ments will provide critical large-scale process understanding to improve earth system models. But, they also offer unique opportunities for microbiologists to collaborate with plant biologists, ecologists and geologists. The scientific opportunities to explore biogeochemical cycles at multiple scales with modern biological, chemical and physical methods is unprecedented and will challenge us to develop new informatic tools to integrate these new data that span disciplines and scales. With these integrative studies we may begin to open up the proverbial black box and quantify important interfacial and molecular biogeochemical processes.

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Metabolic engineering, systems biology and synthetic biology

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In the sunny morning of November 15, 2017, Professor Meteng is having a conversation with one of his graduate students in the lab. 'Have a look at this. I just finished designing the 3.5 kb bacterial genome for polyethylene terephthalate (PET) production. Wow, it took us 2 weeks to design this sequence using our *in silico* MetabolicRegulatorySignaling Designer program. As we discussed, we now optimally positioned all the genes necessary for cell growth and PET production from carbon dioxide and sunlight. We should be able to produce PET with a productivity of 5.5 g l^{-1} h^{-1} and 95% of the maximum theoretical yield. We still need to run several fermentations to confirm the *in silico* predicted performance and collect data in order to further improve this bug's performance by fixing its genome. Once these are all done, I expect that the production cost of this bio-based PET will be about 2.5$ per kg. Later today, I will send this synthetic genome sequence to the National Genetically Created Organisms Committee for approval to synthesize. It usually takes five working days to get approval. Then, I will send the sequence to company X to synthesize it. The synthetic genome will cost $500 and will be delivered to you within 24 h. We might get some discount as we already synthesized two genomes last week. Once you receive the synthesized genome, you can create PET producer using the *in vitro* CELL CREATOR kit we purchased last week. How do we want to name this bacterium? Hmm . . . how about *Plasticomonas superproduciens* KAIST2017?'

Over the last couple of decades, metabolic engineering (Bailey, 1991) has advanced rapidly to design and develop engineered bacteria in order to more efficiently produce drugs, chemicals, fuel and materials. Traditional metabolic engineering started by manipulation of a handful of genes to be amplified, deleted, and/or introduced heterologously. Over the last decade, advances in systems biology have changed the way metabolic engineering is performed. Based on the rapid analysis of the entire genome followed by other omics studies including transcroptomics, proteomics, metabolomics and even fluxomics, metabolic engineers are now equipped with vast amounts of data and simulation tools that can be used in designing the optimally performing cells. A system-wide analysis and engineering of metabolic and other cellular networks are now possible – and thus called, systems metabolic engineering (Lee *et al*., 2007). More recent advances in cost-effective DNA synthesis and synthetic biology are triggering our interest in possibly designing the whole genome followed by actual genome synthesis. Although Craig Venter's the first artificially synthesized genome (Gibson *et al*., 2010) is far away from the creation of true 'designed cell doing something useful', it showed the possibility for the first time.

Are we really interested in creating artificial organisms, such as overproducers of biofuel, plastics, chemicals and drugs? The answer is YES; but first, we might want to define what artificial organisms are. If we start with our favourite microbe *E. coli*, and engineer it by knocking out 50 genes, amplifying 10 genes, altering 7 regulatory circuits, and introducing 10 heterologous genes originated from plants and animals, is the resulting strain an engineered *E. coli* or created artificial cell? What if the number of genes that are altered reaches over 50% of the original genome? What do we call it? One thing for sure is that this

type of engineering (or creation) should be performed for the benefits of human and environment. Ethics, safety and security issues will become increasingly important (Lee, 2010).

Metabolic engineering is an essential paradigm for the environmentally friendly production of chemicals and materials from renewable resources with an aim to save our earth and sustain human race, and developing ways of efficiently producing drugs that are new or difficult to synthesize. Innovative ways of bioremediation using metabolically engineered organisms will also be developed. Looking ahead, it is likely that many sophisticated organisms developed by systems metabolic engineering will appear over the next 7 years, mainly for the enhanced production of drugs, chemicals, fuels and materials. Some of these will be incorporated into the actual industrial biorefinery processes for the mass production. At the same time, organisms that are based on 100% synthesized genomes will continuously appear; the first handful of these will be most likely mimicking the genomes of the organisms already present in nature. We should not think that we are playing God.

It is also likely that systems metabolic engineering approaches will be adapted to new therapeutics and disease prevention. Human body (and other organisms as well) is a truly complex system, which will almost never be completely understood. Our current therapeutic paradigm is a single drug-single target approach, while multiple drugs (a mixture of single drugs) can be administered to treat multiple respective symptoms. An old Korean saying 'the best drug is good food' deserves good attention. The traditional Korean medicine book 'Dong-Eui-Bo-Gam' written by Hur Jun 400 years describes many interesting therapeutic recipes for treating chronic diseases. Obviously, millions of secondary metabolites among others present in these mixed plant extracts cannot be considered as drugs in the current drug administration standards. If multicomponent multi-target interactions are clarified at the systems level, and designer plant combinations without side-effects can be formulated, it will change the human healthcare paradigm – to this end, systems metabolic engineering will play an important role. Ultimately, what we eat (food) will be systematically coupled to our health issues through systems nutrition, and for this, the approaches developed in systems metabolic engineering field will become essential.

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Bioprocess Systems Engineering: bridging the 'scales' between 'molecules, cells & processes'

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Mathematical models of biological systems developed over the last decades incorporate various degrees of structure and mathematical complexity. Focusing on microbial systems, models of single cells, cell populations and cultures have been central in the understanding and improvement of the cellular systems, as well as in the optimization and control of the bioprocesses (Thilakavathi *et al*., 2007). In the last decade especially, the large-scale generation of biological data obtained with the development of a variety of high-throughput experimental technologies enabling system-level measurements, demand for mathematical model building to become a centre of importance in biology (Covert *et al*., 2001). Alas, as Bailey (1998) argued the development of mathematically and computationally orientated research has failed to catch up with the recent developments in biology. The need to bridge this widening gap between mathematically oriented research and system-wide analytical experimentation ('omics' technologies) stimulated *Systems Biology* to emerge as a new and dominant science (Bruggeman and Westerhoff, 2007). Consequently, the logical question is being raised of whether *Systems Biology* has simply rushed into the development of new biological theories in the quest to convert data into knowledge? In a field now shifting from method development to application development (Oberhardt *et al*., 2009), there is now some increasing scepticism regarding the future of *Systems Biology* as understanding of all the collected information has lagged far behind its accumulation because modelling of complex systems is an inverse problem that cannot be solved (Brenner, 2010).

Simply put, even relatively simple microorganisms, which have been extensively studied, are hosts to a complex network of interconnected processes occurring on diverse time scales within a confined volume. The multilevel nature of the regulatory network and the interactions occurring at the intracellular level further augment this complexity (Yokobayashi *et al*., 2003). Therefore, attempts to wholly model the function of even a single cell are non-trivial, if not impossible. The amount of delicate intracellular measurements required to validate such a

