

BBSRC TECHNOLOGY STRATEGY: TECHNOLOGIES NEEDED BY RESEARCH KNOWLEDGE PROVIDERS

1. The Technology Strategy sets out six areas where technological developments are required to push the frontiers of knowledge in the biosciences. In many cases these areas involve technologies that have yet to be developed and therefore they provide research challenges at the forefront of physical sciences and engineering. Others are technologies that have been developed but are not widely available in the biosciences or could be applied to new systems and / or in novel combinations.
2. The six areas were identified in consultation with the research community and together they provide a general overview of technological requirements across BBSRC's remit. A number of the areas are interconnected and complement each other. For example, work on gel spot recognition would be relevant to 'omics technologies' and 'functional analysis and bioimaging' while novel probe design could be relevant to 'functional analysis and bioimaging' and 'chemical biology tools'.
3. The Technology Strategy includes areas of relevance to other Research Councils and, in taking them forward, BBSRC will liaise with other sponsors as exemplified by the recent BBSRC / EPSRC Technology Development Research Initiative.

Omics Technologies for Integrative Biology

4. Integrative Biology is a holistic view of biology as an integrated and dynamic whole. It extends from the study of individual molecules, cellular chemistry/biochemistry and biophysics through to how cells and networks of cells function together in integrated ways in tissues, organs and whole organisms and how populations of organisms function in their environment. Many interrelated omic technologies (including genomics, transcriptomics, proteomics, glycomics, metabolomics, and lipidomics) underpin the construction of a dynamic picture of how a biological system operates at a molecular and cellular level. Improved technology is essential to enable comprehensive definitions of each "ome", taking account of the full range of diverse structures and molecular properties. Integration of these omics tools and the development of multi-omics methods are important, together with integrative bioinformatics analysis. Particular requirements include:
 - Enhanced sensitivity of analytical omics techniques enabling progress towards determinations at the single cell level, improved dynamic range and facilitating the study of components and products of complex cellular populations;
 - An increased emphasis on quantitative omics techniques, enabling accurate and precise determination of the dynamic concentrations of cellular constituents in both time and space;
 - New approaches to identify and quantify the multiplicity of structural modifications of each "ome", such as DNA methylation and post-translational modifications of proteins, including (but not limited to) glycosylation and phosphorylation;

- Analytical omics methods with increased throughput, matched by data processing methods;
- Computational tools for capturing and processing the increasingly large and diverse data-types from omic technologies and converting these high throughput data-sets into knowledge;
- Technology oriented application of new interventionist approaches, such as the use of small regulatory RNAs.

Functional Analysis and Bioimaging

5. This includes the development of imaging technologies that span the entire length scale - all the way from single molecules and single cells through to tissues and organs, living organisms and finally the environment they inhabit. Modern bioimaging requires development of new imaging modalities (spanning the entire electromagnetic spectrum and including other physical means e.g. mechanical and acoustic methods), the creation of novel contrast agents and marker technologies to enable biologists to study: molecular mechanisms and biomolecular interactions; patterning of gene expression; monitoring of complex pathways and networks within live cells; cell-cell interactions; developmental pathways and organ development; functional studies within intact living organisms and localisation of organisms within their environment. The scope of bioimaging therefore includes *in vitro* through to *in vivo* functional and mechanistic studies and the means to obtain complex and quantitative data sets during *in vivo* studies with appropriate spatial and temporal resolution. Bioimaging should aim to rigorously test predictions and models generated by functional genomics and systems biology. Particular challenges include:
 - Development of technologies that allow simultaneous analysis of multiple transcripts, proteins, or metabolites in living cells, tissues or organisms (including within their environment) that yield mechanistic insights;
 - Development and use of higher-resolution techniques that reveal new structures or information that reside beyond the diffraction limit;
 - Development of new chemical and physical probes and associated means of detection and new imaging modalities that will give new mechanistic insights;
 - Correlation of measurements made *in vitro* with those in intact cells leading to a continuum of knowledge, defined by our understanding of the temporal and spatial understanding of pathways and networks critical to systems biology;
 - Length-scale independent themes that include statistical descriptions of data sets, image processing and archiving, and signal analysis that gives detailed mechanistic insights at the level of genes, molecules, cells, intact organisms and their environment. There is also a need to develop platform-independent data warehousing with emphasis on annotation (e.g. technical and experimental meta-data), raw data and compression formats, minimising processing time and storage while maximising resolution and data integrity to enhance data sharing.

Predictive Modelling of Biological Systems

6. The application of predictive mathematical and computational modelling will enable a better understanding of biological complexity at all levels from molecules to populations. As such, it is an integral part of all the technologies required for systems biology. Particular challenges include:
 - Development of approaches to model multi-scale phenomena (e.g. temporal, spatial, across organisational levels);
 - Approaches to (a) bridge the gap between modelling and statistical methods and (b) develop the interface between deterministic and stochastic approaches;
 - Development of approaches to analyse, compare and reduce the complexity of systems models;
 - The application of novel approaches developed in other complex system domains to biology challenges;
 - Creation of resources and standards to enable modelling, model exchange and interoperability as well as automating modelling processes and model visualisation;
7. The modelling must be integrated with a biological system relevant to BBSRC's remit. It should be coupled with experimental programmes through predictive/experimental cycles. This coupling will encourage the development of appropriate mathematics to deal with biological data sets.

Integrative Informatics for Biology

8. Biological research is a data-intensive science challenged with a very significant growth in the volume and variety of data that are available from distributed Internet locations, much of it generated by high-throughput instrumentation. Maintaining the international competitiveness of the Bioscience is critically dependent upon all researchers having timely access to high quality datasets and user-friendly software tools for discovering, integrating and interpreting these datasets in efficient and novel ways.
9. Informatics areas that are considered high priorities for new developments include:
 - New biological data repositories and data exchange formats that facilitate data sharing and advance BBSRC objectives in integrative and systems biology. For example, providing solutions in the area of data provenance, and the sharing and mining of biological models, image/video data and biological chemistry information;
 - Software and database techniques that enable the discovery of new biological insights from integrated, diverse data. For example by exploiting new visualisation methods in the biosciences, and the broad application of advanced data mining and knowledge extraction methods;

- Novel computational and statistical methods for use in omic data analysis such as genome sequence analysis, network inference, and structural and biochemical analyses;
- Approaches to improve and extend data resources by enrichment with added-value information from the scientific literature, from expert users and from specialist resources such as curated biological ontologies, metabolic and signaling pathways and structural and biological chemistry datasets;
- Data management and analysis approaches that address the problems inherent in the study of organisms with incomplete and disparate data resources, particularly organisms of economic or environmental importance;
- User-focused resources that facilitate the use of advanced informatics or computational techniques by scientists working on BBSRC priority research topics, which target a clearly identified requirement and will open up new areas of informatics to biological researchers or create new interactions between informatics and biological scientists.

Chemical Biology Tools

10. The UK has a strong position in the field of chemical biology, which uses chemistry to probe biological systems. To ensure this position is maintained and strengthened, there is a need to develop further the chemical biology tools available to biologists. In particular, the tagging and imaging of individual molecules within intact cells are areas where chemical biology tools would be applicable. Other areas identified where the use of chemical biology tools could have a significant impact are:
 - **New Chemical Probes** There is a need for new approaches to identify novel active compounds for chemical biology research, including:
 - novel chemistries that generate libraries of cell active compounds that bind to particular classes of target
 - further development of fragment-based approaches to develop compounds active against different classes of target
 - innovative strategies that pair compounds with protein mutation as toolkits for selective chemical intervention on a target, interaction or pathway
 - **Molecular Design:** There is a need to develop and make available tools to aid the molecular design process, including quantitative prediction of protein-ligand binding affinities, cheminformatics toolkits and compound databases. Some of the fundamental science underpinning molecular design and informatics is funded in the BBSRC responsive mode and there is a need to translate this into tools that can be used by the biological community.
 - **Synthetic Approaches in Biology:** Novel synthetic approaches are needed to influence the biology of cells to probe the role of particular proteins, interactions and complexes. Recent examples include the introduction of reporter synthetic amino acids, tagging and labelling of macromolecules with reporter groups and the introduction of modified carbohydrates.
11. The focus of this technology priority is the development of new chemical biology tools and associated tools for structural and functional characterisation of their

intermolecular interactions, which should be developed and validated on appropriate biological models and further the understanding of biological systems.

Biomolecular Characterisation

12. This area is concerned with molecular analysis of biological systems and sub-systems and both *in vitro* and *in vivo* measurements from single molecules, molecular systems, single cells and tissues.

Particular challenges include:

- The development of methods that either improve the sensitivity or the type of information collected, including the use of dynamic, polarisation and/or time-resolved methods;
- Technologies for single molecule analysis including increasing both the throughput of analysis and information content;
- The development of new platforms for analysis involving the integration of measurement technologies, including sample preparation and fluid handling to provide faster and better information;
- Developing molecular characterisation techniques having improved resolution and specificity compared to conventional assays;
- New techniques involving analysis at biological interfaces including methods appropriate for solid-solid, solid-liquid and liquid-liquid interfacial molecular characterisation (e.g. dynamic changes in membranes or of biomolecular deposition, adsorption and desorption at surfaces, as might be appropriate for scientists working in biosensors or drug delivery);
- Methods for studying macromolecular interactions, both *in vitro* and *in vivo*, especially dynamic formation of complex assemblies, detailed information on the make-up of the complexes, and the selectivity and nature of the interactions;
- Improvements in the application of newly evolving technologies such as arrays, high resolution mass spectrometry and surface enhanced techniques (e.g. SERS, TIRF, SPR, SIMS and near-field microscopy) for studying biological systems from the level of molecular assembly to tissue.