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Post-genome science highlights systems biology

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The Consortium for Post-Genome Sciences (http://www.postgenomeconsortium.com) held its second conference, *Genomes to Systems*, on 1–3 September 2004 in Manchester, UK. The programme included sessions on systems biology, structural biology, genomics, protein dynamics, new biosensor technologies, gene–environmental interactions, metabolomics, proteomics and bioinformatics.

Network and systems biology

The conference elegantly illustrated the general progression from a characterization of genomics and proteomics to a more system-wide integration of our knowledge of biology (i.e. systems biology). Albert-László Barabási (University of Notre Dame; http://www.nd.edu/~alb) showed that in the past few years the scientific community has learned that networks of all kinds are not random. Indeed, the structure of networks carries the signatures of self-organizing processes that are governed by simple generic rules. Barabási presented the analysis of the metabolic networks of 43 organisms, in addition to the protein interaction network of yeast. These networks display identical topologic and scaling properties, despite significant variation in their individual components. However, cellular networks have a hierarchical architecture, enabling us to identify the organization of the functional modules embedded in the cellular topology.

Other speakers discussed the application of mathematical models to illustrate the behaviour of complex biological networks. In one presentation, Jennie Reed (University of California, San Diego; http://www.ucsd.edu) demonstrated that known constraints circumscribe the list of possible models, thus making the analysis of networks much easier. Novel theorems that illustrate the differential distribution of the control of the period and duration in oscillating systems between 'producer' and 'consumer' reactions, which has significant implications for the selection of drug targets, were described by Hans Westerhoff (Free University; http://www.vu.nl/home). By contrast, Pedro Mendes (Virginia Bioinformatics Institute; https://www.vbi.vt.edu) addressed effective methods for solving the inverse problem – which system caused the observed behaviour? Michael White (University of Liverpool; http://www.liv.ac.uk) provided an illustration of the powerful combination of mathematical modelling and real-time, single-cell imaging, demonstrating that the dynamics of the system are crucial for conveying the message during cellular signalling in the nuclear factor κ-binding pathway.

Advancing proteomics

Proteomics is now 'coming of age'. After the initial hype, a clearer view as to what can be accomplished with the current approaches is emerging, and the recognition of the many dimensions of proteomics was a major theme of the sessions relating to this area. Although there have been significant advances in mass spectrometric techniques in recent years, this technology still lags behind transcript screening in terms of tractability and quantitative capability. These screens have the potential to deliver much more specific and accurate data. Ian Humphery-Smith (University of Utrecht; http://www.uu.nl) gave a thoughtful insight into proteome complexity and the strategies that should be adopted to deal with this issue. The complex nature of the proteome will not begin to be deconvoluted until accurate quantitative data are acquired. Ruedi Aebersold (Institute for Systems Biology; http://www.systemsbiology.org) indicated that isotope-labelled tags can be used quantitatively to compare the concentration of specific peptides in different protein sources. These techniques considerably expand the utility, as well as increase the throughput, of mass spectrometry (MS) methods. Matthias Uhlen (Royal Institute of Technology, Sweden; http://www.kth.se/eng) described a large-scale Swedish project to generate antibodies for all human proteins. These are currently being used to characterize tissue-specific expression and cellular location, but will eventually form the basis for antibody arrays for assessing protein expression.

Despite the promise of antibody-based methods, there is a convincing case for continuing the central role of MS in proteomics. The recurrent theme of the need for quantification was emphasized by Simon Gaskell (Manchester Interdisciplinary Biocentre; http://www.mib.umist.ac.uk) – well-established precepts in analytical chemistry could be used to drive accurate measurement of the amount

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of a protein in a cell. At the same time, enhancements in mass measurement afforded by cutting-edge MS, as described by Alan Marshall (Florida State University; http://www.fsu.edu), serve to reduce the search space in identification proteomics and are crucial for the accurate definition of the complexity dimension caused by posttranslational modifications, which was a theme addressed by Peter Roepstorff (University of Southern Denmark; http://www.sdu.dk). An important strategy in defining complete proteomes is that of complexity reduction, and Rainer Cramer (University College London; http://www.ucl.ac.uk) described elegant new approaches for the selective analysis of the proteome, particularly in the context of the emerging strengths of liquid chromatography used in conjunction with matrix-assisted laser desorption–ionization time-of-flight MS and MS–MS. Rob Beynon (University of Liverpool) emphasized the temporal dynamics of the proteome and described stable isotope strategies for the measurement of the turnover rate of individual proteins inside the cell. Kathryn Lilley (University of Cambridge; http://www.cam.ac.uk) picked up on the theme of proteome spatial dynamics in the assignment of proteins to discrete sub-cellular spaces.

'Omic overviews

DNA microarrays provide scientists with a first step towards uncovering gene function on a global-scale, which might lead to new target molecules in drug discovery. In the opening plenary session of the conference, Stuart Kim (Stanford University; http://www.stanford.edu) commented that genes participating in the same pathway, or as part of the same protein complex, are often co-regulated. Kim's group has assembled all available DNA microarray data from several key organisms (human, mouse, fly, worm and yeast) and found sets of orthologues that are co-expressed in multiple organisms. This conservation implies that the co-expression of these gene pairs confers a selective advantage and therefore these genes are functionally related. Kim uses the 'gene network' to analyse entire sets of genes to understand the system as a whole. For example, some pathways have gene interactions that are evolving rapidly, whereas gene interactions in others are stable. Kim characterized the connectivity properties of the gene co-expression network as an integrated system and has found that some genetic pathways are designed to be large and others are engineered to be small.

In the session 'Metabolomics – the way forward', several diverse technologies and applications were used to exemplify the information and linked-research that metabolomics can provide. In one impressive example, Douglas Kell (Manchester Interdisciplinary Biocentre) demonstrated that a single gene knockout in yeast can be differentiated from the wild-type by MS profiling of the metabolites the yeast secretes into the media. This provides a useful tool for characterizing different mutants in functional genomics studies. Ian Wilson (AstraZeneca; http://www.astrazeneca.co.uk) showed that NMR- and LC–MS-analysis of mouse urine can detect metabolites that can determine age, gender and disease states in different mouse models. These techniques are in their infancy and undoubtedly will be subject to wider exploitation over the next few years as their power becomes more widely appreciated.

Fundamental science of biosensors

Underpinning the use of new genomic-scale approaches to drug discovery is technology, both for miniaturization and increased sensitivity, as well as via increased throughput and expansion to encompass measurements of the entire genome. The rapid pace of technology development was evident. Andrew Cossins (University of Liverpool) showed that a large-scale integration of academic resources between institutions provides the appropriate interdisciplinary environment within which new technologies can be identified. Cossins went on to describe new sensors involving probe-free, electrochemical and voltammetric detection methods, novel functionalized nanoparticle systems and microfluidic platforms that use nanodroplet technology for high-throughput PCR reactions. Geoff Smith of Solexa (merged with Lynx Therapeutics; http://www.lynxgen.com) described the integrated systems developed by Solexa for whole-genome resequencing. In addition, Smith outlined the recent progress made in sequencing biochemistry at Solexa and its application to resequencing genomic DNA. The comprehensive and economical analysis of individual genomes with application in basic research through to the development and implementation of personalized medicine is the target. Advances in the areas of microfluidics and waveguide technologies were illustrated by Jon Cooper (University of Glasgow; http://www.gla.ac.uk) and Markus Ehrat (Zeptosens AG; http://www.zeptosens.com), respectively. Cooper described novel sensors formed by the fusion of microfluidics with optical sensing techniques for DNA arrays and cell-based screening, whereas Ehrat illustrated the use of waveguide technology to enhance the performance of glass microarrays. All these contributions reflect the intense research and development activity in biosensor technologies that is currently ongoing worldwide.

Future prospects

This conference provided a coherent view of the current state-of-the-art in

assessing genomic complexity, and provided insights into the scale of interactions between components. It also showed how the underpinning 'omic technologies are rapidly diversifying, providing deeper insights into mechanisms and also a range of new profiling tools, many of which can transform diagnostic methodology.

Most importantly, the conference showed how rapidly post-genomics is moving conceptually, and how biological systems can be viewed from a network theory perspective, following the same general rules as other, more familiar, networked systems. These insights point to new strategies for manipulating complex systems, or for understanding the mechanisms behind the breakdown of a system when components fail. Thus, genomics has generated far more than just an increase in scale of parallel analysis; it is creating novel concepts concerning the way in which entire systems function, which in turn is leading to a rapid maturation of our appreciation of biological complexity. All these factors have consequences in the search for new druggable targets and the drugs themselves, which will hopefully be on view at the next conference in May 2006.