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Welcome Address

The "Berlin Summer Meeting" is an annual 2-3 days meeting at the interface of experimental molecular biology and computational approaches.

It is designed to create an intense and open atmosphere, aiming at stimulating productive interactions between various branches of biology and bringing together leading scientists and young researchers.

The inaugural meeting in 2008 will be devoted to Systems Biology. Systems Biology is a disperse and newly emerging research area. This meeting will focus on approaches that seem especially promising to elucidate biological function.

The organizing committee for 2008 consists of

Prof. Nikolaus Rajewsky (MDC -Berlin)

Prof. Hermann-Georg Holzhütter (University Medicine Berlin, Charité)

Prof. Dimitris Thanos (Biomedical Research Foundation, Academy of Athens, Greece)

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Speaker Abstracts

Invited speakers abstracts in alphabetical order

SYSTEMS BIOLOGY: NETWORK OF NETWORKS

Ruedi Aebersold

Institute of Molecular Systems Biology, ETH Zurich; Faculty of Science, University of Zurich, Switzerland and the Institute for Systems Biology, Seattle, USA

At a molecular level biological systems such as cell signaling or metabolism can be represented as dynamic networks of interacting molecules. In the living cell multiple such networks are concurrently present and active. These include the gene regulatory (transcriptional) networks, protein interaction networks, networks of enzymes and their substrates (e.g. protein kinase-substrate networks), networks of microRNA and their substrates etc. Notably, most of these types of networks consist of or involve proteins. Therefore, the systematic analysis of the proteins that constitute a biological system and the networks they constitute is a central theme of the emerging field of systems biology.

Mass spectrometry is the most widely used method for the analysis of proteins and proteomes. In this presentation we will discuss new mass spectrometry based technologies for the analysis of different types of cellular networks and their dynamic change as a function of cellular state. These include protein interaction networks, networks of concurrently regulated proteins and networks of protein kinases and their substrates. Selected applications will illustrate the current status of these new technologies.

GLOBAL PATTERNS IN CONDITION- AND TISSUE-SPECIFIC RNA PROCESSING

Chris Burge

Department of Biology, Massachusetts Institute of Technology, Cambridge, MA

Expression of alternative mRNA isoforms increases the regulatory and protein-coding potential of the genome. We are exploring changes in global alternative mRNA isoform expression between tissues and conditions using technologies that assess expression of individual exons genome-wide. These studies have uncovered a number of global patterns in alternative RNA processing regulation. One such pattern is a conserved program of increased expression of mRNAs derived from upstream polyadenylation sites (PAS) following activation of primary murine CD4⁺ T lymphocytes. This program, resulting in shorter 3' UTRs and very often affecting protein expression, is a characteristic of immune cell activation and strongly correlates with proliferation across diverse cell types and tissues. In collaboration with Gary Schroth (Illumina Inc.), we have performed deep sequencing of polyA⁺ mRNA isolated from a panel of 9 normal human tissues and 5 cell lines using the Solexa/Illumina platform and analyzed the ~300 million 32 base pair-long reads obtained. Comparing isoform-specific read densities between tissues allowed identification of thousands of tissue-specific alternative RNA processing events and indicates that a majority of such events are tissue-regulated. Global patterns in tissue-biased isoform usage were also observed. For example, tissues which exhibit increased inclusion of skipped exons also exhibit decreased intron retention and decreased usage of alternative 3' and 5' splice sites. These studies underscore the ubiquity of regulated RNA processing and suggest a high degree of coordination of RNA processing regulation.

SYSTEM LEVEL GENOMIC REGULATORY LOGIC: GENE NETWORK FOR SEA URCHIN DEVELOPMENT

Eric Davidson

Caltech Pasadena, USA

If the premise of system biology is correct then causal explanations of biological phenomena should emerge from system level analyses if they approach completeness in respect to the functional linkages among the parts of the model. The developmental GRN controlling development of the skeletogenic micromere lineage of the sea urchin embryo now includes experimentally established, causal transcriptional links to every regulatory gene expressed specifically in this lineage. It provides the opportunity to challenge directly this argument. We show that at its current level of maturity its structure provides an explanation in terms, of the genomic regulatory system, why all of the functions this lineage executes occur. These functions are: transformation of the initial maternal cues localized in the micromeres into an initial transcriptional regulatory state; activation of downstream genes through a double negative transcriptional gate; presentation of inductive signals to adjacent cells; dynamic lockdown of the definitive transcriptional regulatory state; specific activation of skeletogenic differentiation gene batteries; exclusion of alternative regulatory states. Though the remainder is not as mature, novel technologies have enabled extension of GRN analysis to the oral and aboral ectoderm as well as the whole of the endomesoderm up to gastrulation, and we can look forward to a global GRN for the embryogenesis of this organism. The GRN provides a new way to understand evolution as well as development. For example, the skeletogenic function of the micromere lineage is a derived feature of modern echinoderms that probably arose in the Triassic <250 mya. By mapping onto the topology of the GRN the genes expressed and not expressed in adult skeletogenic centers, we can discern the regulatory linkages that had to be formulated in order to co-opt skeletogenic genetic function to the micromere embryological address. This idea is subject to experimental test.

Transient Differentiation at the Single-cell level

Elowitz, Michael

Caltech Pasadena, USA

Abstract: How do cells make random decisions about whether and when to differentiate? And once they do decide, how do they ensure that differentiation proceeds in an orderly fashion? Both questions hinge on the ability of genetic circuits to manage fluctuations, or noise, within their own components. Noise enables genetically identical cells to make different decisions in the same environment, effectively "rolling the dice." Recently, we have begun to use *Bacillus subtilis* as a model organism to address these questions. In *B. subtilis*, competence is a transient differentiated state in which cells can take up extracellular DNA. The decision to become competent is probabilistic and occurs in at most 10-20% of cells. Using time-lapse fluorescence microscopy movies, we analyzed the dynamics of the genetic circuit controlling competence at the single-cell level. Our results suggest that entry into competence and subsequent exit from it are controlled together by a core module of three genes which generate noise-excitable dynamics in a cell-autonomous fashion. (An excitable system, such as a neuron, is one in which a small perturbation can generate a well-defined response, such as an action potential). Thus, cells can regulate the probability of competence much as a neural system can control the firing rate of action potentials. By re-wiring the circuit, systematically perturbing the basal expression levels of key genes, and reducing global noise levels, we have analyzed quantitative and qualitative plasticity in the circuit. We have also developed a stochastic model of the underlying circuitry that can explain observed behaviors. Together these results show how a cell fate decision system can be understood quantitatively at the single-cell level, and provide a framework for tackling analogous phenomena at other levels of biological organization.

Evolution of bacterial regulatory systems

Mikhail S. Gelfand

Institute for Information Transmisison Problems (the A.A.Kharkevich Institute) RAS

Hundreds of available complete genomes of bacteria make it possible to perform rather detailed comparative genomic studies of regulation even in the absence of high-quality experimental data. Of specific interest in this context is the evolution of regulatory systems. Some recent studies in our lab include:

- (i) regulon dynamics of the LacI family of transcription factor (regulon expansion transforming local regulators into global ones, merging and separation of regulons, change and duplication of transcription factors, etc.);
- (ii) co-evolution of transcription factors from the LacI family and the motifs they recognize in DNA;
- (iii) evolutionary history of the iron-and manganese-dependent regulation in alpha-proteobacteria (changes of regulator specificity and emergence of new regulators leading to complete re-wiring of regulatory interactions);
- (iv) complete description of T-box RNA-level regulation (changes of specificity, lineage of expansion caused by loss of other regulators, new structural and functional classes of T-boxes).

Mapping molecular networks in development: a view from the 3'UTR end

Kris Gunsalus

NYU

The processes through which organisms develop from a fertilized egg to a mature adult involve many layers of coordinated regulation at a molecular level. The importance of post-transcriptional regulation has gained increased attention as an important component of developmental control. In metazoans, much of this control is exerted through the 3'UTR of protein-coding mRNAs, but the regulatory regions within them remain comparatively poorly characterized. Toward the goal of obtaining a better global appreciation of this layer of regulation, we are characterizing 3'UTR isoforms in different stages of development in *C. elegans*. We find that 3'UTR composition varies much more than previously recognized, increasing the combinatorial potential for regulatory interactions through the 3'UTR during development. To complement this effort we are constructing interactive tools to visualize data on 3'UTR isoforms and potential trans-acting factors (utrome.org), and to dynamically integrate these in the context of multidimensional molecular interaction networks (gnetbrowse.org).

Systems biology of the mammalian circadian clock

Hanspeter Herzel

Institute for Theoretical Biology, Berlin

Negative feedback loops regulating clock genes such as *Per2*, *Bmal1* and cryptochromes (*Cry1*, *Cry2*) constitute the molecular basis of endogenous oscillations with a period of about 24 h. About 20,000 synchronized neurons in the suprachiasmatic nucleus (SCN) control daily rhythms of physiology, metabolism, and behaviour. We show that mathematical modelling contributes to an understanding of the complex temporal organization at the levels of single cells, the synchronization of neurons, and the entrainment of organismic rhythms.

Experiments using a luciferase reporter reveal that the interference with *Per2* phosphorylation or the modulation of proteasomal degradation via β -TrCP1 can lead to decreased or increased periods and to damping of the oscillations. Modelling the effects of multisite phosphorylation on degradation and nuclear export explained the observed phenotypes and lead to predictions which were confirmed experimentally [1,2].

Even though the 20,000 SCN neurons exhibit variable internal periods and phases they synchronize in a robust manner with short transients after perturbations such as jet lag. Simulations of coupled neurons show that this can be achieved if neurotransmitters such as VIP play a dual role: they induce self-sustained oscillations at the single cell level via a positive feedback and serve at the same time as coupling agent [3].

We perform a meta-analysis of DNA-array data from rodent tissues and search in the promoter regions of 2065 clock controlled genes for high-scoring transcription factor binding sites. We find that most of the transcription factors with overrepresented binding sites exhibit themselves circadian rhythms. Among the predicted factors are known regulators such as *BMAL1*, *VBP*, *HLF*, *E4BP4*, *CREB*, *RORa* and the recently described regulators *HSF1*, *STAT3* and *HNF4a*. We find additional promising candidates of circadian transcriptional regulators significantly overrepresented in promoter regions of clock controlled genes.

Finally we show by combining experiments with human skin fibroblasts with mathematical modelling that the intrinsic period, oscillation amplitude, and the light input strength determine the entrainment phase in patients with extreme chronotypes [4].

[1] K. Vanselow et al. (2006) *Genes and Development* 20, 2660-2672.

[2] S. Reischl et al. (2007) *J. Biol. Rhythms* 22, 375-386.

[3] S. Bernard et al. (2007) *PLoS Comp. Biol.* 3, e68.

[4] S. Brown et al. (2008) *Proc. Nat. Acad. Sci. USA*, 105, 1602-1607.

Genome wide variation in mutation rates

Greg Lang, Andrew Murray

Harvard Cambridge, USA

We measured the geographic variation in mutation rate by placing the URA3 gene at multiple locations on budding yeast chromosome VI. We find a strong variation in mutation rate that correlates with the timing of DNA replication and propose that this arises because bulky DNA lesions can be replicated in two ways: by strand switching which produces a non-mutated newly synthesized strand and by error prone DNA polymerases that replicate past the lesion but make mutations as they do so. Because error prone synthesis is activated late in S phase, late replicating regions have less time to do strand switching and are thus more likely to produce mutations. Comparing different isolates of *S. cerevisiae* reveals that the density of single nucleotide polymorphisms (SNPs) correlates with the timing of replication, but comparing synonymous SNPs between *S. cerevisiae* and *S. paradoxus* doesn't reveal such a correlation suggesting that replication origins move rapidly during genome evolution.

Towards a systems view of early embryogenesis in *C. elegans* and related species

Fabio Piano

NYU

Fertilization unites two specialized cells, egg and sperm, and activates a coordinated cascade of events to build an embryo. The global mechanisms underlying processes that guide the transition from oocyte to early embryo remain largely mysterious. What is known points to largely post-transcriptional and post-translational regulatory mechanisms derived mostly from tackling each part of the problem such as fertilization, cell cycle progression, establishing polarity, and cytokinesis as separate programs. Yet, we know these are exquisitely coordinated. Combining global functional approaches has revealed a first-draft global map of the molecular networks underlying early embryogenesis in *C. elegans*. We have used this map as a launching point to address three areas: identifying key new regulators that bridge different embryonic processes, tackling how early embryogenesis evolves, and to build a global genetic interaction map. These studies have implications not only to understand the function of uncharacterized proteins but also on how a system is built and how it evolves.

Transcription factor affinity prediction: methods, statistics, and delineation of tissue specific binding sites

Martin Vingron

MPI for Molecular Genetics, Berlin

In this talk we review a biophysical method for prediction of transcription factor affinity to binding sites on the DNA. The affinity prediction is calibrated to reproduce ChIP-chip values where these are available, while also allowing for prediction solely based on a weight matrix description of a binding site. Recently, we also computed statistics for the significance of the affinity values, which allows comparing predicted binding behavior of different factors. Further, we computed tissue specific transcription factors by analyzing promoters from sets of tissue specific genes. Results confirm established knowledge and provide several new predictions.

The first protein interaction networks for human in health and disease

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In 2002, we have started to develop high-throughput technologies for the systematic identification of human protein-protein interactions. We have automated the yeast two hybrid system, establishing a unit of picking and spotting robots as well as a human cDNA library that contains more than 20,000 clones. In a first application, we have created a protein interaction network for Huntington's disease, a fatal neurodegenerative illness, identifying an important modulator of disease progression among more than 180 interactions with the disease protein. Upscaling the concept, we constructed the first genome wide human protein interaction network ever from a screening of 25 million protein pairs. Finally, we developed a database to make interaction network datasets easily accessible to the scientific community. This database serves biomedical researchers around the globe as a highly valuable tool for the study of human protein pathways. However, currently available human interaction data are static and incomplete and do not provide immediate clues about the cellular processes that convert genetic information into complex phenotypes. Integration of interaction data with other qualitative and quantitative information, *e.g.* protein expression or localization data, are therefore required to construct networks of protein function that reflect dynamic processes in the cell. In this way, we have combined PPI networks with gene expression data and generated tissue specific disease networks that were utilized as tools for the identification of disease modulators.

Using Transcriptional Networks in Model Systems to Identify Determinants of Disease

Kevin P. White, Ph.D.

Director, Institute for Genomics & Systems Biology

James and Karen Frank Family Professor, Department of Human Genetics and Ecology & Evolution

Pritzker Fellow, The University of Chicago Biological Sciences Division and Pritzker School of Medicine

IGSB Division Director, Argonne National Laboratory

Investigator, Chicago Biomedical Consortium

I will describe our recent work developing integrated genomic and gene functional analysis approaches to identify cancer biomarkers that can be coupled to drug development. Using a combination of gene expression, ChIP chip, large-scale protein interaction analysis, literature mining and computational modeling we have developed a prediction pipeline for high value candidate genes and proteins. I will describe one case from *Drosophila* and one using a model cancer cell line where we have gone from systems-level analysis, to genetic and biochemical validation, to clinical analysis, to drug development.

Poster Abstracts

P1 MiRseq: An R package to analyze the high-throughput small RNA libraries

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Small RNA guided gene silencing has emerged as an important way of gene regulation. Deep sequencing methods have been used to predict new miRNAs and novel small RNA classes, as well as to profile small RNA populations in several organisms. Those methods produce large amount of reads and they are suitable for multiplex sequencing. The analysis of the libraries is one of the most important steps and requires extensive computational methods to extract the useful information. There is no software package available for the primary analysis of multiplex libraries. Addressing this issue, we developed *miRSeq* as an R package to perform the primary processing and analysis of single and multiplexed small RNA libraries with a special focus on microRNA prediction.

P2 Evolution and function of circadian clock proteins: lessons from bacteria

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Organisms coordinate biological activities into daily cycles using an internal circadian clock. The simplest clock has been described for cyanobacteria where only 3 proteins are sufficient to generate 24-hour oscillations. KaiC, the principal protein of this biochemical oscillator, undergoes rhythmic autophosphorylation and dephosphorylation modulated by KaiA and KaiB. We used a mathematical approach to scan different hypothetical mechanisms for the 3-protein oscillator, starting from experimentally established molecular properties of the clock proteins.

Only one *in silico* reaction network was able to reproduce the experimentally found high amplitude and robustness against perturbations.

Here, a negative feedback synchronizes the phosphorylation level of the individual hexamers and has indeed been realized in *Synechococcus* by KaiA sequestration as confirmed by experiments. Surprisingly, related marine cyanobacteria of the genus *Prochlorococcus* lost the *kaiA* gene by genome reduction. Our recent experiments indicate that the 2 remaining clock proteins of *Prochlorococcus*, KaiB and KaiC, are still functional. Although we did not observe autonomous circadian oscillations of the 2-protein system in a test tube, a minimized but functional clock is likely for the living *Prochlorococcus* cell.

P3 Accurate prediction of protein-protein interactions from sequence alignments using a Bayesian method¹

L. Burger and E. van Nimwegen

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Accurate and large-scale prediction of protein-protein interactions directly from amino acid sequences is one of the great challenges in computational biology. By making use of recent results in Bayesian network theory², we have developed a new algorithm that predicts interaction partners using only multiple alignments of amino acid sequences of interacting protein domains, without tunable parameters, and without the need for any training examples. We apply the method to bacterial two-component systems and comprehensively reconstruct two-component signaling networks across all sequenced bacteria. Comparisons of our predictions with known interactions show that our method infers interaction partners genome-wide with high accuracy. To demonstrate the general applicability of our method we show that it also accurately predicts interaction partners in a recent dataset of polyketide synthases. Analysis of the predicted two-component signaling networks shows that cognates (interacting kinase/regulator pairs which lie adjacent on the genome) and orphans (which lie isolated) form two relatively independent components of the signaling network in each genome. While most genes are predicted to have only a small number of interaction partners, we find that 10% of orphans form a separate class of 'hub' nodes that distribute and integrate signals to and from up to tens of different interaction partners.

¹ L Burger and E van Nimwegen (2008). *Molecular Systems Biology* 4:165.

² Meilá M and Jaakkola T (2006) Tractable Bayesian learning of tree belief networks. *Statistics Computing* 16: 77–92

P4 Disentangling molecular interaction networks for Chorea Huntington

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Chorea Huntington is a fatal neurodegenerative disease with late onset. Common symptoms are loss of motor control, cognitive decline, dementia and pathopsychological behaviour. The disease causing mutation – an CAG repeat expansion in a single gene named *huntingtin* (*htt*) - is well known and can be accurately diagnosed. Despite of intensive research, however, no cure for this devastating disease has been found yet.

Although Chorea Huntington is a classical Mendelian disease following dominant inheritance pattern, strong inter-individual variability in the disease progression suggests the existence of biological modifiers which could provide novel therapeutical targets. A further important feature of Huntington's disease (HD) is the observation of a various molecular changes such as formation of aggregates, excitotoxicity and dysregulation.

To detect novel disease modifiers and to consolidate the seemingly unrelated molecular changes observed, we constructed a *htt*-focused protein interaction network. Introducing a novel multi-level prioritization strategy based on complementary information, we were able to identify a set of potential modifiers. One of the identified modifiers, CRMP1, was subsequently experimentally validated as an important factor for aggregation, neurotoxicity and disease progression in HD models. Complementary to the analysis of the huntingtin neighbourhood, we also applied a global approach for the detection of dysregulated modules. This enabled us to reveal connections between distinct disease-related processes.

Our study demonstrates that not only the elucidation of complex diseases such as cancer but also of apparently 'simple' Mendelian diseases can tremendously profit from a network approach. The strategy proposed here can provide a general framework for the study of a wide class of human diseases.

References

1. H. Göhler et al. , (2004) A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington's disease, 15(6):853-65.
2. G. Chaurasia et al. (2007) UniHI: an entry gate to the human protein interactome, Nucleic Acids Research, Database issue, D590-4
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4. M.E. Futschik, G. Chaurasia and H. Herzel (2007) Comparison of Human Protein-Protein Interaction Maps, Bioinformatics, 23(5):605-611
5. M. E. Futschik et al. (2007) Functional and Transcriptional Coherency of Modules in the Human Protein Interaction Network, Journal of Integrative Bioinformatics, 4(3):76

P5 miRDeep: Discovering miRNAs from deep sequencing data

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Any attempt to model interactions in a biological network must be preceded by an effort to identify the elements in the network. miRNAs are small non-coding RNAs that function in *trans* to regulate a large fraction of animal genes. We have developed miRDeep, a probabilistic algorithm that can discover novel miRNAs from deep sequencing data with high accuracy and robustness¹. Based on a simple model of miRNA biogenesis, miRDeep scores compatibility of the position and frequency of sequenced RNA with the secondary structure of the miRNA precursor. Using miRDeep, we have successfully identified miRNAs in the three main branches of the animal phylogenetic tree, analyzing output from both Solexa/Illumina and 454/Life Sciences sequencing platforms. So far, we have discovered ~300 novel animal miRNAs, many of which we have validated by northern blot analysis. We plan to sequence the miRNA transcript fraction of more than a dozen animals in order to outline the phylogenetic distribution of these regulatory elements in the vertebrate clade.

1 Friedländer M.R., Chen W., Adamidi C., Maaskola J., Einspanier R., Knespel S., Rajewsky N. (2008). Discovering microRNAs from deep sequencing data using miRDeep. *Nat Biotechnol.* 26(4):407-15

P6 Partner discrimination in yeast mating

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Yeast cells exist in two haploid types, **a** and **α**, which can fuse to form diploids. The two mating types sense each others presence by reciprocal sets of pheromones and G-protein coupled receptors. The process of mating involves three steps downstream of pheromone-binding: detecting spatial pheromone gradients, polarized cell growth, and cell fusion.

Mating type **a** cells secrete an aspartyl protease (Bar1) that degrades and inactivates **α**-factor. **a** cells that lack Bar1 have been described as being supersensitive to **α**-factor-induced G1 arrest and exhibit mating difficulties, but even in the complete absence of the protease, the cells overcome the arrest, polarize and grow shmoos.

Past and present work from the group has shown that Bar1 is fundamental in gradient sensing and partner discrimination. We combine theoretical and experimental approaches to ask why yeast cells have evolved such an external desensitization mechanism and we are studying both the external and internal adaptation processes that lead to an appropriate **α**-factor concentration dependent response.

We find that degradation, both uniform and localized, can not only prevent saturation of the receptors but also help in partner discrimination.

P7 Using transcription factor binding site co-occurrence to predict regulatory regions

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Transcriptional regulation is known to be controlled by transcription factors (TFs) that form complexes with each other. Therefore binding sites for transcription factors (TFBSs) contained in these protein complexes often occur in proximity to each other. In this work we exploit this fact to identify TFs that are likely to interact with each other and to predict regulatory regions.

We annotate a set of non-redundant upstream regions of human genes with predicted transcription factor binding sites based on a representative set of vertebrate binding site motifs from the TRANSFAC database. We count co-occurring pairs of putative binding sites using a sliding window. Subsequently, significantly co-occurring pairs are identified using a log-odds score of observed and expected numbers of pairs of binding sites. To calculate the expected number of pairs we shuffle the TFBS labels and count pairs again repeatedly. Then we calculate the average number of co-occurrences. We assess the scoring procedure using known interactions of TFs from the TRANSFAC database. Scores for known combinations of TFs get significantly higher co-occurrence scores than combinations not known to interact. Furthermore we show pairs of TFs with high co-occurrence scores.

Using predicted TFBSs and the co-occurrence scores shown above we construct TFBS-graphs, on which we calculate scores for the regulatory potential subsequently. The methods used include different ways of matching on the graph. We demonstrate the application of the methods on known regulatory regions. Comparison of maximum scores achieved for sets of known regulatory regions with the respective scores of random intergenic regions and artificial sets based on a permutation procedure shows the functioning of the procedures.

References

1. Klein, H., and Vingron, M., (2007), Using Transcription Factor Binding Site Co-Occurrence to Predict Regulatory Regions, *Genome Informatics*, Vol. 18, 109-118.

P8 Evaluation of a mathematical model of the sea urchin endomesoderm network using random parameters

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Limited experimental data is the main bottleneck in creating detailed dynamical models of cellular processes. This holds true for the Endomesoderm Gene Regulatory Network¹, which combines the accumulated knowledge concerning specification and differentiation of endoderm and mesoderm cells in the sea urchin embryo. The underlying data is too sparse to fully parameterize an ODE model. Therefore, we developed a method to evaluate dynamic properties determined by the model topology in spite of sparse data. We simulated the behaviour using randomly sampled parameter sets and compared the results to experimental data. The predictive power of this approach is judged by comparison to randomized network topologies.

We developed a mathematical model that describes the Endomesoderm Gene Regulatory Network on the molecular level². This model was simulated under normal and perturbed conditions as outlined above. While the simulations under normal condition indicate general parameter sensitivities for all components of the network, the differences between normal and perturbed conditions show robust topological features of the network. Nearly half (42%) of these features correspond with experimental data, a significantly greater value than the 23% observed in comparison between randomized versions of the network and experimental data.

The method described in this paper enables the simultaneous detection of robustness to parameter variations and evaluation of the network topology without requiring any parameter values. The benefit of this method is exemplified in the evaluation of the dynamic behaviour of the Endomesoderm Network Model.

References

1. Davidson, E.H. et al., A Genomic Regulatory Network for Development. *Science* 295 (5560): 1669-1678, 2002
2. Kühn, C. et al., Evaluation of Large Developmental Gene Regulatory Networks Using Random Parameters: Encompassing Data Limitations in the Sea Urchin Endomesoderm Network, submitted

P9 An Entropic Characterisation of Biological Networks

Thomas Manke, Lloyd Demetrius and Martin Vingron

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The structure of biological networks is often believed to determine important aspects of their functional and dynamic behaviour, such as their resilience against fluctuations in the operational parameters. One of us (LD) has recently introduced a quantity, called network entropy, as a measure to characterize the diversity of pathways and parameters in a network. The importance of this measure rests on a fluctuation theorem which states that changes in network entropy are positively correlated with changes in network robustness.

Here I present numerical studies to explore the relationship of network entropy with several other measures of network resilience. The entropic formalism also suggests a novel method to rank network elements according to their relative contribution to network entropy and their perceived importance for robust network function. I will present studies on real biological networks which suggest that entropy-based measures provide a better descriptor of biological importance than other heuristic measures, such as node degree.

P10 Universal patterns of purifying selection at non-coding positions in bacteria^[1]

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To investigate the dependence of the number of regulatory sites per intergenic region on genome size, we developed a new method for detecting purifying selection at non-coding positions in clades of related bacterial genomes. We comprehensively quantified evidence of purifying selection at non-coding positions across bacteria and found several striking universal patterns. Consistent with selection acting at transcriptional regulatory elements near the transcription start, we find a universal positional profile of selection with respect to gene starts and ends, showing most evidence of selection immediately upstream and least immediately downstream from genes. A further set of universal features indicates that selection for translation initiation efficiency is the major determinant of the sequence composition around translation start in all clades. In addition to a peak in selection at ribosomal binding sites, the region immediately around translation start shows a universal pattern of high adenine frequency, significant selection at silent positions, and avoidance of RNA secondary structure. Surprisingly, although the number of transcription factors (TF) increases quadratically with genome size, we present several lines of evidence that small and large genomes have the same average number of regulatory sites per intergenic region. By comparing the sequence diversity of the most and least conserved DNA words in intergenic regions across clades we provide evidence that the structure of transcription regulatory networks changes dramatically with genome size: Small genomes have a small number of TFs with a large number of target sites, whereas large genomes have a large number of TFs with a small number of target sites each.

[1] Nacho Molina and Erik van Nimwegen (2007). Universal patterns of purifying selection at non-coding positions in bacteria. 18(1) 148-160. *Genome Research*.

P11 Using drug combinations to construct regulatory models for signaling in cancer cells

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We present a computational method to analyze and predict how combinations of perturbations, such as drugs or genetic changes, act on a cellular system to affect phenotypes. The method builds network models of interacting molecules and processes, represented by non-linear differential equations in which the aggregate influence on the time derivative of a network node is bounded by sigmoid transfer functions. Network connections and interaction parameters in each model are optimized using two criteria, simplicity of model structure and optimal agreement of model predictions with experimental observation. We evaluate the predictive potential of the method for a set of drug-drug treatment experiments in the human breast cancer cell line (MCF7) with observation of levels of phosphorylated proteins and markers of phenotypic outcomes. The best network model for the propagation of perturbations in MCF7 cell lines rediscovers known regulatory pathway couplings and adds concrete predictions. The method may be applicable to network pharmacology (design of targeted combination therapies), cell biology (discovery or 'reverse engineering' of regulatory interactions and network principles) and synthetic biology (validating the effects of engineered modifications).

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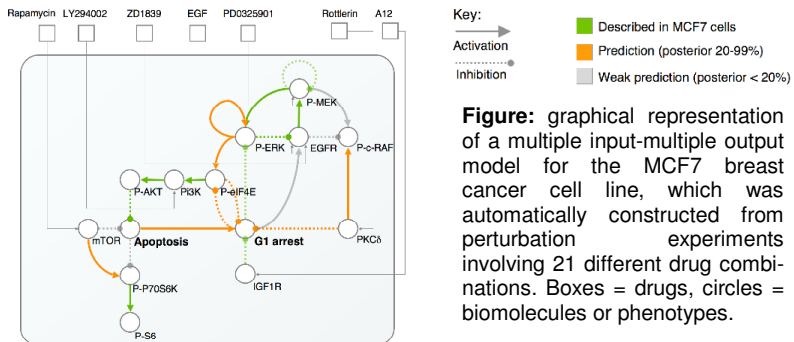


Figure: graphical representation of a multiple input-multiple output model for the MCF7 breast cancer cell line, which was automatically constructed from perturbation experiments involving 21 different drug combinations. Boxes = drugs, circles = biomolecules or phenotypes.

P12 Multiplierz: an open-source, extensible desktop environment for proteomics data analysis

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We present multiplierz, a novel and open-source software for mass spectrometry-based proteomics data analysis. Multiplierz acts as an integrated desktop environment by providing most tools required in a proteomics pipeline. A few proteomics integrated environments exist, most notably the Trans Proteomic Pipeline (TPP). However, multiplierz stands out in its extensibility and ease of use, making it ideal not only for integration into pipelines but also as a stand alone exploratory tool. We leverage existing commercial applications such as Microsoft Excel to generate image-enhanced spreadsheets that serve as information rich reports as well as easily alterable input sources. We have extended multiplierz to interact with OpenOffice.org Calc and are in the process of making multiplierz truly multi-platform software. We have used multiplierz to analyze data from various projects involving signaling downstream of oncogenic kinases, novel differentiation pathways in embryonic stem cells, and remodeling protein complexes. We demonstrate various features of multiplierz commonly used in such projects, including: (i) comparative analysis of protein abundance based on both stable isotope label and label-free approaches, (ii) functional annotation of identified proteins, and (iii) in-depth interrogation and confirmation of spectral features.

P13 The network analysis of *in silico* evolved oscillators

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Molecular oscillators drive many physiologically important processes, such as the cell cycle, circadian rhythms, and hormonal cycles. While the molecular basis of many such systems has been studied in detail, little is known about the evolutionary origin and the general network design principles of these oscillators. For example, it is still unclear how transients in circadian oscillators decay rapidly, and how such oscillators can be robust against gene expression noise. In order to study how different constraints and requirements shape the network design, we perform a large-scale comparison of *in-silico* oscillators. Oscillators in protein-protein and gene-protein networks can be evolved *in-silico* using genetic algorithms, however this has previously been a hard objective in evolutionary computation. We present a new method of rapidly evolving a large number of oscillating networks, which can be studied statistically and further selected for desirable properties. One analytical technique to be presented is a method of identifying the nature of the interlocking positive and negative feedback loops that are found in complex biochemical oscillators. The network analysis will be applied to existing models of biochemical oscillatory systems for comparison. The network design and analysis tools will be of interest to both synthetic and systems biologists.

P14 Mutagenic processes associated with transcription

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Can transcription direct mutations in human germ line cells?

In this work, we quantified the effect of mutational mechanisms associated with transcription in germline cells using a regional analysis of nucleotide substitution rates along human genes and their flanking regions. Our analysis reveals three distinct patterns of substitution rates. First, a sharp decline in CpG methylation deamination rate, which is observed in the vicinity of the 5'-end of genes. Second, a strand asymmetry in complementary substitution rates, which extends from the 5'-end to 1 kbp downstream to the 3'-end, associated with transcription coupled repair (TCR). Finally, a localized strand asymmetry, in form of an excess of C->T over G->A substitutions in the non-template strand. Surprisingly the last asymmetry is confined to the first 1-2 kbp downstream of the 5'-end of genes, requiring that, in addition to TCR, other processes are active in these regions.

We argue that a higher exposure of the non-template strand near the 5'-end of genes leads to a higher cytosine deamination rate. Up to now only the somatic hyper mutation (SHM) pathway has been known to mediate localized and strand specific mutagenic processes associated with transcription in mammalia. The mutational patterns in SHM are induced by cytosine deaminase that just targets single stranded DNA. This DNA conformation is induced by R-loops, which preferentially occur at the 5'ends of genes. Further more, we suggest that transcription induce a gradient of genomic instability along genes; instability that can lead to genomic rearrangements.

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P15 Establishing a system biological framework for molecular mechanisms of neurodegenerative diseases

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Neurodegenerative diseases pose significant health and financial challenges to individuals and society as a whole. Those conditions – with age as single most important risk factor - such as Alzheimer's or Parkinson's disease are particularly confounding. Different neurodegenerative diseases show distinct histological and clinical symptoms caused by neuron loss in selective brain regions¹.

Nevertheless, neurodegenerative diseases are characterized common mechanisms such as the formation and deposition of fibrillar aggregates of specific proteins such as amyloid β and tau protein in Alzheimer's disease, α -synuclein in Parkinson's disease or fragments of the huntingtin protein in Huntington's disease². Increasing evidence indicates that conformational changes followed by protein aggregation are central to the pathogenesis of these disorders³. These similarities suggest common disease mechanisms between neurodegenerative diseases. Here we present a common framework for the pathogenic molecular mechanisms of different neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease. We have performed a first metaanalysis of microarray data sets enabling the characterization of common (and distinct) transcriptional regulatory changes in these diseases. Followup analysis using gene annotation allows illuminating the underlying pathogenic cascades. Moreover, the subsequent integration of the expression with protein-protein interaction data delivered molecular networks for neurodegeneration in general as well as for specific neurodegenerative disorders. We believe that the presented unifying framework will facilitate the development of more targeted interventions for neurodegenerative diseases.

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P16 The Cancer Genome Atlas: Integrated analysis of genomic profiles reveals altered signaling pathways

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The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of various genome analysis technologies. The first phase of the project focuses on glioblastoma, the most common and most aggressive type of brain tumor. More than two hundred primary glioblastoma samples have so far been analyzed for changes in DNA copy number, mRNA expression, miRNA expression, DNA methylation, as well as for germ-line and somatic mutations in protein-coding genes.

Coupled with carefully collected clinical data, the integration of these different data types holds great promise for the identification of new oncogenic mechanisms and for the development of effective diagnostics and therapies. The identification of functional events on the background of massive molecular alterations, however, presents a formidable analytical challenge, complicated by interdependencies, e.g., between DNA methylation and transcript levels, and synergies, e.g., between amplification and activating mutation.

By mapping molecular profiles to known biological pathways, we have identified recurrent altered signaling processes. A substantial fraction of tumors has alterations in one or more of the following sub-pathways: Receptor-tyrosine-kinase/RAS/PI-3-Kinase signaling, P53-signaling, and RB-signaling. While each of these signaling modules is affected in almost all tumors, the exact mechanisms vary. For example, alterations in the EGFR and PDGFRA receptors tend to be mutually exclusive, and are the result of DNA amplification, mutations, or both. Classification of alterations in particular tumors by sub-pathways is likely to greatly simplify the development of sub-type specific therapies.

We will present an overview of salient results from the first phase of the TCGA project and a detailed account of signaling pathways analysis.

P17 Metagenomic evidence of the CRISPR systems, the recently discovered type of the prokaryotic immunity.

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CRISPRs are a new type of prokaryotic anti-phage immunity systems that exist in half of all known bacteria and almost all known archaea. A regularly Interspaced Short Palindromic Repeat (*CRISPR*) system consists of a *CRISPR*-cassette that is a repeat of the basic unit (about 30 nt) with unique spacers that direct the specific anti-phage response, a leader region, and genes encoding the *CRISPR*-associated (*cas*) proteins.

We analyzed the prevalence and distribution of the *CRISPR*-systems in metagenomic sequences. Unfortunately there are no effective tools for *CRISPR*-cassettes search. All three of publicly available programs produce a high level of false positive noise. To search for *CRISPR*-cassettes in metagenomes we developed a filtering method based on a combination of these three programs. Application of this schema to the Sorcerer II metagenome data showed that the frequency of *CRISPR*-cassettes in this metagenome is almost ten-fold lower than the average for completely sequenced prokaryotic genomes.

The identified *CRISPR*-cassettes were collected in a special database. Families of related cassettes were formed by the analysis of similarity between repeat units. Additional analysis of flanking regions allows one to distinguish between the lateral transfer and the parallel evolution of the cassettes in related strains. In many cases the similarity between cassettes is confined to single spacers, and some spacers are similar to known phage sequences. These observations support the hypothesis that this system defends organisms constituting the metagenome against invasion of foreign DNA.

P18 Spatiotemporal cytokine dynamics in TCell regulation a mathematical model of IL2 diffusion and Regulatory TCells (Treg)

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Cytokines mediate complex interactions among immune cells. They are lowmolecularweight signalling proteins apparently capable of manipulating the target cell in very low (picomolar) concentrations. A classic calculation from diffusionlimited reaction theory¹ shows that under such conditions, a signal would take hours to occur. This raises the question how, nevertheless, sensitive cytokine signalling in a noisy environment can be achieved². A twodimensional reactiondiffusion model brings new insights to this question. We consider a wellstudied and physiologically important sample system: Activation of T Helper(Th)cells via Interleukin(IL)2 and immunosuppression by Treg. The model reflects experimentally proven features like autoactivation of Thcells and low IL2 concentrations in the bulk phase. Three major results have been obtained so far: Firstly, the model predicts high local IL2 concentrations at secretion sites, which can possibly be verified experimentally with quantitative secretion assays. Thus, this property may serve to justify the model just as to explain effective signals at low cytokine concentrations. Secondly, we can show a paracrine signal over several cell diameters, confirming recent experimental results which suggest paracrine rather than autocrine signalling in Tcell activation³. And finally, immunosuppression by Treg may be explained by competitive IL2 uptake. With the spatiotemporal modeling approach, we are able to predict the range of a cytokine signal in dependence of important system parameters. The strong localization of cytokine distributions in the model provides a unifying explanation for diverse observed properties of complex cytokine networks.

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P19 Sensitivity-driven model discrimination in the HOG pathway in *S. Cerevisiae*

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In previous experiments the high osmolarity glycerol (HOG) pathway elements Ssk1 and Pbs2 could be identified as highly sensitive towards overexpression using the genetic tug-of-war (gTOW) method. Their severe gTOW phenotype could be rescued by deletion of HOG1, which encodes the MAPK of the HOG pathway, thereby linking overexpression of Ssk1 and Pbs2 to growth-inhibitory constitutive activation of the pathway.

How precisely Ssk1 and Pbs2 are regulated however still remains to be elucidated. The current view of the pathway as well as existing mathematical models of the HOG MAPK cascade cannot account for the distribution of sensitivities observed in the gTOW experiment.

Here we present a number of mathematical models of how the sensitive nodes Ssk1 and Pbs2 might be regulated alternatively. Additional parameters are obtained using standard parameter estimation techniques to ensure that the output of the pathway remains in agreement with experimental data. The impact of different types of regulation on the sensitivity of the nodes is then discussed and proposed for further experimental testing.

P20 Quantification of Single-Cell Bioluminescence Data: The Mammalian Circadian Clock as a Damped Oscillator Driven by Noise.

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Nowadays, the circadian oscillators in the suprachiasmatic nucleus in the brain, and in peripheral tissues such as fibroblasts, are thought to be self-sustained at the single-cell level. This notion is based on recent studies where the clock has been tracked in different tissues at the single-cell level using bioluminescence imaging. We apply established methods from engineering and physics to extract parameters such as period, damping and noise level from single cell data of wild-type and mutant cells¹. Correlation functions are surprisingly well fitted by weakly damped oscillators driven by biochemical fluctuations. We illustrate that visual inspection has limited power to distinguish noisy damped oscillations from self-sustained oscillations. Thus the question of whether single cells are self-sustained oscillators or not is far from being settled. The understanding of the nature of the single-cell oscillator is crucial for understanding entrainment and synchronization properties. Since damped oscillators driven by random fluctuations and neurotransmitter coupling are easily synchronized further experimental studies with long time-series are required to judge whether the damped oscillator idea presented here stands up to scrutiny.

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