The Chaudhuri Effect *

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Accelerating technological changes will make the practice of Medicine unbelievably complex and also challenge our current concepts of evolutionary and species-wide changes in the near future.

This article was originally submitted for publication to the Christmas BMJ 2018. Sadly, it did not make the mark. This was well before He Jiankui announced the birth of Lulu and Nana (maybe BMJ had a premonition about the controversy). I must make it very clear at the outset that I do not condone unethical human or animal experimentation.

Recently, four young dogs with Duchenne Muscular Dystrophy had their DNA modified "In-vivo" using a gene editing tool called CRISPR [Ref 1]. This successfully reversed the molecular defect responsible for their muscle wasting disease. In fact, successful "ex-vivo" human application of a related gene editing technique TALEN was reported not so long ago in a one-year-old girl with advanced leukemia [Ref 2]. These are nascent technologies and one might ask what is so remarkable about them. We have had ground-breaking therapies that marked paradigm shifts in the treatment of disease before. In fact, chemotherapy of cancers was one such technique and again it was first successfully demonstrated in what was then universally fatal childhood leukemia in 1947 [Ref 3].

So, what is different now? The response to this question touches upon a multitude of recent technological advances which are sometimes closely related and sometimes subtly so or not at all. However, the synergy of these approaches is likely to disrupt the way we practice medicine in humans. It will not stop at that point. The juggernaut will then move on into other areas such as cosmetic enhancement and functional improvements. Such changes will challenge our current concepts of the evolution of species, which is inherent in its DNA and the genome.

It is not always possible to reliably predict the future. Popular science journals are peppered with remarkable predictions of technological advances which have either not materialized yet or have fallen by the wayside. Notwithstanding, I shall attempt in this short essay to try to see things from a certain perspective and aim to stimulate discussion amongst peers. I must also apologize for any factual errors in advance as my knowledge about most of these advances is very much akin to that of a dilettante.

In 1859 Charles Darwin published his book *On the Origin of Species* and started us on our current thinking about biological evolution and concept of species. In his book, he explained his theory of Natural selection of species and contrasted it with humankind's limited (yet profound) efforts at Artificial Selection. The genetic basis of evolution was not recognized until later and in fact, it was only in the early years of the 20th Century Charles Darwin's theory of evolution was reconciled with Gregor Mendel's ideas on heredity. In essence, any noticeable effect of natural selection usually takes many generations. Artificial selection such as wolves leading to the domesticated dog would have occurred within a shorter timeframe. Breeding of different pedigrees of dogs takes even less time. However, the common trait between these is that they are not precisely engineered changes in their genes. It is still a selective culture of preferential traits within a species. The potential of gene editing techniques such as CRISPR and TALEN is that they can precisely edit the DNA. It will then be possible to insert other genes at the same (or different) spots to create de-novo characteristics. In the treatment of disease, this is currently broadly grouped as personalized medicine and the gene editing if used in therapy would be called precision medicine. If these techniques were then used to change the color of the Iris to blue or to enhance the limb musculature in an athlete, the effects would be noticeable much quicker and certainly within an individual's lifetime.

Unicellular organisms with synthetic DNA which are able to reproduce have already been created in the laboratory [Ref 4]. However, these are minimalistic and certainly a far cry from the complexity of multicellular organisms. Syn3.0 created by Dr. Venter's

team in California only has 473 genes contrasted with the 20,000–25,000 protein-encoding genes in humans. This is where the synergistic effects of other technologies come in.

The cost of whole-genome sequencing has plummeted in recent years as a result of advancing technology, especially the jump from analog to digital sequencing techniques [Ref 5]. Sequencing the entire human genome for the first-time cost approximately $2.3 billion dollars in 2003. There are companies [Illumina.com] who are currently marketing devices which will be able to sequence my entire genome for just $100. This is an astronomical reduction in costs in only 15 years. Others offer to map our ancestral gene pool and give us full health (and potential disease risk) report based on our personal genetic data [www.23andme.com].

The semiconductor industry is fond of quoting a popular principle called Moore's Law, which states that the cost of semiconductors halves every two years as a result of technological advances [Ref 6]. In comparison, the reduction in the cost of genome sequencing has been even more phenomenal. Ray Kurzweil an engineer, scientist, and inventor with an excellent track record of predicting technological breakthroughs calls this the Law of Accelerating Returns [Ref 7]. He believes while most of us anticipate innovation to follow a linear course most such development actually follows an exponential course over time. If this were true, then we should expect to sequence or edit a fully synthetic human (or variant) genome within a single generation (or so). I shall not complicate matters any further by discussing the potential ethical concerns of such an endeavor. I should, however, point out here that modern plastic surgical techniques were developed for the treatment of soldiers with burns and injuries sustained in the war zone. Yet their single most prevalent use today is enhancing subjective cosmetic appearances in individuals without any prior injury.

Ray Kurzweil has been employed at Google by Larry Page to improve natural language processing by means of artificial intelligence and machine learning since 2012. He has also courted controversy by promoting the concept of the Technological Singularity in his books and publications [Ref 8]. Essentially, he predicts that in the near future (circa 2045) we shall invent superhuman machine intelligence. This landmark point is an event horizon — a point of no return and it is also currently unimaginable what might happen to humans themselves after that landmark event.

Go is a board game which is one of the simplest and at the same time one of the most abstract. It is estimated that the number of possible configurations of the board in a

game of Go exceeds the number of atoms in the known Universe. In March 2016 a computer programme Alphago, trained using a deep convolutional network technique of reinforcement machine learning defeated Lee Sedol a top ranking Go Player 4 –1 in a series of five games. IBM Watson is a computing product which uses a combination of natural language processing and machine learning amongst other allied technologies. In 2011 it won the 1st place in the quiz show Jeopardy defeating other legendary champions. Since then it has found expanding use in Healthcare, assisting physicians by interpreting patient clinical information and laboratory results and then reviewing 10s of millions of pages of relevant peer-reviewed and current medical evidence in seconds and suggesting a personalized management plan for that individual patient [Ref 9]. I doubt any human doctor could compete with Watson for efficiency, accuracy and up to date knowledge. Certainly, if medical advances and knowledge continue to progress at such a dizzy pace we will all require similar cloud-based smart machines to assist and optimize the treatment of every individual patient. What is more, according to the Law of Accelerating Returns [Ref 7] the machines should not only become exponentially intelligent over time but universally accessible and affordable by all.

There has been a healthcare data explosion in recent years, especially with the advent of the Internet of things, wearable technology and developments such as patient experience community apps [Ref10] and AI-enhanced chatbots [Ref 11]. This data can be harnessed and processed in real time using the Cloud. Machines like IBM Watson might then be able to actively monitor and improve our health and even suggest timely diagnostic and therapeutic interventions [Ref 12]. So am I going to become redundant as a doctor, as it is quite clear that I cannot keep pace with a machine? On the contrary, in the foreseeable future, I might become more indispensable to Watson. This brings us to an eponymous principle — Moravec's Paradox — which states "it is comparatively easy to make computers exhibit adult level performance on intelligence tests or playing checkers, and difficult or impossible to give them the skills of a one-year-old when it comes to perception and mobility" [Ref 13]. While recent advances in image recognition, natural language processing, and robotic machine learning may mean that this is no longer entirely true, the principle remains valid. It is far more difficult to teach a machine (at the present moment), what we, humans, do without thinking (and what has probably been ingrained deep within our subconscious over millions of years of evolution) than tasks that we might struggle with (such as complex calculations and memorizing and processing vast amounts of scientific data).

We might not expect our current biological capabilities (as homo sapiens) to progress exponentially in tandem with technological and computational advances. Yet it is also

quite unlikely we are going to sit by and watch the computers take over and bring to fruition the various dystopian futures for humankind that is often popularised in popular media. We could, for instance, acquire cybernetic enhancements. Such developments might include brain stimulating electrodes, brain-computer interfaces, and neuroprostheses. Some of these have already been tried out with varying success in animals as well as in human subjects [Ref 14]. Most of the technology is still at a rudimentary phase [Ref 15] or has been used as a proof of concept in patients with serious debility (locked-in syndrome) or with existing implants (electrodes for deep brain stimulation or refractory epilepsy). In fact, a recent experiment in brain stimulation via implanted electrodes in patients with refractory epilepsy found it boosted their memory by 35% [Ref16].

Other technological advances that may play a significant role in enhancing humans, promoting longevity and curing existing and novel diseases in the near future include bioprinting, DNA computing, nanobots, and quantum computing.

When advancement in an existing technology starts slowing down, we humans simply discover a completely new technology to move things forward again, according to Ray Kurzweil. He explains that Moore's Law is, in fact, the fifth paradigm shift in computing technology.

IGEM is an independent non-profit organization that promotes the open advancement of synthetic biology [http://igem.org/About]. They run an annual global competition where not just University Scientific teams but also college undergraduates and high school students take part. One of the winning projects in last year's competition was a team from Heidelberg who used a mix of computer databases and analytics and gene-editing technology to speed up selective evolution in bacteria [Ref 17].

We are standing at the threshold of an exciting era where we shall partner with advancing technology to give new meaning to the term human. Medicine, as we know it now, will undergo dramatic changes as humankind evolves into a varied species with both biological and technological enhancements to our existing morphology and genetics. We may consider modern medicine as increasingly complex and doctors might struggle to keep pace with developments, it is still only the tip of the iceberg of what is yet to come.

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