

Curriculum Vitae October 2008

Raimund J. Ober, Ph.D.

Education

- 1982: `Vordiplom in Mathematik', `Zwischenpruefung in Physik', Tuebingen University, Germany.
- 1984: `Certificate of Advanced Study in Mathematics', Cambridge University, UK.
- 1985: M.Phil. in Operations Research and Control Engineering, Cambridge University, UK. Thesis title: Problems of Parametrizations in Linear Systems Thesis advisor: J.M. Maciejowski.
- 1987: Ph.D., Department of Engineering, Cambridge University, UK. Thesis title: Balanced Realizations for Finite and Infinite Dimensional Linear Systems. Thesis advisor: J.M. Maciejowski.

Positions

- 1987-1990: Research Fellowship at Girton College, Cambridge, UK and Department of Engineering, Cambridge University, UK.
- 1990-1993: Assistant Professor, Programs in Mathematical Sciences, University of Texas at Dallas.
- 1993-97: Associate Professor with tenure, Programs in Mathematical Sciences and Department of Electrical Engineering, University of Texas at Dallas.
- 1996-: Adjunct Faculty Appointment, University of Texas Southwestern Medical Center, Dallas.
- 1997-1998: Full Professor with tenure, Programs in Mathematical Sciences and Department of Electrical Engineering, University of Texas at Dallas.
- 1999- present: Full Professor with tenure, Department of Electrical Engineering, University of Texas at Dallas
- 2005- present: Member, Graduate Program in Biomedical Engineering, University of Texas Southwestern Medical Center at Dallas.
- 2005- present: Member, Graduate Program in Biomedical Engineering, University of Texas Southwestern Medical Center at Dallas.

Temporary and visiting appointments

- 1984: Two month work experience with Government Statistical Office, Stuttgart, West Germany.
- June, December 1988: Institute of Dynamical Systems, University of Bremen, Germany.
- May 1989 (1 week): Institute for Techno Mathematics, University of Kaiserslautern, Germany
- 1989: Lectured and contributed to lecture notes for a course o `System Identification' given by Cambridge Control Ltd., Cambridge, UK, to industrial engineers.
- 1989-90: Consultancy work with Cambridge Control Ltd., Cambridge, UK.
- February 1990 (2 weeks): Department of Mathematics, Ben Gurion University, Beer Sheva, Israel.
- July 1990 (2 weeks): Dipartimento di Matematica, Politecnico di Torino, Italy.
- June-August 1991: Institute National de Recherche en Informatique et Automatique, Sophia-Antipolis, France.
- May-July 1992: Institute for Techno Mathematics, University of Kaiserslautern, Germany.

- June 1992 (1 week): Department of Econometrics, Free University, Amsterdam, The Netherlands.
- May-June 1993 (6 weeks): Department of Econometrics, Free University, Amsterdam, The Netherlands
- June 1995: Charleston Laboratory, National Marine and Fisheries Service, South Carolina, US.
- July 1995: Department of Econometrics, Free University, Amsterdam, The Netherlands.
- Academic year 1998/99: Cancer Immunobiology Center, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA.

Scholarships, Fellowships, Elections, Awards

- 1982-1983: Scholarship by Friedrich-Ebert-Stiftung for study at University of Tuebingen.
- 1983-1984: Scholarship by German Academic Exchange Service (DAAD) for study of mathematics at Cambridge University.
- 1984-1985: Scholarship by Friedrich-Ebert-Stiftung for study towards a Master's degree at Cambridge University.
- 1985-1987: Scholarship by Markel-Stiftung for study towards a Ph.D. degree at Cambridge University.
- 1987-1990: Research Fellowship at Girton College, Cambridge.
- 1992: Awarded the SERC (Science and Engineering Research Council of UK) Advanced Fellowship (a faculty level appointment) to conduct five years research in the Department of Electrical Engineering at Imperial College, London, UK (not taken up).
- 1995: Elected Senior Member of the Institute of Electrical and Electronics Engineers (IEEE).
- 2007: The paper [Q. Zou, Z. Lin, and R.J. Ober. The Cramer Rao lower bound for bilinear systems. *IEEE Transactions on Signal Processing*, 54:1666-1680, 2006] was awarded the 2007 IEEE Signal Processing Young Author Best Paper Award.

Publications

Journal Publications

- [121] J.Chao, S. Ram, E.S. Ward, and R.J. Ober. Resolution in three dimensional microscopy, submitted.
- [120] S. Ram, P. Prabhat, J. Chao, E.S. Ward, and R.J. Ober. High accuracy 3D quantum tracking with multifocal plane microscopy for the study of fast intracellular dynamics in live cells, *Biophys. J.*, in press.
- [119] W. Mi, S. Wanjie, S-T. Lo, Z. Gan, B. Pickl-Herk, R.J. Ober and E.S. Ward. Targeting FcRn for antigen delivery using engineered Fc fragments, *J. Immunol.*, in press.
- [118] Z. Gan, S. Ram, C. Vaccaro, R.J. Ober and E.S. Ward. Analyses of the recycling receptor, FcRn, in live cells reveal novel pathways for lysosomal delivery, under revision.
- [117] P. Prabhat, Z. Gan, J. Chao, S. Ram, C. Vaccaro, S. Gibbons, R.J. Ober, and E.S. Ward. Elucidation of intracellular recycling pathways leading to exocytosis of the Fc receptor, FcRn, by using multifocal plane microscopy. *Proceedings of the National Academy of Sciences*, 104:5889-5894, 2007.
- [116] C.G. Vaccaro, R. Bawdon, S. Wanjie, R.J. Ober, and E.S. Ward. Divergent activities of an engineered antibody in murine and human systems have implications for therapeutic antibodies. *Proceedings of the National Academy of Sciences*, 103:18709-18714, 2006.
- [115] S. Ram, E.S. Ward, and R.J. Ober. Beyond Rayleigh's criterion: a resolution measure with application to single molecule microscopy. *Proceedings of the National Academy of Sciences*, 103:4457-4462, 2006.
- [114] S. Pastor, C. Vaccaro, A. Minguela, R.J. Ober, and E.S. Ward. Analysis of T cell receptor clustering at the T cell-antigen presenting cell interface and its impact on the activation of naive CD4+ T cells. *International Immunology*, 18:1615-1625, 2006.
- [113] S. Ram, E.S. Ward, and R.J. Ober. A stochastic analysis of performance limits for optical microscopes. *Multidimensional Systems and Signal Processing*, 15:27-57, 2006.
- [112] Q. Zou, Z. Lin, and R.J. Ober. The Cramer Rao lower bound for bilinear systems. *IEEE Transactions on Signal Processing*, 54:1666-1680, 2006.
- [111] C. Vaccaro, J. Zhou, R.J. Ober, and E.S. Ward. Engineering the Fc region of immunoglobulin G to generate reagents to modulate *in vivo* antibody levels. *Nature Biotechnology*, 23:1283-1288, 2005.
- [110] Z. Lin, Q. Zou, E.S. Ward, and R.J. Ober. The Cramer Rao lower bound for parameter estimation in nonlinear systems. *IEEE Signal Processing Letters*, 12:855-858, 2005.
- [109] E.S. Ward, C. Martinez, C. Vaccaro, J. Zhou, Q. Tang, and R.J. Ober. From sorting endosomes to exocytosis: Association of Rab4 and Rab11 GTPases with the Fc receptor, FcRn, during recycling. *Molecular Biology of the Cell*, 16:2028-2038, 2005.

- [108] J. Zhou, F. Mateos, R.J. Ober, and E.S. Ward. Conferring the binding properties of mouse FcRn onto the human ortholog by sequential rounds of site-directed mutagenesis. *Journal of Molecular Biology*, 345:1071-1081, 2005.
- [107] J. Huang, R.J. Ober, and E.S. Ward. The central residues of a T cell receptor sequence motif are key determinants of autoantigen recognition in murine experimental autoimmune encephalomyelitis. *European Journal of Immunology*, 35:299-304, 2005.
- [106] X. Lai, Z. Lin, E.S. Ward, and R.J. Ober. Noise suppression of point spread functions and its influence on deconvolution of three-dimensional fluorescence microscopy image sets. *Journal of Microscopy*, 217:93-108, 2005.
- [105] R.J. Ober, X. Lai, Z. Lin, and E.S. Ward. State space realization of a three-dimensional image set with application to noise reduction in fluorescent microscopy images of cells. *Multidimensional Systems and Signal Processing*, 16:7-48, 2005.
- [104] P. Prabhat, S. Ram, E.S. Ward, and R.J. Ober. Simultaneous imaging of different focal planes in fluorescence microscopy for the study of cellular dynamics in three dimensions. *IEEE Transactions on Nanobioscience*, 3:237-242, 2004.
- [103] R.J. Ober, C. Martinez, X. Lai, J. Zhou, and E.S. Ward. Exocytosis of IgG as mediated by the receptor, FcRn: an analysis at the single molecule level. *Proceedings of the National Academy of Sciences*, 86:11076-11081, 2004.
- [102] L.R. Hunt, E.S. Ward, and R.J. Ober. Approximation of trajectories of nonlinear systems by iterates of systems with linear state dynamics. *Systems and Control Letters*, 51:377-381, 2004.
- [101] R.J. Ober, C. Martinez, C. Vaccaro, and E.S. Ward. Visualizing the site and dynamics of IgG salvage by the MHC class I related receptor, FcRn. *Journal of Immunology*, 172:2021-2029, 2004.
- [100] R.J. Ober, S. Ram, and E.S. Ward. Localization accuracy in single-molecule microscopy. *Biophysical Journal*, 86:1185-1200, 2004.
- [99] R.J. Ober, J. Caves, and E.S. Ward. Analysis of exponential data using a non-iterative technique: application to surface plasmon experiments. *Analytical Biochemistry*, 312:57-65, 2003.
- [98] E.S. Ward, J. Zhou, V. Ghetie, and R.J. Ober. Evidence to support the cellular mechanism involved in serum IgG homeostasis in humans. *International Immunology*, 15:187-195, 2003.
- [97] J. Zhou, J.E. Johnson, V. Ghetie, R.J. Ober, and E.S. Ward. Generation of mutated variants of the human form of the MHC class I-related receptor, FcRn, with increased affinity for mouse immunoglobulin G. *Journal of Molecular Biology*, 332:901-913, 2003.
- [96] R.J. Ober, Z. Lin, and Q. Zou. Calculations of the Fisher information matrix for multidimensional data sets. *IEEE Transactions on Signal Processing*, 51(10):2679-2691, 2003.

- [95] B. Hanzon and R.J. Ober. State space calculations for discrete probability densities. *Linear Algebra and Its Applications*, 350:67-87, 2002.
- [94] V. Ramakrishna, R.J. Ober, K.L. Flores, and H. Rabitz. Control of a coupled two-spin system without hard pulses. *Physical Review A*, 65:063405, 2002.
- [93] R.J. Ober and E.S. Ward. Compensation for loss of ligand activity in surface plasmon resonance experiments. *Analytical Biochemistry*, 306:228-236, 2002.
- [92] R.J. Ober, Z. Lin, H. Ye, and E.S. Ward. Achievable accuracy of parameter estimation for multidimensional NMR experiments. *Journal of Magnetic Resonance*, 157:1-16, 2002.
- [91] R.J. Ober. The Fisher information matrix for linear systems. *System and Control Letters*, 47:221-226, 2002.
- [90] K.C. Garcia, C.G. Radu, J. Ho, R.J. Ober, and E.S. Ward. Kinetics and thermodynamics of T cell receptor-autoantigen interactions in murine experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences*, 98:6818-6823, 2001.
- [89] M. Firan, R. Bowden, C.G. Radu, R.J. Ober, D. Eaken, F. Antohe, V. Ghetie, and E.S. Ward. The MHC class I-related receptor, FcRn, plays an essential role in the maternofetal transfer of gammaglobulins in humans. *International Immunology*, 13:993-1002, 2001.
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- [83] V. Ramakrishna, K. Flores, H. Rabitz, and R.J. Ober. Quantum control by decomposition of SU(2). *Physical Review A*, 6205(5):3409, 2000.
- [82] R.J. Ober. An introduction to the shift realization for finite dimensional continuous time systems. *International Journal of Control*, 72:332-344, 1999.

- [81] A. Gheondea and R.J. Ober. A trace formula for Hankel operators. *Proceedings of the American Mathematical Society*, 127:2007-2012, 1999.
- [80] A. Gheondea and R.J. Ober. Completely J-positive linear systems of finite order. *Mathematische Nachrichten*, 203:75-101, 1999.
- [79] R.J. Ober and E.S. Ward. The choice of reference cell in the analysis of kinetic data using BIAcore. *Analytical Biochemistry*, 271:70-90, 1999.
- [78] R.J. Ober and E.S. Ward. The influence of signal noise on the accuracy of kinetic constants measured by surface plasmon resonance experiments. *Analytical Biochemistry*, 273:49-59, 1999.
- [77] R.J. Ober, V. Ramakrishna, and E.S. Ward. On the role of reachability and observability in NMR experimentation. *Journal of Mathematical Chemistry*, 26:15-26, 1999.
- [76] R.J. Ober. Asymptotic stabilization of infinite-dimensional systems which cannot be exponentially stabilized. *Systems and Control Letters*, 35:61-63, 1998.
- [75] B. Hanzon and R.J. Ober. Overlapping balanced canonical forms for various classes of linear systems. *Linear Algebra and Its Applications*, 281:171-225, 1998.
- [74] B. Hanzon and R.J. Ober. Overlapping block-balanced canonical form and parametrizations: the stable SISO case. *SIAM Journal on Control and Optimization*, 35:228-242, 1997.
- [73] V. Ghetie, S. Popov, J. Borvak, C. Radu, D. Matesoi, C. Medesan, R. J. Ober, and E.S. Ward. Increasing the serum persistence of an IgG fragment by random mutagenesis. *Nature Biotechnology*, 15:637-640, 1997.
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- [70] R.J. Ober. On Stieltjes functions and Hankel operators. *Systems and Control Letters*, 27:275-277, 1996.
- [69] R.J. Ober and E.S. Ward. System theoretic formulation of NMR experiments. *Journal of Mathematical Chemistry*, 20:47-65, 1996.
- [68] R.J. Ober and E.S. Ward. Correcting for phase distortion of NMR spectra analyzed using singular value decomposition of Hankel matrices. *Journal of Magnetic Resonance Series A*, 114:120-123, 1995.
- [67] J.A. Sefton and R.J. Ober. Properties of optimally robust controllers. *International Journal of Control*, 59:1191-1210, 1994.

- [66] J.A. Sefton and R.J. Ober. Hankel norm approximation and control systems. *Linear Algebra and Its Applications*, 205-106:1081-1120, 1994.
- [65] P.A. Fuhrmann and R.J. Ober. A functional approach to LQG balancing. *International Journal of Control*, 57:627-741, 1993.
- [64] J.A. Sefton and R.J. Ober. On the gap metric and coprime factor perturbations. *Automatica*, 29:723-734, 1993.
- [63] J.A. Sefton and R.J. Ober. Uncertainty in the weighted gap metric: A geometric approach. *Automatica*, 29:1079-1100, 1993.
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- [61] R.J. Ober. Balanced parametrization of classes of linear systems. *SIAM Journal on Control and Optimization*, 29:1251-1287, 1991.
- [60] R.J. Ober and J.A. Sefton. Stability of control systems and graphs of linear systems. *Systems and Control Letters*, 17:265-280, 1991.
- [59] R.J. Ober and S. Montgomery-Smith. Bilinear transformation of infinite dimensional state space systems and balanced realizations of nonrational transfer functions. *SIAM Journal on Control and Optimization*, 28:438-465, 1990.
- [58] R.J. Ober. A note on a system theoretic approach to a conjecture by Peller-Khrushchev: the general case. *IMA Journal of Mathematical Control and Information*, 7:35-45, 1990.
- [57] R.J. Ober. Connectivity properties of various classes of linear systems. *International Journal of Control*, 50:2049-2073, 1989.
- [56] R.J. Ober and D. McFarlane. Balanced canonical forms for minimal systems: a normalized coprime factor approach. *Linear Algebra and Its Applications*, 122-124:23-64, 1989.
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- [54] R.J. Ober. Balanced realizations: canonical form, parametrization, model reduction. *International Journal of Control*, 46:643-670, 1987.
- [53] R.J. Ober. A parametrization approach to infinite dimensional balanced systems and their approximation. *IMA Journal of Mathematical Control and Information*, 4:263-279, 1987.
- [52] R.J. Ober. A note on a system theoretic approach to a conjecture by Peller-Khrushchev. *Systems and Control Letters*, 8:303-306, 1987.

Book Chapters and Review Articles

- [51] S. Ram, E.S. Ward and R.J. Ober. Resolution of Optical Microscope Redefined. *Biophotonics International*, pages 42-46, July 2006.
- [50] A. Gheondea and R.J. Ober. Spectral minimality of J-positive linear systems of finite order. In *Operators, Systems and Linear Algebra*, pages 70-80. B.G. Teubner, 1997.
- [49] R.J. Ober. Balanced canonical forms. In *Identification, Adaptation, Learning*, pages 120-179. Springer Verlag, 1996.
- [48] R.J. Ober. System theoretic aspects of completely symmetric systems. In *Operator Theory: Advances and Applications*, volume 87, pages 233-262. Birkhaeuser Verlag, 1996.
- [47] R.J. Ober and P.A. Fuhrmann. Diffeomorphisms between classes of linear systems. In *The IMA Volumes in Mathematics and Its Applications: Linear Algebra and Control Theory*, volume 62, pages 117-157. Springer Verlag, 1994.
- [46] P.A. Fuhrmann and R.J. Ober. State space formulas for coprime factorizations. In *Operator Theory: Advances and Applications: Contributions to Operator Theory and its Applications, The T.A. Ando Birthday Volume*, pages 39-75. Birkhaeuser Verlag, 1993.
- [45] F. De Mari and R.J. Ober. Topological aspects of robust control. In *Control of Uncertain Systems*, pages 57-67. Birkhaeuser Verlag, 1990.

Conference Proceedings

- [44] J. Chao, S. Ram, E.S. Ward, R.J. Ober. 3D resolution measure for multifocal plane microscopy. *2008 IEEE International Symposium on Biomedical Imaging: From Nano to Macro*, in print.
- [43] S. Ram, J. Chao, P. Prabhat, E.S. Ward and R.J. Ober. Overcoming the depth discrimination barrier in widefield microscopes: 3D single molecule tracking with high axial accuracy. In *Imaging, Manipulation, and Analysis of Biomolecules, Cells and Tissues IV. SPIE International Symposium on Biomedical Optics (BiOS) 2008*, in print.
- [42] J. Chao, S. Ram, A.V. Abraham, E.S. Ward and R.J. Ober. Resolution in 3D in multifocal plane microscopy. In *Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XV. SPIE International Symposium on Biomedical Optics (BiOS) 2008*, in print.

- [41] S. Ram, J. Chao, P. Prabhat, A.V. Abraham, E.S. Ward and R.J. Ober. Breaking resolution limits: advances and challenges in single molecule microscopy. In *Proceedings of the 41st Asilomar Conference on Signals, Systems, and Computers, November 4-7, 2007, Pacific Grove, CA*, in print.
- [40] S. Ram, P. Prabhat, J. Chao, E.S. Ward and R.J. Ober. Resolution beyond Rayleigh's criterion: a modern resolution measure with applications to single molecule imaging. In *Proceedings of the 2007 IEEE Dallas Engineering in Medicine and Biology Workshop*, 110-113, 2007.
- [39] J. Chao, P. Long, E.S. Ward and R.J. Ober. Design and application of the Microscopy Image Analysis Tool. In *Proceedings of the 2007 IEEE Dallas Engineering in Medicine and Biology Workshop*, 94-97, 2007.
- [38] S. Ram, E.S. Ward and R.J. Ober. Breaking the resolution barrier in optical microscopy: a new resolution measure with applications to single molecule imaging. In *Proceedings of the 2007 IEEE International Symposium on Biomedical Imaging: From Nano to Macro, 12-15 April 2007, Metro Washington, DC*, 928-931, 2007.
- [37] S. Ram, J. Chao, P. Prabhat, E.S. Ward and R.J. Ober. A novel approach to determining the three-dimensional location of microscopic objects with applications to 3D particle tracking. In *Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XIV. SPIE International Symposium on Biomedical Optics (BiOS) 2007*, 6443:64430-D7, 2007.
- [36] S. Ram, E.S. Ward and R.J. Ober. A novel 3D resolution measure for optical microscopes with applications to single molecule imaging. In *Imaging, Manipulation, and Analysis of Biomolecules, Cells and Tissues IV. SPIE International Symposium on Biomedical Optics (BiOS) 2007*, 6444:6440-D9, 2007.
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- [33] S. Ram, E.S. Ward, and R.J. Ober. A novel stochastic resolution criterion for fluorescence microscopes. In *Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XIII. SPIE International Symposium on Biomedical Optics (BiOS) 2006*, volume 6090, 60900J, 2006.
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- [31] S. Ram, E.S. Ward, and R.J. Ober. How accurately can a single molecule be localized in three dimensions using a fluorescence microscope? In *Imaging, Manipulation, and Analysis of Biomolecules*,

Cells and Tissues II. SPIE International Symposium on Biomedical Optics (BiOS) 2005, volume 5699, pages 426-435, 2005.

[30] Z. Lin, Q. Zou, and R.J. Ober. The Cramer Rao lower bound for nonlinear systems and its biomedical applications. In *Proceedings of the IEEE International Symposium on Circuits and Systems (ISCAS 2005)*, pages 1338-1341, 2005.

[29] R.J. Ober, Z. Lin, and Q. Zou. On the identifiability of bilinear systems. In *Proceedings of the IEEE Conference on Circuits and System (ISCAS 2005)*, pages 3769-3772, 2005.

[28] R.J. Ober, X. Lai, Z. Lin, and E.S. Ward. A state space approach to noise reduction of 3D fluorescent microscopy images. In *IEEE International Conference on Image Processing (ICIP '04), Singapore*, 2:1153-1156, 2004.

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[24] V. Ramakrishna, R.J. Ober, K.L. Flores, and H. Rabitz. Constructive control of a spin system via periodic control. In *Proceedings of the 40th IEEE Conference on Decision and Control*, pages 292-297, 2001.

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[22] V. Ramakrishna, K. Flores, H. Rabitz, and R.J. Ober. Constructive controllability for systems with drift motivated by and applied to quantum control. In *Proceedings of the 39th IEEE Conference on Decision and Control*, pages 955-960, 2000.

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- [15] Hanzon and R.J. Ober. Overlapping block-balanced canonical form and parametrizations: the stable SISO case. In *Proceedings of the 31st IEEE Conference on Decision and Control*, pages 2835-2838, 1992.
- [14] P.A. Fuhrmann and R.J. Ober. A functional approach to LQG balancing. In *Proceedings of the 31st IEEE Conference on Decision and Control*, pages 1034-1038, 1992.
- [13] J.A. Sefton and R.J. Ober. Hankel norm approximation and control systems. In *Proceedings of the 31st IEEE Conference on Decision and Control*, pages 1030-1035, 1992.
- [12] R.J. Ober and P.A. Fuhrmann. Diffeomorphisms between manifolds of linear systems. In *Proceedings SINS '92, Arlington, TX*, pages 139-146, 1992.
- [11] J.A. Sefton and R.J. Ober. Graphs of linear systems and stabilization. In *H. Kimura and S. Kodama, editors, Recent Advances in Mathematical Theory of Systems, Control, Networks and Signal Processing I*, pages 351-356. Mita Press, 1992.
- [10] J.A. Sefton and R.J. Ober. Graphs of linear systems. In *Proceedings of the 30th IEEE Conference on Decision and Control*, pages 545-546, 1991.
- [9] Y. Wu and R.J. Ober. Asymptotic stability of infinite dimensional discrete-time balanced realizations. In *Proceedings of the 30th IEEE Conference on Decision and Control*, pages 3025-3030, 1991.
- [8] B.P. McGinnie, R.J. Ober, and J.M. Maciejowski. Balanced parametrizations in time-series identification. In *Proceedings of the 29th IEEE Conference on Decision and Control*, pages 3202-3203, 1990.
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- [6] F. De Mari and R.J. Ober. Topological aspects of robust control. In *Control of Uncertain Systems*, pages 57-67. Birkhaeuser Verlag, 1990.

- [5] R.J. Ober. Stability and structural properties of infinite dimensional balanced realizations. In *Proceedings of 5th IFAC Symposium on Control of Distributed Parameter Systems, Perpignan*, 1989.
- [4] J.M. Maciejowski and R.J. Ober. Balanced parametrizations and canonical forms for system identification. In *Proceedings 8th IFAC Symposium on System Identification and Parameter Estimation, Beijing*, 1988.
- [3] R.J. Ober. The parametrization of linear systems using balanced realizations: relaxation systems. In *C.I. Byrnes, C.F. Martin, and R.E. Saeks, editors, Linear Circuits, Systems and Signal Processing: Theory and Application. North-Holland*, 1988.
- [2] R.J. Ober. Asymptotically stable allpass transfer functions: canonical form, parametrization and realization. In *Proceedings IFAC World Congress, Munich*, 1987.
- [1] R.J. Ober. Infinite dimensional balanced realizations and their approximation. In *Proceedings of the 25th IEEE Conference on Decision and Control*, 1986.

Software

- [1] R.J. Ober, J. Caves, J. Chao and E.S. Ward. SPRTool: a software environment to analyze optical biosensor data for the determination of interaction constants of protein-protein interaction constants. Website: <http://www4.utsouthwestern.edu/wardlab/sprtool>; Release date: October 2003.
- [2] J. Chao, E.S. Ward and R.J. Ober. MIATool: a software environment to analyze fluorescence microscopy image sets. Website: <http://www4.utsouthwestern.edu/wardlab/miatool>; Release date: June 2004.
- [3] A. Abraham, S. Ram, J. Chao, E.S. Ward and R.J. Ober. FandPLimitTool: a GUI based program to compute localization and resolution measures for single molecule microscopy. Website: <http://www4.utsouthwestern.edu/wardlab/fandplimittool>; Release date: May 2007.
- [4] A. Abraham, S. Ram, J. Chao, E.S. Ward and R.J. Ober. EstimationTool: a GUI based program to estimate the location and distances between objects such as single molecules. Website: <http://www4.utsouthwestern.edu/wardlab/estimationtool>; Release date: May 2008.

Current Grant Support

National Institutes of Health (R01 GM 71048)

Title: High accuracy quantum dot tracking in live cells

Role on Project: Principal Investigator.

Co-Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 July 2008 – 30 June 2012

Total costs: \$1,215,172

National Institutes of Health (R01 GM071048)

Title: Quantitative Aspects of Single Molecule Microscopy.

Role on Project: Principal Investigator.

Co-Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 May 2005 - 30 April 2009.

Total Award: \$1 046 500.

National Institutes of Health (R01 AR 56478)

Title: Mechanistic studies of FcRn inhibitors for the treatment of IgG-mediated diseases

Role on Project: Co-Principal Investigator.

Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 8 July 2008 – 31 May 2013

Total costs: \$1,727,000

National Institutes of Health (RO1 AI/NS42949)

Title: Molecular Analysis of T cell recognition in EAE.

Role on Project: Co-Principal Investigator.

Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 December 2002 - 30 November 2008.

Total award: \$1 530 750.

National Institutes of Health (RO1 AI55556)

Title: Antibody engineering: targeting Bacillus anthracis.

Role on Project: Co-Principal Investigator.

Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 15 September 2003 - 31 December 2008.

Total award: \$1 521 000.

National Institutes of Health (R01 AI39167)}

Title: Structure Function Studies of Human FcRn.

Role on Project: Co-Principal Investigator.

Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 June 2004 - 31 May 2009.

Total award: \$1 930 000.

Past Grant Support

National Institutes of Health (R01 AI50747)

Title: Image processing of immunological microscopy samples.

Role on Project: Principal Investigator.

Co-Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 March 2002 - 28 February 2005.

Total award: \$800 738.

National Institutes of Health (R21 AI53748)

Title: High Performance Fluorescence Microscopy Imaging.

Role on Project: Principal Investigator.

Co-Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 30 September 2002 - 31 August 2005.

Total award: \$408 960.

National Institutes of Health (1R01GM58538-01A2)

Title: Improving Surface Plasmon Resonance Technology.

Role on Project: Co-Principal Investigator. Principal Investigator: E. Sally Ward, Ph.D., UT Southwestern Medical Center at Dallas.

Period: 1 April 2000 - 30 March 2004.

Total award: \$671 824.

University of Texas Southwestern Medical Center - UT Dallas Interagency Agreement

Purpose: Development of Fluorescence Microscopy Image Analysis Software.

Period: 1 February 2002- 31 March 2002.

Amount: \$23 000.

University of Texas Southwestern Medical Center, UT Dallas Interagency Transfer Agreement Period: 1 September 1999- 31 August 2000.

Purpose: To conduct research (80% time) in the Center for Cancer Immunobiology at UT Southwestern.

Amount: \$88 882.

University of Texas Southwestern Medical Center - UT Dallas
Interagency Transfer Agreement

Period: 1 August 1998- 31 August 1999.

Purpose: To conduct full time research in the Center for Cancer Immunobiology at UT Southwestern.

Amount: \$106 031.

National Science Foundation

Title: Balanced realizations in system theory, approximation and stabilization.
Role on Project: Principal Investigator.
Period: 15 June 1998 - 31 May 2001.
Amount: \$82 497.

National Science Foundation

Title: Stabilization and Approximation of Infinite Dimensional Systems.
Role on Project: Principal Investigator.
Period: 1 June 1995 - 31 May, 1998.
Amount: \$90 407.

NATO: Collaborative Research Grants Programme.

Title: Parametrization issues in system identification.
Role on Project: Principal Investigator.
Coinvestigator: B. Hanzon, Department of Econometrics, Free University
Amsterdam, The Netherlands.
Period: 1 August 1994 - July 1997.
Amount: ca. \$6 200.

National Science Foundation

Title: Balanced realizations for infinite dimensional linear systems.
Role on project: Principal Investigator.
Period: 1 June 1993 - 31 May 1995.
Amount: \$40 000.

Current and Future Research Interests

Over the past years my research has focused on biological problems and the development of technology to advance the capabilities of biological research. Currently, the main research interests center on high resolution fluorescence microscopy analyses of processes in living cells. My research group is involved in both the development of methods (hardware, software, image processing and analysis) and in carrying out of experiments to address problems of biological interest.

Biological problems: In collaboration with Prof. E. Sally Ward we are elucidating the intracellular trafficking of immunoglobulin G (IgG) and its salvage receptor FcRn. IgG plays a central role in conferring immunity. FcRn is involved in trafficking IgG within and across cells and, in so doing, controls the levels and distribution of IgG throughout the body. To gain an understanding of the intracellular trafficking of FcRn and its ligand, IgG, we have been using different techniques that include live cell single molecule microscopy. These studies have to date allowed us to gain new insights into the intracellular sorting events and exocytic release processes that are integral parts of the trafficking of FcRn and IgG within cells. In addition, we have recently developed a novel microscope design, multifocal plane microscopy (MUM), which allows us to track fast intracellular trafficking events in three dimensions. Such processes could not be imaged with standard approaches. For example, we have discovered that in some exocytic events a direct tubular connection exists between the sorting endosome and the plasma membrane. With MUM we are exploring the three dimensional tracking in live cells of IgG molecules fluorescently labeled with fluorophores or quantum dots. The overall goal is to combine these approaches with protein engineering to build up a dynamic three dimensional picture of the intracellular behavior of this receptor-ligand system.

Quantitative aspects of high resolution single molecule microscopy: An important aspect of our current work relates to the development of methodology for image analysis for cellular microscopy. Special emphasis is being placed on the development of image analysis approaches for single molecule microscopy, which allows the properties of individual (protein) molecules to be studied. Due to the low signal to noise ratio that is characteristic of fluorescence microscopy and the quantum limited nature of the detection process, this area presents novel problems of both a theoretical and experimental nature.

Breaking Rayleigh's resolution limit: A central component of this work has involved the development of quantitative techniques for the analysis of single molecule data. We have derived a new resolution measure for two point sources/single molecules. This new resolution measure overcomes several deficiencies of classical criteria such as Rayleigh's criterion and has been validated in experimental single molecule studies. Importantly, this work shows that even for a conventional microscope there is no resolution limit and that the accuracy with which two point sources can be resolved depends on the number of photons that are collected. We have experimentally verified this criterion and imaged distances down to 12nm with the accuracy predicted by our new criterion. Similarly, we have extensively studied the question of how accurately a single molecule can be localized, with particular emphasis on the influence of experimental conditions. Future efforts include the development of parameter estimation algorithms that are of importance for the tracking of fluorescently or quantum dot labeled single molecules in, for example, tubules and vesicles within cells. A fundamental aspect of our work has been to incorporate parameter estimation problems in fluorescence microscopy into a well founded analytical framework.

Multifocal Plane Microscopy (MUM): To be able to carry out advanced fluorescence microscopy experiments we have been investing a substantial amount of effort into the design of high performance microscopy imaging stations. Of particular importance is a novel design in which different focal planes can be imaged simultaneously to build up three dimensional, dynamic images of cells. Combining multifocal plane microscopy with a multi-color labeling strategy of the cellular proteins this allows us, for example, to simultaneously investigate processes on the cell surface using the high sensitivity of total internal reflection microscopy together with the intracellular events that correlate with the membrane events. This has allowed us for the first time to visualize the recycling pathway from intracellular sorting endosomes to exocytosis at the plasma membrane. Importantly, using quantum dot labeled molecules, we can for the first time perform single molecule studies in 3D at high temporal and spatial resolution. This has allowed us to, for the first time, image ligand (IgG) molecules, from diffusion on the plasma membrane, over endocytosis to the merging with a sorting endosome at unprecedented spatial and temporal resolution.

Software: Software development is another active component of our work. Novel microscopy technologies, such as fast and high sensitivity imaging detectors generate new challenges for software design, not least of which is the large amount of data that is being produced. For example, due to the lack of appropriate software, biologists often spend an extraordinary amount of time analyzing the acquired imaging data. We are therefore developing software that allows for the efficient acquisition, processing and analysis of the acquired data.

Biosensor data analysis: Additional research interests include data analysis problems for the determination of molecular interaction constants using surface plasmon resonance (e.g. BIAcore instruments). We have addressed problems in data analysis that are encountered by the laboratory scientist, in addition to the study of more fundamental questions. The scientist needs to predetermine the experimental conditions and instrument settings such that the estimated interaction parameters have the required accuracy. This frequently has to be done in the context of limitations in protein availability, instrument time etc. Optimal experimental design therefore provides an important challenge in these studies. In a series of publications we have investigated this problem by calculating the Fisher information matrix/Cramer Rao lower bound for a number of model systems that represent typical biological interactions.

Systems biology and modeling: The question of the regulation of antibody (IgG) transport and dynamics in the body is not only of fundamental interest in immunology but also has important implications for the use of antibodies in therapy. From the point of view of systems biology this provides a fascinating subject. Information is available on very different time and size scales from studies of antibody dynamics in humans or laboratory animals, over knowledge of the intracellular trafficking pathways, to data related to the interaction dynamics between IgG molecules and the transport/salvage receptor FcRn. It is possible to use protein engineering techniques to modulate the interactions between IgGs and FcRn. Experimentally, it has been shown that this influences IgG dynamics *in vivo* and *in vitro*. In addition, the Ward laboratory have recently generated a genetically modified mouse strain in which FcRn can be conditionally deleted. We have initiated a project in which we aim to model the impact of FcRn-IgG interaction properties combined with differential FcRn expression on the intracellular trafficking behavior and *in vivo* dynamics of IgGs.

Professional Activities

Editorial activities

- Associate Editor: Systems and Control Letters (from 1995-2007).
- Associate Editor: IEEE Transactions on Circuits and Systems: Part I: Fundamental Theory (1995-1997).
- Associate Editor: Mathematics of Control, Signals and Systems, (from 1996).
- Associate Editor: Multidimensional Systems and Signal Processing (from 2006).
- 1991-2000: Editor of 'SCAD: Systems and Control Archive at Dallas'. An electronic database for information concerning systems and control theory. The website is being taken over by the IEEE Control Systems Society

Organizational activities

- Organizer (with P.A. Fuhrmann) of invited session: New results on balanced realizations, 1991 Symposium on the Mathematical Theory of Networks and Systems (MTNS), Kobe, Japan.
- Organization of systems and control section of 1992 Texas Systems Day, UTD, November 1992.
- Organizer of invited session: Topological Aspects of Linear Systems, Symposium on Implicit and Nonlinear Systems (SINS '92), Arlington, USA, December 1992.
- Organizer of workshop on 'Systems and Control Theory' as part of the 1993 Distinguished Lecture Series at UT Dallas.
- Member, Program Committee, 1993 Symposium on the Mathematical Theory of Networks and Systems (MTNS), Regensburg, Germany.
- Organizer of invited sessions: New results on balanced realizations I, II, 1993 Symposium on the Mathematical Theory of Networks and Systems (MTNS), Regensburg, Germany, 1993.
- Organizer of invited mini-symposium: Linear Algebra and Systems Theory. Fourth conference of the International Linear Algebra Society (ILAS), 1994.
- Member, International Program Committee, Conference on Stochastic Differential and Difference Equations, Gyor, Hungary, 1996.
- SIAM Representative and Member, International Program Committee, IEEE Conference on Decision and Control, Kobe, Japan, 1996.
- Organizer (with L. Gerencser and G. Michaletzky) of invited session on 'Parametrization and Model Reduction', 1996 Symposium on the Mathematical Theory of Networks and Systems (MTNS), St. Louis, USA, 1996.
- Organizer of invited session on 'System theoretic approaches to problems in biomedicine and the sciences', 1998 Symposium on the Mathematical Theory of Networks and Systems (MTNS), Padua, Italy, 1998.
- Organizer (with V. Ramakrishna) of invited sessions 'Control of Quantum Phenomena I and II', 39th IEEE Conference on Decision and Control, Sidney, Australia, 2000.
- Member, International Program Committee, Fifteenth International Symposium on Mathematical Theory of Networks and Systems, University of Notre Dame, USA, August 12-16, 2002.

- Organizer of Mini-Symposium on Biological Systems: 'Investigation of a central aspect of the immune system: T cell receptor interactions with major histocompatibility complex', 2002 Symposium on the Mathematical Theory of Networks and Systems, University of Notre Dame, USA, August 12-16, 2002.
- Program Committee Member: Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XIV. SPIE International Symposium on Biomedical Optics (BiOS) 2007.
- Organizer of Special Session: 'Resolution and Localization: Challenges in Single Molecule Microscopy'. 2007 IEEE International Symposium on Biomedical Imaging: From Nano to Macro, Washington DC, April 12-15, 2007.
- Program Committee Member: Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XV. SPIE International Symposium on Biomedical Optics (BiOS) 2008.
- Program Committee Member: Three-dimensional and multidimensional microscopy: Image Processing and Acquisition XV. SPIE International Symposium on Biomedical Optics (BiOS) 2009.

Talks in Seminars and Conferences since 2004

- 8 March 2004, National Institutes of Health, Bethesda, MD.
Title: Problems in Fluorescence Microscopy Image Analysis; Accuracy of Single Molecule Localization and Estimation of Point Spread Functions.
- 24 September 2004, Oklahoma Medical Research Foundation.
Title: Problems in Fluorescence Microscopy Image Analysis: Localization of Single Molecules and Point Spread Function Estimation.
- 20 October 2004, Engineering Department, Cambridge University.
Title: Imaging Single Molecules in Live Cells.
- 22 October 2004, Imperial College London.
Title: Problems in Fluorescence Microscopy Image Analysis: Localization of Single Molecules and Point Spread Function Estimation.
- 26 January 2005, Photonics West, San Jose, CA.
Title: Three-dimensional state space realization algorithm: noise suppression of fluorescence microscopy images and point spread function estimation.
- 14 February 2005, Biophysical Society, 49th Annual Meeting, Long Beach, CA.
Title: Analysis of FcRn-mediated trafficking of IgGs at the single molecule level.
- 23 March 2005, Focus on Microscopy 2005, Jena, Germany.

Title: Simultaneous imaging of multiple focal planes in fluorescence microscopy for the study of cellular dynamics.

- 26 January 2006, Photonics West, San Jose, CA.
Title: Simultaneous imaging of several focal planes in fluorescence microscopy for the study of cellular dynamics in 3D.
- 20 February 2006, Biophysical Society, 50th Annual Meeting, Salt Lake City, UT.
Title: Simultaneous multi-plane imaging and analysis: a novel microscopy technique for the study of the 3D trafficking pathways in live cells.
- 9 March 2006, Department of Physics, University of Stuttgart.
Title: Imaging single molecules: theory and practice.
- 8 April 2006, 2006 IEEE International Symposium on Biomedical Imaging: From Nano to Macro, Arlington, VA.
Title: A novel resolution measure for optical microscopes: stochastic analysis of the performance limits.
- 4 December 2006, UT Metroplex Day, UT Arlington, TX.
Title: Breaking limits in fluorescence microscopy: resolution and dimensionality.
- 11 April 2007, Department of Electrical Engineering, University of Glasgow, UK.
Title: New approaches to Localization and Resolution in Fluorescence Microscopy.
- 29 June 2007, Bioquant Center, University of Heidelberg, Germany.
Title: Beyond Rayleigh's criterion: new approaches to resolution and localization in single molecule microscopy
- 14 August 2007, School of Life Sciences, Bio-Op Seminars, EPFL, Lausanne.
Title: Beyond Rayleigh's criterion: new approaches to resolution and localization in single molecule microscopy
- 10 September 2007, University of North Texas Health Science Center, Fort Worth, TX, Department of Molecular Biology and Immunology Seminar Series.
Title: Single Molecule Studies of IgG trafficking by the Fc receptor, FcRn
- 6 November 2007, 41th Asilomar Conference, Circuits, Systems, and Computers, Pacific Grove, CA.
Title: Beyond Rayleigh's criterion: new approaches to resolution and localization in single molecule microscopy
- 3 December 2007, Institut Pasteur, Paris, Department of Cell Biology and Infection Seminar Series.
Title: FcRn mediated IgG trafficking investigated by multifocal plane and single molecule microscopy
- 20 January 2008, Photonics West, Conference on Single Molecule Spectroscopy and Imaging, San Jose, CA.

Title: Overcoming the depth-discrimination barrier in widefield microscopes: 3D single-molecule tracking with high axial accuracy

- 24 January 2008, Photonics West, Conference on Three-Dimensional and Multidimensional Microscopy: Image Acquisition and Processing, San Jose, CA.
Title: Beyond the three dimensional resolution barrier in optical microscopy: a new three dimensional resolution measure for modern imaging applications
- 5 February 2008, Biophysical Society, 52th Annual Meeting, Long Beach, CA.
Title: Resolving Single Molecules in 3D with multifocal plane microscopy: How far can we go beyond the classical 3D resolution limit?
- 16 February 2008, 10th Annual Linz Winter Workshop Advances in Single-Molecule Research for Biology & Nanoscience, Linz, Austria.
Title: 3D Single Molecule Tracking in Live Cells with High Spatial and Temporal Resolution: Endocytosis and Exocytosis
- 18 February 2008, Institute for Applied Physics-Biophysics Ludwig Maximilians Universitaet Muenchen, Germany.
Title: Localization and Resolution in Single Molecule Microscopy
- 19 February 2008, Department of Chemistry and Biochemistry Ludwig Maximilians Universitaet Muenchen, Germany.
Title: Localization and Resolution in Single Molecule Microscopy
- 26 March 2008, Department of Electrical Engineering, University of Southern California, CA.
Title: Beyond Rayleigh's Resolution Criterion: microscopy at the nanoscale
- 14 April 2008, Focus on Microscopy 2008, Osaka-Awaji, Japan.
Title: Resolving single molecules in two and three dimensions: How far can we go beyond Rayleigh's limit?
- 15 April 2008, Focus on Microscopy 2008, Osaka-Awaji, Japan.
Title: 3D Single Molecule Tracking in Live Cells with High Spatial and Temporal Resolution: Endocytosis and Exocytosis
- 17 May 2008, 2008 IEEE International Symposium on Biomedical Imaging: From Nano to Macro, Paris, France.
Title: 3D Resolution Measure for Multifocal Plane Microscopy
- 23 September 2008, High Speed Optical Sectioning Microscopy 2008, Universitaet Bonn, Germany.
Title: 3D Single Particle Tracking in Live Cells with High Spatial and Temporal Resolution using MUM (multifocal plane microscopy): Endocytosis and Exocytosis (Invited Speaker)

- 27 October 2008, 42th Asilomar Conference, Circuits, Systems, and Computers, Pacific Grove, CA.
Title: Localizing single molecules in three dimensions (Speaker in invited session)
- 3-5 June 2009: INSERM workshop, Saint-Raphael, France; Novel imaging techniques for biology: super-resolution and super-localization. (Invited speaker).