Molecular Machines

The distinction between the 'artificial' and the 'living' is being increasingly blurred by new technological advances at the intersection of computing, biology, chemistry and engineering. These advances have the potential to revolutionise not only our ability to model, understand and repair complex living systems, but also to construct new biological parts that may one day be the building blocks of entirely new organisms. This is a world made possible by labs-on-chips, synthetic biology and molecular computers. The implications are truly profound, not only for biology and medicine, but also for human ethics and for protecting our society against future onslaughts of natural (and engineered) diseases.

Labs on Chips

Living cells are the most sophisticated nano-systems known. The speed with which they reproduce belies their intricate intracellular organisation. This organisation gives rise to a very special environment, whose physics is characterised by small length scales, surfaces dominating volume, laminar flows, fast diffusion, and the heat bath, and whose chemistry is dominated by stochastic fluctuations and highly controlled reactions. Recent progress in microfluidics and nanotechnology has now opened this unfamiliar environment to practical engineering experience [29]. Microfluidics has been used to construct systems of channels and vessels equipped with electrodes and optics for detecting, measuring, and manipulating solutions, particles, macromolecules or cells. Simple laboratory work flows, such as sequences of reactions followed by product analysis, can be implemented on a single chip for mass production. Such micro-reaction chemistry within confined volumes offers unprecedented control over reaction conditions. In addition, specific macromolecules or cells can be individually identified and separated using on-chip methods, enabling new types of experiments to be conducted. Since the reactions are in small volumes, they consume very little chemical supplies, enabling extensive studies. Furthermore, high integration on a single chip enables new types of instrumentation that use embedded chemistry to perform analysis at the point of measurement.

Synthetic Biology

Although lab-on-chip technology allows for refined control of molecular interactions, it pales in comparison to the powerful infrastructure and mass production capabilities of a living cell. For over two decades, efforts have been under way to modify cells for factory production of chemicals that are either too complex for classical synthesis, or that can be produced much more efficiently by microorganisms (white biotechnology). So far, most of these examples have been relatively simple and could probably have been identified by classical mutagenesis. However, as genome-wide computational models become more complex, these models will enable the construction of cell factories that could change the very nature of production in the chemical and pharmaceutical industries. The self-replication capability inherent to cells lends itself to convenient mass production. More recently, there has also been a shift from static metabolic engineering towards interfacing with the control structures of cells [30]. The possibility to engineer the dynamics of cellular behaviour opens a path to novel, living biomaterials.

Cells tuned for a particular purpose can be grown in bio-films of communicating elements, going far beyond the conventional idea of DNA computers [31]. This is leading to the emergence of the field of *Synthetic Biology*, focused on 'the design and construction of new biological parts, devices, and systems, and the re-design of existing, natural biological systems for useful purposes'. MIT is leading the evolution of this new field through the BioBricks project (http://parts.mit.edu/), with the development of standard and interchangeable biological parts. These currently include operators, coding regions, transcriptional terminators and logic gates. The aim is to provide powerful abstractions so that bio-engineers can design and build complex biological systems in the same way that electronic engineers have traditionally built complex electronic circuits, by putting together high-level logic gates.

Bio-hybrid chips

Customised cells can also be integrated with conventional technology, and integrated circuits have already been interfaced with microorganisms engineered for sensing [32]. This technology enables the sensing and discrimination of minute traces of a substance (e.g. a toxin) against a complex chemical background. Lab-on-chip technology is capable of maintaining the environment required by the cells resident in such a bio-hybrid chip. The integration of microorganisms into electronic circuits can be expected to expand significantly within the next 5 years.

Molecular computing

Cell simulation through building such artificial cells is viewed as a widely desirable goal by systems biologists. However, an alternative engineering approach would be to design a self-replicating von Neumann machine – natural and artificial cells can be considered as a special case of a von Neumann Universal Constructor [33]. A chemical synthesis version of the constructor has already been described by Drexler [34], and ideas for miniaturisation of machines were discussed still earlier by Penrose and Penrose [35] and Feynman [36]. These can all be viewed as special cases of a *Chemical Universal Turing Machine* (CUTM) – an abstract computational device used to investigate what can be computed. It should be possible to build such an abstract machine with a simple physical realisation. This would be a simple automaton consisting of a large reaction flask, together with a conveyor belt containing an arrangement of chemicals. The chemicals would constitute the 'program' and the automaton would have operations for reading chemicals on the conveyor, adding and removing them from the reaction flask, and controlling the temperature of the reaction. The CUTM is a fundamental concept which unifies lab-on-chip and artificial cell concepts. Clearly, this requires research to establish its viability but, if successful, could have a dramatic effect on combining theoretical, experimental and modelling approaches to understanding and engineering biology.

Much closer to realisation than self-replicating machines are simple molecular computers. Comparable in capability more to a laundry machine controller than to a general purpose computer, simple molecular computers are small enough to operate within a cell. A proof-of-concept of a molecular computer has recently been demonstrated, which senses disease-related molecular symptoms, namely over – and under-expressed genes, analyses the information according to a medical rule and, if a disease is diagnosed, releases the drug molecule it carries [37]; see also the section 'Revolutionising Medicine' in Part 3. This concept is interesting, not least because it illustrates the potential of combining key concepts from computer science with chemistry and biology into a new form of therapy: smart drugs for nano-medicine. In this case, the computer has three modules: an input module that senses molecular symptoms, a computation module that analyses symptoms according to pre-programmed medical knowledge, and an output module that releases the drug. To offset for unreliability of computer components, two types of automata compute in parallel: one that releases a drug upon positive diagnosis, and one that releases a drug suppressor upon negative diagnosis. Many hurdles are to be overcome in developing this into a viable molecular computer for applications in areas such as smart drugs, yet even if this design does not cross these hurdles, it might still inspire future designs that would. The consequences would be dramatic – revolutionising biology and medicine.

Summary

Insights from systems biology combined with an understanding of molecular mechanisms will increasingly enable the tailoring of cells for specific purposes. On a long-term perspective, the possibilities created by the emerging tool set of synthetic biology are enormous. They span from new experimental tools and techniques to the design and synthesis of entirely new forms of drugs [38]. A detailed understanding of the information processing principles operating within cells will be crucial to realising these possibilities.

With the simplification of cells to their minimal set of essential genes [39], the bottom-up implementation of micro-compartmentalised biochemistry [29] and the integration of cells into circuits [32] well under way, we can expect the distinction between biological and technical systems to blur in the coming decade. The computer will be central in this merger of 'the artificial' and 'the living'. Principles from computer science are already proving essential for addressing the immense complexity of such an endeavour.

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