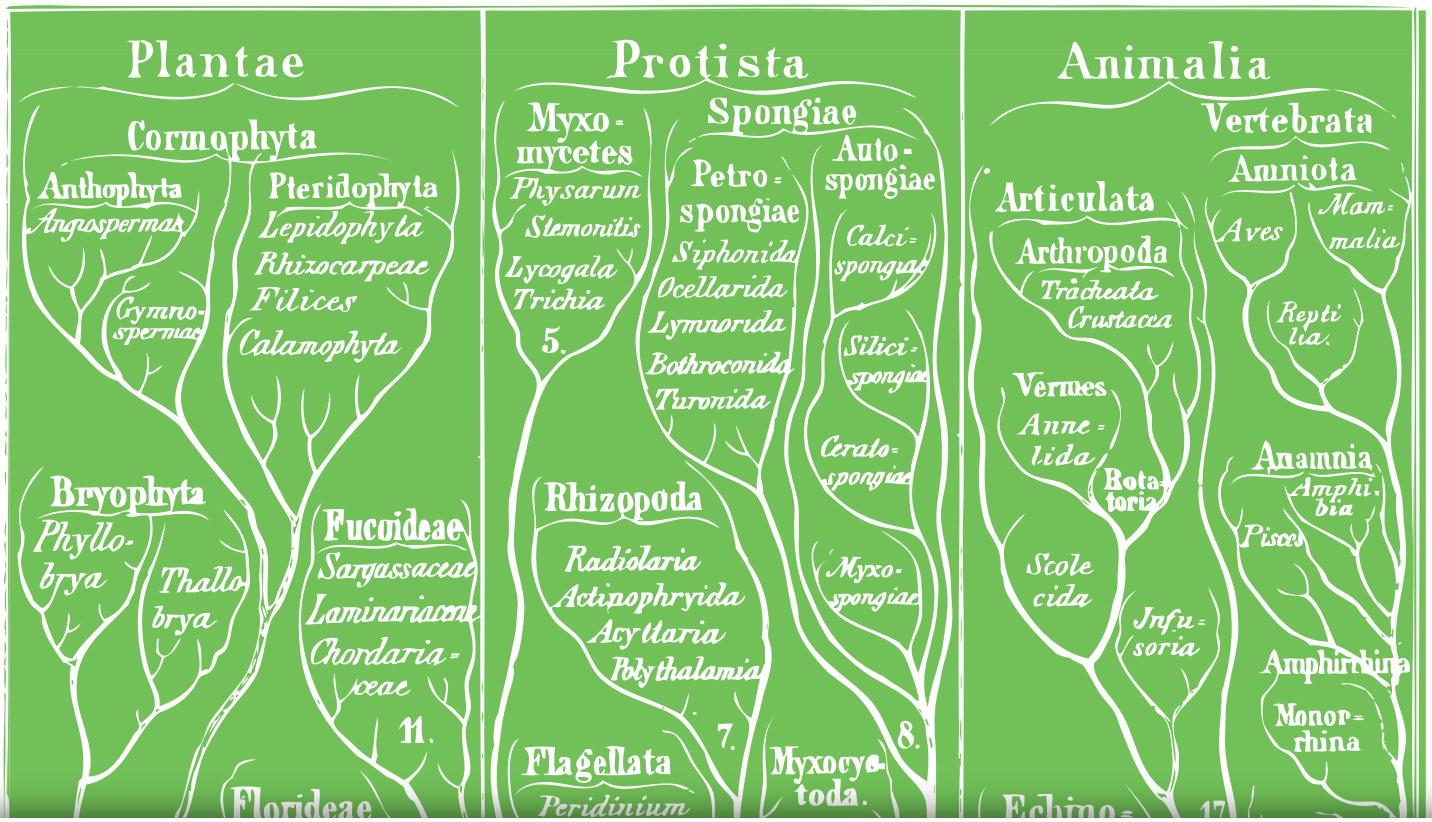

JCB Workshop, March 28–29, 2011

Nucleotides ° Networks ° Novelties

Understanding Evolution Beyond Darwin & Haeckel

Friedrich Schiller University of Jena
Carl-Zeiss-Straße 3, Lecture Room 5

JCB

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The workshop is organised by the Jena Centre for Bioinformatics (JCB) and supported by the Jena School for Microbial Communication (JSMC).

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Programme

Monday, 28 March 2011

Opening and introductory remarks

12:30	Thorsten Heinzel (FSU Jena) Welcome by the Dean of the School of Biology and Pharmacy
12:35	Stefan Schuster (JCB, FSU Jena) Welcome and introductory remarks
12:40	Günter Theißen (JCB, FSU Jena) Nucleotides, networks, novelties

Session 1 Nucleotides I

12:45	Thomas Dandekar (Julius-Maximilians-Universität Würzburg) Genome comparisons: Trace evolution and make use of the insights
13:25	Burkhard Morgenstern (University of Goettingen) Phylogenomics sheds light on deep metazoan phylogeny
14:05	Martin Mascher (IPK Gatersleben) Chargaff's second parity rule in plant genomes
14:25	Lydia Gramzow (FSU Jena) SplamiR - A program for the prediction of spliced miRNAs in plants
14:45	*Coffee break*

Session 2 Networks I

15:15	Andreas Deutsch (TU Dresden) Modelling cancer progression - the emergence of the invasive phenotype
15:55	Ekaterina Shelest (Leibniz Institute for Natural Product Research and Infection Biology, HKI, Jena) Comparative analysis provides insights into the pathogenicity of dermatophytic fungi
16:15	Sarah Werner (FSU Jena) Have ATP stoichiometries been optimized in evolution? Analysis of various ATP-producing metabolic pathways by irreversible thermodynamics
16:35	Katrin Bohl (FSU Jena) Rational redesign of *Escherichia coli* for overproduction of amino acids aiming at mutualistic cross-feeding
17:00 – 18:30	Poster session

Tuesday, 29 March 2011

Session 3	**Novelties I**
9:00	Michael Schroeder (TU Dresden) On the evolution of protein interaction interfaces
9:40	Manuel Than (Leibniz Institute for Age Research, FLI, Jena) Does the E2-domain of APP contain a novel metal binding site?
10:00	Nina Kottenhagen (MPI for Evolutionary Anthropology, Leipzig) Correlations in the evolution of linguistic and genetic relationships
10:20	Hagen Jung (MPI for Evolutionary Anthropology, Leipzig) Evolutionary Wordlist Transformations - Event-based modelling and reconstruction methods for language change
10:40	*Coffee break*
Session 4	**Nucleotides II**
11:00	Mathias Ziegler (University of Bergen, Norway) Generation and signalling functions of subcellular NAD pools
11:40	Pierre-Yves Bourguignon (MPI for Mathematics in the Sciences Leipzig/ Laboratoire de Physique Statistique) Compositionally biased genomes: the extreme case of *Carsonnella ruddii*
12:00	Sascha Winter (FSU Jena) On the detection of approximate gene clusters
12:20	Bryan Downie (Leibniz Institute for Age Research, FLI, Jena) Toward a *de novo* assembly of the highly repetitive *N. furzeri* genome: a novel pipeline for contig scaffolding and assembly
12:40	*Lunch break*
Session 5	**Networks II**
14:00	Martin Middendorf (University of Leipzig) Gene order rearrangement and phylogeny
14:40	Björn Junker (IPK Gatersleben) Central metabolic fluxes in seeds of the legume plant family
15:20	Poster session *with coffee*
Session 6	**Novelties II**
16:30	Wolfgang Marwan (MPI für die Dynamik komplexer technischer Systeme, Magdeburg) Sensory control of cell differentiation in *Physarum polycephalum* (Amoebozoa), a systems-oriented approach

17:10	Florian Rasche (FSU Jena) Computational mass spectrometry for metabolite identification
17:30	Sebastian Müller (Leibniz Institute for Natural Product Research and Infection Biology, HKI, Jena) Gene acquisition, duplication and metabolic specificaton: The evolution of fungal methylisocitrate lyases
17:50	Stefan Schuster (JCB, FSU Jena) Closing remarks

List of posters (in alphabetical order, according to presenting author)

1. M. Bartl, M. Pfaff, D. Driesch, S. Zellmer, R. Gebhardt, S. Schuster, P. Li
   A model-based optimization approach to understand liver zonation

2. S.O. Dahms, D. Roeser, M. E. Than
   Structure and biochemistry of the APP E2 domain

3. M. Eckart, K. Fliegerova, J. Mrazek, K. Hoffmann, A. Liggenstoffer, G. W. Griffith, P. M. Kirk, K. Voigt
   ***In silico* analysis based on the nuclear ribosomal DNA suggests eight novel genera in the anaerobic fungi (Neocallimastigomycota)**

4. S. Diekmann, P. Dittrich, G. Escuela, D, Görlich, G. Grünert, B. Ibrahim, T. Lenser, M. Lohel, N. Matsumaru
   Identifying biological information, rule-based modelling in space, and systems biology of mitosis

5. G. Escuela, P. Dittrich
   Evo-Devo Computing

6. M. Felder
   Assembly of mitochondrial genomes from whole-genome next-generation sequencing data

7. J. Gebauer
   Reconstruction of an eucaryotic genome-scale metabolic model

8. S. Germerodt, S. Halle
   Breeding suppression in small mammals: applying inividual-based models and evolutionary game theory to behavioral ecology

9. L. Gramzow, G. Theißen
   Phylogenomics of MADS-box genes in plants

10. K. Grützmann, K. Szafranski, M. Pohl, S. Schuster
    The alternative messages of fungal genomes

11. K. Bettenbrock, A. Kremling, K. Jahreis, U. Rinas, S. Schuster, M. Pfaff, R. Guthke
Dynamics and regulation of the metabolic balance in *Escherichia coli*

12. I. Heiland, C. Bodenstein, S. Schuster
Temperature compensation and temperature entrainment — amity or enmity?

13. J. Kelm, P. Kießling, O. Voytsekh, S. Schäuble, I. Heiland, S. Schuster and M. Mittag
A systems biology approach to improve nitrate-uptake in *Chlamydomonas reinhardtii* during day-phase

14. P. Dittrich, T. Hinze, B. Ibrahim, T. Lenser, N. Matsumaru
Hierarchically evolvable components for complex systems: Biologically inspired algorithmic design.

15. S. Hoefgen, S. O. Dahms, D. Roeser, M. E. Tha
Structure-function-relationship of the APP-E1-domain

16. P. Koch, B. R. Downie, A. Petzold, K. Reichwald, M. Groth, M. Platzer
Toward a *de novo* assembly of the highly repetitive *N. furzeri* genome: a novel pipeline for contig scaffolding and assembly

17. U. Münchberg, L. Wagner, K. Hoffmann, K. Voigt, P. Rösch, Jürgen Popp
Raman spectroscopy in zygomycetes: Determination of fatty acid content and saturation in distinct lipid enclosures of hyphae from *Mortierella* spp. (Mortierellomycotina, ex Zygomycetes)

18. A. Petzold, B. Downie, M. Platzer, K. Reichwald
***De novo* assembly and annotation of the *Nothobranchius furzeri* transcriptome – a new model for ageing research**

19. S. Reinhard, K. Hoffmann, K. Voigt, L. Olsson, A. Kupfer
Rhizomucormycosis: First records in amphibians

20. S. Richter, F. Centler, M. Thullner, P. Dittrich
Computational inference of metabolic reaction networks for degradation pathways in bacterial communities

21. S. Schäuble, I. Heiland, S. Schuster, O. Voytsekh, M. Mittag
New developments in the diurnal changes of nitrogen metabolism in *Chlamydomonas reinhardtii*

22. J. Schirmeyer, E. Leipold, S. H. Heinemann, C. Mawrin, M. Platzer, K. Szafranski
A novel splice variant of $Na_V1.8$ voltage-gated sodium channel from human dorsal root ganglion neurons leading to skipping of exon 11

23. V. U. Schwartze, T. Heydel, K. Hoffmann, G. Walther, A. Alastruey-Izquierdo, J. L. Rodriguez-Tudela, I. D. Jacobsen, G. S. de Hoog, K. Voigt, W. Schrödl
Direct analysis and identification of opportunistic *Lichtheimia* species by Matrix Assisted Laser Desorption Ionization (MALDI) - Time-Of-Flight (TOF) analyzer-mediated mass spectrometry

24. K. Szafranski, A. Petzold, K. Huse, T. Hildebrandt, H. Burda, P. Dammann, M. Platzer
Evolution of a long healthspan in African mole-rats

25. C. Tokarski, S. Hummert, A. Schroeter, S. Schuster
Interaction of opportunistic pathogenic fungi and human phagocytes: A multi-agent-based modeling approach

26. K. Wagner, J. Sühnel
The Jena Centre for Systems Biology of Ageing - JenAge

27. L. Wagner, T. Griebel, T. Petkovits, L. G. Nagy, I. Nyilasi, K. Hoffmann, R. A. Samson, D. Schnabelrauch, H. Vogel, C. Vágvölgyi, T. Papp, K. Voigt
Reconstruction of the phylogeny of the Mortierellales based on nucleotide sequences of the internal transcribed spacer from the nuclear ribosomal DNA cluster

28. S. Westermeier, L. Gramzow, G. Theißen
Phylogenomics of MADS-box genes in maize

Abstracts of talks

(in order of presentation/programme)

Genome comparisons: Trace evolution and make use of the insights

Thomas Dandekar
Julius-Maximilians-Universität Würzburg, Biozentrum, Lehrstuhl für Bioinformatik

In the age of postgenomics it has become a standard technique to compare genomes including various types of further analysis (differential genome analysis, target search, metabolic network reconstruction). In my talk I will discuss some techniques pertaining to this and the evolutionary results from our work which are suggested by this for different model organisms. In a further part we then look together at application aspects and insights gained from these data.

Phylogenomics sheds light on deep metazoan phylogeny

Burkhard Morgenstern
University of Goettingen, Institute of Microbiology and Genetics, Dept. of Bioinformatics

Genomic data are increasingly used to study phylogeny. A central problem is to select groups of ortholog genes as a basis for phylogeny reconstruction. We developed a software tool called OrthoSelect for this purpose. Our approach was applied in an international collaboration to study the phylogeny of sponges using existing and newly generated sequence data. As a result, our data confirm old viewpoints, namely (a) that sponges are monophyletic and (b) that the ctenophores together with the cnidarians form a so-called `coelenterat' clade.

Chargaff's second parity rule in plant genomes

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The famous first parity rule of Chargaff states that the number of As exactly equals the number of Ts, as well as the number of Gs equals the number of Cs in any piece of double stranded DNA molecules. Since Watson and Crick established the double-helix structure of the DNA, it is well known that Chargaff's first parity rule is the a consequence of the DNA's spatial organization.

A less widely known fact is that a similar parity rule applies to single-stranded DNA, too. After separating the DNA strands in *Bacillus subtilis*, Chargaff and his collegues found out that %A ≈%T and %G ≈ %C within a single strand of DNA. This intra-strand parity has become known as Chargaff's second parity rule in the literature. Although it has been known for more than forty years, no generally accepted explanation for it has been given. The puzzle remains to identify the mechanisms or selective pressures that underlie the rule. While intra-strand parity has been shown to be a global property, local deviations from it do exist and are correlated with functional attributes of a genomic sequence.

In recent years, ever more and larger genomes have been sequenced and Chargaff's second parity rule has been validated in any kind of prokaryotic or eukaryotic genome. In our study, we inquired into patterns of intra-strand parity in large plant genomes that have become available in the last few years, and

compared these to animal genomes. Our study revealed that plant chromosomes complied to Chargaff's second parity rule to a higher degree than animal chromosomes. Furthermore, patterns of local deviations from Chargaff's second rule were different between plant and animal species. In plants, local deviation patterns were similar both in coding and intronic sequences of chromosomes of inter-related species, whereas in animals, divergent patterns were witnessed even among chromosomes of the same species. This plant-specific intra-chromosomal homogenity was not reflected on the scale of individual genes and was not encountered in inter-genic sequences. We conclude that there exist plant-specific selective pressures responsible for a more complex genome-scale organization in plants.

SplamiR – A program for the prediction of spliced miRNAs in plants

Lydia Gramzow, Christoph J. Thieme, Dajana Lobbes and Günter Theißen
Friedrich Schiller University Jena, Department of Genetics, Philosophenweg 12, 07743 Jena, Germany; e-mail: lydia.gramzow@uni-jena.de

MicroRNAs (miRNAs) regulate a variety of biological processes in plants and animals. Detection of miRNAs has been hampered by the recent discovery of miRNAs which cannot be predicted immediately from genomic sequence as their genes contain introns.

In our contribution we will present the first method for the detection of these spliced miRNAs in plants, termed SplamiR. Our method consists of two phases. In phase one, complementary sequence pairs are identified in a given genomic sequence and stored in a database. These sequence pairs may encode for RNAs folding into stem-loop structures. In a second phase, sequence pairs with complementarity to a given target mRNA are retrieved from the database. Furthermore, *in silico* splice variants are generated from the genomic sequence of the identified sequence pairs. Finally, these *in silico* splice variants are classified as to whether they may represent miRNAs.

Our evaluation on simulated datasets verifies that SplamiR has a reasonable sensitivity. We also investigated the performance of our method on genuine miRNAs regulating MADS-box genes involved in plant development. SplamiR identifies all instances of spliced miRNAs in rice and maize, as well as one previously undiscovered miRNA in maize. SplamiR is currently the only available tool for the prediction of spliced miRNAs and will hence prove useful for the identification of more of these regulatory RNAs in other plant genomes.

Modelling cancer progression - the emergence of the invasive phenotype

Andreas Deutsch
TU Dresden, Dept. for Innovative Methods of Computing

Deciphering the principles of cancer invasion is crucial for the development of new therapy concepts. While molecular biology methods are required for a better characterization and identification of individual cancer cells, mathematical modelling and computer simulation is needed for investigating collective effects of cancer invasion. Here, we demonstrate how appropriately chosen rules in lattice-gas cellular automaton (LGCA) models allow for an adequate description of individual invasive cancer cell behaviour. We will then show how analysis of the LGCA models allows for prediction of emerging properties (in particular of the invasion speed). Furthermore, we propose that the transition to invasive tumour phenotypes in some brain tumours can be explained on the basis of the microscopic 'Go or Grow' mechanism (migration/ proliferation dichotomy) and oxygen shortage, i.e. hypoxia, in the environment of a growing tumour. We

test this hypothesis again with the help of a lattice-gas cellular automaton. Finally, we will use our LGCA models for the interpretation of data from in vitro glioma cancer cell invasion assays.

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Comparative analysis provides insights into the pathogenicity of dermatophytic fungi

Ekaterina Shelest
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Millions of humans and animals suffer from superficial infections caused by a group of highly specialized filamentous fungi, the dermatophytes, which exclusively infect keratinized host structures. Two closely phylogenetically related dermatophytes, *Arthroderma benhamiae* and *Trichophyton verrucosum*, both of which induce highly inflammatory infections in humans, have been sequenced by the *Arthroderma benhamiae* genome project consortium. 97% of the 22.5 megabase genome sequences of *A. benhamiae* and *T. verrucosum* are unambiguously alignable and collinear. To unravel dermatophyte-specific virulence-associated traits, we compared sets of potentially pathogenicity-associated proteins, such as secreted proteases and enzymes involved in secondary metabolite production, with those of closely related onygenales (*Coccidioides* species) and the mould *Aspergillus fumigatus*. The comparisons revealed expansion of several gene families in dermatophytes and disclosed the peculiarities of the dermatophyte secondary metabolite gene sets. Our results not only enlighten the genetic basis of putatively virulence-related traits of dermatophytes, but also shed some light on the evolution of these important pathogens.

Have ATP stoichiometries been optimized in evolution? Analysis of various ATP-producing metabolic pathways by irreversible thermodynamics

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The stoichiometry of ATP-producing metabolic pathways had been analysed theoretically by several authors by using evolutionary arguments and optimality principles. Waddell et al. (Biochem Educ 27:12–13, 1999) analysed (lactate-producing) glycolysis and used linear irreversible thermodynamics. The result was that half of the free-energy difference should be converted into free-energy of ATP and the remaining half should be used to drive the pathway. The calculated stoichiometry is in agreement with the observed yield of two moles of ATP per mole of glucose. Using the same approach, we analyse the

following eight other metabolic pathways: glycolysis as leading to ethanol, Entner–Doudoroff pathway, pentose phosphoketolase pathway, respiratory degradation of glucose, heterolactic fermentation, mixture of homolactic and heterolactic fermentations, mixed-acid fermentation in *E. coli* and arginine degradation in *M. pneumoniae*. Although the deviation is not very large, the calculated values do not fit as nicely as for glycolysis as leading to lactate. For example, for O2 respiration, the theoretical ATP yield equals 27.9. The real value varies among organisms between 20 and 38. For mixed-acid fermentation in *Escherichia coli*, the theoretical and experimental values are 2.24 and 2, respectively. For arginine degradation in *M. pneumoniae*, the calculated value is 2.43 mol of ATP, while *in vivo* only one mole is produced. Calculating the ratio of the resulting flux and the maximum flux possible shows that in all cases more than 55% of the maximum flux are reached and in six of nine pathways it is even more than 85%. During evolution, some pathways may not have reached their optimal ATP net production because energy yield is not their only function or there is no strong selection pressure in some pathways. Moreover, it should be acknowledged that the approach by linear irreversible thermodynamics is a rough approximation.

Rational redesign of *Escherichia coli* for overproduction of amino acids aiming at mutualistic cross-feeding

Katrin Bohl[1,2], Anja Schröter[1], Christoph Kaleta[1], Christian Kost[2] and Stefan Schuster[1]
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Mutualisms, meaning that unrelated individuals cooperate and benefit one another, are common in nature. Despite its ubiquity, cooperative behaviours pose a challenge for evolutionary theory because they are always costly to their performer which causes a disadvantage in natural selection. Which ecological factors favour the evolution and maintenance of mutualisms? To answer this question, we use the mutual exchange of essential amino acids between different species of bacteria as a model system in which the costly overproduction of amino acids is defined as the focal cooperative trait.

To artificially trigger such a mutualism in *Escherichia coli* and study it in long-term evolution experiments we redesign the metabolic network model in such a way that the production of a specific amino acid is increased. To this end we use and extend a method from metabolic engineering – CASOP-GS (Computational Approach for Strain Optimization Aiming at high Productivity – Genome Scale). With metabolic engineering the production by microorganisms of certain substances is improved. This is achieved by using suitable intervention strategies, such as knockouts, knockins or overexpressions. CASOP-GS ranks reactions according to their importance for the synthesis of a specific product in a genome-scale network. These importances are estimated using so-called elementary modes that correspond to a mathematical definition of the biochemical concept of pathways. Based on this, knockin- and knockout-candidates can be proposed.

Applying these methods, we obtained rankings of all reactions in the genome-scale model of *Escherichia coli* for the production of different amino acids and, as a test case, succinate. We found, that the proposed strategies in the succinate case resemble known genetic modifications used for its overproduction. Other proposed mutations, both for histidine and succinate, can be clearly explained by the network structure of the metabolic model. The proposed knockouts for amino acids are being currently implemented in *Escherichia coli* and first results are presented.

On the evolution of protein interaction interfaces

Michael Schroeder
Technical University Dresden, Biotec, Bioinformatics group, Dresden, Germany

With the advent of domain interaction networks derived from 3D structures and experimentally determined large-scale protein interaction networks a number of interesting questions arise: Are interaction interfaces more conserved than the rest of the surfaces? Can the structure of protein interaction networks be linked to underlying domain interactions? Can motifs derived from domain interactions predict protein interactions? Can viral domains mimick native human protein interaction interfaces? Do the gene products of fused and non-fused genes use the same domain interfaces to interact?

There is an intricate relationship between domain-domain and protein-protein interactions, whose understanding helps to answer the above questions. In the talk, I will review how to construct networks derived from structural domains and how to complement largeexperimental protein interaction networks with interactions extracted from literature. I will shed light onto the structure of these networks, how to identify functional modules, and how to predict interactions.

The discussed techniques will be used to identify candidate targets in pancreas cancer and to show how viruses interfere with the apoptotic programme of their hosts.

Does the E2-domain of APP contain a novel metal binding site ?

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Alzheimer's disease is one of the most frequent forms of dementia in the elderly population affecting about 25 % of people in the age of 80 to 90 years [1]. As our western society is continuously aging, the medical importance of dementia is increasing. In spite of intensive research it was not yet possible to find an effective drug against Alzheimer's disease (AD). The brain of AD-patients is characterized by the deposition of senile plaques containing the neurotoxic peptide $A\beta_{40\text{-}42}$, that is proteolytically derived from its precursor, the Amyloid Precursor Protein (APP) [2]. In addition to its role in AD, many potential physiologic functions of APP have been shown. While the overall processes leading to the formation of Aβ are well known, rather little is understood about the structure of the entire protein and how this may relate to its physiologic and pathological (mal)function(s).

In our lab we investigate the three-dimensional structure of APP by biochemical and protein crystallographic experiments, analyzing in detail its structure-function relationship. Recently, we identified novel metal binding sites in its Cterminal, folded E2 domain. Interestingly, the physiologic function of APP has been linked to the binding and transport of cupper ions. We currently investigate the structural and functional details of these sites.

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Correlations in the evolution of linguistic and genetic relationships

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Darwin believed that "a perfect pedigree of mankind [...] would afford the best classification of the various languages now spoken throughout the world [...]" [The Origin of Species, 1859]. Intuitively, one might assume that linguistic features and genetic markers should correlate, because both are passed on from parents to children. As populations diverge, so do their genes and languages. However, unlike with genes, horizontal transfer of languages is possible, and indeed common. Where populations come into contact, they may become more similar to each other in both their languages (through bilingualism and language contact) and genes (through interbreeding). Alternatively, in cases of language shift, a population can change its ‚linguistic lineage' entirely, while maintaining its genetic lineage. If contact does not result in combined exchange of genes and linguistic features, the genetic evidence tells a different story to the linguistic evidence.

Since the 1980 a good number of studies have yielded sometimes contradictory results by using various genetic markers alongside diverse at times even subjective linguistic distance measures, and applying them to different regions of the world.

In my project, I am exploring putative correlations between genetic markers and linguistic features using two types of linguistic distances (lexical and structural, including more and less stable subsets of each) as well as genetic and geographic distances, to answer the following questions:

Overall, is there a significant correlation between genetic and linguistic relations between human populations?
Are there differences between more stable and less stable linguistic traits, in how closely they correlate with genes?
How far does geography influence the dispersals of languages and populations?
Is there a difference in how closely the male and female genetic lines correlate with language, as might be expected from their different migration patterns?

I also test a model of how to tell apart convergence in contact situations from divergence within language families to find out more about the co-evolution of genetic markers and linguistic features.

Evolutionary Wordlist Transformations - Event-based modelling and reconstruction methods for language change

Hagen Jung
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Evolution is usually seen as the change over time of organisms differing in inherited traits resulting from gene-environmental interaction. But there are also other interactions which occurred in the more recent history of humans. A powerful and functional interaction among individuals and populations is language. Similar to genes, languages evolve along ancestral generations while the components of language are improved by innovations under environmental pressure. Investigating such linguistic lineages is a big challenge in understanding our cultural legacy. The huge diversity of still-spoken and extinct languages

at all levels of communication motivated us to find automatic and objective methods to classify language groups, to identify relatedness and to reconstruct languages of the past. An important part of languages is the lexicon, viz. the inventory of words used by a speaker. In our approach languages are related when they contain lexical items of the same origin. Words are sequences of characters which change over time like genes in species. Remaining similarities among words can be detected in different languages. In our work, character transformations across lexical wordlist are used to model evolutionary language change and to find plausible lineages.

Simple character transformations like insertion, deletion and substitution are introduced in conjunction with a model of language speciation. Existing methods to find word-to-word transformation sequences are enhanced into methods for computing language-to-language transformation phylogenies. As in other cases of evolution the parsimony principle can be applied. In this sense a history containing as few single transformations as possible is the most likely explanation of the observed data. More precisely, the goal of our study is to find such minimal solutions which are known to be NP-complete. To find reliable explanations for specific word changes some more complex transformations are incorporated into the existing model. Synchronous character substitutions like cluster duplications in biology enable us to identify general change patterns within a language.

In summary, we try to explicitly reconstruct each single step of lexical evolution. Word forms for each step within the reconstruction are calculated. We found that resulting language transformation trees are more precise than language phylogenies calculated by simple word-to-word comparisons. Additionally regular character patterns can be detected, which is of great benefit for linguistic research. Due to the computational complexity a convergence method was developed. Once we estimated a plausible tree we iteratively improved this tree by substituting single transformations. First results for a smaller set of linguistic data provides us with the complete transformation history of estimated character changes and all proto-words of the reconstructed languages.

Gene order rearrangement and phylogeny

Martin Middendorf
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No abstract available

Compositionally biased genomes: the extreme case of *Carsonnella ruddii*

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Celebrated as the shortest microbial genome ever fully sequenced [1], *Carsonnella ruddii* 's chromosome exhibits another striking feature: it is also the most compositionnally biased one, with a GC content as small as 16.5%. Such extreme deviations are made possible by the species lifestyle: *C. ruddii* is a vertically-transmitted endosymbiont of psyllids, hosted in bacteriocytes that apparently compensate for the loss of multiple essential functions. From an information-theoretic point of view, the combination of a short genome with a strong compositional bias results in a dramatic shrinkage of the amino acids diversity of the proteome [2]. Comparing the most diverse amino acid distribution achievable under this informational constraint with the actual amino acid distribution in *C. ruddii* 's proteome, an unexpectedly high level of

agreement is observed, showing that this species genome evolved far beyond limits so far assumed to bear on any cellular organism.

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[2] Claude Shannon. A mathematical theory of communication. The Bell System Technical Journal, 27:379–423, 1948.

On the detection of approximate gene clusters

Sascha Winter (1), Katharina Jahn (2) , Leon Kuchenbecker (2) , Jens Stoye (2) and Sebastian Böcker (1)
(1) Lehrstuhl für Bioinformatik, Friedrich-Schiller-Universität Jena; (2) AG Genominformatik, Technische Fakultät, Universität Bielefeld

Analysis of genomes for co-localized genes that remain clustered in multiple genomes is a popular approach in comparative genomics. Due to micro-rearrangements, gene losses and gene insertions, these gene clusters are often not conserved perfectly. The demand for error-tolerant models makes the detection of approximate gene clusters a computational challenge.

Gecko2, developed by Jahn et al, is a tool for the *de novo* detection of conserved gene clusters in multiple genomes. It is based on models that are robust against incomplete conservation patterns, but still allow for an efficient analysis of large genome sets.

To determine the significance of the predicted clusters, a statistical framework is integrated into Gecko2.

We applied Gecko2 for a comparative analysis of microsporidia, comparing gene cluster occurrences in microspridia with gene cluster in fungi and nucleariids.

Toward a *de novo* assembly of the highly repetitive *N. furzeri* genome: a novel pipeline for contig scaffolding and assembly

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With the advent of next generation sequencing technologies (NGS), whole genome sequencing (WGS) can be conducted for much reduced prices and timescales. However, increased error rate and short read length in NGS introduces new difficulties to *de novo* whole-genome assemblies and to mapping NGS reads to a reference. Moreover, many unassembled genomes remain so due to the high genome complexity introduced by repetitive genome motifs and gene duplication found in higher vertebrates and grains. Using a mixture of Illumina and 454 sequencing technologies, we have developed and utilized a novel masking pipeline to perform *de novo* assembly and scaffolding of a 1.5-2 Gb highly repetitive (>45%) unassembled genome, the turquoise killifish *Nothobranchius furzeri* and validated the assembly against the most up-to-date transcriptome data (see poster of A. Petzold et al.). Additionally, a genome browser for the *N. furzeri* genome assembly is currently under development.

Generation and signalling functions of subcellular NAD pools

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NAD is vital for both bioenergetic conversions and the regulation of major cellular events. Recent discoveries of signalling pathways, which consume NAD(P), have changed the original view that these redox carriers are only reversibly interconverted between their oxidized and reduced states. It is well established now that the NAD-dependent activities of PARPs, sirtuins (NAD-dependent deacetylases), ADP-ribosyltransferases and ADP-ribosylcyclases hold key positions in cellular and organismal signal transduction and necessitate a continuous re-synthesis of NAD (1). Indeed, the selective supply of NAD to compartment-specific signalling processes may have a critical impact on regulatory pathways (2). Therefore, NAD homeostasis is now considered as important link between the metabolic state and signal transduction events such as gene regulation, calcium signalling, circadian rhythm and others.

The enzyme activities of NAD synthesis have been known for decades. However, the corresponding genes have been identified and characterized only within the past years. Tremendous progress has been made regarding catalytic, structural and regulatory properties of these proteins. Notably, several NAD biosynthetic enzymes themselves carry additional regulatory functions, linking NAD generation directly to signalling.

The use of precursors and the corresponding pathways of NAD synthesis have evolved from a preference for nicotinic acid towards the predominant utilization of nicotinamide (both collectively referred to as vitamin B3). This shift may have been accompanied by a more versatile and complex use of NAD in signalling pathways.

In mammals, the key step of NAD synthesis is catalysed by three different isoforms of NMNATs. While they are encoded by individual genes, they are closely related and their subunit structures are highly similar. However, they have acquired individual, unique insertions (isoformspecific targeting and interaction domains, ISTIDs) which mediate subcellular targeting or posttranslational modifications. The ISTIDs of two isoforms have evolved under high selective pressure, apparently to maintain their nuclear and Golgi localisation (3). These isoforms are critical for the maintenance of vital functions, not only because of their NAD biosynthetic capacity. Thus, the increasing complexity of NAD-mediated signalling processes appears to be reflected in new structural and functional properties of the biosynthetic enzymes.

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Central metabolic fluxes in seeds of the legume plant family

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Seeds of the legume plant family are the major source of protein for human nutrition and animal feed worldwide. Furthermore, legumes have evolved a variety of storage compound compositions ranging from starch-dominating (pea) via protein-dominating (soybean) to lipid-dominating (peanut). We have

analyzed central metabolic fluxes in legume seeds with two main approaches: For the first approach, flux balance analysis, we have reconstructed the stoichiometric network of central metabolism and simulated carbon fluxes for seeds with various storage compound compositions. Despite the fact that the carbon backbones of most storage compounds somehow originate from carbohydrate metabolism, glycolysis, or the TCA cycle, the usage of central metabolic pathways is quite different and in some cases contradicts textbook knowledge. In the second approach, steady-state 13C metabolic flux analysis, we have used a combination of computer modeling and stable isotope labeling experiments to quantify metabolic fluxes in pea and *Medicago* seeds. These experiments have confirmed that the usage of central metabolic routes is quite distinct between these two members of the legume family. The flux determinations will be repeated with other members of the legume family in the future. The gained knowledge might facilitate engineering of storage compound composition also in other plant systems, for example cereals.

Sensory control of cell differentiation in *Physarum polycephalum* (Amoebozoa), a systems-oriented approach

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No abstract available

Computational mass spectrometry for metabolite identification

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Some organisms, such as plants, have to adopt to unfortunate conditions, rather than flee from them. Under this evolutionary pressure, these organisms developed a huge number of metabolites to cope with e.g. UV radiation, extreme temperatures and natural enemies. Current estimates are in the range of 4 000 - 20 000 metabolites for any species. Since metabolites cannot be predicted from the genome sequence, metabolite databases remain vastly incomplete. Therefore high-throughput de-novo identification of metabolites is highly sought. Mass spectrometry (MS) in combination with a fragmentation technique is one of the key technologies for their identification, but the manual interpretation of mass spectra is cumbersome and requires expert knowledge. Automated analysis of such spectra is still in its infancy.

Our group has proposed fragmentation trees as a tool for the interpretation of CID tandem mass spectrometry (MS2) data. Here we present how to use fragmentation trees for the classification of compounds or the detection of structurally similar molecules. We also show how to adjust this approach to other types of fragmentation spectra.

For example, additional fragmentation steps (MSn) reveal more information about the molecule. We adjust the fragmentation model to MSn data to reflect the succession of fragmentation reactions. Evaluation of our method on a dataset of 45 reference compounds showed, that almost one quarter of all fragments are changed due to the information from MSn data. As our scoring scheme is “chemically reasonable”, we argue that the trees are actually improved.

Gas chromatography MS (GC-MS) typically uses electron impact ionization (EI) as fragmentation technique. This setup is very common in metabolomics, but has the disadvantage, that the molecule peak

is often not contained in the spectrum. Besides the computation of the fragmentation tree, here we are further interested in the identification of the molecule mass and its explanation.

Using fragmentation trees, we can obtain some structural information about an unknown compound. For this, we build a database of reference trees from an existing spectral database. The fragmentation tree of the unidentified compound is aligned with the reference trees. We can then assume that the compound of interest is of the same class than the best scoring hits. This is an improvement over spectral comparisons, as the tree alignment reveals similarities which are not obvious in the spectra. Additionally, if the hits share common features in their molecular structure, these might also be part of the unknown metabolite.

We offer a tool that can identify metabolites not yet contained in any database and is sufficiently fast to be used in high-throughput analysis. We hope that this tool will help to overcome the limitations of the "known universe of organic chemistry".

Gene acquisition, duplication and metabolic specification: The evolution of fungal methylisocitrate lyases

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AG Systembiologie / Bioinformatik

Gene duplication represents an evolutionary mechanism for expanding metabolic potential. Here we analysed the evolutionary relatedness of isocitrate- and methylisocitrate lyases, which are key enzymes of the glyoxylate and methylcitrate cycle, respectively. Phylogenetic analyses imply that ancient eukaryotes acquired an isocitrate lyase gene from a prokaryotic source, but it was lost in some eukaryotic lineages. However, protists, oomycetes and most fungi maintained this gene and successfully integrated the corresponding enzyme into the glyoxylate cycle. A second gene, encoding a highly related enzyme, is present in fungi, but absent from other eukaryotes. This methylisocitrate lyase is specifically involved in propionyl-CoA degradation via the methylcitrate cycle. Although bacteria possess methylisocitrate lyases with a structural fold similar to that of isocitrate lyases, their sequence identity to fungal methylisocitrate lyases is low. Phylogenetic analyses imply that fungal methylisocitrate lyases arose from gene duplication of an ancient isocitrate lyase gene from the basidiomycete lineage. Mutagenesis of active site residues of a bacterial and fungal isocitrate lyase, which have been predicted to direct the substrate specificity of iso- and methylisocitrate lyases, experimentally confirmed the possibility of direct evolution of methylisocitrate lyases from isocitrate lyases. Thus, gene duplication has increased the metabolic capacity of fungi.

Environmental Microbiology and Environmental Microbiology Reports, 2011

Poster abstracts

(in alphabetical order, according to presenting author)

1| A model-based optimization approach to understand liver zonation

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No abstract available

2| Structure and biochemistry of the APP E2 domain

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The Amyloid Precursor Protein (APP) and its sequential cleavage by the proteases beta- and gamma-secretase are generally believed to be of central importance for the development of Alzheimer's disease (AD) [1]. The resulting neurotoxic peptide Abeta is found in the disease typical senile plaques. Especially the biological function of APP remains mostly unclear until now, not least because of insufficient structural knowledge about the Protein. We will present structural and biochemical data of the E2-domain of APP, which provides new functional insights.

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Keywords: Amyloid Precursor Protein (APP), Alzheimer's Disease (AD), Crystal structure

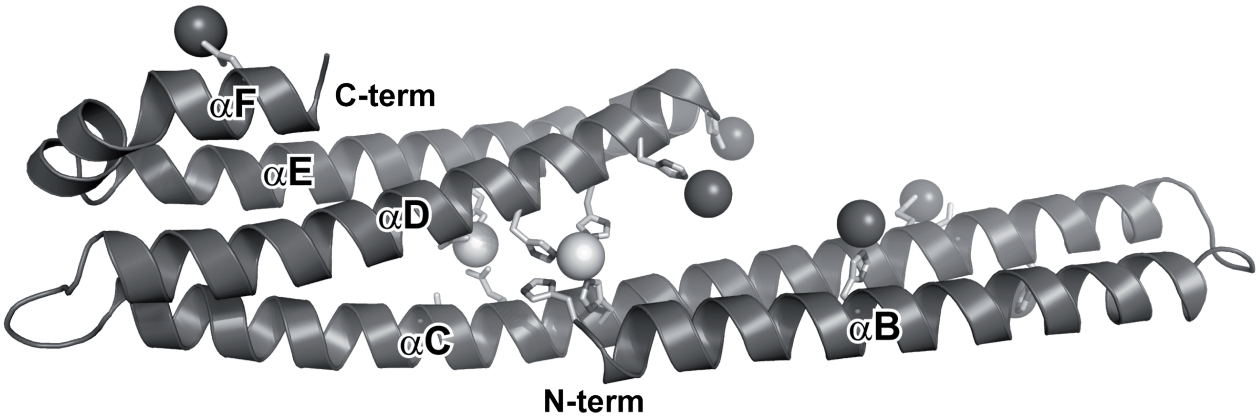

Figure 1: Structure of the APP-E2 domain with intermolecular (dark spheres) and intramolecular (light spheres) bound Cadmium ions.

3| *In silico* analysis based on the nuclear ribosomal DNA suggests eight novel genera in the anaerobic fungi (Neocallimastigomycota)

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Anaerobic gut fungi are evolutionarily extraordinary in the fungal kingdom. Unique traits of gut fungi especially their anaerobiosis, possession of hydrogenosomes instead of mitochondria, multiple flagella and extremely low genomic GC content caused considerable difficulties with their classification within the class of the chytridiomycetes. Modern systematics of anaerobic fungi based on DNA analyses eliminates the problems with extensive morphological variation of gut fungi depending on environmental conditions. Until now, molecular phylogenetic reconstructions answered to satisfaction the relationship neither between aerobic and anaerobic nor within the anaerobic. The present study results in the generation of a nuclear ribosomal DNA-genealogy from all taxonomic groups of the chytridiomycetes in comparison with major clades of other fungal lineages. Since animals and fungi are known to be sister groups and flagellate fungi are accepted to represent the most basal lineage of fungi our project will shed light on the ancient evolutionary history of divergence between animals and fungi. Furthermore, eight novel phylogenetic clades and their cultivation-independent, taxonomic description will be presented.

4| Identifying biological information, rule-based modelling in space, and systems biology of mitosis

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The Bio Systems Analysis Group is concerned with the analysis and design of organic systems. Here we present some examples of current research topics in our group.

In the context of the evolution of developmental processes in natural and artificial systems, a study about the origins of specific mechanisms for floral development was proposed. Additionally, in order to model such systems, we have applied adequate approaches to capture aspects of structural dynamics that characterize developing unities, at a molecular level, for example, using rule-based modelling in space or membrane systems.

We also present a deterministic as well as stochastic dynamical model and simulation of the *Saccharomyces cerevisiae* spindle positioning checkpoint (SPOC). It assures the fidelity of spindle alignment and eventually

the asymmetric cell division by delaying activation of the mitotic exit network until the spindle is correctly aligned along with the polarity axis.

In a JSMC (Jena School for Microbial Communication) funded project we investigate theoretical properties of biological systems with regard to their capacity to be used as signaling and communication systems. In particular we focus on molecular codes that can be implemented by such systems.

5| Evo-Devo Computing

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We present Evo-Devo Computing, a project whose goal is to achieve a system-level understanding on the evolution of developmental programs that gives rise to autonomous unities, in the context of changing environments. Considering them as dynamic, constructive, complex systems, we are interested in identify and abstract components, relations, mechanisms, emergent phenomena and metrics related to developing systems that evolve in time.

We propose an abstraction for Evo-Devo *in silico*, where dynamic genetic and environmental information guides the developmental mechanisms that construct a functional organism or transform its structure (i.e. change its dimensionality). Currently we are working in a minimal model of Evo-Devo in order to study the basic properties that arise in a system, whose developmental mechanisms are affected by evolutionary processes, and, at different time scales, the developmental processes constraint the evolution.

The final aim of this work is to obtain a general framework for Evo-Devo systems whose applicability could be either to assist in the design of artificial artifacts (software, hardware, conceptual and physical things) with desirable self-X properties, and, hopefully, help to answer open questions in natural sciences.

6| Assembly of mitochondrial genomes from whole-genome nextgeneration sequencing data

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Classical approaches to sequence and analyse mitochondrial DNA are based on the separate isolation and/or amplification of mitochondrial DNA. The aim of our approach was to identify and analyse mitochondrial DNA using next-generation data derived from whole-genome shotgun sequencing of *Rhynchosporium secalis* UK7 and 6a.1. These two isolates are of particular interest as pathogens of barley and rye, respectively.

7| Reconstruction of an eucaryotic genome-scale metabolic model

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No abstract available

8| Breeding suppression in small mammals: applying individual-based models and evolutionary game theory to behavioral ecology

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Breeding Suppression in small mammals, especially voles, is interpreted as an anti-predatory behavior. Olfactory cues of their highly specialized ground predators, e.g. the least weasel (*Mustella* spec.), are a possible stimulus to indicate an increased predation risk and may initialize this behavior. Reproductively non-active females tend to avoid micro-habitats visited and marked by their predator, while activity of reproductive active females is decreased. Non-breeding obviously contradicts the principle of fitness-maximization, so this strategy should be a trade-off between actual survival and future reproduction opportunities.

This system of breeding individuals and suppressing ones can be interpreted as a coexistence of two distinct behavioral standards mediated by predator dynamics. With an evolutionary game theory approach we investigated the evolutionary stability of the breeding suppression strategy. We could show that under high predation risk conditions both strategies, breeding and breeding suppression at predation risk, can co-exist.

Further we were interested in the character of the olfactory cues of the predator in time (evaporation) and space (diffusion). For that, we developed an individual-based model (IBM) of a vole population, to model explicitly local interactions between predator, its olfactory cues and the prey. Each female vole had a certain probability to suppress breeding (SSP), this trait was inherited to there offspring. If it was advantageous for the individuals, it become more frequent, if not, it was eliminated after several generations. We used this pseudo-selective approach to investigate the impact of the predator dynamics (temporal and spatial), habitat heterogeneity of the voles and metapopulation structure on the frequency of the breeding suppression as a part of a complex anti-predator behavior.

9| Phylogenomics of MADS-box genes in plants

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MADS-box genes are involved in the regulation of nearly all major aspects of plant development. During the evolution of plants, the number of MADS-box genes greatly expanded from just one in green algae to approximately 100 in flowering plants. This expansion accompanied the evolution of plants with more and more complex structures and life cycles. There are two types of MADS-box genes in plants, type I and type II, which are further subdivided into groups. The different types and groups control different phases of the plant life cycle.

The number of whole genome sequencing projects for plants is increasing rapidly and genome sequences are now available for a variety of plant orders. Annotation and phylogenetic analyses of MADS-box genes in these genomes will give further insights into the expansion of the different types and groups of MADS-box genes. Hence, the association of the evolution of MADS-box genes with the origin of evolutionary novelties will be further clarified.

Here we present a method for the annotation of MADS-box genes in plant genomes and preliminary annotation and phylogenetic results for nine species. Our analyses reveal massive expansion of type I MADS-box genes in *Carica papaya*, as well as numerous examples of recently duplicated and lost MADS-box genes in different plant species.

10| The alternative messages of fungal genomes

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Alternative splicing (AS) is a cellular process that increases a cell's coding capacity from a limited set of genes. With regard to species evolution, AS presumably contributed to phenotypic diversification by introducing additional protein isoforms. Thus, AS opens an unconstrained evolutionary "playground" in the "backyard" of commonly used genes. Although AS is common in higher plants and animals, its prevalence and abundance in the whole eukaryote domain is unknown.

We present a genome-wide comparative study of AS in 26 fungal species from three different phyla. The assay is based on alignments of publicly available EST data to fungal genome sequences.

Our analysis reveals, that a greater part of fungal genes than previously expected is alternatively spliced. With random sampling of two ESTs per genomic locus we find an average AS rate of 5.8% per gene. Higher sampling rates even yield rates of up to 20% for some fungi. In contrast to higher animals, intron retention is the most prevalent AS type in fungi. On average, the investigated Basidiomycetes show higher rates of alternatively spliced genes (6.9%) than Ascomycetes (5.7%). We find hints, that AS may have helped to develop a complex lifestyle. Strict yeasts show nearly no AS, while in multicellular molds, AS is more prevalent. Moreover, it affects genes of the cytoskeleton, which plays an active role in hyphae formation of molds. We find that AS affects genes of many other categories: metabolism, gene expression, organelles and transport. Overrepresented Pfam domains frequently involve the term ribosome, and enzymes as synthase, dehydrogenase and peptidase.

We conclude that AS is a rather common phenomenon in multicellular fungi. It likely affects biological function in fungi, is involved in many cell activities and may have contributed to develop the complex lifestyle of multicellular fungi.

11| Dynamics and regulation of the metabolic balance in *Escherichia coli*

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The FORSYS-partner project is focused on the dynamic modeling of the overflow metabolism of Escherichia coli [1]. Overflow metabolism not only limits biomass yield but also the quality of biotechnologically important products. The quantitative understanding of the regulation of the carbohydrate uptake and of the metabolic fluxes in particular around the pyruvate node is a prerequisite for the optimization of recombinant protein production by *E. coli*.

Within this project six partners collaborate:

- MPI for Dynamics of Complex Technical Systems Magdeburg (MPI, MaCS)
- University of Osnabrück (UOS)
- Helmholtz Centre for Infection Research GmbH Braunschweig (HZI)
- Friedrich Schiller University Jena (FSU)
- Hans Knöll Institute Jena (HKI)
- BioControl Jena GmbH (BCJ)

Results were obtained by integrating physiological, transcriptomic and proteomic data from different strains of E. coli grown at different experimental setup by using gene regulatory network inference and metabolic network analysis. For instance, driven by recent modeling results [2], the production and uptake of acetate after a glucose pulse and during shifts in dilution rates were analyzed by the MPI. Omics-data from the glucose pulse experiments were generated by HZI and analyzed by HKI. The UOS-group analyzed the three different feedback loops within the regulation of the glucose-PTS with respect to their importance to maintain the metabolic balance [3] and found an additional component of PTS-regulation, the metalloprotease MtfA. Transcriptomic and proteomic alterations of the central carbon metabolism in *E. coli* due to the synthesis of the foreign protein hFGF-2 were experimentally studied by the HZI group, thereafter HKI, FSU and BCJ analysed and modelled the obtained data by integrative and genome-wide approaches.

The cycle of systems biological research could be perfectly closed by collaboration of the partners HKI, FSU and UOS: First, a large-scale gene regulatory network model was inferred analyzing publicly available transcriptomic and genomic data. Next, the analysis of the inferred network using prior knowledge from databases and the literature allowed to predict five novel transcription factor - target gene interactions in *E. coli*. One of the model-based predictions, the regulation of lipoate synthase (LipA) by the pyruvate-sensing pyruvate dehydrogenase repressor (PdhR), was experimentally tested and confirmed.

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12| Temperature compensation and temperature entrainment — amity or enmity?

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Most organisms have a circadian clock that helps them to anticipate daily environmental changes. Although, being an endogenous rhythm, it can be entrained by external time cues like light-dark or temperature cycles. Under constant conditions circadian rhythms persists with a period of approximately 24 hours. This endogenous period of the clock is relatively insensitive to temperature. This phenomenon is called temperature compensation. However, single pulses of temperature can shift clock phase.

Whereas light information is usually integrated via specific components — the photoreceptors — temperature permanently influences all processes of an organism. Thus it is difficult to study temperature

regulation of circadian clocks experimentally and the underlying mechanisms are poorly understood. We use mathematical models and control analysis to study temperature regulation of existing clock models from different organisms in order to identify common mechanisms for temperature compensation and temperature entrainment. Additionally, we study how known specifically temperature regulated processes like temperature regulated alternative splicing or phosphorylation contribute to these processes. Furthermore, we try to unravel the interrelation of temperature entrainment and compensation. We are able to show that the latter is an requirement for temperature entrainment in a changing environment.

13| A systems biology approach to improve nitrate-uptake in *Chlamydomonas reinhardtii* during day-phase

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The circadian RNA-binding protein CHLAMY1 from the green alga *Chlamydomonas reinhardtii* recognizes UG-repeat elements situated in the 3'-UTRs of several mRNAs (1). Some of them encode proteins for nitrogen-metabolism, such as nitrite reductase1, glutamine synthetase2 (GS2) or arginino succinate lyase (ASL). Insertion of the UG-repeats of *nii1*, *gs2* and *arg7* into the 3'-UTR of a luciferase reporter can trigger circadian expression of the reporter with a maximum during day-phase (2, 3). We have selected further components of nitrogen metabolism involving a key enzyme, a transporter and a transcriptional regulator to insert UG-repeat elements in their 3'-UTRs. We cloned the chimeric constructs, transformed wild type and mutant strains where these genes are defect and are now on our way to characterize them functionally. With such strains, we aim to achieve an improvement in nitrate uptake and metabolism during day-phase. In parallel, we have started to model pathways involved in nitrogen metabolism of *C. reinhardtii* using the concept of elementary flux modes (4) by analyzing incorporation of compounds via asparagine, lysine or arginine biosynthesis. This should enable us to select further critical components for experimental modulation. Moreover, we simulated three different day times that provide clues about the diurnal behavior of the uptake of nitrogen compounds in *C. reinhardtii*.

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14| Hierarchically evolvable components for complex systems: Biologically inspired algorithmic design

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Biological reaction networks form efficient computational devices capable of controlling information processing in living organisms [1]. Questions about programming techniques for biohardware are of particular interest to explore and substantiate biologically inspired computing paradigms. Research projects

within our group investigate different approaches for modelling, simulation, construction, and validation of biohardware components at specific levels of abstraction. We consider two aspects: Firstly, identification of the function of networks found in pro- or eukaryotic cells providing templates for algorithmic elements. Secondly, development of network engineering techniques can adopt and amalgamate those templates in order to achieve and optimise more complex algorithms. Based on findings and implementations of biological systems, dedicated wetlab experimental data embody a first behavioural description [2]. Here, the huge amount of low structured data reflects its inherent stochasticity as well as redundancy [3]. The next level of abstraction is reached by representations of reaction systems on a submodular level. Consequently, cell signalling and gene regulatory networks provide predefined functional units of high reliability. Balanced inhibiting and activating effects lead to system descriptions at a modular level [4]. Finally, data condensation affords chemical organisations [5]. We exemplify interconnections between these levels as well as their application for algorithmic design by RS flip-flops. Beyond engineering methods for biohardware programming, heuristics like evolutionary network reconstruction tools are incorporated [6].

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15| Structure-function-relationship of the APP-E1-domain

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Alzheimer's disease is one of the most frequent forms of dementia in the elderly population affecting about 25 % of people in the age of 80 to 90 years [1]. Due to the more and more ageing society the importance of dementia is increasing. In spite of intensive research it was not yet possible to find an effective drug against Alzheimer's disease.

The brain of affected patients is characterized by the deposition of senile plaques containing the neurotoxic peptide $A\beta_{40-42}$, that is derived out of its precursor, the Amyloid Precursor Protein (APP) [2]. Beside its role in Alzheimer's pathology many physiological functions, like stimulation of synaptogenesis and signal transduction in a receptor-like manner are discussed for APP [3]. However, until now it was not possible to correlate the known structures of subdomains with most of the proposed physiological functions of APP.

Here we present the structural and biochemical characterization of the APP-E1-domain showing that the growth-factor-like domain (GFLD) and the copper-binding domain (CuBD) form one closed structural and hence functional entity. In biochemical experiments we show the heparin dependent dimerization of the E1-domain which interestingly occurs in a pH dependent manner [4].

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16| Toward a *de novo* assembly of the highly repetitive *N. furzeri* genome: a novel pipeline for contig scaffolding and assembly

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With the advent of next generation sequencing technologies (NGS), whole genome sequencing (WGS) can be conducted for much reduced prices and timescales. However, increased error rate and short read length in NGS introduces new difficulties to *de novo* whole-genome assemblies and to mapping NGS reads to a reference. Moreover, many unassembled genomes remain so due to the high genome complexity introduced by repetitive genome motifs and gene duplication found in higher vertebrates and grains. Using a mixture of Illumina and 454 sequencing technologies, we have developed and utilized a novel masking pipeline to perform *de novo* assembly and scaffolding of a 1.5-2 Gb highly repetitive (>45%) unassembled genome, the turquoise killifish *Nothobranchius furzeri* and validated the assembly against the most up-to-date transcriptome data (see poster of A. Petzold et al.). Additionally, a genome browser for the *N. furzeri* genome assembly is currently under development.

17| Raman spectroscopy in zygomycetes: Determination of fatty acid content and saturation in distinct lipid enclosures of hyphae from *Mortierella* spp. (Mortierellomycotina, ex Zygomycetes)

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Members of the order Mortierellales constitute a remarkable group of the Zygomycetes fungi, which is morphologically, ecologically, chemotaxonomically and phylogenetically distinct from the core Mucoromycotina. Therefore, the Mortierellales were recently classified in a separate subphylum, the Mortierellomycotina Kerst. Hoffm., K. Voigt, P. M. Kirk 2011. This group of filamentous fungi shows

extremely high ecological and physiological diversity and is distributed world-wide. Most species of these fungi are lipid accumulating organisms (such as *Mortierella alpina*) having great biotechnological importance as industrial producers of polyunsaturated fatty acids, like arachidonic acid or eicosapentaenic acid. Both, the content of fatty acids and their rate of saturation are known to be temperature-dependent and vary during utilization of different cultivation media. The aim of the present project is the elucidation of the fatty acid content and composition of twelve *Mortierella* species by Raman spectroscopy. Moreover, fatty acid composition was measured directly in the hyphal lipid enclosures in time course experiments. The data indicate the large potential of *Mortierella* spp. in fatty acid production for 'white biotechnological' purposes.

18| *De novo* assembly and annotation of the *Nothobranchius furzeri* transcriptome – a new model for ageing research

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The turquoise killifish (*Nothobranchius furzeri*) is the vertebrate with the shortest known lifespan in captivity. Furthermore, laboratory strains derived from wild locations showing differences in yearly precipitation have differences in their lifespan in captivity (3 to 9 months). This makes *N. furzeri* a promising model organism for ageing research.

By RNA-seq we want to identify determinants for ageing in *N. furzeri*. One prerequisite for this analysis is an annotated reference sequence of its transcriptome. Towards this, we generated more than 100 million ESTs with Sanger, 454 and Illumina sequencing, comprising a total of 12 Gb raw transcriptome data. Based on a two-step assembly procedure including classical as well as new assembly tools relying on De Brujin graphs, we assembled 118,548 contigs with a total length of 109 Mb (N50: 1,194 bp, largest contig: 11,285 bp). Of these, 36,378 contigs are longer than 1 kb comprising a total of 64 Mb.

To assess complexity and completeness, we compared the *N. furzeri* transcript contigs to the four most closely related fish species with an assembled genome: the zebrafish (*Danio rerio*), the Japanese ricefish medaka (*Oryzias latipes*), the three-spined stickleback (*Gasterosteus aculeatus*) and the green spotted pufferfish (*Tetraodon nigroviridis*). Based on BLAST analyses against protein sequences of the four fish species (ENSEMBL, database version 58.1j), we estimate that the current *N. furzeri* transcript catalogue contains 20,979 unique transcript contigs derived from 18,065 genes. These represent roughly 90% of all protein coding genes in *N. furzeri*.

A transcriptome browser was set up containing the current transcript assembly supplemented with the best currently available annotation. A complex query mask allows to quickly find transcripts of interest and search results can be downloaded. Furthermore, sequence similarity search can be done by an implemented BLAST server. Transcripts are linked to a genome browser currently being set up which allows to examine the genomic structure of the transcript.

Altogether, the presented transcriptome *de novo* assembly and annotation will provide the basis for gene expression analyses in *N. furzeri* of different strains and ages.

19| Rhizomucormycosis: First records in amphibians

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Among the members of the subphylum Mucoromycotina several species are known to be opportunistic pathogens. Those species belong mainly to the genera *Rhizopus*, *Mucor*, *Lichtheimia*, *Apophysomyces* and *Rhizomucor*. Infections caused by these species do occur predominately in immunocompromised hosts and grow at elevated temperatures in axenic cultures. Although few infections in amphibians are known, this is the first report of an infection of amphibians by a member of the genus *Rhizomucor*.

20| Computational inference of metabolic reaction networks for degradation pathways in bacterial communities

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*** represented by Gabi Escuela**

Microbial activity is usually the result of many microbial species interacting with each other, e.g. by metabolite exchange, or via substrate competition. Over the past years information on the metabolic capabilities of many soil and groundwater bacterial species has been investigated in detail and is collected in numerous online databases. Interaction network models allowing for the computation of admissible metabolic fluxes, quantitative estimation of substrate consumption, or contaminant degradation have been developed.

By now, we are going the next step and design algorithms and tools to collect existing knowledge from databases and integrate those data into complex metabolic interaction network models of bacterial communities. Currently we develop a set of tools to predict which substrates are necessary to let certain target compounds be degraded, which undegradable products may remain, and how different strains may be added to avoid accumulation of such terminal substances. This will allow us to investigate how bacteria interact with each other on the metabolic level, and how this interaction influences the communities' performance, for example with respect to contaminant degradation. The obtained theoretical results will be accompanied by laboratory experiments to verify and refine the computational approach.

Ultimately, we aim at the prediction of the degradation potential of bacterial communities at given environmental conditions. In order to achieve these goals, computational methods from different fields are required; this includes graph theory, flux analysis, and linear integer programming. In addition, thermodynamic considerations will be taken into account to constrain the direction of metabolic reactions.

On the poster, we will show first results of the network analysis and our preliminary laboratory experiments.

21| New developments in the diurnal changes of nitrogen metabolism in *Chlamydomonas reinhardtii*

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The capability of plants to assimilate nitrogen plays a crucial role in optimising biomass production. This is of particular interest for maximising crop yields as well as for detoxifying stressed soils.

The green algae *Chlamydomonas reinhardtii* renders a suitable model organism, as it is rather easily accessible compared to higher plants and shows circadian oscillations, which are involved in many metabolic and physiological processes [1]. Furthermore, new findings reveal that several RNAs are alternatively spliced in the green algae [2]. We demonstrate that stoichiometric data are sufficient to provide valuable insight into the nature of the nitrogen uptake system. This is achieved by considering different carbon sources, environmental conditions, the repressive behaviour of the circadian regulated mRNA-binding protein CHLAMY1 [3] and the application of Elementary Flux Mode analysis [4]. We retrieved the most efficient fluxes in regard to the biosynthesis of amino acids that show a high nitrogen to carbon ratio. Moreover, we provide clues for the role of CHLAMY1 in the regulation of nitrogen uptake and show a reasonable time course of nitrogen incorporation throughout the day.

An investigation of the overall distribution of amino acids in *C. reinhardtii* reveals a rather high abundance of simple amino acids in the green algae. Thus, we included these amino acids into our metabolic pathway analysis as they constitute a potential alternative nitrogen deposit.

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22| A novel splice variant of $Na_V1.8$ voltage-gated sodium channel from human dorsal root ganglion neurons leading to skipping of exon 11

Jana Schirmeyer, Enrico Leipold, Stefan H. Heinemann, Christian Mawrin, Matthias Platzer, Karol Szafranski

$Na_V1.8$ voltage-gated sodium channels are expressed in afferent neurons of dorsal root ganglia (DRG) where they are involved in the perception of inflammatory and chronic pain. Various cellular mechanisms, e.g. auxiliary subunits and posttranslational modifications, as well as mRNA processing, allow for specific

functional regulation of these channels. We isolated mRNA from human, rat, and mouse DRG tissue samples and screened them for alternatively spliced isoforms of SCN10A, the gene encoding NaV1.8, using 454 sequencing technology.

We identified a novel splice variant of human SCN10A, which results from skipping of exon 11. The protein encoded by the new splice variant will lack 98 amino acid residues (from serine 488 to serine 585) in the cytoplasmic loop between domains I and II. This region is highly involved in channel regulation as it contains various putative phosphorylation sites. The abundance of the splice event was independently analyzed by capillary electrophoresis of fluorescence-labeled RT-PCR products. The relative amount of $Na_V1.8\_\Delta e11$ compared to $Na_V1.8$ wild-type mRNA in human adult DRGs was 5% in three individual samples. The splice event could be detected in neither rat nor mouse DRG tissue, and thus is not conserved among rodents and human.

We constructed $hNa_V1.8\_\Delta e11$, the gene product of the short splice variant, using a PCR-based strategy. To examine the influence of the splice event on channel function we expressed both isoforms of $hNa_V1.8$ in neuroblastoma cells (Neuro-2A) and compared their functions using the whole-cell configuration of the patch-clamp method. All experiments were performed in the presence of 100 nM extracellular tetrodotoxin (TTX) to suppress TTX-sensitive currents endogenous to Neuro-2A cells. Mutant and wild-type channels reached similar current densities at test pulses to 0 mV (62.5 ± 15.6 pA/pF, n = 13 for $hNa_V1.8\_\Delta e11$ and 62.9 ± 13.1 pA/pF, n = 15 for $hNa_V1.8$ wild type), indicating that the splice event has no effect on the production of functional channel proteins in this expression system. Voltage dependence and kinetics of channel opening and inactivation was assayed by tailored pulse protocols, however, in none of the measured parameters the alternatively spliced isoform deviated from the control channel (n = 13 for $hNa_V1.8\_\Delta e11$, n = 15 for $hNa_V1.8$ wild type, t-test: P-values > 0.25).

As reported in Zhang et al. (J Cell Sci 121 (19): 3243. (2008)), exon 11 contains an ER retention signal involved in the regulation of the cell surface expression of $Na_V1.8$ channels. We therefore compared the expression of $hNa_V1.8\_\Delta e11$ and wild type in HEK 293 cells because $hNa_V1.8$ channels are hardly expressing in these cells. In three of 23 cells transfected with $hNa_V1.8\_\Delta e11$ we detected an average maximum current density of 21.3 ± 6.4 pA/pF at pulses to 0 mV; for $hNa_V1.8$ wild type we only found specific Na^+ current in one cell with 23 pA/pF out of 24 cells tested.

The splice event leading to $Na_V1.8\_\Delta e11$ channels thus does not appear to have an obvious impact on channel function under the given experimental conditions. Different approaches may help to identify effects on targeting and clustering of $Na_V1.8$ channels or on its modulation by phosphorylation, processes that are possibly influenced by skipping of exon 11.

23| Direct analysis and identification of opportunistic *Lichtheimia* species by Matrix Assisted Laser Desorption Ionization (MALDI) - Time-Of-Flight (TOF) analyzer-mediated mass spectrometry

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Zygomycetes can cause life-threatening infections (Zygomycosis) which are characterized by rapid destruction of tissue and a high mortality rate. Moreover Zygomycetes are resistent to many antifungal drugs. Therefore, fast and reliable identification is important. Here we present MALDI-TOF mass spectrometry based method for the identification of *Lichtheimia* species. MALDI-TOF profiles revealed a high resolution on the intergeneric level resulting in a clear discrimination of *Lichtheimia* spp. from other clinically relevant mucoralean fungi. Although resolution decreases on the intrageneric level clinically relevant *L. corymbifera*, *L. ramosa* and *L. ornata* could be discriminated from clinically irrelevant species *L. hyalospora* and *L. sphaerocystis*.

24| Evolution of a long healthspan in African mole-rats

K Szafranski, A Petzold, K Huse, T Hildebrandt, H Burda, P Dammann, M Platzer

As was pointed out recently*, „virtually all research on basic mechanisms of aging has used species that are short-lived and thus demonstrably unsuccessful at combating basic aging processes." This limitation may be overcome with the study of African mole-rats which comprise the longest-lived rodents known. For example, the maximum lifespan of the the naked mole-rat (*Heterocephalus glaber*) is 28.3 years, 6-7 times higher than that of mouse and about 8 times higher than predicted from its body mass. Breeding females („queens") who carry the reproductive burden of an entire colony do not show a decline in fertility and even have an elongated life span compared to non-breeders. Moreover, spontaneous tumors have never been observed in these species. For these reasons, mole-rats are of special interest in the search for mechanisms leading to particularly long, healthy lives.

We have constructed gene catalogs of African mole-rat species and their shorter-lived relatives. Through sequence comparisons and by tracking evolutionary signatures of positive selection we aim at identifying target genes which have undergone lifespan-related adaptation. Alternative pathways of gene evolution, mutation as well as gene duplication and subsequent differentiation, can give rise to complex molecular patterns. On the other hand, the correlation analysis is challenged by the fact that ecological and social traits have coevolved together with long healthspans.

* S Austad. J Geront 64:199 2009

25| Interaction of opportunistic pathogenic fungi and human phagocytes: A multi-agent-based modeling approach

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The fungal pathogen *Aspergillus fumigatus* causes severe systemic diseases in immunocompromised patients [1,2]. Although this fungus is found worldwide and its small conidia are present in air and food [2] it is almost harmless to healthy people, since inhaled conidia are phagocytosed by macrophages and neutrophil granulocytes [1]. However, neither the cellular dynamics, the per-cell efficiency, the outcome of this interaction, nor the environmental impact on this process are known [3]. Live imaging shows that the interaction of phagocytes and fungal conidia is a dynamic process of touching, dragging and phagocytosis [3].

Using multi-agent-based modeling, the interactions of human neutrophil granulocytes and *Aspergillus fumigatus* are simulated to gain knowledge about different behavioral strategies by optimizing parameter settings such as velocity of cells, dragging and phagocytosis efficiency as well as movement directions. Behavior of simulated cells is compared to those of living cells in liquid cultures gained by live imaging data.

Implemented in the multi-agent modeling environment NetLogo [4], neutrophil granulocytes and conidia of *Aspergillus fumigatus* are modeled as distinct agents, whose individual behavior is determined by spatial settings, e. g., density of cells, communication between cells, individual states and is influenced by random effects. Moreover, chemotaxis and random movement of immune cells are compared to get insight into advantages in regard to phagocytosis efficiency.

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26| The Jena Centre for Systems Biology of Ageing - JenAge

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No abstract available.

27| Reconstruction of the phylogeny of the Mortierellales based on nucleotide sequences of the internal transcribed spacer from the nuclear ribosomal DNA cluster

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The basal fungal genus *Mortierella* (Mortierellomycotina) consists of more than 80 described species, many of them with biotechnological applications. E.g. *Mortierella alpina*, *M. alliacea* and *M. parvispora* were identified as high potential producers of polyunsaturated fatty acids (PUFAs). But one species, *M. wolfii*, is also known as a potential pathogen to animals. *M. wolfii* causes abortion in cattle and swine with disadvantages in agriculture. Although *Mortierella* species are common soil fungi, this genus might possess a broader range of potential biotechnological applications then discovered till now. Unfortunately, less is known about the natural family structures within this subphylum. In a first step we analyzed the family structure and searched for a fast method to identify environmental samples. Our analysis based on a total of 90 isolates and clearly indicate that the current classification scheme is highly unnatural.

28| Phylogenomics of MADS-box genes in maize

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MADS-box genes encode transcription factors that consitute a large gene family in land plants identified by containing the DNA binding MADS domain. They have been divided into two major groups, type I and type II, which differ in gene structure, rates of evolution and function. Comprehensive studies of the gene family have been released for *Arabidopsis thaliana*, poplar and rice. In maize, several genes have already been individually identified and studied. However, the recent publication of the maize genome sequence now allows us to characterize the complete gene family in maize. A phylogenic analysis identified members of the major groups and subfamilies proposed in previous studies. Chromosomal localization and a comparison to related genes from rice allowed us to track the consequences of the recent genome duplication in maize on the gene family. Phylogenetic and structural analyses also revealed strong indications of transposon activity.