# Popular science summary

## *Bio-inspired crossover*

Evolution is the mechanism through which nature created all varieties of life on our planet. In order to understand this process, it is crucial to not only catalogue the natural history of species, but also to create deeper insights in the properties and limitations of Darwinian evolution. In natural science, such understanding is typically gained by comparing a wide range of possible scenarios, in the form of experiments that are deliberately designed to verify or falsify a scientific hypothesis. However, experimentation is difficult in evolutionary science, in part because many interesting phenomena tend to occur only over millions of years, but also because we are able to observe life on only one planet, and thus only one natural evolutionary process. Because all species on Earth share common ancestry, it is not always possible to tell which common features are necessary consequences of evolution and natural selection, and which features are random properties of our ancestors that were inherited by all living species. For example, we do not know if genetic information could be stored using other mechanisms than the DNA code. It may be that other molecules besides DNA are not as efficient at carrying hereditary information, and that the evolution of DNA-based life was inevitable on our planet; but we cannot rule out that an early life form evolved to use DNA as a chance event out of many possible alternatives, and then multiplied so that other hereditary mechanisms never arose.

Many shared properties of living species — such as DNA but also details of cell structure, metabolism, and the genetic underpinnings of embryonal development, for example — have great influence on the evolutionary process. They determine which evolutionary adaptations are possible, how populations react to environmental change, how new species can form and which interactions are possible between species. If some of these aspects of life as we know it are the result of random events in our shared evolutionary past, this implies that there are many other ways for evolution to progress, which we cannot observe in nature. Understanding how evolution happens in populations with other hereditary mechanisms, cell structures, and so on, would give us greater insight in the properties and limitations of evolution in general. This knowledge, in turn, would lead to technological innovation in some widely used computational techniques that are inspired by evolutionary theory. Understanding evolution also has consequences for cancer research, since tumours form out of a runaway evolutionary process wherein cells that normally cooperate to form tissues and organs instead compete on an individual basis in natural selection. Finally, if there is life on other planets, most scientists expect that it must have been formed by Darwinian evolution, so that a more general evolutionary theory might give a better idea of what to look for in the search for extraterrestrial life.

When traditional experimentation is difficult, computer simulations are useful as alternative experimental tools. In computational evolution experiments, scientists create virtual environments wherein evolution occurs. This is useful because these evolutionary processes are entirely separate from our own natural history, and are thus not shaped by the same random events. In addition, there are few limitations on the experimental design of an environment that is built with programming code, so that many different kinds of evolutionary processes can be compared.

One of the topics that are studied in evolutionary theory for which this computational approach would be useful is the evolution of how DNA sequence is structured. Over many generations, genes can become ordered differently, or they can be copied or deleted, so that the overall structure of the sequence changes. It is not fully understood what drives these changes and how they in turn affect the evolution of a species. Simulated evolution could be a useful instrument for researchers in this area, because the structural properties of the virtual DNA can be varied in different experiments. Thus, different aspects of the evolution of DNA structure can be explored separately and compared with alternatives, allowing specific hypotheses to be tested. However, there are some structural changes that can occur in natural DNA, which have never been implemented in digital evolution programs. In this dissertation, it is discussed how realistic DNA-like structure can be incorporated in digital genes for use in evolutionary simulations. In particular, we deal with the design of algorithms that imitate sexual reproduction, wherein two genetic architectures are combined into one offspring. Our goal is to enable future research in simulated evolution to uncover the causes and consequences of DNA architecture using virtual experiments.

## *A model of neuronal reprogramming*

The human body is composed of trillions of cells. Despite the fact that all these cells have the same DNA, they come in thousands of different types with different shapes and functions. For example, a white blood cell is specialised in destroying foreign invaders in the blood, while a muscle cell can contract and expand with force. Cells are able to be so varied despite their common DNA blueprint because not all genes are equally active in all cell types, resulting in different kinds of proteins being present in the cell. Crucially, because the activity of genes is itself regulated by proteins, when some groups of genes are activated, they produce proteins that activate themselves and deactivate other genes. Cells maintain their cell type through this mechanism of self-regulating gene activity.

In the past decade, medical scientists have discovered that the specialisation of a cell into a particular type can be undone by destabilising this self-regulation in a lab. Specifically, some viruses can be genetically engineered so that they activate or deactivate a particular gene when they infect cells in a Petri dish, which is a standard laboratory technique in

biomedical science. By applying this technique to manipulate key genes which are crucial for the self-regulation that maintains cell type, cells can be reprogrammed to a different type. When reprogramming human cells, fibroblasts (the cell type that composes most of the skin, excluding hair follicles, blood vessels, etc.) are often used as the source material, because they can be easily gathered from a patient without invasive surgery.

A particularly well-studied and useful kind of reprogramming is to turn skin cells into neurons, which is the type of brain cells and nerves. By giving doctors direct access to a patient's own neurons in a Petri dish, this technology could enable new diagnostic tests and revolutionise the way some brain diseases are studied. Even more spectacularly, it may be possible to inject reprogrammed brain cells into the skull of patients suffering from neurodegenerative diseases such as Alzheimer's, which are characterised by a catastrophic loss of brain matter. Using cells that originate from the patient's own body sidesteps ethical issues associated with sourcing stem cells and organs from other humans, and also minimises the risk of the body rejecting tissue from an incompatible donor.

Fibroblast-to-neuron reprogramming of human cells was first performed in 2012, one year after a critical breakthrough in mice. Since then, much research has been done to improve the efficiency of the method, and some understanding has been gained into which gene activation and deactivation mechanisms are crucial to flip the switch between the two cell types. However, self-regulation of gene activity in the real cell is a complex system that can only be understood as a whole, not as a collection of individual gene regulation mechanisms. In a publication that is included in this dissertation, we created a mathematical model of this gene regulation system, which combines many different activation and deactivation mechanisms, based on the measured activity of certain important genes during a skin-to-neuron reprogramming process. This model is able to predict which experimental procedures can successfully turn fibroblasts into neurons, and gives us more insight in how exactly the cell genes decide to change from one cell type to another. Medical scientists may learn from our model to develop more efficient reprogramming methods in the future, and put neuronal reprogramming one step closer to medical application.