acid-encoded chemicals. (Three publications, four patents).

1. K. R. Riley, J. Gagliano, J. Xiao, K. Libby, S. Saito, G. Yu, R. Cubicciotti, J. Macosko, C. L. Colyer, M. Guthold, K. Bonin "Combining Capillary Electrophoresis and Next Generation Sequencing for Aptamer Selection" *Analytical and Bioanalytical Chemistry* (2015) 6 1527-1532
2. Gassman, N.R., Nelli, J.P., Dutta, S., Kuhn, A., Bonin, K., Pianowski, Z., Winssinger, N., Guthold, M., Macosko, J.C. "Selection of Bead-Displayed, PNA-encoded Chemicals" *Journal of Molecular Recognition* (2010) 23, 414-22.
3. Bonin, K., J. C. Macosko, J. Gagliano, M. Guthold, and R. Cubicciotti. Integrated Compound Discovery Systems and Methods. Wake Forest University, Nanomedica LLC, assignee. **Patent** US 10481153. Nov. 19, 2019
4. Guthold, M., and J. C. Macosko. Compositions, Methods, and Kits for Identifying Candidate Molecules from Encoded Chemical Libraries. Wake Forest University, assignee. **Patent** US 9487774. Nov. 8, 2016.

D. Research Support

<u>Ongoing Research Support</u>

NIH R15, Hudson (ECU), PI; Guthold (WFU) co-PI, PI of Wake Forest portion; 08/01/19 – 07/31/22
"Identifying the function of the Fibrin(ogen) alpha-C connector region", $438,279

The goal is to identify the role of the Fibrin(ogen) alpha-C connector region in fibrin fiber assembly and mechanical properties.

Wake Forest University, Center for Functional Materials (Guthold, PI) 08/26/20 – 06/30/21
"Mechanical Properties of Electrospun Nanofibers for Biomedical Applications", $20,059
The goal is to determine the mechanical properties of electrospun PCL fibers for use in biomedical applications, e.g., tissue engineering scaffolds.

Wake Forest University, Collaborative Pilot Grant (Baker, Guthold, PI, Kucera, co-PI) 8/1/2020 – 7/31/2021.
'Does Cancer Treatment by Chemotherapy Cause a Change in Blood Clot Structure and Mechanics which in turn is Associated with Increased Riskof Thrombosis (Venous Thromboembolism)?", $20,000.
The goal is to investigate a possible correlation of cancer treatment and thrombosis.

Completed Research Support (Selection)

Discovery Institute, (Macosko, PI) 06/01/2016 – 06/30/19
Searching for the Function of Centrioles
In this study an AFM cantilever is used to detect vibrations and forces as cells undergo mitosis. Furthermore it is studied if force can be used to revert mitosis.

NIH-SBIR Phase I: 5R43 GM102987-02 (Cubicciotti, PI, WFU PI, Guthold) 11/01/12 – 04/30/16
National Institutes of Health
NextGen Lab-on-Bead: Harnessing Ion Torrent Sequencing for Cancer Drug Discovery
This grant focuses on Lab-on-Bead™ enabled Ion Torrent sequencing as a high-throughput way to decode single-sequence-per-bead DNA-encoded libraries. Micron-sized beads arrayed in millions of microelectronic wells are used to simultaneously sequence and then functionally select candidate molecules. The project combines programmable DNA-encoded macrocycle synthesis, Lab-on-Bead processing and NGS to identify new ligands that modulate tyrosine kinase signaling by the erb-B family of receptors overexpressed in breast, prostate and ovarian cancers.

NSF-CMMI 1106105 (Bonin, PI) 07/15/11 – 12/31/15
National Science Foundation
Cell Mechanics and Protein Mobility during Neoplastic Transformation
The main goal is to study cells, as they progress through different cancer stages, to determine whether they initially become stiffer than normal cells and interfere with protein mobility (and, thus, genetic stability), and then in later stages become softer and more nimble, which would aid metastasis.
Role: Co-PI

NIH-NCI P30CA012197-4 (Guthold, PI) 02/01/15 – 10/31/15
Pilot award (sub-award) from Wake Forest University Health Sciences Comprehensive Cancer Center
Next-Generation Sequencing for Cancer Drug Discovery
This proposal focuses on further developing Ion Torrent sequencing as a high-throughput way to decode single-sequence-per-bead DNA-encoded libraries. Specific attention will be focused on the binding reactions of target to small-molecule or aptamer library candidates that act as drugs.

2011-MRG-1115 (Guthold, PI) 01/01/11 – 12/31/13
North Carolina Biotechnology Center
Accelerated discovery of small molecules by preselection-coupled NanoSelection® method
The major goal of this project is to integrate our NanoSelection drug discovery method with capillary electrophoresis-based and cell-based pre-screening. The project involves screening two small chemical libraries for src-tyrosine kinase inhibitors.