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RESEARCH CONFERENCES

ESF-UB Conference in Biomedicine

Bacterial Networks 2010

Hotel Eden Roc, Sant Feliu de Guixols (Costa Brava) • Spain

4-9 September 2010

Chair: **Urs Jenal**, University of Basel, CH
Vice-Chair: **Regine Hengge**, Freie Universität Berlin, DE

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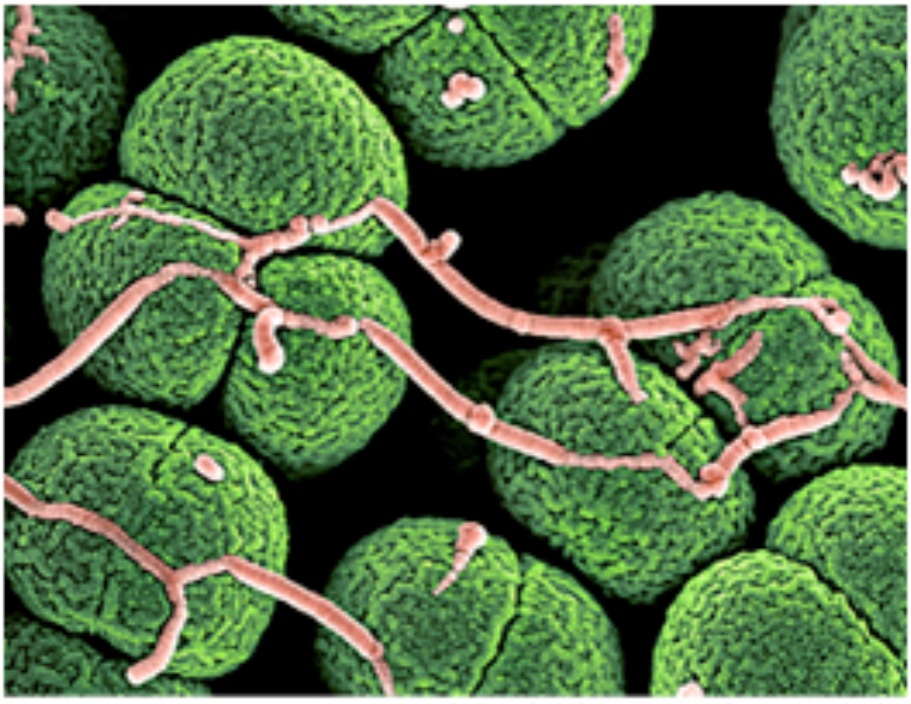
Highlights & Scientific Report



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Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

The conference on Bacterial Networks 2010 (BacNet/10) covered architecture, function and dynamics of regulatory and metabolic networks in bacteria. With a long speaker list of some of the foremost people in the areas of molecular microbiology, modeling, and system engineering in Europe and the US, the conference fully succeeded in its original task to provide a meeting platform at the forefront of new research developments in modern-day quantitative molecular microbiology and to give students a comprehensive overview of the current concepts and state-of-the art technologies of the field. The conference was more than 200% oversubscribed precipitating a discussion on a possible extension of the meeting was discussed but rejected by a clear majority in favor of maintaining highest quality standards in future BacNet meetings.

BacNet/10 had a strong focus on the emerging complexity of genetic, regulatory and metabolic networks in bacteria and featured sessions on global regulation, microbial development and cell biology, stress response, and cell-cell communication. These contributions were interspersed with sessions and talks on mathematical modeling and engineering of bacterial networks. In the following I would like to highlight a few of the meeting's main topics. Several talks addressed the questions of how bacteria perceive environmental signals, how they transfer this information to their interior and how they process and integrated it to produce an appropriate cellular response. This included contributions on how bacteria sense nitric oxide to communicate with its host during symbiosis (Ruby, University of Wisconsin) or how they use light as information to adjust their basic activities with the circadian rhythm (Golden, UC San Diego). Several novel signal transduction mechanisms were introduced based on ECF-type sigma factors (Vorholt, ETH, Zürich; Crosson, University of Chicago), RNA molecules (Hengge, Freie Universität Berlin; Henkin, Ohio State University; van der Oost, Wageningen University), small proteins (Storz, NIH), or second messenger signaling compounds (Dow, University College Cork; Schirmer, University of Basel; Viollier, University of Geneva). As exemplified for two-component sensory systems (Laub, MIT), signal transduction pathways are able to evolve through gene duplication and the formation of new interactions through mutational steps that alter the connectivity between signaling partners. A series of talks identified factors contributing to the sensitivity and robustness of information transfer processes and addressed the question of how this information could be used towards a quantitative and predictive understanding of living systems (Sourjik, ZMBH Heidelberg; Panke, ETH, Zürich; Hasty, UC San Diego). A particularly nice example was given by Jeff Hasty who reported on the engineering of a synchronized genetic clock capable of generating oscillations in a growing population of bacterial cells. With ever-improving power of microscopy techniques, the importance of the spatial organization of bacterial cells has come apparent over the past decade. Several talks addressed the dynamic behavior of proteins and DNA in the three-dimensional context of the cell. Examples included the context dependency of bacterial promoters (Busby, University of Birmingham), as well as spatial organization directing morphological transitions (Rudner, Harvard University; Elliot, McMaster University), conferring directionality to cellular processes like DNA segregation (Jacobs-Wagner, Yale), or contributing to signal transduction processes (Armitage, University of Oxford; Lopez; Harvard University; Briegel, Caltech). Despite of considerable progress made in the functional characterization of cellular components, the role of a large fraction of bacterial genes and proteins remains elusive. Chemical-genetic profiling was introduced as a novel method to define novel gene functions and to assign so far uncharacterized bacterial genes to known cellular pathways (Typas, UC San Francisco). The method is based on exposing libraries of single knock-out mutants to a large variety of metabolic and chemical stress conditions and assigning individual components to specific pathways through the definition of new common phenotypes. Finally, it was discussed how the increasing knowledge on cellular networks

in bacteria can be exploited to chemically counteract their pathogenic exponents. Novel observations on the mechanisms of quorum sensing in *Pseudomonas aeruginosa* have renewed the promise to exploit this cell-cell communication system as potential target for antimicrobials (Greenberg, Washington University). Likewise, modeling of the metabolic network of Salmonella operating during human and animal infections allows certain predictions about metabolic fluxes and uncovers the organism's Achilles heels to be exploited as potential targets for novel antimicrobial substances (Bumann, University of Basel).

☒ I hereby authorize ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

Scientific Report

Executive Summary

(2 pages max)

A total of 32 main talks were given by invited speakers and 14 short talks were selected from conference abstracts. Oral contributions were completed by a total of 97 posters. With a total of 150 people attending the meeting, this amounts to almost all attendees having delivered either an oral contribution or a poster. Apart from the many highlights in the oral sessions, it is worth mentioning that the quality of the poster presentations at BacNet/10 was very high and that poster sessions were exceptionally well attended. This results from the stringent selection of participating students, postdocs and young faculty and is one of the cornerstones of the BacNet meeting series.

One word to the budget: Resources were acutely limiting to such an extent that the chair, the vice-chair and the entire scientific advisory committee were covering meeting and travel costs themselves. A total of €20K were contributed by ESF and €10K were from FEMS, the latter amount being earmarked entirely for student travel grants. Despite of some additional funding from EMBO, SGM, and NEB, it was not possible to cover the local costs of all invited speakers/chair with the available resources. It should be noted that, with one exception, no resources were spent on covering travel costs of invited speakers. The travel costs of Dr. Hasty, a young faculty at UC San Diego, were covered partially.

Scientific Content of the Conference

(1 page min.)

- Summary of the conference sessions focusing on the scientific highlights
- Assessment of the results and their potential impact on future research or applications

Session on **Global Regulation**:

Steve Busby (University of Birmingham) impressively illustrated that bacterial promoters are context-dependent. He showed that both strength and induction kinetics of a model promoter critically depends on its location on the bacterial chromosome. This indicates that the landscape of RNA-Polymerase accessibility in bacteria is not homogeneous and that RNA-Polymerase might be limited at distinct loci of the bacterial chromosome. These results will add to a more in-depth view of gene expression and nucleoid organization within the three-dimensional context to the bacterial cell. A total of three talks in this session centered on the molecular and cellular role of the global bacterial second messenger c-di-GMP. Regine Hengge (Freie Universität Berlin) reported on a novel molecular switch mechanism that in *E. coli* stationary phase mediates between capsule biosynthesis and biofilm formation. The switch is based on a small regulatory RNA that antagonizes the c-di-GMP network to globally control surface attachment and biofilm formation. Max Dow (University College Cork) reported on the role of the second messenger c-di-GMP in the plant pathogen *Xanthomonas campestris* and Tilman Schirmer gave a broad overview on structural and mechanistic aspects of c-di-GMP signaling components. Together with a series of poster contributions to the same prominent signaling topic, these talks significantly advanced our understanding of the molecular details of c-di-GMP signaling in bacteria and direct the efforts of the research community towards a systems-level understanding and exploitation of c-di-GMP signaling as target for chemical interference with chronic infections. In the last two talks of this session RNA-mediated cellular processes were discussed. Tina Henkin (Ohio State University) gave an overview on riboswitches and explained how these RNA elements regulate gene expression in cis through direct monitoring of physiological signals. Johan van der Oost presented

the latest developments in understanding the molecular mechanisms of ‘clustered regularly interspaced short palindromic repeats’ (CRISPR), an RNA-based adaptive immunity-like defense system that protects bacteria and archaea against mobile genetic elements.

Session on **Development**:

David Rudner (Harvard University) presented data on how the coordinated action of cell wall biogenesis enzymes mediates spore morphogenesis in *B. subtilis*. Similarly, Marie Elliot (McMaster University, Hamilton) reported on the role of peptidoglycan hydrolysis enzymes in sporulation and spore germination in Streptomycetes. Tam Mignot reported on the molecular dissection of the *Myxococcus xanthus* gliding motor and presented preliminary evidence that the surface gliding machinery is powered by proton motif force. Susan Golden (UC San Diego) gave a comprehensive overview on the cyanobacterial circadian clock mechanism that allows these organisms to tell time. Like most cellular processes, cell division and cell cycle processes is gated by the central KaiABC circadian oscillator circuit. These analyses not only recognized the key circadian clock components as being involved in gating cell division, but also identified increased ATPase activity of one of the oscillator proteins as being responsible for closing the cell division gate.

Session on **Molecular Cell Biology**:

Christine Jacobs-Wagner (Yale University) reported on the molecular dissection of chromosome segregation in *Caulobacter crescentus*, where TipN, a protein positioned at the new cell pole, confers directionality to the ParS/ParB/ParA centromer complex to drive movement of one of the newly replicated Cori regions to the opposite pole. This work provides a mechanistic framework for a self-organizing oscillator that is able to create motion suitable for chromosome segregation. The cell wall is an essential structure for virtually all bacteria forming a tough outer shell that protects the cell from damage and osmotic lysis. Jeff Errington (Newcastle University) reported on *Bacillus subtilis* L-forms, specific morphotypes that can grow and divide without a cell wall. The generation of viable L-forms is linked to distinct mutations in components of cell wall homeostasis that predispose cells to growth without a wall. Growth and division without cell wall strongly deviates from classical forms of bacterial cell proliferation and may provide insights into cell proliferation of early forms of cellular life. Richard Losick (Harvard University) presented data on the regulation of biofilm formation and disassembly in *B. subtilis*. A self-reinforcing double negative feedback loop that acts as epigenetic switch controls biofilm assembly and disassembly in this organism. The same switch was shown to control the expression of amino acid racemases and D-amino acids were identified as key regulatory compounds of biofilm dissolution in *Bacillus* and a range of other gram-positive and gram-negative bacteria. This discovery exposed D-amino acid metabolism as an attractive target for chemotherapy directed against microbial biofilms in a wide range of bacteria. Dirk Schüler gave an overview on the molecular and cellular basis of magnetotactic behavior in bacteria and on the recent progress in understanding magnetobacterial cell biology. The formation of magnetosome organelles requires compartmentalized biomineralization within a specialized intracellular membrane system providing proteins for iron transport and crystallization. These studies will not only reveal novel aspects of cellular compartmentalization in microorganisms but will contribute to a cellular understanding of iron mineralization in bacteria.

Session on **Networks and Switches**:

Tom Silhavy (Princeton University) reported on some new results analyzing the specific role of the Crl protein in E. coli nitrogen and carbon starvation. Crl facilitates RNA polymerase holoenzyme formation in stationary phase. Judy Armitage (University of Oxford) introduced a system responsible for chemoreceptor segregation during cell division that is analogous to the Par system involved in DNA segregation during division. Michael Laub (MIT) outlined how novel signal transduction pathways could evolve through duplication of genes coding for sensor histidine kinases and response regulators and the formation of new specific interactions through mutational steps that alter connectivity between these direct signaling partners. Sandy Parkinson (University

of Utah) reported on some recent discoveries on the molecular function of HAMP domains that act as hinges between signal input domains and output helices of chemoreceptors or sensor histidine kinases.

Session on **Bacterial Stress Response**:

Gisela Storz (NIH Bethesda) discussed the annotation and function of small proteins of 50 or fewer amino acids in bacteria. These proteins were often missed by classical genetics or proteomic analysis and thus are poorly characterized. Many of these proteins accumulate under specific growth conditions or are stress induced, indicating that they are an overlooked set of stress proteins, with a diverse range of functions. It is proposed that some of these proteins could act as modulators of the activities of their specific target proteins. Julia Vorholt (ETH Zürich) summarized work that led to the identification of the PhyR stress response regulon in *Methylobacterium extorquens* as novel signal transduction paradigm that relies on sigma factor mimicry. This system, which is wide-spread in alpha-proteobacteria makes use of NepR-like anti-σ and PhyR-like anti-anti-σ factors that control the activity of EcfG-type sigma factors. PhyR homologs contain a C-terminal receiver domain typical for bacterial response regulators. Upon phosphorylation, PhyR titrates NepR away from EcfG, thereby releasing the σ-factor to recruit RNA polymerase and initiate transcription of its target genes. The presentation of the first three-dimensional structure of a PhyR anti-anti- σ homolog by Sean Crosson (University of Chicago) provides an entry point into understanding the mechanism of the reversible, phosphorylation-dependent partner switching module that orchestrates general stress response. Nassos Typas (UC San Francisco) introduced chemical-genetic profiling as a novel method to define novel gene functions and to assign so far uncharacterized bacterial genes to known cellular pathways. Clones of an *E. coli* single gene deletion library were exposed to a large variety of unique chemical and physical stress conditions and respective genes were assigned to specific pathways by cluster analysis. This strategy allowed identifying phenotypes for so far uncharacterized orphan genes, thereby significantly expanding functional knowledge on bacterial proteins. E.g. two so far uncharacterized outer membrane lipoproteins were identified to functionally interact with and modulate enzymes involved in cell wall biogenesis.

Session on **Cell-cell Communication/Sociomicrobiology**:

Ned Ruby (University of Wisconsin) reported on the role of nitric oxide (NO) in the squid-vibrio symbiosis. During squid colonization Vibrio fischeri encounters host-derived NO, which has been hypothesized to serve as a specificity determinant. The studies presented strongly suggest that V. fischeri uses NO as host signal to appropriately modify its own gene expression profile during the associations with its host. Peter Greenberg (University of Washington) reported on aspects of microbial sociobiology and the fact that intercellular signaling by quorum sensing controls “public goods” in bacteria. Many bacteria have an orphan gene coding for a HSL receptor (R) that lacks a cognate HSL synthase (I) counterpart. Interestingly, QscR, a member of the orphan R family in P. aeruginosa is activated by LasI-derived C12 HSL. In contrast to C12 binding to LasR, binding to QscR is reversible. This raises the chance for anti-QS receptor based drugs, as normal R proteins fold around the HSL ligand irreversibly and therefore require very high antagonist concentrations.

Sessions on **Network Modeling and Engineering**:

Martin Howard (John Innes Center, Norwich) modeled the distribution of the critical morphogen DivIVA and its impact on branching, tip splitting and curvature during Streptomyces hyphal growth. Jeff Hasty (UC San Diego) reported on the engineering of a genetic circuit capable of generating synchronized oscillations in a growing population of cells. The synchronized genetic clock is based on positive feedback loops that confer robust oscillatory behavior. Sven Panke (ETH Zürich) reported on the optimization of catalytic pathways by selectively removing enzymes from a complex mixture with proteases recognizing engineered protease sites. Luis Serrano (EMBL Barcelona) reported on the progress towards a fully quantitative and predictive understanding of a

living system. Quantification of protein and RNA abundance and turnover of Mycoplasma pneumoniae, with 680 open reading frames one of the smallest self-replicating organisms, revealed an unexpected complexity of gene regulation with frequent antisense transcripts and alternative transcripts. Victor Sourjik (ZMBH, Heidelberg) addressed the factors affecting network robustness and sensitivity of a biological system using the example of bacterial chemotaxis. Both experimental and modeling studies revealed how translational coupling of opposing enzyme activities within a given pathway contributes to network robustness. Dirk Bumann used modeling tools to predict target sites for antimicrobial compounds interfering with *Salmonella* metabolism in the host situation. Kelly Hughes (Université de Fribourg) presented experimental evidence in favor of codon context effects on ribosome speed. By demonstrating that synonomous mutations are not neutral, these data strongly argue against the neutral theory of selection and favor of a selectionist view of evolution.

Forward Look

(1 page min.)

- Assessment of the results
- Contribution to the future direction of the field – identification of issues in the 5-10 years & timeframe
- Identification of emerging topics

While participants agreed that BacNet/10 (like previous BacNet conferences) was the best European conference in the field of bacterial molecular and systems biology in 2010, it also became apparent that some organizational details require improvement for future BacNet conferences. During past years, September has developed into a month now literally crowded with international scientific meetings. Moreover, the deadline for applying for future ESF Conferences is in September as well, with the consequence that there is no time available to integrate the discussions and decisions taken during the conference about the content or organization of future meetings. In other words, it is not possible to have the meeting community participate in the planning of the next meeting, or e.g. also to vote for future chairs and/or vice-chairs.
In order to solve this problem, it was decided to apply in September 2011 for the next meeting to take place in spring 2013. Moreover, while the future Chair for BacNet/13 (Regine Hengge, Freie Universität Berlin) had already been determined and was active as a Vice-Chair in 2010, the BacNet/10 community voted for a new Vice-Chair for 2013 and prospective Chair for 2015 (Kelly Hughes, Université de Fribourg). The entire community definitely agreed that the size of the BacNet Conference (max. 150-160 participants) and, if possible, the location (Eden Roc, Sant Feliu de Guixols) should remain the same for BacNet/13. In particular, it was pointed out that moving future BacNet Conferences to an Eastern European location would significantly reduce the number of participants from the US and thereby endanger the international standing of the BacNet Conference.
In addition, the scientific content of future BacNet meetings was intensely discussed during BacNet/10. It is clear that architecture, function and dynamics of regulatory networks will remain perhaps the most important field for understanding molecular structure and function of bacteria, their role in pathogenesis and ecology and their use in biotechnology. Blending the perspectives of molecular and systems biology on bacterial regulatory networks has been and will continue to be immensely successful. In addition, two new trends will be integrated into the future planning of BacNet Conference topics. These are an increasing importance of bacterial cell biology and metagenomics. Both have been made possible by dramatic technical developments, i.e. in microscopic technology and in large-scale DNA sequencing. These now allow us to begin to see the spatial architecture of intra- and intercellular networks and to get an idea of the breath-taking multitude, variability and evolutionary adaptation potential of regulatory networks in the bacterial world. Thus, broadening the perspective of approach while maintaining the focus on bacterial regulatory networks will make the BacNet Conference even more attractive and the most important European meeting in the field of microbiology.

- Is there a need for a foresight-type initiative?

Atmosphere and Infrastructure

▪ The reaction of the participants to the location and the organization, including networking, and any other relevant comments

From the manifold feedback that I received about the conference venue, the available infrastructure and the conference atmosphere, it is absolutely clear that a large majority of attendees very much appreciated the location and would like to come back to the same place for future conferences. The organization of the meeting was extremely smooth and professional on all levels and, at least to my knowledge, was viewed very positively by the conference attendees. Although I have not had insight into the meeting evaluations, I would be very much surprised if there was not a clear trend towards such a very positive view from most people attending BacNet/10.
The meeting program was deliberately set up to provide ample time for interactions and networking between students, postdocs and established researchers before and after oral presentations and poster sessions. This was very much facilitated by the meeting facilities, which offer enough quiet space at the pool or at the bar for informal gatherings right next to the lecture hall. As a regular member of Gordon Research Conferences I do find the organization of these ESF meeting series fully competitive with if not superior to the GRC meetings.

Date & Author:

Basel, 13.12.2010

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