

**Japanese Competence Centers in Bioinformatics and Computational Biology:
A primer for European SMEs**

May 2015

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Terms used:

Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data. As an interdisciplinary field of science, bioinformatics combines computer science, statistics, mathematics, and engineering to study and process biological data, <http://en.wikipedia.org/wiki/Bioinformatics>.

Computational biology involves the development and application of data-analytical and theoretical methods, mathematical modeling and computational simulation techniques to the study of biological, behavioral, and social systems. The field is broadly defined and includes foundations in computer science, applied mathematics, animation, statistics, biochemistry, chemistry, biophysics, molecular biology, genetics, genomics, ecology, evolution, anatomy, neuroscience, and visualization, http://en.wikipedia.org/wiki/Computational_biology.

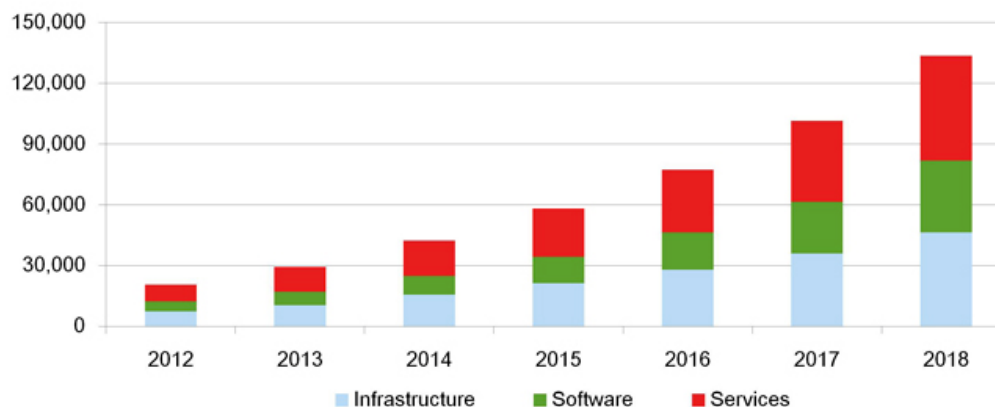
Systems biology is the computational and mathematical modeling of complex biological systems. An emerging engineering approach applied to biomedical and biological scientific research, systems biology is a biology-based inter-disciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach (holism instead of the more traditional reductionism) to biological and biomedical research, http://en.wikipedia.org/wiki/Systems_biology.

Biobanks are a type of biorepository that stores biological samples (usually human) for use in research. Since the late 1990s biobanks have become an important resource in medical research, supporting many types of contemporary research like genomics and personalized medicine, <http://en.wikipedia.org/wiki/Biobank>.

1. Introduction

Japan is a global hub for electronics, computers, robotics and software. Electronics from Sony or Canon, computers from NEC or Fujitsu, robots from Epson, Honda or Panasonic, or telecommunication and internet software from, e. g., SoftBank are widely sold beyond Japan and have much contributed to Japan's image as a high-tech nation. Details of her science, technology and business in these areas have already been provided in this series of reports from the EU-Japan desk. In addition, Japan has a strong stake in the life sciences industry which has entered an era of "big data": genome sequencing, quantitative and systems biology, personalized medicine or drug design are just a few examples of cutting-edge technology developments where "big data" originating from life-science research are being used for product developments or services. Japan is also an "information society". The government plays an active role in the continuous upgrading of Japan's competitiveness through science and technology. This also translates into R&D expenditure into public and individual health, agriculture, environmental protection, but also into new sustainable production methods based on renewable raw materials. To this end, the collection of "big data" based on, e. g., genome sequencing, their processing by supercomputers and their storage and retrieval in databases are considered a key resource which must be administered and financially supported by the government. The BioBank project (see 2.1.5), administered by RIKEN and centered in the Tohoku area (which was struck by the Great Eastern Earthquake in 2011) is just one, if a particularly important example. Against this background, it is of little surprise that computational biology is a very important component of Japanese technology development, as reflected in a recent market forecast by IDC, http://www.idc.com/getdoc.jsp?containerId=IDC_P31404.

Japan Big Data Technology and Service Market Forecast 2012–2018



Source: IDC

I will first describe the Japanese landscape in this area, followed by reflections how Europe's SMEs might gain access to this very active business field. It must be stated, however, that this field is quite scattered among various ministries and regions, and that unfortunately most of the documents cited here and relevant for a deeper understanding are only available in Japanese.

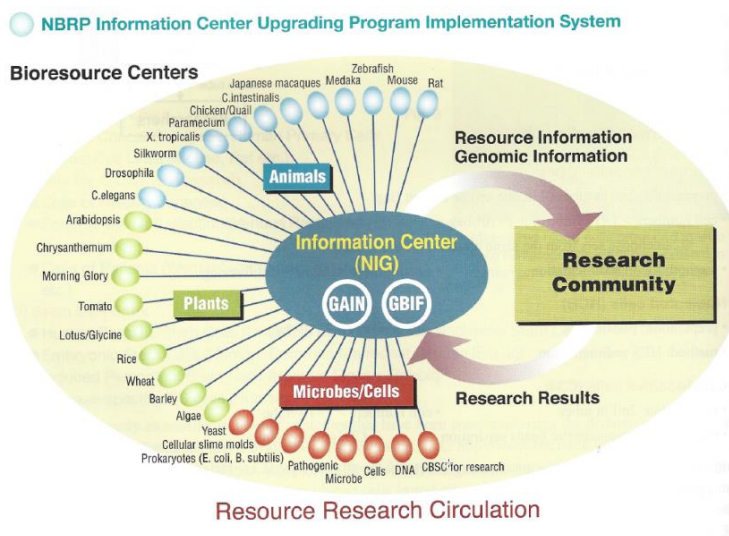
2. Governmental institutions and their stakes in bioinformatics

2.1 The Ministry of Science and Education (MEXT) and its Science and Technology Agency JST

In her annual "White papers", MEXT reiterates the view that S&T is the fundament of Japan's economic growth, and specimen- and bioinformatics-related databases are essential to ensure progress in the life sciences. As a consequence, several programs were implemented as early as 2002 and are being continued until now.

2.1.1 MEXT National Bioresource Project, <http://www.nbrp.jp>

The program was implemented in 2002 and is presently in its 3d term from 2012 – 2016. Its objective is to strategically organize the bioresources of Japan in order to promote the life sciences. In 2014, there were 29 core facilities distributed throughout Japan which had a focus each on the collection, preservation and provision of a specific bioresource, e. g., mice, Drosophila, silkworm, Medaka fish, yeast etc. The information about all 6.3 million bioresources in these core facilities is stored and distributed by the Information Center at the National Institute of Genetics (NIG) in Mishima, Shizuoka Prefecture. PI is Yukiko YAMAZAKI. Each month, 240.000 users on average access the database, and some 12.000 papers have been published citing access to these resources. The Great Ape Information Network (GAIN) on primates living in Japan, <http://www.shigen.nig.ac.jp/gain/>, is included in this network, as is the Japan node for the Global Biodiversity Information Facility (GBIF Japan), <http://www.gbif.jp/v2/>.

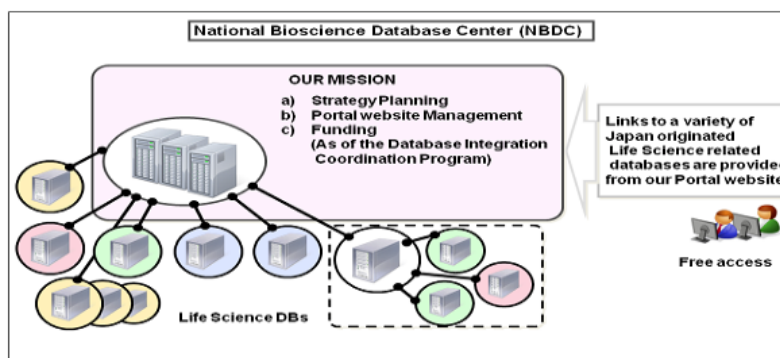


2.1.2 National Bioscience Database Center (NBDC), <http://biosciencedbc.jp/en/>

The NBDC is operated by the Japan Science and Technology Agency, an institution under MEXT.

It is the national database center of Japan, integrating the scattered life science related databases from Japan and beyond, with an aim to optimize the value of scientific data. The mission of NBDC is

- to do strategic planning for database research and development
- to integrate and improve existing databases related to the life sciences,
- to share R&D-related data nationally and internationally



Starting from the NBDC (English version available), a considerable number of Japanese databases can be accessed, as shown in the list.

One of the pillars of NBDC is the

2.1.3 JST Bird Institute, http://www.jst.go.jp/nbdc/bird/index_e.html

The Institute for Bioinformatics Research and Development (BIRD) is located at the National Bioscience Database Center (NBDC) and administered by the JST. Its mission is to aid the progress of bioinformatics and promote creation of new biology, which has computational, deductive, predictive, and theoretical features. A brochure of BIRD, issued in Nov. 2011, http://www.jst.go.jp/nbdc/bird/files/pdf/BIRD_seikasyu.pdf (in Japanese) outlines in much detail the major Japanese databases accessible under BIRD, and the key scientists involved in their creation and maintenance.

2.1.4 The National Institute of Genetics and DNA Database of Japan, <http://www.ddbj.nig.ac.jp>

The National Institute of Genetics is a public research organization under MEXT, located in Mishima, Shizuoka Prefecture. A pioneer in Japanese bioinformatics, it hosts, since 1984, the DNA Databank of Japan (DDBJ) <http://www.ddbj.nig.ac.jp/intro-e.html>, one of the 3 mirror sites of the International Nucleotide Sequence Database Collaboration (INSDB) with 2 other mirror sites at the National Center for Biotechnology Information (NCBI), USA, and the European Bioinformatics Institute (EBI), UK. By now, Japan contributes about 12 % to the 188 billion nucleotides incorporated in sequences documented by INSDB. The National Institute of Genetics also hosts the **Database Center for Life Sciences (DBCLS)** <http://dbcls.rois.ac.jp>. Established in April 2007, it forms a base for integrating databases in life science field. Positioning itself as a specialized institution to provide biological databases and related services, DBCLS integrates and maintains biological databases mainly within Japan, conducts R&D of information technology and develops new services to enhance usability.

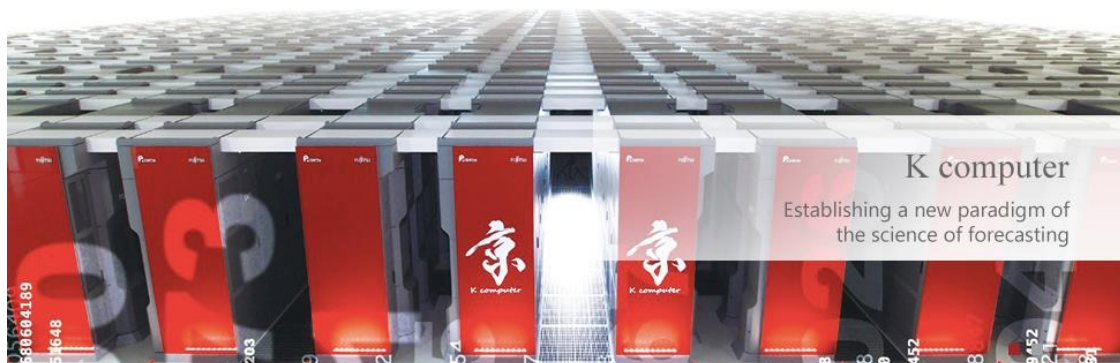
2.1.5 RIKEN and associated programs

RIKEN is Japan's largest and most comprehensive research organization for basic and applied science in a diverse array of scientific disciplines, from developmental biology and neuroscience to quantum physics and computer science, <http://www.riken.jp/en/>. It is an institute under MEXT.

RIKEN encompasses a network of world-class research centers across Japan, with main campuses in Wako, Tsukuba, Yokohama, Kobe and Harima offering state-of-the-art facilities that rank among the best in the world. Significant parts of RIKEN are dedicated to the Life Sciences, e. g., the RIKEN Center for Sustainable Resource Science, and its BioResource Center in Tsukuba, RIKEN's Center for Developmental Biology in Kobe, its Brain Science Institute in Wako, the RIKEN Center for Integrative Medical Sciences, the Center for Life Science Technologies in Yokohama, and also RIKEN's Spring-8 Center in Harima. All this program handle big data, and thus it is no surprise that RIKEN is also a Japanese hub for biocomputing.

RIKEN's K computer

This computer, which is on top of many international supercomputer rankings, is located on the campus of the RIKEN Advanced Institute for Computational Science in Kobe. It is being used in a broad range of fields including drug discovery, earthquake/tsunami research, weather forecasting, space science, manufacturing and material development. It is built on energy efficiency with features including solar power generation, use of heat from cogenerators and reuse of rainwater. It has a peak performance of 10.62 pFLOPS. Its construction features and performance have been summarized in an English-language leaflet, http://www.aics.riken.jp/en/wp-content/uploads/system_handout.pdf.



RIKEN's Operating System and Software

As the cluster system for RIKEN with its many diverse tasks, the institute established the RIKEN Super Combined Cluster RSCC, operating since 2004, and, from 2009, the RIKEN Integrated Cluster of Clusters RICC. This was followed in 2015 by the HOKUSAI-GreatWave. This massively parallel computing system performs up to 1000 trillion floating point operations per second and will service RIKEN's physics, chemistry, biology, and medical science departments. The HOKUSAI-GW system aims towards the fusion of experiment / simulation / data analysis and connects three computing systems having different functions in a high-speed network InfiniBand (FDR 4X), as if it were just one computing system. In 2016, it will be complemented by "HOKUSAI BigWaterfall (HOKUSAI-BW)", http://www.riken.jp/pr/press/2015/20150403_1/ http://www.riken.jp/pr/press/2014/20140310_1/.

Quite recently, RIKEN has published another achievement in software development: GENESIS, a software package for molecular dynamics (MD) simulations of macromolecules, allows for the highly parallel simulation of very large biological systems consisting of more than one million atoms. It is released as free software under the GPLv2 licence and can be easily modified for the development of new algorithms and molecular models, <http://wires.wiley.com/WileyCDA/WileyArticle/wisId-WCMS1220.html>.

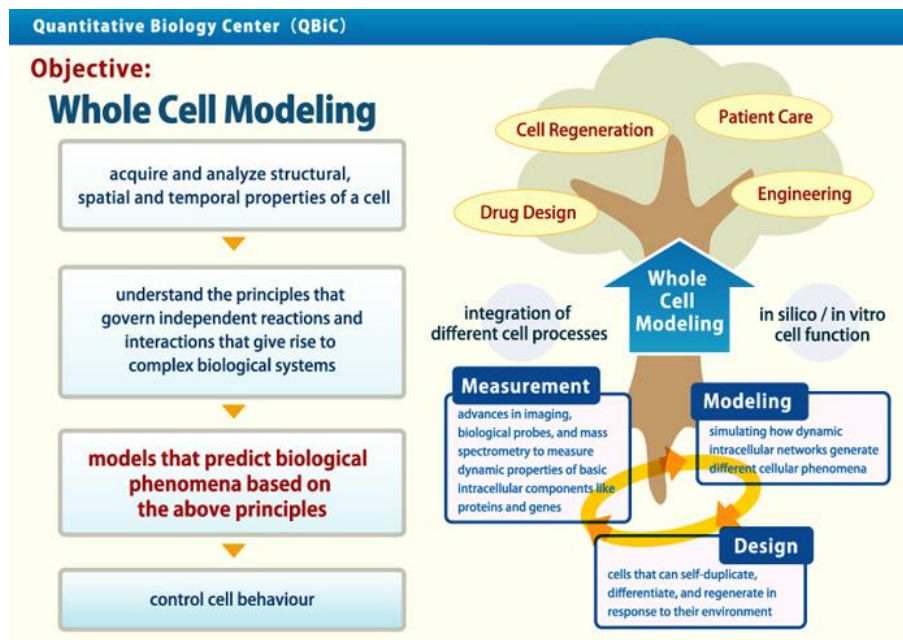
RIKEN Meta Database

RIKEN Meta Database is a service to publish metadata of databases published by RIKEN researchers in an organized way so that RIKEN's research results are widely used by researchers, <http://metadb.riken.jp/metadb/front>.

RIKEN BioResource Center DNA bank, Tsukuba

The DNA Bank of RIKEN BioResource Center <http://dna.brc.riken.jp/index.html> is located at RIKEN's Tsukuba institute. It is a member of the National BioResource Project of MEXT (see 2.1.1) and collects and provides DNA from man, animals, plants, microorganisms, viruses etc.

RIKEN's QBic Center, Osaka



In 2011, RIKEN has formed its Quantitative Biology Center (QBic), with its virtual headquarter in Osaka. The focus of this center, with about 20 delocalized laboratories, is on various aspects of whole cell modelling, helping in drug design, cell regeneration and patient care,

<http://www.qbic.riken.jp/english/overview/index.html>. The Center hosts a Computational Biology Research Core under direction of Makoto TAJI.

RIKEN Omics Center, Yokohama

RIKEN's Omics Science Center <http://www.osc.riken.jp/english/> is developing a comprehensive system called "Life Science Accelerator"(LSA) for the advancement of omics research. Apart from bioinformatic tools, the LSA consists of biological and human resources, technologies and know-how. A key project of the LSA is FANTOM, an international research consortium established in 2000 to assign functional annotations to the full-length cDNAs that were collected during the Mouse Encyclopedia Project at RIKEN. FANTOM has since developed and expanded over time to encompass other fields of transcriptome analysis. The object of the project is moving steadily up the layers in the system of life, progressing thus from an understanding of the 'elements' - the transcripts - to an understanding of the 'system' - the transcriptional regulatory network, in other words the 'system' of an individual life form.

RIKEN Center for Integrative Medical Sciences and the Biobank project

The RIKEN IMS, formerly Center of Genomic Medicine <http://www.src.riken.jp/english/project/person/index.html> , is also located at RIKEN Yokohama. It investigates individual gene variation in the genome and identifies the relationship to disease onset and drug response, in order to develop preventive and therapeutic techniques to suit each individual. It also administers the BioBank project <http://biobankjp.org/english/plan/summary.html> , which collects genomic data and SNPs from patients in 53 cooperating Japanese hospitals suffering from 38 target diseases. Started as early as 2003, after the Great Eastern Earthquake a significant part of this program was handed over to the disaster-stricken Tohoku region where now an important part of sequencing and data acquisition for this project takes place.

RIKEN's E-CELL project

The E-Cell Project develops general technologies and theoretical supports for computational biology with the grand aim to make precise whole cell simulation at the molecular level possible.

Some of the research projects include:

- modeling methodologies, formalisms and techniques, including technologies to predict, obtain or estimate parameters such as reaction rates and concentrations of molecules in the cell.
- E-Cell System, a software platform for modeling, simulation and analysis of complex, heterogeneous and multi-scale systems like the cell.
- numerical simulation algorithms.
- mathematical analysis methods.

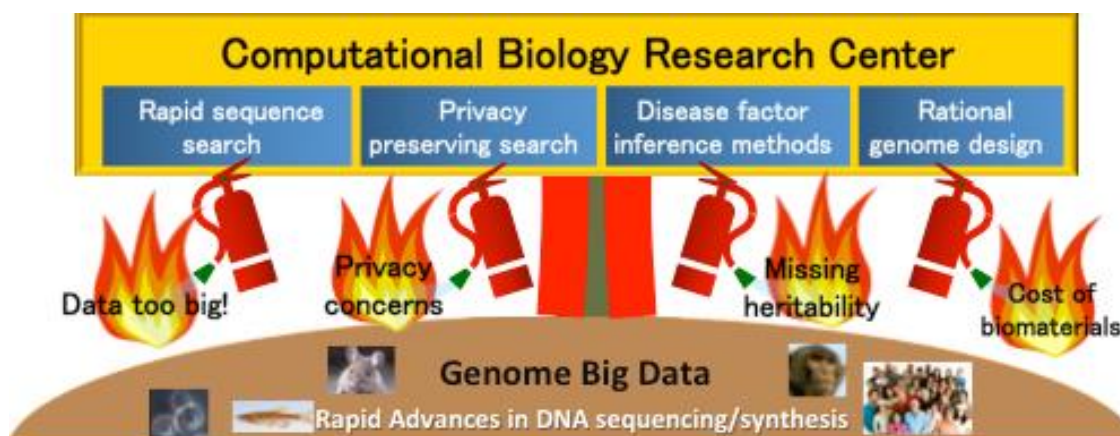
The E-Cell Project was started in 1996 by Masaru TOMITA, then at the Sony Corporation, and is co-developed by TOMITA's Institute of Advanced Science at Keio University, Tsuruoka Campus, and by RIKEN, <http://www.e-cell.org>.

2.2 The Ministry of Economics, Trade and Industry (METI) and its S&T organizations (AIST and NEDO)

As METI and associated institutes are concerned with Japan's economy and trade, the bioinformatics-related institutions under METI cover applied and business-related issues.

2.2.1 Computational Biology Research Center (since April 1st, 2015: Computational Biology Research Consortium).

The Center is under the Agency of Industrial Science and Technology (AIST), the R&D arm of METI. It is located on an artificial island at Tokyo Waterfront, near the Tokyo International Exhibition Center. CBRC is, since April 1, 2014, under the direction of Dr Paul Horton, a US computer scientist who started his career at Kyoto University. An important target of CBRC is to remove various bottlenecks in the application of genome big data, as shown below.



To this end, the Center has developed a range of software tools (see 7.) and also established various databases which are described on a detailed and well-run English-language website, <http://cbrc3.cbrc.jp/eng/intro/index.eng.html>. CBRC is structured into two research groups, one on **Genome Control information**, and the other on **Functional Genomics**. The CBRC website *in Japanese* also indicates a number of external partners to this group, namely

- the Laboratory of Yutaka AKIYAMA at the Tokyo Institute of Technology Department of Computer Engineering, <http://www.bi.cs.titech.ac.jp/web/>
- four laboratories at the University of Tokyo School of Frontier Sciences, Dept. of Computational Biology, located on the Kashiwa Campus (see 4.), namely
- the Laboratory of Kiyoshi ASAI, <http://asailab.cb.k.u-tokyo.ac.jp>
- the Laboratory of Shinichi MORISHITA, <http://mlab.cb.k.u-tokyo.ac.jp/en/>,
- the Laboratory of Koji TSUDA, http://tsudalab.org/en/member/koji_tsuda
- and the Laboratory of Hisanori KIRYU, <http://www.cb.k.u-tokyo.ac.jp/kiryulab/?lang=en>
- and the Laboratory of Michiaki HAMADA, Waseda University, Laboratory for Advanced Electrical and Bioinformatics Engineering, <https://sites.google.com/site/hamabioinflab/home>

2.2.2 AIST Intelligent Systems Research Institute

AIST operates several research institutes within its AIST cluster in Tsukuba, Ibaraki Prefecture. Robotics-related research is an important issue, and computing and software development plays a key role, https://unit.aist.go.jp/is/cie/outline/outline_e.html . As these developments are not in the core area of bioinformatics, they will not be described in more detail here.

2.2.3 NEDO programs

NEDO is a major project support agency under METI and handles in particular large public-private partnerships (PPPs) for the development of innovative industrial technology. Below is a shortlist of bioinformatics- and database-related programs of NEDO which were done over the last 10 years.

Program name and duration	Contents	URL
Next-generation cancer diagnostic system, 2014-2018	role of non-coding RNAs	http://www.nedo.go.jp/content/100083816.pdf
Human genome diversity database, 2011	database on the diversity of healthy Japanese population	http://www.nedo.go.jp/news/press/AA5_100003.html
Systems biology: standardization of graphical notation, 2009	Cooperation with Nature Biotechnology	http://www.nedo.go.jp/news/press/AA5_0096A.html
JBic: collection of cloned human proteins, 2008	Collection of 15.000 expressed human proteins	http://www.nedo.go.jp/news/press/AA5_0459A.html

2.2.4 Japanese Agency for Marine-Earth Science and Technology, JAMSTEC,
<http://www.jamstec.go.jp/e/>

The Earth Simulator consists of NEC SX-ACE, 5120 nodes.



Node	
Number of CPU	1
Number of cores	4
Peak performance / core	64 GFLOPS
Main memory	64 GB
Memory band width	256 GB/s
System	
Total number of Processor nodes	5120
Total number of CPUs	5120
Total number of cores	20480
Total peak performance	1.3 PFLOPS
Total main memory	320 TB
Total memory band width	1.3 PB/s

Founded in 1971 as a research system for oceanographic research, with strong support by then MITI, JAMSTEC by now has become an independent research organization. The research focus, originally on deep-sea research and oceanographic exploration, has broadened and now encompasses the oceans, earth and the environment, in view of making Japan “an entirely ocean-based nation in the future”. JAMSTEC entertains one of the largest fleets of deep-sea vessels and marine observation systems, including a Core Sample research station in Kochi. At its Yokohama Institute for Earth Sciences, JAMSTEC has established **The Earth Simulator** supercomputer, one of the most powerful parallel computers built so far, <https://www.jamstec.go.jp/es/en/>. The SUPER-UX software is an operating system that takes the function from BSD and SVR4.2MP as an operating system based on UNIX System V, and strengthens the function necessary for the super computer in addition. Details on the software system used can be found under the above URL. The main use of

this NEC-built supercomputer is for calculations on the risks of climate change, but simulations of chemical reactions and of evolutionary science and technology have also been performed. Among the many databases which have been built by JAMSTEC, the BISMAL data (Biological Information System for Marine Life), <http://www.godac.jamstec.go.jp/bismal/e/> are the most relevant for this review. BISMAL contains some 70.000 datasets on marine species, with close to a million occurrence records. In addition, the JAMSTEC repository of marine specimen contains about 45.000 marine specimen. JAMSTEC’s Marine Biological Sample database contains metadata on all expeditions made by JAMSTEC’s surface or underwater vessels, including the expeditions of KAIKO 7000 II which can dive 7000 m deep and CHIKYU which can perform deep sea floor drilling at 7000 m deep, <http://www.jamstec.go.jp/e/about/equipment/ships/>.

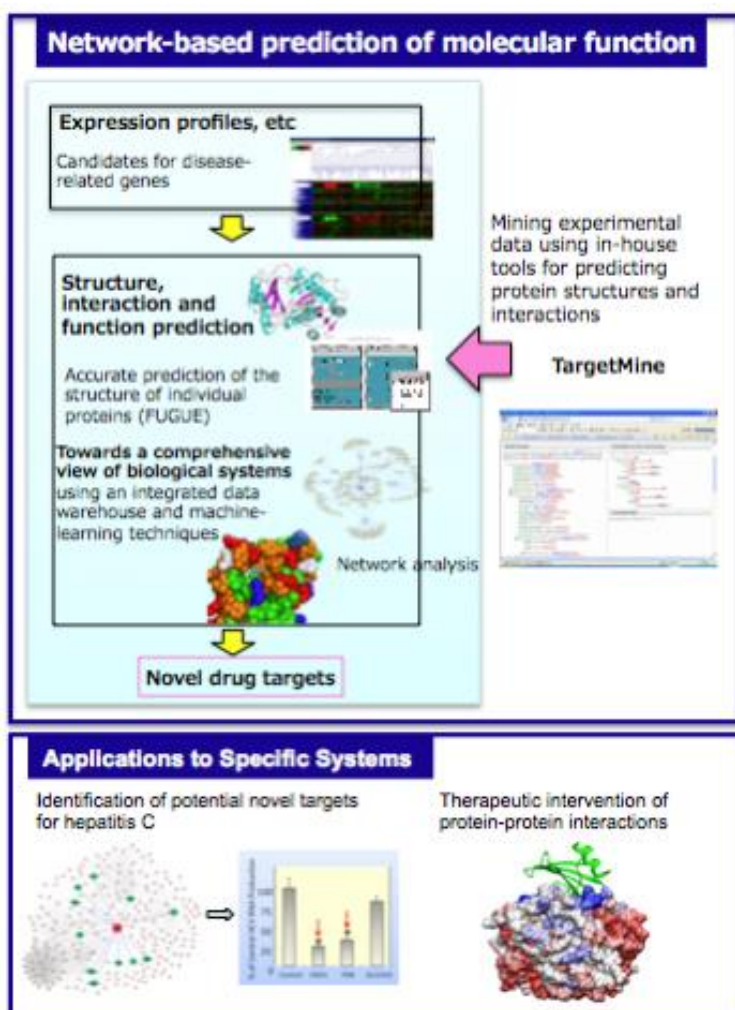
2.3 The Ministry of Health, Labor and Welfare and its S&T organizations

2.3.1 The National Institutes of Biomedical Innovation, Health and Nutrition

http://www.nibiohn.go.jp/index_e.html

The organization was newly formed as of April 1, 2015, from its two predecessors, the National Institute of Biomedical Innovation in Osaka and the National Institute of Health and Nutrition in Shinjuku, Tokyo. One of the predecessors, the National Institute of Biomedical Innovation (NIBIO) was established in 2005 for the purpose to contribute to the creation of innovative pharmaceuticals and the improvement of national health. The Osaka branch of National Institute of Health Sciences formed then the nucleus, and aspects of the National Institute of Infectious Diseases and the Pharmaceuticals and Medical Devices Agency were integrated. The focus is on research on basic technology of pharmaceuticals and on biological resources, <http://www.nibio.go.jp/english/index.html>. The other predecessor, the National Institute of Health and Nutrition (NIHN) has similar responsibilities as the NIH in the USA, http://www0.nih.go.jp/eiken/english/about/eiken_leaflet2014.pdf.

By combining these two predecessors into the National Institutes of Biomedical Innovation, Health and Nutrition



(QBNIBIO), located in Osaka, it is attempted to bring all responsibilities for assisting innovative pharmaceutical and food research and technologies by an open innovation process, but also monitoring safety and usefulness of drugs and health food materials under one roof and to speed up innovation.

Bioinformatics and computational biology in this center is done in the Laboratory of Kenji MIZUGUCHI, <http://mizuguchilab.org/members>. The laboratory carries out research into drug discovery and development, with special emphasis on early-stage target discovery and safety prediction. This involves both the analysis of real-life experimental data and the development of novel computational techniques, aiming to establish systems approaches to drug discovery, <http://mizuguchilab.org/overview> drug function prediction.

2.4 Ministry of Agriculture, Forestry and Fisheries (MAFF)

2.4.1 The Metabolome research network,

http://www.s.affrc.go.jp/docs/metabolome/kentoukai/pdf/taisei_image.pdf (in Japanese)

MAFF has not established its own databases but resorts to the MEXT National Bioresource Project (2.1.1). However, MAFF has set-up in 2014 a public-private partnership on metabolome analysis with a strong link to food production and quality control. The focus is on speeding up innovation in the agriculture- and food-related industries, and typical research targets are

- Identification of functional ingredients
- Technologies to achieve higher quality of the fermented food products by metabolic profiling
- Development of analytical technologies for taste components by metabolic profiling
- Development of discrimination technologies for raw materials used in food production
- Development of discrimination technology for advanced sterilization methods
- Sophisticated methods for food raw materials processing, storage and distribution technology

Information on this program, which is run through the Agriculture, Forestry and Fisheries Research Council Secretariat, is only available in Japanese, <http://www.maff.go.jp/j/supply/hozyo/gikai/150114.html>.

3. Major academic activities

3.1 Early academic centers in bioinformatics

A good survey from 2010 is available on the web, though in Japanese, http://www.spc.jst.go.jp/hottopics/1012fusion/r1012_akutsu.html. It is written by Akutsu TATSUYA, Head of Kyoto University's Bioinformatics Center which is located at Kyoto University's Institute for Chemical Research, the Uji campus. Professor TATSUYA provides a good account of bioinformatics development in Japan starting with the Human Genome Project (to which Japan joined in 1991). Interestingly, the article is published by JST on their Science Portal China (<http://www.spc.jst.go.jp>) because Professor TATSUYA is also one of the coordinators of Japan-China cooperative projects in bioinformatics.

The first Japan Human Genome Center was established at the University of Tokyo Institute of Medical Science in 1991, but the field began to expand only after the year 2000 when, in 2001, Kyoto University's Bioinformatics Center was started in Uji and an AIST Bioinformatics Research Center (precursor of the present Computational Biology Research Consortium CBRC, see under 2.2.1) in Tokyo. From 2002, other universities followed, notably Hokkaido University, the University of Tokyo, the Nara Institute of Science and Technology (NAIST), Osaka University, Kyushu University, Keio University and Ritsumeikan University.

University	Lead professor	URL
Kyoto University, Uji Campus	Akutsu TATSUYA	http://www.bic.kyoto-u.ac.jp/takutsu/
Hokkaido University, School of Information Science and Technology	Yoshikazu MIYANAGA (dean)	http://www.ist.hokudai.ac.jp/english/about/
University of Tokyo, Dept. of Computational Biology, Kashiwa Campus	Shinichi MORISHITA, head	https://www.k.u-tokyo.ac.jp/pros-e/cb-e/index-e.htm
Nara School of Information Sciences	Several groups	http://www.naist.jp/activity/c01_04_01_03_e.html
Osaka University, Protein Research Institute	Haruki NAKAMURA	http://www.bio.sci.osaka-u.ac.jp/en/dbs01/re-paper-temp.php?id=31
Osaka University, School of Information Science and Technology	Ktsuro INOUE, dean	http://www.ist.osaka-u.ac.jp/english/research/majors/bio/
Kyushu University, Medical Institute of Bioregulation	Misata SUYAMA, dean	http://www.bioreg.kyushu-u.ac.jp/mib/about_education_e.html
Keio University, Dept. of Biosciences and Informatics	Tojiro AOYAMA (dean)	http://www.st.keio.ac.jp/english/departments/faculty/faculty_bios.html
Ritsumeikan University, College of Life Sciences, Kusatsu Campus	Several groups	http://www.sysbio.sk.ritsumei.ac.jp/bioinfo/teachers.html

This list is somewhat historical and not comprehensive. As bioinformatics have become such an important technology in life-science related R&D, many national and private universities in Japan have established groups in this area but cannot be comprehensively covered in the format of this review.

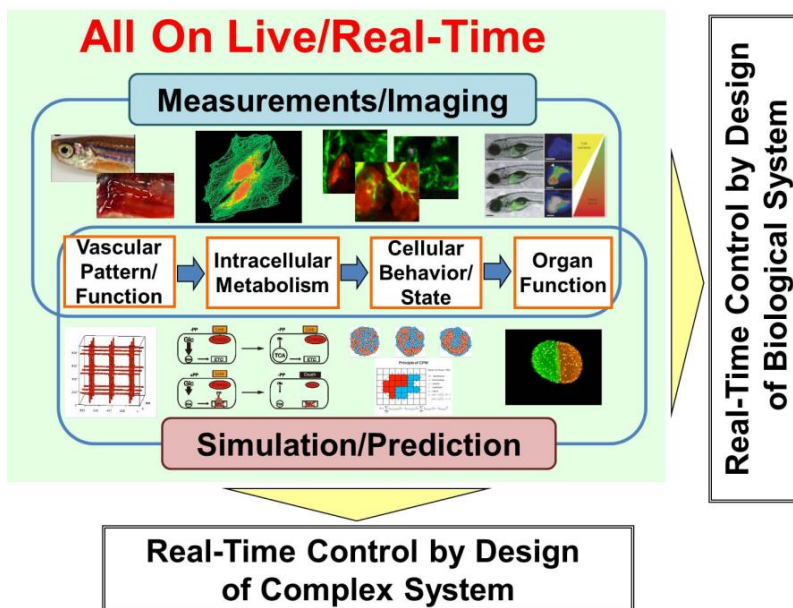
3.2 Systems Biology

In the late 1990ies, Masaru TOMITA, then at the Sony Corporation Computer Science Laboratories, coined the term “systems biology”, meaning the computational and mathematical modeling of complex biological systems. A first International Conference of Systems Biology was held in Tokyo in 2000 and triggered international research in this field. Around this period TOMITA started E-cell, a project to describe E. coli by a software platform comprising modeling, simulation and analysis and which is now jointly done by Keio University’s Institute of Advanced Biosciences (see 4.3), to which TOMITA has moved, and at RIKEN Quantitative Biology Center QBIC (see 2.1.5)

<http://www.e-cell.org/about/>). Other early activities in systems biology were by Hiroyuki KURADA, Kyushu Institute of Technology, <https://www.kyutech.ac.jp/professors/iizuka/i5/i5-1/entry-730.html>, who developed a **CADLive Software**, and by Satoru MIYANO at the University of Tokyo, Laboratory of DNA Information Analysis, <http://dnagarden.hgc.jp/en/doku.php>, who developed a software called **Cell Illustrator**. Recently, it is attempted to expand this approach to a systems-based description of whole organs, e. g., by Akinori NOMA at Ritsumeikan University, who simulates heart cells, http://research-db.ritsumei.ac.jp/Profiles/44/0004330/prof_e.html, or by Masanori ARITA at the University of Tokyo, School of Science, and at the RIKEN Plant science team, who studies the metabolic network of whole plants, <http://www.s.u-tokyo.ac.jp/ja/rigakuru/3639/>, <http://www.csr.s.riken.jp/en/labs/mirt/index.html>.

3.3 ERATO's SATO Life Forecasting Project

http://www.ist.go.jp/erato/en/research_areas/ongoing/sly_P.html. Since 2013, an ERATO project with even more ambitious goals was started, the **SATO Life Bio-Forecasting project**,. Research Director is Thomas N. SATO from the BioMEC-X Laboratories of Advanced Telecommunications Research Institute International (ATR), http://www.ATR.jp/research/research_info_e.html, and the research term is from 2013 to 2019. The project group proposes to realize Live Bio-Forecasting, allowing to control by design the future states of the complex, dynamic and stochastic biological processes with unprecedented efficiency and precision. The "Live Bio-Forecasting" works like



weather forecast to predict the future state of physiological processes while the current state is monitored/ measured/ imaged and simultaneously also to control them by design, all on live (i.e., real-time). This project will particularly focus on putative alterations of metabolic states of cells of organs conferred by the changes in vascular patterns and functions, which are eventually being manifested as organ functions. To this end, molecular and cellular principles and logics underlying such interactions between vascular pattern/function and metabolic state/function of the organ will be deciphered, and predictive computational models, and eventually real-time online prediction/forecast of the future states of

such processes will be developed, based on the real-time and quantitative imaging and measurements of their current states. The project will first use developmental and disease models of zebrafish to demonstrate the proof-of-concept of the Live Bio-Forecasting and will form foundation for its future applications to human biology and disease.

3.4 Kyoto University's GenomeNet, <http://www.genome.jp>

Among the many academic database developments – which are all accessible under the National Bioscience

- **Main entry point to the KEGG web service**
 - KEGG2** KEGG Table of Contents [Update notes](#)
- **Data-oriented entry points**
 - KEGG PATHWAY** KEGG pathway maps [[Pathway list](#)]
 - KEGG BRITE** BRITE functional hierarchies [[Brite list](#)]
 - KEGG MODULE** KEGG modules [[Module list](#) | [Statistics](#)]
 - KEGG ORTHOLOGY** Ortholog groups [[KO system](#) | [Annotation](#)]
 - KEGG GENOME** Genomes [[KEGG organisms](#)]
 - KEGG GENES** Genes and proteins [[Release history](#)]
 - KEGG COMPOUND** Small molecules [[Compound classification](#)]
 - KEGG REACTION** Biochemical reactions [[Reaction modules](#)]
 - KEGG DISEASE** Human diseases [[Cancer](#) | [Pathogen](#)]
 - KEGG DRUG** Drugs [[ATC drug classification](#)]
 - KEGG MEDICUS** Health information resource [[Drug labels search](#)]
- **Organism-specific entry points**
 - KEGG Organisms** Enter org code(s) [hsa](#) [hsa eco](#)
- **Analysis tools**
 - KEGG Mapper** KEGG PATHWAY/BRITE/MODULE mapping tools
 - KEGG Atlas** Navigation tool to explore KEGG global maps
 - BlastKOALA** Genome annotation and KEGG mapping
 - GhostKOALA** Metagenome annotation and KEGG mapping *New!*
 - BLAST/FASTA** Sequence similarity search
 - SIMCOMP** Chemical structure similarity search

Database Center (NBDC) of STA, see 3.1.2 – Kyoto University's GenomeNet is outstanding due to its early and wide collection of bioinformatics tools. It is probably the Japanese bioinformatics software which is best-known outside Japan. GenomeNet was established in September 1991 under the Human Genome Program of the then Ministry of Education, Science and Culture (Monbusho) and developed by Minoru KANEHISA and his group at Kyoto University. Its major feature is the Kyoto Encyclopedia of Genes and Genomes KEGG, <http://www.kegg.jp>, which comprises a large set of databases. The Center is formally organized as NGO Bioinformatics Japan, a non-profit organization, <http://www.bioinformatics.jp/en/>.

3.5 University of Tokyo's Frontier Science Cluster, <https://www.k.u-tokyo.ac.jp/pros-e/cb-e/index-e.htm>

At the University of Tokyo, the Department of Computational Biology, located in the Graduate School of Frontier Sciences on the Kashiwa Campus, has established a wide range of data-driven biological disciplines such as databases, machine learning, simulation, ontology, and systems biology. The targets are cellular functional analysis, analysis of genetic diseases, genomics, and analysis of proteins' three-dimensional structures. Facilities include a Center for Omics and Bioinformatics, a Bioimaging Center and a Functional Proteomics Center. The Cluster keeps a strong link to the AIST Computational Biology Research Consortium, see 2.2.1

3.6 Keio University Institute of Advanced Biosciences IAB <http://www.iab.keio.ac.jp/en/>

When systems biology became popular around the year 2000, Keio University was quick to establish experimental and computational facilities in Tsuruoka (Yamagata prefecture, in northern Japan) which closely cooperate with the the bioinformatics laboratory of Keio University on the SFC campus, Kanagawa Prefecture. IAB and his director, Masaru TOMITA, are recognized worldwide as a pioneer in cell simulation based on their flagship project „E-Cell system“ which was awarded the IBM Shared University Research Award in 2003. IAB's technology is mainly based on high-throughput and quantitative CE-MS methods, which can measure thousands of charged metabolites. This competency led to the foundation of Human Metabolome Technologies Inc. (HMT) in July 2003, <http://humanmetabolome.com>, which also operates in Boston, USA, <http://humanmetabolome.com/en/>. HMT technologies make it possible to measure over 1,600 metabolites in cells and organisms simultaneously and comprehensively, at high speed and with high resolution. Apart from software used in systems biology and cell simulation, IAB has developed „G-language“, a generic genome analysis environment aiming to construct an

integrated environment for the development of analysis software that allow users to avoid redundancy in the process of analysis.

4. Professional networks

4.1 Japan Society of Bioinformatics (JSBI) <http://www.jsbi.org/en/>

The Japanese Society of Bioinformatics (JSBI) was founded in 1999 and consists of some 600 regular (individual) members and some 20 corporate members. The most important event of the Society is the General Meeting, which is held once a year and to which all the members are requested to participate. The official language of the annual meeting is English and participants from outside Japan are welcome. Two important activities of JSBI are the activity of Special Interest Groups (SIGs) and that of (regional) Working Groups. At present, there are 3 SIGs, namely on Bio-Systems Theory, on Pharma-Informatics and on Agribioinformatics. There are five Working Groups in various areas of Japan and their existence is expected to stimulate local activities on bioinformatics. Other activities include the proposal of a standard curriculum for bioinformatics education in universities and graduate schools and the editing of an **encyclopedia of bioinformatics** (in Japanese). The encyclopedia, written by hundreds of JSBI members and researchers in related areas, was published by Kyoritsu Shuppan. Co. Ltd. in 2006. Newsletters are delivered to JSBI members twice a year. Summer schools for students and young scientists are organized and financially supported annually by JSBI. There is an Annual Japanese Society for Bioinformatics Prize which is shared by Oxford Journals.

4.2 Association of Asian Societies for Bioinformatics (AASBI) <http://www.aasbi.org>

JSBI is a member of AASBI which in turn holds a membership to the International Society for Computational Biology (ISCB) <http://www.iscb.org> which serves over 3,200 members from more than 70 countries. AASBI was founded in 2003 by the Association for Medical and Bio Informatics, Singapore, Association of Australian Bioinformatics, Bioinformatics Society Taiwan, Japanese Society for Bioinformatics, and Korean Society for Bioinformatics hereby agree to cooperate to form the Association of Asian Societies for Bioinformatics, in order to promote mutual understanding between the societies through academic and research collaboration and exchange, and to contribute to the advancement and progress of bioinformatics in Asia-Oceania. Since 2010, the annual meetings of AASBI proceed as ISCB Asia Conferences, and the past 4 meetings were held in Asian nations accordingly

- GIW/ISCB-Asia International Conference on Genome Informatics, December 15 - 17, 2014, Tokyo, Japan
- ISCB Asia Translational Bioinformatics Conference 2013, Oct 2 - 4, 2013, Seoul, Korea
- ISCB-Asia and Shenzhen Conference on Computational Genomics, December 17 - 19, 2012, Shenzhen, China
- InCoB/ISCB-Asia Joint Conference 2011, November 30 - December 2, 2011, Kuala Lumpur, Malaysia

4.3 Information Processing Society of Japan, <http://www.ipsj.or.jp/english/index.html>

This large IT-related academic society has absorbed, in 2005, the Japanese Society for Artificial Intelligence, <http://www.ai-gakkai.or.jp>.

5. Public-private partnerships (PPP)

Many of the programs mentioned above are operated in the manner of public-private partnerships. Usually, a Ministry offers seed money to organize a temporary research association (usually for 3 – 5 years); successful PPPs may be extended for even longer periods. This is, for instance, true for the

5.1 Japan Biological Informatics Consortium JBic <http://www.jbic.or.jp/english/about/>

JBic was initiated in 1998, and established in July 2000 as a non-profit organization under the control of four ministries including the Ministry of Economy, Trade and Industry. The core research facility of JBic is in the Tokyo

Waterfront Bio-IT Research Center of the National Institute of Advanced Industrial Science and Technology (AIST) located at Odaiba, Tokyo. The participating parties are about 60 private companies from the pharmaceutical, IT, food, chemistry and diagnostics industries, universities such as the University of Tokyo, Osaka University, Nagoya University and Fukushima Medical University, as well as public research organizations such as AIST and Riken. JBic is coordinating research activities among these industry, university and public research organizations.

Present R&D programs are

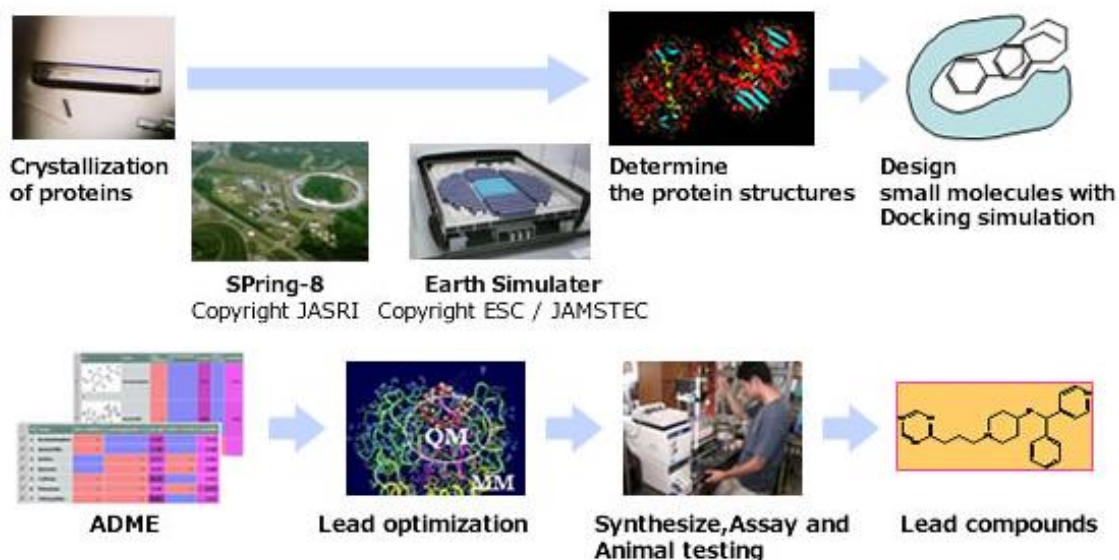
- Fukushima Translational Research Project
- Construction of resources for cell system-control gene expression of regenerative medicine
- Technology Development for Drug Discovery Platform Based on the Mechanism of Epigenetic Genome Modification
- Development of Innovative Drug Discovery Platform Utilizing Information Technology
- Development of Technology for Producing Next-generation Useful Natural Compounds

Whereas JBic is mostly based in the Kanto region (Tokyo and surrounding prefectures), a smaller PPP is operating in Kansai, covering the region of Osaka, Kobe and Kyoto, where many pharmaceutical companies are located:

5.2 BioGrid Center Kansai <http://www.biogrid.jp/eng/>

The NGO was established in 2004 by Osaka University and a small number of companies such as NEC and Mitsui Knowledge Co. for promoting bio-related projects, in particular for translational research from academia to industry. Director is Shinji SHIMOJI, Director of Osaka University's Cybermedia Center. An important target is the structure-based discovery of pharmaceutical lead structures,

Structure based Drug Discovery



6. Foreign bioinformatics organizations active in Japan

6.1 BGI Japan, http://www.genomics.cn/en/navigation/show_navigation?nid=3781

Beijing Genomics Institute (BGI), located in Shenzhen, China, provides the world's largest sequencing platform and superb bioinformatics analysis. BGI markets her services in many countries such as the USA, Europe (Copenhagen) or SE Asia (Singapore). BGI Japan was founded at the end of the year 2010 with its headquarter in Kobe and provides quality-ensured services with short turnaround time. It coorganizes scientific meetings such as the China-Japan Symposium on Cancer Research meeting at Shenzhen in 2011, and the "2nd Japan-China Symposium on Cancer Research in Chiba, Japan, in 2012.

6.2 Eurofins Genomics

<http://www.eurofins.com/en/about-us/laboratory-contacts/japan.aspx> Eurofins was founded 1986 in Nantes, France, as an analytical service company. Today, it operates about 200 laboratories worldwide with over 17.000 staff and a portfolio of over 130.000 validated analytical methods. Services include radioactivity assays in food and various genomic assays related to pharma, diagnostics, agriculture and food which rely strongly on the use of bioinformatics. Eurofins is the only foreign-owned laboratory which is accredited by MHLW for the stringent testing requirements of imported food products. In 2012, Nihon Kankyo, a company with 250 staff specialized in environmental testing, was acquired, strengthening the company's business in Japan.

6.3 BIOBASE Japan and CLC Genomics, two Qiagen companies

BIOBASE, a spin-off of the former Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig and now a Qiagen company, operates an office in Tokyo, <http://www.biobase.co.jp>. They provide access to various databases and knowledge libraries related to genomics, metabolomics and proteomics. CLC Genomics was founded in Aarhus, DK, and acquired by Qiagen in 2013, <http://www.clcbio.com>. They provide several software service packages such as CLC Genomics Workbench and drug-discovering software and run a Tokyo office. Since 2010, they cooperate with RIKEN <http://www.osc.riken.jp/english/press/100507/> and in 2011 have offered researchers in the earthquake-stricken Tohoku region free access to their software through RIKEN, <https://www.genomeweb.com/informatics/riken-clc-bio-provide-free-hosted-bioinformatics-tools-researchers-japans-disast>.

7. Software and databases

Many of the websites cited in this report contain information on software packages and databases, which often can be freely downloaded and used according to international research customs. The AIST-run Computational Biology Research Consortium (CBRC, see 2.2.1) offers a good English-language website on such software packages <http://www.cbrc.jp/cbrc-software> and biology-related databases <http://www.cbrc.jp/cbrc-databases>.

8. Opportunities and challenges for European stakeholders

Japan is among the most developed industrialized nations in terms of science and technology. As both IT and life sciences have long-standing priorities in her national S&T policy, it is of little surprise that also bioinformatics and computational biology are highly developed. This statement is also true for many European nations, and academic interactions in this field among European and Japanese researchers may be considered good. Thus, Oxford University, UK, which is very active in promoting interactions with Asia, has organized in 2011 a "Bioinformatics Road Show" as an EMBL-EBI training course, <http://www.ebi.ac.uk/training/course/bioinformatics-roadshow-japan>.

Consequently, one might also expect excellent opportunities for technology trade in this field. However, there are still quite few examples for this to happen. Why?

A very helpful attitude of the Japanese for international cooperation is their interest in useful innovations, accompanied by pragmatism. Thus, if a European SME can provide a useful innovative technology or service, it can rely on initial interest from a Japanese counterpart (I consider the “not-invented-here” barrier in Japan as being much lower if compared to, e. g., Germany). Unfortunately, there are also difficulties to realize such opportunities. For one, Japanese researchers are much absorbed by communication and duties within their own networks (“clubs”) and it may prove difficult to obtain membership in such clubs. A visible token for this has come up again in this study: there is abundant information on the subject of this review but I was more than surprised to find that even in an IT-related area so little information is available in English. In fact, English mirror websites of many institutes and most scientists covered in this report are rather the exception than the rule. This is, of course, a considerable obstacle for international technology trade and makes it rely heavily on match-makers. Finally, it is well-known that the Japanese standards for precision, quality and non-failure are extremely high, and a product or service made-in-Europe aiming at the Japanese market must comply to these standards.

The success of, e. g., Eurofins Co. in the Japanese analytical markets seems to be a good token how all these difficulties can be surmounted, and European companies active in the areas of this review should be encouraged to consider entering the Japanese market, using the help of the EU-Japan Desk, JETRO or other matchmakers such as the Steinbeis Center for Asia Technology Consulting www.asia-tech.eu.

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