# Preface

## Bioarchitect – A new concept in bioscience for the new century

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The era of post-genomics has come. It is only six years since the whole genomic DNA sequence of the bacteria *Haemophilus influenzae* was first determined,[1)] but now dozens of organisms have their entire (or almost entire) genome information available in databases. They include *E. coli*,[2)] yeast,[3)] nematode,[4)] fruit fly,[5)] Arabidopsis,[6)] and human.[7,8)] In other words, the sequence information of these organisms, which is believed to be sufficient to draw the blueprints of cell and body architecture, is now easily accessible for everybody, even for small kids if they can operate computers and access the Internet.

### Does genomics solve all problems?

How much has this situation changed the style of life sciences? A lot? Yes, perhaps. For example, molecular biology technologies are facing drastic innovation. Cloning of a novel gene does not make sense anymore. You can just read the end sequence of your DNA fragment and then look into the database. The excitement of unveiling new amino acid sequences is now devoted only to high-throughput DNA sequencing factories. Instead, the need for comprehensive analysis of genomes has given rise to the DNA chip technology. Development of information science to handle the enormous amount of sequence information, which is called bioinformatics, is also remarkable. Benefited by these advances of technologies, people appear to be rushing to the next stage of genomics, structural genomics, functional genomics and proteomics.

In this trend of comprehensive sciences, are the roles of individual researchers disappearing? Are small sciences in small laboratories only the hobbies of poor scientists now? No, absolutely not.

When the genome sequence of the yeast *Saccharomyces cerevisiae* was determined for the first time as a eukaryotic organism,[3)] about one third of the 6000 genes were reported as "function unknown". This is more or less true for other organisms and the elucidation of their functions is still very slow. For example, we identified the yeast gene, *RER1*, as a gene involved in the correct localization of an endoplasmic reticulum (ER) membrane protein in 1993.[9)] Cloning of the gene and the characterization of the product led us to propose that it is required for retrieval of ER proteins from the Golgi apparatus,[10)] but another several years were needed for us to finally conclude that the Rer1 protein is a sorting retrieval receptor in the Golgi [11)] (see also the section of Ken Sato *et al.*). It took a long time because both the receptor and the ligand are integral membrane proteins and the demonstration of their transient interaction required very tricky experiments, but this is what a very able researcher can achieve by his full devotion.

Let's forget about the reality and assume that you can reveal the function of each gene in one month (I know it's almost impossible). The yeast chromosome III, the third smallest chromosome of *S. cerevisiae*, contains 183 open reading frames (ORF) including *RER1*. If you work very hard and analyze all of them at the pace of one gene per month, it still takes more than 15 years to complete it. Of course many people can collaborate, but if you think about all the 6000 ORFs of yeast or 32000 ORFs of human, the estimated figures of years x persons will be astronomical. Even if you focus on unknown

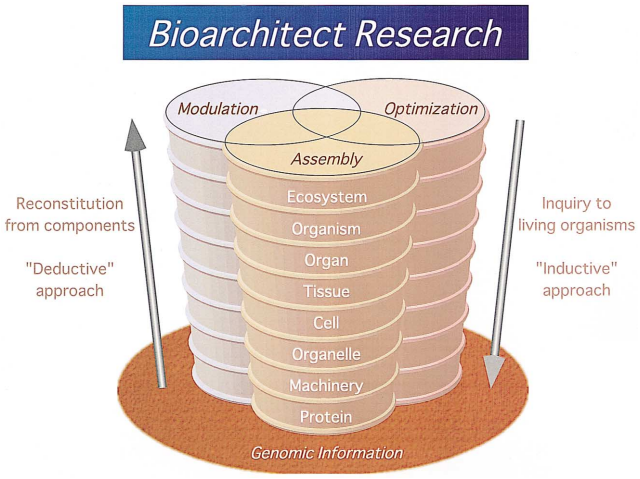


Fig. 1. The Bioarchitect Research Project likens the layers of life to stories of a building. Three teams, Assembly, Modulation and Optimization, work in cooperation to understand how the adjacent levels are connected and regulated. Both the top-down "inductive" or inquiring approach and the bottom-up "deductive" or reconstitutional approach are utilized.

genes only and substantially improve the speed, one-by-one analysis of 10000 genes may not be practical using our current technology. Complexity will diverge to infinity if you calculate their interactions. The many serious biological problems that human beings are facing now, such as diseases, food shortage and environmental degradation, cannot wait many decades to be solved.

## Hierarchy – Stratified life

A variety of metaphors are used for living organisms and life, such as societies, cities, or maybe the universe. We imagine that life is a building, a big building with many stories (Fig. 1). Naturally, the genome provides the plan of the building. Gene products, or proteins, constitute the ground floor. Proteins work together to form complexes or machinery. Assembly of machinery on a membrane constructs an organelle. This kind of stratum or hierarchy is very convenient to consider how the whole organism is made from the genomic information. Next to organelles come cells, and tissues and organs follow. Sometimes above the organism level, groups of organisms or populations may exist.

It is interesting to note that these different levels of life are very strictly organized in space and time by independent principles. Random mixture of proteins never gives rise to a functional complex and you need a good combination of different cell populations to obtain a functionally differentiated tissue culture. Every level of life appears to require particular rules to become truly living.

This is the beginning of the concept of the Bioarchitect Research. By likening the layers of life to stories of a building, we wish to understand how the adjacent levels are connected and regulated. Once we know the principles, we will be able to design, modify and even optimize the whole architecture of the building, like architects.

## Two opposite approaches

It is easy to say that the connection of different levels is important. What is then a practical approach to studying them? *In vitro* reconstitution is a very powerful strategy for building the upper floor using a particular set of components. Reconstitution of machinery and organellar functions has already been successful for many biological reactions. Indeed, a former project of RIKEN, Biodesign Research (1991–2000), aimed at reconstitution of organellar functions from molecules and made great achievements.[12)] One of the ultimate goals of life sciences may be to reconstitute a cell or even an organism from the genomic information. However, as discussed above, reconstitution from 10000 different components is far beyond reality at the moment. Reconstitution between particular two layers would still be very useful

in investigating the principles and regulations connecting higher levels of the building, but at the same time we will take another strategy. In contrast to the reconstitutional "deductive" approach, we call this the "inductive" approach. Instead of looking from the lower to the upper levels, the inductive approach looks from the top to the bottom. Genetics provides great tools for this approach. By inquiring directly into living cells or organisms, we can infer which gene is responsible for the macroscopic phenomenon we are looking at. Use of chemicals, inhibitors, activators or modulators, can also be applied to a similar approach. Such top-down strategies are highly complementary to the bottom-up reconstitutional studies and would strengthen the overall Bioarchitect Research Project.

## Three Bioarchitect teams

To realize such a project with a wide scope, we decided to form three teams, Assembly, Modulation and Optimization. The Assembly Team will study the principles on how components function, assemble and cooperate in the right places at the right timing to produce living relationships in various levels of life. The Modulation Team will deal with how such components interact with and modulate each other in certain boundary conditions, space and time, in the hierarchy. The Optimization Team will try to understand the integration principles of different layers and further pursue to improve or optimize the principles. This bold exploration may lead to the realization of artificial designing of biological functions in the future.

To envisage such a big project, it is inevitable to incorporate a wide variety of laboratories with a common concept and philosophy. RIKEN is ideal for this purpose because it harbors a wide range of biological sciences, from molecular biology of DNA to cell biology of organellar dynamics and even to symbiosis in termites. More than forty members are participating in this project, not only from RIKEN laboratories but also from the outside. The objective of this issue of RIKEN Review is to publicize how this project is planned and organized and to show what each member aims at, has performed and further attempts to perform under the concept of Bioarchitect. Although each article is short because of the limitation of pages, I hope the readers will feel the new trend of bioscience in the post-genome era of the new century.

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