Beyond the Natural
A Comprehensive Guide to Synthetic Biology

KCL, Warwick, Cambridge, Oxford, Edinburgh, Exeter iGEM Teams

Preface

Welcome to Beyond the Natural: A Comprehensive Guide to Synthetic Biology.

This textbook expands King's College London's 2021 iGEM team *Renervate Therapeutics*' educational project, The Biologix Competition. King's 2023 iGEM team *ColoEcho* brings back the spirit of accessible knowledge with The Biologix Project, consisting of 6 lecture series and a collaborative textbook.

This textbook was written by iGEM teams of six universities in the United Kingdom, including

Chapter 1 - **King's College London**
Chapter 2 - **University of Warwick**
Chapter 3 - **University of Cambridge**
Chapter 4 - **University of Oxford**
Chapter 5 - **University of Edinburgh**
Chapter 6 - **University of Exeter**

This textbook aims to provide secondary school students, especially those who study in the UK, with a comprehensive and accessible introduction to *synthetic biology*– a fascinating field that is mostly untouched in the secondary school curriculum.

We include pop-up information boxes, UK-relevant statistics and stories, interactive quizzes with guided answers, as well as a further readings list after each chapter.

Contents

Chapter 1: The Synthetic Biology Landscape

1.1 Definition, history, and goals of synthetic biology

What is synthetic biology?

Synthetic biology is the redesign or construction of biological parts, devices, and systems.

Let's imagine synthetic biology as the **Lego of Life**. Biological systems, regardless of bacteria, plants, or animals, almost always share some common biological components on the microscopic level, such as reserved DNA and protein sequences. They can be perceived as basic Lego blocks.

Fig 1.1 *The Bioneers*, Lego Biology

A synthetic biologist's role is to act as a Lego architect and reassemble these Lego bricks in a meaningful way. It allows them to be creative and **make biology more customisable**, ultimately contributing to larger causes such as producing biological compounds more effectively, developing novel therapeutics, and tackling issues like pollution and contamination.

Fig 1.2 French chemist Stéphane Leduc (1853-1939)

History of synthetic biology

The term "synthetic biology" was first coined in 1912 by the French chemist **Stéphane Leduc** in his paper *La Biologie Synthétique* (Leduc 1912). Before the naming of this field, scientists in the late 19th century proposed a series of theoretical frameworks that involved creating "artificial cells" (Traube 1866) and artificial organic forms (Monnier and Vogt 1882).

Story time!

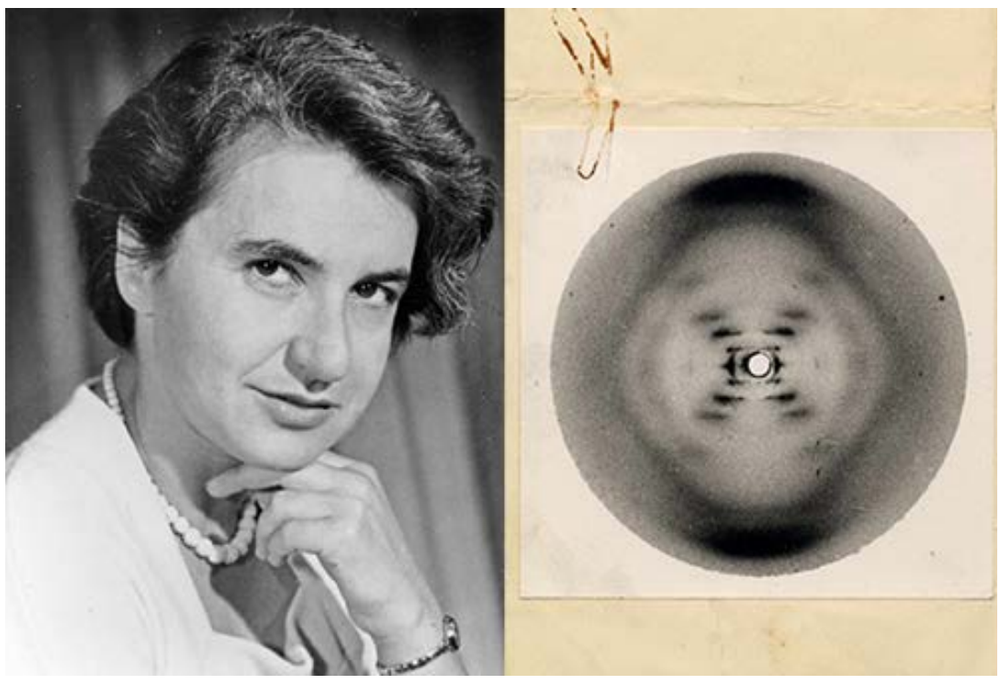


Fig 1.3 Rosalind Franklin and *Photo 51*

In May 1952, the famous ***Photo 51*** (Fig 1.3, right) that displayed the X-ray diffraction pattern of DNA was taken by Raymond Gosling, a graduate student working under **Rosalind Franklin** at **King's College London**. After Franklin left, **Maurice Wilkins** became Gosling's new advisor and obtained the image.

Wilkins showed this to **James Watson**, who worked on the structure of DNA with **Francis Crick** at the **University of Cambridge**. In April 1953, by building on top of features in Photo 51 and knowledge from other sources, Watson and Crick published their key findings of DNA's double helix structure in Nature. In 1962, Wilkins, Watson, and Crick joint received the **Nobel Prize** in Physiology or Medicine. With the reveal of the DNA structure, synthetic biology started to take off in the late 20th century followed by molecular cloning, DNA amplification, and synthetic biological circuits.

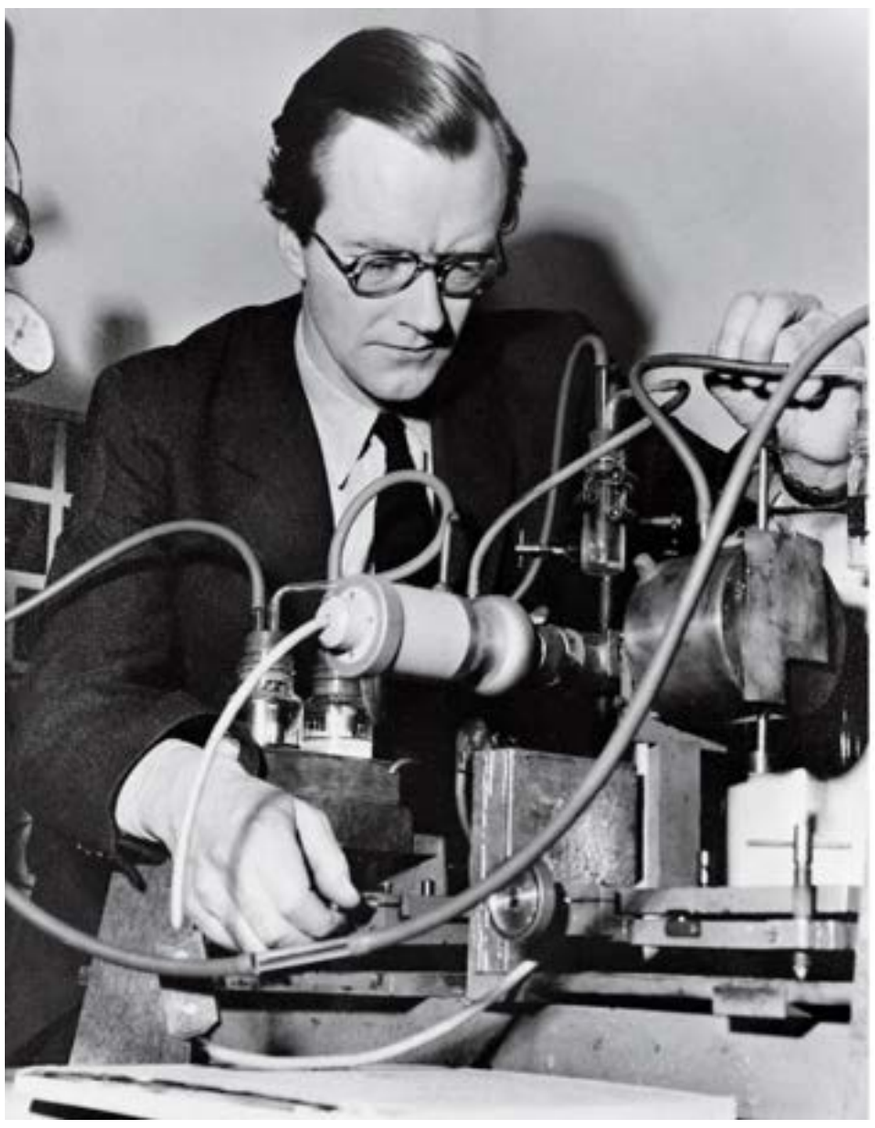


Fig 1.4 Maurice Wilkins

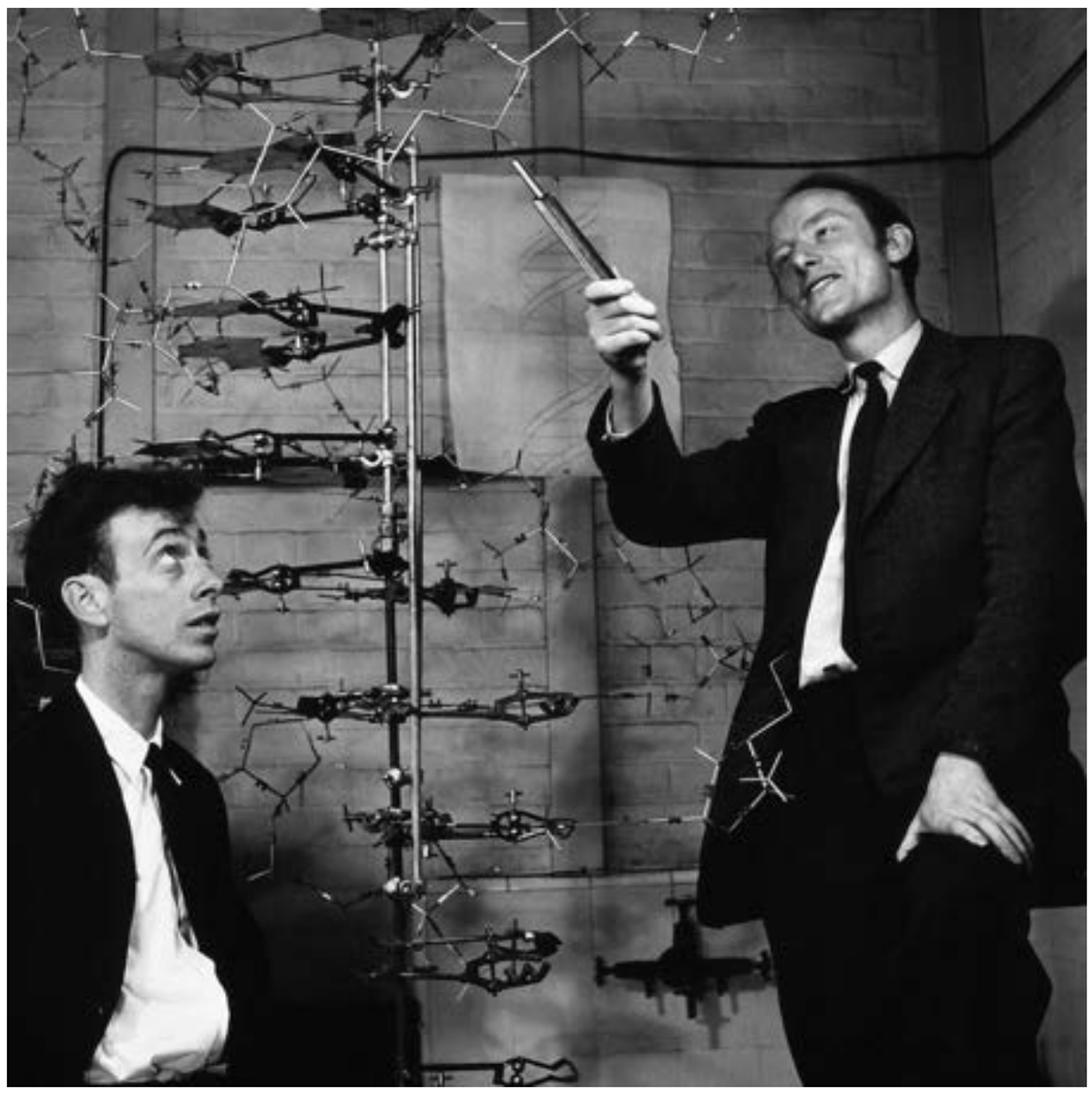


Fig 1.5 James Watson (left) and Francis Crick (right)

Scientists working in synthetic biology harness engineering techniques for a wide spectrum of challenges. Perhaps the most prominent applications are in agriculture, medicine, and environment, which will be outlined in detail in *Chapter 3*.

1.2 How synthetic biology work with other disciplines

Synthetic biology and AI

More recently, the emergence of **AlphaFold** surged a new wave for computational biology and individualised medicine. AlphaFold is a protein structure prediction technology developed by **DeepMind, a London-based AI company under Google**. AlphaFold uses the primary structure of proteins (i.e., the sequence of amino acids) to predict their tertiary structures (i.e., the three-dimensional structure of proteins) computationally using machine learning algorithms.

AlphaFold entered the **Critical Assessment of protein Structure Prediction (CASP)**, which is known as “the Olympics of protein folding,” in 2018 with their first version. They made headlines with its outstanding results, rivalling against other teams using traditional X-ray crystallography and cryo-electron microscopy methods.

Delve in deeper!

If you are interested in learning about how AI can help science, DeepMind has its own intriguing and comprehensive podcast.

Then, it re-entered in 2020 with AlphaFold2 and ranked first with an exceptional performance of an approximate 90% accuracy, allegedly **solving the protein folding problem** that remained one of the grandest challenges in biology. With the development of novel technologies like AlphaFold, synthetic biologists can engineer proteins and model molecular constructs more effectively. This accelerates synthetic biology research and pushes the field to new heights.

1.3 Working in the synthetic biology sector

The synthetic biology industry

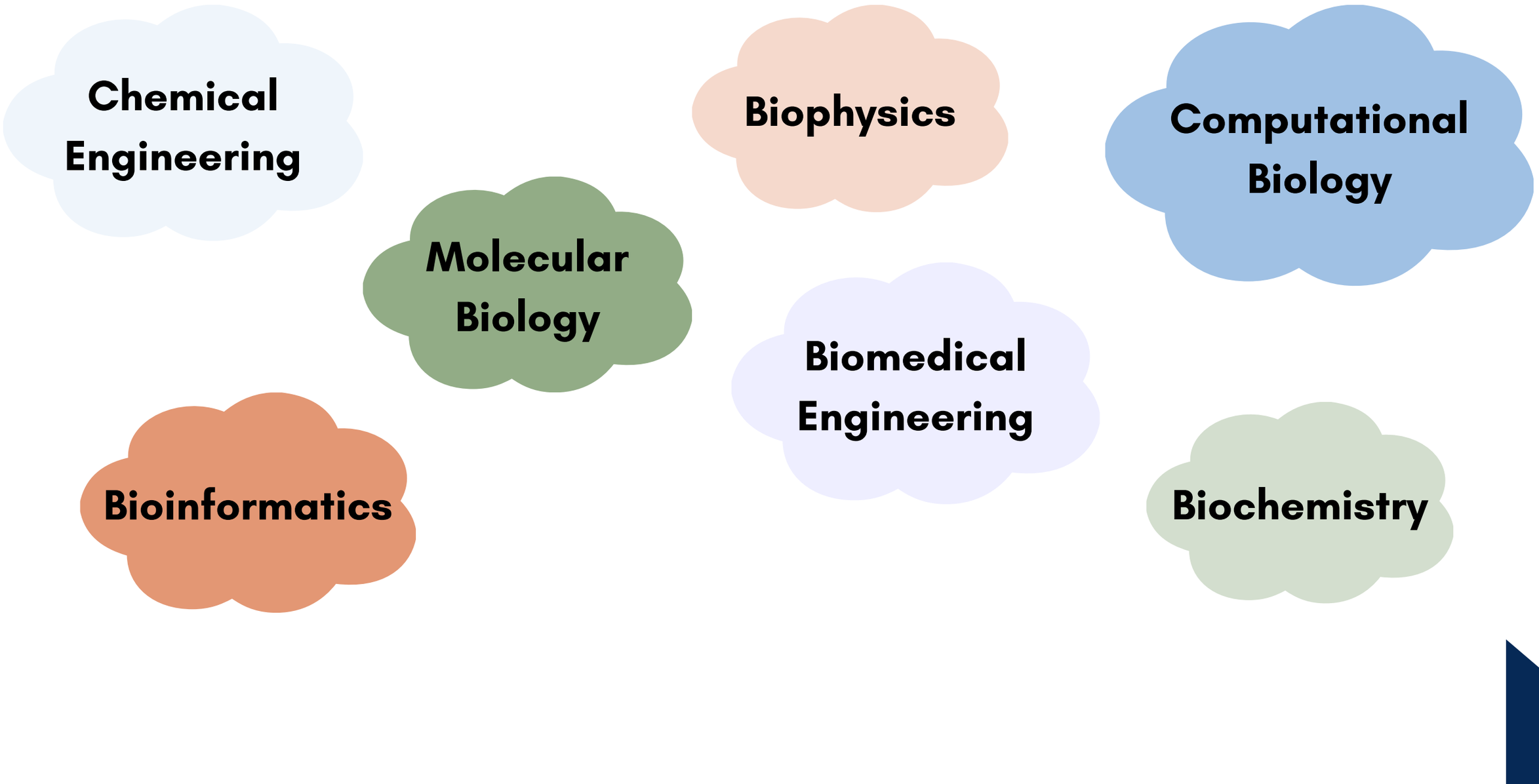
The synthetic biology ecosystem is established with a multitude of disciplines. More often, biotechnology companies will harness synthetic biology techniques for bigger purposes such as developing novel therapeutics or scaling the production of desired biological compounds. In other words, they are not often branded as a “synthetic biology” company. Instead, they can be **pharmaceutical corporations**, **biotechnology start-ups**, and even **robotics companies**.

In essence, you can be a molecular biologist operating wet lab experiments, working with agar plates and bacteria. You can also be a computer scientist, using modern genetic engineering tools and 3D modelling software to predict molecular docking and reaction kinetics.

We provide further details on companies that started as iGEM teams in *Chapter 6*. It specifically highlights two UK companies **Colorifix** and **BentoLab**, which started in **University of Cambridge** and **University College London (UCL)** respectively.

Relevant degrees

If you are thinking of stepping into the world of synthetic biology, you may consider the following degrees that are commonly provided by universities at an undergraduate level.



Relevant courses in UK universities

Based on the six authoring universities, the following **undergraduate degrees** and **relevant modules** are worth a look if you are interested in what synthetic biology offers.

University	Undergraduate Course	Relevant Modules	A-Levels Requirements
King's College London	Molecular Genetics	Molecular Basis of Gene Expressions	AAA, with grade A in Biology and Chemistry
		Protein Structure & Design	
	Biomedical Engineering	Mechanics for Biomedical Engineering	AAB, with grade A in Mathematics and grade B in one from Biology, Chemistry, Computer Science, Further Mathematics or Physics.
		Synthetic Anatomy	
		Biomechanics & Neurorehabilitation	
University of Warwick	Biomedical Science	Virology	AAB, including Biology and another Science
		Synthetic Biology	
	Biomedical Systems Engineering	Medical Device Design	AAA, with grade A in Mathematics and Physics
		Biomechanics	
University of Cambridge	Natural Sciences	Cell and Developmental Biology	A*A*A, usually including Mathematics and two other Sciences
		Mathematical and Computational Biology	
University of Oxford	Biochemistry (Molecular and Cellular)	Cellular Biochemistry	A*AA, including Chemistry and another Science or Mathematics
		Physical Biochemistry	
	Biomedical Sciences	Genes and Molecules	A*AA, including two from Biology, Chemistry, Mathematics, and Physics
		Intra- and Intercellular Signalling	
University of Edinburgh	Biological Sciences (Biotechnology)	The Microbial World	AAA-ABB, including Biology and Chemistry, both at B or above
		Biotechnology	
		Molecular and Synthetic Plant Biology	
University of Exeter	Biochemistry	Advanced Microbiology	AAB-ABB, including Biology and Chemistry, both at B or above
		Organic Synthesis and Drug Design	
	Biological and Medicinal Chemistry	Horizons of Biochemical Research	
		Frontiers in Molecular Cell Biology	

Table 1 Detailed table displaying relevant undergraduate degrees and modules

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Chapter 2 : Basic Principles of Synthetic Biology

2.1 DNA, genes, and genetic engineering

What is DNA?

Deoxyribonucleic acid (DNA) is a polymer composed of two polynucleotide chains that coil around each other to form a double helix. DNA is tightly packed into the nucleus of cells and carries **genetic instructions** for development, function, growth and reproduction. In bacteria, DNA can also be stored in a circular fashion as **plasmids** that are separate from the normal genome but are still transcribed like native DNA.

What is a gene?

A gene is a **segment of DNA** containing coding and non-coding regions, many genes act as a blueprint to code for one specific protein (although there are some exceptions). There are anywhere from 500-7500 genes in bacteria and over 20,000 in human cells. Genes play an important role in encoding everything from our **cellular inner-workings** to even the **colour of our eyes**.

Fun fact!

Genetic engineering has been used to create a **green fluorescent cat**.

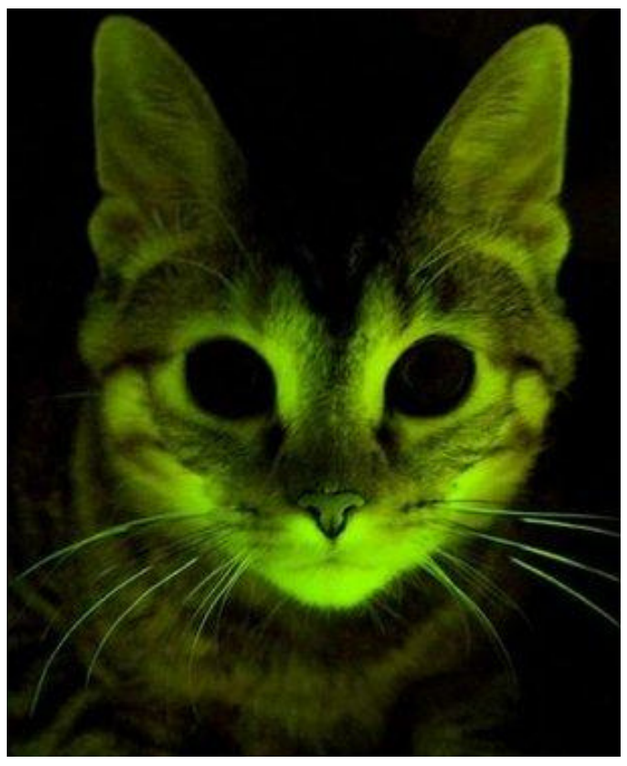

Fig 2.1 Green fluorescent cat

What is genetic engineering?

Genetic engineering is the **modification and manipulation of DNA** using technology. It is commonly used to alter the genetic makeup of an organism which, in turn, will impact its functions. This may involve changing a single base pair, deleting or adding a new segment of DNA. Common examples of genetic engineering in our day-to-day lives are genetically modified fruit and vegetables, to produce higher yield or nutrition. There is a guideline that must be followed when using this technology– an incorrect application can cause damage to the ecosystem and even the safety of human life.

2.2 Techniques and software: From PCR to CRISPR-Cas9

What is PCR?

Polymerase Chain Reaction (PCR) is a technique involving short synthetic DNA fragments called **primers** that select a complementary segment of the genome and **amplify that segment over many cycles**.

Primers provide a starting point for DNA polymerase enzymes to start DNA synthesis. Put simply, a high temperature (95°C) separates the double strands, then the temperature is lowered so that primers can bind. A final temperature change to 72°C allows the DNA polymerase to make an exact copy of the DNA strand.

This cycle of **denaturation**, **primer annealing** and **extension of product** usually repeats for 20-40 cycles to secure a large amount of product. PCR machines can automate temperature, time and other factors. This lowers the chance of primers accidentally binding elsewhere at an inaccurate temperature, or the polymerase enzymes failing to synthesise all of the DNA.

Sequencing

Sequencing is a technique used to read DNA and precisely **determine the order of nucleotides** (A,T,C,G) that make it up. It is crucial to see whether there are mutations in the DNA, since even a single base misplacement may impact the function of proteins.

Fun fact!

Sequencing equipment can range from the size of a **fridge** to the size of your **phone**.

Fig 2.2 MinION PCR machine

The most used method of DNA sequencing is **next-generation sequencing**. DNA is replicated and cut into clusters. Each base has a **unique light signal**; this helps to read each individual nucleotide, and a full sequence is eventually revealed. Normally, we send off DNA to be sequenced at a lab with specialised equipment.

Transformation

Transformation is the process of **inserting external DNA** (often a desired plasmid) into a cell. This gives you the power to **add a completely new pathway or function** to the cell that is not originally coded for in its native genome.

Transformation requires specific cells called **competent cells** - these cells are special as they can withstand the stressful transformation conditions and are viable to take up the plasmid. There are two common methods: **heat shock** (high temperature) and **electroporation** (high voltage) that both require their own unique competent cells.

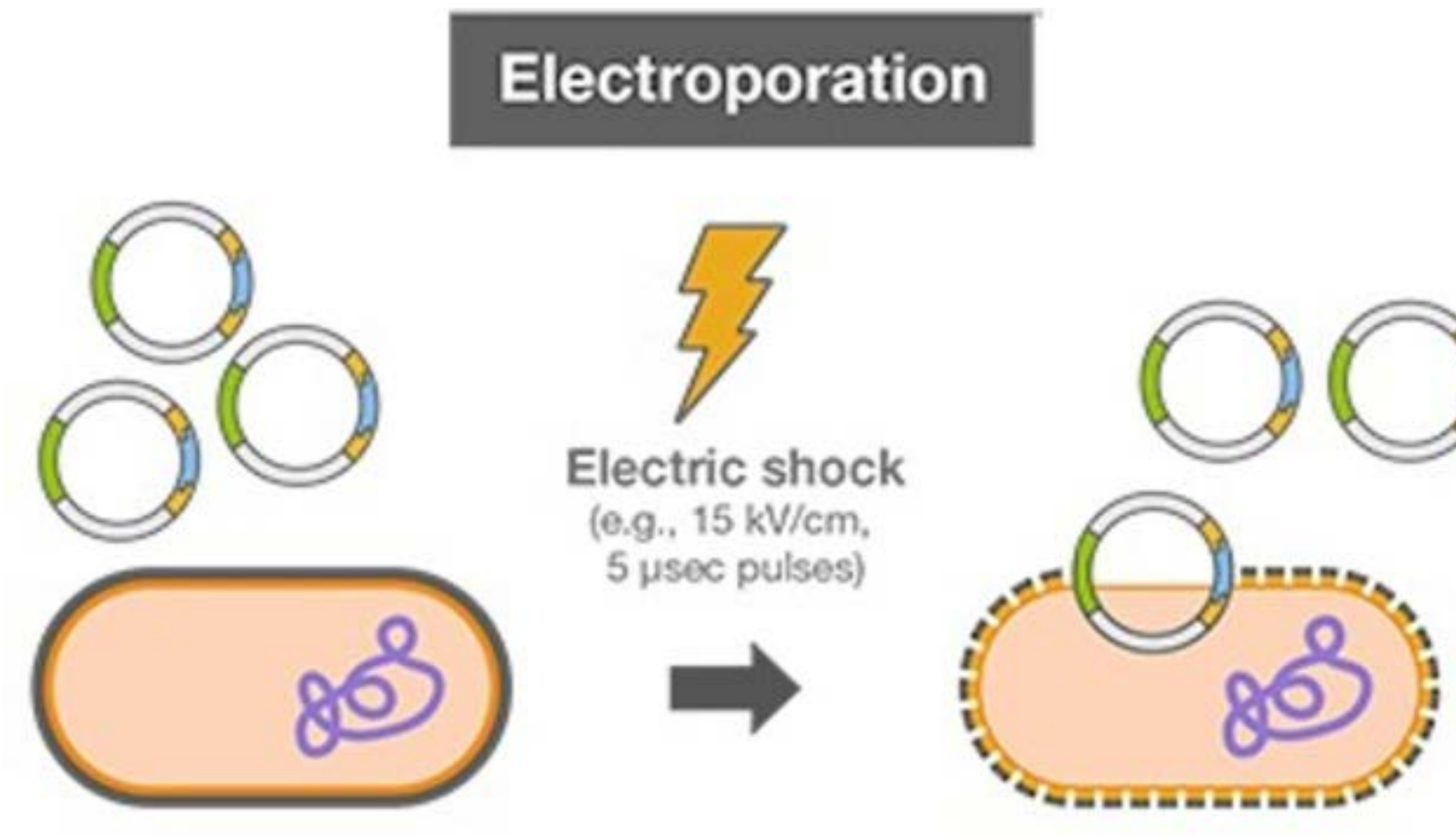

Fig 2.3 Schematic of electroporation transformation

Heat shock transformation takes competent cells with plasmid in a solution that have been kept on ice and immediately plunging them into a 42°C water bath for 30 seconds. This **instantaneous temperature** change fluctuates membrane fluidity and forms pores in the cell membrane, which allows plasmids to move into the cell. The, the cells are put in growth media and shaken for recuperation and time to express any antibiotic resistance genes.

Electroporation achieves a similar goal by utilising a high voltage (>50V). In a special electroporation cuvette, suddenly **zapping** the competent cell and plasmid mixture forms pores in the cell membrane, allowing free plasmids to move into the cells. Just like heat shock, growth media is then added, and the cells are incubated for 45 minutes before being grown on a plate.

CRISPR-Cas9 genetic editing

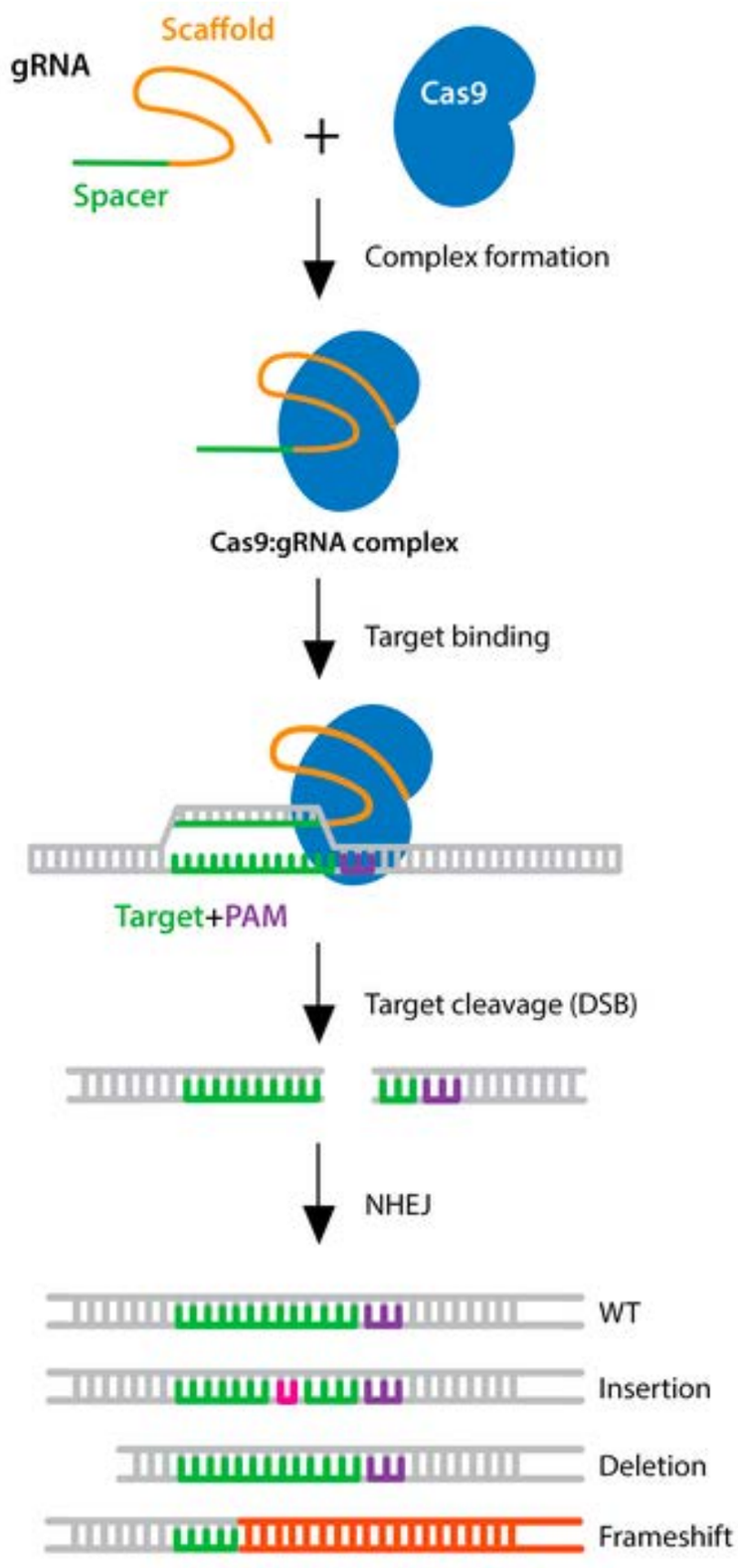

Fig 2.4 CRISPR-Cas9 gene editing system

CRISPR-Cas9 is a more recent technology developed using mechanisms that were **first found in a bacterial defence system** used against viruses, this technique enables us to make changes to DNA by **cutting at desired locations**. Clustered regularly interspaced short palindromic repeat (CRISPR) sequences found in the bacterial genome are transcribed to RNA upon viral infection.

This system is made of two key components: a **guide RNA (gRNA)** uses a large scaffold sequence to find and bind to a specific region in the DNA that it is complementary to. The 20bp pre-designed sequence on the gRNA then guides the **Cas9 enzyme**, which acts a “pair of scissors" and cuts both strands of DNA at specific locations. This allows DNA to be inserted or removed in between the cuts.

Gibson cloning

Gibson cloning is a procedure that allows us to **clone two or more fragments together** and doesn’t rely on compatible restriction sites being present – it instead uses overlapping ends.

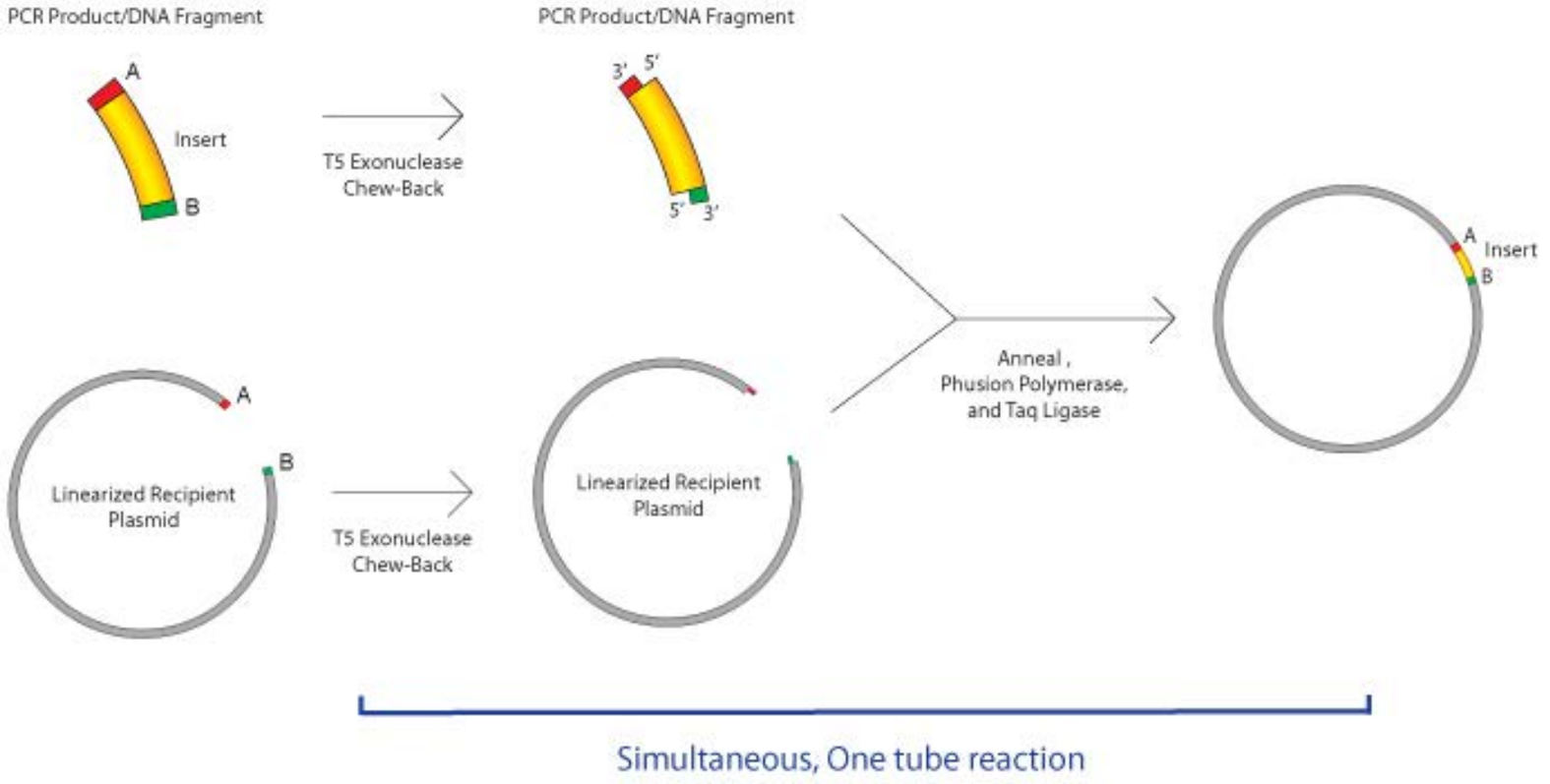

Fig 2.5 Gibson cloning technique

Gibson cloning

First, the recipient plasmid is cut open using two restriction enzymes and linearised while the insert is amplified by PCR. The insert and plasmid share 30 base pairs of **overlaps** on either side that are made into single stranded overhangs by an **exonuclease**. Incubating at 50°C gives the insert and plasmid the time to anneal with their complementary ends, and a **ligase** is used to fully seal it up. A weakness of Gibson assembly is frequent repeats in the overlap sequence, at which point Golden gate cloning may be favoured.

Golden gate cloning

Normal enzymes will recognise a palindromic sequence and cut within it. Golden gate cloning uses **type IIs restriction enzymes** that cut outside of their recognition sequence, therefore they can cut DNA fragments and form roughly 4bp overlapping ends. This unique property allows us to anneal these overlapping sequences together to form a complete plasmid in one reaction. The DNA fragments must be multiplied via PCR just like Gibson cloning.

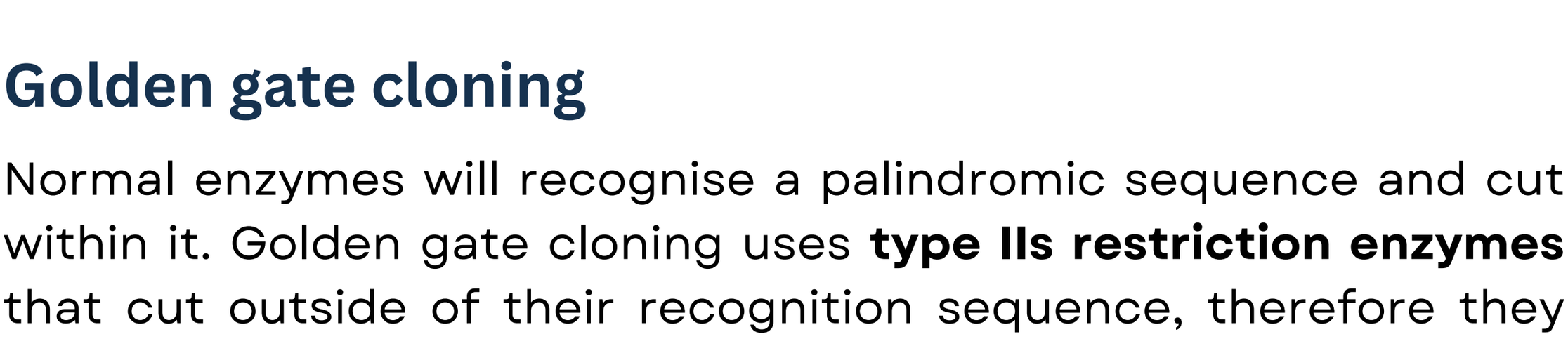

Fig 2.6 Golden gate cloning schematic

Fun fact!

PCR was used to find a **teddy bear thief!**

Because of the unique cutting method, you must ensure that the recognition sites are oriented correctly and only the sites required are present in the plasmid and insert. Gibson is very effective at assembling multiple fragments even if sequence repetitions are present – provided all the sequences contain restriction sites in the correct place.

2.3 BioBricks and standardised genetic elements

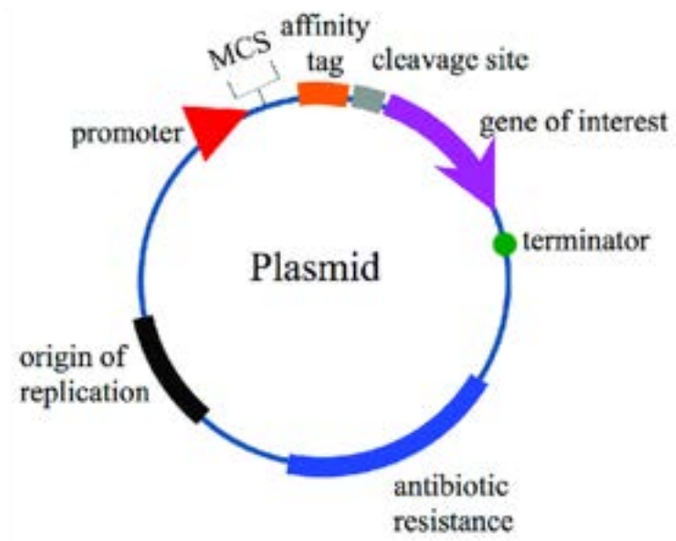

Fig 2.7 Schematic plasmid map showing the major features present in common expression vectors.

What are BioBricks?

BioBricks are like DNA lego, they contain a specific DNA sequence and easily click together through complementary “sticky” ends of DNA, which are small single stranded overhangs made by cutting using a restriction enzyme. Gibson assembly can easily join multiple BioBrick simultaneously, resulting in a fully formed plasmid containing the BioBrick sequences joined to the backbone. BioBricks can contain things as simple as terminators or binding sites, or more complicated coding sequences.

iGEM also has a **Registry of Standard Biological Parts**. This is a repository of many different parts that different teams and labs submit in a specific pSB1C3 plasmid backbone, with a specific BioBrick prefix and suffix. BioBricks have a level of standardisation in their “backbone”. For example, BioBrick parts must have a common antibiotic resistance marker such as ampicillin or kanamycin. These genes specifically means the modified organism gains resistance to the specific antibiotics and makes testing for its presence quite easy.

Genetic element – promoters

The promoter is a small specific region of DNA upstream of the coding region where RNA polymerase (and transcription factors) will bind to **initiate transcription into mRNA**. Promoters can range from 100-1000 bases long. Without a promoter (or with a dysfunctional promoter sequence), the enzymes cannot tell where to bind to start transcribing mRNA.

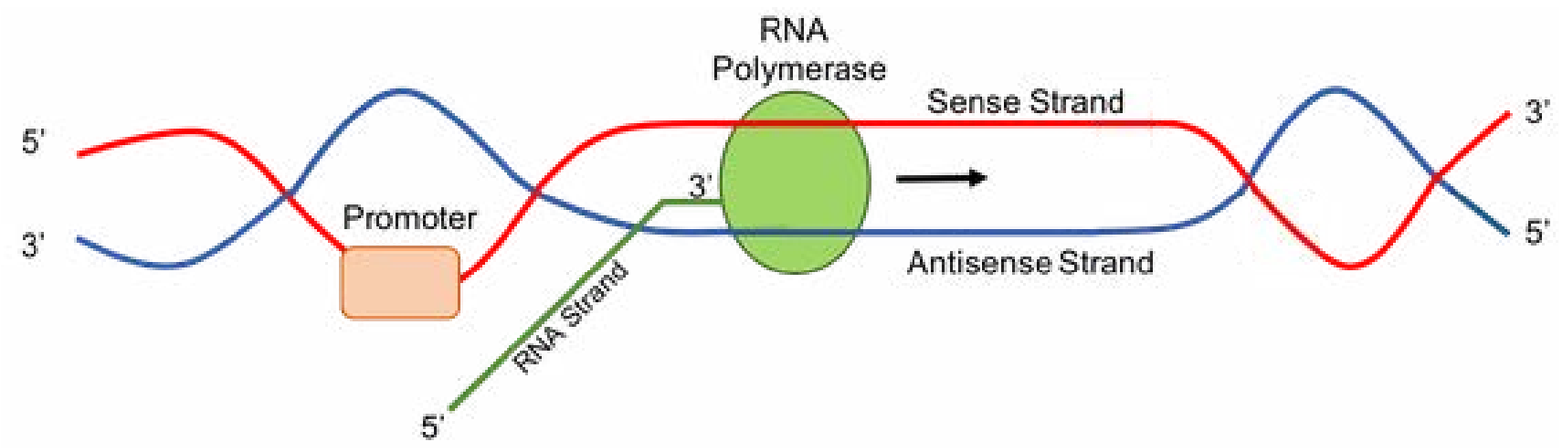

Fig 2.8 Schematic displaying promoters in process of transcription

Genetic element – origin of replication

The origin of replication (ori) is found in every plasmid (as well as in chromosomes) and is **where DNA replication begins**. Due to its circular structure, the plasmid can have many polymerases going around at the same time, all starting from the ori. The ori can determine the amount of copies of this specific plasmid that can exist within the cell - known as the **copy number**. The ori also acts as barcode for the plasmid so they cell can recognise that it is there. Having two plasmids with the same ori is bad, because it means they will compete for the cellular machinery.

Genetic element – RBS

The ribosome binding site (RBS) is found just before the start codon in mRNA. It is known as the **Shine-Dalgarno sequence** in prokaryotes and the **Kozak sequence** in eukaryotes. Here, the ribosome components can bind and form its 70S or 80S complex for prokaryotes or eukaryotes respectively. The fully assembled ribosome can then translate the mRNA sequence into a protein. Ribosome reads the mRNA sequence and adds amino acids using tRNAs.

Genetic element – terminator

The terminators quite simply tell translation to stop. Usually, an mRNA codon tells the ribosome to add a specific amino acid anticodon to the product; however, the stop codon tells it to add water instead. This causes the translated protein and thus the ribosome to dissociate from the strand.

In prokaryotes there are two types of termination. **Rho-dependent terminators**, where a helicase protein – rho factor is involved in the disruption of mRNA-DNA-RNA polymerase transcriptional complexes which are downstream of the stop codon. **Rho-independent terminators**, instead of binding of a protein, mRNA-DNA-RNA polymerase transcriptional complex is disrupted by self annealing hairpin, a physically modified RNA structure.

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Chapter 3: Application of Synthetic Biology

3.1 Agriculture and food production

Meat production

Cultured meat, an innovative concept in biotechnology and food science, offers a sustainable solution to issues in traditional meat production like ethical concerns, dietary problems, food-borne illnesses, and methane emissions. Creation of large-scale cultured meat offers a possible solution, and cutting-edge technologies like 3D/4D bio-printing, biophotonics, and cloning are under active investigation to enable this. However, before **commercialisation**, cultured meat must overcome societal and regulatory hurdles, with the primary obstacles being **high production costs** and **consumer acceptance**. Nonetheless, it is viewed as a crucial long-term solution to meet the growing demand for meat sustainably.

Crop production

In crop production, a significant portion of global land is used for farming, leading to problems in biodiversity and soil depletion. Synthetic biology can help **create nutrient-rich crops** and **enhance characteristics** like heat tolerance and disease resistance without introducing new elements. Ongoing advances offers hope for efficient ways to feed the growing global population while addressing ethical and environmental concerns.

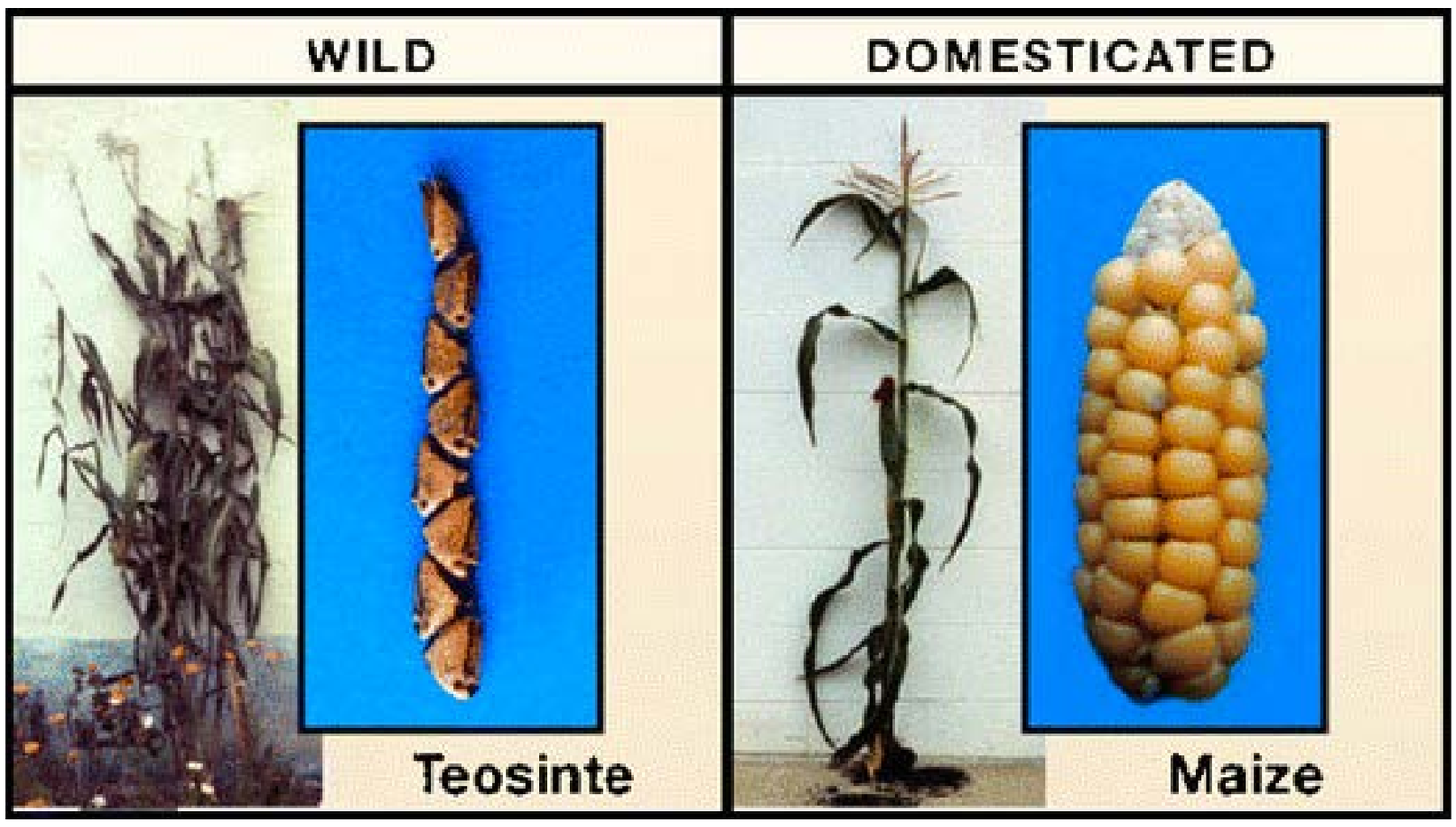

Fig 3.1 Wild and domesticated maize

Soil engineering

An annual loss of 24 billion tons of fertile soil poses severe threats to ecosystems and agriculture. Soil microorganisms, particularly **Plant Growth-Promoting Rhizobacteria (PGPR)**, **nitrogen-fixing bacteria**, and **mycorrhizal fungi**, have shown potential for restoring land, enhancing soil properties, and combating hydrophobicity. **Synthetic microbial communities** offer innovative solutions by reshaping soil microbial structures, thereby increasing microorganism survival rates and improving soil remediation efforts, with applications extending to **plant disease resistance** and overall **soil health enhancement**.

Fig 3.2 A spectrum of soil diversity

Fig 3.3 The roots of nitrogen-fixing plants

3.2 Healthcare and medicine

iPSCs and smart cells

Synthetic biology is at the forefront of developing **induced pluripotent stem cells (iPSCs)** from regular adult cells, offering versatile applications in medical research. iPSCs allow for the creation of disease-specific cell lines for drug testing, can be transformed into various cell types for therapies, and they hold promise for addressing age-related concerns and treating conditions like brain injuries and severe heart problems. Advances in synthetic biology have also led to therapeutic human cells.

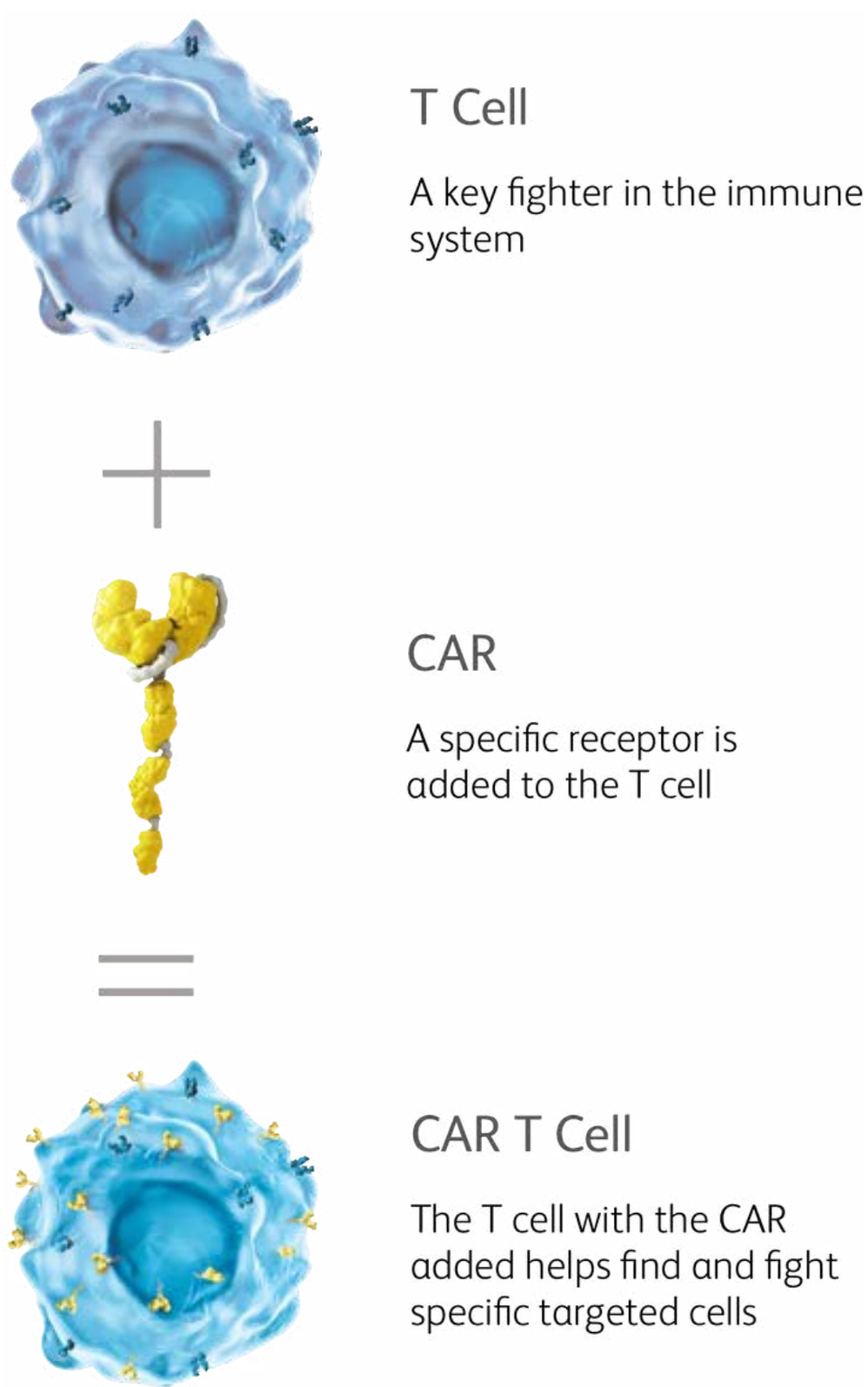

Fig 3.4 Simple schematic describing CAR T cell therapy

CAR T-cell therapy is transforming cancer treatment by utilising genetically enhanced T cells to precisely target cancer cells, achieving remarkable success in the treatment of leukaemia and lymphoma, often resulting in complete cancer elimination. Despite challenges such as high costs, CAR T-cell therapy has become a standard and crucial component of modern cancer care, particularly for patients with aggressive lymphoma.

Tissue engineering

Tissue engineering repairs damaged tissues, while synthetic biology improves it by controlling cell behaviour with artificial genetic tools. Smart genetic systems like CRISPR/Cas9 switches and synthetic mRNAs help precisely turn genes on and off. Genetic circuits like the **Tet system** sense molecules on cell surfaces. **Optogenetics**, using light to control cells, is another advanced technology. Synthetic biology enhances tissue engineering and paves the way for advanced treatments.

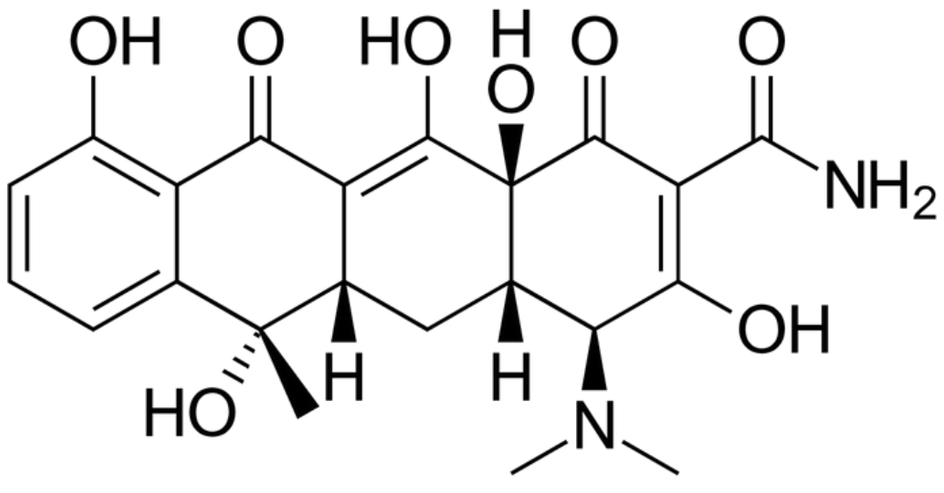

Fig 3.5 Tetracyline, by which its administration act on target promoters

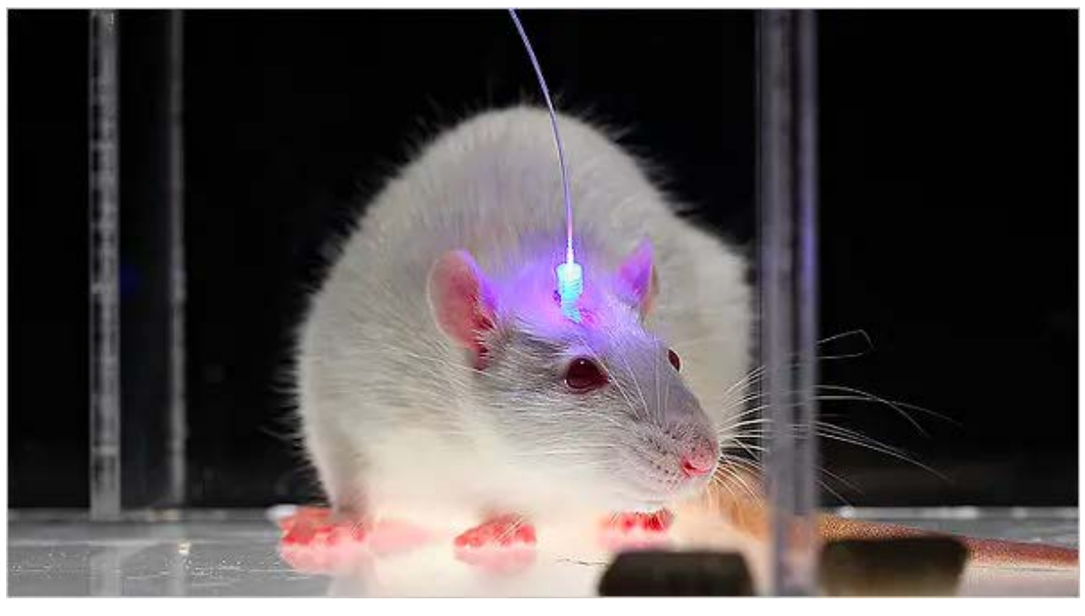

Fig 3.6 Optogenetics, by which researchers can engineer neurons to express opsin genes

Vaccine development

Synthetic biology is transforming vaccine development. It offers innovative approaches like **genomic codon deoptimisation**, **DNA-based**, and **RNA-based vaccines** for diseases. These methods enhance vaccine stability, antigen expression, and immunogenicity. Clinical trials of mRNA vaccines utilising synthetic biology techniques have shown promise, speeding up vaccine creation and bolstering our defences against infectious diseases.

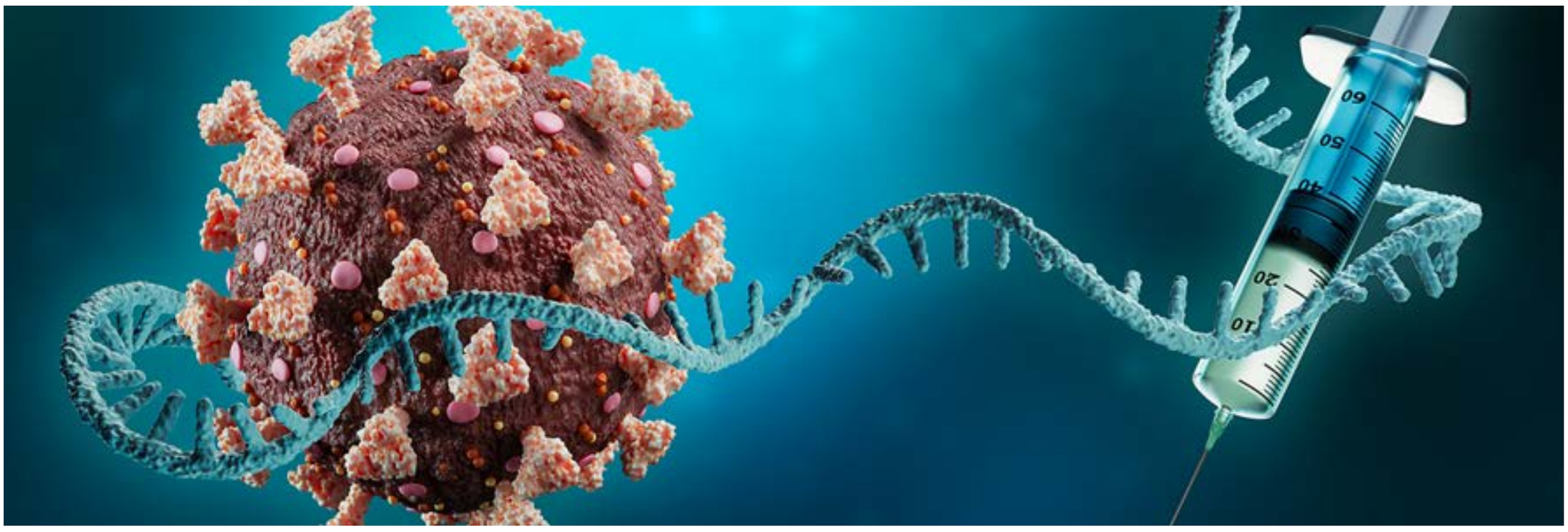

Fig 3.7 Artistic visualisation of mRNA-based vaccines

3.3 Environment and sustainability

Biosensors

The World Health Organisation sounded the alarm in 2012, reporting that 12.6 million lives were lost due to unhealthy environments, representing nearly a quarter of global deaths. In some developing countries, **pollution in the soil** is a big problem due to poor controls and practices. Certain bacteria can **create conductive biofilms** and are used in devices called **microbial fuel cells (MFCs)** that produce electricity while breaking down pollutants in wastewater. MFCs can be used to make biosensors for **detecting pollutants** like p-nitrophenol, atrazine, formaldehyde, and copper.

Bioremediation

Synthetic biology is advancing bioremediation, mainly in microbial systems, and explores potential applications in more complex organisms like plants. Efforts against **mercury contamination** include mercury biosensors and engineered bacteria. An innovative study **integrated mercury-absorbing nanofibers into E. coli**, creating on-demand biofilm materials for **heavy-metal absorption**. Challenges include E. coli's mercury sensitivity and the need for resistant microbes. In addressing plastic pollution, enzymes like PET hydrolase and MHET hydrolase show promise, but research is ongoing for other plastic polymers.

Carbon sequestration

To combat rising CO_2 levels, various methods like physical, chemical, and biological CO_2 sequestration have been explored. Among various methods, **biological CO_2 fixation** stands out as an energy-efficient and eco-friendly solution. Microbes like bacteria, with their ability to synthesise valuable biomaterials from CO2, are at the forefront of this approach. Optimisation of CO_2 fixation pathways in microbes, including the **Calvin-Benson-Bassham (CBB) cycle** is a promising strategy.

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Chapter 4: Biosecurity and Ethics in Synthetic Biology

4.1 Hazards and risks in a biology lab

Hazards in a biology lab

As we delve deeper into the realm of designing and engineering living organisms, the first thing to be aware of is the safety of yourself and the people around you. To do so, you need to be able to identify, prevent, and deal with the potential hazards and risks associated with working in a biology lab.

What are hazards?

Definitions

Hazards = the entity that has the ability to cause harm or damage to people, property, or the environment.

Risks = the likelihood of that harm or damage (hazard) being realised.

Note that, while one can easily confuse these two related concepts, it is important to distinguish them.

Hazards are the entity that has the ability to cause harm or damage to people, property, or the environment, which can be a phenomenon, substance, human activity or condition. Hazards are a crucial concept in safety and risk management, as mitigating them is essential for preventing accidents and minimizing harm.

Fig 4.1 Chemical reagents with hazard labelling (left), Bunsen burner (middle), and gel electrophoresis image of radioactively labelled DNA fragments obtained under UV radiation (left), exemplifying chemical, physical, and radiation hazards in a biology lab, respectively.

Potential hazard categories

- **Chemical Hazards**: Chemical reagents are commonly used in biological experiments for tasks like DNA extraction, cell culture, and protein purification. Examples include liquid nitrogen (extremely cold), acids, corrosive chemicals, mutagens/carcinogens, heavy metals, or explosives.
- **Physical Hazards**: Lab equipment such as glassware, microscopes, centrifuges, Bunsen burners, and autoclaves can pose physical hazards if not used correctly. For example, some can cause fire and some have sharp edges.
- **Radiation Hazards**: Experiments that require imaging may involve the use of radiation sources like UV light. It's important to understand the risks associated with radiation exposure and take appropriate precautions.
- **Biological Hazards**: You should be aware of potential risks associated with the biological agents you are working with, including the potential for infection or contamination.

Health and safety signs

The colours of the signs are indications of the nature of the information the signs convey.

Red means prohibition;
yellow means warning;
blue means mandatory;
green means safe condition.

Try it out!

Can you categorise them into the 4 types of hazards (chemical, physical, radiation, biological) seen in a lab?

Fig 4.2 Health and safety signs

Story time!

Pasteur Institute (Paris, France) 1980s – 10 Deaths

The lab was working with early cDNA technology and was trying to express myb oncogenes. For unclear reasons – it could be their insufficient occupational hygiene or their containment measures, or, more likely, it could be their incorrect supposition that the expressed DNAs could not be harmful – 10 lab researchers **died from blood tumours** in the following few years. This incident demonstrates the importance of obtaining a correct understanding of the nature of materials one is working with.

Western General Hospital (Edinburgh, UK) 1999 – 1 Death

The lab required working with liquid nitrogen to keep samples frozen. On the day of the incident, the low oxygen alarm in the basement where liquid nitrogen tanks were placed was triggered first by an unapproved procedure carried out by two other lab members to speed up the process of filling storage vessels. The alarm was then switched off before the lab member went down alone to the basement, performing another speedy yet unapproved procedure to fill storage vessels. The oxygen level continued to drop without alarms, causing the lab member to **lose consciousness**, while the hoses kept pumping liquid nitrogen from tanks into storage vessels so that the gas overflooded and covered the entire facility for a couple of centimetres deep.

When the leakage was finally noticed after some time, several lab members tried rescuing the unconscious person, who **died from asphyxiation**, and got severely injured themselves as well. This incident covers several principles in biosafety measures – one should always observe instructions and safety procedures in place (they may be less efficient but are there for a reason) and ensure warning alarms are functional and switched on.

Biological safety level (BSL)

Biology laboratories are classified into four corresponding Safety Levels – Biological Safety Level (BSL) 1, 2, 3, and 4 – based on the level of containment (prevention or control of exposure of workers and the environment to the agents) attainable.

Safety Level	Pathogenicity	Transmissivity	Treatment/ Prophylaxis	Example	Working Space
1	Unlikely to cause disease	No	N/A	Lab strains of E.coli, yeasts, algae	Open bench
2	May cause disease	Likely	Usually available	S.aureus, Herpes virus, most mammalian cell lines	Biosafety cabinet
3	May cause severe disease	Presents risk	May be available	Dengue virus, HIV, HepB/C, SARS-1 virus	Class 3 biosafety cabinet
4	Known to cause disease	High risk	Usually none	Ebola, Variola, Lassa, Marburg	Full isolation suits

Table 2 Risk groups and biological safety levels

Fig 4.3 Laboratories of different Biological Safety Levels – BSL1 Lab (top left), BSL2 Lab (top right), BSL3 Lab (bottom left), and BSL4 Lab (bottom right).

Managing risks

Remember, all biological lab work, even simple experiments, carries some risk to the experimenter, and lab safety is everyone's responsibility. By being vigilant and following safety guidelines, you can enjoy your experiments in synthetic biology while minimizing risks.

Test yourself!

What do you think Peter and Rose are doing wrong in the lab in terms of biosafety measures? There are **15 things** captured in this picture. Try to spot as many as possible yourself before checking the answers!

Fig 4.4 iGEM Responsibility Safety Quiz

Answers

The boy's coat is open (**#1**), and the girl has the sleeves coiled (**#2**). A spill on the bench (**#3**), a centrifuge open with a spill on the rotor (**#4**), open Eppendorf tubes with bacterial cultures (**#5**), an opened petri dish (**#6**). Clean spills at once to prevent further contamination. Coffee on the bench is not allowed (**#7**). Don't apply cosmetics or contact lenses, and don't use smartphones/laptops (**#8**). Before leaving the lab, one should wash their hands with soap and refill a nearly empty soap dispenser (**#9**). Don't have lab journals on the working bench (**#10**). Paperwork hanging on the wall (**#11**) needs protection from contamination. Don't block the air vents (**#12**) with glassware or boxes. When pipetting the pipet with tip is kept within the cabinet (**#13**). Sending biological material needs specific packaging. Beware of spills and contamination (**#14**)! Plants are allowed in the lab when they are part of an experiment and housed properly. Don't keep flowering plants (**#15**) in this way!

4.2 Prevention of misconduct with biosecurity practices and policies

Understanding biosecurity

Over the past two decades, the rate of development and research in synthetic biology has increased for both industry and academia. However, with the promising prospect synthetic biology has revealed, also comes the **raised concern of how its technology can be adapted for malicious purposes** to harm people, organisms, environments, or nations.

Indeed, **35 cases of biological weapons deployment** between 1970 and 2014 have already been confirmed, and the future development in synthetic biology will only enable the creation and modification of biological weapons, calling for the need for biosecurity practices.

There are two requirements for malevolent dual-use or negligent misuse of synthetic biology technology by any party.

Firstly, one has to **obtain and understand the information and techniques**, and, secondly, one has to be able to **use such knowledge and tools to reproduce the technology**. As the second is hard to enforce control, biosecurity practices and policies in synthetic biology, therefore, focus on the first, involving measures to protect biological materials, data, and information from theft, misuse, or unauthorized access.

Additionally, it also involves **preventative actions** such as developing screening mechanisms for malicious uses, as well as **proactive assessment** and identification of how, by whom, and to whom a synthetic biology technology can be deployed for ill intentions.

Dual-use research

Dual-use research refers to **scientific studies that have the potential for both beneficial and harmful applications**, and many related to synthetic biology fall into this category. Let's explore an easy example of how synthetic biology can be used for harmful purposes in depth.

Say you are a microbiologist working with **pathogenic bacteria**. Your research focuses on a newly arisen and slowly spreading strain of bacteria that can be very deadly yet is not very virulent. To figure out the mechanisms of the bacteria attacking healthy human cells and establish the disease model - knowledge crucial for treatments and vaccine development - you have to make the bacteria more virulent so that it is easier to observe and study how they interact with healthy human cells, evades the immune system, and causes severe symptoms or even death. This step would require synthetic biology to introduce a virulence factor into the bacteria.

Can you see how this resultant genetically engineered new strain of bacteria with its original trait of high host mortality and introduced trait of high virulence combined **could be a potential threat?** Within the hands of righteous scientists in the research labs, this strain can be beneficial for promoting understanding and facilitating treatment/vaccine development, but, once this strain - or even just the detailed information of how to make this strain - falls into the hands of the biohackers or bioterrorists, the bacteria can be released into the community, bringing forward the next pandemic with their enhanced transmissivity.

If you look at the width of different fields synthetic biology applications have penetrated, you will see how much synthetic biology technology has enlarged the dual-use threat space. The presence of dual-use research is like **yin-yang**, the **benefits and the dangers co-existing and inseparable**. Ultimately, synthetic biology is just a **tool**, albeit one with great power, and it will be up to us humans to determine how we will use its potential.

Vaccines and Therapeutics

- **Beneficial Use**: Attenuated designer viruses can be used as transportation vessels for gene therapy or vaccines. They target specific cells, but they are not supposed to replicate as normal, unattenuated viruses do.
- **Harmful Use**: The designer viruses can be used to transport and deliver materials that are not for therapeutics or vaccines but, instead, disease-causing genes (e.g. oncogene). If the designer viruses are not even attenuated, they can easily cause widespread disease outbreaks.

Diagnostics

- **Beneficial Use**: Biosensors can be used for early disease detection or monitoring environmental conditions by sensing the presence/absence of specific small molecules and giving corresponding indications (usually a change in colour, fluorescence, or electrostatics).
- **Harmful Use**: In the wrong hands, biosensors could be used to develop bioweapons capable of detecting specific individuals or sub-populations, thus enabling precision targeting and attacking.

Environmental Remediation

- **Beneficial Use**: Engineered bacteria can be used for cleaning up oil spills or environmental pollutants, such as heavy metals and microplastics.
- **Harmful Use**: These same engineered bacteria may also be able to disintegrate/absorb materials that could be essential components of ecosystems or properties and commodities.

Food Production

- **Beneficial Use**: Crops can be improved to promote their growth, increase their production, or enhance their environmental tolerance so they can survive better and across wider areas. This could increase food production, reduce hunger and malnutrition, and benefit global food security.
- **Harmful Use**: The same technology can be used on weeds instead of crops. The weeds can be made more productive and adaptable, thus increasing their invasiveness and competitiveness.

Industry

- **Beneficial Use**: Microorganisms can be engineered to act as a “factory,” manufacturing certain products (drugs, biofuels, silk/leather alternatives, etc.) in bulk.
- **Harmful Use**: The same microorganisms can be manipulated to produce harmful toxins or other more dangerous chemicals that could be used in acts of bioterrorism.

Reference Answers

Food Production

Environmental Remediation

Diagnostics

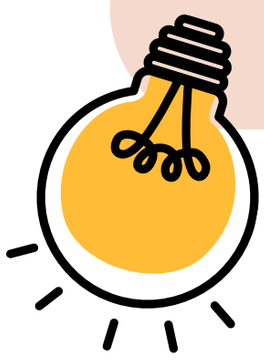
Industry

Vaccines and Therapeutics

Think and discuss!

You are given some applications of synthetic biology and challenged to think about what they can be potentially exploited to do for malicious purposes.

Discuss them with your friends!



4.3 Ethical Considerations in Synthetic Biology

Biodiversity and environmental impact

With the promising prospect synthetic biology has revealed, also comes the **raised concern of how its technology can be adapted for malicious purposes** to harm people, organisms, environments, or nations.

When engineered organisms are **put into real-life usages**, you must break the containment and expose the natural environment and ecosystem to them, calling for your acute awareness of the potential consequences. For example, **genetically modified mosquitoes** are released into the environment to combat diseases that use mosquitoes as dissemination vectors. However, what will these newly introduced modified mosquitoes do to the local ecosystem? Would they affect the survival and proliferation of other non-target species? Another example can be **oil-cleaning bacteria** for removing oil spillage in the ocean. Could the bacteria pose potential harm to marine, disrupting the ecosystem and reducing the biodiversity?

Fig 4.5 Exemplification of GM mosquito

Fig 4.6 Exemplification of oil-containing ocean

The ethical duty of scientists is centred on minimising any unintended ecological disruptions and striving for harmony with the natural environment. It is thus essential to conduct rigorous risk assessments and consider long-term environmental and ecological implications when deploying synthetic organisms.

Human genetic engineering

While synthetic biology technology on humans has the potential to revolutionise healthcare by preventing and treating traditionally incurable genetic disorders, it also raises complex ethical questions that demand our careful consideration.

Ethical dilemmas often surround the concept of "designer babies." Think about it, if genetic traits are chosen and modified for non-medical reasons, such as eye colour or intelligence, **would it actually make a better and happier world?** We must grapple with questions of fairness, equity, and the potential for genetic discrimination.

Interestingly, this moral debate was already portrayed in an old movie **Gattaca** (1997, directed by Andrew Niccol) well before the famous gene-editing technology CRISPR-based system was invented.

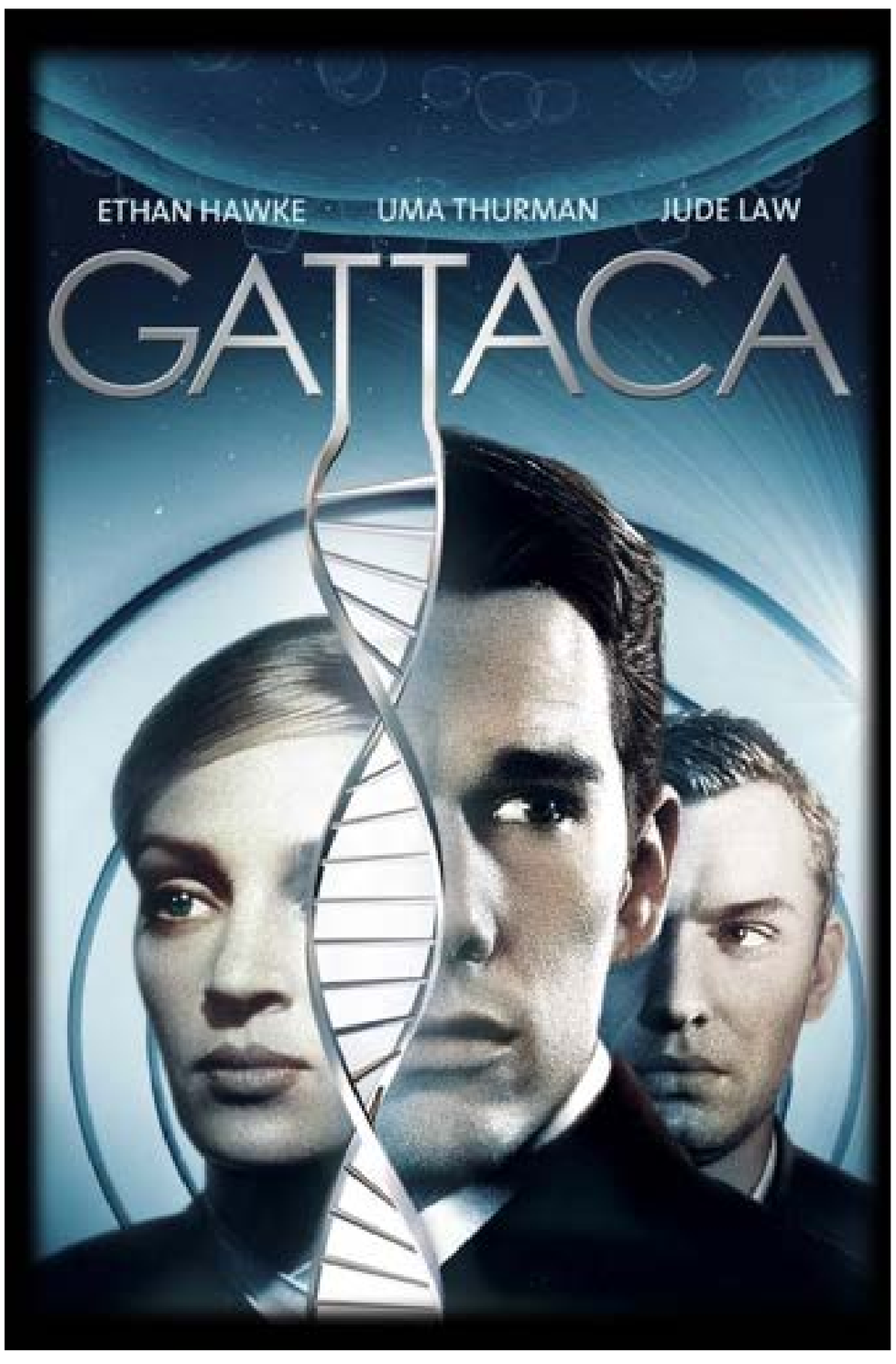


Fig 4.7 Poster of the movie Gattaca (1997)

The movie depicts a future world where everyone's genetic information is publicly registered from birth and is regarded as the only qualification factor for one's physical and intellectual capabilities. The protagonist Vincent Freeman (Ethan Hawke) did not go through the process of "genetic perfection." Due to his inferior genetics, he was discriminated against, referred to as the "invalid" by society, and ended up purchasing the genetic identity of a genetically perfect man.

Social and cultural implications

The increasingly connected world challenges us to navigate a diverse tapestry of cultures and populations. As we introduce new technologies and innovations, we must be sensitive to the varied beliefs held by and the distinct socioeconomic statuses of different communities. In the very end, **the people are the ultimate beneficiaries of scientific advancements**, so we must have the capability to see the problem from a humanitarian perspective.

First of all, given the diversity of cultural norms, ethical frameworks, and social values, what might be morally acceptable in one population might be a concern in another. For example, the use of **synthetic meat** in food production raises questions about cultural preferences and dietary traditions. Similarly, other lab-grown products, such as **leather, fur, and silk**, can also encounter very different cultural attitudes – while some cultures may embrace this as an ethical choice and a cruelty-free alternative, others may have deep-seated traditions tied to the use of natural animal materials.

Synthetic organs for transplantation are another example: some cultures/religious groups may see it as a welcome solution to the organ shortage crisis, while others may view it as tampering with the natural order or the sanctity of the human body. This is not a judgement of who is right and who is wrong, because we should understand the challenges new technologies such as synthetic biology often bring against established **cultural practices and traditions**. The introduction of synthetic biology applications and its integration into society should always be responsible for local cultural heritage.

Understanding and respecting this diversity is paramount, reminding us to approach our scientific endeavours with cultural humility, foster open dialogue, and facilitate cooperation across borders.

Secondly, we should ensure **equitable distribution of the benefits of synthetic biology**. As scientists, we bear the responsibility to develop technologies that benefit all of humanity, irrespective of socioeconomic or geographical factors, rather than limited to a privileged few. Striving for **affordability and accessibility** in healthcare, agriculture, and other synthetic biology applications is an ethical imperative. By addressing issues of equity, we can work towards a more just and inclusive global society where the benefits of our scientific innovations are shared by all. That being said, achieving a state of equity is harder than one thinks.

The Matthew Effect, a term borrowed from sociology, describes a phenomenon where advantages and opportunities tend to accumulate for those who are already privileged, while those with fewer advantages may face barriers to entry. Let's look at an example.

Genetically modified (GM) crops offer the potential for increased yields, reduced pesticide use, and improved resilience to environmental stress, but **their adoption is not uniform across the globe**. In more developed regions where GM crops are often engineered, farmers tend to have **access to the resources and infrastructure** necessary to cultivate GM crops, such as advanced farming equipment and the knowledge of modern agricultural practices, such that the advantages of these crops can be readily realised to improve income, invest in resources, and promote GM crop research, positively reinforcing their initial advantage. Conversely, **in less developed regions** with limited access to these resources, small-scale farmers **faced challenges in adopting GM crops**. They lacked the financial means to invest in genetically modified seeds or the infrastructure needed for their cultivation. Additionally, **regulatory hurdles and intellectual property rights** often placed GM technology out of reach for these farmers. As a result, they missed out on the potential benefits, perpetuating a cycle of disadvantage.

Fig 4.8 Artistic visualisation of the Matthew Effect

Think and discuss!

How can we break this vicious cycle of negative reinforcement?

Frankly, it is a daunting task requiring the **collaboration of multiple parties** on the international, national, and local levels. But as scientists, our role in the process is indispensable. Our synthetic biology system can be designed in a way so that its deployment can be achieved with as **less prerequisites** (of highly technical skills, stringent conditions, human resources, financial investment, equipment, and infrastructures) as possible.

We can also devote ourselves to **public engagement and outreach** to disseminate the knowledge of synthetic biology to the generally less accessible population. By actively working to **address disparities** in access to education, resources, and technologies, we can help mitigate the Matthew Effect and strive for **a more equitable future in synthetic biology**.

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Chapter 5: Recent Advances and the Future

5.1 State-of-the art facilities

Next generation sequencing

Next generation sequencing (NGS) is an incredibly **high throughput method of sequencing DNA**. It allows the simultaneous sequencing of many DNA fragments in parallel, which can greatly increase research output and save time due to the large volumes of data generated. The introduction of NGS has also helped to decrease the cost of DNA sequencing, making the technology much more **accessible** within the field. Many different NGS techniques exist, but the key technology for synthetic biology is Illumina Next Generation Sequencing.

Uses of NGS include **determining whole genomic sequence of organisms** and **identifying potential drug targets** quicker by providing detailed information on pathogen genotypes in less than a day.

Biofoundries

Biofoundries are a key **infrastructure** in testing organisms made using synthetic biology quickly. **The Global Biofoundry Alliance** was formed for researchers to share resources and experiences and there are institutes across the world.

In the UK, there are 6 institutes that belong to the Global Biofoundry Alliance. Of these 6 institutes, some are also multidisciplinary Synthetic Biology Research Centres (SBRCs) that have been built to accelerate synthetic biology innovation.

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Institution	Biofoundry	SBRC	Aims
BrisSynBio			Biomolecular design & engineering
Centre for Mammalian Synthetic Biology			Developing expertise in mammalian synthetic biology
Earlham DNA Foundry			Development of microbe-derived high value compounds
Edinburgh Genome Foundry			DNA construction and synthesis: designing, constructing, and verifying gene constructs of up to 1,000,000 bp.
Genemill			Automated robotics facility that can assemble DNA parts grown in bacterial colonies into genes that can be expressed.
London Biofoundry			Design, engineering and functional characterisation of synthetic DNA and organisms.
OpenPlant			Using synthetic biology to develop sustainable agriculture solutions.
SYNBIOCHEM			Applying the ‘Design, Test, Build, Learn’ cycle to engineer systems that can sustainably produce fine and specialty chemicals.
Warwick Integrative Synthetic Biology Centre			Developing Nextgen synthetic biology tools, engineering biosynthetic pathways, engineering microbial communities
SBRC Nottingham			Reduce global fossil fuel reliance by engineering organisms to harness greenhouse gases to produce valuable chemicals.

Table 3 Table providing a comprehensive catalog of biofoundries and SBRCs

5.2 Impact on Society

Many synthetic biology generated products are in the works, and some are **already on the market for consumer use**. Let's take a look at some synthetic biology products you may or may not have come across, and discuss the impact they have.

Impossible™ meat

If you are keeping up with plant-based meat alternatives, you will have heard of **Impossible™**. The iron-containing molecule heme is what gives meat it's characteristic flavour. To help give their product a meat-like-taste, scientists at this company **engineered yeast** to produce soy leghaemoglobin – a heme protein originally derived from plants. The heme is sourced from genetically engineered yeast instead due to inability of plant-based heme to feed the current population.

Fig 5.1 Impossible™ plant-based meat products

Through their innovation, Impossible™ have developed a tasty **plant-based meat alternative** that uses 75% less water, generates 87% less greenhouse gases and requires 95% less land, all while maintaining the same balance of nutrients you would get from regular meat.

PROVEN® – Pivot Bio

Pivot Bio has developed a **microbe-based corn fertiliser** using microbes that fix nitrogen from the air as **nitrogen fertilisers**. The microbes attach strongly to the corn to prevent runoff and leaching during rainy seasons, making PROVEN® **less polluting** and **more predictable** than chemical fertilisers. The nitrogen fixing microbes are not naturally compatible with corn, so synthetic biology was used ensure nitrogen fixing genes would be expressed in the presence of corn waste products.

5.3 Challenges ahead in the field

Synthetic biology is a relatively new field of study that has many hurdles to overcome. From technology to regulation, there is much to be done if we want to see more synthetic biology products hitting the market in the coming decades. So, **what needs to be done?**

Technological challenges

Synthetic biology is reliant on the concept of DNA parts that can be assembled into devices that can express genes according to how we design. The benefits of this are that downstream processing is extremely streamlined, as parts can be pieced together and tested quickly. However, we do not have the physical capacity to go through iterations of the cycles as quickly as required for innovation. As mentioned in *Section 5.1*, biofoundries play a key role in creating a high throughput method of generating and testing new parts. **Maintaining and developing biofoundries** will be the key to rapid development in the field, but commercial biofoundries may choose to close access to their software due to competing interests with other companies.

Machine learning is also becoming an important aspect of the Design, Build, Test, Learn cycle. Designing DNA can be a difficult and slow task for scientists. However, with machine learning and AI, we can **leverage software to help us design optimal DNA sequences** using the plethora of data they collect from experiments. This would greatly **increase the efficiency** of the design process, and we may even be able to develop programs that can learn to **mimic biological evolution much faster** than humans would be able to.

Regulation

Synthetic biology products are regulated in a similar way as GMOs and members of the public can be worried about the possible effects of these products on our ecosystem, or the ethical implications of constructing new genetic material. The negative public response to GMOs has led to **heavy regulation on synthetic biology products**. However, the tight regulation can also stifle innovation and prevent products with potentially enormous impacts (such as Impossible meat and PROVEN) from entering the market.

For the appropriate regulations to be put in place, there needs to be **more dialogue between scientists and the public**. **Science communication** efforts to direct debates about the risks of technology and prevent misconceptions of the technology will be integral to this.

Fig 5.2 Artistic visualisation of science communication and public engagement

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Chapter 6: iGEM and the World

6.1 History of iGEM

iGEM (International Genetically Engineered Machines) was founded in **2003** in **MIT, USA**.

It didn't begin life as the competition it now is, but instead as a 4 week long program held during academic breaks to give students something to work on. The first iteration of iGEM focused on **making cells blink** through a method called Elovitz's Repressilator.

Fig 6.1 iGEM Founders Randy Rettberg, Tom Knight and Drew Endy.

In **2004**, iGEM spread (rather aptly) out of MIT, becoming an **intercollegiate competition** between some of the USA's top universities. Some people might say that this marks the true beginning of iGEM as we know it.

Fig 6.2 The iGEM Distribution kit, containing physical DNA parts

2005 brings some of the founding principles of modern iGEM, including distribution kits filled with useful DNA, these kits were sent to each team now in several different countries. iGEM had become an international competition and adopted the iGEM branding.

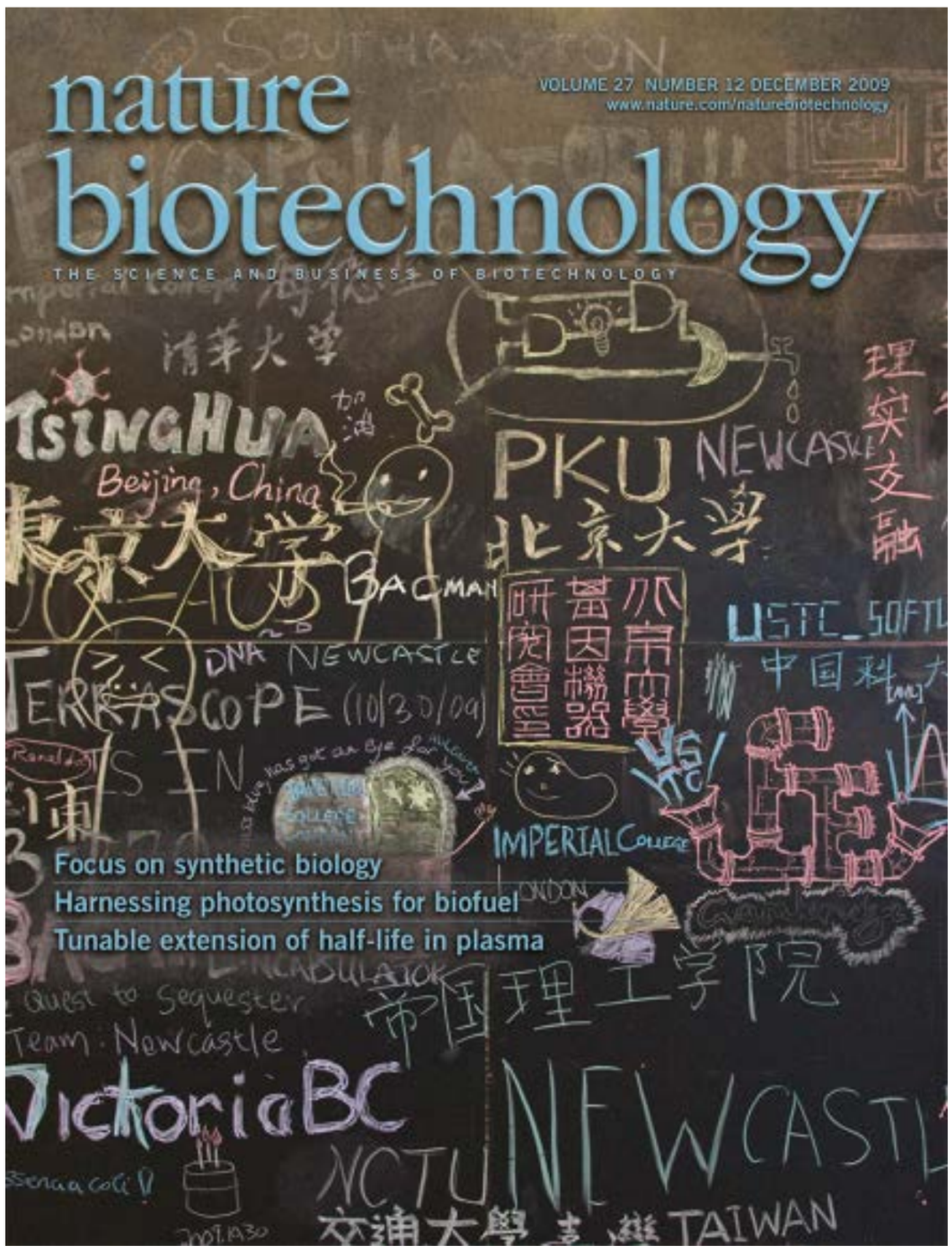

Fig 6.3 *Nature* Journal Volume 27 Issue 12, December 2009, artwork drawn by participants at iGEM

The competition only continued to grow over the next few years, with **over 100 teams participating in the 2009 competition**.

In 2014, there were over 200 teams involved, so the iGEM Giant Jamboree moved venues from MIT to Hynes Convention Center, Boston.

In **2016**, over 300 teams compete in iGEM.

In **2019**, iGEM makes the **cover of The Economist**.

Fig 6.4 Cover of *The Economist* Magazine, 6th April 2019

Fig 6.5 Virtual group photo for iGEM 2020

In **2020**, the Covid-19 pandemic greatly affected the competition, being held online with a significant reduction in teams participating. The ability of teams to complete lab work was reduced due to local lockdowns and restrictions, so this year's competition was judged based on a number of other factors

By **2022**, iGEM was still recovering from the pandemic, and iGEM held a hybrid online/in-person Jamboree in Paris, which also allowed for some major changes to the way the competition worked and teams were judged, such as the removal of project posters and recorded presentation videos.

Fig 6.6 Snapshot of the 2022 Grand Jamboree at Paris, France, with over 3,500 people

6.2 iGEM founded companies

Fig 6.7 4 companies that originated as iGEM teams: *Ginkgo Bioworks* (all 5 founders were advisors of MIT 2006), *Benchling* (UC Berkeley 2012), *ASIMOV* (MIT 2009), and *Eligo Bioscience* (Paris Bettencourt 2010).

There are **hundreds of companies that started as iGEM projects**, these are just some of the biggest ones; together they have a **net worth of almost $1 billion**, and are some major players in the bioscience and biotech industries.

iGEM offers support to start-ups and provides business ideals and knowledge to teams throughout the competition, fostering an environment where ideas can be turned into marketable, profitable endeavors.

Colorifix

Fig 6.8 Dress by Stella McCartney using Colorifix dye

Colorifix makes **eco friendly dyes** for clothing using synthetic biology, this dress here is actually a Stella McCartney piece that has been dyed using a Colorifix product in a collaboration they had for a fashion show in the Victoria and Albert Museum.

Colorifix started as the **iGEM project for Cambridge, UK in 2009**, and in 2019 they exceeded $37 million in funding.

Bentolab

BentoLab makes **portable lab kits the size of a bento box** (or a KFC box meal– they're the same size). This box contains all the useful things you might need; a pipette, electrofluresis gel, a PCR machine and a centrifuge. These are great for places that don't have permanent labs but still need to do testing on DNA.

BentoLab started with the **UCL, UK iGEM project in 2013**, and has grown into a small biotechnology company completely through crowdfunding, not having any investors to potentially detract from their goals.

6.3 What is being in an iGEM team like?

Being in an iGEM team is:

- Fun
- Challenging
- Engaging
- Interestin
- Varied

Fig 6.8 Collage of the 2023 Exeter iGEM team

Quotes from iGEMers

“No two days of iGEM are the same, one day I’m **coding** a website and the next I’m **working in the lab**.”

“I didn’t know anything about synthetic biology before iGEM started, now I’m presenting our idea in front of **5000 people**.”

“**There’s something for everyone**. The team is built around its members, not the other way around.”

“I’ve had so much **fun** over the last few months, I don’t want it to end!”

“iGEM has given me **work and research experience**, as well as so many skills I never even thought about.”

“It really lets you be in control, for some of us this is the first **real research project** we’ve done.”

“I liked petting the campus **cat** during our breaks.”

“Your **lucky numbers** are 3, 12, 15, 36 and 42.”

“I know I’m now considering **pursuing synthetic biology** more as a result of doing iGEM.”

“Getting to speak to **teams across the world** all in the same situation as you is great, I can’t wait to **meet some of them at the Jamboree**.”

“Going in to iGEM, I was afraid I wouldn’t be good at anything because I’m not a biologist, but I’ve realised that **iGEM is so much more than that**, I’ve been **coding** and **modelling** and **organising meetings**, I don’t even have to step in the lab at all!”

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Attributions

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