# Developing Design Tools for Biological and Biomedical Applications of Micro- and Nano-technology

Jacob White (white@mit.edu)
C. H. Green Professor of Electrical Engineering and Computer Science
Associate Director, Research Laboratory of Electronics
Massachusetts Institute of Technology 50 Vassar Street., Cambridge, MA 02139

## ABSTRACT

This short paper, an update of [75], is intended to provide a brief summary and extensive references on biological applications for micro- and nano-machining, as well as the computer-aided design challenges generated by those applications.

## Categories and Subject Descriptors

J.6 [**Computer-Aided Engineering**]: Computer-Aided Design

## General Terms

Design, Algorithms

## Keywords

bioMEMS, lab-on-a-chip, CAD, Numerical Techniques

## 1. INTRODUCTION

It has long been recognized that techniques developed for fabricating nanometer-sized semiconductor devices can be used to generate mechanical structures, a process referred to as micro- or nano-machining. Electrostatic forces are commonly used to manipulate these small structures because such forces are sufficiently large, owing to their quadratic scaling with inverse length, and because electrostatics is easily controlled electronically. Devices which combine small structures and electrostatic manipulation are often referred to as MEMS or NEMS, which are mnemonics for Micro(Nano)-Electro-Mechanical Systems. These mnemonics have become quite popular, and now MEMS and NEMS are used quite liberally to refer to a wide range of micro- and nano-machined devices that are not primarily electromechanical [1].

MEMS and NEMS can be combined to create single-chip systems that perform complicated procedures on micron- and nanometer-sized objects, making the technology a natural candidate for processing biological cells, bacteria, and even larger proteins [2, 3, 4]. The potential of MEMS and NEMS in biological and biomedical applications inspired a subfield, often referred to as bioMEMS. The bioMEMS field is currently undergoing a dramatic expansion thanks in part to the very visable commercial success of microarrays for collecting gene expression data [6]; and the development of biologically-neutral rapidly micromachinable materials [5]. What has not kept pace is the development of the appropriate computer-aided design (CAD) tools.

The impact of inadequate CAD tools in micro- and nanotechnology is well-known. Researchers will not as aggressively examine the design space of a new idea, because they will have to rely on slow-to-construct physical prototypes. Product developers will struggle much longer to create manufacturable designs, because generating multiple physical prototypes is an extremely inefficient approach to determining design sensitivities. Even though there is consensus on the impact of inadequate CAD, the reason the situation has not changed is that bioMEMS design is so technologically diverse that new CAD strategies are needed. In this short paper, really an update of [75], the author is trying to point out both application and CAD literature that will help make clear some of the design tool challenges. Below, applications are mentioned first, to show the diversity of bioMEMS technology, followed by brief descriptions of some of the associated CAD issues.

## 2. APPLICATIONS

The biological applications of micro- and nano-machining fall into three broad overlapping categories: providing faster or extended experimental capabilities for researchers in molecular, cellular and system biology; improving detection capabilities either for medical diagnosis or biohazard applications; and developing implantable devices for managing chronic diseases [7, 8].

### 2.1 Research

In the area of biological research, one of the major successes of microtechnology is the microarray [6]. A microarray is a two-dimensional array of individually programmable patches that can be made to "light up" in response to gene expression levels. The two dimensional array then creates a characteristic picture which represents relative expression levels for many different genes. One important use of microarray data is to construct or calibrate network models for cellular signal transduction and regulation [9, 10, 11]. These networks are then used to gain insight into cell normal and disease responses, as well as to identify treatment targets.


*CODES+ISSS'05,* Sept. 19–21, 2005, Jersey City, New Jersey, USA.

Microarrays are relatively straight-forward devices to design, because most of the cell processing is done externally. In order to accelerate that cell preparation, complicated microfluidic devices are being developed that can store arrays of cells and select them electronically [12], or lyse cells to release proteins for later detection [13]. In addition, new "living cell" devices are being developed which can yield single-cell time-series data, which can be much more informative than the single-timepoint, multicell-aggregate data provided by microarrays [14].

## 2.2 Biomedical Applications

In the area medical diagnosis, micro- and nano-machining offers the promise of rapid and inexpensive testing by creating a single device that is the equivalent of an entire diagnostic lab [15, 4, 16, 17]. Some labs-on-a-chip are essentially detectors; they combine mixers, reservoirs of reagents, separators, and reaction product sensors. Single-chip labs intended for processing cells are significantly more complicated; they may include techniques for screening and lysing the cells, preconcentrators or filters for resulting biomolecules, and specialized arrays of sensors [18].

There has been considerable success in designing and optimizing basic lab-on-a-chip components, and there are a variety of alternative designs for cell manipulators, mixers, separators, preconcentrators, filters and sensors. There has been less success in designing complete single-chip labs, in part because of the difficulty in modeling the entire complicated system.

Additional medical applications for micro- and nano-machining include DNA sequencing [19, 20, 21, 22, 23], cell separating and isolation [24, 12], and blood testing [25, 26].

## 2.3 Implantable Devices

Many of the implantable, or in-vivo, applications of micromachining are ones for which there is little or no treatment alternative. Such applications of micromachining are inspiring, and include approaches for continuous glocose monitoring [27], neural-stimulation [28], retinal implants [29], and artificial livers and other tissues [30, 31]. In-vivo micromachined devices are unlikely to appear in the near term, there are many difficult challenges such as the problems of energy havesting and developing biocompatible processing [32, 33, 34, 35].

# 3. CAD CHALLENGES

For surface-micro-machined polysilicon, a popular and relatively mature MEMS technology, existing design tools are reasonably complete. There are low-level simulation tools which, given either 3-D geometry or 2-D layout, can perform fast coupled 3-D electromechanical analysis of a single device. In addition, there are higher-level tools that extract more abstract models from 2-D layout and can be used for system simulation [36, 37, 38]. The situation is very different for bioMEMS. The tools are nowhere near as complete, primarily because the technology, and therefore the physical effects, are much more diverse. This diversity impacts strategies for low-level simulation as well as for model extraction. Finally, generating manufacturable designs in these new technologies have proved to be extremely difficult, suggesting that recent techniques in robust design might be important avenues to pursue [39].

## 3.1 Simulation

For many bioMEMS devices, the important physics can be reasonably accurately modeled using coupled continuum models. For example, many microfluidics devices can be simulated by coupling a Stokes equation model for the fluid, Poisson or Laplace's equation for the electrostatic fields, and the continuum elastostatics equation for mechanical deformation. For devices described by coupled continuum models, there are finite-element [40, 41] and volume-element [42] simulation tools which allow substantial flexibility in multiphysics simulation. When faster computational performance is needed for 3-D field simulation, Green's function independent fast solvers [43, 44, 46, 45] can be combined with finite-element simulation using matrix-implicit multi-level Newton methods [47], though there is little available software.

Although some bioMEMS devices can be described by coupled PDE's and simulated using existing or emerging multiphysics simulators, many devices have more complicated physics. In devices intended for use in molecular separation, the length scales are such that noncontinuum fluid effects must be considered [48, 49, 50], and therefore hybrid approaches which combine molecular and continuum models are being developed [55, 56, 57, 58]. For devices used in processing cells, faster techniques are needed for analyzing cells in flow [51, 52, 53, 54]. For devices that perform droplet chemistry, methods are needed for rapid surface evolution [59].

# 4. MODEL EXTRACTION

The application of micromachining to systems which use bioMEMS, such as labs-on-a-chip, require complicated combinations of individual bioMEMS devices which process fluids, cells and molecules (e.g. mixers, separators and pumps). In order to simulate systems of these devices, models have been developed for common components, such as mixers and separators [60, 61]. The wide variety of devices currently in development, and the need to rapidly assess the impact of candidate device performance on system behavior, will accelerate the demand for techniques which more automatically extract models of these bioMEMS devices from detailed physical simulation. The required automatic techniques may include approaches similar to the robust nonlinear model order reduction strategies developed for classical MEMS and nonlinear circuits [62, 63, 64, 65, 66, 67, 68], but may also require new approaches where the interaction is a surface or region, rather than a few ports [69, 70, 71]. Finally, automated device optimization, particularly to improve robustness, will likely require some form of parameterized model reduction[72, 73, 74].

# 5. CONCLUSIONS

The field of micro- and nano-machining for biological applications has progressed considerably since the publication of [75], but the CAD tools have changed little. In the author's opinion, the lack of adequate CAD tools is the key reason for this field's near decade long delay between research prototype and commercial product. And since the technology is scaling ever downward, eventually delays in product development will halt research progress, because the delays will cascade. That is, without a previous generation's technology in useable form, it is unlikely that the next generation technological investigation can thoroughly begin.

The author hopes that this brief paper will provide enough pointers to the literature to motivate students to contribute to CAD tool development and thereby help avoid technology stagnation.

This summary was supported by the Singapore-MIT Alliance, the National Science Foundation, Grants from the Semiconductor Research Corporation, the MARCO Interconnect Focus Center. In addition, much of the research described above was supported under a variety of DARPA-sponsored programs.

## 6. REFERENCES

[1] S. D. Senturia, "Microsystem Design," Kluwer Academic Publishers, Norwell, Massachusetts, 2001

[2] Kricka, L. J.; Wilding, P. Micromechanics and Nanotechnology. In Handbook of Clinical Automation, Robotics, and Optimization; Kost, G. J., Welsh, J., Eds.; John Wiley and Sons: New York, 1996; p 45.

[3] Manz, A., Becker, H., Eds. Microsystem Technology in Chemistry and Life Sciences; Springer-Verlag: Berlin, Germany, 1998.

[4] D. J. Harrison and P. G. Glavina, "Towards Miniaturized Electrophoresis and Chemical Analysis Systems on Silicon: An Alternative to Chemical Sensors, Sens. Actuators B 10, 1993

[5] David C. Duffy, J. Cooper McDonald, Olivier J. A. Schueller, and George M. Whitesides* Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane) Anal. Chem.1998, 70,4974-4984

[6] M. Schena, D. Shalon, R. W. Davis, P. O. Brown "Quantitative Monitoring of Gene-expression Patterns with a Complementary-DNA Microarray," Science, Vol. 270, 1995, Pp. 467-470

[7] W. Tang, "MEMS for Biomedical Applications," Presentation, NSF workshop on Control and System Integration of Micro- and Nano-Scale Systems, March, 2004

[8] J. Voldman, M. L. Gray, M. A. Schmidt, "Microfabrication in Biology and Medicine," Annu. Rev. Biomed. Engr., 1999, Vol 1.

[9] H. S. Wiley, S. Y. Shvartsman and D. A. Lauffenburger "Computational modeling of the EGF-receptor system: a paradigm for systems biology," Trends in Cell Biology Vol.13 No.1 January 2003

[10] A. J. Hartemink, D. K. Gifford, T. S. Jaakkola, R. A. Young, "Using graphical models and genomic expression data to statistically validate models of genetic regulatory networks." Pac. Symp. Biocomput. 2001, 422-433 (2001).

[11] Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors B. Schoeberl, C. Eichler-Jonsson, E. D. Gilles, and G. Mller

[12] Voldman, J., R. A. Braff, M. Toner, M. L. Gray, and M. A. Schmidt (2001). Holding Forces of Single-Particle Dielectrophoretic Traps. Biophys. J. 80(1): 531-541.

[13] S. Song, P. Mela, A. Berg, and B. J. Kirby, "Microfluidic Architectures for Integrated Cell Lysis, Lysate Dialysis, and Cell Stimulus," Eighth International Conference on Miniaturized Systems for Chemistry and Life Sciences, September 2004, Malmo, Sweden

[14] K. R. Kling, D. M Thompson, K. J. Wieder, M. Toner, M. L. Yarmush, and A. Jayaraman, "Living Cell Gene Expression Assays in a Microfluidic Device," Eighth International Conference on Miniaturized Systems for Chemistry and Life Sciences, September 2004, Malmo, Sweden

[15] van den Berg, A., Bergveld, P., Eds. Micro Total Analysis Systems; Kluwer Academic Publishers: London, 1995.

[16] C. H. Ahn, J. -W. Choi, G. Beaucage, J. Nevin, J. -B. Lee, A. Puntambekar, and J, Y. Lee, "Disposable Smart Lab on a Chip for Point-of-Care Clinical Diagnostics", Proceedings of the IEEE, Special Issue on Biomedical Applications for MEMS and Microfluidics, Vol. 92, pp. 154 - 173, 2004.

[17] Pourahmadi, F., Lloyd, K., Kovacs, G., Chang, R., Taylor, M., Sakai, S., Schafer, T., McMillan, W., Petersen, K., and Northrup, M. A., Versatile, Adaptable and Programmable Microfluidic Platforms for DNA Diagnostics and Drug Discovery Assays, Proceedings of the MicroTAS 2000 Symposium, May 14 - 18, 2000, Enschede, Netherlands, pp. 243 - 284.

[18] J. Fritz, E. B. Cooper, S. Gaudet, P. K. Sorger and S. R. Manalis "Electronic detection of DNA by its intrinsic molecular charge" Proceedings of the National Academy of Science, October 2002, vol. 99, no. 22, pp. 14142-14146

[19] Ehrlich, D. and Matsudaira, P. (1999) Microfluidic devices for DNA analysis. Trends in Biotechnology, Vol. 17, 315-318.

[20] Salas-Solano, O., Schmalzing, D., Koutny, L., Buonocore, S., Adourian, A., Matsudaira, P., and Ehrlich, D. (2000) Optimization of high-performance DNA sequencing on short microfabricated electrophoretic devices. Anal. Chem., 72, 3129-3137.

[21] Han, J. and H. G. Craighead (2002). Characterization and Optimization of an Entropic Trap for DNA Separation. Analytical Chemistry 74: 394-401.

[22] J. Fritz, E.B. Cooper, S. Gaudet, P.K. Sorger, and S.R. Manalis, Electronic detection of DNA by its intrinsic molecular charge, Proceedings of the National Academy of Sciences, vol. 99, no. 22, p. 14142-14146 (2002).

[23] D. Di Carlo and L. P. Lee, Mechanical Cell Lysis Results of a Sample Preparation Module for Functional Genomics, 2nd Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology, p. 527-530, Madison, Wisconsin, USA

[24] Voldman, J., M. Toner, M. L. Gray, and M. A. Schmidt (2002). A Microfabrication-Based Dynamic Array Cytometer. Analytical Chemistry 74(16): 3984-3990.

[25] Wilding P., Kricka L.J., Cheng J., Hvichia G., Shoffner M.A. and Fotina P. (1998). Integrated cell isolation and polymerase chain reaction analysis using silicon microfilter chambers. Analytical Biochemistry, 257: 95-100.

[26] Yuen P.K., Kricka L.J., Fortina P., Panaro N.J.,

Sakazume T., and Wilding P. (2001) Microchip module for blood sample preparation and nucleic acid amplification reactions. Genome Research, 11: 405-412.

[27] S. Simmermann1, B. Stoeber, D. Fienbork1 and D. Liepmann "Diabetes under control: a microneedle-continuous glucose monitor" Proceedings, BMES 2003 Annual Fall Meeting, October 2003, Nashville, USA

[28] Andy Hung, David Zhou, Robert Greenberg, and Jack W. Judy, "Dynamic Electrochemical Simulation of Micromachined Electrodes for Neural- Stimulation Systems", 1st International IEEE EMBS Neural Engineering Conference, Capri, Italy (March 20-22, 2003).

[29] D. Shire, M. Gingerich, K. Karcich, A. Buck, R. Sweitzer, C. Scholz, S. Montezuma, J. Loewenstein, J. Wyatt, and J. Rizzo, Packaging Developments for Retinal Prostheses, in IOVS Vol. 44, No. 4, March, 2003

[30] L. Griffith, A. Sivaraman, K. Domansky, SR Tannenbaum, A. Capitano, and J. Roberts, "Microfabricated liver for metabolism and toxicity," Chemical Research in Toxicology, 15 (12): 25 DEC 2002.

[31] S. N. Bhatia and J. W. Allen, "Improving the Next Generation of Bioartificial Liver Devices," Seminars in Cell and Developmental Biology 13(6):447-454, 2002.

[32] M. Schmidt, "Research Directions in MEMS" Presentation, NSF workshop on Control and System Integration of Micro- and Nano-Scale Systems, March, 2004

[33] J. Tien, Y. Xia, and G. M. Whitesides, "Microcontact Printing of SAMs", Thin Films, vol.24, Ulman, A., Ed. Academic Press, 1998 , 227-253.

[34] R.J. Jackman, T.M. Floyd, R. Ghodssi, M.A. Schmidt, and K.F. Jensen, "Microfluidic systems with on-line UV detection fabricated in photodefinable epoxy," J. Micromechanical and Microengineering, 11, 263-269 (2001)

[35] H. Lu, Lecture Notes for 6.152, Massachusetts Institute of Technology, 2003

[36] S. D. Senturia, N. Aluru, and J. White. Simulating the behavior of MEMS devices: Computational methods and needs. IEEE Computational Science and Engineering, 4:30-43, 1997.

[37] S. Senturia, "CAD Challenges for Microsensors, Microactuators, and Microsystems," *Proc. IEEE*, vol. 86, August 1998.

[38] item T. Mukherjee, G. Fedder and J. White, "Emerging Simulation Approaches For Micromachined Devices", *IEEE Trans. on Computer-Aided Design*, December, 2000

[39] l. Bitsch, H. Bruus, and J. P. Kutter, "Minimization of Performance Variation in Microfluidic Components Using the method of Robust Design," Eighth International Conference on Miniaturized Systems for Chemistry and Life Sciences, September 2004, Malmo, Sweden

[40] O. C. Zienkiewicz and RL Taylor, "The Finite Element Method, Volumes 1 and 2", (5th edn). Butterworth-Heinemann: Oxford, 2000

[41] FEMLAB, http://www.femlab.com

[42] M. R. Pinto, D. M. Boulin, C. S. Rafferty, R. K. Smith, W. M. Coughran Jr., I. C. Kizilyalli, M. J. Thoma, "Three-dimensional characterization of bipolar transistors in a submicron BiCMOS technology using integrated process and device simulation," IEDM Tech. Dig., pp. 923-926, 1992.

[43] V. Rokhlin, "Rapid solution of integral equation of classical potential theory," *J. Comput. Phys.*, vol. 60, pp. 187–207, 1985.

[44] K. Nabors, F. T. Korsmeyer, F. T. Leighton, and J. White. Preconditioned, adaptive, multipole-accelerated iterative methods for three-dimensional first-kind integral equations of potential theory. *SIAM J. Sci. Statist. Comput.*, 15(3):713–735, 1994.

[45] J. R. Phillips and J. K. White, "A Precorrected-FFT method for Electrostatic Analysis of Complicated 3-D Structures," *IEEE Trans. on Computer-Aided Design*, October 1997, Vol. 16, No. 10, pp. 1059-1072.

[46] L. Ying, G. Biros, and D. Zorin. A kernel-independent adaptive fast multipole algorithm in two and three dimensions. Journal of Computational Physics, 196(2):591-626, 2004.

[47] D. Ramaswamy, N. Aluru and J. White, "Fast Coupled-Domain, Mixed-Regime Electromechanical Simulation" Proc. Int'l Conference on Solid-State Sensors and Actuators (Transducers '99), Sendai Japan, June, 1999 pp. 314-317

[48] L. Zhang, J.-M. Koo, L. Jiang, M. Asheghi, K.E. Goodson, J.G. Santiago, and T.W. Kenny, "Measurements and Modeling of Two-Phase Flow in Microchannels with Nearly Constant Heat Flux Boundary Conditions", Journal of Microelectromechanical Systems, Vol.11, No.1, Feb 2002, pp.12-19.

[49] G. Han, J.C. Bird, K. Johan, A. Westin, and K.S. Breuer "Infrared Diagnostics for Measuring Fluid and Solid Motion Inside MEMS," Solid-State Sensor, Actuator and Microsystems Workshop, Hilton Head Island, South Carolina, June, 2002

[50] G. Karniadiakis and A. Beskok, Micro Flows, Springer Verlag, 2001

[51] N. R. Aluru and J. White. "A Fast Integral Equation Technique for Analysis of Microflow Sensors Based on Drag Force Calculations." Proc. of MSM, pp. 283-286, 1998.

[52] W. Ye, X. Wang, W. Hemmert, D. Freeman and J. White, Viscous Drag on a Lateral Micro-resonator: Fast 3-D Fluid Simulation and Measured Data. Solid-State Sensors and Actuators Workshop, Hilton Head Island, June, 2000: 124-127

[53] Pozrikidis, C.(Ed) Modeling and Simulation of Capsules and Biological Cells. Chapman and Hall/CRC Press., 2003

[54] C.P. Coelho, J.K. White and L.M. Silveira Dealing with Stiffness in Time-Domain Stokes Flow Simulation Proceedings of Nanotech, Boston, March 2004.

[55] Allen , M. P and D. J. Tildesley (1989). Computer Simulation of Liquids. Oxford Science publications.

[56] Hadjiconstantinou, N. G. and A. T. Patera (1997). Heterogeneous Atomistic-Continuum Representations

for Dense Fluid Systems. International Journal of Modern Physics C 8:967-976.

[57] Hadjiconstantinou, N. G. (1999). Hybrid Atomistic-Continuum Formulations and the Moving Contact-line Problem. Journal of Computational Physics,154: 245-265.

[58] Aktas, O. and N. R. Aluru (2002). A combined Continuum/ DSMC Technique for Multiscale Analysis of Microfluidic Filters. Journal of Computational Physics 178:342-372.

[59] T. Korsmeyer. Design tools for bioMEMS. Proceedings of the Design Automation Conference, pages 622-627, 2004.

[60] Y. Wang, Q. Lin, and T. Mukherjee, "Applications of behavioral modeling and simulation on a lab-on-a-chip: micro-mixer and separation system,"Proceedings of the 2004 IEEE International Behavioral Modeling and Simulation Conference, 2004. BMAS 2004., pages 8-13, 2004.

[61] Y. Wang, Q. Lin, and T. Mukherjee. System-oriented dispersion models of general-shaped electrophoresis microchannels. Lab-on-a-chip, 4(5):453-463, 2004.

[62] E. Huang, Y. Yang, and S. Senturia, "Low-Order Models For Fast Dynamical Simulation of MEMS Microstructures," IEEE Int. Conf. on Solid State Sensors and Actuators(Transducers '97), Chicago, June 1997, Vol. 2, pp. 1101-1104.

[63] Joel R. Phillips. Projection-based approaches for model reduction of weakly nonlinear, time-varying systems. IEEE Trans. Computer-Aided Design, 22:171-187, 2003.

[64] P. Li and L. T. Pileggi. NORM: Compact model order reduction of weakly nonlinear systems. In 40th ACM/IEEE Design Automation Conference, pages 472-477, Anaheim, CA, June 2003.

[65] N. Dong and J. Roychowdhury. Piecewise polynomial nonlinear model reduction. In 40th ACM/IEEE Design Automation Conference, pages 484-489, Anaheim, CA, June 2003.

[66] Rewienski, M. and White, J. A Trajectory piecewise-linear approach to model order reduction and fast simulation of nonlinear circuits and micromachined devices. IEEE Transactions of Computer-Aided Design 22(2):155-170, 2003

[67] A. Oliveira, J. R. Phillips, J. Afonso, and L. M. Silveira. Analog macromodeling using kernel methods. In International Conference on Computer Aided-Design, Santa Clara, CA, November 2003.

[68] S.K. Tiwary and R.A. Rutenbar. Scalable trajectory methods for on-demand analog macromodel extraction. In Proceedings of the 42nd annual conference on Design automation, pages 403-408, New York, NY, USA, 2005. ACM Press.

[69] Gabbay, L.D., Mehner, J.E., Sentura, S.D., "Computer-Aided Generation of Nonlinear Reduced-Order Dynamic Macromodels-II:Stress-Stiffened Case" IEEE/ASME J. Microelectromechanical Systems, Vol. 9, No. 2, June 2000.

[70] Computational Methods for Reduced Order Modeling of Coupled Domain Simulations, Bebbini, F., Mehner, J., Dtzel, W., 11th Intl Conf. on Solid-State Sensors and Actuators, Tranducers 2001, Munich 2001.

[71] Willcox, K., J. Peraire and J.D. Paduano, Application of Model Order Reduction to Compressor Aeroelastic Models', Journal of Engineering for Gas Turbines and Power, Vol. 124, January 2002.

[72] Prud'homme, C., D.V.Rovas, K. Veroy, L. Machiels, Y. Maday, A.T. Patera, G. Turinici. Reliable real-time solution of parametrized partial differential equations: Reduced-basis output bound methods, Journal of Fluids Engineering-Transactions of the ASME, 124 (1): 70-80, March 2002.

[73] Daniel, L., O. C. Siong, L. S. Chay, K. H. Lee, and J. White, A Multiparameter Moment Matching Model Reduction Approach for Generating Geometrically Parameterized Interconnect Performance Models," IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems.

[74] Bui-Thanh, T., Murali, D., Willcox, K. E., "Proper Orthogonal Decomposition Extensions for Parametric Applications in Compressible Aerodynamics", AIAA paper 2003-4213, 21st Applied Aerodynamics AIAA conference, Orlando, FL, 2003.

[75] J. White, "CAD Challenges in BioMEMS Design," Proceedings of the Design Automation Conference, June, 2004, pp. 629-632.