MENDEL'S LEGACY: EXPLORING BACTERIAL GENOMICS THROUGH ART

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ABSTRACT

My artworks investigate our relationship to bacteria and infectious diseases by looking at their cultural, societal and personal impact from historical perspectives to radically new technologies. I focus on the visceral and aesthetic aspects of the subject, communicating on an emotional as well as an intellectual basis and playing with notions of a 'bacterial sublime'. I work with traditional craft techniques, such as textile work and carving as well as with digital technologies, using the tools and techniques of microbiology and bioscience as a physical medium. I also develop participatory performances and large and small scale hands-on public workshop activities that involve the making of collaborative installations that grow over time. This paper describes key projects and outlines the narrative conceptual threads that run through my work indicating how they connect to the legacy of Mendel.

Keywords: Art; Science; BioArt; Mendel; Biology; Genomics; Synthetic Biology

INTRODUCTION

In 2015, 150 years after Gregor Johann Mendel shared his principles of heredity at the Natural Science Society in Brno, Czech Republic, I was invited to respond to his work by sharing my explorations as an artist into the contemporary fields of bacteriology, genomics, and synthetic biology. I was honoured to present my work in the very room where Mendel performed his pioneering research breeding peas and other plants for many years in the Augustinian monastery in Old Brno.

In those intervening 150 years Mendel gained posthumous fame as the founder of the modern science of genetics and kick-started a biotechnological revolution of which we are only now starting to see the fruits.

It is becoming possible to read and understand all the genes in a living thing and to alter or 'hack' the fundamental building blocks of living organisms to our own ends. Improving synthetic biology techniques enables us to edit the genomes of living organisms more rapidly and even offer the potential of creating novel organisms entirely from scratch. The promise of the antibiotic age is becoming hollow and increasing antimicrobial resistance has led to wide concerns around untreatable infectious diseases, the emergence of global pandemics and the lack of new treatments. However new biotechnological tools such as whole genome sequencing allow us to understand bacteria at the deepest level, track their evolution and revolutionize approaches to epidemiology.

The impact that these contemporary biotechnological tools are now having, and will continue to have on all our lives raises the need for an inclusive public debate. The (non-scientific) public do not currently have a clear understanding of the cultural, societal, and ethical issues involved in such emerging biotechnologies, or even sometimes the basic science behind them. More broadly we have forgotten the past and need to uncover histories and narratives that may have a bearing on us today, lest history repeats itself. We need to reflect on how scientific knowledge, personal beliefs, and health care behaviours are currently, and have been previously, constructed.

Infective Textiles and The MRSA Quilt

In 2011 I developed the *Infective Textiles*[1] project as part of the Laboratory Life Project at Lighthouse in Brighton, UK. The project was hugely significant for the development of my work as it enabled me to create a major piece of work and bring in new techniques that I had not previously used at scale. I led a group of artists, doctors and scientists who collaborated on the development of a textile-based artwork which takes the form of a Regency style dress stained with bacterial pigments and patterned by antibiotics. The work used 'garage science' methods and 'DIY' microbiological processes to explore the notion of infection control. During the project we cultured microbes from the local environment including soil, buildings and other public places. We then stained silk thread with natural and clinical antibiotics - including cloves, turmeric, green tea and vancomycin, - and used them to create embroidered patterns (based on microscopic images of bacteria and historic Regency designs) on fabric. The dress was then placed in a 'giant Petri dish' filled with DIY bacteria culture media made from supermarket products, upon which environmental bacteria, selected on the basis of the attractive natural pigments they were producing (burnt oranges, rose pinks etc), were grown. Finally, the dress was made sterile prior to its exhibition. The piece was created in close collaboration with Rosie Sedgwick. Melissa

[1] Infective Textiles: http://annadumitriu.tumblr.com/InfectiveTextiles

Grant, Brian Degger and Sarah Roberts Dr John Paul, Dr Simon Park, Dr James Price and Alex May.

Fig. 1: Infective Textiles project.

Nowadays there is an increasing issue of antibiotic resistance, the wonder drugs of the past are beginning to fail us on a much more significant scale than before. Unlike the pea plants Mendel worked with, bacteria reproduce by splitting into two identical cells, rather than two 'parents' producing an offspring. In order to evolve they may receive genes transferred from another different bacterium (for instance to gain a useful antibiotic resistance gene), they may pick up DNA from their environment (often from dead bacterial cells), or via infection by bacteriophages (viruses that can infect bacteria) which can carry DNA from previous bacteria they have come in contact with. Some bacteria can evolve and become antibiotic resistant rapidly and some more slowly. The use of natural antimicrobials and even other antibiotic-producing bacteria in I*nfective Textiles* shows that this is not a new issue, but a rapidly increasing one as the pressure for a bacterium to evolve resistance in order to survive has been greatly increased by the 'antibiotic age' we (just about) still live in.

The MRSA Quilt [2] tells the story of a highly problematic antibiotic-resistant organism that has specifically evolved to do damage in the ecological niche of hospital patients. The artwork was

[2] The MRSA Quilt: http://annadumitriu.tumblr.com/ModMedMicro

created by embedding squares of cotton calico in chromogenic agar. This bacterial growth medium contains a dye that is taken up by *Staphylococcus aureus* bacteria, causing them to grow blue in colour and stain the calico. The patterns on the squares are created using different tools and techniques used in the treatment and diagnosis of infections caused by this bacterium and its drug resistant form, known as MRSA (Methicillin or Multi drug resistant *Staphylococcus aureus*). The patterns I made included stripes and polka dots created using antibiotic susceptibility tests, such as vancomycin susceptibility discs and cefoxitin strips, and embroideries made using natural antibiotic dyed threads. Quilts are a traditional way of passing down stories and the piece works as an artwork and also a storytelling discussion tool to facilitate dialogue between the wider public and scientific researchers.

Fig. 2: The MRSA Quilt.

Tuberculosis: The Romantic Disease

My ongoing project *The Romantic Disease*[3] investigates mankind's strange relationship with Tuberculosis (TB), from early superstitions about the disease, through the development of antibiotics, to the latest research into whole genome sequencing of the disease. Tuberculosis has been the greatest enemy of microbiologists as it is able to become antibiotic resistant very quickly meaning nowadays patients need to be treated with a cocktail of drugs for at least six months to recover. As part of a series of artworks, I traced a number of histories of the disease that was strongly linked to creativity, poetry, and art throughout history, earning it the nickname 'the romantic disease'.

[3] The Romantic Disease: http://annadumitriu.tumblr.com/RomanticDisease

I created an artwork from an altered original pneumothorax machine originally used to collapse the lungs of tuberculosis patients in order to rest them. Prior to the antibiotic age, and specifically the discovery of streptomycin, rest was the only available treatment for the disease. The carved case reminds us of the texture of the lung tissue as the immune system attempts to 'wall off' the 'foreign' TB bacteria that it cannot eliminate. The engraving represents a positive sputum smear test made using a Ziehl–Neelsen staining technique. This relatively rapid diagnostic test can be used to diagnose patients with active pulmonary TB, though it is not always easy to find bacterial cells in a sample. The bacteria stain red with Carbol Fuchsin against a background of Methylene Blue and may give the appearance of scattered red ribbons.

Fig. 3: Pneumothorax Machine.

Another work in the series is an engraved *Blue Henry*, a sputum flask carried by tuberculosis (TB) patients in order to collect infected sputum coughed up from their lungs, rather than spit it out. The engraving, I placed on the lid, shows a transmission network of tuberculosis patients revealed through new research by Modernising Medical Microbiology at The University of Oxford (where I am artist in residence) using whole genome sequencing. A collection of TB samples taken from patients from the English Midlands between 1994 and 2011 was sequenced and the method revealed many previously unrecognised links between patients. By identifying minor changes in the bacteria's genome as it moves between people it is possible to reveal who passed the disease to whom. This diagram shows the possible occurrence of what is known as a 'super spreader', numbered '1', who caught the disease from patient '0' and proceeded to spread it widely. Patient 1 is known to be a drug dealer and therefore a member of a recognised high-risk group for TB.

Fig. 4: Blue Henry.

Where there's dust there's danger is a set of small needle-felted lungs made from wool and household dust impregnated with the extracted DNA of killed Mycobacterium tuberculosis (TB). The organisms have been rendered sterile using a validated kill protocol used in whole genome sequencing of TB. The lungs show various stages of the disease and forms of treatment. Around the turn of the 20th Century it was widely believed that household dust was one of the main transmission vectors. Sufferers would cough up sputum from their lungs and spit it out.
The sputum would dry and become mixed with dust. But it seems very unlikely that the disease could be spread effectively in this manner, as the particles are far too large.

Fig. 5: Where there's dust there's danger.

Rest, Rest, Rest! is a tiny altered antique model of a hospital bed and screen, impregnated with the extracted DNA of tuberculosis and dyed with natural dyes, which were historically used as treatments for tuberculosis. It reinforces the idea that until the discovery of the antibiotic streptomycin in 1943 there was no effective treatment for tuberculosis and medical treatments were directed towards enhancing the immune systems of sufferers through a regime of regular meals and rest and fresh air. Some of the rest regimes were very extreme. Calculations were made as to the number of breaths required to perform specific tasks and patients would be confined to bed, sometimes in just one position until they recovered, rebelled or succumbed to the disease.

Fig. 6: Rest, Rest, Rest!

One of the latest works in the series is *Burden* which focusses on the ongoing global health crisis of tuberculosis. It is made with carved Zimbabwean lemon opal stone and fruit stone, embroidered calico dyed with madder root (used as an ancient treatment for TB), and impregnated with TB DNA. Tuberculosis currently infects around one third of the world's population, mainly in low to middle income countries and Westerners often perceive it as a disease of history. However, increasing drug resistance may mean that the disease could have an equally big impact on countries where it is perceived to have been almost eradicated. The artist carved the work whilst in conversation with a Zimbabwean artist about the powerful impact of the disease on his country and his family. Modernising Medical Microbiology are working with a large number of international collaborators to improve diagnosis in low to middle income countries.

Fig. 7: Burden.

The Microbiome and the Gut

I am currently investigating the dramatic impact of antibiotics and antimicrobial resistance on our gut microbiota, through the creation of a new body of artworks, which enable stories of scientists, medics, patients and members of the public to be told and shared. With my collaborators I am developing a large-scale, evolving participatory artwork through a series of workshops that enable the sharing of individual stories, allowing participants to talk about the impact that infection has had on them through making 'votive offerings' based on images of bacteria. The result will be a spectacular collection of small drawings on aluminium, hung on ribbons stained with gut bacteria grown pink and blue on chromogenic agar, as well as other bacteria and antibiotic stained ribbons. These will be exhibited alongside textile works that reflect our changing gut microbiota in relation to antibiotic use and will employ the tools and techniques of bacteriology in their making.

The Hypersymbiont Enhancement Salon - Self Improvement Through Infection?

I used the format of a beauty consultation to demonstrate and discuss the potential ways in which our harmless bacterial flora could be enhanced to create human superorganisms (with better appearances, better health and even better personalities) through our active colonisation with hypersymbionts; bacteria that not only happily co-exist on and inside our bodies, but which actively improve us. Research (in mice) may now indicate that our gut microbiota can

potentially influence our weight and our mental health[4]. We have naturally co-evolved with bacteria but now, through new technologies, we are starting to have the power to understand and enhance these bacterial symbionts and to perhaps develop 'hypersymbionts' so that we may actually begin to drive our own evolution at a cellular level. I worked with Dr John Paul, Dr James Price and Kevin Cole (from the UKCRC Modernising Medical Microbiology Project) and Dr Simon Park (University of Surrey) for their advice and support in creating this performance artwork.

The Hypersymbiont Enhancement Salon[5] was originally commissioned for the *Superhuman* exhibition at The Wellcome Trust Gallery in London, and first performed in October 2012, and then at The Wellcome Trust in London in November 2013 and at Princeton University (USA) in March 2016. The work involves discussions around the complex relationship we have with bacteria (both pathogenic and non-pathogenic) including conversations focussed on the (often discussed) relationship of Tuberculosis and creativity. The work is being further developed in collaboration with The Modernising Medical Microbiology Project and Wellcome Trust Brighton and Sussex Centre for Global Health Research to investigate the drug trial process through the speculative production of "Hypersymbiotics", make with "extract of tuberculosis DNA".

In 2015 I began to develop some new products for the *Hypersymbiont Enhancement Salon*, using genuine psychobiotic bacteria genetically engineered by Paloma Portela Torres and her colleagues of the *UCL iGEM 2015* team who invited me to collaborate with them. Their genetically modified *E. coli* expresses a gene that increases serotonin production and points the way to the possibility of genuinely augmenting our bodies and minds using bacteria which can make us 'better' (in this case happier). I also worked with Heather-Rose Macklyne at The University of Sussex to freeze dry the bacteria to make a dust (which was given some added sparkle for cosmetic purposes) and incorporated into toothpaste, lipstick, and food: "smile with the hypersymbiont enhancement salon!" was my call to action. Also working with Macklyne I made some fresh jellies containing the necessary antibiotics to enable the bacteria to keep the serotonin producing plasmid active. They were grown and decorated with the living bacteria.

[4] De Palma, Giada, et al. Microbiota and host determinants of behavioural phenotype in maternally separated mice. *Nature Communications*, Vol. 6, Article number 7735, 2015.
[5] The Hypersymbiont Enhancement Salon: http://annadumitriu.tumblr.com/HypersymbiontSalon

Fig. 8: Hypersymbiont Enhancement Salon - Lipstick containing freeze dried psychobiotic bacteria.

The Human Super-organism

Super-organism[6] originally began as an interactive installation (originally commissioned for Cinekid Festival in Amsterdam) where visitors imprint themselves onto a screen, which takes the form of a 'virtual Petri dish', and slowly reveals the shape of their bodies made of colonies of (digital) bacteria, which grow before their eyes. I collaborated with artist Alex May on the project and we cultured and filmed the growth of the bacteria from our bodies using DIY biology techniques and created high definition time-lapse videos of their growth.

The interactive installation was made using custom software written in C++ and uses infrared sensor technology to track participants in the space. The resulting 'virtual Petri dish' images are made up of collages of hundreds of the stop motion films of bacterial colonies, that are being generated in real time for each participant to create the effect that the bacteria from their bodies has been cultured in a Petri dish. The bacteria are, in fact, grown from the artists' own bodies using DIY microbiology techniques. The growth is speeded up from three days to about twenty seconds to give a meaningful experience. I want participants to understand that bacteria are an important part of what it means to be human and integral to our immune system. We are, in fact, super-organisms - our bodies contain a significant percentage of bacterial cells.

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[6] Super-organism: http://annadumitriu.tumblr.com/Super-organism

Fig. 9: Super-organism - interactive installation. Cinekid Festival in Amsterdam.

Versions of the installation have been accompanied by participatory bioart workshops that enable visitors to work hands on with their own microflora. A version of the installation which uses the hands rather than the whole body called *The Human Super-organism* is on permanent display at *Eden Project* in Cornwall, UK in their ground-breaking exhibition *Invisible You: The Human Microbiome*.

Sequence

Sequence[7] is a continuing project that aims to artistically investigate the emerging technology of whole genome sequencing of bacteria, and consider what it means to us personally, culturally and socially. A genome means all the different fragments of DNA guanine, adenine, thymine, or cytosine that go to make the basis for a living organism.

I have embedded myself in the research of Modernising Medical Microbiology who are sequencing the whole genomes of clinically important bacteria. I wanted to begin to understand my own microbiome better and study one of the organisms that lives on my own body using the state of the art technology of next generation sequencing.

I have shadowed the work of Modernising Medical Microbiology intensively, and have learned to perform the entire process myself from end to end. The aim of their research is to fully integrate whole genome sequencing technology into clinical microbiology over the forthcoming decade so that it becomes an integral part of the diagnostic process in healthcare settings. As an artist I wanted to understand and respond to this research, which is revolutionising microbiology and healthcare; shifting the practice of bioscience from hypothesis testing to hypothesis generating through big data bioinformatics; and raising issues of privacy, access, ownership and ethics.

[7] Sequence: http://annadumitriu.tumblr.com/Sequence

Whole genome sequencing of bacteria builds on the work of the Human Genome Project and before that the work of Mendel, but as bacterial genomes are much smaller they are easier to work with. Sequencing can provide the precise diagnosis and also reveal drug resistances, pathogenesis, and virulence. It replaces the current range of tests with one single test.

My research has culminated in my preparing, sequencing and assembling the whole genome (around 2.8 million base pairs) of the bacteria that lives in my anterior nares (the very front part of my nose), one of billions of bacteria with which I share my life and my body and that I know almost nothing about.

I learned that the probability of this bacterium, that thrives on me, being a human pathogen is estimated 0.983, so the organism is predicted to be a human pathogen. Though it lives on me at the moment without any problem, it is possible that in different circumstances it could make me ill or potentially kill me.

I found out that organism is resistant; it contains the blaZ gene, which confers resistance to beta-lactams, such as penicillin. It can be treated with methicillin and so is not a form of the famous methicillin resistant *Staphylococcus aureus* (MRSA) mentioned above.

It has been a challenging project. It is a hugely complex area and the researchers I collaborate with work on very different parts of the process, which means it is very difficult to get the whole story of what is going on without talking to lots of people. Both myself, and my collaborator on the work, digital artist Alex May, found ourselves frequently confused and continually having to journey further down the rabbit hole.

The preparation of the DNA for sequencing is difficult, time consuming, and very high precision is required (I needed to dilute the DNA so precisely that 1 000 000 fragments of it would cover 1mm of the flow cell used in the sequencer). However, this pales in comparison to working with the data. Initially the sequencer (we used an *Illumina MiSeq*) records images of light signals originating from fluorescent chemical compounds attached to nucleotides. Each nucleotide A T G or C binds to a different coloured compound, and at each stage a digital image is taken. The machine then builds up a picture of what DNA is there and outputs a raw file of data.

This data can then be assembled using software. I used a trial version of *Geneious* to assemble the sequence de novo from my raw data of around 2.8 million base pairs in length. There are two kinds of DNA assembly used in whole genome sequencing of bacteria: mapping and de novo.

Mapping maps to a reference strain, a known, fully sequenced strain of the bacteria. A metaphor for this can be thought of as a jigsaw puzzle with a picture on the box, except the picture is slightly different from the one on the pieces. De novo assembly, on the other hand, is like a jigsaw puzzle when you have lost the box with the picture on it. Assembled genomes can then be compared to other assembled genomes to reveal how infections spread as minor changes in the DNA show how closely related one organism in a species is to another.

Engineered Antibody

In late 2015 I was awarded a residency at The Liu Lab for Synthetic Evolution and The University of California, Irvine. There I created *Engineered Antibody*[8], a beaded necklace based on an antibody purified from the blood of an HIV positive patient. Made up of 452 hand-made beads, it both represents and physically contains the actual 21 amino acids of the antibody in the precise order and folded into the precise protein structure. An antibody is a protein that is produced by the immune system in order to combat foreign bodies and viruses, which it can bind to. This antibody has been engineered to better block HIV infections through the introduction of an additional amino acid called sulfotyrosine. I drew on the image that all forms of organic life are made of amino acids, which join together like strings of beads to form proteins that fold into three-dimensional structures essential to their function. The beads are then attached to textiles that have been dyed using Coomassie Brilliant Blue, originally a wool dye nowadays used as a stain in laboratories to visualize and separate proteins in synthetic biology. The form of the embroidered calico is based on the diagram of the antibody structure.

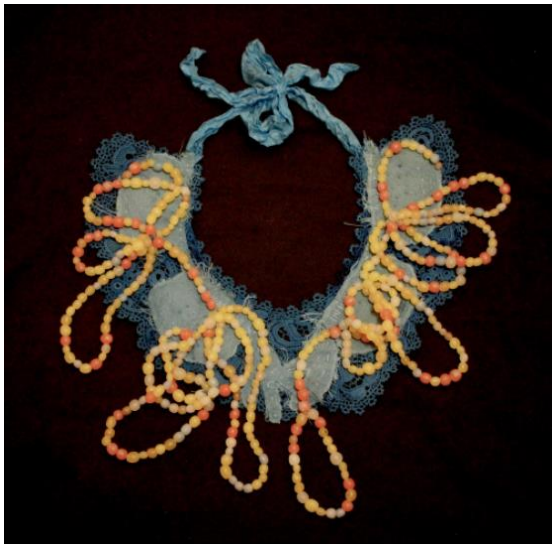

Fig. 10: Engineered Antibody.

[8] Engineered Antibody: http://annadumitriu.tumblr.com/UCI

Conclusion

When Mendel undertook his experiments he founded an area of research that has led to a revolution in science and our increasing understanding gives us the potential to combat antibiotic resistance in entirely new ways. Synthetic biology techniques are also being used now to work on antibiotic pathways in existing known antibiotic producing bacteria, such as *Streptomyces*, which produced streptomycin to treat TB and many other infectious diseases. My very latest work now with Professor Maggie Smith's lab at the University of York in the UK is focussed on learning more about these processes and their hunt for new antimicrobials using synthetic biology techniques derived from bacteriophages. In this constantly changing area of research, art is able to become a means of engaging and reflecting on science enabling far wider audiences to participate in influencing research directions by giving them the tools to better understand the world they inhabit, along with so many other diverse invisible life-forms.

Biography

Anna Dumitriu (1969) is a British artist whose work fuses craft, technology, and bioscience to explore our relationship to the microbial world, biomedicine and technology. She has a strong international exhibition profile, having exhibited at The Picasso Museum in Barcelona, The Science Gallery in Dublin, The Museum of Contemporary Art (MOCA) Taipei, and The V&A Museum in London. Her work is held in several major public collections, including the Science Museum London and The Eden Project. She is the founder and director of "The Institute of Unnecessary Research", a group of artists and scientists whose work crosses disciplinary boundaries and critiques contemporary research practice. She won the 2012 Society for Applied Microbiology Communication Award. Her book "Trust Me, I'm an Artist" which investigates the novel ethical problems that arise when artists create artwork in laboratory settings, co-authored with Professor Bobbie Farsides, was published in 2014.