The Future of Biotechnology: Confluence of Next-Generation Experiment, Software, and Hardware for Deciphering and Rewriting Biological Systems

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Less than 250 years after the conclusion of the Enlightenment, we have reached a point in human history where science has given us seemingly mystical abilities. We interact across thousands of kilometers nigh-instantaneously, we hold millions of libraries of knowledge in the palms of our hands, and hosts of shining buildings tower into the sky. Despite popular conceptions of doom and gloom, we are healthier, more peaceful, and less impoverished than ever before (Pinker, 2018). Our medicines can perform miracles such as making the blind see (Kumar et al., 2016; Lu et al., 2020), repairing damaged organs (Attanasio et al., 2016; Fioretta et al., 2018), and eradicating smallpox and rinderpest (Njeumi et al., 2012; Willis, 1997). When reflecting on all that is possible today, Arthur C. Clarke's famous statement that "any sufficiently advanced technology is indistinguishable from magic" takes on more truth now than ever. But the next revolution, the revolution where we decipher biological complexity and rewrite biology itself for the better, has only just begun.

The convergence of new experimental methods, software, and hardware may act as a driving force for *deciphering* complex biological systems at a vastly deeper level than ever before. Enormously data-intensive experimental techniques in areas such as spatial transcriptomics and high-resolution volume and video microscopy will provide the foundation for advancing our understanding of biological systems (Liao et al., 2021; McDole et al., 2018; Titze & Genoud, 2016; Vogt, 2020; Wan et al., 2019). Robotic laboratory automation may further enhance the throughput of such methods (Angelone et al., 2021; HamediRad et al., 2019; Holland & Davies, 2020). In the realm of software, artificial intelligence (AI) advances will facilitate interpretation of patterns in massive amounts of biological data (Motta et al., 2019; Scheffer et al., 2020; Topol, 2019). At its heart, AI is a technology which extracts patterns from data. This means that AI can automate the process of sifting through oceans of complex multidimensional data and isolating a manageable number of insights with relevance to human affairs. In addition to AI, detailed integrative simulation techniques will aid prediction and description of biological mechanisms (Bezaire et al., 2016; Billeh et al., 2020; Karr et al., 2012; Markram et al., 2015; Singharoy et al., 2019; Yu et al., 2016). Some examples of these include large-scale molecular dynamics (MD) simulations (Singharoy et al., 2019; Yu et al., 2016), kinetic simulations of whole cells (Karr et al., 2012), and neurobiological simulations with tens of thousands of detailed virtual neurons (Bezaire et al., 2016; Billeh et al., 2020; Markram et al., 2015). As essential supporting technologies for these software innovations, key hardware advances may take the forms of quantum computing architectures (Cao et al., 2019; Outeiral et al., 2021), neuroscience-optimized neuromorphic computing architectures (Brown et al., 2018; Indiveri et al., 2011; Schemmel et al., 2017), and neuromorphic tensor processing unit architectures (Bains, 2020). Quantum computing may support quantum mechanical MD simulations as well as MD simulations with more particles and longer timescales (Cao et al., 2019; Outeiral et al., 2021), neuroscience-optimized neuromorphic computing may support realistic brain simulations (Brown et al., 2018; Indiveri et al., 2011; Schemmel et al., 2017), and neuromorphic tensor processing unit architectures may support much more powerful AI (Bains, 2020). The advent of exascale supercomputing will also play a central role in aiding the outlined software methods for the biological sciences (Lee & Amaro, 2018; Service, 2018). These changes will facilitate massive enhancement of our ability to make accurate predictions of how biological systems behave.

The convergence of experimental methods, software, and hardware may further act as a driving force for *rewriting* complex biological systems in a scalable and reproducible manner. The previously mentioned hardware advances could enable a surge in computer-aided design (CAD) software for engineering biology with nanoscale precision. To design new biology, these CAD innovations particularly may leverage AI (Kriegman et al., 2020; Zielinski et al., 2020), *in silico* directed evolution (Benson et al., 2019; Kriegman et al., 2020), kinetic modeling of cellular signaling and metabolic networks (Karr et al., 2012; Zielinski et al., 2020), and molecular dynamics (Benson et al., 2019; Shi et al., 2017) as well as improved graphical user interfaces (Grun et al., 2015). On the experimental side, laboratory automation and novel experimental tools may align to rapidly synthesize, validate, and iteratively improve biological inventions (Angelone et al., 2021; Chao et al., 2015; HamediRad et al., 2019; Schneider, 2018). These changes will facilitate tremendous strides in our collective capacity to create entirely new biology and to interface this new biology with existing biology.

Advances in our capacity to decipher and rewrite biology will dramatically advance the biomedical sciences. For instance, immunotherapies have the potential to eventually cure most or all cancers (Eggermont et al., 2013; 'Mac' Cheever, 2008; Yong et al., 2017). Medical nanorobots, some of which will consist of an exciting material known as DNA origami (Jiang et al., 2019), may also contribute to cancer treatment (Tregubov et al., 2018) and treatment of other diseases. In the case of DNA origami especially, CAD and MD will likely play a significant role (Benson et al., 2019; Douglas et al., 2009; Shi et al., 2017). AI, classical MD, and quantum MD will also enable the creation of numerous protein-based nanomachines with diverse applications by enabling rational design of proteins which have sophisticated dynamics (Kuhlman & Bradley, 2019; Melo et al., 2018; Pirro et al., 2020). Experimental automation and computational methods involving AI and integrative simulations could enable extremely rapid responses in the form of treatments, vaccines, and diagnostics to future outbreaks of infectious disease (Angelone et al., 2021; Chao et al., 2015; Schneider, 2018; Singh et al., 2020). While the threat of antibiotic resistance is concerning, phage therapy and synthetic biology treatments may further combat future forms of bacterial infection (Collins et al., 2019; Kortright et al., 2019). AI may automate a large portion of biomedical image analysis in the clinical setting (Topol, 2019). Donor organ shortages may end with the advent of bioprinted replacement organs (Cui et al., 2017; Mir & Nakamura, 2017). CAD methods may help improve the quality of bioprinted organs (Fay, 2020). AI and integrative simulations might help unlock the secrets of aging, allowing development of treatments for aging as a disease. This could both greatly increase human longevity and greatly decrease the incidence of aging-related illnesses (Fontana et al., 2014; Zhavoronkov et al., 2019). Wearable medical devices such as electronic tattoos could monitor health and prevent tragedies by giving people early warnings before physiological dysfunctions occur (Jeong & Lu, 2019). These represent some of the many possible biomedical technologies which may make us happier and healthier in the relatively near future.

One biomedical technology which may particularly make gains throughout the coming decades is gene therapy. Through synthetic biology manufacturing techniques (Le et al., 2019), gene therapies may shake off their currently prohibitive level of expense. Multiscale computational methods for understanding the human body at general and personalized levels (through AI and integrative simulations), CRISPR tools (Doudna, 2020), and superior nanobiotechnology delivery systems (Lundstrom, 2018; Wang et al., 2019) may allow gene therapy to start treating complex polygenic disorders (Carlson-Stevermer et al., 2020). These factors may even someday enable genetic modifications which make the human body more suited to space colonization (Norman & Reiss, 2020). If political polarization declines and the specter of genetic inequality loses its imminence, gene therapy could even enhance cognitive abilities and empathy in humans. While these prospects may seem frightening to some, it is important to realize that even a few more highly intelligent and empathetic people may make dramatic positive changes in our world (Rinn & Bishop, 2015). Gene therapy may also make major contributions to increasing human longevity (Bernardes de Jesus et al., 2012). Gene therapy could result in many positive transformations to our lives and even help to preserve the long-term future of humanity.

Neurotechnology may also soon come of age. Connectomics techniques, AI, and integrative simulations may give far better understanding of how to treat brain diseases in precisely targeted ways (Bullmore & Sporns, 2009; Markram, 2006; Markram et al., 2015; Mizutani et al., 2019). In particular, nanoscale connectomics might soon undergo a revolution as 4th generation synchrotrons (Pacchioni, 2019) and the relatively cheap miniature synchrotrons called Lyncean Compact Light Sources (Hornberger et al., 2019) facilitate rapid imaging of brains at nanoscale resolution (Kuan et al., 2020). On the neuroelectronics side, brain-machine interfaces and electronic neural prostheses could treat traumatic brain injuries and sensory and motor ailments as well as extend human abilities to interface with the cloud and the physical environment (Acarón Ledesma et al., 2019; Flesher et al., 2016; Gaillet et al., 2020; Hampson et al., 2018; Liu et al., 2015; Musk, 2019). Optogenetic methods, which enable control of genetically modified neurons with pulses of light, might synergize with gene therapy to create much more precise and complex brain-computer interfaces (Balasubramaniam et al., 2018; Chen et al., 2018). Though currently in its infancy, neurotechnology will likely grow rapidly into a mature discipline which grants us new abilities in neuromedicine and beyond.

Novel biotechnologies will also have great influence on manufacturing and environmental conservation. Biological CAD methods, integrative simulations of metabolism and gene regulation, and laboratory automation may allow synthetic biology to create a panoply of new microorganisms which can cheaply and rapidly produce medicines (Meng & Ellis, 2020), nanostructures (Bhaskar & Lim, 2017; Furubayashi et al., 2020), and even useful macroscale materials (Tang et al., 2020). Engineered microorganisms may also act to clean up pollutants and greenhouse gases (Gong et al., 2016). Molecular CAD methods, MD simulations, and laboratory automation may further revolutionize manufacturing through the creation of artificial molecular factories (Krause & Feringa, 2020). These molecular factories could involve immobilizing optically programmable supramolecular complexes such as certain rotaxanes and catenanes (Bruns & Stoddart, 2014) on metal-organic frameworks or similar crystalline structures (Krause & Feringa, 2020). With these miniscule factories, the dream of molecularly or even atomically precise construction at scale might be in reach. In addition, molecular factories which clean up pollutants and greenhouse gases could also make great contributions to combatting environmental degradation (Aithal & Aithal, 2020; Subramanian et al., 2020). Another suite of emerging technologies for ecoengineering are gene drives. These propagate gene editing tools which modulate the reproduction of populations of mosquitos and other disease vectors, potentially helping to stop illnesses like malaria (Gantz et al., 2015; Noble et al., 2017). Synthetic biology may also provide “off switches” for these gene drives, preventing them from causing environmental problems if they get out of control (Xu et al., 2020). In the realm of food production, gene edited plants can be made more suited to vertical farming (Kwon et al., 2020; O’Sullivan et al., 2020), indoor farming on the moon or Mars (Cannon & Britt, 2019), or ocean-based agriculture (Simke, 2020). *In vitro* meat may eventually transform meat production into a much more sustainable industry while decreasing the prevalence of animal cruelty (Bryant & Barnett, 2020; Zhang et al., 2020). These innovations and others could go a long way towards combatting global challenges such as hunger and climate change.

The confluence of advances in experiment, software, and hardware will enable many exciting biotechnological changes in the coming decades. Clever new experimental techniques will couple with automation to produce oceans of biological data. AI and integrative simulations extract meaningful insights from those otherwise unmanageable data point oceans. Hardware advances in neuromorphic computing, quantum computing, and exascale supercomputing could enable the titanic computations necessary to push software to its full potential. With this trinity of drivers of scientific progress, a plethora of new biotechnologies may enter common use and radically transform how we live. Some major areas of impact for these biotechnologies will include biomedicine, neurotechnology, gene therapy, manufacturing, agriculture, environmental remediation, and space colonization. Some may raise objections about the risks of such rapid technological changes. To answer these objections, consider that any kind of human progress, technological or social, must involve missteps. Yet human ingenuity and determination corrects these missteps in an ever-evolving trajectory, leading to an overall better world. Technology will synergize with the indomitable human spirit to build a bright and beautiful future.

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