E-CELL: Towards integrative modeling of cellular processes

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E-CELL Project (http://www.e-cell.org) was launched in 1996 and is currently carried out at the Institute for Advanced Biosciences (IAB) of Keio University (http://www.ttck.keio.ac.jp/IAB/english/index.htm) with the ultimate goal of simulating the cell as a whole. E-CELL System, a generic software package we have developed, enables us to model not only metabolic pathways but also other higher-order cellular processes such as protein synthesis and signal transduction.

Using the system, we have successfully constructed a virtual cell with 127 genes sufficient for ``self-support''. The gene set was selected from the genome of Mycoplasma genitalium, and the metabolisms include transcription, translation, membrane transport, the glycolysis pathway for energy production, and the phospholipid biosynthesis pathway for membrane structure. Since all its proteins and membrane structure are modeled to degrade spontaneously over time, the virtual cell must keep synthesizing proteins and phospholipid bilayer to sustain its life. It thus uptakes glucose as its energy source, and emptying glucose in the environment would result in "cell death from hunger" [1,2].

Modeling Group in our institute are now developing many different models of cellular processes, including bacterial chemotaxis, circadian rhythms, photosynthesis, as well as cell cycle and cell division. For organelles, a quantitative model of mitochondria is nearly complete, and we will be soon developing chloroplasts in the context of e-Rice Project funded by Japanese ministry of agriculture. For human cells, we have already developed a quantitative model of erythrocytes, and being used in pathological analyses of enzyme deficiencies causing anemia. Other human cells now being developed include myocardial cells, neural cells, and pancreatic beta-cells [3].

A major bottleneck in cell modeling is lack of quantitative data, such as kinetic parameters, dissociation constants, steady state concentration, and flux rates. Metabolome Group of our institute is developing methodologies for mass-production of those quantitative metabolic data. We analyze metabolic flux distributions (MFDs) with different conditions such as dissolved oxygen (DO) concentration, pH, temperature, and media composition. We also label certain substrates with U-13C or 1-13C, and measure isotope distribution of intercellular metabolites using NMR and GC-MS. For high-

throughput measurement of metabolites, we have developed a novel analytical device based on capillary electrophoresis and mass spectrograph, which can measure hundreds of metabolites at the same time [4]. Based on data collected by those means, we are developing a quantitative and dynamic model of E. coli energy metabolism as a part of Cell Modeling Project funded by New Energy and Industrial Technology Development Organization (NEDO) of the Ministry of Economy, Trade and Industry of Japan [5]

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[2] Science 284:5411, 80-81 (1999)
[3] Trends in Biotechnology, 19:6, 205-210 (2001)
[4] Analytical Chemistry, 74: 2233-2239 (2002)
[5] Bioinformatics 17: 1091-1092 (2002)