Биографски подаци и научни резултати Проф. Др. Србољуба Мијаиловића

Др. Србољуб Мијаиловић је рођен у Тополи 1951. године. Основну школу је завршио у Тополи, а средњу школу у Средњој техникој школи у Крагујевцу. Машински факултет у Београду завршио је 1975., и на истом факултету је магистрирао 1982. године. Докторирао је на МИТ-Massachusetts Institute of Technology, Boston, 1991. из области биоинжењеринг.
Даље су наведени у најкраћем облику подаци о запосењу и научни допринос. Коришћен је документ на енглеском језику који је посвећен једном концепту истраживања. Из њега се може видети научна заснованост и образложење, а такође и научни допринос Др. Мијаиловића. Није превођен текст ради аутентичности.

A. Positions, Scientific Appointments, and Honors

Positions and Employment

2021-	President and C.E.O., FilamenTech Inc., Newton, MA
2016-2022	Associate Research Professor, Illinois Institute of Technology
2016-2017	Associate Professor, Wentworth Institute of Technology
2013-2016	Research Professor, Northeastern University
2012-2013	Associate Research Professor, Northeastern University
2010-2012	Assistant Research Professor, Tufts School of Medicine
2011-2012	Senior Investigator, Steward St. Elizabeth's Medical Center
2010-2011	Senior Investigator, Caritas St. Elizabeth's Medical Center
2006-2010	Instructor, Harvard Medical School
2003-2010	Senior Research Scientist, Physiology Program, Harvard School of Public Health
1998-2003	Research Scientist, Physiology Program, Harvard School of Public Health
1997-1998	Research Associate in Physiology, Harvard School of Public Health
1995-1997	Research Associate/Research Fellow in Physiology, Harvard School of Public Health, Boston, MA
1992-1995	Research Fellow, Department of Biomedical Engineering, Massachusetts General Hospital, Boston, MA
1991-1993	Research Fellow in Physiology, Harvard School of Public Health, Boston, MA
1991-1992	Research Scientist, The Biomechanics Institute, Boston, MA
1982-1986	Research Engineer, Institute "Gosha", Yugoslavia
1979-1982	Research Engineer, Institute "Mihailo Pupin", Belgrade, Yugoslavia
1978-1979	Military Service
1975-1978	Research Engineer, Institute "Mihailo Pupin", Belgrade, Yugoslavia

Peer review activities (last 5 years)

2015-2018 **UO1** Review Committee, NBIB, NIAMS, NIH

Professional Society memberships:

1999-present Biophysical Society,
2006-2012 Biomedical Engineering Society
1991-1997 *American Society of Mechanical Engineers*

Honors:

1997 NIH Postdoctoral Fellowship

B. Contributions to Science

1. *Multiscale Computational Modelling of Striated Muscle Mechanics*
   The current applications developed using the MUSICO platform primarily focus on studies of cardiomyopathies, muscle weakness, and disorders affecting skeletal muscle function. The integration of new capabilities into MUSICO has facilitated the onset of several novel projects: (i) Mechano-chemical regulation of troponin-actin bonds and their role in delayed stretch activation during muscle contraction; (ii) Modulation of crossbridge cycling kinetics and length-dependent calcium sensitivity by titin and nebulin; (iii) X-ray Diffraction Patterns of Non-Uniformly Stretched helices of DNA, actin, myosin and other helical proteins and filaments (in living cells). (iv) Kinetics of myosin binding to human cardiac thin filaments

containing tropomyosin carrying DCM and HCM mutations; (v) Activation and relaxation kinetics in skeletal and cardiac muscles; (vi) Modulation of twitch kinetics in skeletal and cardiac muscle by mutations of contractile and regulatory proteins; (vii) Estimation of local forces in myofilaments in living cells using X-ray diffraction; (viii) Effect of mutations in cMyBP-C on sarcomere mechanical function. (ix) Using computational approaches to elucidate relationships for translating the observations from rat and mouse, as model organisms, to human heart function. (x) Developing multi-scale models of muscle contraction in muscular organs based on mesoscale imaging by diffusion spectrum imaging (DSA). Research progress has been reported in multiple publications and presented at numerous national and international conferences. The relevant references are:

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a) **S.M., Mijailovich**, O. Kayser-Herold, B. Stojanovic, D. Nedic, T.C. Irving, and M. A. Geeves. "Three-dimensional stochastic model of actin-myosin binding in the sarcomere lattice. *J. Gen. Physiol.* 148(6):459-488, 2016. PMCID: PMC5129740
b) M. Prodanovic, M.A. Geeves, C. Poggesi, M. Regnier, **S.M. Mijailovich**. "Effect of Myosin Isoforms on Cardiac Muscle Twitch of Mice, Rats and Humans," *Int. J. Mol. Sci.* 23 (3), 1135, 2022 doi.org/10.3390/ijms2303113
c) **S. M. Mijailovich**, M. Prodanovic, C. Poggesi, J. D. Powers, J. Davis, M. A. Geeves, M. Regnier. "The effect of variable troponin C mutation thin filament incorporation on cardiac muscle twitch contractions," *J. Mol. Cell. Cardiol.* 155, 112-124, 2021. PMCID: PMC8240760
d) **S. M. Mijailovich**, M. Prodanovic, C. Poggesi, M. A. Geeves, and M. Regnier. **"**Multiscale Modeling of Twitch Contractions in Cardiac Trabeculae," *J. Gen. Physiol.* 153 (3), e202012604, 2021. PMCID: PMC7852458
e) Tomasevic, S., Milosevic, M., Milicevic, B., Simic, V., Prodanovic, M., **Mijailovich, S. M.**, Filipovic, N. (2023): "Computational Modeling on Drugs Effects for Left Ventricle in Cardiomyopathy Disease". Pharmaceutics, 15(3):793. https://doi.org/10.3390/pharmaceutics15030793
f) Ma, W., Del Rio, C. L., Qi, L., Prodanovic, M., **Mijailovich, S. M.**, Zambataro, C., Gong, H., Shimkunas, R., Gollapudi, S., Nag, S., Irving, T. C. (2024): "Myosin in autoinhibited off state(s), stabilized by mavacamten, can be recruited in response to inotropic interventions". PANS, 121(8), e2314914121. https://doi.org/10.1073/pnas.2314914121

2. <u>*MUSICO Simulations of X-ray Diffraction Patterns.*</u>

The limiting factor in the field of interpretating X-ray diffraction patterns in striated muscles has been the lack of suitable analysis and modeling tools for muscle diffraction. Significant progress in the modeling of X-ray contraction was recently achieved by adapting the MUSICO simulation platform to predict X-ray diffraction patterns in collaboration with Prof. T. Irving and associate M. Prodanovic. So far, these achievements have been focused exclusively on the generation of X-ray diffraction patterns of relaxed and deformed actin filaments during isometric muscle contraction. These developments can be considered as an initial step toward the development of a tool for interpreting the abundant amount of X-ray diffraction data related to myosin filaments and associated accessory proteins such as titin and MyBP-C, as well as actin accessory proteins like tropomyosin, troponin, and nebulin. This work provides the basis for significant improvements in X-ray diffraction technology at BioCAT, enabling the study of muscle diseases simultaneously at the protein and whole muscle scales. Relevant references are:

a) M. Prodanovic, Y. Wang, **S.M. Mijailovich**, T. Irving. "Using Multiscale Simulations as a Tool to Interpret Equatorial X-ray Fiber Diffraction Patterns from Skeletal Muscle," *Int. J. Mol. Sci.* 24 (10), 8474, 2023. PMCID: PMC10218096 DOI: 10.3390/ijms24108474
b) **S. M. Mijailovich**, M. Prodanovic, T. Irving. "Estimation of Forces on Actin Filaments in Living Muscle from X-ray Diffraction Patterns and Mechanical Data." *Int. J. Mol. Sci.* **2019**, *20*(23), 6044. PMCID: PMC6928692
c) B. Kiss, E. J. Lee, W. Ma, F.W. Li, P. Tonino, **S.M. Mijailovich**, T.C. Irving. "Nebulin stiffens the thin filament and augments cross-bridge interaction in skeletal muscle," *PNAS* 115 (41), 10369-10374. PMCID: PMC6187167
d) M. Prodanovic, T.C. Irving, and **S.M. Mijailovich**. "X-ray diffraction from nonuniformly stretched helical molecules," *J. Appl. Cryst.* 49:784-797, 2016. PMCID: PMC4886979

3. <u>*Tissue Mechanics and Fiber-Fiber Kinetics Model*</u>

Understanding the mechanical behavior of tissues is essential for studying organ function in health and disease. A major effort in this direction was initiated in doctoral research at MIT and continued during postdoctoral studies at Harvard. As a result, I have developed Fiber-Fiber Kinetics Model (FFKM), which was a major innovation in the early 1990s, connecting microstructural interactions between collagen and elastin fibers to complex connective tissue behavior. The model can successfully predict viscoelastic and viscoplastic behavior observed in connective tissues. The model shifted the prevailing practice at the time, which involved fitting phenomenological viscoelastic models to experimental data in order to obtain relevant rheological material characteristics, to a structurally based model with strong predictive power. The main difference between the FFKM and viscoelastic material models is that FFKM's input parameters are physically measurable parameters, rather than material constants obtained from best fits to observations, often without physical meaning. Here are relevant references:

a) M. Kojic, **S. Mijailovic**, and N. Zdravkovic. "A Numerical Algorithm for Stress Integration of a Fiber-fiber Kinetics Model with Coulomb Friction for Connective Tissue," *Computat. Mech.*, 21: 189-198, 1998.
b) **S.M. Mijailovich**, D. Stamenovic, R. Brown, D. Leith and J.J. Fredberg. "Dynamic Moduli of Rabbit Lung Parenchyma and Pigeon Ligamentum Propatagiale Undergoing Uniaxial Cyclic Loading," *J. Appl. Physiol.* 75(2): 773-782, 1994.
c) **S.M. Mijailovich**, D. Stamenovic and J.J. Fredberg. "Toward a Kinetic Theory of Connective Tissue Micro Mechanics", *J. Appl. Physiol.* 74(2): 665-681, 1993.
d) D. Navajas, **S.M. Mijailovich**, G. Glass, D. Stamenovic and J.J. Fredberg. "Dynamic Response of the Isolated Relaxed Rat Diaphragm Strip," *J. Appl. Physiol.* 73(6): 2681-2692, 1992. PMID: 1490986 DOI: 10.1152/jappl.1992.73.6.2681

4. *Multiscale Models of Skeletal and Cardiac Muscles*

Recent developments in experimental techniques and new technologies have provided large amounts of data ranging from basic structural and biochemical kinetics to functional behavior of tissues and organs. These advances have provided an opportunity to revise models of muscle behavior, including kinetics models of muscle contraction and finite element models of muscular organs. Previously, simulations of tissue or organ behavior were performed using computational program packages developed for classical engineering materials such as rubbers and other solid materials. These simulations found application in studying the mechanical behavior of muscular organs such as the lungs, heart, and various skeletal muscles. However, these simulations were completely disconnected from the complex behavior of muscular tissue, which involves complex mechano-chemistry, calcium regulation and the fine fibrous muscle mesoscale structure. We were inspired by new discoveries and initiated the development of multiscale models by revising the basic models of muscle contraction. For example, this involved myofilament extensibility, and developing models of organs using newly developed multiscale approaches, which include crossbidge kinetics and mesoscale orientation of muscle fibers from diffusion spectrum magnetic resonance imaging. The software developed by my group provides opportunities for applications in surgical planning and personalized evaluation of patient's loss of performance due to disease or aging. The relevant references are:

a) **S.M. Mijailovich**. "Biophysical and Biochemical Determinants of Contractile Force Generation, Regulation, and Function," In: *Cell and Tissue Engineering,* edited by B. Obradovic. New York: Springler, 2012, p. 44–91.
b) T.T. Wang, H.S. Kwon, G. Dai, R. Wang, **S.M. Mijailovich**, R.L. Moss, P.T. So, V.J. Wedeen, Gilbert RJ. "Resolving myoarchitectural disarray in the mouse ventricular wall with diffusion spectrum magnetic resonance imaging". Ann Biomed Eng. 38(9):2841-50, 2010. PMCID: PMC5775481
c) M. Kojic, **S. Mijailovic** and N. Zdravkovic. "Modeling of Muscle Behavior by Finite Elements Using Hill's Three Element Model," *Int. j. numer. methods eng.*, 43: 941-953, 1998.
d) **S.M. Mijailovich**, J.J. Fredberg and J.P. Butler. "On the Theory of Muscle Contraction: Filament Extensibility and the Development of Isometric Force and Stiffness," *Biophys. J.* 71: 1475-1484, 1996.
PMCID: PMC1233614, DOI: 10.1016/S0006-3495(96)79348-7

5. *Thin Filament Regulation*

The contractility of striated muscle is regulated by calcium-dependent azimuthal movements of tropomyosin-troponin (Tm-Tn) complexes over the surface of the actin filament. Calcium regulation of muscle contraction is essential for understanding impaired muscle function in most of neuromuscular diseases. We have developed the most comprehensive models of calcium regulation that allow the translation of data from experiments in solution to the muscle contraction dynamic in fibers and whole muscles. The most important advancement is the development of a computational model for the cooperative regulation of myosin binding to actin filaments by a continuous flexible Tm-Tn chain. The model is based on the physical characteristics of Tm-Tn chains and their interaction with actin. An important outcome of this research project is that the cooperativity factors are intrinsic features of the model reflecting physical changes in Tm-Tn chain elasticity and the chain's interaction with the actin surface. As such, this model is suitable for studying the effect of numerous mutations in regulatory proteins on muscle dysfunction in many neuromuscular diseases and cardiomyopathies. The concepts reported in the references below are implemented in the MUSICO platform, and they have the potential to find applications in personalized medicine. By tracing alterations in genes, protein structure, and protein-protein interaction kinetics across multiple scales, this approach provides essential information for the effective development of new drugs and therapies for neuromuscular diseases and cardiomyopathies. Relevant references are:

a) **S.M. Mijailovich**, D. Nedic, M. Svicevic, B. Stojanovic, J. Walklate, Z. Ujfalusi and M.A. Geeves, "Modeling the Actin. myosin ATPase cross-bridge cycle for skeletal and cardiac muscle myosin isoforms," *Biophys. J.* 112 (5): 984-996, 2017. PMCID: PMC5355499
b) **S.M. Mijailovich**, X. Li, J.C. Del Álamo, R.H. Griffiths, V. Kecman and M.A. Geeves. "Resolution and uniqueness of estimated parameters of a model of thin filament regulation in solution," *Comput. Biol. Chem.* 34: 19–33, 2010. PMCID: PMC6089521
c) **S.M. Mijailovich**, O. Kayser-Herold, X. Li, R.H. Griffiths and M.A. Geeves. "Cooperative Regulation of Myosin-S1 Binding to Actin Filaments by a Continuous Flexible Tm-Tn Chain," *Eur. Biophys. J.* 41: 1015–1032, 2012. PMCID: PMC3509328
d) M.A. Geeves, H. Griffiths, **S.M. Mijailovich** and D. Smith. "Cooperative [Ca^{2+}]-Dependent Regulation of the Rate of Myosin Binding to Actin: Solution Data and the Tropomyosin Chain Model," *Biophys. J.* 100:1–9, 2011. PMCID: PMC3117182 DOI: 10.1016/j.bpj.2011.04.020

C ПУБЛИКОВАНИ РАДОВИ И ЦИТИРАНОСТ

Др. Србољуб Мијаиловић има преко 100 публикованих радова у престжним светским часописима. Према Google Scholar цитираност је 6169, а h индекс је 33.

Complete List of Published Work
A complete list of published work can be found at:
https://pubmed.ncbi.nlm.nih.gov/?term=Mijailovich%20SM&sort=pubdate