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Systems Biology – From model organisms to complex disease

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Course page in pdf format [[click here](#)]

Course organizers:

- **Jesper Tegnér & Johan Björkegren (Computational Medicine)** [Course content and Course programme]
- **Lena Lewin & Bengt Persson** [Administration of the PhD Programme in Medical Bioinformatics (**FMB**) funded by **KK stiftelsen**]

Course content : This course provides an overview of systems biology. The course is given within the national programme - Forskarskolan för Medicinsk Bioinformatik (FMB) but the course is also open for other graduate students. The course is given at the Karolinska Institute (KI) in Stockholm. An intensive 3 day lecture operation covers work ranging from simpler model organisms to more complex diseases including cancer and cardiovascular diseases. The students will be oriented of different levels of analysis and exposed to a “smorgasbord” of system identification methods and different approaches to systems biology. Bayesian networks, modular analysis, network inference algorithms based on bayesian or ordinary differential equation models are presented. Strategies and examples of computational modeling of biological circuits at different levels of details are also discussed. An overview of systems biology software is also included. 3-4 weeks after the lectures students will, during two days (i) present and critically discuss original research papers and (ii) individually perform an oral (and written) examination of your proposed system biology study.

Advice to students: This is a unique opportunity to have access to such a distinguished group of teachers. It is therefore in your interest to prepare yourself thoroughly in order to maximally benefit from the lectures. Therefore, read the recommended review papers and check the

web links (listed at the end of this document). Try to read some of the original papers before the lectures. You will not understand everything but you will appreciate the difficult parts and you are therefore in better shape for the lectures.

Students - list of participants: [Click here](#)

Contact Information:

- For questions on course administration contact - Lena Lewin (lena.lewin@ki.se) at **Strategy and Development Office** Phone +46852486064, Cell +46703646064
- For questions on course content contact - Jesper Tegnér (jesper@karlavagen90.se or jespert@ifm.liu.se), Cell +46703282989

Instructions for applying :

- Application should be sent before 1 October to Lena Lewin.
- Priority for FMB students
- Limited to 50 students
- If you are not an FMB student and you would like to increase your chances of being accepted to the course please add a paragraph on how you would benefit from the course.

Course format:

- 31 october - 2 november. Lectures.
- 29-30 november. Student presentation of research papers (29/11). Examination (30/11).
- The course is equivalent to 2p.

Teachers

- **Erik Aurell**, Professor, Biological Physics [[link](#)]
- **Johan Björkegren**, Docent, Molecular Medicine [[link](#)]
- **Måns Ehrenberg**, Professor, Molecular Biology [[link](#)]
- **Ingemar Ernberg**, Professor, Microbiology and Tumor Biology [[link](#)]
- **Michael Hörnqvist**, Docent, Physics [[link](#)]
- **Jose Pena**, Ass Professor, Computational Biology [[link](#)]
- **Henning Schmidt**, Researcher, Systems Biology [[link](#)]
- **Jesper Tegnér**, Professor, Computational Biology [[link](#)]
- **Karl Tryggvason**, Professor, Matrix Biology [[link](#)]
- **Olaf Wolkenhauer**, Professor, Systems Biology and Bioinformatics [[link](#)]

Schedule for the lectures

	TUESDAY 31 October Lennart Nilsson salen	WEDNESDAY 1 November Lennart Nilsson salen	THURSDAY 2 November Lennart Nilsson salen (8-12)
8-9		Johan Björkegren [you got handouts]	Erik Aurell
9-10		Cardiovascular Systems Biology	Networks & Computational Modeling, Phage Lambda modeling
10-11	10-10.15 Jesper Tegnér & Johan Björkegren, Welcome & Admin	Karl Tryggvason	Måns Ehrenberg
11-12	10.15-12 Jesper Tegnér [ppt] A students guide to systems biology - a comprehensive map in which to place the lectures	Kidney & Systems Medicine	Experimental and computational analysis of gene regulation - E Coli
12-13	LUNCH	LUNCH	LUNCH Note ! Atrium salen (13-18)
13-14	Jose Pena- Bayesian Models	Olaf Wolkenhauer [lecture slides part A, B, C, D]	Michael Hörnqvist [you got handouts]
14-15	hugin software - bayesian analysis	Systems Biology, Networks, Computational modeling.	Network Identification - overview of ODE based techniques, Hands on & Examples
15-16	Network Inference		15.00-15.30 Jesper Tegnér - Instructions for the second part of the course
16-17	Henning Schmidt		15.30-17.00 Ingemar Ernberg, [ppt] Cancer Systems Biology
17-18	A systematic modeling framework and related computational tools + live demo		Jesper Tegnér - Summary & Questions from Students

Social events:

- Dinner. Down town. *Tuesday* (31/10) 6.45 PM. Host: Lena Lewin.
- Wine and beer. Outside the lecture hall. *Wednesday* (1/11) 6-6.45 PM. Host: Lena Lewin.

Schedule for presentation of research papers and examination:

- 29/11 **Lennart Nilsson salen** (KI), 10-18. Presentation and discussion of original research papers
- 30/11 **Lennart Nilsson salen** (KI), 8-17. Examination.

Examination:

- November 29. Groups, Schedule and instructions for examination on papers [[click here](#)]
- Your individual task is to design a novel system biology study. Write up a *short* report (0.5-1 page) where you have a title, an abstract (150 words) and a short outline of your study.
- You should aim for a top-journal paper.
- A "novel" idea & realistic budget. Nothing like "I like to screen all molecules within the Asian population and see what happens".
- You send your report to Jesper Tegnér (November 27 at latest) and you present your study orally for everyone (30/11) during 4 minutes and then 8 minutes (max) discussion follows. A detailed schedule will appear here soon.

Suggested research papers (to be selected for critical discussion 29/11)

- **[Olaf Wolkenhauer]** *Control, exploitation and tolerance of intracellular noise*, Christopher V. Rao*, Denise M. Wolf† & Adam P. Arkin **Nature** November 2002 [[pdf](#)]
- **[Olaf Wolkenhauer]** *DiMSim: A Discrete-Event Simulator of Metabolic Networks* Xiao-Qin Xia and Michael J. Wise*, **J. Chem. Inf. Comput. Sci.** 2003, 43, 1011-1019 [[pdf](#)]
- **[Olaf Wolkenhauer]** Olafs suggestion for questions to think about & discuss [[pdf](#)]
- **[Olaf Wolkenhauer]** You may find more papers at Olafs excellent page [[click here](#)]
- **[Michael Hörnqvist]** D di Bernardo, et al., *Chemogenomic profiling on a genome-wide scale using reverse engineered gene networks*, **Nature Biotech** vol 3, no 3, 377-383, 2005 [[pdf](#)]
- **[Michael Hörnqvist]** M Gustafsson, M Hörnqvist and A Lombardi, *Constructing and Analyzing a Large-Scale Gene-to-Gene Regulatory Network*, **IEEE/TCBB** vol 2, no 3, 254-261, 2005 [[pdf](#)]
- **[Michael Hörnqvist]** LFA Wessels, EP van Someren, MJT Reinders, *A comparison of genetic network models*, **PSB** 6: 501-

- 519, 2001 [\[pdf\]](#)
- [Erik Aurell] Jeong, S. Mason, A.-L. Barabási and Zoltan N. Oltvai *Lethality and centrality in protein networks*, **Nature** 411, 41-42 (2001) [\[pdf\]](#)
 - [Erik Aurell] R Milo, S Shen-Orr, S Itzkovitz, N Kashtan, D Chklovskii & U Alon, *Network Motifs: Simple Building Blocks of Complex Networks* **Science**, 298:824-827 (2002) [\[pdf\]](#)
 - [Jose Pena] *Using Bayesian Networks to Analyze Expression Data* Nir Friedman, Michal Linial, Iftach Nachman, Dana Pe'er **Journal of Computational Biology**. Aug 2000, Vol. 7, No. 3-4: 601-62 [\[pdf\]](#)
 - [Jose Pena] Husmeier D. (2003) "Sensitivity and specificity of inferring genetic regulatory interactions from microarray experiments with dynamic Bayesian networks" **Bioinformatics** 19: 2271-2282. [\[pdf\]](#)
 - [Jose Pena] Adriano V. Werhli, Marco Grzegorzczak, and Dirk Husmeier *Comparative evaluation of reverse engineering gene regulatory networks with relevance networks, graphical gaussian models and bayesian* **Bioinformatics**, 15 October 2006; 22: 2523 - 2531. [\[pdf\]](#)
 - [Jose Pena] *Derivation of Causal Protein Signaling Networks from Multiparameter Single-cell Data.* with Karen Sachs, Omar Perez, Doug Lauffenburger, and Garry Nolan. **Science** , 308:523-529, April 2005 [\[pdf\]](#)
 - [Jose Pena] *Module networks: identifying regulatory modules and their condition specific regulators from gene expression data* with Eran Segal, Micha Shapira, Aviv Regev, David Botstein, Daphne Koller, and Nir Friedman. **Nature Genetics** 34:166-176, June 2003. [\[pdf\]](#)
 - [Jose Pena] *Learning Module Networks.* with Eran Segal, Aviv Regev, Daphne Koller, and Nir Friedman. **Journal of Machine Learning** , 6:557-588, April 2005 [\[pdf\]](#)
 - [Jesper Tegnér] *Mathematical and theoretical biology for systems biology, and then . . . vice versa* Hans V. Westerhoff **J. Math. Biol.** 2006 [\[pdf\]](#)
 - [Jesper Tegnér] *The evolution of molecular biology into systems biology* Hans V. Westerhoff & Paulsson **Nature Biotechnology**. 2004 [\[pdf\]](#)
 - [Jesper Tegnér] *Dynamic Complex Formation During the Yeast Cell Cycle* Ulrik de Lichtenberg,^{1*} Lars Juhl Jensen,^{2*} Søren Brunak,¹ Peer Bork **Science** 2005 [\[pdf\]](#)
 - [Jesper Tegnér] *Genomic analysis of regulatory network dynamics reveals large topological changes* Formation During the Yeast Cell Cycle Luscombe et al **Nature** 2004 [\[pdf\]](#)
 - [Jesper Tegnér] Reverse engineering of regulatory networks in human B cells Basso et **Nature Genetics** 2004 [\[pdf\]](#)

- [Jesper Tegnér] *Network dynamics dynamics and cell physiology*, **Nature Reviews Molecular Cell Biology** 2, 908-916, 2001. John J. Tyson, Kathy Chen & Bela Novak [\[pdf\]](#)
- [Jesper Tegnér] Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. **Curr Opin Cell Biol.** 2003 Apr;15(2):221-31. Review. [\[pdf\]](#)
- [Jesper Tegnér] Goldbeter: **Computational approaches to cellular rhythms**. **Nature** Volume 420 November 2002, 238-245 [\[pdf\]](#)
- [Jesper Tegnér] System-level identification of transcriptional circuits underlying mammalian circadian clocks. Ueda et al **Nat Genet.** 2005. [\[pdf\]](#)
- [Jesper Tegnér] Feedback repression is required for mammalian circadian clock function.. Sato et al **Nat Genet.** 2006. [\[pdf\]](#)
- [Jesper Tegnér] *Just-in-time transcription program in metabolic pathways* **Nature Genetics** 2004. [\[pdf\]](#)
- [Jesper Tegnér] *Using a Quantitative Blueprint to Reprogram the Dynamics of the Flagella Gene Network* **Cell**, 117:713–720, (2004).. [\[pdf\]](#)
- [Jesper Tegnér] *Peeling the yeast protein network* **Proteomics** (2005). [\[pdf\]](#)
- [Johan Björkegren] *From signature to models: understanding cancer using microarrays*, . Segal, N. Friedman, N. Kaminski, A. Regev, and D. Koller **Nature Genetics**, 2005 June, 37(6 Suppl): S38-45 [\[pdf\]](#)
- [Ingemar Ernberg] Sandberg R, Ernberg I. The molecular portrait of in vitro growth by meta-analysis of gene-expression profiles. **Genome Biol.** 2005;6(8):R65. Epub 2005 Jul 27. [\[pdf\]](#)
- [Ingemar Ernberg] Huang S, Eichler G, Bar-Yam Y, Ingber DE. Cell fates as high-dimensional attractor states of a complex gene regulatory network. **Phys Rev Lett.** 2005 Apr 1;94(12):128701. Epub 2005 Apr 1. [\[pdf\]](#)
- [Ingemar Ernberg] Eichler GS, Huang S, Ingber DE. Gene Expression Dynamics Inspector (GEDI): for integrative analysis of expression profiles. **Bioinformatics.** 2003 Nov 22;19(17):2321-2 [\[pdf\]](#)
- [Ingemar Ernberg] Reya T, Morrison SJ, Clarke MF, Weissman IL Stem cells, cancer, and cancer stem cells. **Nature.** 2001 Nov 1;414(6859):105-11. [\[pdf\]](#)
- [Ingemar Ernberg] Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The consensus coding sequences of human breast and colorectal cancers. **Science.** 2006

- Oct13;314(5797):268-74. [\[pdf\]](#)
- **[Måns Ehrenberg]** What Makes Ribosome-Mediated Transcriptional Attenuation Sensitive to Amino Acid Limitation? Johan Elf, Ma°ns Ehrenberg T Plos Comp Biology 2005 [\[pdf\]](#)
 - **[Måns Ehrenberg]** Fast Evaluation of Fluctuations in Biochemical Networks With the Linear Noise Approximation Johan Elf, Ma°ns Ehrenberg T Genome Res. 2003 13: 2475-2484 [\[pdf\]](#)
 - **[Måns Ehrenberg]** Selective charging of tRNA isoacceptors induced by amino-acid starvation Kimberly A. Dittmar¹, Michael A. Sørensen², Johan Elf³, Ma°ns Ehrenberg³& Tao Pan¹+ EMBO 2005 [\[pdf\]](#)
 - **[Måns Ehrenberg]** Selective Charging of tRNA Isoacceptors Explains Patterns of Codon Usage Johan Elf,¹ Daniel Nilsson,² Tanel Tenson,³ Måns Ehrenberg¹* Science 2003 [\[pdf\]](#)
 - **[Måns Ehrenberg]** Ribosome bypassing at serine codons as a test of the model of selective transfer RNA charging Dale Lindsley¹, Paul Bonthuis¹, Jonathan Gallant¹+, Teodora Tofoleanu¹, Johan Elf²&Ma°ns Ehrenberg² EMBO 2005 [\[pdf\]](#)
 - **[Måns Ehrenberg]** Over Expression of a tRNA^{Leu} Isoacceptor Changes Charging Pattern of Leucine tRNAs and Reveals New Codon Reading Michael A. Sørensen¹†, Johan Elf²†, Elli Bouakaz²†, Tanel Tenson³ Suparna Sanyal², Glenn R. Bjork and Ma°ns Ehrenberg²* JMB 2005 [\[pdf\]](#)
 - **[Henning Schmidt]** Cell Designer [\[link here\]](#)
 - **[Henning Schmidt]** Virtual Cell [\[link here\]](#)
 - **[Henning Schmidt]** Copasi [\[link here\]](#)
 - **[Henning Schmidt]** SB Toolbox [\[link here\]](#)

Additional recommended reading (reviews)

A. Algorithms and strategies for inferring regulatory networks from experimental data

- Review paper on *network reconstruction*, focus on pathways. Papin, Hunter, Palsson, Subramaniam, **Nature Reviews Molecular Cell Biology** 2005. [\[pdf\]](#)
- *Inferring Cellular Networks Using Probabilistic Graphical Models.* Nir Friedman. **Science** 2004 [\[pdf\]](#)
- Bayesian network analysis of signaling networks: A primer. Dana Peér, Science 2005 [\[pdf\]](#)
- Perturbations to uncover networks, Tegnér & Björkegren, Trends in Genetics 2007 [\[pdf\]](#)

B. Computational modeling of pathways and networks

- *Network dynamics dynamics and cell physiology*, **Nature Reviews**

- Molecular Cell Biology** 2, 908-916, 2001. John J. Tyson, Kathy Chen & Bela Novak [[pdf](#)]
- *Toward predictive models of mammalian cells*, Avi Ma'ayan, Robert D. Blitzer, and Ravi Iyengar **Annual Review of Biophysics and Biomolecular Structure** 2005. [[pdf](#)]
 - *The Role of Modeling in Systems Biology*, Douglas B. Kell and Joshua D. Knowles from *System Modeling in Cellular Biology, From Concepts to Nuts and Bolts* MIT Press 2006. [[pdf](#)]
 - Réka Albert and Albert-László Barabási *Statistical mechanics of complex networks* **Review of Modern Physics** 2002 [[pdf](#)]

C. Clinical systems biology

- *Toward a biological network for atherosclerosis*. Aldons Lysis et al. **Journal of Lipid Research**. 2004 [[pdf](#)]
- *From signatures to models: understanding cancer using microarrays* Eran Segal, Nir Friedman, Naftali Kaminski, Aviv Regev & Daphne Koller **Nature Genetics** 2005. [[pdf](#)]
- *Hereditary Proteinuria Syndromes and Mechanisms of Proteinuria*. Karl Trygvasson et al.. **New England Journal of Medicine**. 2006 [[pdf](#)]
- *DISEASE GENE DISCOVERY THROUGH INTEGRATIVE GENOMICS* Cosmas Giallourakis,^{1,2} Charlotte Henson,¹ Michael Reich,¹ Xiaohui Xie,¹ Vamsi K. Mootha^{1,3,4} **Annu. Rev. Genomics Hum. Genet.** 2005. 6:381–406 [[pdf](#)]

D. General reviews

- *Computational systems biology*, **Nature** 420, 206-210, 2002 Hiroaki Kitano [[pdf](#)]
- *Modeling cellular machinery through biological network comparison*. Roded Sharan & Trey Ideker. **Nature Biotechnology** 2005 [[pdf](#)]
- *Systems Biology: An overview*. A review from the **Science Creative Quarterly** July 2005 [[link](#)]
- *A new approach to decoding life: systems biology*. Ideker, Galitski, Hood. **Annual review genomics human genetics** 2001. [[pdf](#)]
- *Network Biology*. Very readable review from Barabasi. **Nature Reviews Genetics** 2004. [[pdf](#)]
- *The model organism as a system: integrating 'omics' data sets* Andrew R. Joyce* and Bernhard Ø. Palsson‡ **Nature Reviews Molecular Cell Biology** 2006 [[pdf](#)]
- *Exploring complex networks* Steven Strogatz ‡ **Nature** 2001 [[pdf](#)]

Web resources:

- **Systems Biology - Wikipedia (loads ! of links, history, groups, centers, researchers, companies, meetings, tools)**
- **Systems Biology Organization**
- **Institute for Systems Biology (Leroy Hood)**

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