Yeast Systems Biology – 2nd Workshop

May 14-16, 2004 Copenhagen, Denmark

Background

21st century biology will gradually move from studying individual cellular components to addressing how functional modules interact to make the cellular system function as a whole. Thus, there will be a trend towards a systems view of cellular function based on an understanding of the molecular mechanisms of individual processes.

In order to generate accurate descriptions of the interaction and operation of different components and to understand at a quantitative level the relationship among genotype and phenotype it will be necessary to develop a research environment in which experimental and theoretical scientists work together. Hence, we will see an integration of experimental research with efforts to generate and optimize computer models of cellular networks and processes. This integration represents a real challenge for researchers in the future. In particular, in order to describe the dynamic operation of biological systems, it requires the generation of quantitative data, time courses and spatial information. In fact, generating such data often constitutes a true experimental challenge. Therefore, Systems Biology will also encompass the development of tools and experimental approaches to produce quantitative data. This type of information will help to better understand diseases and hence Systems Biology will become an integral part of drug target identification and drug design.

In the development towards quantitative biology – or Systems Biology – the study of suitable model systems will be pivotal. The yeast *Saccharomyces cerevisiae* represents an obvious model system for a concentrated research effort in this area to significantly advance biological sciences, just as it has been for genomics and functional genomics.

The idea to combine forces in Yeast Systems Biology was first discussed at the yeast2003 conference (XXI Int Conf Yeast Genet Mol Biol, Göteborg, Sweden, July 2003). A first brain storming workshop took place after the Systems Biology Conference in St. Louis in Nov 2003. It was decided to explore the possibilities for setting up the global network. Following this first workshop a White Paper (Annex III) was drafted and distributed to a number of members of the yeast as well as the modeling community.

Workshop goals

The objectives of the second workshop on systems biology of the yeast *Saccharomyces cerevisiae* were to discuss and define conditions and needs for an integrated systems biology effort on this yeast. In particular, the goal was to define an action plan for the near future to set up the network, create visibility and interest, to involve a wider community in the discussion and to open the possibility for fund raising.

The conclusions of the workshop will be written up as publication(s) and as a synopsis summarizing requirements for a focused effort on systems biology on a given organism. Hence this network will serve as a paradigm both scientifically as well as in terms of organisation and management of a global effort.

Participants

	Participant	E-mail	Affiliation Remarks
1	Marco Vanoni	Marco.vanoni@unimib.it	University of Milano
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2	Kara Dolinski	kara@genomics.princeton.edu	Princeton University
		botstein@princeton.edu	Representing David Botstein and Mike Cherry/SGD
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5	Betul Kirdar	kirdar@boun.edu.tr	University of Istanbul
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7	Edda Klipp	klipp@molgen.mpg.de	Max Planck Institue for Molecular Genetics Berlin
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9	Pedro Mendes	mendes@vt.edu	Virginia Polytechnic Institute and State University
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19	Hans Westerhoff	hw@bio.vu.nl	Free University of Amsterdam
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Several additional people had been invited but were unable to attend due to other obligations.

Agenda

Friday, May 14

19:00 Get together dinner

Saturday, May 14

09:00 Presentations by all participants

12:00 Lunch

13:00 Discussions in three groups

Group 1: Data acquisition and databases

Group 2: Modelling efforts

Group 3: Possible action plans and training

16:00 Drafting of conclusions and initial plenum discussions

18:00 Dinner

Sunday, May 14

09:00 Discussions in plenum – drafting of action plan and distribution of tasks

11:00 Conclusions and round off

12:00 Lunch and departure

Summary report: Setting up a global YEAST SYSTEMS BIOLOGY NETWORK (YSBN)

The yeast community, and the research community in general, is confronted with two seemingly contradictory problems: on the one hand massive amounts of global analysis data are produced that need to be rationalized to achieve an understanding of cellular networks. On the other hand, we are lacking quantitative, time-dependent data and spatial information to understand the dynamic operation of many cellular pathways and processes. Both issues can be addressed with the help of mathematical descriptions that enable, for instance, generating network maps from large data sets and predicting the operation of cellular processes even if certain parameters are lacking. While the specific mathematical models addressing both problems are different, the present fragmentation of efforts calls for a wider collaboration between scientific disciplines. Those disciplines encompass experimental scientists that generate data and aim at an understanding of biological function as well as mathematicians, engineers and computer scientists that elucidate the characteristics of the systems underlying biological networks and processes. It should be noted that data generation as such is a multidisciplinary endeavor involving not only biologists or medical researchers but also, for instance, chemists and physicists. With the awareness that the challenges of modern, post-genomic biology require novel ways of scientific interactions some 20 scientists met in Copenhagen to discuss actions the yeast community could take to be at the forefront of the systems/quantitative biology.

The workshop participants each briefly introduced their own research as well as their individual expectations from future research in the area and the contributions the Yeast Systems Biology Network could make (see Annex I for summaries and Annex II for ppt presentations). It was generally agreed that the White Paper (Annex III) was a suitable starting point for the discussions. Discussions in small groups (leading to the generation of working groups, see below) as well as subsequent plenum discussions resulted in the definition of the needs, including needs for funding, for the YSBN:

Data access: Relevant global analysis data (any sort of –omics) are stored in different places and formats. Larger existing repositories should provide filters enabling to locate yeast data. Data access needs to be centralized and facilitated. SGD may be an ideal place for making yeast data available, where SGD restricts to published data. Modes have to be found to store and make available metabolomics data.

Data generation: Data needed for dynamic modeling (i.e. quantitative, time-course data etc) are scarce and not stored in relevant databases. To obtain such data text and data mining in the scientific literature needs to be done. The research community will have to be encouraged to generate such data and to deposite those using certain formats and standards in a specific data repository.

Scope of models: So far only relatively few cellular modules have been subjected to mathematical description, those however often several times in different ways (e.g. glycolysis, cell cycle,. MAPK signaling). To eventually cover the entire cell further modules should be addressed and reference models for individual modules have to be generated.

Model connectivity: The goal is to connect models for individual modules to arrive, eventually, at whole cell models. This requires application of certain modeling standards for building reference models and significant research and development to connect models. Moreover, ways (and standards) for presenting and animating simulations via the internet have to be developed. The Network will have to invest significant research in this area or coordinate existing research efforts and mobilize those for the objectives of the network.

Training: Scientists trained in quantitative biology plus mathematics are scarce but needed in the near future by academia and industry. The network sees it as an obvious task to strongly contribute to train at an international level the "new biologist" by a number of different means.

Dissemination: The network has to reach out to and motivate the relevant research communities to achieve highest impact. The network will have to mobilize the scientific and technical resources to generate relevant data and to iteratively improve mathematical descriptions effectively.

Much of the discussions at the workshop centered around the question of how the yeast research community can be mobilized, motivated and involved in a joint yeast systems biology effort. The general consensus was that the community needs to be encouraged to participate and that the forces of scientific freedom and creativity need to drive the process. The Yeast Systems Biology Network needs to offer an environment for interactions between yeast biologists, other experimental disciplines and theoretical scientists. This environment should evolve using the scientific forces from the research community. Success stories in systems biology will have highly important advertising effects. "Success stories" can be defined as such: novel biological information obtained by research using both experimental and mathematical approaches that any of the disciplines alone would not have yielded.

While providing maximal scientific freedom, the environment generated by the Network should be driven by the goal to achieve an *understanding* of biological function, i.e. cellular networks and processes. For this, different types of data are required and the community needs to be encouraged to generate such data in the process of their normal research projects. Providing data suitable for modeling will require an awareness of the needs within the community as well as certain standards/formats for information on data. This could follow the example of the MIAME standards for micro array data. Designing such standards for different types of data can easily become a daunting task and hence it will be necessary to set those out in quite general format.

At the same time it will also be needed to set certain standards for model generation and presentation and here the Network will enter new scientific territory. The Network will start from modules, i.e. descriptions of certain cellular subnetworks and processes such as a metabolic or signaling pathway, or the cell cycle. Presently, there are several different mathematical descriptions available for e.g. the cell cycle or for glycolysis. Those might live and evolve in parallel for some time but eventually should converge to reference models. This is necessary for modules to be connected to arrive at whole-cell network or process models. How this can be achieved will be a prime task of the YSBN.

The workshop has defined the framework for how the YSBN can function and it has decided an action plan for the coming months to drive the processes of implementing the infrastructure.

Central to the Network will be a web resource as an interface between the yeast research community (data acquisition), the community of bioinformaticians, mathematicians, computer scientists and engineers (modeling) and back to the yeast research community (use and improvement of models). This web resource (forming a "virtual research community") will be closely linked to (and collaborate with) but distinct from the *Saccharomyces* Genome Database SGD, the Yeast Resource Center at Washington University and the Munich Institute for Protein Sequences MIPS. The models that are made available on this web site shall be described based on widely accepted standard representation schemes. Building and maintaining the resource (coordinator, curators) will require dedicated funding. It does not need to be physically located at one place. http://www.YSBN.org/ will be used as a gateway for the resources of this initiative. An overall structure of the website has been discussed and

tasks have been distributed to set up the website (see action plan). The website will be hosted, at least initially, at Göteborg University.

The workshop has also decided on and implemented a set of working groups with members and chairpersons from different continents as well as sets of dedicated tasks:

1. The data acqusition and database working group headed by Uwe Sauer, Takashi Ito and Charlie Boone. The group will closely collaborate with SGD and also with the Washington Resource Center. It will work out the general standards on data presentation, documentation and quality that are required for deposition at either SGD or YSBN's own data repository. Those data will be of value and useful for mathematical modeling. The group will, in this context, also define the type of data required for instance for generation of dynamic models and call for generation of and providing such data. Moreover, the working group will host a database (or link to relevant resources) listing a set of recommended protocols for generation of relevant types of data.
2. The modeling working group headed by Edda Klipp, Hiroaki Kitano and Pedro Mendes. The group will work out strategies to present to the community different models and modules. It will also discuss and design standards for modeling and approaches that will allow generating reference models and connection of models and modules. As indicated above, this will require extensive research and may serve as paradigm for other, organism-driven systems biology projects. It has been discussed that a possibly ideal scenario would be establishing a dedicated research group that could also be in charge of the web site, similar to the SGD setup. The working group will meet in October 2004 in Heidelberg.
3. The training working group headed by Karl Kuchler, Ian Dawes and Bernard Palsson will steer the organization of dedicated international training courses and training networks in the area of systems and quantitative biology. Ideally, the Network should organize a yearly prestigious course following the example of the Cold Spring Harbor Yeast Genetics Course, that has helped shaping the yeast community. Training is an important way to reach the research community and to raise interest and funding.
4. The dissemination working group headed by Stefan Hohmann will overlook activities to spread information on the Network as well as systems/quantitative biology in general. This includes certain aspects of the YSBN website (for the public), activities at relevant conference and production of information material.

The working groups have started their activities already during the workshop and members are in frequent contact. Tasks for the immediate future include setting up the www.ysbn.org website and produce an information flyer. Both will be available by the end of July for the Seattle yeast conference. Contacts with journal editors have already been taken to publish a position paper on the Network plans and activities and to highlight why this activity goes clearly beyond simply setting up a website. The White Paper still serves as a reference and has been updated. Potential members of the advisory board are being contacted.

Discussions in Göteborg on how to possibly setup the web resource, including databases and model base, have been started and could soon involve other Network members (e.g. DTU).

International conferences are major opportunities for interacting with the research community. Several have been listed in the action plan and contacts with members of the organizing committees (some are part of the Network) have been initiated to discuss the most appropriate way to represent the Network. In the nearest future this will be the Seattle yeast conference

(end July 2004) as well as the Heidelberg systems biology conference (October 2004), where the 3rd workshop is planned.

In fall 2004 there are several opportunities to apply for support at the EC level. In particular, the Network will apply for a set of complementary Specific Targeted Research Projects (STREPs, max 2 million each) to secure some resources both for the data acquisition and the modeling parts. Also applications for Training Networks are planned. Using EC support could also be one possibility to establish a team that does research on model development with an emphasis on reference models, connectivity, simulation animation etc.

While the action plan lays out the activities and goals for the coming months those for 2005 will have to be defined at the 3rd workshop in Heidelberg

The long term vision of the Network is to become a crucial part of yeast research, to establish yeast as a model for systems biology and to provide a paradigm for systems biology on other organisms. The Network is aware of the fact that this requires wide acceptance by the research community.

Report Data collection working group

By Jens Nielsen

The following comments were made during the discussions of databases:

Transcriptome data

SGD provides published data (http://www.yeastgenome.org/)

Other databases provide repository-type data:

(Array Express: http://www.ebi.ac.uk/arrayexpress/; GEO)

The only transcription database with a page dedicated to yeast is http://transcriptome.ens.fr/ymgv/. Also this side only has published data.

Standards have been worked out: MIAMI at http://www.mged.org/

It is needed to establish a filter to enable search in ArrayExpress/GEO

Proteome data

EBI/Oliver work on standard format for proteome data (2D-gels and MS)

Metabolome data

Standards needed to metabolite profiling/metabolite data

Perhaps too early (journals need to enforce the standards, concerted effortis needed to establish such standards)

The group should prepare a position paper on metabolite data (quality control important)

Adapt concepts from MIAME (http://www.mged.org/) for metabolome data on experimental protocols

Fluxome data

Data base for C13 data and estimated fluxes needed

Uwe Sauer and Jens Nielsen to discuss concerted effort on this

Interactome data

GRID (http://biodata.mshri.on.ca/yeast_grid/) has yeast data separate and they can be accessed through SGD

GRID – no Kd's (binding constants); BIND (http://www.blueprint.org/bind/bind.php) has Kd's included; YPD is the best repository database but not freely available

Perhaps establish a filter on interactome data from GRID and BIND

Locasome data

SGD presents these data via a link to http://yeastgfp.ucsf.edu, including data on molecules per cell

Specific tasks

EC-nomenclature is not updated, needs to be updated.

There are several metabolites in yeast that are not present in any database. Also there is knowledge of enzymes present in yeast where the corresponding genes have not yet been identified. Based on a reconstructed metabolic network this information is collected and it will be relatively easy to implement this into the SGD database.

Specific action points

List all metabolites present in yeast cells (dynamic process) in SGD (showing need to identify relevant enzymes)

List all enzymes known to exist in yeast cells in SGD (showing need to identify relevant genes)

Report Modelling working group

By Hiroaki Kitano

The goal of systems biology, as well as modeling and simulation need to be clearly defined at the outset of the project. Systems biology is a field that aims at systems-level understanding of biological systems. While there are several undefined words such as "understanding" and "system-level", the operational definition may be to identify dynamic properties and principles behind the biological systems. In this context, modeling and simulation are powerful approaches to reveal dynamical properties. However, caution has to be made not to pursue "simulation for the sake of simulation".

Aside from the understanding of principle of life, the direct implication of a computational model is the capability to predict biological phenomena using the model and relevant analysis methodologies.

In addition, it was made clear that there is not such thing as “general simulation model”. Simulations are problem specific, so that abstractions, grain size of modeling, and the scope of modeling heavily depends upon the problems that are addressed in the context of the research. Thus, attempt to create one ultimate model need careful examination.

By the same token, the notion of “whole cell model” has to be taken with careful examination. Truly building “whole cell” implies that it must model even lipid bi-layer, cytoskeleton, and all other details of cell, not just networks of molecular interactions. Any researcher may come up with a question “where is my gene?” Alternatively, an integrated model captures the essential aspect of the initiative that tries to reveal biology that are enabled only by putting pieces together, rather than isolated studies. In addition, the notion of “the reference model” emphasizes the model as a common infrastructure shared by numbers of research groups serving as common language.

One of the initial programs will be to create the reference model that describes all known molecular interactions within a cell, but no kinetic constant is yet assigned. SBML and diagram notations proposed by Kitano will be the basis of computer-readable and human-readable model representation, respectively. Palsson’s proposal on systemic annotation is along the same direction, but with different representation.

The other program to be initiated is identification of the set of experiments necessary to obtain parameters for numerical simulation. The modeling working group is in agreement that the network should challenge to establish a model-driven data acquisition where model based analysis and experimental design drive experiment programs. This requires extensive collaboration between computational/theoretical biologists and experimental biologists. In particular, experiments shall be done to identify dynamical properties of the cell. At the early stage of the project, a list of experiments and conditions shall be created with specific ideas of how such data are processed to construct the model. Numerical simulation will be attempted initially using existing knowledge from current experimental data and literature, but standardized and well managed experimental data set shall be used.

Web service to the network, as well as to the yeast community is critical and essential for the success of the project. The web site shall incorporate model repository, interactive simulation applets, software and data resources, molecular and pathway pages that are particularly designed for model construction.

The success story will be the essential aspect that needs to be identified and highlighted as soon as possible.

The project has two aspects: one is infrastructure development in both experimental technique development and data acquisition, and software development and model construction; the other is research on yeast biology that is enabled by the use of infrastructure created.

The success story shall be the one feature a kind of biology that is enabled by creation of infrastructure in this project. This is called “Enabled Project”. Other projects shall be conventional biology, but significantly accelerated by the use of infrastructure.

Report Training working group

By Stefan Hohmann

It has been made explicit that international training in systems biology is crucial because

- It provide a means for dissemination of the goals of the YSB network
- It provides a means for involving further groups in the network
- It provides a means to create awareness of the importance to create quantitative data
- It is one step towards the education of a new generation of biologists, i.e. scientists trained in more than one discipline
- It provides one means to raise funds for activities of the YSBN

Hence, international training should be a prime activity of the network. Peter Philippsen pointed to the importance for the yeast community of the Cold Spring Harbor Yeast Course. A quantitative/systems biology counterpart should be set up in Europe as a central network activity.

The following activities within training are envisaged:

- Karl Kuchler and Hans Westerhoff already organise a training course in 2005, that will involve many members of the community. This course should take place regularly, possibly at different locations.
- Stefan Hohmann and Marja Makarow (Helsinki) recently agreed to set up a course that shuttles between Göteborg and Helsinki and takes place every other year, starting in 2005. Emphasis on yeast systems biology.
- An application to EC is pending on PhD student training in the field. It involves Amsterdam, Berlin and Göteborg and can involve PhD students from anywhere.
- One or two applications for EC Research Training Networks should be handed in at the fall deadline.
- A list of relevant local training activities should be set up and courses open to students from outside the organising institution should be advertised through the network.

Action plan

1. Preparation of a summary report of entire meeting.

To be done by Stefan Hohmann by end of May.

2. The report will be processed into:

A report containing (copy-paste) all contributions from the workshop participants (this report).

A two-page abridged summary written by Stefan Hohmann (edited summary report incl specific actions).

Short meeting report about establishing the YSBN for *Nature*: Hiraoki Kitano will discuss possible publication with Nature editors (e.g. form of ”communication”) June/July.

Longer paper describing the needs and goals for the YSBN for Nature Biotechnol. Section on Computational Biotechnology (Karl Kuchler will e-mail Gaspar Taroncher, who indicated that reports of developments in the field of systems biology should be welcome. May/June.

3. Name of the initiative:

Yeast Systems Biology Network: YSBN.org

Hiraoki reserved the name.

4. Website management & design

A website should be set up until about mid/end June. Hans Westerhoff and Stefan Hohmann will be responsible for design and content. Stefan has web designer employed in an EC project that could help.

The basic look of the site was discussed:

Left hand side: buttons for [documents, members, models, data, training]

In the centre text boxes with [below each other: Title, Mission, Invitation text (with button in this 'to join'), definition of SB, disclaimer].

Top of page: buttons guiding to [News, Hot applications, etc].

5. Website section 'Models'

There will generally be two types of models

I. Network models (connectivity models) based on genetic or protein interactions, array data etc

II. Process models, i.e. dynamic models on processes operating in time (and space)

There are two possible, non-exclusive ways of model presentation:

I. Link to a page curated by the researchers that generated the model

II. The model is curated at the site of the YSBN. At least in the long run, this should be the goal of the network, especially for reference models.

Main page for Models will be made (Jacky Snoep, Hans Westerhoff) with the following setup (before Seattle (July 27-August 1)).

Website should illustrate that the main plan is to arrive at whole cell models and should emphasise what is already possible at this point: modules.

Therefore a central diagram about all of the yeast cell; then point for instance at metabolism and zoom to the glycolytic models (this to prevent the impression that this is too complicated/technical).

Or point at cell cycle and go to cell cycle models etc.

Also simplified models (core models) and training model

Link to JWS glycolysis models (present relevant addresses: www.siliconcell.net, jjj.biochem.sun.ac.za , Jacky Snoep: jls@sun.ac.za or js@bio.vu.nl)

Link to cell cycle models: Bela Novak

Link to signaling models: Edda Klipp

Link to interaction map-models: Hiraoki Kitano

It will be important to illustrate from the start different models, not showing too many models from the same pathway (such as glycolysis).

6. Model working group

The task of this group is content development for website node 'models', definition of reference models and establishment of model integration.

Present members (underlined: responsible persons): Hans Westerhoff, Jacky Snoep, Pedro Mendes (in charge of the mailing list), Hiraoki Kitano, Edda Klipp (chair), Mats Jirstrand, Matthias Reuss, Bela Novak, Bernard Palsson, Matej Oresic.

The group will meet in Heidelberg at the systems biology conference in Oct 2004.

The group may apply for EC funding in fall.

7. Data content committee

Group will set up a system to select sets of data that are well defined. Before Seattle: description of what type of data are needed; short text on the website.

Further tasks of committee:

Requirements for data submission; definition of the criteria including quality of experiments, controls, validation, also structural data. Content of the relevant section of the website.

SGD can store published data sets.

Filter for yeast will/may be installed in other relevant data repositories.

Kara will provide FTP site address where the data are; will collect datasets.

Data content committee (underlined: responsible persons): Jens Nielsen, Uwe Sauer (chair), Takashi Ito (vice-chair), Kara Dolinski, Steve Oliver, Pedro Mendes, Matej Oresic, Charlie Boone (vice-chair), Trey Ideker, Karl Kuchler, Peter Philippsen, Stefan Hohmann.

8. Training committee

The committee will be in charge of organising training courses and networks as well as coordinating and overseeing/advertising local training activities. This should lead to a broader strategy in training in the field and opening of local courses to many participants from abroad.

International projects envisaged: Early stage training EST, research training networks RTN, EXT (4 years start up group), MSc programs curricula

The Network should organise a yearly flagship course 3 weeks. Could rotate or in one specific place.

Committee members (underlined: responsible persons): Karl Kuchler (chair), Hans Westerhoff, Stefan Hohmann, Matthias Reuss, Marco Vanoni, Peter Philippsen, Edda Klipp, Betul Kirdar, Jens Nielsen, Bernard Palsson (vice chair), Charlie Boone, Marja Makarow, Ian Dawes (vice chair) plus to be identified by Hiraoki: Singapore, China ??

9. Dissemination

Stefan Hohmann is coordinating dissemination

Future conferences of relevance to the Network:

IEcA meeting: mention Network at that meeting

Seattle July 2004: panel discussion future of yeast as model organism

Flyer describing the initiative: Karl Kuchler

10 minutes dedicated presentation (ideally by someone from the US?) to be negotiated by Karl Kuchler with Stan Fields

Heidelberg: workshop: Stefan Hohmann, Hans Westerhoff, dates to be defined

Biotechnology 2005 Copenhagen August: Heavy SB content. Jens Nielsen

Yeast 2005 in Bratislava: Hans Westerhoff will contact them:

Metabolic Engineering Conference Jim Liao

ISSY in Finland 2006, Merja Penttilä

Yeast Cell Biology August 2005 Cold Spring Harbor: PeterPhilippsen to talk to Brenda Andrews

10. Committees:

Advisory committee; suggestions for names (invitor between brackets; underlined: confirmed at time of report)):

Brenner (Hiroaki Kitano), Botstein (Stefan Hohmann), Hartwell (Steve Oliver), Paul Nurse (Bela Novak), Sakaki (Takashi Ito), Kirschner (Hans Westerhoff), Gilman (Hans Westerhoff), Aebersold (Uwe Sauer), Frank Gannon (Karl Kuchler)

11. Possible applications for money:

USA running grants, others?

EC: plan for a ”Coordination Action” discussed. Focus on yeast or more general with yeast as a focus (paradigm, model), possibly as extension to the existing EUSYSBIO network (SSA)

SysMo (Germany) to be extended transationally

EC FP6, third call: STREP possibilities (max 2 million Euro): identifying correlation of biochemical data and gene function, system biology of complex cellular pathways. We should submit a set of complementary proposals, each of 5 groups and each 2 MEuro max., companies SME’s needed:

Metabolomics to identify gene functions, dynamics (Hans, Steve, Mattias, Uwe?)

Glucose sensing pathways (Stefan, Jens)

Cell Biology [Imaging, generating quantitative data; Something on bioimaging, cell growth; interaction between metabolism and cell proliferation]; to be dfined who will do this

Coupling cell cycle to metabolism (might be too close to a project under negotiation)?

Others....

Annex I: Summaries of individual presentations

Alberghina/Vanoni

This work is aimed at molecular understanding of cell cycle control in budding yeast using a modular systems biology approach. *Saccharomyces cerevisiae* cells grown in glucose have larger size than cells grown in ethanol. In order to enter S phase at Start, they must reach a carbon source-modulated critical cell size. We showed that an increased level of the cyclin dependent inhibitor Far1 increases cell size, while in *far1*Δ cells, bud emergence and DNA replication start at a smaller size relative to wild type cells. Stabilization of Far1 explains the delay in the onset of S phase observed during a nutritional shift-up despite the concurrent increase in Cln3. Taken together these findings indicate that Cln3 has to overcome the available Far1 in order to activate Cln•Cdk1 activity required for SBF and MBF activation thereby indicating the presence of a Cln3/Far1 threshold involved in the mechanism of the cell sizer. A second threshold given by Sic1 degradation, is required for the onset of DNA replication. Carbon source modulation of cell size at Start is completely abolished only when both thresholds are inactivated The newly described two-threshold control of cell cycle transition from G1 to S is able to reconcile a wealth of literature data and its modeling and simulation analysis correctly predicts major features of the G1 to S dynamics and the behaviour of known cell cycle mutants such as a delay in Start execution brought about by *CLN3* deletion, lethality of a *cln1,2,3* deletion and its rescue by concurrent deletion of the *SIC1* gene. The major system properties of the network are under study in collaboration with Edda Klipp's group.

In its current implementation, our model of the G1/S transition is working as a backbone that starting from a simple blueprint is adding deeper and deeper molecular details in the computational model in a form that can be directly tested experimentally. Quantitative measurements of levels, phosphorylation state and affinity constants of relevant Cdk, Cki, SCF, subcellular localization of the relevant molecules and proteosomal activities as well as genome-wide analysis during transitory states is underway and should allow to improve quantitative agreement between experimental and simulated data, to further test this mathematical model of the G1/S transition and to iteratively refine - and expand - its underlying molecular structure. The interconnection of cell cycle with signal transduction and metabolic pathways in setting the thresholds regulating the G1/S transition will also be studied.

Dolinski

See PowerPoint presentation

Hohmann

The Hohmann group is interested in the control of signal transduction pathways, in particular MAPK pathways (and here in particular the HOG pathway) as well as nutrient-controlled signalling (and here in particular the Snf1 pathway). We are doing quantitative analysis of different events in signalling and cellular responses. Particular questions we are addressing in this work include:

How is pathway activation controlled and what are the underlying mechanisms?

What are the specific feedback mechanisms and how are they controlled?

How do different pathway branches and even different pathways interact and how does this interaction contribute to the response profile?

How are different signals integrated and how do individual signals divert to generate different responses?

In the future we will further emphasise analysis at the level of the single living cell.

We collaborate with mathematicians locally and abroad (Edda Klipp). We see modelling as a tool to rationalise experimental data, to get an insight into system properties and to phrase hypotheses for further experimental work. We are interested in kinetic modelling, i.e. resolving events on a time scale.

Göteborg is presently planning a centre for quantitative biology in which biologists (incl many of the groups of the Göteborg Yeast Centre with some 50 researchers), physicists, chemists, engineers, computer scientists anbd mathematicians will work together within close vicinity. Hence, we could contribute to the YSBN both with data collection, database management, modelling and website management.

In addition the Göteborg groups are keen to take part also in the overall management of the network.

Ito

The group led by Takashi Ito at the University of Tokyo is putting particular emphasis on comprehensive and quantitative measurement of both transcriptome and proteome as well as development of novel methodologies required for such measurements. For the transcriptome, his group has established a genome-wide PCR system to competitively amplify each ORF from cDNA and genomic DNA. Since genomic DNA contains every gene at exactly the same copy number, it serves as an ideal standard to normalize the difference in amplification efficiency of each amplicon, thereby leading to the description of transcriptome on the scale of number of transcripts per cell or absolute quantification. For the proteome, the group developed a method for comprehensive identification of polyubiquitinated proteins based on a unique parallel-affinity purification method followed by LC/MS/MS (PAP-MS). The PAP-MS with stable isotope labeling is currently applied to the profiling of protein ubiquitination. They are also aiming at absolute quantification of particular protein phosphorylation and interactions using isotope-labeled synthetic standard peptides and LC/MS/MS. The group is willing to provide these technologies for the collection of basic data for various modeling, whereas the target of their own is nutritional stress response, in particular, the well-known general amino acid control response.

Kirdar

Current Members of the Systems Biology Group:

Professors : B.Kirdar, K.Ulgen, Z.I.Onsan

PhD Students : P. Pir, K.Y. Arga, T. Cakir, E. Nikerel, H.Taymaz

MSc students : D. Dikicioglu, F.B Kavun, D. Rende, H. Kinis, S.Tiveci, S.Alsan

Collaborations : Steve Oliver(UK), Jens Nielsen (Denmark)

Projects : Our present research is focused on a system level understanding of the cell and establishment of new strategies for the rational design through identification of target sequences for the development of new products and improved processes in yeast and/or mammalian cells using a system biology approach. We have an integrated PhD program sponsored by TUBITAK(Turkish Scientific Research Council). The aim of this project is to establish international collaborative research projects in Systems Biology and to develop them through PhD students.These students will be sponsored by TUBITAK to spend a limited time to carry out one part of the planned research as part of their thesis in a well known collaborator's laboratory.

Our on-going project are;

1.Integrated Analysis of Metabolomics and Gene Expression in *S.Cerevisiae* (in collaboration with S.Oliver)

The aim of this project is to have a an improved understanding of respiratory metabolism and to reconstruct the pathway to include all components acting on the assembly of respiratory chain complexes and regulation. The ultimate goal of the project is to develop a rational design of an ethanol overproducing strain

We are conducting a series of perturbation experiments using respiratory deficient strains under different environmental conditions in strictly controlled fermentors.Metabolome and transcriptome data are analyzed using advanced multivariate statistical tools. Genome scale models are expected to be devloped and tested.

2.Integration of Transcriptomics to Fluxomics

(in collaboration with J.Nielsen)

We have already analyzed the central carbon metabolism of *S.cerevisiae* using MPA tools. Elementary Flux Modes (EFMs) for three substrates were determined using the catabolic reactions occurring in yeast. Resultant elementary modes were used for gene deletion phenotype analysis and for the anlysis of rrobustness of the central metabolism and network functionalaity. Control effective fluxes, determined by calculating the efficiency of each mode were used for the prediction of transcript ratios of metabolic genes in different media. Our current studies are focused on the extension of the stochiometric model and development of a genome scale model to predict the transcription of the genes in deleted strains (e.g. genes deleted in the signaling pathway or encoding isoenzymes). In future applications this analysis will be extended to the area of proteomics, with an aim toward theoretical prediction of protein ratios.

3.Analysis and Modelling of Glucose-Sensing and -Signaling Pathway (in collaboration with J.Nielsen)

The aim of this project is to understand how the components of the glucose-sensing and -signaling cascade work together as a system to produce cellular responses with respect to a change in the the extracellular environment. Signal transduction pathways are considered as linear chains of biochemical reactions from the sensor molecules to the intracellular targets.

Sinaling pathways interact with each other and the final biological response is shaped by interactions between pathways. These interactions result in networks that are quite complex with many levels of interconnectivity of large number of molecular components.Our efforts are focused on the reconstruction of glucose signaling pathway as part of the complex signaling network topology and design of the experiments. Our goal is the development of a model to link the interactome to fluxome and metabolome.

Klipp

The profile of research of the group fits well with YSBN. One focus is the modeling of signaling pathways in yeast, especially High Osmolarity Glycerol (HOG) pathway and pheromone pathway, as well as modeling of the complex stress response including not only the signaling pathway but also receptor activation, gene expression changes, metabolic changes, or biophysical changes. The means of modeling is mainly description with ordinary differential equations and analysis of the resulting systems. Modeling relies on strong collaborations with experimental groups also involved in the YSBN (Hohmann, Alberghina).

We perform also theoretical studies of biochemical networks and respective models, which can be a contribution to an important aim of the YSBN, the build-up of comprehensive models of yeast biochemical networks.

One challenge is the existence or development of individual models for certain pathways that need to be linked. We work on developing rules how to link models (integrate overlapping components, match of behavior, time scales, dynamic properties, and so on).

Another problem is insufficient data and/or parameters for comprehensive kinetic description. Thus we analyze networks to find out how far dynamic behavior is determined by network structure (stoichiometry, effector pattern) and/or by kinetics.

Nevertheless, a lot of information is already stored somewhere in literature. We develop text-mining strategies for systems biology in order to find respective literature and to extract kinetic types and kinetic data in full text (text classification (ongoing), automated information extraction (open problem)).

To store the information we build up the database Kinetikon for kinetic types and related data for enzymatic reactions (mainly) and all cellular biochemical processes. Data come from text mining (see above) and from community (hopefully).

Expectations to YSBN: First, we see model development as an iterative process: experimental investigation – mathematical description – hypothesis generation – experimental verification/falsification. Results need a critical discussion by the community. Second, common effort and distributed focus may accelerate build up of more and more integrative view of cellular regulation and maintenance pattern. Third, the network aspect: an organized community has more power to support actions (training, fund raising, public awareness, and so on) as well as to set and develop standards.

Kuchler

See PowerPoint presentation

Mendes

The Mendes, Shulaev and Laubenbacher groups at the Virginia Bioinformatics Institute are part of a collaborative Yeast Systems Biology project, funded by the NIH. This project's aim is to develop a novel approach to modeling biological systems with a combined discrete and contiuous top-down approach. At the same time the team is investigating the response of *S. cerevisiea* to oxidative stress. The experiments, run in the Shulaev lab, consist of the application of a toxic dose of cumene hydroperoxide to yeast cultures in controlled batch conditions (pH 6, 30^{o} C, dissolved oxygen above 90%). Experiments are run in triplicate, with controls, and several deletion mutants are studied. The data consists of time courses of absolute or relative levels of mRNA, proteins and metabolites, during the first two hours after elicitation. RNA analyses are carried out with Affymetrix, proteins with 2D-gels and MALDI-TOF, and metabolites with a series of techniques: GC-MS and CE-MS in untargeted modes, and LC-MS targeted for a number of metabolites using a triple-quad mass spectrometer (which provides quantitative results). Importantly, all the analyses are carried out from a single sample, so that the three data types are comparable.

To reconstruct the underlying dynamics of a time series assuming continuous time, the Mendes group uses a linear dynamics approximation. A method is being developed to reconstruct a qualitative version of the Jacobian matrix from a minimal set of time series data, which reveals the pairs of molecules that do *not* interact. This is very important since it reduces the dimensionality of the problem drastically (most known systems have sparse Jacobians). A second stage uses least-squares methods to fit a set of differential equations to the time series data, producing a quantitative model of the system.

The second modeling approach (Laubenbacher group) simplifies the system further by categorizing the data, resulting in a time-discrete dynamical system with a finite state set. This is chosen in a way to support standard arithmetic (modular arithmetic) and then the system can be described via polynomial functions. We are then in a position to bring to bear the power of the well-developed machinery of computational polynomial algebra. It allows us to study the whole space of models consistent with the given data, and we have developed methods for model selection that work particularly well with the mutant data to be collected for this project. The results obtained from this modeling approach are then combined with the ODE models described above.

This interdisciplinary team is interested in the using Systems Biology approaches to oxidative stress response, sulfur assimilation, and associated phenomena in *Saccharomyces cerevisiae*. We are also intersted in applying our modeling methods to any other yeast Systems Biology studies.

Nielsen

Center for Microbial Biotechnology focuses on the development of novel cell factories for the production of chemicals through biotechnology. In connection with this it is essential to have a detailed insight into the function of cell factories, and within the center there is therefore a substantial interest in systems biology. Systems biology research activities within the center encompass:

- **Metabolome analysis**. CMB has several LC-MS and GC-MS systems, and the center is developing new methods for high-throughput analysis of specific metabolites. There have recently been developed a new GC-MS method for analysis of 80 metabolites of

the central carbon metabolism, and there is currently work ongoing on using LC-MS for high-througput profiling *S. cerevisiae*.

- **Transcription analysis**. CMB is performing transcription analysis, using the Affymetrix system, for yeast growing at well controlled conditions. A substantial database of transcriptional profiles at these conditions is currently being established. This includes data generated at TUD (by the group of Jack Pronk). Hereby we will have data on many different carbon sources, different nitrogen sources, different D-values in chemostat cultures for CEN.PK113. We also have data for several deletion mutants, particularly of genes involved in glucose repression.
- **Bioinformatics algorithms**. CMB is developing novel algorithms for extracting information about co-regulation of genes. These algorithms involve new clustering methods that enables analysis of data series (D-value series or time series) or methods using structural information, e.g. provided by metabolic models. Some of these algorithms have shown to identify completely new patterns in transcriptional data, and in the context of systems biology this will be important for model reduction.
- **Modelling of transcriptional pathways**. Current CMB is working on reconstructing signal transduction pathways based on protein-protein interaction data. These maps may be used to construct models that can simulate dynamic responses, and so far different model approaches have been evaluated (stochastic versus mechanistic).

Novak

Systems biology of the yeast cell cycle engine, Béla Novák[1] and John J. Tyson[2]

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1111 Budapest, Gellért tér 4, Hungary

[2] Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, VA 24061, USA

One goal of systems biology is to obtain an integrated understanding of the physiological properties of cells from the detailed molecular machinery (the genes, proteins and metabolites) that carry out these functions. Cell cycle regulation in yeast is an appropriate test case for this ambition, because the scientific community has amassed much information about the molecular components and functional properties of the control system. The major events of the cell cycle (DNA synthesis, mitosis and cell division) are regulated (activated and inhibited) by cyclin-dependent kinases. The activity of Cdk's is regulated by cyclin proteolysis, by binding of stoichiometric inhibitor and by enzymatic modifications. All of the processes and the underlying proteins that influence Cdk activity, are regulated (directly or indirectly) by Cdk's, thereby creating feedback loops (positive ad negative ones) in the mechanisms. These regulatory mechanisms can be translated into differential-algebraic equations, which contain many kinetic rate constants. Although most of these rate constants have never been measured directly, parameter estimation is still possible, because we have a huge amount of quantitative and qualitative information about the control system. Yeast geneticists have mutated, deleted and overexpressed most of the genes involved in cell cycle control and the physiological characteristics of these mutants (cell size, cell cycle phases etc.) can be used indirectly to estimate the values of rate constants. After parameterization we study solutions of these equations by one-parameter bifurcation diagrams where we use cell

mass as bifurcation parameter. The general characteristics of this bifurcation diagram are consistent with all the features of the yeast cell cycle controls.

Selected reviews:

Tyson, J.J., Csikász-Nagy A. & Novák B. (2002). The dynamics of cell cycle regulation. Bioessays, 24, 1095-1109.

Tyson, J.J., Chen, K. & Novák B. (2001). Network dynamics and cell physiology. Nature Rev. Mol. Cell Biol. 2, 908-916.

Oresic/Penttilä

VTT Biotechnology has a long tradition in yeast molecular biology and genetics, with primary interest in metabolic engineering applications. The institute has already started two complementary yeast systems biology programmes, funded by Academy of Finland and National Technology Agency Tekes, respectively.

The yeast systems biology platform at VTT Biotechnology includes technologies for proteomics (gel based, LC/MS based, Maldi-ToF for identification, phsophoproteomics), transcriptional profiling (Affymetrix, TRAC), metabolomics (LC/MS, GC/MS, NMR), and physiology measurements and control. The bioinformatics system is set up on native XML server, enabling easy integration of experimental data and external bioinformatics resources. Modelling efforts are starting.

The primary research interest is studies of physiological responses of yeast to a variety of environmental and genetic interventions. In regards to the Yeast Systems Biology Network, we have strong interest in:

1. Data standards, particularly development of new standards for metabolomics
2. Modelling efforts, particularly integrative approaches for predictive modelling of cell physiology

In particular, we could contribute to YSBN the following expertise:

1. Metabolomics (experimental, algorithms for data processing and analysis, databases)
2. Bioinformatics (data integration and standard development)
3. Modelling (approaches based on non-equilibrium physics)

Philippsen

EVOLUTION OF CELL CYCLE AND GROWTH CONTROLS IN YEASTS

Peter Philippsen, Applied Microbiology, Biozentrum, University of Basel, Switzerland

S.cerevisiae is a unicellular ascomycete which grows by budding and cell separation. A. gossypii is a filamentous ascomycete which exclusively grows by tip extension of multinucleated hyphal and lateral as well as tip branching. Despite these differences in life style the genomes of both organisms revealed a surprisingly high level of gene order conservation (synteny). For 95 % of the 4720 A. gossypii ORFs we found homologues in S. cerevisiae. Both ascomycetes diverged prior to the duplication of the S. cerevisiae genome. Despite the over 4000 gene deletions and 300 genome rearrangement following the duplication, synteny relations could be reconstructed because of the low level of genome rearrangements in the A. gossypii lineage. Always two S. cerevisiae chromosomal regions

align with short or long A. gossypii regions. This double synteny pattern covers 95 % of the A. gossypii genome and reveals sites of former gene deletions and genome rearrangements.

In the context of Yeast Systems Biology it is a challenging question whether present and future mathematical models of cell cycle control and polar growth control developed for S. cerevisiae can be applied to the filamentous growth of A. gossypii including asynchronous mitoses. Both ascomycetes have a common ancestor (yeast-like growth or filamentous growth?) and A. gossypii carries syntenic homologues for all S. cerevisiae genes controlling cell cycle and polar growth. We hypothesize that evolutionary differences in wiring of key components due to alterations of protein domains or expression signals rather than differences in gene contents lead to the life styles of S. cerevisiae and A. gossypii. Thus, in silico evolution of S. cerevisiae models can potentially yield models applicable to A. gossypii.

Reuss

The yeast biology group at Stuttgart addresses important issues within the two complementary and strongly interconnected approaches of systems biology: (1) The bottum up, knowledge driven inductive procedure in which biological knowledge about components and their interactions, modulations etc. are aggregated to functional modules. The modules are then interconnected to architectures suitable for holistic analysis. (2) The data driven, top down deductive approach by applying inverse engineering strategies to the huge quantities of experimental data to eventually extract the biological knowledge about topology and behaviour of large scale networks. Activities are focussing at toplogical analysis of metabolic, regulatory and signaling large scale networks and dynamic modeling and simulations of small as well as large scale networks.The approach in Stuttgart is characterized by stronk links between experimental and simulation work. Since the beginning of the ninties the stimulus response methodology is pursued. This approach is based on environmental instead of genetic perturbation and experimental observation of the intracellular response in various state variables such as metabolites. Recent activities focus on problems of linking modules of the energy and carbon metabolismus like glycolysis, pentose-phosphate shunt, TCA and respiration with the progression of the cell cycle. This work addresses the important question of understanding and modeling the different energy demand and supply during the progression of the cell cycle. As such, the horizon is widened to modeling problems of the lifelines of individual cells. Again the strong link between experimental observations and modeling is sustained by measuring metabolites and signal substances during the cell cycle (synchronous cultures). A comprehensive mathematical model of these processes has been developed, which aims at capturing the dynamics of the cAMP-PKA signal transduction cascade during the cell cycle as well as that of central metabolism and the cell cycle machinery itself.

Sauer

Genome-wide analyses of mRNA, protein, or metabolite complements of biological systems produce unprecedented loads of static data on cellular network composition. As the functional output of the complex biochemical and regulatory interactions between these metabolic network components, in vivo molecular fluxes through a network link genes and proteins to higher-level functions. Intracellular fluxes thus are key quantities for systems biology. Beyond detailed interrogation of network operation in few particular conditions/mutants, steady state fluxes become now tractable at a higher throughput due to recent advances in analytical accuracy and sensitivity, mathematical frameworks, and experimental design

(Fischer et al., 2004; Sauer, 2004). Accumulating data on flux responses to hundreds of genetic or environmental changes start to reveal new pathways (Fischer and Sauer, 2003; Gunnarsson et al., 2004) and modes of network operation (Blank and Sauer, 2004) but also general design principles and system properties of metabolic network operation (Sauer et al., 2004).

Blank, L. M., and U. Sauer, 2004, TCA cycle activity in Saccharomyces cerevisiae is a function of the environmentally determined specific growth and glucose uptake rate: Microbiology, v. 150, p. 1085-1093.

Fischer, E., and U. Sauer, 2003, A novel metabolic cycle catalyzes glucose oxidation and anaplerosis in hungry Escherichia coli: J. Biol. Chem., v. 278, p. 46446-46451.

Fischer, E., N. Zamboni, and U. Sauer, 2004, High-throughput metabolic flux analysis based on gas chromatography-mass spectrometry derived 13C constraints: Anal. Biochem., v. 325, p. 308-316.

Gunnarsson, N., U. H. Mortensen, M. Sosio, and J. Nielsen, 2004, Identification of the Entner-Doudoroff pathway in an antibiotic-producing actinomycete species: Mol. Microbiol., v. 52, p. 895-902.

Sauer, U., 2004, High-throughput phenomics: experimental methods for mapping fluxomes: Curr. Opin. Biotechnol., v. 15, p. 58-63.

Sauer, U., F. Canonaco, S. Heri, A. Perrenoud, and E. Fischer, 2004, The soluble and membrane-bound transhydrogenases UdhA and PntAB have divergent functions in NADPH metabolism of Escherichia coli: J. Biol. Chem., v. 279, p. 6613-6619.

Wernersson/Brunak

About The Center for Biological Sequence Analysis (slides 1-3):

The Center for Biological Sequence Analysis (CBS) at the Technical University of Denmark was formed in 1993, and conducts basic research in the field of bioinformatics and systems biology. The group of +50 scientists, working in six specialist research groups, has a highly multi-disciplinary profile (molecular biologists, biochemists, medical doctors, physicists and computer scientists) with a ratio of 2:1 of bio-to-nonbio backgrounds. CBS represents one of the large bioinformatics groups in academia in Europe.

In the last decade, CBS has produced a large number of computational methods, which are offered to others via WWW servers [www.cbs.dtu.dk/services].

Besides the computational effort CBS has it’s own lab facilities, which is specialized in gene expression and RNA handling using both Affymetrix and the Febit Geniom One platform.

Case story (slide 4):

I have chosen one of our ongoing studies of the Yeast cell cycle to illustrate how the different areas of expertise at CBS are working together. The slide shows a “feature wheel” depicting how different protein features is over/under represented during the yeast cell cycle.

Initially using existing data a neural network based prediction method was build for predicting cell cycle regulated genes using only protein features. Follow up array experiments (custom designed oligo array) where conducted using the suggested genes as a guideline. The plot shows the dynamics of proteome in feature space through out the cell cycle based on expression data from our experiments.

Possible contributions to the Yeast Systems Biology Network:

Protein and gene feature prediction. Integration of different kinds of data – both predicted and experimental. Advances array analysis (algorithm development).

Westerhoff

Jacky L. Snoep, Hans V. Westerhoff and (many) friends

Centre for Research on bioComplex Systems, BioCentrum Amsterdam, EU & Department Biochemistry, University of Stellenbosch, South Africa)

Systems Biology addresses the issue of how functional properties of biological systems arise in the interactions between system components. Because of the revolutionary progress in molecular biology and genomics, much of the present emphasis is on molecular systems biology, i.e. on how molecular interactions lead to the simplest complete forms of life, i.e. autonomous living cells. The methodology of Systems Biology comprises quantitative experimentation and mathematical modeling and analysis, and is still under development. A single model system at which a number of teams of systems biologists collaborate should be a great asset also for the systems biology of all other organisms including man. *S. cerevisiae* may well be the best candidate for such a model system. We illustrate our possible contribution to a corresponding network below.

Important of course is precision, and therefore quantitative experimentation. Probably all molecule-types are always present in living cells; the issue is not whether they are present but at which levels. The analytic (top-down) approach to Systems Biology is valuable vis-à-vis the massive amounts of genomics data that need to be classified and interpreted. It has led to improved diagnosis, and to our FANCY approach to gene-function identification in yeast. The analytic approach does not usually lead to understanding of how system properties arise in interactions. Therefore we here illustrate the other, integrative (bottom up) approach. This may not only discover mechanisms but also new principles, 'laws' of systems biology. Principles or laws include the ones that address control and regulation. Vis-a-vis yeast glycolytic oscillations for instance the sum of the control exerted by each individual enzyme on the frequency must equal 1. The decrease in glycolytic capacity upon starvation, may be be metabolically regulated or by gene expression, but the total of the corresponding regulatory coefficients must equal 1.

Perhaps the ultimate systems biology is a computer replica of a living organism in which the response of the organism to various challenges can be calculated. The silicon cell initiative (cf. www.silioncell.net) with its European hub http://www.jjj.bio.vu.nl through which everyone can experiment *in silico* with a number of pathways, is putting replica together of pathways in living cells. We propose that this strategy will also be used for the Yeast Systems Biology Network.

Annex II: Individual PowerPoint presentations (pdf file on request)

Annex III: White Paper (version May 2004)