Infrastructure for Systems Biology Europe

Deliverable No: 4.2

"Report on existing high throughput data generation centres"

Main/responsible Authors: Dimitris Thanos, Sissy Kolyva, Ioannis Michalopoulos
Institution: Biomedical Research Foundation Academy of Athens (BRFAA)
Country: Greece

Project funded by the European Commission under the Seventh Framework program for Research and Technological Development

Project ref. no.	INFRA-2012-2.2.4: 312455
Project title	ISBE – Infrastructure for Systems Biology Europe
Nature of Deliverable	R= Report
Contractual date of delivery	Month 20
Actual date of delivery	Month 20
Deliverable number	D4.2
Deliverable title	Report on existing high throughput data generation centres
Dissemination Level	PU
Status & version	Version 3
Number of pages	21
WP relevant to deliverable	WP4
Lead Participant	BRFAA, Dimitris Thanos
Author(s)	S.Kolyva, I.Michalopoulos
Project coordinator	Richard Kitney
EC Project Officer	Andreas Holtel

Dissemination level: PU = Public, RE = Restricted to a group specified by the Consortium (including Commission services), PP = Restricted to other programme participants (including Commission Services), CO= Confidential, only for members of the Consortium (including the Commission Services)

Nature of Deliverable: P= Prototype, R= Report, D=Demonstrator, O = Other.

Table of Contents

Background Information on WP4

Objectives of WP4

Systems approaches require the collection, integration and storage of large data sets from genomics, proteomics, metabolomics and other –omics fields as well as molecular imaging with the goal to model life processes. The aim of the Data Generation work package (WP4) is to develop the appropriate institutional infrastructure and scientific mentality to support the collection of high throughput quantitative data in the biomedical and biotechnology fields in a way that is fit for systems biology. The overall objective of WP4 is to translate the strategic vision developed in WP3 (Overall Infrastructure, Eligibility and Accessibility) into an infrastructure plan for the construction phase of ISBE. Specifically, this document aims:

- To document the existing physical infrastructures providing high throughput data generation of partner institutes in order to identify those that are relevant to ISBE.
- To develop a long-term, strategic vision of the role of high throughput data generation centres for systems biology research;
- To develop a distributed infrastructure prioritised plan to renovate existing infrastructures and build new infrastructures. To determine their contribution and impact on ISBE by constructing a roadmap of integrating relevant proposals for national and pan-European construction plans.
- To design and define standards and harmonise procedures in the operation and management of the data generation centres and to ensure implementation of harmonised and standardised operating practices among users.
- To define the needs of the European scientific community regarding access to the Data Generation Centres.
- To develop a plan for the implementation of European access and to develop the strategies that will establish the rules for providing European access to the Data Generation Centres of ISBE.
- To assess the needs, survey existing solutions and define the future strategy for developing a distributed data storage infrastructure for systems biology that can efficiently cope with unprecedented data volume and will be linked closely to the data generation centres and modelling hubs of ISBE (in cooperation with WP3).

Relationship of WP4 to other work packages:

WP4 aligns closely with the following ISBE WPs:

- WP1 Project Management and Co-ordination: WP1 and WP3 will work together on the cross-cutting topics and responsibilities to integrate results and information of all WPs to generate the overall concept of ISBE.
- WP2 Model and Data Management: Considerations around the model and data management are a central topic for the overall ISBE concept, e.g. standardisation and SOPs have a high relevance and influence the strategy development how cooperation with other infrastructures, projects or initiatives might be implemented.

- WP3 Overall Infrastructure, Eligibility and Accessibility: This is a core activity of ISBE and is therefore vital for the vision, strategy and even advocacy of ISBE Also the definition of the ISBE user concepts mainly dependent on the WP3 results.
- WP5 Community Building and Synergies: Synergy and interaction with different projects, infrastructures and communities are vital for ISBE, for the preparatory phase the interaction with the different user/provider communities is highly important to optimise the concept and strategy plan for ISBE.
- WP8 Modelling Infrastructure and Expertise: Input of WP8 is required on the definition of the modelling for the ISBE vision.
- WP9 Technology and Science Watch: Input of WP9 is required to incorporate new technologies and applications to Data Generation Centres.
- WP10 Training and Education: Together with WP10, WP7 will provide a strategic basis for identification of educational needs across fields in Europe.
- WP11 Funding, Governance and Legal: WP7 will feed into WP11 with respect to the definition of funding needs and strategies, as well as with respect to advocacy at the level of funding agencies and governance.
- WP13 (Connections): on the vision of the essential role that the connections between centres and between centres and users play in achieving the integrative aims of ISBE
- WP15 Innovation, Impact and Exploitation: Liaison with WP15 to assist in providing information for the pipeline for technology and methodology exploitation and IP management, as well as a European expertise and technology matrix; the results of WP15 will also feed back to the WP3 centre structure discussion and the overall concept.

What is systems biology?

Systems Biology is an integrated experimental, informational, and computational science aiming to understand the dynamics of living systems. It has benefited from advances in fields such as genomics, proteomics, metabolomics, and others that employ high throughput technologies and is driven by innovations in mathematics, computational analysis and simulation. Biologists may now pay more attention to understand how biological components work together to produce system behaviours rather than focusing exclusively on the properties of individual molecules and pathways. The adoption of a systems approach is providing new knowledge in many areas of Life Sciences and biomedical research, including cell dynamics and signalling networks, global metabolic fluxes, and responses to drugs (and guidance in their development). It is expected that new, fundamental rules governing systems behaviour at various organisational levels – and how these levels are integrated - will emerge from these studies. However, there continue to be significant conceptual, technological, and cultural challenges to the realisation of the systems biology goals. It is the purpose of this initiative to promote innovative responses to these challenges.

The Data Generation Centres

Currently, technological gaps existing in mathematics, computation and experimentation prohibit data integration into valid models to predict biological functions. These include lack of standards and quality control measures in data collection and software engineering. Growing volumes of data from diverse high throughput experiments provide unprecedented opportunities for computational biologists. However, a high level of heterogeneity in data quality and experimental conditions hampers data comparison, integration, and application in computational modelling. Similar issues exist in software development. The lack of software engineering standards and sufficient documentation has limited software re-use, resulting in unnecessary duplication of efforts, and difficulty in comparing one program to another. The scientific concept of systems biology, arising during the last decade, is based on the quantitative analysis of complex biological networks, where high-throughput data, computational analysis and modelling of molecular functions result in a deeper understanding. Diversity, development, disturbances and diseases of molecular networks are analysed at different molecular levels, engaging different technologies and experimental systems. This implies that existing research infrastructures will be able to contribute to, and to benefit from, systems biology infrastructures. Systems approaches in imaging, quantitative analysis, single cell time lapse, and 3-dimensional imaging, will greatly contribute to the analysis of biological questions in development, motility, signalling and organogenesis. Chemical biology and large scale screening facilities may provide the infrastructures for quantitative and qualitative screens and genome wide analysis of pharmaceutical effects.

Data generation in systems biology is increasing rapidly with the rise and combination of high-throughput –omics and imaging analyses, which will require a close collaboration of ISBE with ELIXIR, to ensure the proper data management, combination and harmonisation of data resources. Experimentally, there is a demand for the development of novel (and low-cost) methodologies to miniaturise, standardise, and automate high throughput data collection such that computational models can be populated with data specifically selected for tests of those models. In some cases, measurements from single cells are of great value. It is particularly important to sample living systems dynamically, at multiple scales, if realistic models are to be constructed. The systems biology centres are encouraged to develop innovative approaches to address these and other technological challenges.

Building cohesive multi-disciplinary research teams by integrating expertise across traditional disciplinary boundaries at the institutional level is not a simple undertaking. ISBE's goal is to encourage leadership in creating such teams. In the larger research community, there is a need for leadership to disseminate new knowledge and to reduce excessive overlap and redundancy in project selection and tool development. Centres are expected to promote communication, collaboration, and technology and data sharing. Another aspect to be nurtured is the dialog between theory and experiment. Transforming data into systems knowledge and principles will require iterative cycles of data collection, model generation, and model testing. Thus, the goal is to develop continuous communication and feedback among experimentalists and theoreticians. Finally, the emergence of a new science demands an adequate, diverse workforce of appropriately trained scientists. The future leaders of systems biology research will be knowledgeable and skilled in both experiment and

computation. Innovation in education, therefore, is a significant task of the Systems Biology Data Generation Centres.

Defining the Data Generation Centres

A first approach has been made to define the outline of the Data Generation Centres. We adopted a three-pronged strategy by focusing on:

1. critical computational challenges arising from the development of new technologies – next-generation DNA sequencing, proteomics, metabolomics, imaging, single cell technologies etc.

2. fundamental and long-term research pursuits – systems biology driven by heterogeneous data-intensive approaches, and

3. development of bioinformatics methods for advancing technologies

The goal of WP4 is to provide an integrated infrastructure to allow European scientists to collect high throughput biological data and to verify model systems using state-of-the-art technologies, including high throughput genomics and transcriptomics (DNA array systems, highly parallel DNA sequencers and advanced multiplexing technologies), advanced proteomics, metabolomics, high throughput imaging systems including microscopy, flow cytometry, automated cell analysis, etc. The ISBE Data Generation Centres will build on existing resources (physical infrastructure including buildings, large scale equipment, human resources, scientific and management expertise) distributed among partner institutes. These resources will provide the basis to develop a state-of-the-art distributed infrastructure to satisfy the needs of the European research and biotechnological communities for systems biology resources.

ISBE Survey

In this context specific questions regarding the use and need for high-throughput data collection were included in the wide survey organised by the ISBE management team. Systems Biology research requires collection and processing of data from large numbers of biological experiments using automated procedures and requires the ability to obtain, integrate and analyse complex data sets from multiple experimental sources using interdisciplinary tools.
This report addresses four specific questions:

1. What existing technologies are considered as state-of-the-art or key technology in the specific fields of Systems Biology?

2. Would it make sense to have these technologies available within an infrastructure?

3. What emerging technologies will be important in the near future for Systems Biology research?

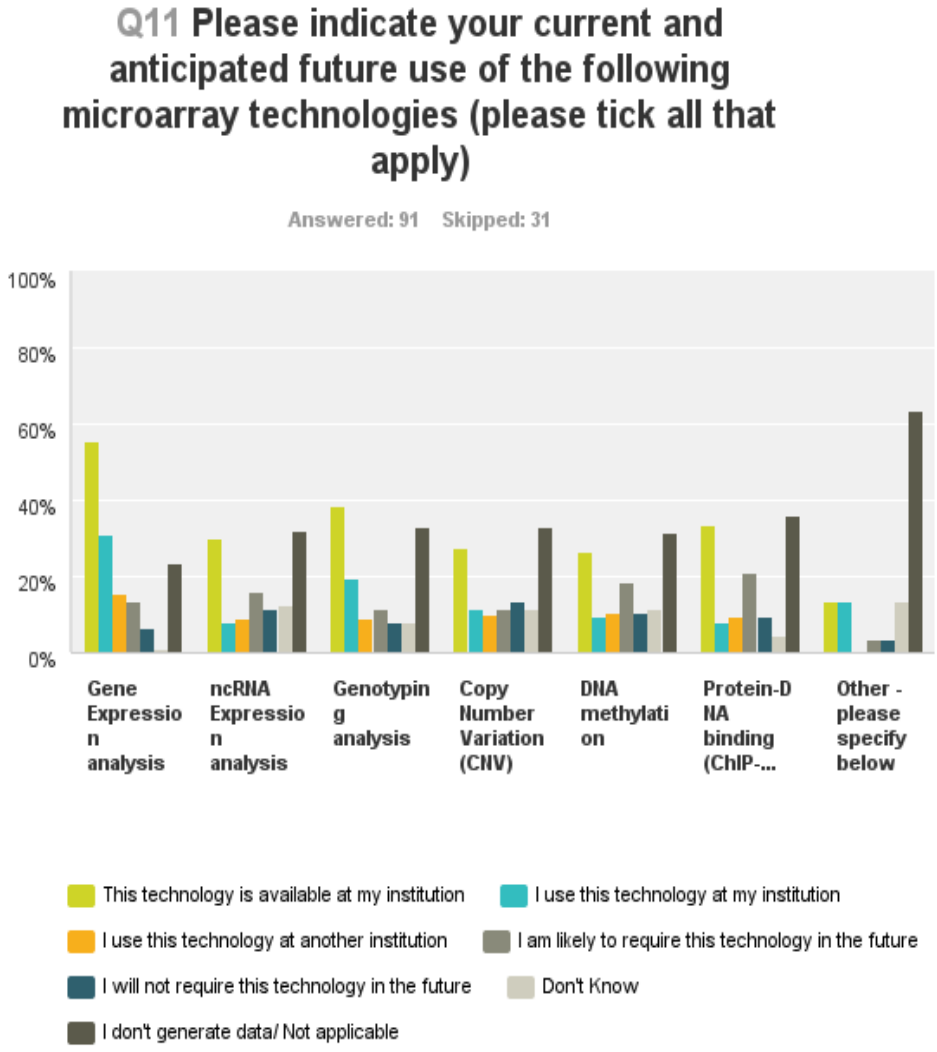
4. How can these new technologies be integrated into Systems Biology and how an infrastructure might help with this?

In addition to technology literature watch and the data extracted and analysed from the survey, we have compiled statistical data obtained during Systems Biology conference

proceedings, abstracts and interviews (lasted approximately 30 min) and conducted with selected leading scientists of the field (Modelling, microscopy & image analysis, live single-cell imaging & modelling, mass spectrometry, proteomics, RNAi screens, genomics & sequencing, metabolomics) all of which were used in our analyses and interpreations.

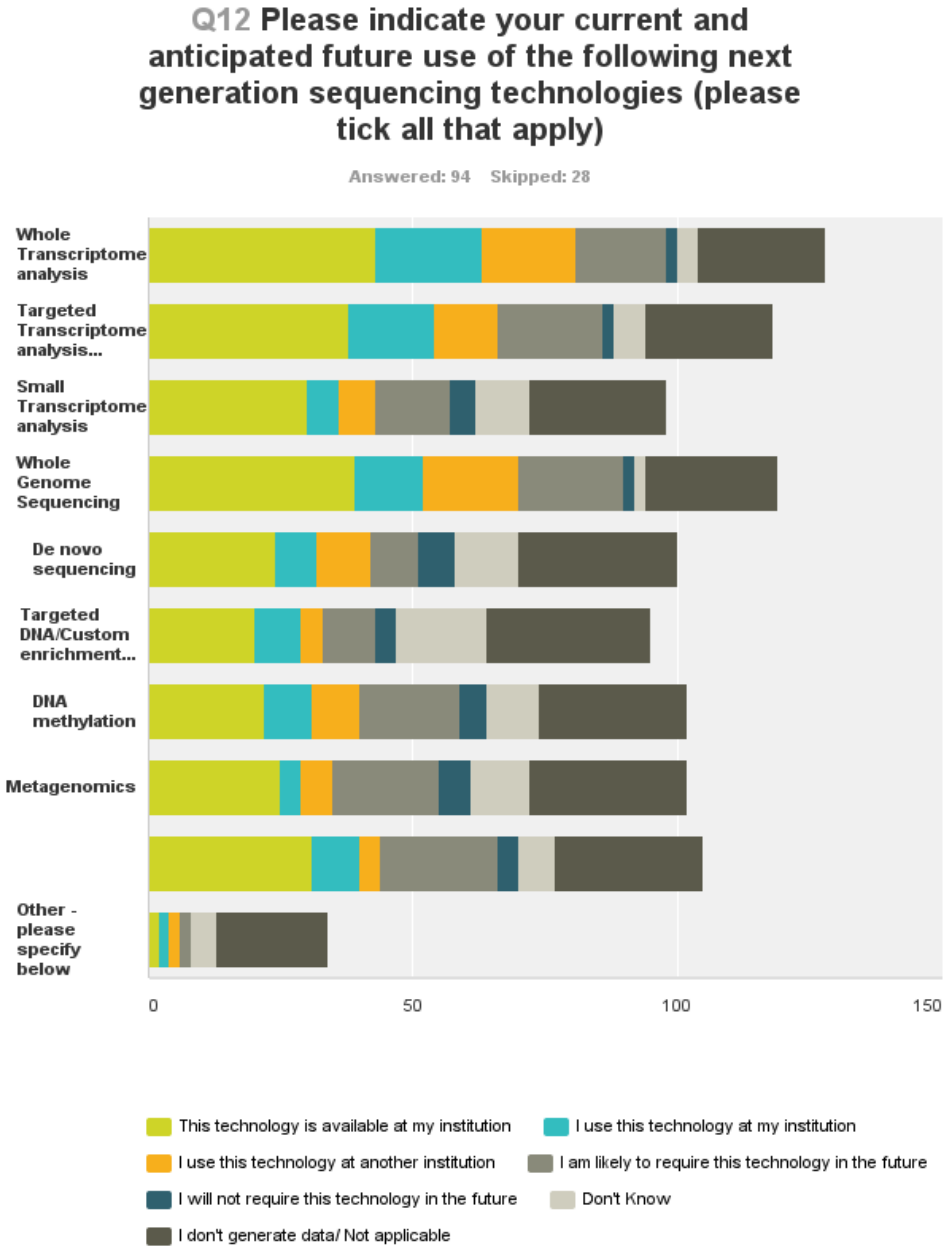
Microarray technologies

A large number of **microarray-dependent technologies (127 Institutes out of 180)** is available in the majority of institutions that carry out systems biology research in Europe (copy number variant, gene expression analysis, genotyping analysis, ChIP-chip etc.). The survey revealed that 16% of the responders use these technologies at a different institution and an additional 14% will need this technology in the future, thus, expressing a need for having access to this methodology in-house.



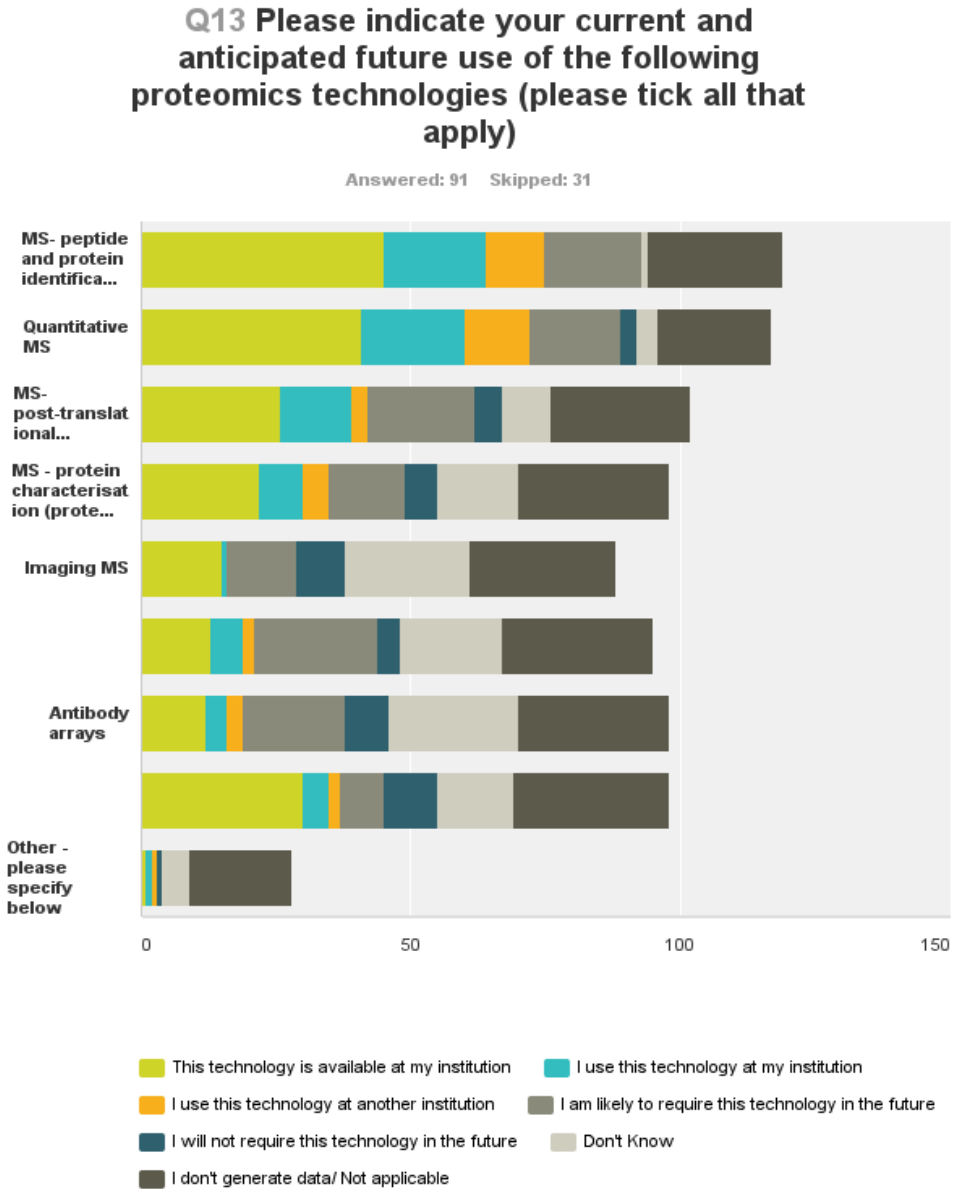
Next generation sequencing technologies

Next generation sequencing technologies are available in **121 Institutes out of 180** participated in the survey**.** More specifically, these technologies are used for **Small Transcriptome analysis, Whole Transriptome Analysis, Targeted Transcriptome analysis (e.g. mRNA-seq or miRNA-seq), Whole Genome Sequencing** and ***De novo* sequencing** is currently available in-house and covers their demands. **Metagenomics** which is likely to be required by more than 22% of survey respondents and used by 6% at different institutions, and by the 4% of respondents at their institutions together with **DNA methylation** is likely to be required in the future by almost 23% of the respondents, it is used by 11% of respondents at other institutions and it is available only in 26% of institutions.



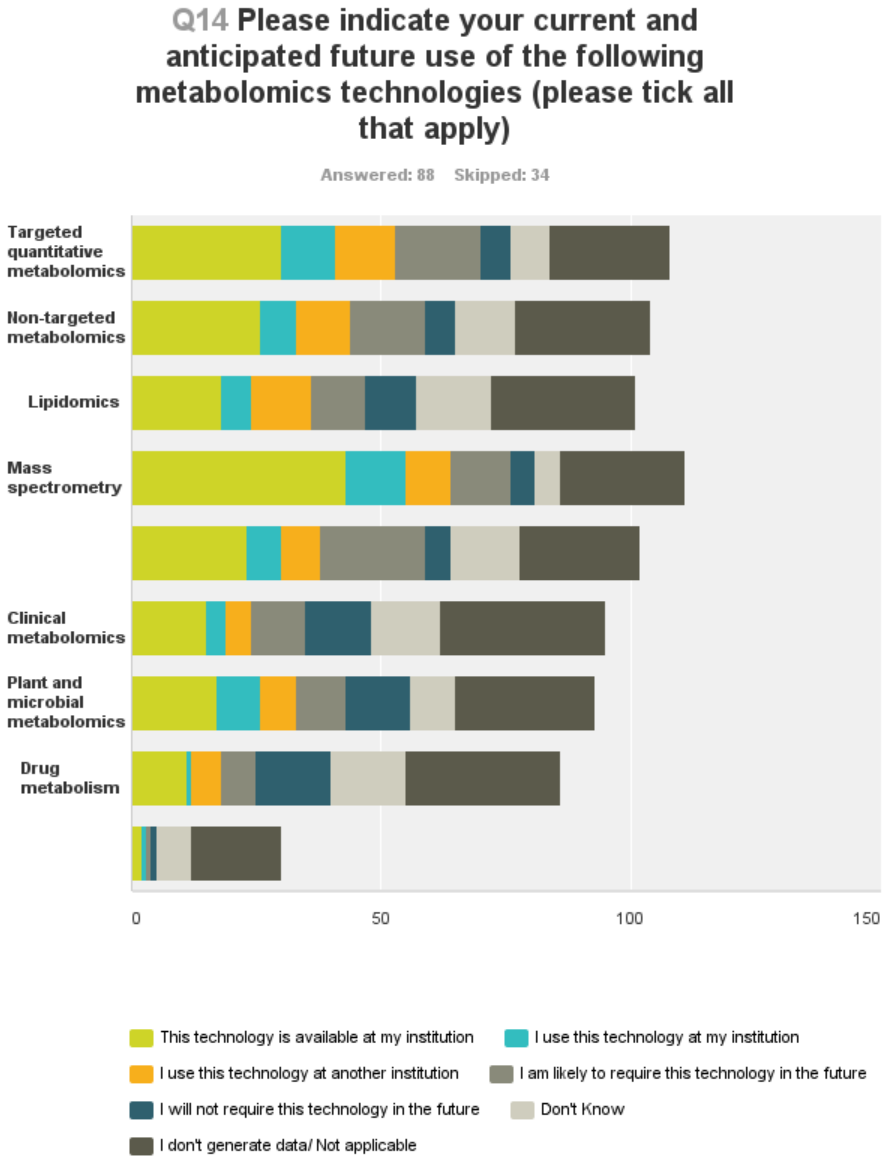
Proteomics technologies

Mass spectrometry based techniques have become widely available through out European Institutions. More specifically, **176 out of 180 institutes** can offer these technologies to their research personnel. , **MS-peptide and protein identification, Quantitative MS, MS posttranslational modifications, Protein and peptide arrays, Antibody arrays** and **2-Dimensional electrophoresis** for **proteomics** are available in the majority of responding institutions and fully cover their demand.



Metabolomics technologies

Targeted quantitative metabolomics, and mass spectrometry are **metabolomics technologies** available in **144 out of the 180 institutions** participated in the ISBE survey. We identify **mass spectrometry** (52%) as the main proteomics technology available at institutions. Surprisingly, however, only 15% (**Mass spectrometry**) and 13% (**Targeted quantitative metabolomics**) of the respondents use these techniques at their institution. Interestingly, other technologies (**on-targeted metabolomics, plant and microbial metabolomics, High throughput metabolomics, Clinical metabolomics**) appear to be in balance between their availability in the institutions (33%) and the possibility to be required in the future. 24% of respondents are likely to use High throughput metabolomics technologies in the future and 10% already use this technology but at other institutions.

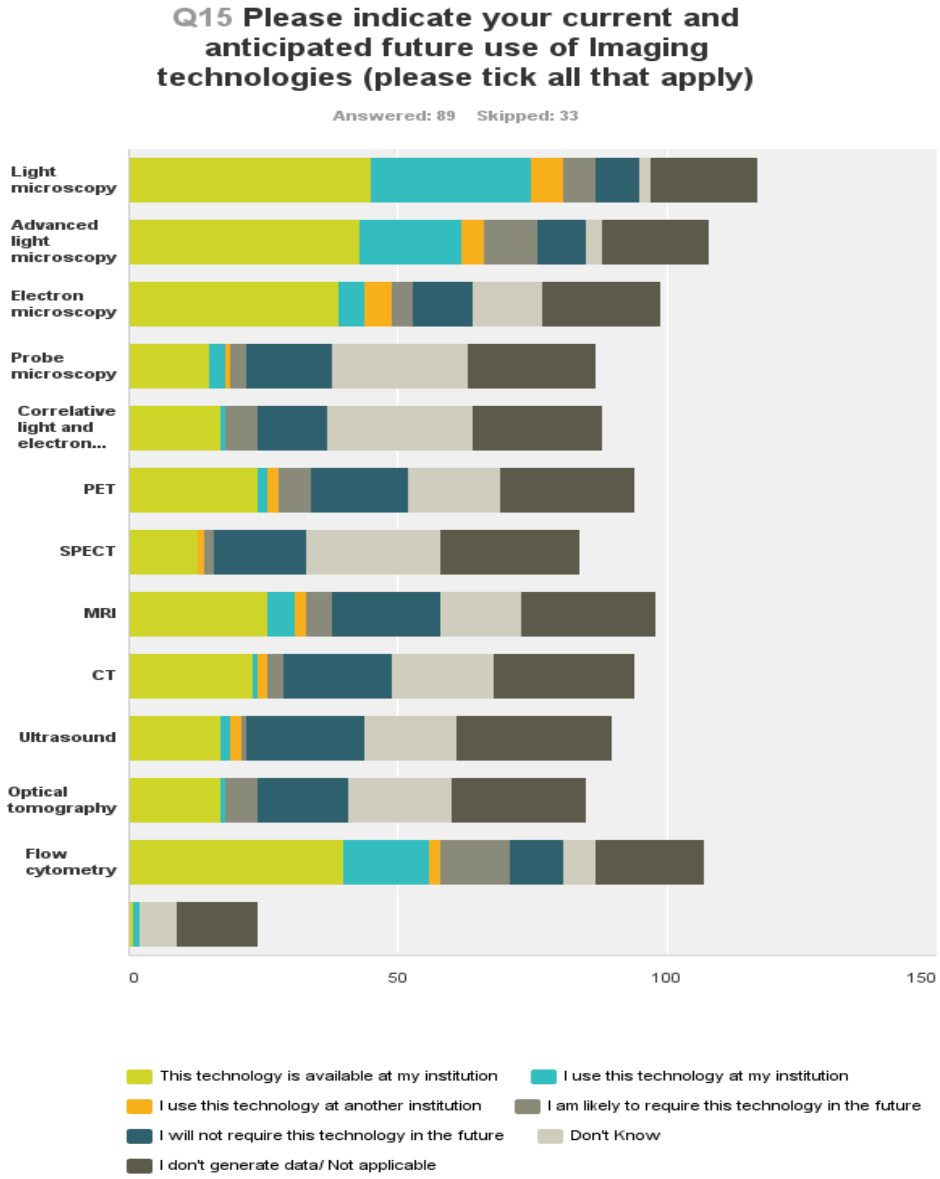


Single cell technologies

A large number of systems biology scientists appreciate the significance of single cell DNA and RNA sequencing. Single cell approaches are increasingly receiving important attention for proteomics, transcriptomics and functional genomics. Although these techniques are currently available, the cost is still a big issue. The general consensus among the scientists participated in our interviews is that next generation sequencing is not yet at the peak of its usage, and that in the near-future the main technological developments will also involve Next gen sequencing but focusing to develop library technologies to read longer pieces of DNA, to improve the accuracy of sequencing and to capture as many transcripts as possible from single cells.

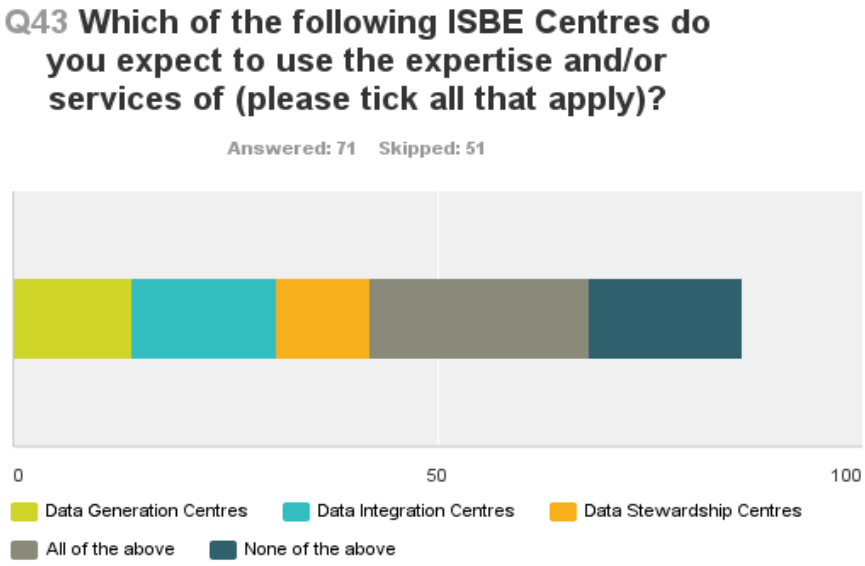
Imaging technologies

Most imaging technologies (**Light microscopy** – 52%, **Advanced Light microscopy** – 52%, **Electron microscopy** – 48%) are available in the participating institutions and appear to fully cover the demands. In comparison to these technologies, other **Imaging technologies** (**Probe microscopy, Correlative light and electron, PET, SPECT, MRI, CT, Ultrasound, Optical tomography**) are not generally available in European institutions but they seem to fully cover the demands, or that the scientists are not currently aware that they might need these technologies in the future. Some advanced microsope technologies (eg 2PPM) are currently in the fermentation phase, and it will be necessary to continuously monitor whether there is an increasing demand in the future.

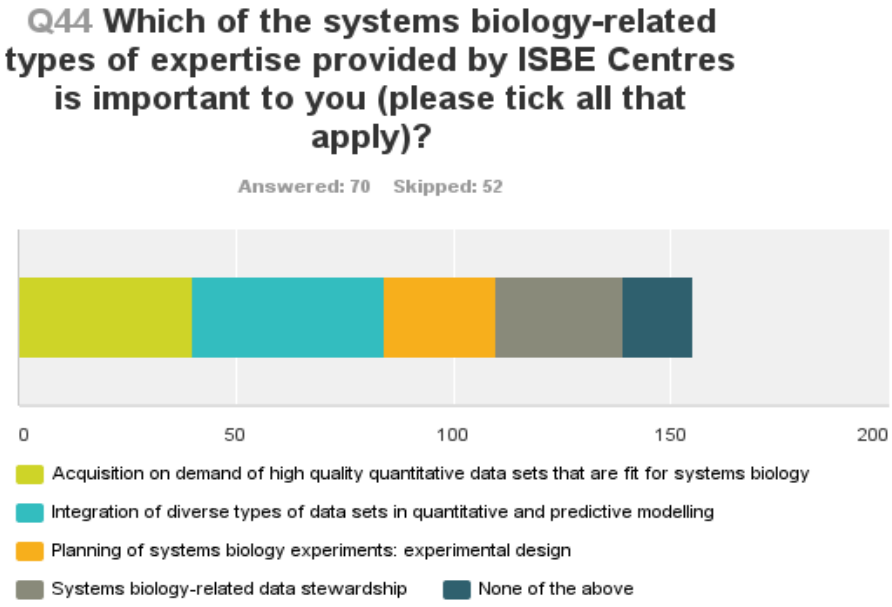


Prospective use of ISBE centers

The mission of ISBE is to provide a state-of-the-art infrastructure to the European Research community for conducting fundamental and applied research in modern computational genomics and systems biology arising from the emergence and increasing prominence of high-throughput instrumentation. The expertise to be offered by ISBE will cover two tightly

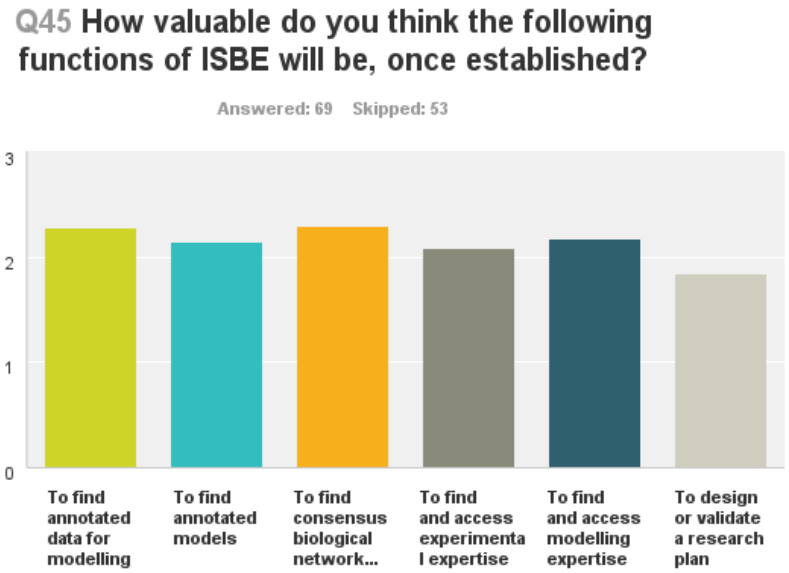


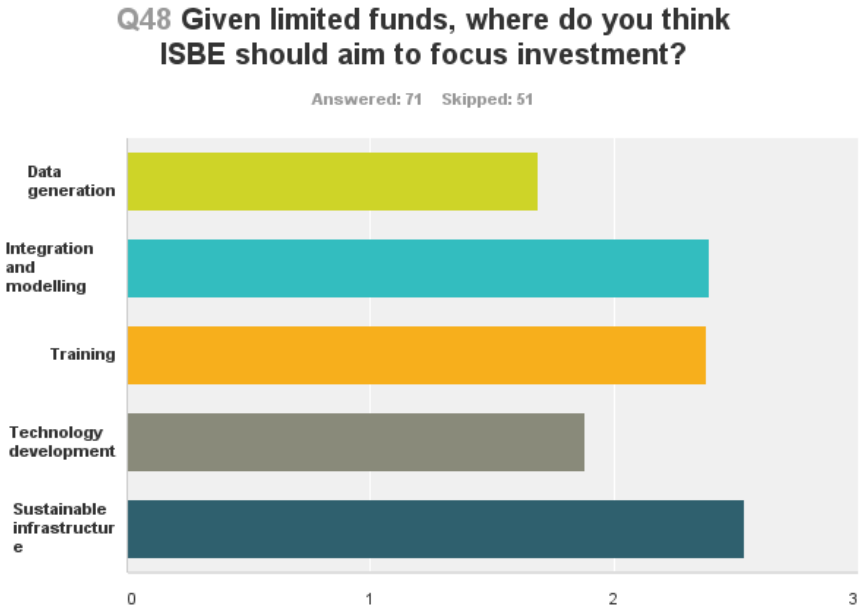
related



activities: high throughput data generation on the one hand, and data stewardship and modelling on the other hand. In order to audit the Systems Biology landscape and the user needs ISBE undertook a survey of the community, for the possible use and need for the three types of centers proposed by ISBE: a) the data generation centers supporting the systematic collection of data under physiological and standardized conditions; b) the

stewardship centers offering collection for standards, formats and ontologies used in Systems Biology, data and model repositories used for deposition and c) the model integration centers offering a wide range of modelling approaches ranging from the molecular to the physiological level.





Generation of model-compliant data is essential for systems biological approaches. Therefore, expertise in the generation of Systems Biology suitable data is critical to ISBE activities. Indeed, **Q43** and **Q44** of the survey addressed this issue. It was reassuring that from the analysis of the survey data, the Data Generation Centers are equally important to users as the modelling and stewardship centers. Interestingly, one third of the users replied that they will use all

three types of ISBE centers, thus justifying ISBE's main proposal for three types of centers. Similarly, the answers from Q45 and Q48, further reinforce ISBE's **"central dogma"** regarding the integrated activities of different types of centers throughout Europe. The main argument is that data generation centres seek to effectively solve current data-intensive scientific challenges and maintain broad applicability by harnessing emerging computing technologies including cloud computing and inexpensive high performance computing devices such as multicores and GPUs. This combination of high-throughput data-driven biology and high performance computing provides a unique mission to the data generation centres enabling them to tackle many challenges of scientific and societal importance. Systems approaches require the collection, integration and storage of large data sets from genomics, proteomics, metabolomics and other –omic fields as well as molecular imaging with the goal to model life processes.

ANALYZING THE ISBE SURVEY OF SYSTEMS BIOLOGY TECHNOLOGIES IN EUROPE

To map existing physical infrastructures providing high throughput data generation of partner institutes with the aim to identify those that are relevant to ISBE, a questionnaire has been elaborated comprising questions for researchers and stakeholders as well. A number of questions have been placed into the ISBE-wide survey. The relevant answers have been be analysed. We collected raw data from 119 individual data sets. We only selected the 108 eponymous answers from researchers working in 83 institutes throughout Europe. We analysed the data on the basis that all Institutes (participating in the survey) house Systems Biology research activities and that in every institute a specific Systems Biology technology is used given that at minimum one of the Institute researchers testifies that at least one of the Systems Biology associated technologies is used at the Institute.

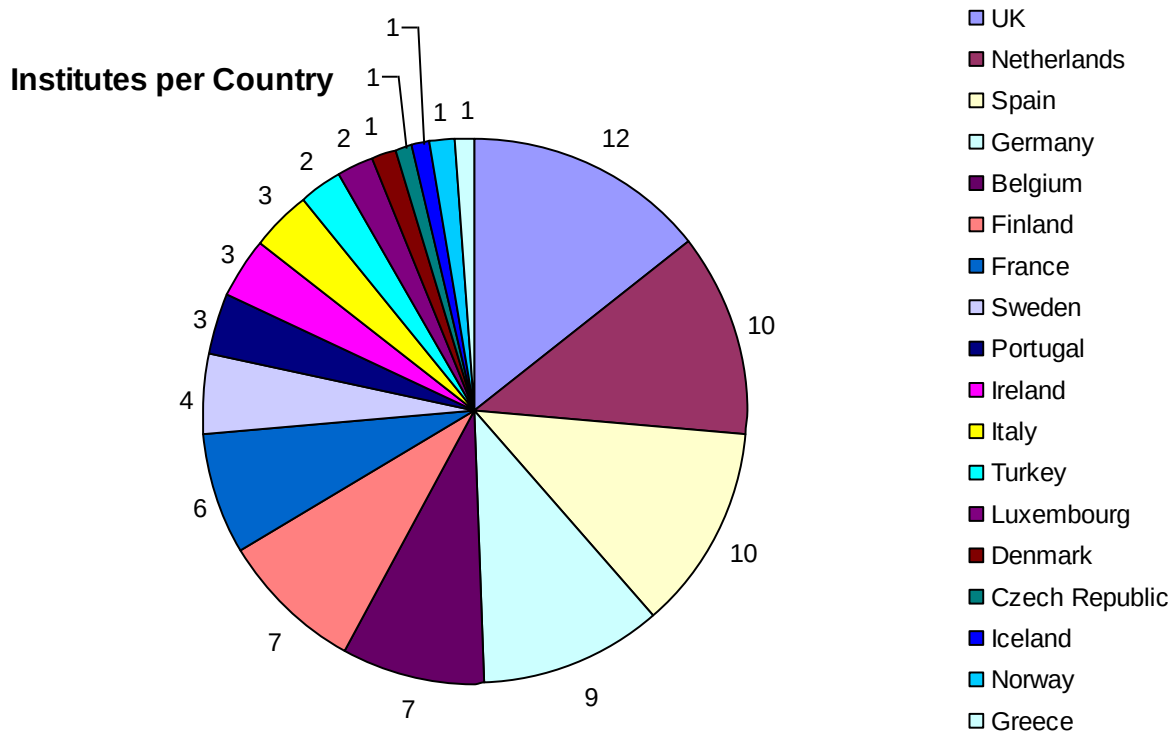
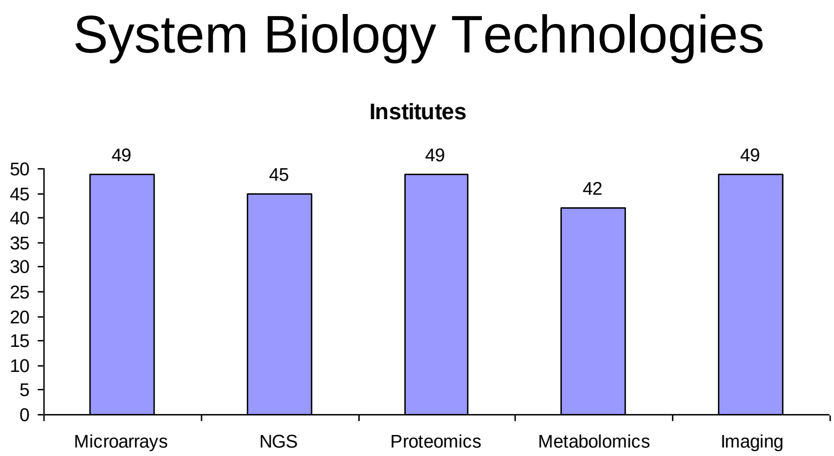


Figure 1: Pie chart of the geographical distribution of Systems Biology institutes using data from the ISBE survey. UK, Netherlands, Spain and Germany share half of the 83 Systems Biology.

Figure 1 clearly shows that more than half of the European Systems Biology-related activities are clustered in only 4 countries (UK, Netherlands, Spain and Germany).

Next we analysed the data of the survey focusing on the use of the different types of high throughput technologies essential for Systems Biology research. Figure 2 (bar graph) shows that the 83 European institutes evenly share the 5 main system biology technologies: Microarrays, Next Generation Sequencing (NGS), Proteomics, Metabolomics and Imaging. The Venn diagram shown at the bottom of the figure illustrates the distribution of the main technologies within the 83 institutes. One third of the institutes use all five dta genetaing technologies, while more than a quarter do not have these technologies in house.



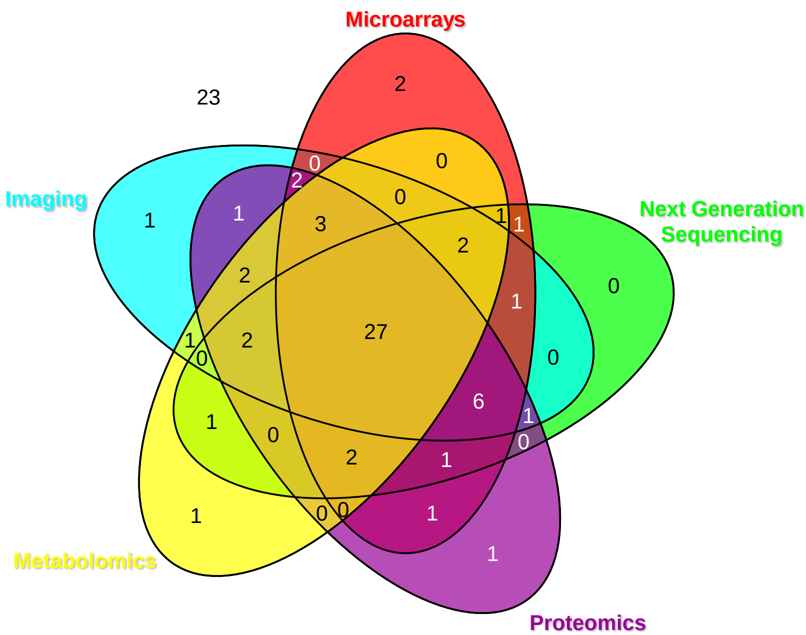


Fig.2: Use of high throughput technologies in Systems Biology Institutes

Next, we analysed the specific usage of each of the high throughput technologies. As seen in Figure 3, expression analyses together with genotyping and protein-DNA analyses are the main uses of DNA microarray-based technologies. Venn diagram representing the main use of microarray technologies applied in the 49 institutes of the survey. Five institutes are specialised in Expression Analysis while more than a third uses Expression Analysis, Genotyping or Copy number variation analysis, DNA Methylation and Protein-DNA binding technologies.

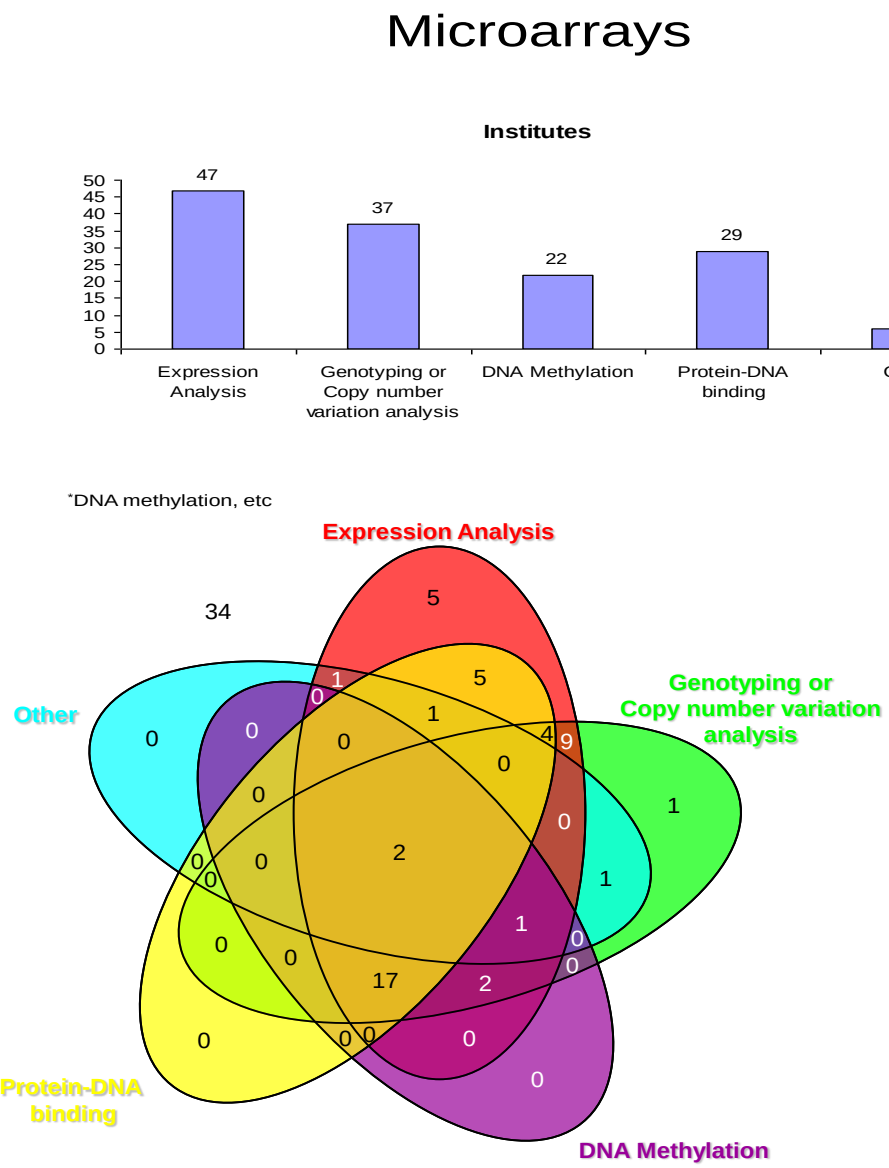


Fig. 3:Application of DNA Microarray technologies. Almost all institutes use Microarray technologies to study gene expression.

Next Generation Sequencing technologies are widely used by European Institutes predominantly for Whole Transcriptome analysis (Fig. 4). Two thirds are interested in the analyses of Protein-DNA binding. The Venn diagram shown at the bottom of the Figure depicts that NGS technologies are used in the 45/83 of the institutes participated in the survey. Half of the institutes use NGS for Whole Transcriptome analysis and Targeted Transcriptome analysis. Whole Genome Sequencing, Protein-DNA binding and other NGS technologies are also used in high frequency by European Systems Biology Institutes. Two institutes are specialising in Whole Transcriptome analysis and one in Targeted Transcriptome analysis.

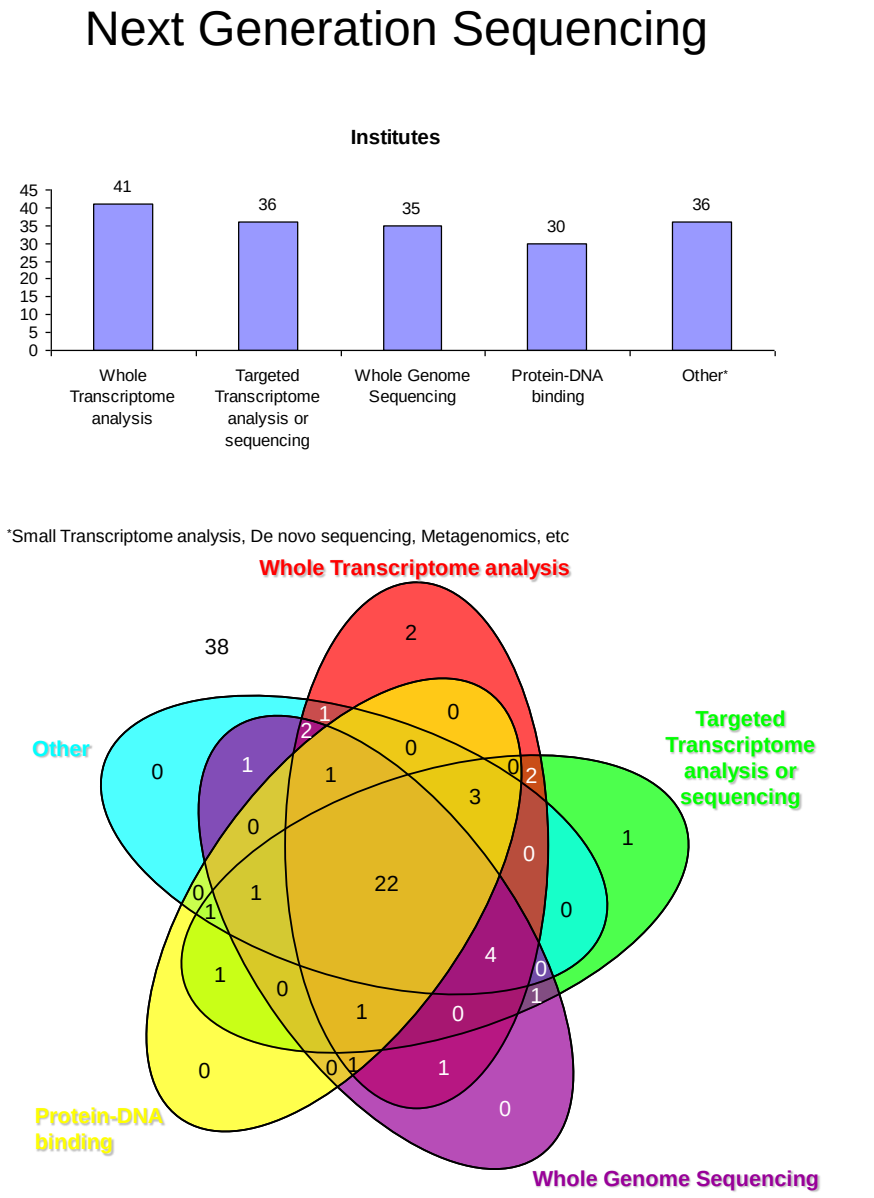


Fig. 4: Applications of Next Generation Sequencing technologies by European Systems Biology Institutes

Proteomics technologies are also evenly distributed between different Institutes. Most of the institutes support MS-peptide and protein identification technologies (Fig. 5). One third of the Institutes applies protein and peptide arrays. The Venn diagram at the bottom of Fig 5 depicts the distribution of the main Proteomics technologies used in the 49 institutes of the survey. It is interesting to note that there are only 9 institutes where all proteomics applications are in place.

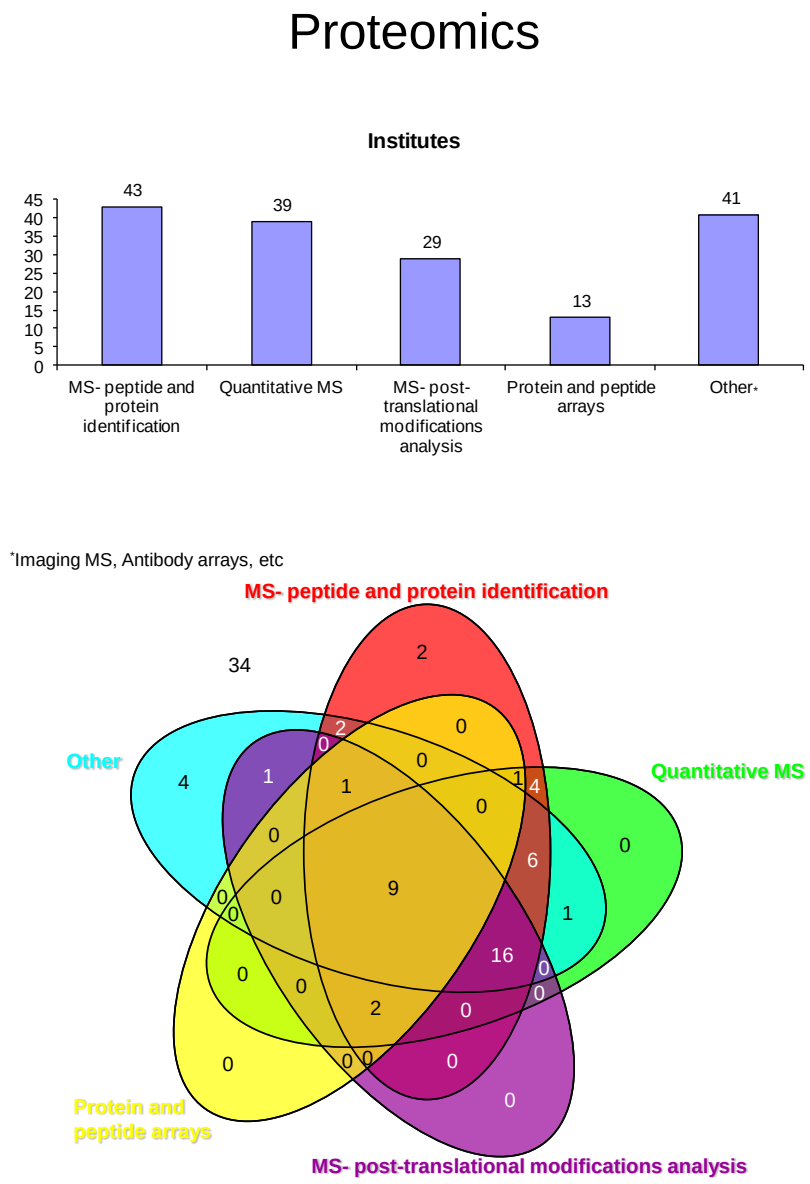


Fig.5 Applications of Proteomics technologies by European Systems Biology Institutes

Figure 6 shows that there is a wide interest among the European Systems Biology Institutes in interested in Targeted quantitative metabolomics and more than half of those also use all other related technologies. The Venn diagram depicts the distribution of the main Metabolomics technologies among the 42 institutes of the survey using Metabolomics technologies. One third of the institutes use Targeted quantitative metabolomics, Non-targeted metabolomics, Lipidomics, High-throughput metabolomics and other technologies are also used quite often by European Systems Biology Institutes..

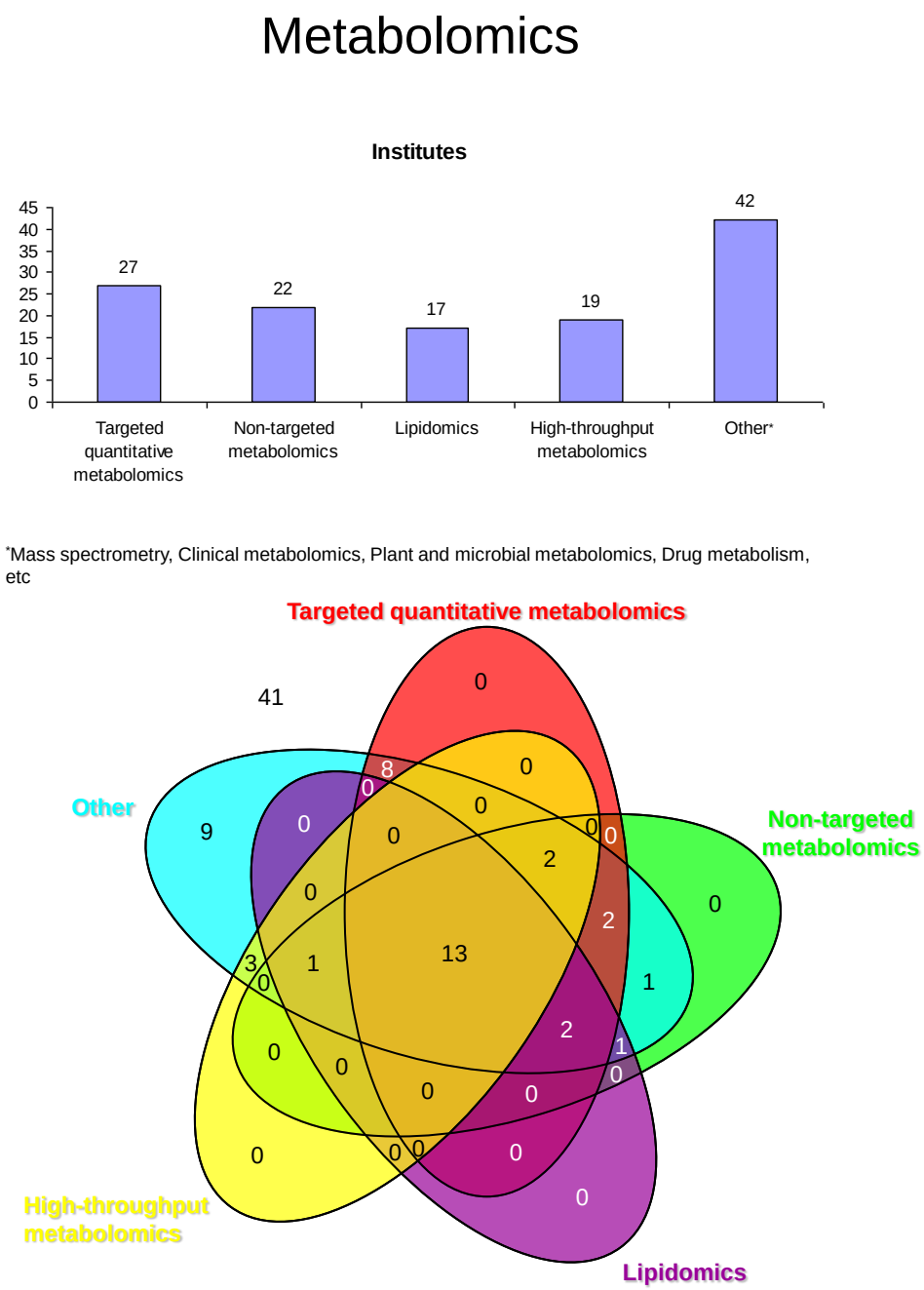


Fig.6: Applications of Metabolomics technologies by European Systems Biology Institutes

The distribution and use of various Imaging technologies is depicted in Figure7. Almost all institutes with Imaging technologies have incorporated Advanced light microscopy. One third is also focusing in Medical and Optical tomography. The Venn diagram illustrates the main Imaging technologies which are used in the 49 institutes of the survey. Besides Advanced light microscopy, Correlative light and/or electron microscopy, Medical and Optical tomography, Ultrasound and other Imaging technologies are also widely used by European Institutes.

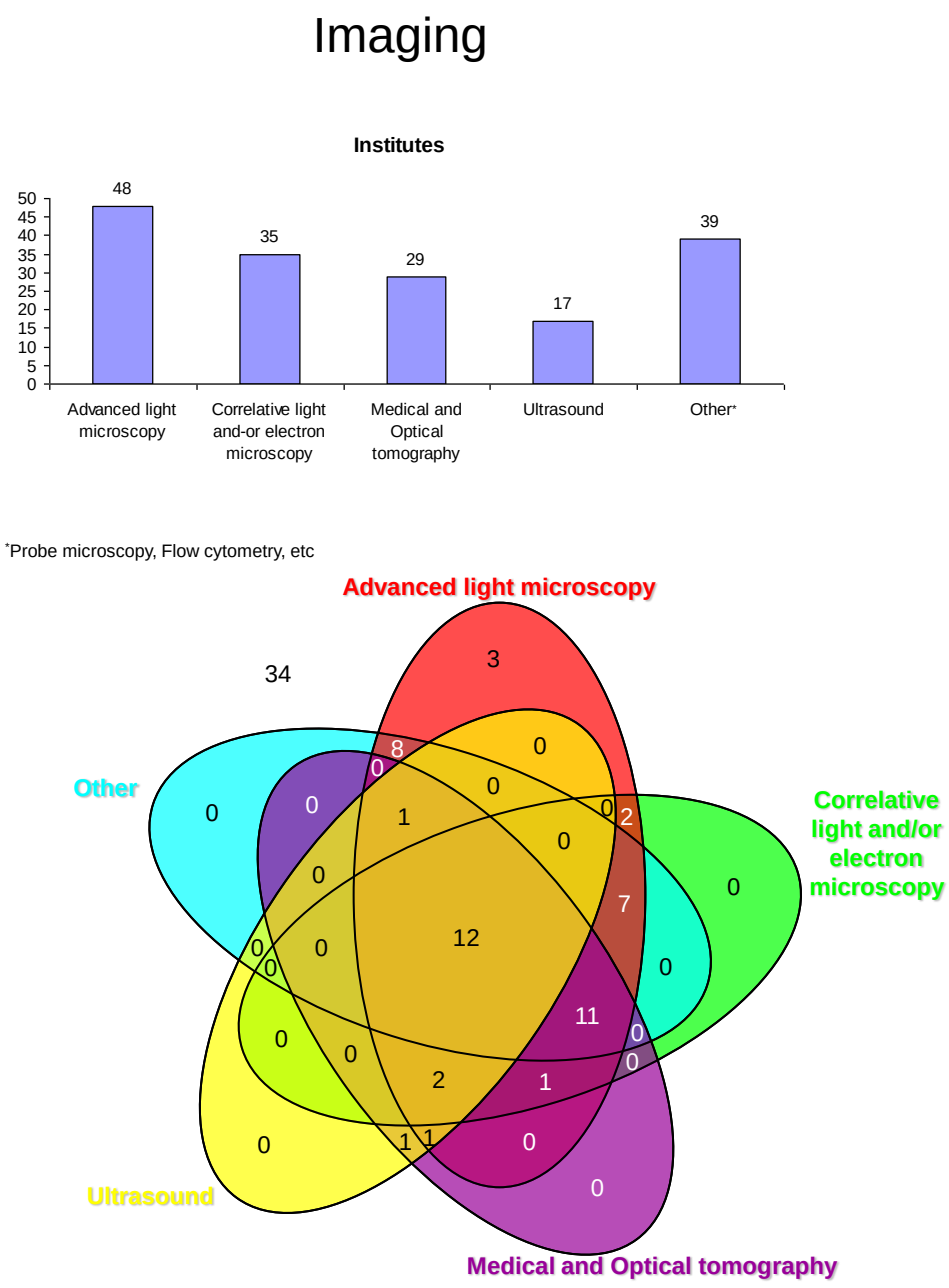


Fig. 7: Distribution and use of Imaging technologies among European Systems Biology Institutes

ISBE WP4 WEB SEARCH

WP4 undertook an additional approach to map the data generation laboratories in and Institute through out Europe capable of producing Systems Biology useful data. The approach undertaken is based on extensive Web searches at European level and national level aiming to map the research teams working on Systems Biology. This study led to the identification of 4 categories of data generation centres:

- Genomics centres
- Proteomics centres
- Eco-Plant centres
- Metabolomics centres

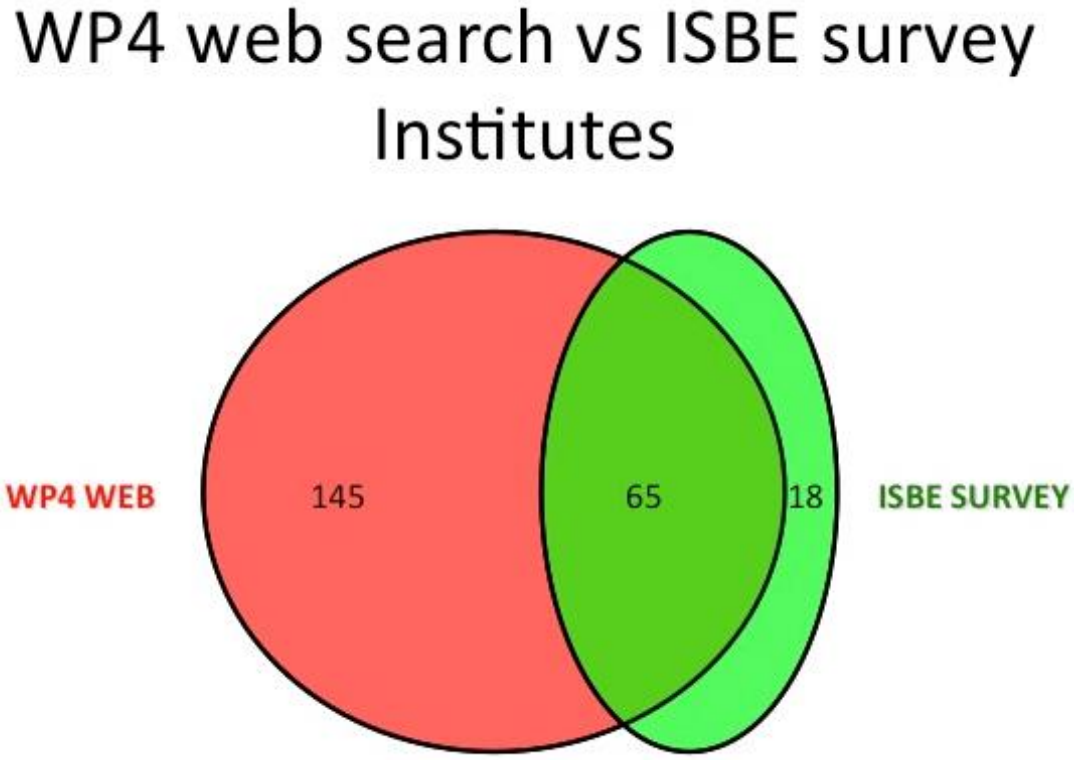


Fig. 8:Comparison of the Institute identified by the ISBE survey and the WP4 WEB searches.

Figure 8 depicts that our inventory of Systems Biology research teams at European revealed 210 systems biology units, 65 of which had been also identified by the ISBE survey. This remarkable similarity between the two different approaches further justifies the validity of our overall planning. More specifically, the results are as follows:

Institutions/Divisions/Companies/Consortia/

- 126 Universities
  - 65 Institutes
  - 61 Divisions
- 60 Institutes
  - 8 Systems Biology Dedicated
  - 52 Divisions
- 7 Companies
- 16 Consortia

Individual Groups

- 155 Life Sciences
- 26 Computer Science
- 5 Science & Technology

We analysed the data from the web search similarly to the analysis we carried out for the survey data described above (Figs 1-7). As seen in Fig. 8 the distribution of the Systems Biology activities is not evenly distributed through out Europe, in agreement with the data presented in Fig. 1

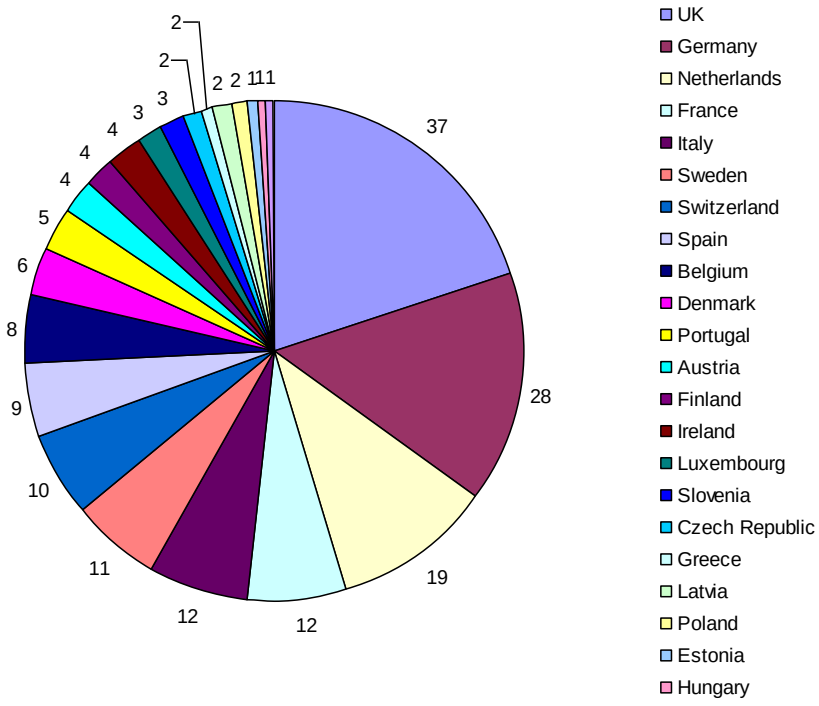
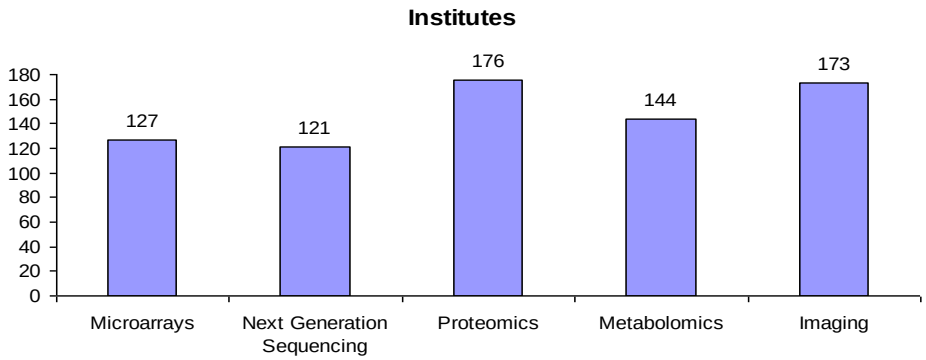
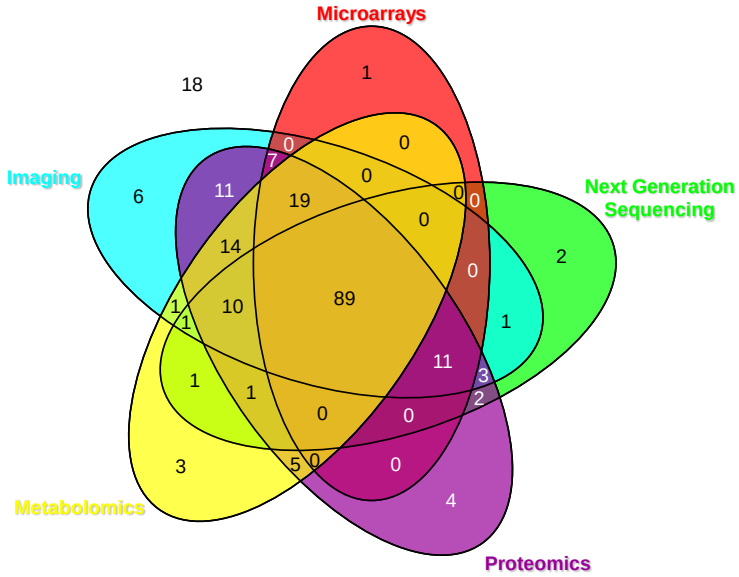


Fig. 8: Geographical distribution of Systems Biology groups/institutions in Europe

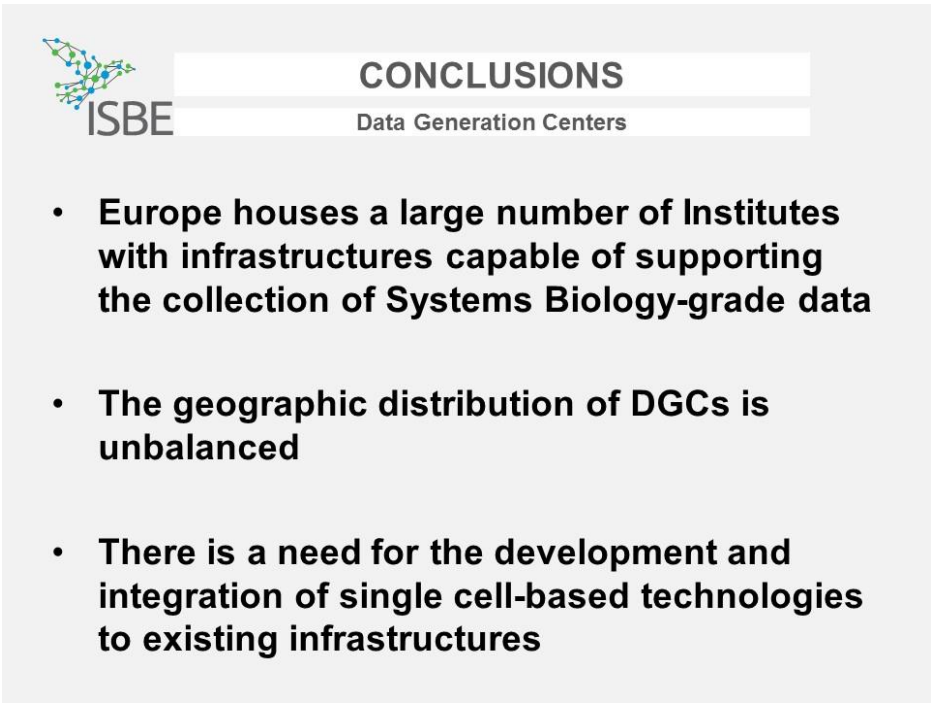
The use of the main Systems Biology technologies in all entities (210) identified by our web survey is indicated in Fig. 9. The Venn diagram of Fig. 10 depicts the distribution of the main Systems Biology technologies across all entities (210). Almost half of the groups/institutes house and use all five main Systems Biology technologies, whereas less than a tenth of the institutes use none of these technologies in house. .



Top, Fig. 9:Use of the main Systems Biology Technologies
Bottom, Fig.10. Distribution of the five main Systems Biology technologies across all 210 Institutes



CONCLUSIONS



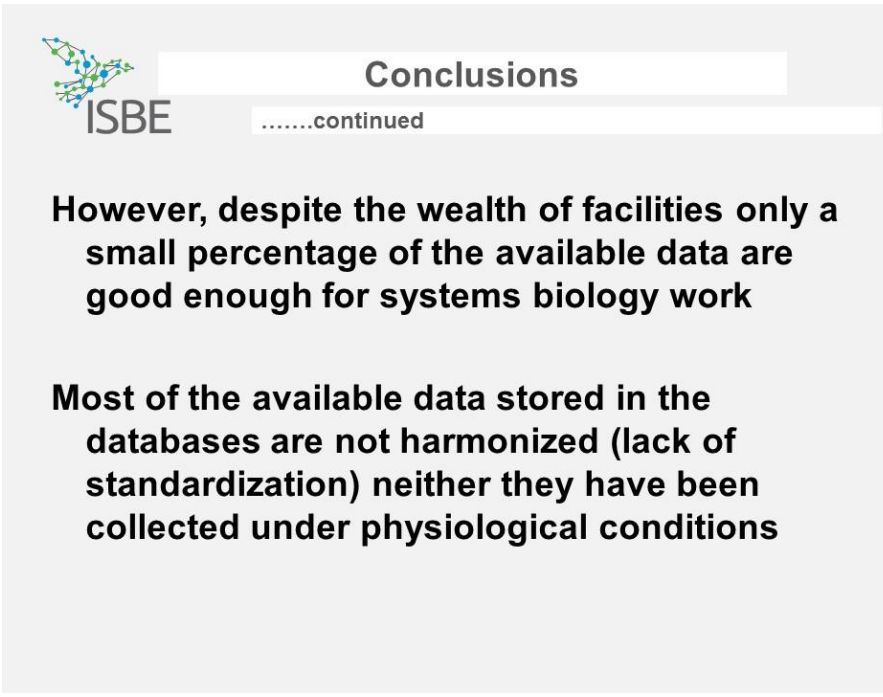
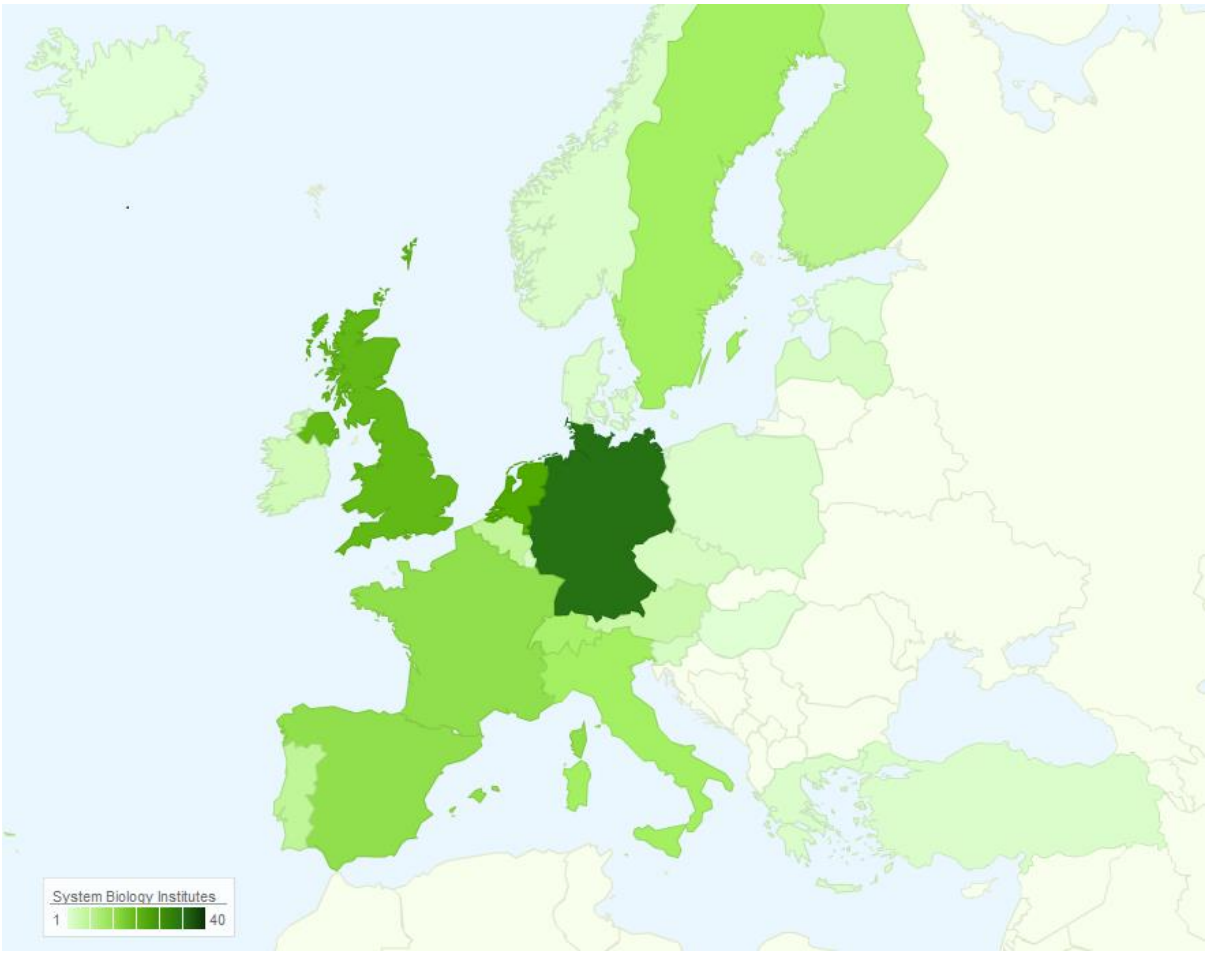
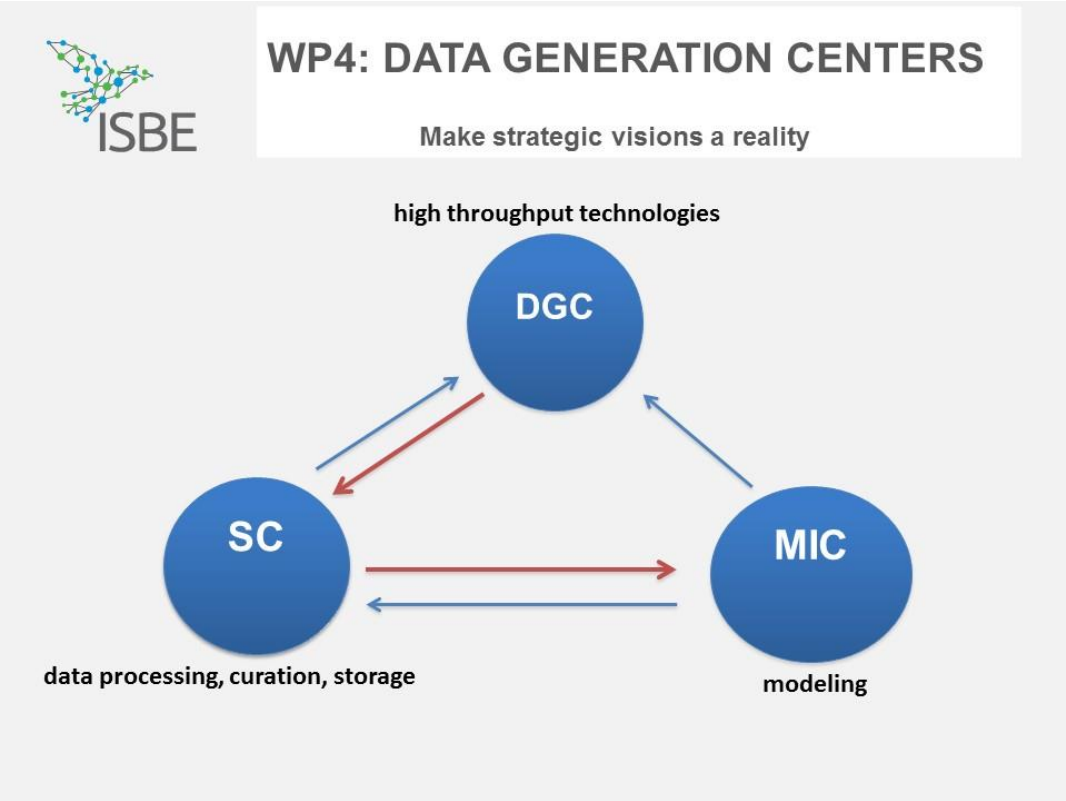


Figure 11 shows a "heat map" of the geographical distribution of Systems Biology Data Generation Laboratories in Europe. It is quite clear that the majority of Systems Biology – related activities are housed in Northern Europe with Germany, UK and the Netherlands being the focal points. A complete list of the data generation infrastructure laboratories is shown on Table 1.



DRAFT POLICY SUMMARY ON DATA GENERATION CENTERS

The aim of the Data Generation work package (WP4) is to develop the appropriate institutional infrastructure and scientific mentality to support the collection of high throughput quantitative data in the biomedical and biotechnology fields in a way that is fit for systems biology. The overall objective of WP4 is to translate the strategic vision developed in WP3 (Overall Infrastructure, Eligibility and Accessibility) into an infrastructure plan for the construction phase of ISBE (Fig.12).



To build competitive Data Generation Centers, ISBE should foster, among others, the following strategic decisions:

- **Expand state-of-the-art omics capabilities**
- **Standardize and normalize procedures**
- **Ensuring interoperability between data generation centres**
- **Provide comprehensive training**
- **Encourage public-private synergy**
- **Ensuring efficient allocation of resources**
- **Meeting data management challenges**

These issues will be discussed on the Policy paper (Deliverables 4.1, 4.3 and 4.5) delivered on month 30.

TABLE 1

Table 1 lists all laboratories/institutes/entities bearing laboratory facilities capable of producing Systems Biology Data. The list has been compiled by combining the data from the IISBE survey and WP4 Web searches.

Intitute	Country	URL
Computational Systems Biology, University of Vienna	Austria	http://cube.univie.ac.at/
Institute of Technology Assessment, Austrian Academy of Sciences	Austria	http://www.oeaw.ac.at/ita/en/projects/reflexive-systems-biology
Molecular Systems Biology, University of Vienna	Austria	http://www.univie.ac.at/mosys/
Systems Biology of Mitosis	Austria	http://www.mitosys.org
The Systems Biology Researcher Database	Austria	http://www.sysbioldb.org/
Vienna Institute of BioTechnology	Austria	http://www.systemsbiology.at/
Centre for Human Genetics	Belgium	http://gbiomed.kuleuven.be/apps/cme/index.html?en
Computational Omics and Systems Biology Group, VIB-Ugent	Belgium	http://compomics.com/
Facility for Systems Biology based Mass Spectrometry	Belgium	http://www.sybioma.be/
Faculty of Medicine KU Leuven	Belgium	http://med.kuleuven.be
Groupe Interdisciplinaire de Genoproteomique Appliquee, University of Liege	Belgium	http://www.giga.ulg.ac.be/jcms/c_5415/giga-systems-biology-chemical-biology
KU Leuven Center for Computational Systems Biology	Belgium	http://www.kuleuven.be/symbiosys/
Plant Systems Biology, Ghent University/VIB	Belgium	http://www.psb.ugent.be/
Systems Biology, VIB	Belgium	http://www.vib.be/en/research/scientists/Pages/default.aspx?category=Systems%20biology
Global Change Research Centre, Academy of Sciences of the Czech Republic	Czech Republic	http://www.czechglobe.cz
Institute of Nanobiology and Structural Biology	Czech Republic	http://www.nh.cas.cz/
Masaryk University	Czech Republic	http://www.muni.cz/
Animal Breeding, Quantitative Genetics and Systems Biology, University of Copenhagen	Denmark	http://qsg.dk/ http://www.systemsgenetics.dk/
Center for Disease Systems Biology	Denmark	http://www.cdsb.dk/
Department of Disease Systems Biology	Denmark	http://www.cpr.ku.dk/research/dsb
Department of Systems Biology, DTU	Denmark	http://www.bio.dtu.dk/english
Integrative Systems Biology, DTU	Denmark	http://www.cbs.dtu.dk/researchgroups/ibiology.php
Systems Biology, University of Kopenhagen	Denmark	http://bmi.ku.dk/english/research/systemsbiology
Laboratory of Systems Biology, Tallinn University of Technology	Estonia	http://sysbio.ioc.ee/
Abo Akademi	Finland	http://www.abo.fi/public/en/
Computational Systems Biology Research Group, TUT	Finland	http://csb.cs.tut.fi/
Institute for Molecular Medicine Finland (FIMM), University of Helsinki	Finland	https://www.fimm.fi/
Institute of Biomedical Technology	Finland	http://www.uta.fi/admissions/exchange/schools/ibt.html
Quantitative Biology and Bioinformatics group	Finland	http://sysbio.vtt.fi/
SBW	Finland	http://www.sbw.fi
Turku Centre for Systems Biology	Finland	http://sbrp.btk.fi/
University of Helsinki	Finland	http://www.helsinki.fi/university/
University of Turku	Finland	http://www.utu.fi/en/Pages/home.aspx
Bacillus Systems Biology	France	http://www.basysbio.eu/
Bio-Modeling Systems	France	http://www.bmsystems.net/
Chemistry Systems Biology, Pasteur Institute of Lille	France	http://csb.ibl.fr
CNRS	France	http://www.cnrs.fr/?lang=en
Computational Systems Biology of Cancer group, Bioinformatics Unit, Institut Curie	France	https://sysbio.curie.fr/
Ecole Normale Superieure	France	http://www.ens.fr/?lang=en
EPI Contraintes, INRIA	France	http://contraintes.inria.fr/
European Institute for Systems Biology & Medicine	France	http://www.eisbm.org/
Ibis, INRIA	France	http://ibis.inrialpes.fr/
Institute of Systems & Synthetic Biology	France	http://www.issb.genopole.fr/
Laboratoire International Associe	France	http://www.edam.uhp-nancy.fr/
Systems Biology Lab, Institut Pasteur	France	http://www.proteomics.fr/Sysbio/
Systems Biology, Mathematique, Informatique et Genome Laboratory	France	https://mig.jouy.inra.fr/?q=en/node/49
Systems biology, SOBIOS	France	http://www.sobios.com/about-us/research-developpement/systems-biology/
University of Evry	France	http://www.univ-evry.fr/en/index.html
University of Montpellier 2	France	http://www.univ-montp2.fr/
UTC	France	http://www.utc.fr/the_university/index.php
Aquatic Systems Biology, Technische Universitat Munchen	Germany	http://fisch.wzw.tum.de/index.php?id=10&L=1
Bio System Analysis Group, University of Jena	Germany	http://www.biosys.uni-jena.de/
Center for Biological Systems Analysis, University of Freiburg	Germany	http://www.zbsa.uni-freiburg.de/
Center for Systems Biology, Dresden	Germany	http://www.mpg-sysbio.de/
Center Systems Biology, University of Stuttgart	Germany	http://www.bioregio-stern.de/en/our-services/corporate-database/center-systems-biology-csb
Center Systems Biology, University of Stuttgart	Germany	http://www.centersysbio.uni-stuttgart.de/
Centre for Structural Systems Biology	Germany	http://www.cssb-hamburg.de/
Comparative Systems Analysis, EMBL	Germany	http://www.bork.embl.de/
Computational Systems Biology, Bayer	Germany	http://www.systems-biology.com/
Department of Plant Systems Biology, Technische Universitat Munchen	Germany	http://sysbiol.wzw.tum.de/index.php?id=2&L=1
ERASysAPP - ERA-Net for Systems Biology Applications	Germany	https://www.erasysapp.eu/
ERASysBio - ERA-Net for Systems Biology	Germany	http://www.erasysbio.net/
FH Stralsund	Germany	http://www.fh-stralsund.de/fh_stralsund/powerslave,id,224,nodeid,.html
Freiburg Initiative for Systems Biology	Germany	http://www.frisys.biologie.uni-freiburg.de/
German Cancer Reseach Center - DKFZ	Germany	http://ibios.dkfz.de/tbi/

Group of Systems Biology of Molecular Networks, Charite Universitatsmedizin Berlin	Germany	http://www.sys-bio.net/
HITS /Heidelberg Univ	Germany	http://www.h-its.org/english/
Institute of Biochemistry of the Charite, Universitatsmedizin Berlin	Germany	http://www.charite.de/sysbio/
Institute of Bioinformatics and Systems Biology	Germany	http://www.helmholtz-muenchen.de/en/ibis
Leibniz Research Centre for Working Environment and Human Factors	Germany	http://www.ifado.de/systembiologie/
Medical Systems Biology, Universitat Ulm	Germany	http://sysbio.uni-ulm.de/
ProteoSys AG	Germany	http://www.proteosys.com/
Systembiology / Bioinformatics, Ernst-Moritz-Arndt-Universitat Greifswald	Germany	http://www.mikrobiologie.uni-greifswald.de/index.php?id=33
Systems Biology / Bioinformatics, Leibniz Institute for Natural Product Research and Infection Biology	Germany	http://www.hki-jena.de/index.php
Systems Biology and Bioinformatics, University of Rostock	Germany	http://www.sbi.uni-rostock.de/
Systems Biology of Ageing Cologne	Germany	http://www.sybacol.org/
Systems Biology of Hepatocytes	Germany	http://www.hepatosys.de/
Systems Biology of Stem Cells and Reprogramming	Germany	http://syboss.eu/
Systems Biology, Leibniz-Institut fur Pflanzengenetik und Kulturpflanzenforschung	Germany	http://www.ipk-gatersleben.de/en/dept-physiology-and-cell-biology/systems-biology/
The Berlin Institute for Medical Systems Biology	Germany	https://www.mdc-berlin.de/13800178/en/bimsb
The Hutt Group, Jacobs University	Germany	http://sysbio.jacobs-university.de
The Institute for Medical Informatics and Biometry, Technische Universitat Dresden	Germany	http://tu-dresden.de/med/imb
The Magdeburg Centre for Systems Biology, University of Magdeburg	Germany	http://www2.mpi-magdeburg.mpg.de/MaCS
The Systems Biology Group, University of Stuttgart	Germany	http://www.sysbio.de/
Theoretical Systems Biology Group, University of Jena	Germany	http://tsb.uni-jena.de/
Theoretical Systems Biology, Friedrich Schiller University of Jena	Germany	http://www.jcb-jena.de/
University of Heidelberg	Germany	http://www.uni-heidelberg.de/index_e.html
University of Hertfordshire/Universitat Passau/University of Debrecen/University of Dundee	Germany	http://www.biomicsproject.eu/
University of Tubingen	Germany	http://www.uni-tuebingen.de/en/
Virtual Liver Network	Germany	http://www.virtual-liver.de
Centre for Systems Biology, Biomedical Research Foundation, Academy of Athens	Greece	http://www.bioacademy.gr/
Systems Biology & Bioengineering Research Laboratory, NTUA	Greece	http://users.ntua.gr/leo/index-People-v01.html
Synthetic and Systems Biology Unit, Biological Research Centre	Hungary	http://group.szbk.u-szeged.hu/sysbiol/
University of Iceland	Iceland	http://english.hi.is/
Bioinformatics and Systems Biology Unit, Deri	Ireland	http://www.deri.ie/content/bioinformatics-and-systems-biology-unit
Centre for Systems Medicine, Royal College of Surgeons in Ireland	Ireland	http://www.systemsmedicineireland.ie/
Systems Biology Ireland, University College Dublin	Ireland	http://www.ucd.ie/sbi/
Systems Biology, Hamilton Institute	Ireland	http://www.hamilton.ie/systemsbiology/
Bioinformatics CORE at Biogem Research Center	Italy	http://bioinformatics.biogem.it/
Center for BioMedical Computing	Italy	http://www.cbmc.it/
Center for Genomic Science, IIT	Italy	http://genomics.iit.it/
Centre for Systems biology	Italy	http://www.sysbio.it/
Centro Interdipartimentale Molecular Systems Biology	Italy	http://www.unito.it/unitoWAR/page/centri1/X026/X026_data_mining1
Centro Ricerca e Innovazione	Italy	http://cri.fmach.eu/Research/Computational-Biology
Computational Systems Biology research center	Italy	http://www.cosbi.eu/
Department of Informatics, Systems and Communications, University of Milan-Bicocca	Italy	http://bimib.disco.unimib.it
Fondazione Edmund Mach	Italy	http://www.fmach.it/
Systems and Computational Biology, Institute of Biomedical Technologies	Italy	http://www.itb.cnr.it/web/bioinformatics/systems-and-computational-biology
Systems Biology and Biomedical Systems, University of Perugia	Italy	http://www.sira.diei.unipg.it/research-area/systems-biology-and-biomedical-systems.html
Systems Biology Group Lab, University of Rome	Italy	http://www.sbglab.org
Systems Biology, International School for Advanced Studies	Italy	http://www.math.sissa.it/content/systems-biology
Telethon Institute of Genetics and Medicine	Italy	http://www.tigem.it/
Biosystems group, Latvia University of Agriculture	Latvia	http://biosystems.lv/
SIA Tibit	Latvia	http://tibit.lv/index.php/research/systems-biology
Systems biology: genomes to life	Latvia	http://www.sysbio.lv/
Faculty of Science Technology and Communication, University of Luxembourg	Luxembourg	http://wwwen.uni.lu/research/fstc/life_sciences_research_unit/systems_biology
Le Centre de Recherche Public - Gabriel Lippmann	Luxembourg	http://ecosystemsbiology.org/
Luxembourg Centre for Systems Biomedicine, University of Luxembourg	Luxembourg	http://wwwen.uni.lu/lcsb/research/computational_biology
BioModeling and bioInformatics, Eindhoven University of Technology	Netherlands	http://bmi.bmt.tue.nl/sysbio/
Cancer Systems Biology Center	Netherlands	http://csbc.nki.nl/
Centre for Medical Systems Biology	Netherlands	http://dial.liacs.nl/
Centre for Systems Biology and Bioenergetics	Netherlands	http://www.csb-bioenergetics.nl/
CNCR, VU University Amsterdam	Netherlands	http://www.cncr.nl/expertise/systemsbiology
Erasmus University Medical Center	Netherlands	http://www.erasmusmc.nl/?lang=en

Faculty of Mathematics and Natural Sciences, University of Groningen	Netherlands	http://www.rug.nl/research/molecular-systems-biology/
Genetics and Systems Biology of the Metabolic Syndrome, Leiden University Medical Center	Netherlands	https://www.lumc.nl/con/3098/85419/124277/?setlanguage=English&setcountry=en
Hubrecht Institute and UMC Utrecht	Netherlands	http://www.umcutrecht.nl/research/collaborations/regional/hubrecht-institute.htm
Kluyver Centre for Genomics of Industrial Fermentation	Netherlands	http://www.kluyvercentre.nl/pro1/general/start.asp?i=5&j=0&k=0&p=0&itemid=164
Life Sciences, Centrum Wiskunde & Informatica	Netherlands	http://www.cwi.nl/Systems_biology_of_molecular_regulatory_networks
Mitochondrial Systems Biology, Nijmegen Center for Mitochondrial Disorders	Netherlands	http://www.ncmd.nl/page/535/systems-biology.html
Netherlands Consortium for Systems Biology	Netherlands	http://www.ncsb.nl/
Netherlands Genomics Initiative	Netherlands	http://www.genomics.nl/
Netherlands Institute for Systems Biology	Netherlands	http://www.sysbio.nl/
Netherlands Metabolomic Centre	Netherlands	http://www.metabolomicscentre.nl/
NUTRIM School for Nutrition, Toxicology and Metabolism, Universiteit Maastricht	Netherlands	http://www.maastrichtuniversity.nl/web/Institutes/FHML/NUTRIM/SystemsBiology.htm
Phenotype Foundation	Netherlands	http://phenotypefoundation.org
Radboud University	Netherlands	http://www.ru.nl/english/
Swammerdam Institute for Life Sciences	Netherlands	http://sils.uva.nl/
Systems Biology of the Synapse - Genes & the Brain, Neuroscience Campus Amsterdam	Netherlands	http://www.neurosciencecampus-amsterdam.nl/en/research/research-activities/genes-and-the-brain/systems-biology-of-the-synapse/index.asp
Systems Biology, Innovation for Life	Netherlands	https://www.tno.nl/content.cfm?context=kennis&content=etp_content&laag1=7&item_id=7&Taal=2
Systems biology, Wageningen UR	Netherlands	http://www.wageningenur.nl/en/Expertise-Services/Research-Institutes/plant-research-international/Research-topics-Plant-Research-International/Systems-biology.htm
The Systems Biology Biology Centre for Metabolism and Ageing, University of Groningen	Netherlands	http://www.rug.nl/research/centre-for-systems-biology/research
Universiteit Utrecht	Netherlands	http://www.uu.nl/en/pages/default.aspx
University of Amsterdam	Netherlands	http://www.uva.nl/en/research/content/systems-biology/systems-biology.html
VU University Amsterdam	Netherlands	http://www.vu.nl/en/
Norwegian University of Life Sciences	Norway	http://www.umb.no/frontpage/
The Centre for Integrative Genetics (CIGENE), Norwegian University of Life Sciences	Norway	http://www.cigene.no/
Institute of Genetics and Animal Breeding, Polish Academy of Sciences	Poland	http://www.functionalgenomics.pl
The International Institute of Molecular and Cell Biology	Poland	http://www.iimcb.gov.pl/
CBS Computational Biology Services	Portugal	http://systemsbiologyservices.com/
Center for Neuroscience and Cell Biology	Portugal	http://www.cnbc.pt/default.asp?lg=2
Center for Neuroscience and Cell Biology, University of Coimbra	Portugal	http://cnc.cj.uc.pt/~salvador/
Centre of Biological Engineering, University of Minho	Portugal	http://sysbio.di.uminho.pt/bisbii/
Institute for Molecular and Cell Biology, University of Porto	Portugal	http://www.ibmc.up.pt/research/research-groups/evolutionary-systems-biology
Instituto Gulbenkian de Ciencia	Portugal	http://www.igc.gulbenkian.pt/
Systems Biology and Bioinformatics Laboratory, University of Algarve	Portugal	http://www.sysbiolab.eu/
Systems Biology and Engineering, Departamento de Quimica da FCT/UNL	Portugal	http://www2.dq.fct.unl.pt/SBEgroup/
Biotechnical Faculty, University of Ljubljana	Slovenia	http://www.integratomics-time.com
Computational Biology Group, University of Ljubljana	Slovenia	http://lrss.fri.uni-lj.si/bio/
Department of Biotechnology and Systems Biology, National Institute of Biology	Slovenia	http://www.nib.si/eng/index.php/oddelki/oddelek-za-biotehnologijo-in-sistemsko-biologijo.html
Anaxomics, System biology solutions	Spain	http://www.anaxomics.es/our-technology/systems-biology/
Autonomous University of Barcelona	Spain	http://www.uab.es/english/
Complex Systems and Networks Lab, Institute for Biocomputation and Physics of Complex Systems	Spain	http://cosnet.bifi.es/research-lines/systems-biology
Computational Systems Biology Group, National Centre for Biotechnology	Spain	http://www.pdg.cnb.uam.es/
Computational Systems Biology, UPM-BBVA	Spain	http://www.ctb.upm.es/?page_id=207
Dept. Ciencies Mediques Basiques, Universidad de Lleida	Spain	http://www.systemsbiology.cat/
Dynamical Systems Biology, Universitat Pompeu Fabra	Spain	http://dsb.upf.edu/
EMBL-CRG Systems Biology	Spain	http://www.crg.es/systems_biology
Organisms and Systems Biology, University of Oviedo	Spain	http://www.uniovi.es/en/departamentos/bos
Polytechnic School / Universitat de Vic	Spain	http://www.uvic.es/en/centres/EPS
Spanish Network of Systems Biology	Spain	http://www.sysbiol.net/
Systems Biology Program, CNB-CSIC	Spain	http://sysbiol.cnb.csic.es/SysBiol/
Systems Biology, Centre for Genomic Regulation	Spain	http://pasteur.crg.es/portal/page/portal/Internet/02_Research/01_Programmes/06_Systems_Biology
Systems Biology, Centro de Investigacion Principe Felipe	Spain	http://www.cipf.es/biologia-sistemas
Univ of Cordoba	Spain	http://www.uco.es/internacional/extranjeros/
Universidad de La Laguna	Spain	http://www.ull.es/
Universitat Politecnica de Valencia	Spain	https://www.upv.es/index-en.html

Center for Molecular Medicine, Karolinska Institutet	Sweden	http://compmed.se/
Centre for Systems Biology, University of Gothenburg	Sweden	http://www.systemsbiology.gu.se/
Chalmers, Chemical and Biological Engineering	Sweden	http://www.sysbio.se/ https://www.chalmers.se/chem/EN/divisions/systems-biology
Computational Biology & Biological Physics Group, Lund University	Sweden	http://cbbp.thep.lu.se/
Department of Cell and Molecular Biology, Uppsala University	Sweden	http://www.icm.uu.se/research/csb/
Department of Plant Biology, Swedish University of Agricultural Sciences	Sweden	http://www.slu.se/en/departments/plant-biology-forest-genetics/research/groups/lars-hennig/research/bioinformatic-and-transcriptomics/
Eukaryotic unicellular organism biology	Sweden	http://www.unicellsys.eu/
Fraunhofer-Chalmers Centre for Industrial Mathematics	Sweden	http://www.fcc.chalmers.se/
Mathematical Sciences	Sweden	http://www.science.gu.se/english/education/mathematical-sciences/
Science for Life Laboratory, Uppsala University	Sweden	http://scilifelab.uu.se/Research/Systems_Biology/
Systems Biology of Colorectal Cancer	Sweden	http://www.genexplain.com/syscol
Systems Biology of Microorganisms Research Group, Linnaeus University	Sweden	http://lnu.se/research-groups/systems-biology-of-microorganisms-research-group?l=en
Systems Biology Research Centre, University of Skovde	Sweden	http://www.his.se/en/Research/Systems-Biology/Systems-Biology/
Systems Microscopy Network of Excellence	Sweden	http://systemsmicroscopy.eu/
Basel Computational Biology Center [BC]2	Switzerland	http://www.hpc-ch.org/basel-computational-biology-center-bc2/
Biozentrum, University of Basel	Switzerland	http://www.biozentrum.unibas.ch/
Computational Systems Biology Group, ETH Zurich	Switzerland	http://www.csb.ethz.ch/
Institute of Molecular Life Sciences, University of Zurich	Switzerland	http://www.imls.uzh.ch/
Institute of Molecular Systems Biology, ETH Zurich	Switzerland	http://www.imsb.ethz.ch/
Institute of Plant Sciences, University of Bern	Switzerland	http://www.botany.unibe.ch/associated/systemsx
Model Organism Proteomics, University of Zurich	Switzerland	http://www.mop.unizh.ch/
Research Group Environmental Genomics and Systems Biology, Zurich University of Applied Sciences	Switzerland	http://www.lsfm.zhaw.ch/en/lsfm/institutes-centres/iunr-biologicalfarming/environmental-genomics-and-systems-biology.html
Swiss Institute of Bioinformatics	Switzerland	http://www.isb-sib.ch/
Systems Biology / Functional Genomics, University of Zurich	Switzerland	http://www.sysbio.uzh.ch/
Systems Biology, Roche	Switzerland	http://www.roche.com/de/research_and_development/what_we_are_working_on/research_technologies/translational_technologies/systems_biology.htm
The Swiss Initiative in Systems Biology	Switzerland	http://www.systemsx.ch/
The Systems Optimization group	Switzerland	http://www.tik.ee.ethz.ch/sop/
Gebze Institute of Technology	Turkey	http://www.gyte.edu.tr/
Koc University	Turkey	http://www.ku.edu.tr/en
Biocomputing Group, Hertfordshire University	UK	http://strc.herts.ac.uk/bio/
Cancer Systems Biology, Abertay University	UK	http://www.abertay.ac.uk/research/schools/scs/cansystems/
Cell and Systems Biology, University of St Andrews	UK	http://biology.st-andrews.ac.uk/groupProfile.aspx?gc=CELLSYS_AREA&mp=BIO07&jc=academic&nt=1
Centre for Systems Biology, University of Birmingham	UK	http://www.birmingham.ac.uk/research/activity/csb/index.aspx
Centre of Excellence for Integrative Biology of Crops, University of Nottingham	UK	http://www.cpib.ac.uk/
Centre SynthSys	UK	http://www.synthsys.ed.ac.uk/
Computational Modelling Group, University of Southampton	UK	http://cmg.soton.ac.uk/research/categories/life-sciences-simulation/systems-biology/
Department of Computational and Systems Biology, The John Innes Centre	UK	http://www.jic.ac.uk/corporate/science-departments/comp-bio.htm
Experimental Network for Functional INtegration	UK	http://www.enfin.org/
Francis Crick Institute/University College London	UK	http://www.crick.ac.uk/
Institute of Integrative Biology, University of Liverpool	UK	http://pcwww.liv.ac.uk/~aging/
London BioScience Innovation Centre	UK	http://www.lbic.com/
Newcastle University	UK	http://www.ncl.ac.uk/
NHLI Imperial College	UK	http://www1.imperial.ac.uk/nhli/
Oxford University	UK	http://www.ox.ac.uk/
SULSA	UK	http://www.sulsa.ac.uk/
Systems Biology Integrative Centre, University of Aberdeen	UK	http://www.abdn.ac.uk/systemsbiology/
Systems Biology of Neuronal Signalling, EMBL-EBI	UK	http://www.ebi.ac.uk/compneur-srv/
Systems Biology, Innogen	UK	http://www.innogen.ac.uk/research/projects/83
Systems Biology, University of Exeter	UK	http://biosciences.exeter.ac.uk/research/systemsbiology/
Theoretical Systems Biology, Institute of Food Research, Norwich Research Park	UK	http://www.ifr.ac.uk/Staff/thomas-wilhelm/TSB/default.html
University of Glasgow	UK	http://www.gla.ac.uk/
University of Manchester	UK	http://www.manchester.ac.uk/
University of Strathclyde	UK	http://www.strath.ac.uk/