Interviewer (EP): Synthetic Biology is often depicted as part of a new technological revolution. Can you give us some tools to understand the scope of this technological pace? How would you explain synthetic biology for the uninitiated?

Kaustubh Bhalerao: To understand how Synthetic Biology contributes to the new technological revolution, we should first place it in the context of the ‘New Biology’ approach advanced by the National Academies of Sciences you have mentioned above. One of the highlights of the approach is that we have awoken to the incredible complexity of the natural world around us. Rather than the hitherto reductionist approach to understanding the natural world, we must now seek to exploit the complexity to solve the most pressing problems of today. Since global problems such as developing a resilience to climate change and feeding a growing population do not fall neatly into specific disciplines, our proposed solutions must also integrate ideas and concepts from numerous disciplines spanning physical, natural and social sciences.

Synthetic biology represents a convergence of biological sciences and systems engineering principles. It is a rapidly-growing engineering discipline that seeks to provide a coherent technological foundation for designing novel living processes. By modeling living organisms as dynamic systems comprised of discrete biochemical processes, synthetic biologists seek to recapitulate natural complexity in order to develop tools and theories for designing novel biochemical functions or modifying existing ones.
It is an advanced form of genetic engineering, where gene networks are designed to operate inside living hosts, not only to graft a desired function (as is the perceived notion behind present-day genetic engineering), but also exercise precise spatial and temporal control on the expression behavior of native or non-native genes.

The common phases of an engineering design cycle comprising of design → build → test → redesign have close analogs in synthetic biology. There have been remarkable technological breakthroughs in the ‘build’ phase, allowing the construction of sequences of DNA (JCVI work). It is now possible to construct any reasonable length of DNA and it is expected that the fidelity and cost with which sequences of DNA can be constructed will decline steadily as the technology matures.

However, the community lags behind in knowing what to design, and in predicting whether a given design will function as expected. In other words, we can build any arbitrary structure, but we cannot yet identify a structure that would engender a specified function, nor predict the function within a biological system, given a specific structure.

Assuming that the capacity to construct synthetic organisms will continue to outstrip the collective capacity to design such organisms, we need to establish the parameters that define ‘design for sustainability’ in the context of synthetic biology.

**Interviewer (EP):** Synthetic Biology is also often staged by the scientific communities as the solution to a range of social ills, including the problematic sustainable development. Can you give us an idea of how synthetic biology can be harnessed for sustainability?

**Kaustubh Bhalerao:** With the population of the planet heading towards 9 billion by 2050, there is an urgent need to rethink present notions of agricultural productivity within the context of environmental sustainability.

The majority of arable land in the most productive nations is already under agriculture (e.g., China ~76%, India, ~94%, U.S.A., ~97%). Water is a serious resource limitation in many parts of the world due to supply and distribution challenges. In addition, resources significant to agriculture are scarce, e.g., phosphorous, or expensive to obtain, e.g., nitrogen. Increases in standard of living lead to corresponding increases in the consumption of meat, milk, and eggs. The resulting shift in agricultural production patterns implies that agricultural systems of the future must be agile to respond to changes in climate, resource input and demand variables.

Sustainable development in this context involves vastly improving the efficiency of our agricultural systems. Increasing agricultural yields while simultaneously decreasing inputs are central to reducing the environmental footprint of agriculture. Achieving a sustainable agricultural system means driving a deliberate transition to agricultural systems that can tolerate reduced inputs, drought, flooding and salinity stresses as well as resist competition from weeds and pathogens.

The traditional approach to food security relies on input-intensive agriculture, where the primary metric of food security is yield per unit land area. While agricultural inputs such as nitrogen have steadily increased over the last 40 years, the same is not true for the per capita increase in productivity. In other words, in order to maintain the same level of food security (in terms of agricultural production per capita), nitrogen input levels have increased by a factor of ~17 for India and China and about ~2.2 for the U.S. (Gapminder.org / FAO). Nitrogen fertilizer can be produced directly from atmospheric nitrogen using the Haber-Bosch process. Its cost of production is directly linked to the cost of producing energy. Since there is a very strong correlation between product yield and the rate of fertilizer application, there is very little incentive for reducing nitrogen input.

The increased yields however, come at a tremendous environmental cost. Excess nitrogen finds its way into surface runoff causing algal blooms. The proliferation of algae in regions such as the Gulf of Mexico results in hypoxia causing widespread destruction of aquatic ecosystems. Growing awareness of
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