

Biotech

THE NEW AGE OF GENOMICS



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DAWN FIELD & NEIL DAVIES



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*This book is dedicated to
Ryan, Suse, John, Felipe, Mesude, and Katja (DF),
and to Maheata (ND)*

PREFACE

DNA is a biological code elegantly composed of only four letters: A, C, G, and T. From this simplicity comes all the complexity of life. The key message of this book is that despite all the tremendous achievements the era of genomics is only starting. We are still seeing just the earliest, fuzziest glimmers of deep insight compared to the richness of life on Earth and the questions we can use it to answer. We stand on the cusp of sequencing the Earth from genome to ecosystem, from our own guts to our oceans.

In the course of eight chapters we attempt to span the breadth of the study of genomics from the discovery of the DNA double helix to the impending promise of planetary-scale genomics. Breakthroughs came in thick and fast during this project and we hope that the breadth of topics helps convey how fast the field is moving. A complete set of endnotes and references provides links to further reading or use in the classroom.

We need to thank many people. Top of the list is Latha Menon, editor extraordinaire. She shepherded this book through all steps from first enquiry to published form, often graciously sharing her wisdom over coffee. Likewise, we are indebted to her assistant Emma Ma for her help and advice and to Oxford University Press for making the project possible.

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for doing so from the perspective of being colleagues driving so much of the science that is shaping the emerging field of 'biodiversity genomics'. Hillary Gilbert and Martha Beeman provided outstanding proofing and comments. We are appreciative to many others for engaging with us by reading and discussing, including Lita Procter, Adrienne Minock, C. J. Cramer, Larry Minock, Robert Possee, Gina Crivello, Peter Sterk, Antonio Fernandez-Guerra, the Monterey Writers' Group, and Aidan Hansell.

All omissions or mistakes are solely ours. The scientific passion, excitement, and achievements of this field are the contributions of the scientists who have published pioneering papers in the field of genomics since its inception in 1995. Recognition must also go to those who have funded this work, and Neil would personally like to thank the Gordon and Betty Moore Foundation for their support of research in Moorea. We appreciate the help of all those who helped us improve our portrayals of their science, including Nikos Kyrpides, Ollie Ryder, Martin Blaser, Paul Hebert, Scott Edmunds, Eske Willerslev, Camilo Mora, George Roderick, David Liittschwager, Chris Meyer, George Roderick, Jonathan Coddington, Leslie Lyons, Eric Alm, Lawrence David, Joakim Larsson, Robert May, Rob Dunn, James Ostheimer, Nick Loman, Larry Smarr, Morten Allentoft, Linda Amaral-Zettler, Nick Loman, Noah Fierer, Karen E. Nelson, Hans-Peter Klenk, Jonathan Eisen, Owen White, Stuart Kim, Gary Wolf, Mike Snyder, Heather Dewey-Hagbord, Tim Smyth, and Nick Goldman. We also thank the hundreds of scientists of the Moorea Biocode Project, the Genomic Standards Consortium, the Genomic Observatories Network, Ocean Sampling Day, and the Moorea Avatar Project for working with us over the past years to make these initiatives possible. Combined, you are all de facto leaders of the unannounced Planetary Genome Project.

DAWN FIELD AND NEIL DAVIES
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DNA

Immortal coil

In 1869, Friedrich Miescher published a quietly received paper entitled 'On the chemical composition of pus cells'. It contained his account of isolating a substance that he called 'nuclein'. Miescher, a Swiss doctor, made the discovery while searching for proteins in white blood cells from patient bandages. He had found the fourth major class of cellular molecules, after proteins, fats, and sugars. It would take almost a century, until 1953 to be precise, for scientists to describe the chemical structure of nuclein, by then relabelled deoxyribonucleic acid, or DNA. With this information, science would finally crack the 'secret of life'.

'WE WISH to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.)' hardly promises a riveting read, but so began one of the most momentous scientific papers ever published.¹ James Watson and Francis Crick's consciously unassuming article followed Miescher's tradition for understatement, but the co-authors fully understood the significance of their breakthrough. As Crick wrote to his 12-year-old son in a handwritten letter, they had found the copying mechanism 'by which life comes from life'.

For the 60th anniversary of the double helix paper, Michael Crick auctioned off his father's letter. The publicity material of Christie's auction house read: 'More than one month before the first published announcement, Francis Crick, the co-discoverer of the structure and function of DNA, details one of the most important scientific discoveries of the 20th century—the "Secret of Life"—to his son.' The lot

became the most expensive epistle in history—it sold for US\$5.3 million.

In seven pages, Crick, a future Nobel Laureate, provides a scientific explanation of his accomplishment: ‘Now we believe that the D.N.A. is a code. That is, the order of the bases (the letters) makes one gene different from another gene (just as one page of print is different from another).’ Crick describes the discovery as ‘beautiful’. One of the pages has a simple sketch of DNA’s double helix structure and the letter is signed ‘Lots of love, Daddy.’ Watson and Crick had started a revolution: within 50 years the human genome was sequenced, heralding what many consider the ‘century of biology’.

Nobel Prizes are bestowed on advances that change our view of the universe and our place in it. Sometimes the transformative nature of the discovery is immediately apparent. More often, the full impact blossoms over time. Choosing the double helix as worthy of a Nobel Prize was a good bet; the rewards associated with human possession of this profound knowledge continue to accrue. Today, we are witnessing the advent of personal, or individualized, genomics and the creation of synthetic life. We stand in the best position yet to reap rich rewards.

The double helix is embedded in us all and in our culture. The immortal coil² has long escaped the ivory tower and is increasingly accessible via over-the-counter services and through the creative outputs of artists, fashion designers, musicians, and writers. Thoughts on DNA are expressed carefully in the most profound works of philosophy, and, on the lighter side, across a wide range of media from pop songs to cartoons. While we rewrite the landscape of biology through laboratory research on DNA, the molecule weaves itself deeper into our social fabric.

Salvador Dalí pioneered DNA-as-art. He celebrated the 10th anniversary of Watson and Crick’s discovery with *Galacidalacidesoxyribonucleic acid*, a painting whose title mixes his wife’s name and an earlier version of the chemical name for DNA. In the painting, his wife, Gala, looks up to the heavens and Dalí mused that the double helix is ‘the

only structure linking man to God'.³ Soraya de Chadarevian, the historian of science, put it thus in an article for *The Economist*: 'DNA has taken on an almost sacred status as the central blueprint for life, and the double helix has become the instantly identifiable secular equivalent of a modern religious icon.'⁴ DNA was there from the beginning and it connects all life—two characteristics historically reserved for deities.

A world in your wardrobe

DNA has a profound ability to encode information: enough to build even the most complex organism. It is also capable of encoding any other type of information. Technologists are mimicking the exceptional storage properties of DNA to store digital data. There is no gene for Dalí's *Galacidalacidesoxyribonucleicacid* or any other work of art, but DNA is being explored as a type of molecular hard-drive.

The first book to be 'printed' in DNA was created in 2012. Fittingly, it was a book on synthetic biology, *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves*,⁵ co-authored by genomics pioneer George Church of Harvard University. In what was at the least a magnificent marketing gimmick, Church used an algorithm to translate over 53,000 words and 11 images from digital form into the four-letter language of genetics; he then fabricated the corresponding DNA molecule using the technologies of synthetic genomics. The contents of Church's book, heavy in the palm of the hand, in DNA are smaller than a dust speck.

It is not likely that DNA books will ever replace hard copy or digital books. Nevertheless, we can only imagine what entrepreneurs will come up with if, or some would say when, DNA sequencers are as accessible as smart phones and we invent DNA printers.

DNA storage might be a way to keep pace with 'big data'. Just considering the output of scientific research alone, information storage needs are escalating rapidly. Data is streaming in from environmental sensors, particle physics experiments, and image processing, to name but a few. DNA sequencing machines, for example, are churning

out ever-growing quantities of information that must be stored in a global public database if all are to benefit from the new genetic knowledge.

We have a global molecular library of DNA mirrored in the United States, Europe, and Japan. In its first decade, it grew from almost 700,000 base pairs in 1982, to over 148 trillion.⁶ If we imagine the sequences aligned in one long strand, the resulting DNA molecule would have stretched 1 per cent of the way to the sun in 1982. By 2012, it would be long enough to reach the sun and back—10,000 times over.⁷

Public DNA holdings are currently doubling every nine months, a remarkable rate that seems set to fall to five months soon.⁸ Genetic sequences are just one of the types of information on the planet. Worldwide digital storage overtook the amount of information stored on paper and other analogue media for the first time in 2002. By 2007, 94 per cent of our information was digital, and in 2011, we stored more than 300 exabytes of information globally. One exabyte has 18 zeros after it. This means that there were over 300 times more digital bytes on our hard drives than grains of sand in the world. Or to think about it another way: if a star were considered 1 byte of data, then we have a galaxy of digital data for each person on Earth.⁹

We are now into zettabytes (10^{21} bytes). For those responsible for archiving human knowledge, these statistics are at once exciting and terrifying. At the current rate, it will soon be impossible to archive every cultural artefact we produce. DNA might be part of the solution. Church and colleagues achieved a storage density of 700 terabytes of information per gram of DNA—six orders of magnitude more dense than contemporary computer hard-disks. In 2013, a research team led by Nick Goldman and Ewan Birney of the European Bioinformatics Institute (EBI) outside Cambridge, UK masterminded a new approach that upped storage capacity to 2.2 petabytes.¹⁰

Importantly, their algorithm was able to reduce errors to such an extent that they could sequence, or 'read' it back out again, with close to 100 per cent accuracy. Showing that the information could be read

back with minimal loss of fidelity was a crucial proof of concept. They wrote and read a variety of digital icons, including a photograph of the institute where they work, a text file with all of Shakespeare's Sonnets, a 26-second audio snippet of Martin Luther King's 'I Have a Dream' speech, and a PDF of Watson and Crick's paper describing the DNA double helix.

DNA offers a future-proof technology. One challenge for storage media, as anyone who has tried to get data from a floppy disk could testify, is ensuring that the information format is still decipherable to people, even thousands of years from now. DNA is the language of life; knowledge of how to read and write it will never go out of fashion. Kept cold, dry, and dark, an airtight test tube on a nice safe shelf is enough to store properly prepared DNA for hundreds to thousands of years without substantial degradation. After all, it is possible to get genetic information from woolly mammoths frozen in ice 10,000 years ago.

One gram of DNA can hold half a million DVDs' worth of information, or about 2 petabytes. This is 27 years of high-definition video. The current contents of the US Library of Congress could be stored 50 times over in a teaspoon. Thus a 'pinch of DNA', dried as a white powder, would offer an intriguing new way to consume the world's culture; the DNA edition of the Library of Congress would taste salty, not sweet.

Cells still read and write DNA far better than we do and DNA synthesis is still prohibitively expensive: synthesizing the DNA in Goldman and Birney's modest experiment was performed by the company Agilent and cost about US\$20,000. A second obstacle is searching across a body of information stored in DNA. There is no equivalent of a Google search that would find a given text in the molecular Library of Congress—not yet anyway. The best use of DNA storage at the moment still seems to be for long-term archiving; for example, to put all human knowledge into 1,000-year 'time capsules' for posterity—perhaps safe in orbit around the Earth. The sum of current human knowledge could be stored in about 500 kilograms

of DNA.¹¹ Perhaps C. S. Lewis was right after all, and whole worlds might one day be kept in the back of a wardrobe.

The molecular narcissist

DNA sequences of any substantial length are nearly infinitely variable. Even though there are only four building blocks paired along the double helix—A, C, T, and G—the potential variation in their order is virtually endless. Furthermore, each human genome is reshuffled every generation as those of our parents mix in novel ways when sperm and egg come together. As a result of this recombination, no two people share a genome sequence, except for identical siblings.

Each of us has our moniker written inside our cells. All our names start with *Homo sapiens* but then they diverge; our individual identity is revealed long before reading the 3 billion letters that make up our genome. This variability in our DNA is a treasure trove for unique identification—the ultimate fingerprint. Researchers, governments, and entrepreneurs alike are mining and exploiting our DNA diversity in myriad ways. Innovations range from the sublime to the ethically worrisome and the downright disturbing. Others are just fun: Decorating your apartment? How about a rug emblazoned with your dog's 'DNA portrait'?

'DNA-as-art' companies are capitalizing on the genotyping technologies at the heart of molecular biology. They want us to stamp our uniqueness on everything from mugs to wedding bands to private jets. The images are nothing like the ones we are used to seeing in portrait galleries. Rather, they are linear, minimalist sets of horizontal rectangles that nobody would associate with a person unless they knew it was a DNA profile. A radical new way to view ourselves is precisely what seems to appeal.

The DNA portraits offered are most often based on the use of two Nobel Prize winning discoveries: restriction enzymes and the polymerase chain reaction (PCR). The resulting technologies enable us to tap into the endless genetic variation found among humans, whether for forensics, medicine, or art. Restriction enzymes are special proteins

found in bacteria. They act as genetic wire cutters, chopping DNA at specific sequences.

Treating DNA with these enzymes yields fragments of different length. When run out under an electrical current across a chunk of a jelly-like substance called agarose, the fragments move at different speeds according to their sizes and the bands of DNA separate. These bands are the rungs of the ladders in the images. Since different genomes have different sequences, the enzymes cut at different locations, yielding characteristic banding patterns that reflect the genetic differences between individuals.

PCR adopts the machinery of life to copy DNA. A highly simplified version can be done in a test tube with just a polymerase, the enzyme that copies DNA, and individual bases, A, C, T, G and short stretches of DNA, called primers, that bookend exactly which short stretch of DNA should be copied.¹² From even a single copy of DNA, billions of copies can be produced, called 'amplifying'. It is an exponential process as one piece of DNA is made into two, which then form the templates for another set of copying reactions leading to four copies and so on. About 40 cycles is usually enough to enable easy manipulation of the amplified DNA. With enough copies of a gene, we can easily manipulate it, for example to read its code or put it into another organism, thus pasting and cutting it, or 'recombining' it, with a different organism.

Together, PCR and the ability to cut and paste DNA constitute the so-called 'recombinant DNA' technologies. Developed in the late 1980s, they underpinned the explosive growth of the biotechnology industry. DNA is changing business models everywhere, and it is having a profound influence on our culture. Much as some now regard the brain as the seat of the modern soul, our genomes are becoming central to our concept of 'self'.

'Who's Your Daddy?'

The unique code within us is a boon for a range of personal identification services. These DNA identity tests hold great promise, but also

risk playing havoc with our relationships, insurance industries, and legal systems. Increasingly access to public DNA sequencing has already exposed shocking cases of forged identities. One case involved a father who found out that his child was not his biological offspring.¹³ Investigations found that a male receptionist at a fertility clinic the couple had used had substituted his sperm for that of the husband's. Since this discovery, the Reproductive Medical Technologies Clinic in Salt Lake City has encouraged all couples who used their services between 1986 and 1995 to also submit to DNA testing.

Human DNA testing is becoming so widely accessible that there are now mobile labs roaming major US cities offering a range of DNA services. A pioneer of this concept is the 'Who's Your Daddy?' truck.¹⁴ Brainchild of Jared Rosenthal, founder of Health Street, the truck offers a range of kerbside services including drug screening and background checks, as well as DNA-based tests of relatedness or kinship, including paternity testing. This innovative service was launched in New York in 2010 and quickly spread to other major cities. When in 2013 the truck made its debut in Boston 1,000 people lined up.

The nature of reproductive biology often makes it quite difficult to be sure who has fathered a particular offspring. This inherent uncertainty of fatherhood has important evolutionary consequences across the animal kingdom. In species considered to be monogamous, like many birds for example, the father should be obvious. Many studies, however, reveal a startling number of what biologists dispassionately refer to as 'extra-pair copulations'. Such goings-on are not entirely unknown in human society either, but their prevalence has been difficult to measure—until now. Roadside services, and perhaps one day the routine screening of babies, can make the paternity of offspring immediately evident. The broad availability of such data could have far-reaching, and possibly disruptive, social consequences. It will put to the test as never before vows of marital fidelity.

DNA testing goes far beyond paternity testing. Matching fathers to offspring is just one of the many relationships between humans that

can be established by comparing DNA profiles. The Health Street website, for example, highlights a number of stories. Some are heart-warming, others upsetting. Among the former are DNA tests to support immigration requests for relatives or to find long-lost children or parents. On the disturbing end of the spectrum are a married couple who discovered they shared the same father.

The universality of DNA and associated genetic machinery—a lingua franca of life—means that most of the DNA technologies developed for humans are immediately applicable to other species. As a consequence, we are now applying them to the animals and plants we love best: those domesticated species we share our lives with—or eat.

Most US states ban wolf–dog hybrids as being too aggressive and unpredictable to serve as pets. Might a litter of puppies result from your pet’s illicit tryst with a wolf? This could sound far-fetched and yet it is estimated that there are more than 300,000 wolf–dog hybrids around today. To find out, a swab from a puppy’s cheek can be sent to labs such as the Veterinary Genetics Laboratory (VGL)¹⁵ at University of California Davis, a world-leading animal genotyping laboratory. Scientists have studied the DNA of enough dogs and wolves now to know the differences.

What goes for dogs goes for cats. While there isn’t much fear of cat–tiger or cat–lion hybrids, there are plenty of interesting things to learn from your tabby’s DNA. According to the Cat Ancestry Test website, developed by Leslie Lyons, most of the 50–60 breeds of cats are less than 100 years old and all cats can be traced back to eight geographic regions of origin: Western Europe, Egypt, East Mediterranean, Iran/Iraq, Arabian Sea, India, South Asia, and East Asia. She has used samples from cat shows held all over the world to create a cat DNA database of ~170 DNA markers that can be used to assign all 29 of the major fancy cat breeds and major geographic regions. Now you can resolve whether your cat is truly from the alley, or if it harbours a more exotic bloodline: Persian, Abyssinian, or—if a bit large—Maine Coon.

Other ingenious applications of DNA testing include checking food quality and nabbing litterbugs. When worried about the contents of

hamburger meat, submit your sample to a DNA test for the presence of 12 mammalian species, including horse and dog as well as cow. If you are mad about the dog mess in your town, perhaps you should follow the example of communities that are mandating the entry of neighbourhood dogs into a local canine DNA database. They can now identify the owners who fail to scoop.¹⁶

Plant and animal breeding is now relying more and more on DNA. Analysis of DNA is one reason why milk yield in cows has improved so significantly over recent years. DNA can also tell whether a male stud will produce horned or hornless offspring. Mating any female with a stud carrying two copies of the *pulled* gene guarantees horn-free offspring, a highly desirable trait in cows, sheep, and big animals kept in high numbers in tight quarters.

One of the goals of genomics is to link genetic sequence variation to physical, mental, and behavioural characters. Knowing the 'genetic quality' of economically important animals (and plants) is paramount, especially given the strains on global food security. Leaving livestock to choose their own mates was abandoned at the dawn of the agricultural revolution, as farmers sought to optimize traits like milk yield and numbers of eggs laid through selective breeding programmes. Livestock today are conceived by artificial insemination and DNA analysis is emerging as the power tool for finding the best genes. Using DNA means supplementing, or even abandoning, years of successful 'gut instinct'. We are quickly moving into an era where all our farmed food will be the result of comparisons and calculations of the DNA kind.

The case of the unusual cat

Every new technology needs a 'killer application', though DNA testing is perhaps the first sector to take that business adage so literally. The first widespread use of DNA profiling for personal identification was in the domain of forensics. Today, DNA testing is a staple of popular TV shows like *CSI: Crime Scene Investigation*. The benefit of using

DNA-based testing as judicial evidence is now firmly established. Analysis of the most variable regions of the human genome from tiny amounts of biological material found at crime scenes can provide a unique match to the perpetrator. Based on past successes the use of DNA testing continues to ramp up and in many countries is now blending into the broader concept of genetic surveillance.

Many American states, for example, now maintain a growing database of genetic profiles that has proven a powerful investigative tool for solving crimes. Use of DNA-based identification was thought to be the same as matching tattoos to known gang members to establish criminal affiliations. Just like fingerprinting or photographing it is legitimate. Civil liberties campaigners in the US were concerned about the breach of privacy, however, and the question ended up before the US Supreme Court in 2013. In the case of *Maryland v. King*, the Court ruled to uphold the routine collection of DNA samples from criminal suspects.¹⁷ The Court had been asked to decide whether a recently collected DNA profile could be used to convict the arrestee for his six-year-old crime. The justices ruled by a narrow 5–4 majority that the analysis of an arrestee’s DNA is consistent with the US Constitution’s Fourth Amendment prohibiting unreasonable searches and seizures.

The ruling risked opening a Pandora’s box. Dissenting justices in the minority report agreed that DNA testing could help to solve cold cases, but were concerned about its use to flag potential suspects. While it might be reasonable to ‘search the DNA’ of someone accused of a serious crime, the definition of a serious crime can be a slippery slope. Might police be able to collect DNA from those committing traffic violations in the future?

Another issue is more intellectually intriguing, and goes to the heart of DNA’s power. What about the rights of relatives to privacy? The genotyping of someone under arrest could be considered a reasonable search of that person, but it could conceivably lead to the conviction of a sibling who has not been accused of anything. The genetic signatures of close relatives are naturally very similar, so when police

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