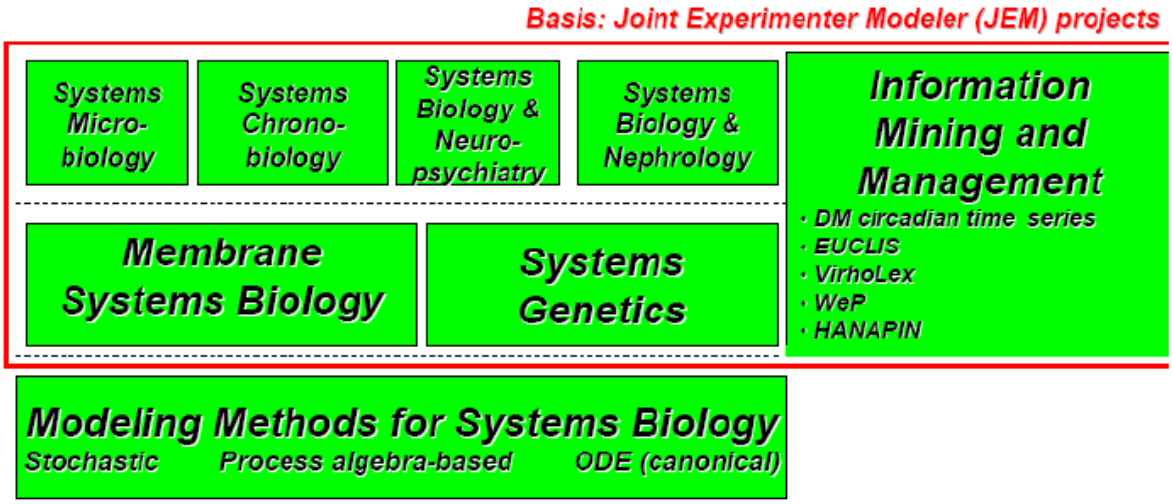
Computational Systems Biology

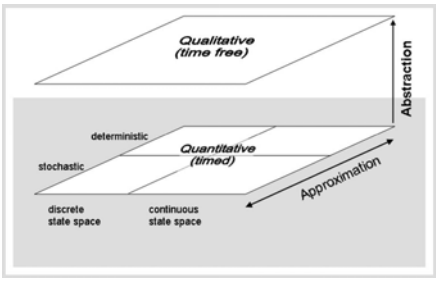
Our group is interested in understanding the structure and dynamics of biological systems through computational and theoretical approaches. We work with various experimental groups very closely in Joint Experimenter-Modeller (JEM) projects. Our group has members and associates in Munich and in Metro Manila, Philippines.

Current research areas are summarized in the following diagram:



Research Areas & Projects

Modelling Methods for Systems Biology (MMSB)



We work with a broad spectrum of modelling methods from stochastic approaches to ODE-based techniques. We select the approach best suited to the experimental partner's questions and the available data. We also prefer to use techniques which are most easily understood by bioscientists in order to optimize the interaction and communication with them. A growing focus is applying theories of concurrent processes such as Petri Nets and process algebra, which smoothly bridge the discrete (qualitative), stochastic and continuous (ODE-based) worlds. In the ODE-based domain, we work extensively with canonical models, in particular the S-Systems and GMA models from Biochemical Systems Theory (BST). Hybrid models also increase in importance with the growing complexity of models being constructed.

Collaborators: L. Cardelli(Microsoft Research), E. Voit (Georgia Tech), R. del Rosario, Genome Institute of Singapore, P. Naval (UPD), E. Rodriguez (UAP), C. Talaue (UPD)

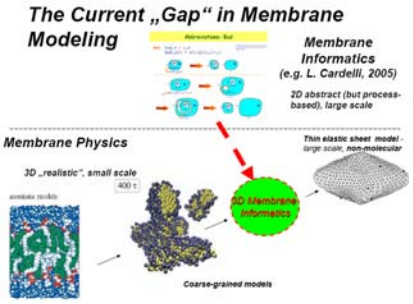
Information Managenent and Mining (IMM)

Data integration is a further important part of building the right infrastructure for systems biology . This line of research should be viewed as a further development of the data-oriented achievements of traditional bioinformatics. Experimental data from various –omics technologies and traditional methods, a variety of information from external sources as well as repositories of mathematical and computational models need to be integrated in a useful way for both experimenters and modellers. Our strategy is a focus on Community-ORiented Information (CORI) Systems,that is, through close cooperation a particular Systems Biology research community,

establish a customized, integrative system, which would also be sustained by the community. A first example of such a project is EUCLIS, the information system being built for the EUCLOCK research network, a 5-year Integrated Project of the EU 6th Framework Program, but envisioned as an information infrastructure for the worldwide (Systems) Chronobiology community. The architecture of such systems will evolve into a digital-library based Common Information Space (or "Collaboratory") in order to effectively handle the diverse multimedia objects dealt with by broadly multidisciplinary systems biology research. Further projects include:

- VirhoLex (Virus-host interaction Lexicon) - an information system for virus-host interactions (U. Reichl, MPI Magdeburg)
- theWeP (Worldwide experimental Platform), a project which adds a qualitatively new level of investigation to biomedical studies through systematic use of the Web (T. Roenneberg, LMU)
- HANAPIN (Health Applications of NAtural Products INformation) System (G. Concepcion, E. Ramos, UPD)
- Data mining of *N. crassa* circadian time series (T. Roenneberg, LMU)

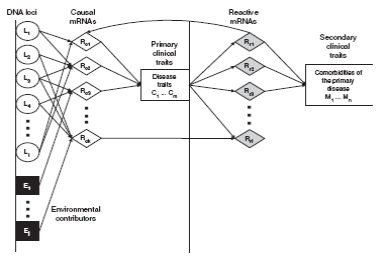
Systems Biology of Membranes (SMEM)



Computational modelling of membrane processes has traditionally been carried out by biophysicists and physical chemists, with a spectrum of methods from atomistic molecular modelling (MD) to the phenomenological "thin elastic sheet" approach. More recently, so-called "coarse-grained" methods have become popular. In parallel, new approaches from computer scientists have emanated from the fields of process algebra and automata theory and successfully been applied to biological problems, including modelling of membrane-mediated processes. Our main approach is based on brane calculi (BC), which were introduced by L. Cardelli in 2005 and allow through the dynamic evolution of compartments in the models. PABM (Projective Activate, Bud and Mate) uses a minimal set of primitive actions while extending the functionality through domains and projective equivalence constructs considerably. A long term vision is to contribute novel spatial process-based methods and thus close the current gap in membrane modelling.

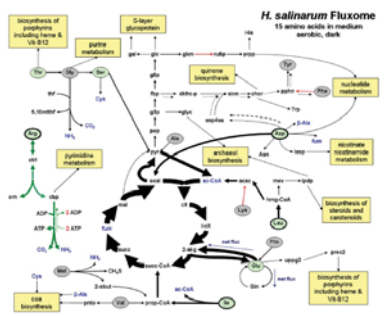
Current projects include the quantitative analysis of synthetic gene transfer and vesicle lysis (J. Rädler, LMU).

Systems Genetics (SGEN)



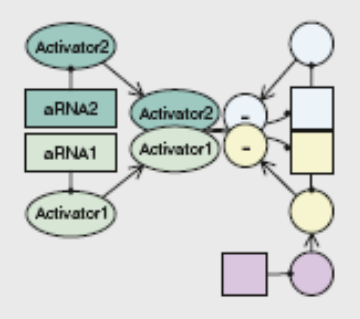
The concept of "Systems Genetics" was introduced by E. Schadt et al (2007) for approaches that integrate population-based techniques (e.g. GWAS) with various 'omics" techniques. The study of metabolic diseases under this perspective has demonstrated its effectiveness and encouraged us to adapt it to study other complex traits. As a first attempt, we are studying pigmentation and related diseases from this point of view. Our long term interest is to apply such techniques to complex mental disorders. Our main collaborator is S. Detera-Wadleigh (NIH Bethesda).

Systems Microbiology (SMIC)



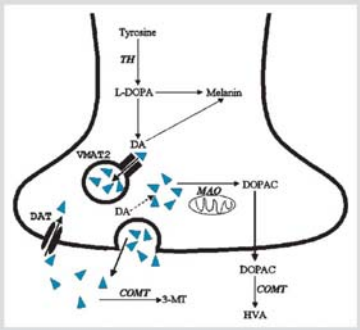
Our research in this area has two major topics: the first is the systems biology of halophilic archaea in close collaboration with the Department of Membrane Biochemistry led by D. Oesterhelt at the Max-Planck-Institute of Biochemistry. Models of various networks in the model organism *Halobacterium salinarum* were developed, including a genome-scale metabolic network, which thru a novel hybrid extension, generated predictions and guided new eyperiments. The second area of focus is a multi-institutional collaboration on the dynamics of herpesviral infection. Collaborative work on HSV-1 dynamics involved S. Bailer and J. Haas (LMU), B. Sodeik (Hannover Medical School), J. Rädler (LMU) and U. Reichl (MPI Magdeburg).

Systems Chronobiology (SCRO)



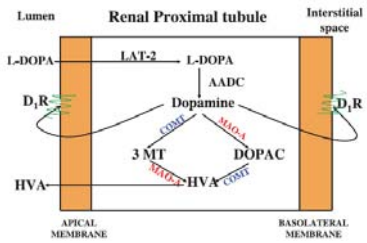
The group has been involved in the FP6 EUCLOCK project in the last four years and has developed 2 novel information systems for the Chronobiology research community, EUCLIS and the WeP. A recent additional focus involves the relationships between shift work and health, particularly in relation to productivity improvement and risk reduction. A further activity concerns the study of the complex mammalian network of clocks (incl. the pacemaking SCN and peripheral clocks in various organs and cells) – here a hybrid modelling approach is being adopted, to cope with the different levels of knowledge (and supporting data) regarding the different subnetworks. The main collaborators are: T. Roenneberg (LMU), A. Wirz-Justice (University of Basel) and M. Merrow (RU Groningen).

Systems Biology and Neuropsychiatry (SNEU)



Our research focus involves modeling the synapse, especially the dopaminergic synapse, in the context of mental disorders. Our current models are ODE-based (specifically GMA systems) but future work will incorporate important spatial aspects such as vesicle formation, etc. We are also experimenting here with the "concept map method" as a systematic way of extracting deep experimental and clinical knowhow from experts and incorporate the results into computational models. We contribute to the annual Munich International Workshop in Computational Neuropsychiatry event. Our main collaborators are F. Tretter (Isar-Amper Clinics Munich), D. Rujescu (LMU Munich) and P. Gebicke-Härter (ZSG Mannheim).

Systems Biology and Nephrology (SNEP)



The dopaminergic system in the kidney is an important regulator of salt-related essential hypertension. Discussions with P. Jose (Children's National Medical Center, Washington DC) led to the insight that neuronal models of the dopamine synapse could be adapted to the various parts of the nephron and provide the first molecularly-based computational models, e.g. for the renal proximal tubule cells there. Main collaborators are P. Jose and I. Armando (CNMC and George Washington University).

Publications

2010

- Schwake G, Youssef S, Kuhr JT, Gude S, David MPC, Mendoza ER, Frey E, Rädler JO, Predictive modeling of non-viral gene transfer
  March 2010. Journal of Biotechnology and Bioengineering . 105: 805-813

- Dulam-Banawa B, Marin-Sanguino A, Mendoza ER. The evolution of synapse models: from numbers to networks to spaces.
  Computational Neuropsychiatry Vol.5, Pharmacopyschiatry May 2010.

- Mendoza ER. From communicational to computational: systems modeling approaches for psychiatric research.
  In "Systems Biology and Psychiatric Research" Tretter F, Gebicke-Härter P, Winterer G, Mendoza ER (Eds) Wiley VCH, June 2010.

- Gonzalez O, Oberwinkler T, Mansueto, L, Pfeiffer F, Mendoza ER, Zimmer R, Oesterhelt D. Characterization of growth and metabólism of the polyextremophile Natronomonas pharaonis.
  June 2010, PLoS Computational Biology

- Mendoza ER and Aguila MER. Social jet lag, shift work and senior citizens.
  NAST Transactions 2010 (Proceedings of NAST ASM, Manila, July 14-15, 2010).

- Naval PC, Sison LG, Mendoza ER. Parameter estimation with Term-wise Decomposition in Biochemical Network GMA Models by Hybrid Regularized Least Squares-Particle Swarm Optimization.
  Proceedings of the IEEE Conference on Evolutionary Computation (CEC) 2010, July 18-23, 2010, Barcelona, Spain

- Marin-Sanguino A, Mendoza ER, Voit EO, Flux Duality in Non-Linear GMA Systems: Implications for Metabolic Engineering.
  Journal of Biotechnology 149, Issue 3, Sept 2010

- Talaue CO, del Rosario RCH, Pfeiffer F, Mendoza ER, Oesterhelt D. Model Construction and Analysis of Respiration in Halobacterium salinarum.
  2010 (submitted to PLoS Computational Biology)

Editorials in co-edited Journals/Books

- Tretter F, Rujescu D, Pogarell, Merndoza ER. Editorial.
  Computational Neuropsychiatry Vol.5, Pharmacopyschiatry May 2010

- Tretter F, Gebicke-Härter P, Winterer G, Mendoza ER Introduction.
  Systems Biology and Psychiatric Research. Wiley VCH, June 2010.

- Dress A, Mendoza ER, Voit EO. Advanced Methods in Molecular Systems Biology.
  Speciall Issue, Journal of Biotechnology, 149, Issue 3, Sept 2010.

2009

- A. Marin-Sanguino, N.V. Torres, E.R. Mendoza, D. Oesterhelt, Metabolic Engineering with Power-law and linear-logarithmic Systems, *Mathematical Biosciences,* 2009, Vol. 218, p. 50-58

- O. Gonzalez, S. von Gronau, F. Pfeiffer, E. Mendoza, R. Zimmer, D. Oesterhelt, Systems analysis of bioenergetics and growth of the extreme halophile *Halobacterium salinarum*, *PLoS Computational Biology,* 2009, Vol. 5, Issue 4

- A. Marin-Sanguino, R.C.H. del Rosario, E.R. Mendoza, Concept maps and Canonical Models in Neuropsychiatry, *Pharmacopsychiatry*, 2009, 42 Suppl 1, p. 51-58

- R.C.H. del Rosario, E.R. Mendoza, D. Oesterhelt, Modeling the Bioenergetics of *Halobacterium salinarum* with Petri Nets, Journal of Computational and Theoretical Nanotechnology, Aug 2009

- E.M. Rodriguez, A. Rudy, R.C.H. del Rosario, A. Vollmar, E.R. Mendoza, A discrete Petri Net model for cephalostatin 1-induced apoptosis in leukemic cells, *Natural Computing, Special Issue on "Petri Nets and Biosystems"*, Aug 2009

- E.R. Mendoza, Systems Biology: Its Past, Present and Potential. Phil Science Letters, Vol 2, No 1 , Aug 2009

- M.P.C. David, J.Y. Bantang, E.R. Mendoza. A Projective Brane Calculus based on Activate, Bud and Mate Primitives, 2009, *LNCS Transactions in Computational Systems Biology*, Special Issue on "Computational models for cell processes", Sept 2009

- M.P.C. David, J.Y. Bantang, E.R. Mendoza. Modeling atonal membrane reactions with the projective brane calculus PABM, Electronic Proceedings in Theoretical Computer Science, Sept 2009

2008

- O. R.Gonzalez, S. Gronau, M. Falb, F. Pfeiffer, E.R. Mendoza, R. Zimmer and D. Oesterhelt, Reconstruction, Modeling & Analysis of Halobacterium salinarum R-1 metabolism, Molecular Biosystems, 2008, 4, pp.148-159

- M.P.C. David, C. Lapid, V. Daria, An efficient visualization tool for the analysis of protein mutant matrices, *BMC Bioinformatics,* April 2008, 9: 218

- R. C.H. del Rosario, E. R. Mendoza, E. O. Voit, Challenges in Lin-log modeling of Glycolysis in Lactococcus lactis, *IET Systems Biology*, 2008, 2: 136-150.

- A. Marin-Sanguino, E. R. Mendoza, Hybrid Modeling in Computational Neuropsychiatry, *Pharmacopyschiatry, Supplement,* 2008, 41 Suppl 1, p. 85-88

- T. Roenneberg, E.J. Chua, R. Bernardo, E.R. Mendoza, Modelling biological rhythms, *Current Biology,* 2008, Sep 18; R826-835.

2007

- O. R. Gonzalez, C. Küper, K. Jung, P.C. Naval Jr. and E. R. Mendoza, Parameter estimation using simulated annealing for S-System models of biochemical networks, Bioinformatics, 23, February
  2007, pp. 480-86

- R. C.H. del Rosario, W.F. Staudinger, S. Streif, F. Pfeiffer, E. R. Mendoza and D. Oesterhelt: Modelling the CheYD10K,Y100WHalobacterium salinarum mutant: sensitivity analysis allows choice of parameter to be modified in the phototaxis model, IET Systems Biology, July 2007, Vol. 1, (4), pp. 207-221

- R. B. Batista, D. B. Ramirez, R. D. Santos, M.C. I. del Rosario and E. R. Mendoza, EUCLIS-An Information System for Circadian Systems Biology, IET Systems Biology, September 2007, Vol.1 (5), pp. 266-273. Selected as the "Featured Paper" for the journal issue.

Group Members

Eduardo Mendoza	Group Coordinator
Maria Pamela David	PhD student

Associated Members

Riza Theresa Batista-Navarro	Manchester University
Johnrob Bantang	University of the Philippines Diliman
Arjay Cayetano	MS student (University of the Philippines Diliman)
Joseph Elias Co	PhD student (University of the Philippines Diliman)
Betty Dulam-Banawa	PhD student (University of the Philippines Diliman)
Orland Gonzalez	Postdoctoral Researcher (LMU Informatik)
Dranreb Earl Juanico	Postdoctoral Researcher (Humboldt Fellow, LMU München)
Alberto Marin-Sanguino	Postdoctoral Researcher (TU M ünchen)
Florence Balagtas-Fernandez	PhD student (LMU Informatik)
Elaine Jane Chua	PhD student (TUM Informatik)
Angelyn Lao	PhD student (University of the Philippines Diliman)
Kevin Manansala	MS student (University of the Philippines Diliman)
Locedie Mansueto	PhD student (MPI Biochemie)
Roselyn Santos-Gabud	PhD student (LMU Informatik)
Jan-Michael Yap	PhD student (University of the Philippines Diliman)

Alumni

Celeste del Rosario	Standard and Chartered Bank, Singapore
Ricardo del Rosario	Genome Institute of Singapore
Prospero Naval Jr.	University of the Philippines Diliman
Eva Rodriguez	University of Asia and the Pacific
Cherryl Talaue	University of the Philippines Diliman
Akos Dobay	University of Zürich

Members and Associates of the Mendoza group in Munich (April 2009)