Synthetic Biology and Responsible language Use

An Anthology of Blog Posts

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FOREWORD

Synthetic biology is a rapidly maturing area of research which can be described as the design and construction of novel artificial biological pathways, organisms or devices. In the United States and the United Kingdom, in particular, synthetic biology is being heralded as a new avenue for delivering significant economic benefits, as well as providing innovative technological solutions for environmental and health predicaments currently facing humanity.

Over the last two years six synthetic biology research centres have been created in the UK, funded by the public purse via Research Councils, with investment currently over £60 million. The centres are located at the Universities of Nottingham (where the authors of this article are located), Cambridge, Bristol, Manchester, Warwick and Edinburgh. In addition, there is a Synthetic Biology Innovation and Knowledge Centre at Imperial College London. These centres are engaged in a broad range of synthetic biology research, with the aim of producing novel products such as, sustainable biofuels and platform chemicals, and new medicinal products and pharmaceuticals.

All six research centres have been tasked with embedding an equally rapidly maturing governance framework which aims for a closer connection between science and societal needs, called 'Responsible Research and Innovation' (RRI for short). By adopting this approach, research funders in the UK, Europe and the US hope that scientific research can be opened up at an early stage, allowing a wide range of societal issues and concerns to steer or shape innovation pathways. In doing so, it is also hoped that any new technologies and products guided by RRI will be socially desirable and undertaken in the public interest.

The success of synthetic biology as part of an emerging and flourishing new field of science and industry, depends on public engagement with this new field. The success of RRI, which has been highlighted within the EU Horizon 2020 programme as part of a tool for carrying out research 'with and in society', is also reliant on interactions with the public. Both in turn depend, at least to some extent, on wider and ongoing public conversation about synthetic biology.

In 2014 a UK report on *Public Attitudes to Science*, which surveys attitudes to science, scientists and science policy among the UK public at regular intervals, found that synthetic biology was a topic about which people generally felt least well informed, and this has remained the same since the last survey in 2011. Other surveys have found that there is also a general lack of awareness about synthetic biology. A 2013 Woodrow Wilson Center poll, based on 800 US adults, found that public awareness of synthetic biology and nanotechnology has not changed since previous surveys. In the poll, only 23 percent of adults say they have heard a lot or some about synthetic biology, compared with 31 percent who say the same about nanotechnology. Those surveyed mainly associated synthetic biology with being un-natural, artificial and having to do with reproducing life. A poll carried out for the Parliamentary Office of Science and Technology in the UK also found that awareness of synthetic biology was low.

Research in the many fields associated with synthetic biology is, it seems, being carried out in a context where large parts of the general population are not aware of it, feel they are not well-informed about it, and have very stereotypical impressions of what it entails.

In order to open up a public conversation about both synthetic biology and RRI Brigitte Nerlich, the RRI lead within EPSRC/BBSRC funded Synthetic Biology Research Centre at the University of Nottingham has begun to write a number of blog posts discussing many aspects of synthetic biology and RRI, focusing in, in particular, on the role of language and of the metaphors used in framing synthetic biology in the public media, from 'book of life' and 'gene editing' to 'Prometheus' and beyond. These posts were initially published on the Making Science Public blog which is linked to a Leverhulme funded research programme of the same title, directed by Brigitte Nerlich.

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Some more academic reading material can be found here:

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1. ON THE HISTORY OF SYNTHETIC BIOLOGY

Fermenting thought: A new look at synthetic biology

I have become involved in a new project related to synthetic biology. The University of Nottingham has received funding for a big Synthetic Biology Research Centre. I am a social scientist within the new team and in charge of keeping an eye on 'responsible research and innovation'. This is not what this post is about though (but see here and here and, more importantly, here).

Fermentation

I recently (August 2014) went to a workshop related to this new centre during which the words 'fermenting' and 'fermentation' were used a lot. For the people involved in synthetic biology this is totally unsurprising, but for me it was a bit of a wake-up call. In the past I had kept an eye on synthetic biology headlines around the creation of cells, the tinkering with genomes and the like. I even did a tiny bit of media analysis of a first wave of coverage (and hype) of synthetic biology in the mainstream press. While carrying out this research I had never become aware of the importance of the words 'ferment' or 'fermentation'. I suspect that for me as for many other lay people synthetic biology as the new big science thing evokes the 'creation of artificial life' rather than 'beer'.

Synthetic biology in the news

All this made me look again at English language news coverage of synthetic biology in 2010. Why 2010? Some background: In the year 2000, the first draft of the human genome was announced in a flurry of publicity, a publicity that involved Craig Venter as one of the lead scientists working on the sequencing of the human genome. About a decade later scientists announced the creation of artificial or synthetic cells, such as the synthetic bacteria *Mycoplasma genitalium* in 2008 and *Mycoplasma mycoides* in 2010, with Venter, again, being one of the

lead scientists. In May 2010 Venter published an article in *Science Express* announcing that his research group at the J. Craig Venter Institute (jcvi.org/) had created the first self-replicating 'artificial cell'. This was heralded in many mainstream media articles as the creation of artificial life and as scientists playing God.

When I checked the news database Lexis Nexis for all English language news again today (13 August 2014) for 2010 as a whole, I found nearly a thousand (991) articles on 'synthetic biology'. I then added the search terms 'ferment' and 'fermentation' and discovered that only 61 of these articles contained the words 'ferment' or 'fermentation'. The majority of these were published in obscure trade journals (apart from one in the more popular *New Scientist*) – many focusing on work within *Amyris*, a renewable products company providing sustainable alternatives to a broad range of petroleum-sourced products. Only a handful of articles mentioning 'fermentation' appeared in the mainstream press; interestingly two were in the Scottish press.

One article by Emma Cowing written on 23 May, 2010 for *Scotland on Sunday,* was entitled 'The power to create' and was particularly interesting. It quotes UK's foremost expert on cloning, Ian Wilmut, as saying: "It's probably hard to imagine all the applications of this technology… Our view is that we're going from 6.8 billion to 9 billion people in the next 30 to 40 years, and we can't provide the food, the energy, clean water or medicines for the 6.8 billion, so we need some radical new technology to be able to do that without destroying the planet for 9 billion people." Wilmut then goes on to compare the new technology to fermentation: "As we learn more about the mechanisms that regulate cell function it may then become possible to change cells in order to give them new abilities that are useful to us … Human beings have done this in different ways for many years. Yeasts have been changed to make them more suitable for production of wine, beer or bread." Comparing synthetic biology to making wine, beer or bread is a good move, I think.

The *New Scientist* (20 February, 2010) article also had a powerful headline: "Genetic code 2.0: Life gets a new operating system". It goes on to say: "A new way of using the genetic code allows proteins to be made with properties never seen before – it could lead to new or 'improved' life forms. … Doing so should lead to the creation of whole new classes of materials, Chin says. And because they could be churned out by bacteria grown in large fermentation vats, it would probably be a cheaper way of producing them than chemical synthesis." Here fermentation doesn't quite evoke mundane food stuffs like beer; on the contrary, the word 'vat' probably triggers negative images, from witches cauldrons ('toil and trouble') to babies in vats, brains in vats, vats of artificial meat and so on. But still, fermentation may be an interesting conceptual anchor for creating an understanding of synthetic biology.

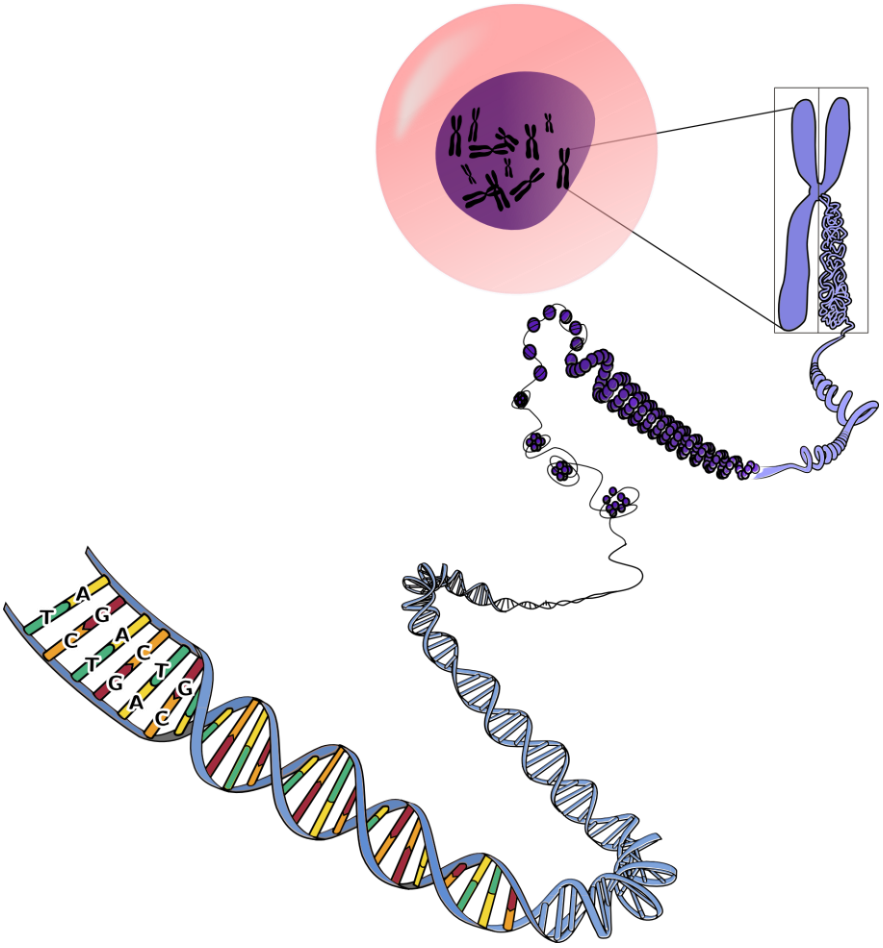
Biotechnology in the past

While musing about these things, I came across a book on the history of biotechnology which had escaped me so far, just as much as fermentation had. And lo and behold, it all began with fermentation. The book is by Robert Bud and

entitled *The Uses of Life: A history of biotechnology* (1993). As Susan Lindee says in her review of the book, Bud stresses that the term biotechnology was coined in 1919 by "Hungarian agricultural engineer and pig farmer Karl Ereky". But he begins his history of biotechnology even earlier "with seventeenth-century zymotechnology – G. E. Stahl's term for practical fermentation – and its ramifications in the development of organic chemistry, agriculture, brewing, and the biological sciences. …. He explores the American chemurgic ('chemistry at work') movement, the rise of industrial fermentation processes in the American chemical industry, scientific and industrial microbiology, chemical engineering (penicillin); the green revolution, and so on." Really interesting and new, at least, to me (ok, old!)!

Fermentation, not creation

Stressing the link between synthetic biology and fermentation (but not vats!) rather than only the 'creation' of artificial or improved life forms (a way of talking which hogged the headlines in 2010 and evoked images of scientists playing God) may be a way forward in engaging ordinary people with this new technology, one that the University of Nottingham excels in.



2. ADVANCES IN SYNTHETIC BIOLOGY

Making synthetic biology public: The case of XNAS and Xnazymes

On 1 December a group of scientists at the University of Cambridge led by Dr Philipp Holliger published an article in the journal *Nature* in which they presented new findings within the field of synthetic biology. Both the *Biotechnology and Biological Sciences Research Council* (BBSRC) and the *Medical Research Council* (MRC), who funded the research, published press releases, and, by 3 December, according to Google News, 21 news items had been published about this research in various outlets. Surprisingly, only three articles appeared in the mainstream press: one in *The Independent*, one in the *Financial Times* and one in *The Daily Mail*. And there is surprise in store for those thinking, ah… *The Daily Mail*…

I was actually astonished by how little this announcement was picked up by the press who had lapped up Craig Venter's advances in synthetic biology about five years ago, and this despite the fact that the Cambridge research seems to be quite exciting. I'll try to explain why, but, of course, I might get things quite wrong, as I am not a synthetic biologist.

XNA and XNAzymes

Scientists have studied the alphabet of life for quite some time, namely the letters or chemical bases A, T, G, C, letters that stand for adenine, thymine, guanine, and cytosine. In the 1950s they discovered the structure of the DNA molecule or deoxyribonucleic acid, where pairs of letters or base pairs, attached to a sugar-phosphate backbone, form the so-called building blocks of the double helix. They realised, as my husband puts it, that the book of life has a spiral binding. Since the 1990s scientists have used the letters to 'read' entire books of life or genomes, culminating in the reading of the human genome in 2003. Around 2010 they began to 'write' new synthetic DNA using these letters or bases. This was the beginning of synthetic biology and Craig Venter's creation of a synthetic cell. The exciting thing now is that scientists are able to create entirely new letters or bases, that is, to extend the alphabet of life. Scientists at the Scripps Research Institute accomplished this in work published in May this year.

Two years earlier, in 2012 *Nature News* published an overview fo such research entitled "Chemical biology: DNA's new alphabet". Earlier that same year the Cambridge group had demonstrated this ability to extend the alphabet by using nucleic acids called XNA (Xeno nucleic acid), in which the sugars normally present in DNA or RNA had been replaced by other ring structures. The scientists changed the backbone of DNA, meaning that the bases A, T, G, and C, which in DNA are attached to the sugar deoxyribose, are now attached to something else which replaces the sugar. So instead of sugar-phosphate-sugar-phosphate, this polymeric strand now goes 'something else'-phosphate-'something else'-phosphate and so on. Building on this work, the Cambridge team have now shown that XNAs, folded into defined structures, can also act as enzymes which they called 'XNAzymes'. How was this discovery made public?

Making XNA public

In this post I'll try to follow the XNA story from the article in *Nature* through the press release to the stories in the news and see how the story and the language with which the story is told changed and how it is anchored in cultural representations of life and disease, as well as, in this particular instance, potential alien life on other planets. I am following in the footsteps of Jeanne Fahnestock (1998) who studied the 'rhetorical life of scientific facts' and examined how the language of science changes in relation to a text's intended audience, describing the phenomenon as the 'accommodation' of science from expert to lay publics.

The *Nature* article

The article in *Nature* is entitled Catalysts from synthetic genetic polymers. It reads mainly like this: "We dissected contributions of individual nucleotides in the FR17_6 XNAzyme, defining a 26 nucleotide (nt) catalytic core (FR17_6min). As all four FANA nucleotide phosphoramidites are commercially available, this minimized XNAzyme could be prepared by solid-phase synthesis (see Methods) and was found to retain near full activity (Fig. 2a–c; k_{obs} = 0.026 min^{-1} at 25 °C), including multiple turnover catalysis (Fig. 2d). FR17_6min shows a pH optimum

(pH_{opt}) of 9.25 (Extended Data Fig. 4h), consistent with a mechanism involving deprotonation of the cleavage site-proximal 2′ hydroxyl."

As one can see, this article is written by scientists in this particular field for scientists in this particular field. Reading through the article as a lay person, a few words jumped out at me that have an ordinary language meaning, but obviously mean something more specific for the scientists, such as 'catalyst', 'scaffold', and 'backbone'. Some of these words were picked up in the press release and the newspapers, as we shall see. The *Nature* article contained other words, such as 'cleave' and 'ligate' which were translated in the press release into 'cutting' and 'stitching together', words which are commonly used by synthetic biologists when they are not writing articles for *Nature*. Two sentences in the article were elaborated further in the press releases, namely: "implications for the definition of chemical boundary conditions for the emergence of life on Earth and elsewhere in the Universe" and "potential applications ranging from medicine to nanotechnology".

Press releases

The BBSRC press release announced that "BBSRC funded scientists have created the world's first enzymes made from artificial genetic material. Their synthetic enzymes, which are made from molecules that do not occur anywhere in nature, are capable of trigging chemical reactions in the lab." To elaborate further, they refer to the artificial DNA called XNA as 'building blocks' (a metaphor translated into a visual image on the Cambridge University announcement of this result). The XNAzymes are said to 'power' simple reactions and be able to cut and stitch together small chunks of RNA. (In scientific jargon the phrase 'building block' normally refers to individual nucleotides)

The press release quotes three scientists: Dr Holliger, who led the research, points out that the chemical reactions on which life depends are normally 'kick-started' (catalysed) by enzymes. He also refers to 'building blocks of life' and says that the building blocks created by his team don't exist in nature but might show that life on other planets could use such 'unnatural building blocks'. The reference to 'other planets' extends the reference the 'Universe' in the *Nature* article. Professor Patrick Maxwell, Chair of the MRC's Molecular and Cellular Medicine Board, speaks of 'designer biological parts' that might be used for therapy or diagnosis in medicine. In terms of applications, the press release expands on the *Nature* article and points to "new therapies for a range of diseases, including cancers and viral infections". Nanotechnology is not mentioned.

The MRC press release quotes an additional voice, Dr Alex Taylor, the study's first author and post-doc at St John's. He also used the phrase 'building blocks' and talks about the possibility of life on other planets.

University news

The University of Cambridge reported on 'The world's first artificial enzymes created using synthetic biology'. Again, we hear of 'building blocks', of 'cutting' and 'joining' and of 'powering' reactions. Dr Taylor is quoted as saying: "This

research shows us that our assumptions about what is required for biological processes – the 'secret of life' – may need some further revision." Dr Holliger refers again to possible "life on other planets" and of these results widening "the possible number of planets that might be able to host life." ~Again, reference is made to applications – cancer, viral infections, designer biological parts.

Medical and science news outlets

Various medical and science outlets reported on this paper, such as popular science magazine *New Scientist*, the *Bioscience Technology* newsletter, *The Pharmaletter*, and others. Most articles stayed close to the press releases.

New Scientist adds some pieces of information to the emerging news jigsaw puzzle, which are quite interesting: Dr Holliger works at "the Laboratory of Molecular Biology in Cambridge, UK, the same laboratory where the structure of DNA was discovered in 1953 by Francis Crick and James Watson" (and Rosalind Franklin). The article briefly summarises previous work by Dr Holliger and, without using the 'backbone' metaphor, the article makes clear that Holliger's team replaced the usual 'sugars' in this backbone with artificial ones.

Interestingly, *New Scientist* refers not only to life on other planets, but to 'exoplanets', a speculation thrown into the mix by Nobel prize-winner Jack Szostak of Harvard University "who studies the origins of life on Earth".

As is usual when reporting on scientific 'advances', the article uses conventional journey metaphors such as 'big steps', 'major step'. Other mainstream newspapers papers would talk even more conventionally about a 'breakthrough' (*The Independent*, *The Daily Mail*) and a 'milestone' (*The Independent*).

Mainstream media

The BBC was quick to announce this advance in synthetic biology and used a metaphor that has become quite popular since around 2010, namely making biological entities, in this case enzymes, 'from scratch' – meaning basically from nothing. The article too uses the metaphors of 'building blocks', 'cutting' and 'joining' etc, but also says that researchers could 'jump-start' simple reactions, similar to the 'powering' metaphor used in the press release. The BBC uses one of the rare metaphors used within the *Nature* article, namely that of the man-made molecular 'backbone' but doesn't explain what it means. XNAs are talked about as 'hardy' (the press release had said 'robust'), as capable to "evade the body's natural degrading enzymes", and as "disrupting disease-related RNAs". Three articles in the mainstream press go beyond these rather sober descriptions.

The Independent

Steve Connor, the *Independent's* science correspondent, calls this advance a 'breakthrough' and 'milestone' in synthetic biology that may enable scientists to cure not only cancer but also "Ebola" and "HIV". Both are very much in the news at this moment, thus creating nice human interest anchoring points for an abstract scientific news story. The article uses the now familiar words 'cutting' and also 'pasting'; it quotes Professor Maxwell and his reference to 'designer

biological parts' and Dr Holliger and his reference to other planets and also exoplanets.

Financial Times

Anjana Ahuha, a science commentator, wrote an article for the *Financial Times* entitled "Artificial ingredients for a primordial soup and recipe for life" that goes beyond this relatively restrained and conventional science reporting. Using the metaphor of a recipe which is well-established in genomic discourse, she links it to the primordial soup and thus the origins of life on earth and elsewhere: "While nobody has yet cooked up a living organism from scratch…the ingredients are coming along nicely." She speculates about new drugs based on an "alien organism that is immortal". There is talk about 'go-faster chemicals', 'off-the-shelf synthetic molecules', and for the first time reference is made to Craig Venter, to his claims of 'rebooting nature' as well as to claims about him 'playing God'. However, there is a proviso: "Controversial though synthetic biology is, it is generally not conducted by chuckling megalomaniacs seeking purely to prove their supremacy over nature" and any "malign intent to manufacture a monster is likely to be thwarted". Thank God for that!! This article for the FT was not illustrated with an image. However, in a post for the SingularityHub which reports on this latest 'creation of artificial life', we find a nice portrait of Frankenstein's monster!

The Daily Mail

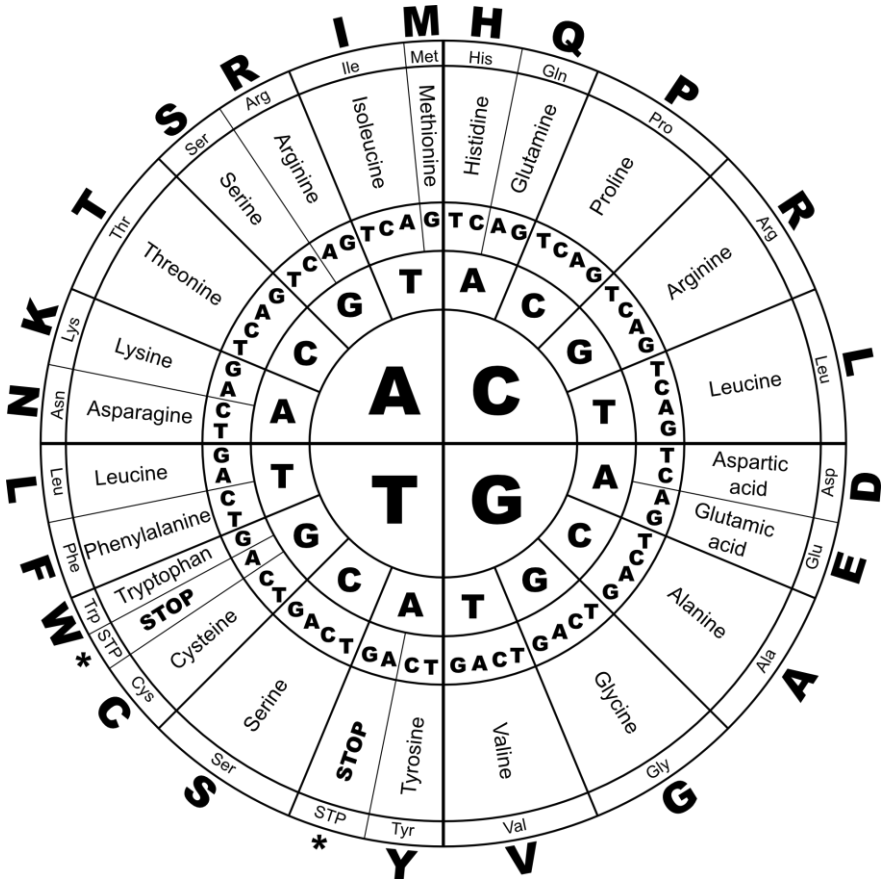
This brings us to the final mainstream media article I'll discuss here, one published in the *Daily Mail*. As far as I can make out, this article by Richard Gray, entitled "Do we really need DNA to form life", is, I think, quite a really good summary of the work by Holliger and his team. It is illustrated not only with a double helix and planets but with some of the original images used in the *Nature* article. It quotes Holliger, Maxwell and Szostak ('as quoted in New Scientist'), refers to Holliger's previous research, talks about 'building blocks', 'cutting' and 'stitching' and quotes Holliger on possible applications – cancer and viral infections. There is also a nicely informative little side box on 'WHAT WOULD LIFE ON OTHER PLANETS MADE FROM XNA BE LIKE?' Overall, it stays within the science, does not go over the top and ends with a question, quoting Szostak: "'But the primordial biopolymer for any form of life must satisfy other constraints as well, such as being something that can be generated by prebiotic chemistry and replicated efficiently. 'Whether XNA can satisfy these constraints, as well as providing useful functions, remains an open question.'"

The rhetorical life of XNA and XNAzymes

When studying how scientific findings are communicated in popular science magazines, Fahnestock observed a shift from establishing the validity of observations to focusing instead on the 'wonder' and 'application' of the findings. She also observed attempts to connect findings to publics' existing values (Fahnestock, 1998, p.334) and cultural stocks of knowledge. Part of this process of 'accommodating science' might involve scientists and journalists sensationalising scientific findings in order to attract readers' attention. As we have seen, this did not happen extensively in the journey I have described here from scientific article to press coverage.

In case of the XNA story we saw that the *Nature* article is essentially a series of equations interspersed with some words that lay people may understand. Only two of these words were picked up in the press releases, none was really explained: 'catalyst' and 'backbone'. Two words in the article, 'cleave' and 'ligate', were translated into 'cut' and 'stitch', thus making the discovery slightly more understandable. 'Wonder' and 'application' were the focus of the press releases and even more so the press coverage talking about alien life on exoplanets on the one hand and the possibility of curing not only cancer, but also Ebola and HIV. Framing this research in terms of these currently widely talked about topics connects it to publics' existing values and interests. Throughout the press coverage, metaphors such as 'building blocks', 'powering', 'kickstarting' or 'jump-starting' were used to convey the workings of DNA and enzymes – some more transparent than others. The 'science is a journey' metaphor was also used when talking about milestones and major steps having been taken. These are all quite conventional metaphors. The only article that veered into hype and sensationalism was the one published in the *Financial Times*, especially when it used such old clichés as Craig Venter playing God and 'chuckling megalomaniacs' *not* creating 'monsters'! The only article that tried to explain the science in some depth without too many rhetorical flourishes was, surprisingly, the one published in *The Daily Mail*.

In the next section of the anthology, we'll home in on some major rhetorical flourishes that are endemic to synthetic biology (and genomics in general). We'll also reflect on their impliations for RRI or more specifically responsible language use.



3. RESPONSIBLE LANGUAGE USE AND METAPHORS

Synthetic biology, metaphors and ethics

As some of you know, I have been interested in metaphors for a long time and more recently have become intrigued by metaphors used when talking about synthetic biology, gene drives, gene editing and so on. This has led to a meeting in Cambridge (Downing College) between Steven Burgess, who edits the PLOS Synbio community blog, Carmen McLeod and myself to talk about a little project we are hatching together (more about that soon; March 2016).

A few days before the meeting I started to dig around a bit more to see whether other people had written about synthetic biology and metaphors. I knew, of course, that my old friend and colleague, Martin Döring, had done so some years ago, around 2012. He has, for example, contributed a chapter on metaphors in systems biology to a book edited by himself and his colleagues in 2015 and he has also written a wonderful chapter on metaphors and morals relating to synthetic biology in 2014 - a systematic metaphor analysis, including reflections on ethical implication, normative assumptions etc. However, I didn't expect to so many other German scholars in particular to home in on the topic.

In this short post I just want to start a little list of books, chapters and articles that deal with metaphors and synthetic biology. There are probably loads of

others around which I have overlooked and I would be grateful to readers for sending me references to put on 'the list'.

Transparency

The first book I found is entitled Genetic Transparency? Ethical and Social Implications of Next Generation Human Genomics and Genetic Medicine. It appeared in 2016 and is edited by Malte Dreyer, Jeanette Erdmann, and Christoph Rehmann-Sutter, whose work I knew from the time we were both interested in stem cells and in the ethical challenges of communication the biological sciences. Here is the blurb for the book: "Genetic Transparency? tackles the question of who has, or should have access to personal genomic information. Genomic science is revolutionary in how it changes the way we live, individually and together, and how it changes the shape of society. If this is so, then – the authors of this volume claim – the rules that regulate genetic transparency should be debated carefully, openly and critically. It is important to see that the social and cultural meanings of DNA and genetic sequences are much richer than can be accounted for by purely biomedical knowledge. In this book, an international group of leading genomics experts and scholars from the humanities and social sciences discuss how the new accessibility of genomic information affects interpersonal relationships, our self-understandings, ethics, law, and healthcare systems."

Christoph and Malte Dreyer have contributed a really interesting chapter to this book, which deals with the idea of 'genes' - a sort of intellectual history of the word, with a lot of metaphorical reflections on the way. It also discusses modern and metaphorical ramification around gene editing, but focuses of course in particular on new ways of 'inspecting' ones genome and the promises and pitfalls of this new transparency. Well worth reading!

Worldviews

The second book I found has the word 'metaphor' in the title: Synthetic Biology: Metaphors, Worldviews, Ethics and Law. It is edited by Joachim Boldt and appeared in 2016. Here is the blurb: "Assessing synthetic biology from a societal and ethical perspective is not only a matter of determining possible harms and benefits of synthetic biology applications. Synthetic biology also incorporates a specific technoscientific understanding of its research agenda and its research objects that has philosophical and ethical implications. This edited volume sets out to explore and evaluate these synthetic biology worldviews and it proposes appropriate governance measures. In addition, legal challenges are discussed."

The book contains a chapter by Joachim Boldt himself, entitled "Swiss watches, genetic machines and ethics: An introduction to synthetic biology's conceptual and ethical challenges". The concluding remarks are intriguing and really worth thinking about: "When we, literally or conceptually, aspire to turn living nature into our tool, we ultimately turn our own origin into a tool. The inconsistency of this project comes to the fore most clearly when we direct it at our own nature. We are, and must always be, simultaneously the subject and object of our nature. By being unaware of this reality we risk fixating our own development on arbitrary ends. The effect would be that we would become prone to falling victim

to those arbitrary ends. Setting ourselves apart from the world of non-human life is easier. But still, that very world has given birth to us. It contains the seeds of all of our highest human abilities. We do not know what other valuable states it may lead to. If we attempt to fixate nature's ends on our own, we may, to our own disadvantage, miss important developmental properties of living beings and hinder the evolution of many sources of unexpected value. That is not what synthetic biology need or ought to be about."

Ambivalences

A third book I found is entitled: Ambivalences of Creating Life: Societal and Philosophical Dimensions of Synthetic Biology. It was published in 2015 and has been edited by Kristin Hagen, Margret Engelhard, and Georg Toepfer. Here is the blurb: "'Synthetic biology' is the label of a new technoscientific field with many different facets and agendas. One common aim is to 'create life', primarily by using engineering principles to design and modify biological systems for human use. In a wider context, the topic has become one of the big cases in the legitimization processes associated with the political agenda to solve global problems with the aid of (bio-)technological innovation. Conceptual-level and meta-level analyses are needed: we should sort out conceptual ambiguities to agree on what we talk about, and we need to spell out agendas to see the disagreements clearly. The book is based on the interdisciplinary summer school 'Analyzing the societal dimensions of synthetic biology', which took place in Berlin in September 2014. The contributions address controversial discussions around the philosophical examination, public perception, moral evaluation and governance of synthetic biology."

This book contains a fascinating chapter by Daniel Falkner, based in his PhD thesis and entitled "Metaphors of Life: Reflections on Metaphors in the Debate on Synthetic Biology". We even get an appetising abstract: "Metaphors play a constitutive and mostly underestimated role in science in general, in the modern life sciences and bio-technologies in particular, and also in the accompanying ethical debates. The current discussion on synthetic biology can be seen as a prime example for the different ways metaphors enter into an area of conflict between science, technology, society and ethics. There seems to be a connection between the paradigm shift in the epistemological approach, the technological development, the societal discourse and the metaphors that have been used to describe, explain and argue the new field of synthetic biology and its revolutionary nature. The goal of my paper is to outline an analytical frame to determine and decipher the specific role and functions of metaphors in the intersection of science, technology and society. I aim to analyze and criticize the innovative, critical, and argumentative functions of metaphors of 'life' in synthetic biology. This analytical frame will then be applied to the example of the metaphor of the genetic code which is the common reference point and driving force in a reconstructed story from Erwin Schrödinger to Craig Venter. This leads to a reassessment of synthetic biology between science and art and focusses on the obscuring and ideological dimension of metaphorical speech about the revolutionary nature of synthetic biology."

Conclusion
There seems to be quite a wave of interest, especially in Germany, in the ways that metaphors frame synthetic biology and in exploring the ethical, legal and social implications of such framings. This is a topic that began to intrigue me in around 2008/2009 and led to a chapter by Andy Balmer and Camille Herreman ("Craig Venter and the Re-programming of Life: How Metaphors Shape and Perform Ethical Discourses in the Media Presentation of Synthetic Biology") which I included in a book co-edited with Richard Elliott and Brendon Larson on Communicating Biological Sciences: Ethical and metaphorical dimensions. It would be nice to revive that project in light of all these new and fascinating developments and in view of the new interest in 'responsible language use' that Carmen and I have developed in our work for the SBRC here in Nottingham.

As Martin Döring said in his 2014 chapter: "Es metaphert gehörig im Kontext biotechnologischer Innovationen, und umso erstaunlicher ist es, dass selten eine kritisch-diskursive […] und systematische Analyse moralisch-ethischer Implikationen und normativer Annahmen […] in Metaphern vorgenommen wurde." (It's metaphorising immensely in the context of biotechnological innovations, and it is therefore quite surprising that the moral and ethical implications of and the normative assumptions inherent in the metaphors used are only rarely studied systematically." (pp. 216-217)

In some of the following posts I have tried to do just that.

The book of life: Reading, writing, editing

I have been observing the use of the 'book of life' metaphor in genetics and genomics since the year 2000, when it was used to announce that the human genome, our entire DNA, had been roughly sequenced. The Human Genome Project had begun in 1990 and was completed in 2003. Its achievement consisted in finding all genes in our human DNA (as it turned out, there were fewer than expected, only around 25,000 instead of the expected 100,000) and figuring out the order of the 3 billion building blocks of DNA, the nucleotides or bases. DNA, the well-known double helix, is strung together by the bases adenine and thymine, and guanine and cytosine: A-T and G-C. These are what is often called the 'letters' in which 'the book of life' (the genome) is 'written'.

This all sounds rather straightforward, but it's not. It also sounds rather neat, but it's not. As it turns out, this 'sequence' of 'letters' (bases), 'words' (codons) 'sentences' (genes), 'chapters' (chromosomes) and so on that seemingly make up the book of life is a real mess. I'll come back to this issue later – and to what it means for communicating about reading, writing and, most recently, editing 'the book of life'.

In this post I want to briefly look at how people have used 'the book of life' metaphor, from the 1960s to the present and see what, if anything, has changed. It would, of course, take a whole research project to do this properly. Some scholars have laid the foundations for such a research project, in particular Lily Kay in her (rather dense but well researched) volume *Who Wrote the Book of*

life?, a book published the year that a first reading of the human book of life was achieved. And there are other interesting books one can consult, such as Judith Roof 's 2007 *Poetics of DNA* and the older 1997 book by Richard Doyle entitled *Beyond Living: Rhetorical Transformations of the Life Sciences*, as well as Robert Pollack's 1994 book *Signs of Life: The language and meaning of DNA*. You can find more reading material at the end of this post.

Reading

In 1953 James Watson, Francis Crick, Maurice Wilkins and Rosalind Franklin figured out the structure of DNA, and in 1962 Watson, Crick and Wilkins received the Nobel Prize for this discovery. They laid the foundations for modern genetics and genomics and for 'reading the book of life'.

It's difficult to say who used the 'book of life' metaphor for the first time (if anybody knows, please leave a comment!). One of the first attestations that I have been able to find is Robert Sinsheimer's booklet entitled explicitly *The Book of Life* from 1967, in which he said: "In this book are instructions, in a curious and wonderful code, for making a human being. In one sense – on a subconscious level – every human being is born knowing how to read this book in every cell of his body. But on the level of conscious knowledge it is a major triumph of biology in the past two decades that we have begun to understand the content of these books and the language in which they are written." (Sinsheimer 1967: 5-6)

As Doyle pointed out, the metaphor of the book of life "transfers the reading practice out of the double helix and into the lab" (1997: 62). (The biological 'reading' practice is of course as metaphorical as the scientists' reading practice…) The metaphor also links this 'book of life' to the older 'book of life', namely that of the Bible, the book of Revelation, and implies that revelation can be achieved when scientists read our genomic book of life.

A year before, in 1966, Sinsheimer's colleague, George Beadle, had published, together with his wife Muriel, a book entitled *The Language of Life: An introduction to the science of genetics*, in which they speculated, for example, that errors could be erased from the gene pool (Kay, 2000: 291), an active intervention into the book of life that goes beyond being able to read or decipher it. It would take a few decades to flesh out this metaphor. (If you can, read this delightful review of this book by Albert Szent-Györgyi).

About two decades later, scientists involved in the Human Genome Project began to sequence the human genome, to decipher the 'book of life' and understand, to some extend, the 'language of life'. And now we come to an interesting bit of this post. In 'All English Language News' (as stored on the new database Lexis Nexis) the 'book of life' metaphor was first used in 1989 and the article that used it is entitled "Ethical questions plague gene research" (Tim Friend, *USA Today*, 4 October, 1989). Let's see what these questions are and whether they have changed over the lifetime of the book of life metaphor from the beginnings of the science of genetics to now, the age of gene or genome editing. I'll quote the article's summary of a meeting at length (leaving out paragraphs).

"But project leaders say that without giving our descendents [sic] guidelines for using the 'book of life,' its rewards could be overshadowed by conflicts. Among dilemmas raised at the meeting this week on the Human Genome Project:- Which fetuses should be sacrificed because of a defect? – When is it ethical to improve normal genetic traits? – Who is genetically unsuitable for certain jobs and insurance coverage? – When is a person's genetic profile no longer private? James Watson, head of the National Institutes of Health's arm of the project, says 3 percent of his annual budget – expected to be more than $ 60 million in 1990 – will be used to fund public education and studies of the issues. Dr. Daniel Koshland, meeting co-chairman, says there are no new moral problems raised by the work, 'but the increased visibility and the scale of the project will perhaps make the problems larger.' Koshland says people already face tough choices as a result of prenatal screening and tests for inherited conditions. But the most difficult issue to be resolved, he says, is how to use information that could exclude many from jobs that may be dangerous because of their genetic makeup. […] Says Dr. C. Thomas Caskey, Baylor College of Medicine, Houston, 'The public will benefit by open discussions of the issues. If they don't take place, people could become extremely suspicious of the project.'"

Guidelines for the use of 'the book of life' are still being written today and debates still rage around issue of enhancement, scale, alternatives, privacy and of course the involvement of 'the public' in these debates (see for example this project by the *Nuffield Foundation on Bioethics*).

Writing

In 2010, seven years after the full decipherment of the human genome, one of the leaders of the Human Genome Project, Francis Collins, published a book with the same title as George and Muriel Beadle's, but with a different subtitle: *The Language of life: DNA and the revolution in personalised medicine*. In 2003 Collins had said: "Today we celebrate the revelation of the first draft of the human book of life… it is humbling for me and awe inspiring to realise that we have caught the first glimpse of our own instruction book, previously known only to God", establishing a rather close link between the two books, the book of revelation and the book of life and feeding the hype that was swirling round the human genome project at the time, a hype that, until now has not quite been fulfilled, especially in terms of personalised medicine.

2010, the year that Collins published his book, was also the year when excitement about the genome and our increasing ability to 'read' the book of life was replaced by excitement about synthetic biology and the prospect of 'writing' and rewriting the book of life which means the prospect of writing new, synthetic DNA, rather than just reading DNA written by evolution.

In 2010 Craig Venter, one of the pioneers involved in the Human Genome Project, managed to create a first synthetic cell. In an interview with *Wired* magazine he said: "As the industrial age is drawing to a close, I think that we're witnessing the dawn of the era of biological design. DNA, as digitised information, is accumulating in computer databases. Thanks to genetic engineering, and now the field of synthetic biology, we can manipulate DNA to an unprecedented

extent, just as we can edit software in a computer." And more importantly: "All the information needed to make a living, self-replicating cell is locked up within the spirals of DNA's double helix. As we read and interpret that software of life, we should be able to completely understand how cells work, then change and improve them by writing new cellular software." The book of life has become the software of life and supercomputers are brought in to decipher it as well as (re)assemble it.

Editing

Five years later, we are reaching another crucial stage in the evolution of the 'book of life' metaphor. In 2003, when the human genome had been sequenced, I made a diagram for myself in which I tried to keep track of the cloud of meanings swirling around the book of life (see above). At the time, I thought that 'editing' the book of life was 'just' a metaphor. However, over the last decade or so, this metaphor has moved closer to reality.

In 2015 the book of life is being discussed in the context of 'genome editing', which involves a range of new technologies, such as CRISPR, which allow experts to edit genomes with much greater precision than before, i.e. to engage in almost literal cutting and pasting using 'molecular scissors'. They can insert, replace or remove DNA quite precisely and efficiently – and relatively easily. When baby Leyla recently received cancer treatment that involved gene editing it was announced by some as: "Gene editing: A cut-and-past cure for cancer".

Lots of people have written about 'gene/genome editing' and, as in 1989 (see above in the section on 'Reading'), have asked for a public debate about the matter. However, a public debate about what should be done or not be done to 'life' can only happen if people can distinguish between metaphor and reality, as well as between what's doable and what's not doable.

As Anjana Ahuja, wrote in the *Financial Times* (June 28, 2015), in an article entitled "Geneticists' quest for crisper prose in the book of life", "Imagining ourselves as glorified books, penned in the language of genes, is a fitting analogy as we muddle on. At some point, society must decide whether any person deserves to be a perfect piece of prose, or whether we should each remain an unedited thriller with an unpredictable ending."

"Don't forget the introns"

There is talk again about the creation of designer babies and this brings me to the 'mess' I alluded to at the beginning of this post. In a blog post entitled "Ethics of editing the book of life", we find this ominous paragraph: "One possible application that has been suggested [for genome editing] is 'correcting' the germline: changing the genetics of sperm, eggs and embryos, to eliminate diseases not just in individuals, but in future generations. The designer baby is in production."

In 2003, when drifting into the social and cultural study of science from linguistics, I was writing about the designer baby debate that raged already at that time. In my usual suck it and see manner, I emailed Lord Winston (then

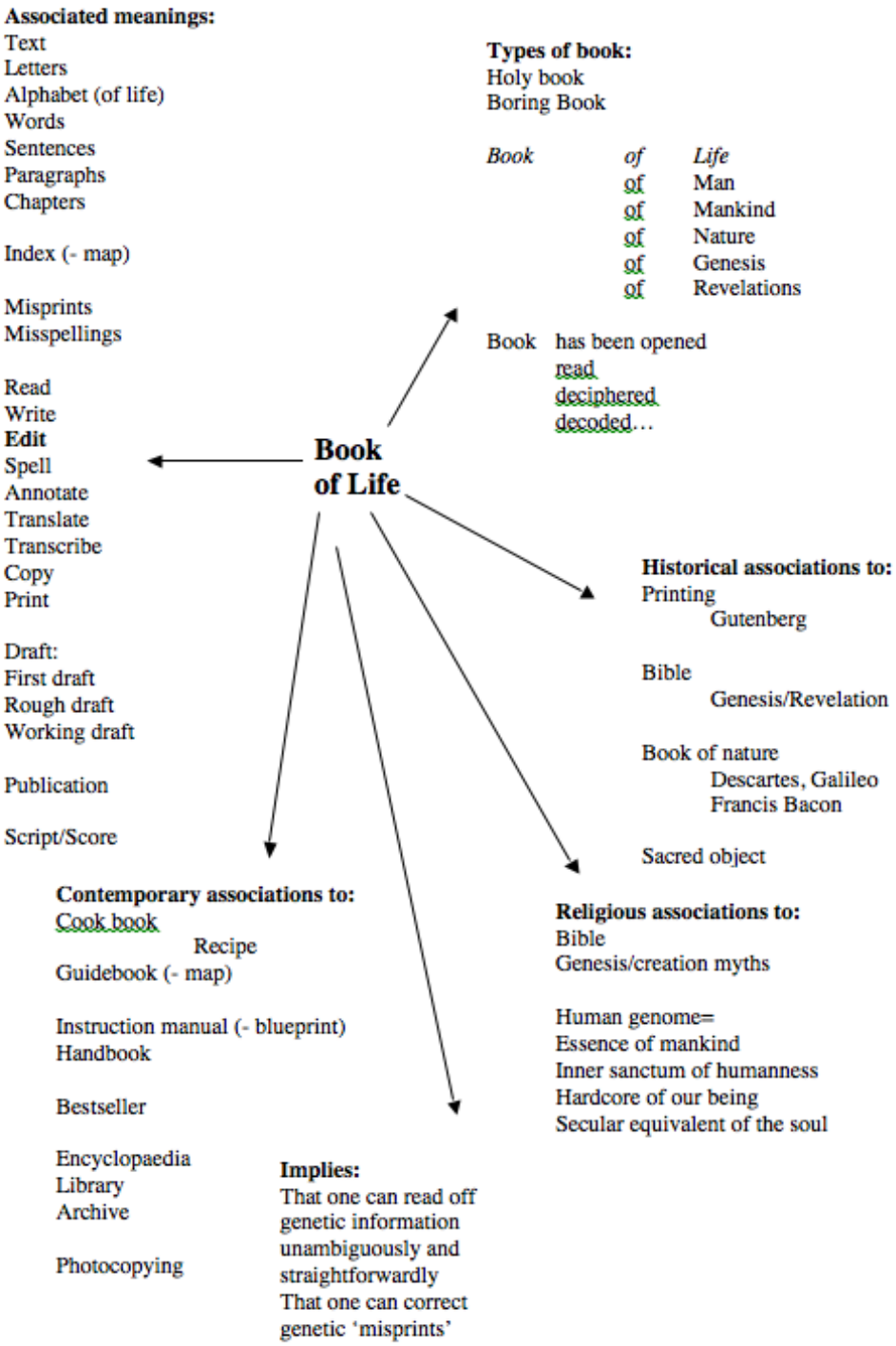
Professor of fertility studies and now Professor of Science and Society at Imperial College) and asked him about things. I still remember, but no longer have, his email in which he said basically: "Don't forget the introns". At the time, I had no idea what he meant. In the meantime I have learned a bit more.

I was reminded again of Lord Winston's advice when reading the following sentences, penned by Jerry Coyne, and provoked by an xkcd cartoon that claims 'rightly' (in my view) that biology should be impossible: "Our genes are ***not*** perfectly adapted and beautifully designed. They are a horrible, historical mess". And: "For reasons we don't understand, many eukaryotic genes (that is, genes in organisms with a nucleus – so all multicellular organisms and some single-celled forms, too) are sometimes split up, interspersed by apparently meaningless sequences, called 'introns'." And that's of course only the tip of the iceberg, an iceberg made of junk and dark matter that litters our cherished book of life – to mix a few metaphors ….. As Steven Pinker recently said: "Genetic editing would be a droplet in the maelstrom of naturally churning genomes."

Complexity and communication

So, biology is practically impossible, the genome is incredibly complex and although genome editing or editing the book of life is getting more and more precise, its application interferes with radically complex biological and moral systems, and its consequences cannot yet be anticipated or controlled. The question is: How do you talk about all this in an open public debate? To this question I have so far not seen an answer. As Professor Joan Leach, a science communication expert from Queensland University, Australia has pointed out, there are, of course, dangers in telling simple stories (using, for example the simple metaphor of the book of life or the simple story of genome editing), but so far we don't know what the advantages are of embracing complexity in public communication. This too is an experiment. And like genome editing itself, a public debate about genome editing has to take into account a very complex and, in this case, culturally, linguistically and morally diverse context, where outcomes are difficult to anticipate and control.

As we have seen, the hopes, hypes and concerns surrounding the book of life metaphor have remained almost constant over time, while, at the same time, the metaphor has moved closer to reality. However, we should still be careful to not confuse hype with reality. The book of life will always be complex, complicated and messy, and reading, writing or editing it will never be as straightforward as it might appear to be or to become. Metaphors like 'the book of life' or 'genome editing' are useful in encapsulating all this complexity, but they can only afford us glimpses of what's going on. They should not be taken as literal representations.



Gene editing, metaphors and responsible language use

Last week I was following the progress of the International Summit on Human Gene Editing, which took place in Washington between 1 and 3 December, 2015. On the last day, I was looking at my twitter timeline and saw that Megan Allyse (a former PhD student) had posted information on a special issue devoted to gene editing published by the *American Journal of Bioethics*. This issue not only

contained an article by Megan herself on reproductive CRISPR, but also an article by Meaghan O'Keefe and others on gene editing and metaphors.

For a long time, I have been interested in how metaphors are used to make genetics, genomics, microbiomics, epigenetics and synthetic biology public. So I was of course excited to read this article, especially since I had quite recently blogged about the 'book of life' metaphor in the context of CRISPR gene (genome) editing.

As people who read this blog know, I am a keen observer of metaphors in public discourse and I think that metaphors are extremely important in science and society. Metaphors provide us with ways of seeing the world in certain ways, for good or for ill. They represent "inferential shortcuts" and help us form and sustain basic "reasoning patterns" as O'Keefe et al. have pointed out quoting work by Dncygier and Sweetser (2014) (O'Keefe et al., 2015: 4). If we want to engage openly and critically with advances in genomics and gene editing in particular we should keep an eye on the language we use to speak about these developments. Metaphors can open our eyes to new developments but they can also blind-side us.

As this is a bit of a long read, here are some sign posts. First I'll briefly summarise some of the insights from the O'Keefe et al. article based on analysing American press coverage of CRISPR (but obviously you should read the article yourself!), then I'll do a rough and ready run-through the UK press coverage. Both the US and UK press seem to use similar metaphors (but more research is needed). I'll then home in on the 'designer babies' metaphor and urge people to think about responsible language/metaphor use.

Gene editing metaphors in the American press

O'Keefe and her colleagues have been the first to look systematically into the role of metaphors in shaping the emerging public meaning of gene editing by investigating the use of metaphors in American newspapers and popular science publications. They searched a selection of American newspapers and popular science sources and found that CRISPR was first mentioned in their sources in January 2013 and they stopped their search on July 11 2013. They found 45 articles dealing with CRISPR, 22 from newspapers and 24 from popular science publications, such as *Popular Science* for example. These articles were analysed qualitatively and metaphors were extracted.

The overarching metaphors they found were both old and new ones. The old 'blueprint' metaphor, which has been used for the human genome for decades, is still in use, as well as the 'code' and 'map' metaphors. Newer ones are 'gambling', 'mechanism', 'medicine' and 'origami' (some, i.e. my son, tell me that the metaphor of 'kirigami' might be better in this context, as it includes cutting of the paper, rather than solely folding the paper). 'War and fight' metaphors were found as well, as in 'CRISPR system to block the attack of…". Under the overarching metaphor of 'medicine' we find talk of 'scalpel', 'surgery', 'snipping' and so on. The authors also say that the most common metaphor they found is that of the genome as 'text' and that the idea of 'editing' appears in nearly very

article. There are of course also references to 'cutting and pasting' (p. 7), 'scissors' and so on. A new metaphor found in the articles they studied is that of 'targeting' (a rather popular metaphor in the discourse of nanomedicine), used "both to emphasize precision and to warn of the dangers of unintended cuts", that is, 'off-target' mistakes in the editing process (p. 8). (Sir Mark Walport, the UK's Chief Scientific Advisor, recently extended that metaphor nicely in a thoughtful newspaper comment on gene editing when he asked: "whether this is a magic bullet or whether there will be off-target effects", 9 December).

The article concludes that "[o]verall, although CRISPR metaphors are not settled, the metaphors that are gaining traction obscure and mislead in important ways. They do not accurately describe what CRISPR does: CRISPR alters cells and Cas9 can chop up the wrong DNA. Questions about the prevalence of 'off-target' effects and whether they will extend to germ cells can fail to gain adequate traction in public debates. This is compounded by editing metaphors that inaccurately convey precision on the one hand and obscure what is not currently known about CRISPR on the other."

Like John Avise in 2001, the authors speculate about whether one can find better metaphors, such as ecological ones that might capture the complexity of interfering with genes and genome more accurately (p. 8).

But can the 'editing' metaphor be put back into its metaphorical bottle? I doubt it – the authors of the article and I myself are, for example, using it in the title of our article/post! However, I'd advocate that scientists who use it take care to contextualise it and provide some nuanced information about the metaphor's limits.

Gene editing metaphors in the UK press

I wish I had time to do an equally thorough analysis of the UK newspaper output on gene editing as O'Keefe et al. did for the American press, and one day I might sit down and do this. In the meantime this nice paper inspired me to take a quick look at things.

Instead of looking at a selection of newspapers, I went to Lexis Nexis and probed 'All English Language News' items in their entirety (about 3100 articles). I found that the word CRISPR was first used on 26 March 2007 in a press release by Danisco which announced that "Researchers from Danisco have published what it has described as groundbreaking research into microbial acquired immunity which could open new perspectives in the battle against viral infections. Scientists from the food group's Cultures Division have established for the first time the relationship between Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and resistance against bacterial viruses, known as bacteriophages. CRISPR form peculiar regions in the genome of numerous bacterial species." (just-food global news, March 26, 2007)

Between 2007 and 2012 'CRISPR' seems to have been used mainly in press releases and news-wires about research dealing with bacteria (viruses, phages), in particular the microbial immune system. Here we find some of the 'war/fight'

metaphors discussed in O'Keefe et al.'s article such as bacterial defense system, how bacteria fend off invaders and so on. Research is linked to the microbiome project as well as research into antimicrobial resistance. As a recent article in New Scientist pointed out, the new gene editing technique is "derived from a mechanism that bacteria use to fight off viruses", an unexpected spin-off of basic science.

On June 28 2012 there is a first headline announcing "Programmable DNA scissors found for bacterial immune system discovery could lead to editing tool for genomes" (States News Services, June 28, 2012). More and more articles begin to discuss this new 'gene probing' or 'gene editing tool' (also a tool that can turn genes 'off and on'). In August 2013 the company Sigma Life Sciences was reported to have launched a CRISPR/cas editing tool (PR Newswire). Genes are now seen as almost under the 'control' of scientists.

In November 2013 mainstream media, the UK's Independent in particular, began reporting on gene editing, at the same time as scientists called for a public debate. This debate has now started in earnest with the recent gene editing summit. In figure 1 you can see the rise in interest over time from 2007 to 4 December 2015.

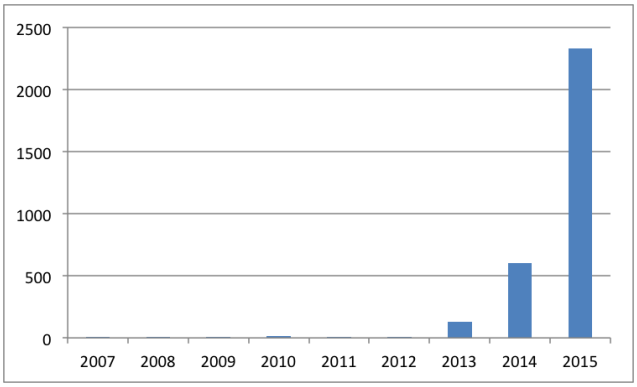


Figure 1: Rise in coverage of 'gene editing' in 'All English Language News'.

But what about the UK coverage of gene editing in particular? As one can see, the Independent seems to be in the lead in covering gene editing, followed by the Daily Mail and the Guardian.

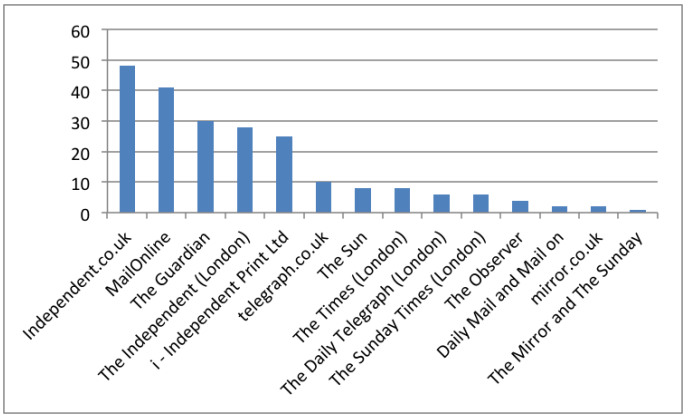


Figure 2: Distribution of newspapers covering CRISPR in the UK, 2013-2015

In the UK Press news paper coverage starts with a comment piece on a 'triumph of basic science' by Craig Mello (2006 Nobel Prize for physiology or medicine for the joint discovery of RNA interference) (The Independent, 6 November, 2013). Like many attending the human gene editing summit last week, Mello argued that "I wouldn't be surprised if someone at some time does suggest using Crispr on human IVF embryos because the technology is so easy to do. But I certainly think this kind of germline gene therapy should continue to be banned for the foreseeable future. There are so many other great ways to use Crispr for the common good."

In the end the summit "ruled out a ban on modifying human embryos that are destined to become people. But the experts made clear that altering the DNA of human embryos for clinical purposes was unacceptable given the unknown risks today and noted that even the most compelling cases to use the procedure were limited." (Guardian, 3 December). But what sort of metaphors were used in the UK press over the last two years? I can, of course, only do a very cursory analysis for this blog post, based on quickly scanning the headlines of the circa 200 articles that were published in the UK press up to the 4th of December.

Two routine metaphors in reporting on scientific advances were used frequently, namely that of 'breakthrough' and 'revolution'. Such metaphors have been critically analysed in the past by Nik Brown and myself.

The word 'editing' is of course employed throughout the press coverage, and we hear about editing (the DNA of) monkeys, wheat, woolly mammoths, pigs, dogs, embryos, insects, mosquitoes, even (metonymically) "humanity" as a whole (The Independent 24 April 2015).

The metaphor of (molecular) 'scissors' was used from the start. The same day that Craig Mello published his comment in The Independent, Steve Connor, the Independent's science editor published an article on CRISPR which explains this new technology really well, delves into its history (and its links to research on bacterial immune systems) and uses a well-entrenched genomic metaphor, namely that of 'junk DNA'. It also uses the now standard metaphor for CRISPR as a pair of molecular scissors (The Independent, 6 November, 2013):

"Crispr stands for 'clustered regularly interspaced short palindromic repeats', a devilishly contrived acronym which just about sums up why it was ignored for so long. For nearly two decades after Japanese researchers first discovered Crispr in bacteria in 1987, scientists mostly dismissed it as 'junk DNA'. In fact, the apparently nonsensical sequences within Crispr, which were repeated in palindromic order (the same backwards as forwards), did have a purpose and were far from junk. About six years ago, scientists discovered that these DNA sequences matched the genetic sequences of various viruses that attack bacteria, which led to the discovery of a sophisticated bacterial immune system. Far from being junk, Crispr was actually a way of storing the genetic information of an

invading virus in the form of a palindromic DNA sequence. The bacteria used this genetic memory to target the viral invader by chopping it up with powerful 'Crispr-associated' (CAS) enzymes capable of 'cleaving' its DNA molecule, just like a pair of molecular scissors." (I have left out paragraphs)

On March 11, 2015, the Mail Online speaks of "cellular scissors". In this context, the phrase 'cut-and-paste' is used quite frequently, as in "cut-and-paste DNA (Guardian 30 January, 2014); "cut-and-paste gene slicing technique" (Mail Online, 31 January 2014); "'cut and paste' technique for precision editing of human genome" (i-Independent, 28 July, 2015).

As observed in the analysis of American press, precision is claimed to be possible. On 21 April 2014 The Independent talks about "pinpoint accuracy". There is talk of a "gene correction technique" (Independent, 5 August, 2014), of "gene repair" (Mail Online, 6 November, 2015), of "find, replace – and cure" (Guardian, 2 September, 2015), of being able to "upgrade our DNA" (The Observer, 10 May, 2015). All this conjures up images of control even, as a Sunday Times headline proclaimed, a "Battle for control of gene editor that rewrites species" (6 September, 2015) – using the ubiquitous metaphor of reading, writing and editing the genome as a text.

However, quite early on, the Independent's Editorial, published on 6 November 2013 (together with Mello's and Connor's articles mentioned above), cautions against conjuring up the spectre of the metaphorically named 'designer babies'. Designer babies have loomed large in ethical debates about gene editing. On 20 January, 2015 The Mail Online carried the headline "Designer babies could one day be created 'with 100% efficiency' says leading scientist – and warns society needs to think through the consequences", quoting, I should stress a scientist, namely, "Dr Tony Perry, a geneticist at the University of Bath", who "said that society needed to be prepared for the day parents can choose certain traits in their children." The Times had a headline: "GM embryo brings designer babies a step closer" (24 April, 2015); and The Mirror talked about "designer baby fears" (18 September, 2015). Reporting on the conclusions of the recent summit, the Mail Online reported "'Designer babies' are ruled out FOR NOW – but experts fall short of banning use of gene editing in humans in the future" (4 December, 2015). Even New Scientist couldn't quite stay away from the topic of designer babies in an article that online carries the headline "Will CRISPR gene editing lead to designer babies?" (2 December, 2015). In the print version the title is: "The Life Editor".

Responsible language use

Talking about banning things… I think it will be impossible to 'ban' the metaphor 'gene editing', however misleading it might be in conjuring up visions of precision and control. We should however 'ban' the metaphor designer babies, I believe, as jokingly suggested by Megan Allyse in a recent tweet (4 November) (she used the word 'eliminate', not 'ban'). The metaphor of designer babies evokes images of being able to control all human traits and tweaking them at will, which is simply scientifically impossible. I agree with A Cecile JW Janssens

who wrote a very good piece for *The Conversation* entitled "Forget about designer babies – gene editing won't work on complex traits like intelligence".

We should not only try to think about the potential impacts of science and innovation on society when, as we are now all supposed to do, engaging in 'Responsible Research and Innovation'. We should also reflect on responsible language use! As Christoff Kueffer and my friend and colleague Brendon Larson have argued, "metaphors should be carefully chosen and evaluated alongside empirical evidence, because they shape data interpretation and how science influences society" – and, I would add, how society influences science! We should also not forget the power of visual metaphors. Scissors are becoming quite ubiquitous when reporting on gene editing for example.

Calling for a social and ethical debate about CRISPR and gene editing is not enough. We have to understand not only how this new technology really works, but also how it is being socially, culturally and metaphorically framed – and most of all what the political implications of such framings are. Focusing on designer babies might not be conducive to the global ethical debate that people are yearning for.

PS: If somebody wants to carry out an analysis of metaphors used in the context of the emerging debate about 'gene drives', they could start with this article entitled, nicely metaphorically "Gene drives spread their wings" (and have a look at the visual metaphor too!)! Research into gene drives has been overshadowed by debates about gene editing, especially human gene editing, but also deserves social, political and linguistic attention.

On the metaphorical origin of gene drives

This morning I woke up to a bit of chat about 'gene drive' – this year's science breakthrough of the year –, first on twitter, then on the radio. This made me think about the use of terms like *gene drive*, *gene driver*, *gene driving* and where they come from. It also made me think about the metaphorical and visual images they conjure up, that is, about the issue of scientific and cultural imagination.
Gene drives on twitter and Radio 4.

At about 06.55 I saw a tweet from Jack Stilgoe saying that he was on his way to York to talk about gene drives on the Radio 4 Today programme. Roland Jackson then asked Jack whether he had listened to Huw Jones earlier on in the programme. I looked at the schedule. I had missed Huw's item by a few minutes:
"0650: Science magazine's breakthrough of the year is 'gene editing' but scientists are now excited about 'gene driving' because it offers the potential to eradicate some deadly viruses. Huw Jones is professor of molecular genetics at Rothamsted Research."

I then tuned in to listen to the next item on the schedule which focused on 'gene drives', a genetic engineering technology which has recently received a boost and become much easier to develop with the advent of the gene editing tool

CRISPR/Cas9. It potentially allows scientists to eradicate diseases like malaria by eradicating the insect population that spreads the disease.

"0810: Science magazine's breakthrough of the year is 'gene editing' but scientists are now excited about 'gene driving' because it offers the potential to eradicate some deadly viruses. Tom Feilden reports and we hear live from Charles Godfray, Hope Professor of Zoology at the University of Oxford and Jack Stilgoe, senior lecturer at the UCL Department of Science and Technology Studies."

Gene drives are attracting a lot of attention, most recently in a House of Lords report which argued for field trials in Britain, followed by an article for *The Guardian* by Jack and Sarah Hartley here at the Making Science Public programme arguing for more caution and an approach based on 'Responsible Research and Innovation'. The 8.10 item on Radio 4 is worth listening to in this respect, as caution is advocated by both experts interviewed for the programme and as Tom Feilden sets out the pros and cons nicely in his introductory piece.

A few minutes into the programme, at 8.16 I saw a tweet from Oliver Morton, entitled 'gene drive prehistory' which showed the cover page of a 2003 issue of New Scientist illustrated with a wonderful pen and ink drawing of a mosquito with malaria written through it (probably by Belle Mellor, as Oliver Morton told me). The title page also carries the phrase 'genetic annihilation' which, like the word 'extinction' used in the Radio 4 programme, evokes some fears alongside the hope of eradicating fatal diseases like malaria, using GM insects/gene editing/gene drives. (This blog post was written before the Zika outbreak swept through the news)

As I am always interested in the origins of words, phrases and concepts, all this radio and twitter chat made me think about two things: (1) The etymology of the words 'gene drive' (and associated words used in announcing the Radio 4 Today item during which Jack Stilgoe was interviewed, namely 'gene driver' and 'gene driving', which were new to me), and (2) the images used to think and talk about this new technology. Basically, how are gene drives verbally and visually imagined? When trying to find out about these things, they nicely came together.

Gene drive's locomotive metaphor

Gene editing and *gene drive* are not yet in the *Oxford English Dictionary* and I can't yet find any useful information about their etymology. I therefore asked on twitter whether anybody knew who first used the term and got a totally truthful answer from *Synthetic Future(s)* (at 8.41): "I first used the term in 1983. After a luncheon of devilled pike and several glasses of port…" (I was just typing this, when my husband came in and asked me whether I wanted a glass of port to "stiffen the sinews"! I said it was a bit too early for that… but anyway… "Once more unto the breach, dear friends, once more"… with a cup of coffee).

As far as I can make out by looking at the news database Lexis Nexis, 'gene drive' was first used only quite recently in *All English Language* news, namely on 25 July 2007 in *US State News* in an article based on a press release. It starts by

saying: “A decade ago, scientists announced the ability to introduce foreign genes into the mosquito genome. A year ago, scientists announced the successful use of an artificial gene that prevented a virus from replicating within mosquitoes. But how does one apply what can be done with a small number of mosquitoes in a lab to the tens of millions of mosquitoes that spread disease worldwide?”

The article uses the phrase *gene drive* here: “Working with Aedes aegypti, the mosquito that carries yellow fever and dengue fever viruses, the researchers are working to create a ‘gene-drive system’ by using instructions copied from the nanos (nos) gene, which is essential for germline formation. ‘Think of the nanos instructions as a key to a room,’ Adelman said.”

I then tracked down Oliver Morton’s March 2003 article for *New Scientist* entitled “Splat!” and that proved very useful indeed (New Scientist177.2387 Mar 22, 2003: 32,34-35). In fact, it led me to the metaphorical source of ‘gene drive’ (I believe). Here is the abstract of the article: “Strange properties of DNA sequences called homing endonuclease genes (HEG) can be used to eradicate the whole species of mosquito. These genes have the capability to evade the normal rules of heredity, exploiting a loophole to get extra copies of themselves into the next generation. Morton discusses further the characteristics and behavior of HEG and its effects on mosquitoes.”

Oliver Morton reported on research carried out by Austin Burt at Imperial College London, especially on his 2003 article entitled “Site-specific selfish genes as tools for the control and genetic engineering of natural populations.” But he also points out that “Burt is not the first person to consider messing around with mosquito genes in order to tackle malaria. Chris Curtis of the London School of Hygiene and Tropical Medicine, has been publishing on the subject since the late 1960s, and recently the field has been positively swarming with ideas.”

I won’t summarise the whole article, which is well worth reading, if you can get access to it. What’s important is the following paragraph which seems to show that the phrase ‘gene drive’ has its metaphorical source in thinking about trains and locomotives!

“To solve this problem [spreading genes that make mosquitoes less likely to transmit malaria through a population at large], the resistance genes need to be hitched to a ‘driver’ – a piece of DNA that spreads for some other reason. Various drivers have been discussed, including transposons and parasites that live within the mosquitoes’ cells, but they all share a significant drawback. ‘The crunch problem,’ says Curtis, ‘is how you make sure that the thing you want driven remains linked to the driving system.’ If you think of the driver as a locomotive and the things you want driven as the carriages, he says, then if the coupling between them breaks, the locomotive will drive off into the distance while the carriages start to roll backwards. There’s always a risk that a new mutation will uncouple the driver and its carriages, and even if the chances of this happening are very small, it’s still a fatal flaw. Work by some of Curtis’s colleagues suggests that if the engineered mosquitoes are just 20 per cent less fit than wild ones, and even if the chance of uncoupling is as low as one in a million, the locomotive

always runs away and the resistance genes die out. To Curtis, that looks like the end of the line. 'If we don't have a reasonable prospect of driving those genes into wild populations, there's no point.'"

However, only with the advent of the gene editing tool called CRISPR/Cas9 could gene drives 'take off', and edited genes can now potentially be 'driven' through a whole population of insects relatively easily.

Visual metaphors

So now that we have discovered the verbal metaphorical source for 'gene drive' (which however no longer seems to drive modern thinking/imagination about gene drives), what about visual metaphors? The only one I have found so far is an illustration that depicts a mosquito made up of cog wheels (unfortunately not quite locomotive parts) and which accompanies the imaginatively entitled article "Gene drives spread their wings" from December 2015.

I also put 'gene drive' into Google images to test the waters and only got boring diagrams, nothing imaginative, interspersed with now ubiquitous images of blood sucking mosquitoes, also used to illustrate the Radio4 Today programme featuring gene editing and gene drives. Does anybody know about more metaphors and images related to 'gene drive'? I'd be interested to collect them! And of course, if anybody knows who really used 'gene drive' for first time….probably somewhere around 2005…

On books, circuits and life

I have recently been trying to understand CRISPR, gene editing and genome editing. While reading about these new developments in genomics, I noticed that in the avalanche of news reports reference is only rarely made to synthetic biology (on 5 January there were 188 articles on CRISPR in *Major World Newspapers* on the LexisNexis news database; of these only 12 mention synthetic biology). I am not quite sure why this is, but when musing about this, I began to wonder whether the language used in the media to talk about CRISPR and gene editing doesn't quite mash with the language used to talk about synthetic biology. I then began to look more closely into how synthetic biology and gene editing are being framed. I found some interesting similarities, but also some differences. I'll report on these before reflecting on some problems with the master metaphors that are circulating in science and society and through which we tend to see synthetic biology and gene editing.

The book of life – take 1

Gene editing (which I'll use here as an umbrella term for genome editing, DNA editing etc.) is rooted in an old metaphor according to which a genome is a 'book of life' or a 'code of life'. For a long time, the metaphorical reader, writer and editor of that book or code was 'nature' or 'evolution'. In their book on the Human Genome Project (HGP) entitled *The Book of Man* (1997), Bodmer and McKie talk for example about the fact that bits of DNA are "snipped out and

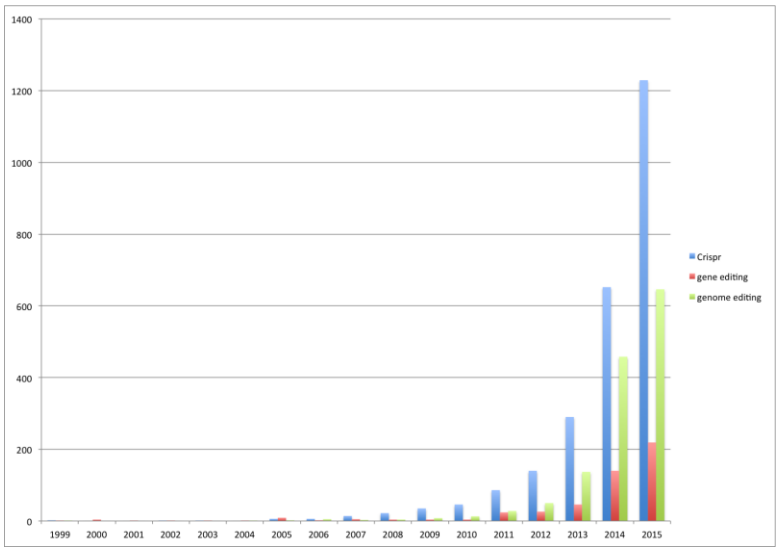
dropped on the cutting room floor" – here the book becomes a film – "during the business of gene editing when DNA is turned into messenger RNA" (p. 81).

Some twenty or so years ago we humans gradually began to master the language in which the book of life was written and began read it ourselves, to decipher or decode it during the era of the HGP. In fact the 'book of life' metaphor evokes almost instantly the human genome, although every living organism has, of course, its own book of life. During and after the HGP (1990-2003 and beyond) there was much talk about us being able to edit this book of life, something that in the case of the human genome is however rather difficult.

Cutting and pasting

A decade or two before the beginning of the HGP, 'gene editing' had begun to be practised by scientists but without reference to the 'book of life' or indeed 'gene editing' as it's metaphorically used today (I believe). During the era of recombinant DNA, in the 1970s, scientists began to 'cut and paste' DNA using restriction enzymes. They also used bacteria as tiny factories to mass-manufacture products, a metaphor that is still being used in synthetic biology.

"Precise edition of a genome with controlled DNA modification at a targeted location was first performed in the 1980s by gene editing through homologous recombination." Later on, more efficient and reliable methods or tools were developed for gene editing, such as zinc-finger nucleases, Transcription Activator-Like Effector (TALE) nucleases, and most recently CRISPR (see also here for good overview). From the early 2000s onwards, and with a spurt in the last few years, 'gene editing' and 'genome editing' began to be used increasingly in scientific articles as metaphors/technical terms. (Figure based on numbers of articles found on the SCOPUS database)



It is interesting to note that to describe these gene editing tools, analogies are still based on rather old-fashioned editing technologies (and their images), such as scissors and erasers, while in real-world book editing these have long been replaced by the word-processor!

The book of life – take 2

The HGP focused on reading and deciphering the human 'book of life'. Recombinant DNA research and the gene editing practised then focused initially on bacteria. Bacteria also became the focus of an enterprise that started when the HGP ended in around 2003, namely synthetic biology. Synthetic biology was heralded as availing scientists with the power to write or re-write 'the book of life'. This metaphor was used quite prominently around 2010 when Craig Venter built or 'wrote' the genome of a bacterium and almost literally left his team's signature on it. Synthetic biologists have been writing or trying to write synthetic genomes ever since. However, this work has been framed not only by the book metaphor, but also, and even more so, by engineering metaphors.

The circuit of life

We can now cut and paste, indeed edit, genes in and out of (human, animal, plant, bacterial etc.) genomes; we can, of course, also turn or switch genes on and off. And here we enter a different metaphorical field governed by a different master metaphor to 'the book of life' one. We might call it the 'circuit of life' (this is a metaphor I invented, not one in general use!). This metaphor shifts the way we talk and think about genes and genomes away from the book (and cutting and pasting and editing paper) and towards the machine and the computer. We have all heard about the *International Genetically Engineered Machine competition* (iGEM), the gateway to synthetic biology. Circuit and machine metaphors (and the older factory metaphors) dominate thinking and talking about synthetic biology, which has, indeed, been defined as the "application of rigorous engineering principles to biological system design and development".

The first inroads into synthetic biology were made when scientists created 'synthetic genetic circuits'. And it is synthetic biology's ambition to build or create circuits/machines/organisms that do not yet exist and to make them programmable and able to perform certain tasks. This is not what a book does, but it is linked to what a computer does and what one does with computer code.

The code of life

The metaphor of the 'code of life' (probably first used by Schrödinger) bridges the two master metaphors of the 'book of life' and the 'circuit of life'. Although gene editing by its very name focuses our metaphorical attention on editing genes in and out of genomes, CRISPR is also said to be able to turn genes on and off. It can be used in synthetic biology to build more complex synthetic biology circuits, that is, to scale things up more easily and also to test, control and measure things more easily. CRISPR as a new gene editing tool provides scientists with precision 'molecular scissors' that can be better targeted and better controlled. Some people talk about this tool as "a programmable machine for DNA cutting. Compared to TALENs and zinc-finger nucleases, this was like trading in rusty scissors for a computer-controlled laser cutter".

The book of life – take 3

And here we are circling back to the 'book of life' and in particular the 'book of man'. Over and above making better and more complex 'circuits' for synthetic biology, CRISPR can also be used, potentially, to 'edit' genetic disorders in

humans affected by them (in vivo, so to speak), or to create 'gene drives' that drive an edited gene through a whole population of disease spreading insects – all uses that go well beyond synthetic biology's engineering ambitions. The most controversial issue relating to gene editing is that it potentially could be used to change the 'germline', that is, the genetic material that is passed on to the next generation – this could really change 'the book of life'.

Artefacts and organisms

It is common practice to examine the ethical, social, legal, regulatory etc. issues posed by bio-technologies used to create or change living organisms, be they humans or bacteria. It is not so common, but, I contend, should be more common, to also inspect the linguistic 'technologies' we use to talk and think about them, that is, the metaphors we use, especially those that make the rewriting and redesigning of life look so easy.

We should keep in mind that books and circuits (and machines) are man-made artefacts. While such artefacts afford us with man-made metaphorical lenses through which to study life (and genes and genomes), they don't always provide us with an altogether clear vision of our objects of study, of those (the scientists) who study them, and of the futures they will shape.

Artefact-based metaphors overexpose our power and control over genes and genomes and they underexpose the messiness and clumsy 'architecture' of living things. They foreground control and background complexity.

Some people have therefore tried to find new 'master metaphors', while others have proposed to just create awareness of the bewitching power of the sometimes "misleading" metaphors in circulation, so that scientists can get on with their work after having thrown them away. In their article "The mismeasure of machine: Synthetic biology and the trouble with engineering metaphors", Boudry and Pigliucci (2013) argue that: "While we acknowledge that metaphorical and analogical thinking are part and parcel of the way human beings make sense of the world in some highly specialized areas of human endeavour, it may simply be the case that the object of study becomes so remote from everyday experience that analogies begin to do more harm than good." (p. 667)

Or, to quote Wittgenstein, probably inappropriately (and I replace 'propositions' with 'metaphors'): "My [metaphors] serve as elucidations in the following way: anyone who understands me eventually recognizes them as nonsensical, when he has used them—as steps—to climb up beyond them. (He must, so to speak, throw away the ladder after he has climbed up it.)" (*Tractatus Logic-Philosophicus*, 6.54)

Precision metaphors in a messy biological world

The promises of nanoscience and nanotechnology have been framed by a variety of future oriented metaphors, such as the those of the fantastic voyage or the

master builder. The former metaphor has been especially prominent in early reports on the promises of nanomedicine, but it is still in use today. What happens when real breakthroughs are announced? Is this fictional backdrop still used, or do other metaphors become more prominent, especially those used traditionally to talk about the work of medicine? What does this mean for the public understanding of nanomedicine? And what can current developments in gene editing and, what one may call, genomic medicine learn from thinking about these metaphors?

Nano-bullets

I have been interested in the visual and metaphorical framing of nanotechnology for a long time and these questions popped back into my head when I came across an article in *The Times* by Tom Whipple. The article was entitled "Microcannon firing nanobullets: The future of targeted medicine" (1 February, 2016). The first paragraph of the article reads like this: "The idea of 'targeting disease' just got less metaphorical. Scientists have developed microscopic cannons that can be injected into patients and triggered remotely, firing drugs deep into tissue." Overall, the word (nano)*bullet* is used 9 times (we even get told about a 'magic bullet'!) in this 525 word article, and the word (micro)*cannon* is used 12 times (mostly in quotes from scientists).

This reminded me of an essay I once wrote in which I studied a similar article published in *The Times* written by Mark Henderson and entitled "New attack on cancer with nano-weapon" (5 November 2009). In this article we don't hear about *bullets* but about *warheads* and *smart bombs*. Both articles are about 'targeted' drug delivery using nanotechnology. The target metaphor is of course also used in synthetic biology, as O'Keefe and her colleagues have shown.

In my 2012 essay I tried to grapple with the way 'evil metaphors' (relating to military weapons) are used to talk about improving human health and whether the knowledge they convey is more illusionary than real. A more thorough analysis of this dilemma (evil metaphors for the good of human health) was written two years later by the French philosophers of science Bernadette Bensaude Vincent and Sacha Loeve. Their article, published in *NanoEthics,* is entitled "Metaphors in Nanomedicine: The Case of Targeted Drug Delivery". As they point out: "No matter whether you want to heal people or kill them, no matter whether your action is good or bad, the ultimate values are control and precision." (p. 4)

The two philosophers summarise the framing of precision nano-medicine in the following way: "The missile metaphor, reminiscent of Paul Ehrlich's 'magic bullet', has framed the problem in simple terms: how to deliver the right dose in the right place at the right moment? Chemists, physicists and engineers who design multi-functional devices operating in vitro can think in such terms, as long as the devices are not actually operating through the messy environment of the body." (p.6)

In their view this metaphor blends out the messiness of the bodily environment into which the bullet, bomb, warhead or missile enters. They therefore suggest a

more ecological way of thinking that "requires dealing with nanoparticles as relational entities (defined by their potential for interactions) rather than as stable substances (defined by intrinsic properties)". (p. 1)

Promises of precision

Since the 1980s, many promises have been made about nanotechnology's abilities to alleviate human suffering and increase human health. The term 'nanocapsule' or rather 'Nanokapsul' was first used by Helmut Kopf in 1975 in a thesis on sub-molecular medicine. The term 'nanomedicine' seems to have first appeared in print in Eric Drexler et al.'s 1991 book *Unbounding the Future*. A search of the newspaper database Lexis Nexis reveals that the term was first used in English speaking news in an article for *The Philadelphia Inquirer* on January 1, 1996 which claimed that "Nanomedicine will use very small mechanisms to target problem spots in our bodies. For example, a tiny bulldozer of sorts would clear out cholesterol, like so much rubble, from arteries, making angioplasty obsolete."

The first targeted nanoparticle-drug delivery systems were developed in the 1980s, but it has been difficult to create systems that work consistently. However, talk of magic nano-bullets and images of nanobots or of nanosubmarines or, indeed, nanobulldozers scouring the blood vessels or delivering drugs began to proliferate alongside the emergence of nanomedicine, and reached a crescendo in the early 2000s. Such words and associated images, both metaphorical and real, tried to convey the exciting future potentials of nanomedicine for the treatment of common diseases, especially heart disease and cancer – and still do so today.

But is this militaristic framing actually a good framing, both in terms of ethics and in terms of knowledge transfer? The use of militaristic metaphors in science, policy and medicine has attracted growing criticism over the last two decades, with repeated calls for less problematic alternatives, and for greater attention to the possible implications of such framing in policy making and political discourse. Among the charges laid against militaristic metaphors are that they can motivate overly strong actions and can have unforeseen consequences such as the stigmatization of the ill or the promotion of shame and guilt amongst sufferers. Among policymakers and public health officials, military thinking may focus attention only on the physical, see control as central, and may encourage the expenditure of massive resources to achieve 'targets'.

Yet, the opacity of much scientific and medical knowledge to most non-specialists means that attempts to disseminate it outside its original context in the laboratory and academy unavoidably depend on metaphors. As a well-entrenched cultural resource, military metaphors continue to be a dominant framing device employed by governments, scientists, journalists, and the public, especially in the context of medicine. However, exactly because such metaphors are so compelling, ubiquitous, and seemingly natural, it is all the more important to scrutinize the role they play at the interfaces between science and society and nature and culture.

Off-target effects

Much of medicine is still permeated by war metaphors, from the war against cancer to the battle against antibiotic resistant bacteria. Targeting disease is still a dream dreamed by many and rightly so. However, such precision metaphors might blind us to the complex bodily and social environments in which this precision warfare is being fought - and sometimes we need to be reminded of that complexity and messiness so as not to succumb too quickly to hype and hubris.

There are some lessons here, perhaps, for synthetic biology, but more importantly perhaps for the creation of expectations regarding genome editing, 'genome surgery', precision-genetic manipulation and what one might call genomic medicine.

The backdrop to nanoscience has been the story of 'fantastic voyage' and breakthroughs in nanomedicine draw on militaristic metaphors. By contrast, the backdrop to genomics has been the 'book of life' (or the map or blueprint) and breakthroughs in genomic medicine employ less militaristic metaphors. But control and precision are still the focus. We hear not so much about bullets but more about precision molecular scissors and erasers, and we see images of knives, spanners and robots with lasers that provide efficient and reliable ways to make precise and targeted changes to the genome of living cells. We also read about 'guide RNA' molecules homing in on their target DNA, and so on. Genome editing is said to bring "gene targeting to the masses".

As Tom Whipple noted, reality is gradually catching up with metaphors, but we are not quite there yet. I agree with Steven Pinker who quipped: "Genetic editing would be a droplet in the maelstrom of naturally churning genomes." An article on nanomedicine rightly points out: "Targeted drug delivery to tumor sites is associated with highly complex biological, mechanical, chemical and transport phenomena, of which characteristics vary spatiotemporally." And, of course, in both nanomedicine and genomic medicine there can be off-target effects and (collateral) damage. This means, according to Mark Walport, "that more research is needed. We need to know you are modifying the gene you want to and you aren't modifying other things as well, whether this is a magic bullet or whether there will be off-target effects."

Some readings...

Nerlich, B. (2005). From Nautilus to nanobo(a)ts: The visual construction of nanoscience. *AZojono: Journal of Nanotechnology Online*:
Nerlich, B., Clarke, D.D, Ulph, F. (2007). Risks and benefits of nanotechnology: How young adults perceive possible advances in nanomedicine compared to conventional treatments. *Health, Risk and Society*, special issue on nanotechnology 9(2), 159-171.
Nerlich, B. (2008). Powered by imagination: Nanobots at the Science Photo Library. *Science as Culture* 17(3), 269 - 292
Image: Wikimedia Commons

Science hype and fun

In one of my early posts for the Making Science Public blog, I talked about hype and about how hype can be used honestly and fraudulently. In one of my later posts I talked about CRISPR and how scientists are trying to deal with this gene editing technology responsibly. So I should have known better!

Following the fun

While still savouring the Pluto flyby on my twitter stream last week, I came across some tweets saying things like this: "It is a truth universally acknowledged, that a single man in possession of a good fortune, must be in want of CRISPR". (Thomas Levenson @TomLevenson Jul 22); "In Wales, CRISPR is pronounced 'Steve'". (Drug Monkey @drugmonkeyblog Jul 22); "Who's the cat that won't cop out, when there's danger all about? CRISPR. (Right on.)" (Ed Yong @edyong209 Jul 22); "It does seem that are stranger than Hilary Sutcliffe @hilarysutcliffe Jul 23); and indeed, making a reference to the Pluto mission: "New Horizons was powered by CRISPR". (Dr Adam Rutherford @AdamRutherford Jul 22) These tweets all used the hashtag #crisprfacts. I went to the whole hashtagged list of tweets and images and enjoyed myself.

According to Rebecca Harrington, writing for Popular Science, the whole thing "started when Daniel MacArthur, a geneticist at Harvard Medical School and the Broad institute, tweeted that *Wired*'s August cover story may have gone too far. […] Chris Dwan, also from the Broad Institute, replied to MacArthur with a joke using the hashtag, and Twitter took it from there."

Questioning the fun

Of course, I retweeted some of these #crisprfacts. Then #crisprfacts began trending. I emailed the hashtag to a friend of mine who looked at the tweets, was amused, but not so amused and emailed back that he'd seen more hyperbolic articles on CRISPR than this one. He also didn't like the purple grass on the cover. Ha, I thought, I should perhaps read the article!

Reading the article

The article was published in *Wired* magazine and was written by Amy Maxmen. When I opened the online version, I saw a rather psychedelic eye and the strap-lines "The Genesis Machine. We now have the power to quickly and easily alter DNA. It could eliminate disease. It could solve world hunger. It could provide unlimited clean energy. It could really get out of hand". Lots of 'coulds'; so not so much hype I thought. Then, further down, there was the August print cover with the purple grass (which I quite liked) and the headline "No hunger, no pollution, no disease. And the end of the world as we know it. The Genesis engine". Ah I thought, typical headline speak – quite hyperbolic, but that's headlines for you.

Then I read on. The article starts with Asilomar 1975 and goes on to discuss Asilomar 2015 – two reference points that I had also used in my blog post on

recombinant DNA and CRISPR. I started to like the article. It was short and to the point and raised some important ethical issues without making a meal of them.

After reading the article, I still liked the fun tweets but I had to agree with Dietmar Scheufele who tweeted: "#crisprfacts targets the scientific hype … and missed the #ELSI point." (Dietram A. Scheufele @scheufele Jul 23) By this he means the point actually made in the article about Ethical, Legal and Social Issues.

Learning something

So what did this teach me? Two things: First: Twitter can be fun and reading the #crisprfacts tweets was indeed fun. But: It's always a good idea to look beyond the twitter-stream and not be swept away by it – to raise one's head once in a while and see what's going on outside. Second: Popular Science suggested that the hashtag turned down the crispr-hype or, as Jack Stilgoe tweeted, "I'm enjoying the bubble-puncturing hype-taking tool that is #crisprfacts" (Jack Stilgoe @Jackstilgoe Jul 22) However, didn't we all, while enjoying ourselves and inventing CRISPR facts, also contribute to the hype? Were we not swept away by anti-hype that was a bit of hype itself?

Like so often in journalism, we have to look beyond the headlines and the hashtags and READ THE ARTICLES too. We should not blame journalists alone for 'the hype' that we all enjoy and feed on. As Tim Radford, free lance journalist and science writer, has made clear, it is almost impossible to tell (indeed sell) a science story without engaging in some sort of 'hype': "You don't grab headlines by describing embryo stem cell research as an expensive laboratory-based technology of unproven merit guaranteed to lead to many years of frustration punctuated by small flashes of enlightenment."

And you don't get tweets trending with a stale discussion of ethics.

Musings on language and life, with special reference to 'programming'

This morning (1 April, 2016) I opened the newspaper and read an article about a new language that lets researchers design novel biological circuits. I mumbled something about this over coffee and my husband said, oh but wasn't that old hat, we all knew that DNA was a language, code etc. So what was new? I looked again at the article and stumbled upon the word 'compile'. So I said that all this apparently had something to do with programming and compilation. Ah, he said, now that is interesting, if it's about compilation. I was none the wiser, being no computer or programming aficionado. Once the coffee was ingested and I had woken up a bit more, I read the newspaper article properly. For more detailed info see New Scientist, for example; and for even more detail, read the article in Science - but I didn't read those this morning...

A programming language for living cells

Instead I looked at this press release by MIT News entitled "A programming language for living cells", published on 31 March, 2016. This is the quote that made me think – especially about my ignorance:

"It is literally a programming language for bacteria," says Christopher Voigt, an MIT professor of biological engineering. "You use a text-based language, just like you're programming a computer. Then you take that text and you compile it and it turns it into a DNA sequence that you put into the cell, and the circuit runs inside the cell." (I suppose 'literally' means 'literally' here, but I don't know)

(Com)Piling on the confusion

For me, as a naïve reader, the word 'compile' conjures up images of 'compiling an index for a book' or 'compiling some notes', or producing "(a list or book) by assembling information collected from other sources". But of course, there is another meaning, which my mind only rarely accesses, as I don't do or practice the stuff associated with that meaning, namely 'convert (a program) into a machine-code or lower-level form in which the program can be executed'.

What does that mean? I then looked up that second meaning in the Oxford English Dictionary and discovered that the examples used to illustrate this meaning, just don't mean anything to me either! Here are just a few:

1952 Proc. Assoc. Computing Machinery 1/2 UNIVAC compiled the program in one and one half minutes.
1960 R. H. Gregory & R. L. Van Horn Automatic Data-processing Syst. viii. 273 After check-out, the final version of the program..can be compiled into the numerical code of the machine.
1961 Communications Assoc. Computing Machinery 4 74 The method..for compiling Boolean expressions is an alternative to the usual method which would compile an object program that performs all logical operations indicated in the expression.
1972 M. D. Freedman Princ. Digital Computer Operation xi. 181 When the complete program has been compiled, the programmer can request that it be executed.
1979 M. S. Carberry et al. Found. Computer Sci. iii. 58 The internal program compiled by the computer is called the object program.
1982 Sci. Amer. Dec. 94/2 Fortran programs are compiled.

Challenges to science communication

So, if I didn't understand a word of this gobbledygook (more here and here), how could I understand the MIT press release? By the way, in the case of the work done by the MIT people, the language they use is neither Fortran, nor Python, nor C++ …., but Verilog…

This made me think a bit more about challenges to science communication. 'Normally' when using words like 'language' and 'code' and 'editing' etc., 'normal' people like me use their understanding of these words to somehow get some understanding of particular aspects of genetics, genomics, synthetic biology and so on. We map our concrete and familiar knowledge of language onto an abstract and unfamiliar domain of knowledge and create a semblance of understanding.

However, in the case of this new research that metaphorical matching and mapping process becomes quite difficult. For two reasons: firstly, not everybody knows what programming and compiling is; and secondly, not everybody knows what 'building biological circuits' means (unless we have already cracked THAT metaphor in our ordinary minds!). So mapping one onto the other and generating new understanding might be difficult.

Black box building of biological circuits

But what if you DID understand something about programming and compiling? Then you might be in clover, as you don't seem to need to understand the biology behind the building of biological circuits. You just build them! As the press release says:

"Over the past 15 years, biologists and engineers have designed many genetic parts, such as sensors, memory switches, and biological clocks, that can be combined to modify existing cell functions and add new ones.
However, designing each circuit is a laborious process that requires great expertise and often a lot of trial and error. "You have to have this really intimate knowledge of how those pieces are going to work and how they're going to come together," Voigt says.
Users of the new programming language, however, need no special knowledge of genetic engineering.
"You could be completely naive as to how any of it works. That's what's really different about this," Voigt says. "You could be a student in high school and go onto the Web-based server and type out the program you want, and it spits back the DNA sequence."

As all school kids (unlike me!) are now encouraged to engage in 'programming' and 'coding', the possibilities are endless. These kids might even understand the phrase 'type out the program you want'! And, apparently they don't need 'special knowledge of genetic engineering' (a type of root metaphor for 'synthetic biology')… they can keep that in a 'black box' and just get on with things. Is that a good thing? I am not totally sure...

Synthetic biology and biological engineering

I'll end on a final linguistic note. The MIT press release never mentions 'synthetic biology' in its text but only talks about 'biological engineering'. Is it time to retire the term 'synthetic biology' and replace it with 'biological engineering' which seems to be much more transparent, descriptive and accessible to the uninitiated - unlike the rest of the article?!

4. SYNTHETIC BIOLOGY, THE MEDIA AND THE BIOECONOMY

Synthetic biology markets: Opportunities and obstacles

As some people know from my previous posts on synthetic biology, I am interested in tracing how synthetic biology is made public in the news media and whether or how it is becoming a matter of public debate.

"Synthetic biology is an emerging area of research and is broadly described as the design and construction of novel organisms or devices, artificial biological pathways, and the redesign of existing natural biological systems." (MarketsandMarkets Analysis, 2014) (more definitions here)

I have argued that synthetic biology has not attracted much attention in the press and has not led to any major news-mediated public debates, for example in comments underneath news articles or blogs. I also argue that only once this happens a more public debate about synthetic biology, including science and society issues such as responsible research and innovation, can happen; although that might also, paradoxically, be too late.

Synthetic biology in the 'news'

In this post I want to dig a bit deeper into this conundrum. I therefore went back to my trusted source for all things related to news data, namely LexisNexis. I used 'synthetic biology' as a search term to search 'All English Language News' and charted recent developments over the last 16 years, that is, from two years before Craig Venter's major announcement about synthetic biology to now. I disaggregated news items according to news sources, such as, for example,

'Newswires and press releases', 'Newspapers', 'Magazines', 'Industry and Trade press' and so on. As you'll see from the following graph, the 'news' about synthetic biology is generally dominated by 'newswires and press releases' (blue), which include news about the ups and downs in share values for business such as Amyris, for example.

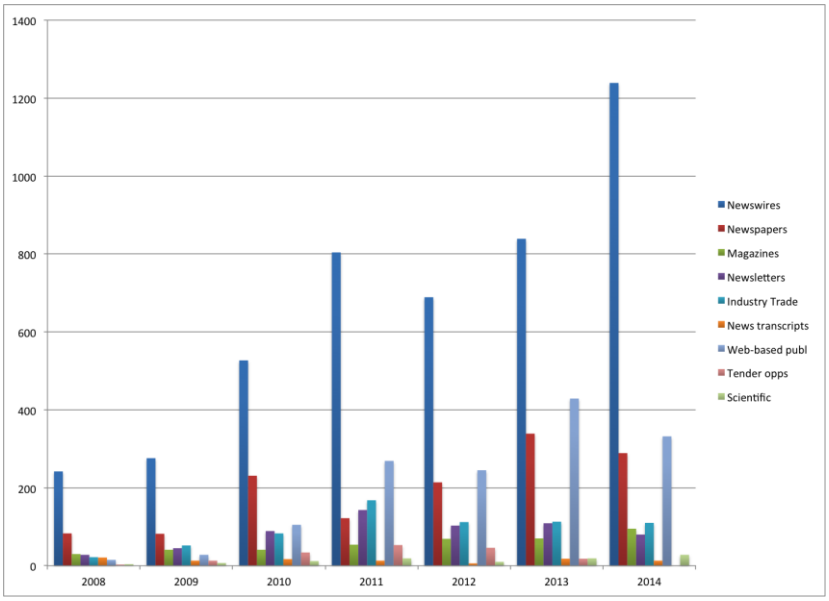


Figure 1: 'Synthetic biology' in All English Language News (LexisNexis, high similarity setting)

Newspapers (red) only make up a small part of the 'news' about synthetic biology, and, although interest hasn't been dwindling since 2010, as I expected, it has also not increased massively. This seems to indicate that synthetic biology does not yet attract a lot of 'public interest' but does attract a lot of market interest.

Synthetic biology: opportunities for growth

When looking through some reports on synthetic biology published towards the end of this year, my eyes fell on a short market report published by *M2 PressWIRE*. I then followed the link to the press release online, which proved very interesting. Unfortunately, I could not consult the whole report, as that would have cost me about $5000.

The article by *M2 PressWIRE* appeared on 23 December 2014 and was entitled "Synthetic Biology Market worth $ 5,630.4 Million by 2018". It makes some interesting points about the reasons why there is such a growth in the synthetic biology market: "Over the years, the demand for synthetic biology is likely to increase owing to the increasing R&D expenditure in pharmaceutical and biotechnology companies, growing demand for synthetic genes, rising production of genetically modified crops, and *incessantly rising funding* in the field of synthetic biology." (Italics added)

Synthetic biology: obstacles to growth

The article highlights that there are however also some obstacles to growth. It points out that "*ethical and social issues such as biosafety and biosecurity are major factors that are restricting the growth of this market*. Furthermore, rising concerns over fuel consumption and increasing demand for protein therapeutics are likely to create opportunities for the synthetic biology market. However, standardization and integration of biological parts at system-level still remains a challenge for this market." (Italics added)

In the online version of the press release the word 'restraining' is used instead of 'restricting': "However, ethical and social issues such as biosafety and biosecurity are the major factors restraining the growth of this market." (MarketsandMarkets Analysis, 2014)

What sells? Who sells?
Not withstanding such obstacles, where does growth in synthetic biology occur? The online overview sorts potential growth areas in terms of tools, technology and application (and if you have the money you can of course order the report and read more about each item on the list).

Tools
Xeno-nucleic Acids (XNA)
Oligonucleotides
Chassis Organisms
Enzymes
Cloning and Assembly kits
Technology
Enabling Technologies
Bioinformatics
Gene Synthesis
Genome Engineering
Microfluidics
Measurement and Modeling
Nanotechnology
Cloning and Sequencing
Site-saturation Mutagenesis
Enabled Technologies
Pathway Engineering
Next-generation Sequencing
Application
Environmental Application
Bioremediation
Whole-cell Biosensors
Medical Application
Artificial Tissue and Tissue Regeneration
Drug Discovery and Therapeutics
Pharmaceuticals
Industrial Application
Biofuels and Renewable Energy
Biomaterials and Green Chemicals

Industrial Enzymes

Who are the biggest players in the synthetic biology market? It appears that North America is the market leader, followed by Europe, Asia and the Rest of the World. "Some of the major players in the global market include Amyris, Inc. (U.S.), DuPont (U.S.), GenScript USA Inc. (U.S.), Intrexon Corporation (U.S.), Integrated DNA Technologies (IDT) (U.S.), New England Biolabs, Inc. (NEB) (U.S.), Novozymes (Denmark), Royal DSM (Netherlands), Synthetic Genomics, Inc. (California), and Thermo Fisher Scientific, Inc. (U.S.)."

Synthetic biology, markets and responsible research and innovation

What does all this mean in terms of responsible research and innovation, an issue that interests me as a social scientist embedded in a Synthetic Biology Research Centre? As the newswire said, *research* in synthetic biology attracts "incessantly rising funding" and *innovation* in synthetic biology in the US, and increasingly so in Europe, is moving steadily ahead. How can this research and innovation be carried out 'responsibly' – a question asked by all major research funders in Europe?

The concept of Responsible Research and Innovation (RRI) is still hotly debated, but the following aspects of RRI, as sumarised by the think-tank MATTER provide a general flavour of what RRI is all about: RRI has "a deliberate focus on socially or environmentally beneficial results"; it stipulates "the continuous and consistent involvement of society in the research and innovation process"; it involves the assessing of "*social, ethical and environmental impacts alongside commercial and scientific considerations*"; it also involves the "use of oversight mechanisms to anticipate and manage problems and opportunities"; and more generally, RRI should ensure that "openness and transparency are an integral component of research and innovation" (italics added). How can this work within a growth industry and a growing market in synthetic biology tools, technologies and applications?

As we have seen, ethical and social issues are regarded as obstacles, restrictions and restraints that might hamper commercial growth, rather than as integral to a responsible innovation and commercialisation process. This industrial perception of 'ethical and social issues' may hamper, restrict and constrain more open and transparent public deliberations about synthetic biology and might be difficult to overcome.

Despite a very long list of tools, technologies and applications, ranging from medicine to alternative fuels and beyond, only biosafety and biosecurity are mentioned by market researchers as potential ethical and social issues related to synthetic biology. This is interesting in a context where, as some social scientists have argued, "concerns about the biosecurity threat posed by synthetic biology are not only exaggerated, but are, more importantly, misplaced" (Marris et al., 2014).

If indeed any of the businesses mentioned above were to get involved in RRI (beyond considerations of Corporate Social Responsibility, business ethics, and

legal and environmental safeguards), a much wider array of social and ethical issues would have to be tackled over and above biosafety and biosecurity. These would be specific to the 'synthetic biology' in question, and differ substantially between say, "bioinformatics", "tissue regeneration" and "biofuels" and "green chemicals".

Talking with members of the public about such issues may be quite difficult for two reasons: first, there is arguably a real news vacuum about most of these technologies, so getting trusted information might be difficult; second, the market might be growing and diversifying faster than RRI efforts around synthetic biology. What can be done in such a situation? Suggestions welcome!

Epilogue
No sooner had a drafted this post, when an item appeared in my twitter stream that is important in this context: An EU "Public Consultation on the preliminary opinion on Synthetic Biology II".

On p. 14 of the document, just underneath a definition of RRI, one reads: "It is vital to recognise the importance of maintaining public legitimacy and support. To achieve this, scientific research must not get too far ahead of public attitudes and potential applications should demonstrate clear social benefits. Furthermore, the potential benefits of the technology and the risks must not be overhyped creating unrealistic hopes that cannot be fulfilled and/or public anxiety" etc. – these pages are worth reading in the context of RRI and the hopes invested in this approach, especially its use to steer innovation towards social benefits.

The bioeconomy in the news - or not

At meetings of the BBSRC/EPSRC funded *Synthetic Biology Research Centre* here at Nottingham the word 'bioeconomy' crops up now and again, which is not surprising, as synthetic biology is supposed to be part of this new economy. In a blog post written in December last year the BBSRC's Chief Executive Jackie Hunter pointed out that: "One can think of the bioeconomy as encompassing all the economic activity derived from bio-based products and processes. Such products and processes can provide sustainable and resource-efficient solutions for a range of industrial sectors including food, agriculture, chemicals, energy production, health and environmental protection. The size of the bioeconomy is truly staggering – in the EU alone the bioeconomy is estimated to be worth two trillion euros accounting for 22 million jobs, which is about 9% of the EU labour market."

Origins of the term
While thinking about this, I came across an announcement in the context of a recent synthetic biology conference, *Synbiobeta*, which said: "Speaker Rodrigo Martinez, Life Sciences Chief Strategist at IDEO, is not new to the intersection of art and science. He originally coined the term 'bioeconomy' with Juan Enriquez in 1997."

So I became curious and wanted to dig a bit more into the history of the term 'bioeconomy', where it comes from and what its current appeal may by. I first looked at Wikipedia and the *Oxford English Dictionary*. Wikipedia has a short entry on the concept which repeats the origin story told above and informs us that Martinez coined the term "at the Genomics Seminar in the 1997 AAAS meeting". We also learn that 'bioeconomy' stands for bio-based economy, had an early rival in the expression 'biotechonomy' and "refers to all economic activity derived from scientific and research activity focused on biotechnology".

The OED has not yet incorporated the word in its dictionary but one can find an entry for 'bioeconomics' which means "The interaction between economics and biological systems (including human families), usually taking into account the economic value of natural resources; any of various fields of study concerned with this; (now usually) *spec.* a mathematical field of study concerned with the optimization of the biological and economic productivity of living resources (such as plant or animal populations) which are used commercially".

Bioeconomy in the news

I then went and looked for the term on the news data base Lexis Nexis. As one can see, a first little surge in usage occurred around 2008 and a second in around 2012, but the term really got a boost in 2014. However, amongst the 644 articles published last year only 14 were written for Major World Newspapers, of which 10 appeared in the *New Straits Times*, Malaysia, and two appeared in a UK national newspaper, namely in *The Guardian*. So, the bioeconomy is not yet a popular news item. Interestingly, the names Martinez and Enriquez are never mentioned in the news coverage I looked at since 1990.

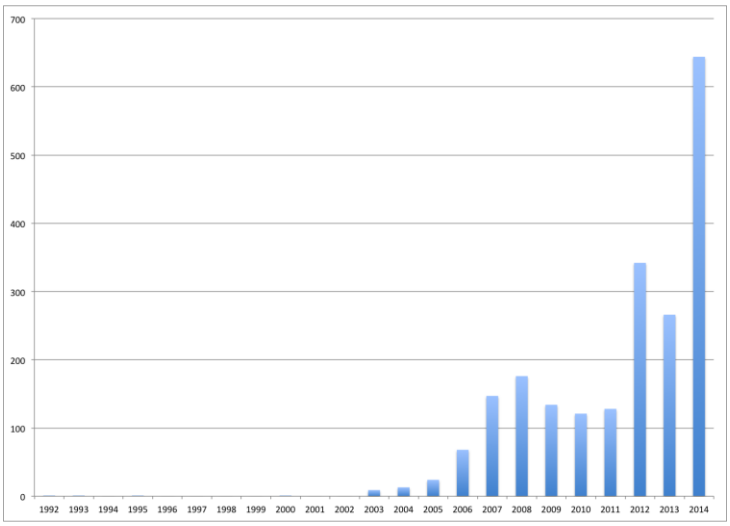


Figure: *Bioeconomy* in All English Language News (Lexis Nexis)

In the news the term 'bioeconomy' was first used in 1992 by Bernadine Healy in the context of early speculations about the promises of biotechnology. In 1993 we find reference to 'bioeconomy of the lakes'. Here the meaning of bioeconomy seems to be closer to the OED's 'bioeconomics'. The same goes for one reference

made to bioeconomy in 1995 in the context of a book by Stephen Budiansky *Nature's Keepers*.

In 2003 we find a new spelling of the term as 'BioEconomy' and from then onwards the term is increasingly used in the context of talking about the promises and later perils of biofuels and bioenergy, with a peak in 2008. This was the time when, in 2001, in the US government released a policy document entitled ''Fostering a Bioeconomic Revolution'', while in 2002 and 2004 the European Union began to focus on a ''knowledge-based bioeconomy''.

Things changed in 2012, when the focus seems to have shifted a bit from biofuels and environmental concerns to synthetic biology, innovation and growth. 2012 was the year that the UK Parliament highlighted the 'huge potential' of the UK's bio-based economy and when the EU published ''Innovating for Sustainable Growth: A Bioeconomy for Europe", "in which the bioeconomy is described as 'a unique opportunity to comprehensively address inter-connected societal challenges such as food security, natural resource scarcity, fossil resource dependence and climate change, while achieving sustainable economic growth'" (for more information on various policies see this recent article by Goven and Pavone).

In the news around 2012 we find talk of "life as a technological project", "plant based plastics", a "post-oil bioeconomy" and much more. However, out of 1308 articles published between the beginning of 2012 and the end of 2014, 406 still refer to biofuels and only 42 to synthetic biology and 43 to genomics. It should also be pointed out that of these 1308 articles 874 are Newswires and only 176 are proper newspaper articles. This shows again that the drivers of bioeconomy news, just as with synthetic biology, are industry and academia, not yet popular interest or controversy.

Growth and responsibility – can they go together?

One of the biggest promoters of the bioeconomy in Europe is Horizon 2020, where it is seen as a way to stimulate growth and assume responsibility for how humans live on this planet: "Over the coming decades, the world will witness increased competition for limited and finite natural resources. A growing global population will need a safe and secure food supply. And climate change will have an impact on primary production systems, such as agriculture, forestry, fisheries and aquaculture. A transition is needed towards an optimal use of renewable biological resources. We must move towards sustainable primary production and processing systems that can produce more food, fiber and other bio-based products with fewer inputs, less environmental impact and reduced greenhouse gas emissions. […] With its cross-cutting nature, the Bioeconomy offers a unique opportunity to address complex and inter-connected challenges, while achieving economic growth."

Creating such a bioeconomy, which can square the circle between growth and responsibility for us and the planet we live on, can therefore also be seen as being at the heart of Europe's and Horizon 2020s' parallel drive for Responsible Research and Innovation (RRI). However, as public dialogue and deliberation are

at the heart of RRI, a lot still needs to be done to foster such public involvement in the context of a media silence on the topic.

5. RESPONSIBLE INNOVATION AND SYNTHETIC BIOLOGY

Making synthetic biology public

Recently (2014) two reports have been published which made me think about the (non-existent?) public debate about synthetic biology. Jessica Mazerik and David Rejeski wrote a guide for the Wilson Center on how to communicate synthetic biology and Virgil Rerimassie and Dirk Stemerding wrote a report for the Rathenau Institute entitled 'Synbio Politics: Bringing synthetic biology into debate'. The intention of this report is to stimulate "political and societal opinion making" (p. 78) around synthetic biology.

Both documents deal with 'making synthetic biology public', in one case communicating 'it', in the other intending to create 'public opinion' around 'it'. Both reports have appeared in a societal context where, as Rerimassie and Stemerding point out, "synthetic biology may still be in its infancy and is still unknown to the general public" (ibid.), and where, despite many efforts by science communicators, policy makers and intermediaries, including social scientists, "a broader societal and political debate on synthetic biology has not yet started" (p. 11).

This poses real problems for synbio science communication, synbio media coverage and also for synbio 'responsible research and innovation'. The big questions for me are: What do we communicate 'about' with relation to synthetic biology, what do we write about it and what do we get people to think about in terms of responsible research and innovation. Can one debate an issue or set of issues in the absence of knowledge (of whatever kind!)? And what responsibility

do social scientists have in this process? Should they stimulate debate before it occurs naturally (engage in 'upstream' debating if you like)?

Mazerik and Rejeski say: "Scientists need to get over trying to tell people what synthetic biology is, and talk about how it is going to be applied and why people should care". This advice seems to be sensible at first glance. However: Applied to what? Are there any applications that 'people' are aware of, should be aware of and why? And: Care about what? Before they care about something, 'people' might first ask: What is synthetic biology (all about)?

What is synthetic biology?

When you put 'synthetic biology' into Google, which is what ordinary 'people' may do, you get the following definition: "Synthetic biology is an interdisciplinary science, combining disciplines such as biotechnology, evolutionary biology, molecular biology, systems biology and biophysics. The definition of synthetic biology is heavily debated not only among natural scientists but also in the human sciences, arts and politics." Where do people go from here? Let's go a couple of links down to a FAQ page maintained by syntheticbiology.org. Here we find the following definition: "Synthetic biology refers to both: the design and fabrication of biological components and systems that do not already exist in the natural world [and] the re-design and fabrication of existing biological systems." The article goes on to say that: "There are two types of synthetic biologists. The first group uses unnatural molecules to mimic natural molecules with the goal of creating artificial life. The second group uses natural molecules and assembles them into a system that acts unnaturally." The words 'unnatural molecules' and 'creating artificial life' might make people think – and even start to care about – synthetic biology …. but where might they get better informed?

What do people care about?

As the 2014 Public Attitudes to Science survey found, people don't feel very well informed about synthetic biology. There are however some people who are perhaps better informed. These are people who have been involved in various initiatives (surveys, dialogues etc) undertaken by research councils and other organisations. Participants in these events seem to begin to care about general regulatory and ethical issues of which they will have become aware during the engagement process (see 2009 Royal Society report). Whether this translates into public debate is another matter.

Eleonore Pauwels found in her 2013 article dealing with 'public understanding of synthetic biology': "US public perceptions toward synthetic biology are ambivalent. Members of the public show enthusiasm for synthetic biology applications when those applications are developed to address societal, medical, and sustainability needs, whereas engineering biology is seen as a potential concern if this research is done without investigations of its potential risks and long-term implications. Members of the public also support funding for research that leads to applications that actually meet social and sustainability goals. When it comes to oversight, their priorities are to promote transparency and

accountability and to ensure a form of tailored governance in which diverse knowledge sources help address the uncertainty surrounding new technologies." But where do people not involved in public engagement projects get their public understanding, perceptions or attitudes from? They probably rely on the media. So what's out there?

What do the media tell us about synthetic biology?
An article on 'Trends in American and European Press coverage of Synthetic Biology: 2008-2011' found that media coverage has significantly increased over that time span. However, the "coverage … remains largely driven by events like the May 2010 announcement by the J. Craig Venter Institute of the creation of the first synthetic self-replicating cell and, immediately following that, the Obama administration tasking the Commission for the Study of Bioethical Issues to examine the implications of that discovery." Over and above Craig Venter playing God, "[e]thical concerns garner the most coverage in Europe, followed by biosafety and biosecurity issues. In the United States, biosafety is the top concern; in the 2003–2008 period, the top concern was biosecurity."

A quick search on the news database Lexis Nexis reveals that there was a slight dip in coverage in 2012 but another increase in 2013. However, it would be worth investigating further who drives this increase in coverage, whether it reaches a general readership and whether it stimulate any public debate online or offline?

Is there public debate and if not should one stimulate it?
A quick look at some articles online reveals that synthetic biology articles don't seem to garner a lot of comments and debate, but again this needs further investigation (as Tim Ingham told me when I visited Plymouth this week – see image) (here is an article he found that generated lots of comments and here is one with none, despite it mentioning an application). Our overall impression is that the Rathenau report is right: there is no public debate. The authors of the report therefore want to stimulate debate. Is that the right thing to do?

Much of the background material gathered for the Rathenau report seems to be gleaned from the media and in particular from coverage of the more spectacular aspects of synthetic biology. The authors of the report repeat, quite uncritically, words, clichés and metaphors, such as 'unnatural', 'artificial life', 'playing God', 'nature as machinery', 'improving on nature', 'Jurassic park', and 'Creation 2.0'. They also say that all this "testifies to the ambitions of synthetic biologists dreaming of making synthetic life" (p. 28) or even "that in the future organisms will be 'created' with a higher level of cuddliness" (p. 37)!

Rerimassie and Stemerding make one reference to an actual application of synthetic biology that people might 'care about', namely an Ecover product which caused some controversy (p. 37), a controversy partially related to the vagueness of the term 'synthetic biology'. However, in the absence of other concrete applications and in the presence of very speculative references to playing God, for example, inspiring "a further process of formulating political and societal views on synthetic biology" (p. 15) might be quite difficult and even

perhaps irresponsible. I believe the responsible research and innovation agenda should not only be applied to the natural but also to the social and communication sciences involved with synthetic biology.

Making life and making opinion

Making life is difficult and scientists are always told to think carefully and responsibly about what they do and how they talk about what they do. As Steve Jones said in 2003 in an article that, on Lexis Nexis at least, used the term 'synthetic biology' for the first time in English Language News: we might have deciphered the human genome but "we are far from being able to perform miracles" (Daily Telegraph, 16 April). A decade later we are still far from being able to perform miracles, but, fortunately, we haven't yet created any monsters either. That's perhaps why we haven't yet had a public debate about synthetic biology. The questions is: Should we 'make' public opinion in the absence of public awareness of and interest in this new science and in the absence of monsters and miracles? Natural and social scientists dealing with responsible research and innovation in the context of synthetic biology might have to tread carefully both when trying to make life and when trying to make public opinion.

From recombinant DNA to gene editing: A history of responsible innovation

In this post I shall report on a recent call for ethical and regulatory reflection by scientists engaged in a new genomic technology. I'll then put this into a historical context of previous initiatives of that kind, and finally ask whether this can be called 'Responsible Research and Innovation'.

CRISPR

Recently, a new controversy has emerged within genetics and genomics, fields that have had their fair share of controversy. This one is centred around a new technology to cut and splice DNA that would allow scientists to edit genomes. This technology has been applied to bacterial, plant and animal genomes but could also be applied to the human genome. This could lead to eliminating heritable diseases (similar to promises made around gene therapy), but could also enable the creation of 'designer babies' or 'perfect babies'. And, of course, the technique could also be used to resurrect the woolly mammoth, as reported in newspapers on 23rd March 2015. The real issue is perhaps that mistakes can be made in this cutting and splicing and that these mistakes could lead to unintended changes to the human genome. As *New Scientist* reported: Editing human embryos is genetics new battleground. Questions around interfering in evolution and around human enhancement are being asked again.

The controversial cutting and splicing technique is called CRISPR, which stands for: Clustered Regularly Interspaced Short Palindromic Repeats. (And as a social scientist, not biologist, I find it quite difficult to get my head round it) The acronym was first used in 2002 and CRISPR was first shown to work as a genome engineering/editing tool in human cell culture in 2012 (wiki). Two scientists in particular have been involved in developing a particular variant of this technique: CRISPR-Cas9 (and here on YouTube). They are Emanuelle

Charpentier, an immune biologist who works at the Helmholtz Centre for Infection Research at the University of Braunschweig and Jennifer Doudna, a specialist in molecular and cell biology at UC Berkeley (see their article in Science, 2014). Both have expressed worries about the potential misuse of this technique and Doudna organised a meeting in Napa, California in January this year to talk about ethical challenges ahead.

On 20th March 2015 the American science magazine *Science* published a special section on the 'CRISPR revolution' (online 19th March). This contained a 'policy focus' piece by 18 scientists and ethicists, entitled "A prudent path forward for genomic engineering and germline gene modification" (corresponding author: Doudna). The paper advocates a moratorium on "any attempts at germline genome modification for clinical application in humans"and calls for a "framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome".

One of the authors of the article, the Nobel laureate David Baltimore, spoke to the New York Times. Interestingly, Baltimore was involved in the famous 1975 Asilomar conference on recombinant DNA in which a "group of about 140 professionals (primarily biologists, but also including lawyers and physicians)" came together to "to draw up voluntary guidelines to ensure the safety of recombinant DNA technology" (wiki). In the NYT interview Baltimore said: "'In 1975, scientists worldwide were asked to refrain from using a method for manipulating genes, the recombinant DNA technique, until rules had been established. We asked at that time that nobody do certain experiments, and in fact nobody did, to my knowledge,' said Dr. Baltimore, who was a member of the 1975 group. 'So there is a moral authority you can assert from the U.S., and that is what we hope to do'" in the case of genome editing.

The warnings expressed by the scientists writing in the journal *Science* echo those by scientists involved in a complementary enterprise using a slightly different approach who published their views in an article for the UK science journal *Nature* a week earlier under the title "Don't edit the human germ-line". Similarly, the International Society for Stem Cell Research (ISSCR) urges scientists "to stop the tampering and editing of the human germline genome in order to get involved with a larger discussion among scientists along with the public that will tackle ethical issues."

Are these warnings exceptional or part of a pattern of scientists reflecting on their impacts on society? In the following I'll show how they are part of a pattern that began, at least, in 1975 with the Asilomar conference. The conference happened in the context of the responsible science movement and early calls for what later became bioethics (see also this article by Alice Bell).

Asilomar, synbio and beyond

The Asilomar conference was organized by Paul Berg who had created the first recombinant DNA molecules in 1972 to review scientific progress in research on recombinant DNA molecules and to discuss appropriate ways to deal with the potential biohazards of this work. Scientists were worried about the dangers

posed by this new technology, as it allowed the combination of genetic information from very different species. The statement they issued became a landmark which reverberated through the ages, not only in biotechnology, but also nanotechnology and, more recently, also in the context of geoengineering.

Synthetic biology, which makes use of recombinant techniques and in some instances may also involve the use of the CRISPR system, began to emerge in the early 2000s. "Like conventional biological engineering, synthetic biology rests on revolutionary advances in DNA sequencing and synthesis technologies. Unlike most recombinant DNA work, synthetic biology seeks to do biological engineering with standardized biological parts, modularized design, and routinized methods of assembly." (Oye, 2012) From the very beginning, scientists and science educators involved in synthetic biology, especially those organising the famous iGEM competitions, have not shied away from discussing ethical and regulatory issues around synthetic biology. Now, movements are afoot to implement more stringent regulations.

As early as 2004 a news item in *Science* entitled "Should there be a synthetic biology Asilomar?" reported on key scientists and ethicists talking together about "responsibilities to society," and a desire to hold a meeting "modeled on the 1975 Asilomar Conference, at which biologists defined safeguards needed to contain genetically engineered microbes." In 2006 risks and ethical issues surrounding synthetic biology were discussed at a Synthetic Biology 2.0 conference, which again was framed as a synthetic biology version of Asilomar, and in 2007 a synbio governance report was published. In 2014 a policy group within the seminal synthetic biology Institute led by Craig Venter published a Report on Challenges and Options for Oversight of Organisms Engineered Using Synthetic Biology Technologies. In the same year, George Church, one of the leaders in the field and contributor to the *Science* article led by Doudna, spoke about the risks and benefits of genome editing at the Harvard Museum of Natural History. (He is also the one talking about using CRISPR for exploring cold resistant genes in the woolly mammoth)…

Responsible innovation

Can all these long-standing ethical, social and regulatory reflections initiated by scientists collaborating with ethicists in the context of biotechnology and synthetic biology be entitled 'Responsible Research and Innovation' (RRI), a new approach to ethics, regulation etc. advocated for the democratic governance of emerging technologies? The article in *Science* calling for a moratorium on CRISPR says that "scientists should avoid even attempting, in lax jurisdictions, germline genome modification for clinical application in humans" until the full implications "are discussed among scientific and governmental organizations". Supporters of RRI would surely applaud all the ethical work and reflection scientists have already been carrying out for so many years together with ethicists and governmental organisations. However, they would also urge them to engage more and earlier with members of the public. As the UK's Synthetic Biology Roadmap famously said: 'engagement' "means genuinely giving power to a wide range of diverse social groups, including those who will be the end users or presumed beneficiaries of the technologies, taking their concerns seriously,

and enabling them to participate throughout the whole pathway of technological development". How to implement this aspiration is another matter.

Ta(l)king responsibility

In social science and policy circles there has been a lot of talk about Responsible Research and Innovation (RRI). However, nobody quite knows yet what this means and how it works in the context of harsh economic realities. In the meantime, natural scientists have taken responsibility for their research and innovations in the context of new developments in genomics and synthetic biology: gene editing using CRISPR.

This is not new. Forty years ago, scientists also took responsibility in the context of recombinant DNA, made their concerns public, sought public views and implemented guidelines, regulations and so on. In the following I'll first explain how scientists took responsibility 40 years ago, then how they are doing so now and what this might mean for RRI and making science public. This is quite a long post. However, I think it needs to be, as it shows us how much still needs to be thought about and done to make RRI work, not only with 'the public' but also with 'the scientists'.

Recombinant DNA

In 1974, molecular biologists expressed their concerns about possible dangers posed by new methods they had developed to splice and recombine DNA. They also temporarily stopped work using this new technology. A year later, in 1975, and together with the US National Institutes of Health (NIH) and the National Academy of Sciences, they organised a conference in Asilomar, California. At that conference "the biologists decided among themselves what restrictions should apply to various types of genetic manipulation" (Rasmussen, 2015). As scientists, they focused, of course, first and foremost "on laboratory safety but not wider social concerns" (ibid.). However, their reflections on the risks and benefits of this new bio-technology were very detailed, wide-ranging and thorough, as can see when looking at a few letters published in *Science* in 1976 and 1977.

I came across these letters by accident after a twitter exchange about designer babies and the slippery slope (topics that are quite popular in this era of CRISPR), when somebody tweeted something about 'genetic meddling' and the *Daily Mail*. I hadn't come across this phrase before, so I put it into a certain search engine and almost the first item that came up was a 1976 letter to *Science* entitled "On the dangers of genetic meddling", arguing that the Asilomar group, as one might call it, had neglected to think about the fare-reaching dangers of recombinant DNA and just wanted, like "Dr Frankenstein", to continue producing "little biological monsters" – this certainly sounds quite Daily Mailish, *avant la lettre*!

Immediately following that letter appears one by a member of Friends of the Earth calling for opening up debate about all sorts of issues the scientists had neglected to tackle, including "the imposition of complex medical decisions on

individuals and society, and the inherent fallibility (not to mention corruptibility) of inspection, enforcement, and regulator bodies". A tall order!

More interestingly, two letters by those involved in Asilomar took up the gauntlet. One expressed surprise to find that what "began as an act of responsibility by scientists" had now become "the breeding ground for a horde of publicists" (one might call it hype today). The author, Stanley N. Cohen, tried to correct some misunderstandings about both the risks and benefits of recombinant DNA, but, more importantly, he tried to dispel some worrying myths which were circulating at the time. One myth relates to people thinking that scientists wanted to protect their freedom of inquiry and continue with experiments regardless of the dangers they may pose. "Instead", Cohen writes, "the history of this issue is one of self-imposed restraint by scientists from the very start". Importantly "their concern was made public" so that those less well informed could also use restraint.

These actions of restraint, self-regulation and risk communication had some unforeseen and un-anticipated consequences. "The scientific community's response has been to establish increasingly elaborate procedures to police itself – but these very acts of scientific caution and responsibility have only served to perpetuate and strengthen the general belief that the hazards under discussion must be clear-cut and imminent in order for such steps to be necessary."

This is interesting, as RRI is intended to anticipate the unexpected. So this is one aspect of the future that we need to keep a close eye on when anticipating the effects of RRI and its implementation.

I'll now come to the last letter that appeared in *Science* in response to the 'genetic meddling' one, written by Maxine F. Singer and Paul Berg, key members of the Asilomar group. They again stress that "we were among those who first publicly expressed concern over the potential hazards of recombinant DNA experiments" and to call for "a voluntary deferral of certain experiments". They point out that they "intervened early and assumed responsibly", rather than any other agency did or could have done at that time, given that the research into recombinant DNA was not widely known or understood. They also stress that "[a]cceptance of responsibility in this matter by the past and present directors of NIH was courageous, farseeing, and proper".

What is important here is that they took responsibility as soon as ethical and regulatory concerns presented themselves to them – this is what one may call 'upstream (ethical) engagement'. What about openness and 'making science' and responsibility public? This is what they have to say on that point: "The discussions on recombinant DNA have been public since their beginning. The matter has been widely reported by the public press. The publicity permitted all concerned individuals and groups to enter the deliberations. No datum has been classified and no commentary has been withheld from the public. Indeed, most policy has been developed in public sessions."

(For people interested in delving into the history of "Recombinant DNA Technologies and Researchers' Responsibilities, 1973-1980", these Paul Berg papers might be a good starting point.)

This little bit of historical research into early discussions around recombinant DNA (which involves "[p]recisely snipping bits of DNA from one organism and transposing them into others, using enzymes as molecular 'scissors'"; Jasanoff, 2011), opens up a new vista on responsibility and openness and should give us pause for thought when dealing with similar issues today.

Gene editing

Scientists have now developed a new gene snipping technology called CRISPR, which allows them not only to recombine DNA but, in a sense, precision engineer it. Again scientists, taking responsibility, have called for a moratorium and a 'prudent path' forward. And not only that. As Sheila Jasanoff points out in an article published in the *The Guardian* at the beginning of April 2015, the scientists also recommend four actions: "a hold on clinical applications; creation of expert forums; transparent research; and a globally representative group to recommend policy approaches".

However, even before all this could be implemented and well before a more democratic approach of public deliberations recommended by Jasanoff could get into gear, Chinese researchers had experimented with CRISPR to 'edit' a human embryo. And again, they took responsibility. At the end of April they made their (mainly negative) results public, a decision that was, one can argue quite courageous, honest and ethical. They published their results in the online journal *Protein & Cell* whose editor then wrote in an editorial defending the decision to publish, but calling for restraint and ethical, social and legal reflection: "Until a consensus on new regulatory rules can be reached, it is in the best interest of all parties that the research field should voluntarily avoid any study that may pose potential safety and/or ethical risks. Only by holding themselves to the highest standards will scientists retain the public's trust in biomedical research, and at the same time, provide the best service for the well-being of our society." You can read the paper about the failed experiments here. Carl Zimmer has published an excellent summary of this affair here.

Conclusion

In a letter to *Nature* Filippa Lentzos of King's College London said: "The original Asilomar meeting failed to engage the public in discussions, which we now know is crucial to the regulatory decision-making process. Had it done so, the resulting guidelines on recombinant DNA might have extended to legislation covering all users – including the military and commercial sectors – and not just those funded by the US National Institutes of Health." (Lentzos, Nature, 21 may 2015, vol. 521, p. 289). This might be so. However, is it realistic to ask scientists, who voluntarily call for guidelines to govern their *research*, which is their domain of expertise, and who call on the public to judge it, to also take responsibility for establishing guidelines that reach well beyond their domains of expertise and into all sectors of society? Would that not be arrogant and hubristic? Isn't this rather the time and place for social scientists and policy makers, as well as ethical and

forecasting experts, to step in and, instead of talking about responsibility and openness, to take responsibility, 'do' RRI in the way they see fit, and involve the public, and of course scientists too, in that enterprise, drawing on and learning from (some) scientists' long experience in taking responsibility.

PS
I had just finished drafting this post (25 May), when the results of a survey of public opinion on gene editing was published by the Synthetic Biology Project. The findings are interesting. Also: "Many respondents initially did not feel they knew enough about the technology to have an opinion about it."

'Pathways' in science and society

"Two roads diverged in a yellow wood; And sorry I could not travel both; And be one traveler, Long I stood, And looked down one as far as I could, To where it bent in the undergrowth." (Robert Frost, 1916)

I have walked along many paths, even pathways, on my journey through life. Recently, I have come across new pathways, indeed two different types of pathways, which have made me curious and thoughtful.

I was sitting in a meeting on Responsible Research and Innovation (RRI) and synthetic biology the other day and heard a lot about 'innovation pathways', 'commercial pathways', 'translational pathways', 'pathways to innovation' and, of course, 'pathways to impact'. Some weeks beforehand I had been sitting in various synthetic biology meetings surrounded by people who study 'metabolic pathways' (or as some call them, 'paths of life'). In both cases I was puzzled, but in different ways. What are these pathways we are talking about? How do we journey along them or make others embark on them? How do we map what they are and where they go? How are they made and changed?

Of course, these pathways are very different, but as we shall see, they cross over (might even come into conflict) in the life of natural scientists (who explore metabolic pathways and are supposed to find pathways to [industrial] growth) and in the life of social scientists (who are tasked with embedding RRI into this process and "help avoid lock-in to innovation pathways that do not serve individual patient or public benefit").

It might be useful to look more closely at these pathways, the micro ones and the macro ones, and see how they function in the life of science, technology and (responsible) innovation. I should say that they both perplex me enormously for different reasons. When I started to look at some 'maps' of metabolic pathways I was horrified to find how little I knew about this topic. I tweeted one of the maps expressing my anxiety, whereupon Jon Turney helpfully tweeted that this was what scientists now optimistically call systems biology. Maps of innovation pathways are no less confusing!

Both the micro and the macro, the metabolic and the innovation pathways, are parts of systems, systems of life and systems of society, that have come into contact in an age of biological industrialisation as well as responsible innovation.

Micro

The word 'metabolism' comes from the Greek 'metabole', which means change and refers to the total of an organism's chemical reactions. The metabolism is essential to maintaining the living state of the cells and the organism. These chemical reactions are organised into 'metabolic pathways'. These pathways convert chemicals derived from nutrition, such as sugars for example, into other (useful) chemicals. This conversion is helped along the way by a sequence of enzymes. Inside cells enzymes (protein molecules) break down or build up other molecules. "These enzymes are similar to traffic lights in that they can slow, speed up, and stop metabolic processes." So we have traffic going along these pathways - at varying speed!

In the past metabolic pathways were laboriously mapped by biochemists and microbial physiologists. Nowadays, these pathways are not only mapped but also 'engineered' using metabolic engineering techniques as part of genomics, systems biology and synthetic biology. To be more precise: "Metabolic engineering is the targeted and purposeful alteration of metabolic pathways found in an organism. […] Metabolic engineering uses organisms such as yeast, plants or bacteria that are genetically modified to make them more useful in biotechnology and aid the production of drugs such as antibiotics or industrial chemicals […]. These modifications are aimed at reducing the amount of energy used to produce the product, increase yields and reduce the production of wastes. Metabolic engineering draws principles from chemical engineering, computational sciences, biochemistry, and molecular biology. It involves application of engineering principles of design and analysis to the metabolic pathways in order to achieve a particular goal."

This is essentially what some of our scientists do at the Synthetic Biology Research Centre (SBRC) here in Nottingham. As it says on our website about 'synthetic biology': "Central to the synthetic biology concept is the development tool kits and interchangeable components which can be combined to construct metabolic pathways and networks."

The scientists study the 'behaviour' of cell 'systems' and the role of metabolic pathways and networks within them. But, as the quote above indicates, they do this not only to create more understanding of how things work; the also put their organisms (bacteria) and metabolisms to work in order to produce useful products.

The study of metabolic pathways, although speeding up in an age of mathematical modelling, genome sequencing and so on, can still be quite slow and painstaking. The pathway to products is however, envisaged to be quite fast, and there are expectations, pressures, to scale-up the metabolic engineering processes from the micro level to the industrial level, to move forward quite quickly from blue sky to more directly applied research. This 'pathway' from the

study of DNA to products through metabolic engineering, is depicted on figure 4 of the Synthetic Biology Roadmap for the UK published in 2012 (and just being re-drafted as we speak).

Macro

And so we get to innovation pathways, pathways to growth, commercial pathways and so on. These too are discussed in the Synthetic Biology Roadmap. On p. 4 we find a use of the pathway metaphor embedded in an extended metaphorical network - we also see a focus on speed. "To accelerate the contribution synthetic biology could make towards a vibrant economy, it will be necessary to build upon the many factors that make the UK an excellent location to progress synthetic biology, whilst identifying and reducing the commonly encountered stumbling-blocks anticipated along the pathway to commercially viable products and services".

Micro, macro and RRI

What does this mean for RRI? Is RRI there to anticipate and remove stumbling-blocks along the path from metabolic to innovation pathways? To get more clarity, I went to the RRI section of the roadmap. Here the gaze shifts from industry and commerce to the general public: "The direction taken by innovation pathways, and their perceived social consequences, themselves shape public responses. The responses and decisions of many and varied social groups – alongside those of academic researchers and firms – help to determine technological pathways and the realisation of benefits. [...] All of these groups need to be actively engaged, throughout the process, in the governance of synthetic biology research and innovation". This is a great ambition, but how can it be fulfilled, and how can this happen in a context of a speedy pathway from discovery to impact?

When listening into the meeting on RRI and synthetic biology, which set me on the path to reflecting on 'pathways', somebody wondered whether RRI had more in common with 'slow science' rather than fast innovation and whether there might be a conflict between doing science, doing innovation and doing RRI, or not.

This leads to a question worth thinking about more deeply in the future: What are the pathways for implementing RRI within the science/technology/industry innovation system? Can RRI become part of an innovation process, where, for example, "the organization makes decisions concerning which innovation pathways to support in the context of the organisations' values, mission and / or business strategy"? Ideally, this would be one of many roles that RRI has in the overall innovation governance process, but practically there might be some 'stumbling-blocks'... When thinking about the two 'pathways', the metabolic one and the innovation to growth and commercial viability one, I began to wonder whether these two pathways can be joined up as smoothly as the roadmap envisaged, helped along by RRI.

In a recent article by Paul Jump for the THE, Helga Nowotny, until 2013 President of the European Research Council, points to an "inherent

tension" between the two pathways, that is, "the demands of policymakers for practical innovation, seen as the undisputed motor of...economic growth" and the scientific process of discovery and the emergence of scientific breakthroughs which can't be foreseen or targeted. The scientific process is normally slow, meticulous, uncertain and full of unexpected surprises.

As Richard Owen, a core expert on RRI, has said on 14 January (2016) during a speech to the entire European RRI community: "Scientific freedom, the objective search for truth, is a value held by most scientists. But we know this is a fiction, overshadowed by the tyranny of urgency where there is simply no time for wider reflection; with the rise of the entrepreneurial scientist; by the need for demonstrating impact, for innovation; and for contributing to a strong, competitive knowledge economy."

Owen ended his speech by quoting Philippe Goujon (Director of the Laboratory for Ethical Governance of Information Technology, University of Namur, Belgium), who had pointed out at the same conference that "we need to change the cognitive frame for innovation" - and, I would add, to do that we need to reflect on, and perhaps, change the language we speak about innovation and responsibility.

Acceleration, autonomy and responsibility

In recent emails and meetings there has been a lot of talk about 'acceleration', both about the rhetorical use of acceleration in the context of Responsible Research and Innovation (RRI) and about the reality of living in an accelerated academy. In this post I will examine 'acceleration' a bit further, especially in the context of synthetic biology. This is a topic that I have begun to explore in a previous post on 'pathways' - pathways to impact, innovation, growth - pathways which are gradually becoming speedways, at least rhetorically. This is also a topic that was discussed at a a workshop organised on 8 March 2016 by Sujatha Raman and Warren Pearce on the 'Responsive-Innovative University', part of a University of Nottingham Discipline Bridging Award.

Acceleration and synbio

In 2012 a UK Government advisory panel drafted a 'Synthetic Biology Roadmap' which laid out five key recommendations for the development of synthetic biology: (1) Invest in a network of multidisciplinary centres to establish an outstanding UK synthetic biology resource; (2) Build a skilled, energised and well-funded UK-wide synthetic biology community; (3) Invest to accelerate technology responsibly to market; (4) Assume a leading international role; (5) Establish a leadership council.

In 2016 a new version of the roadmap, a strategic plan entitled 'Biodesign for the Bioeconomy', was published. This document focuses in particular on recommendation (3) of the previous 'roadmap', now that the network of multidisciplinary centres and the leadership council have been established. The new strategic plan hopes that acceleration in 'biodesign' (a new word for synthetic biology?) will lead to a faster growth in the 'bioeconomy', one driving

the other. The plan highlights five key areas of strategic importance, putting acceleration in first place: (1) Accelerating industrialisation and commercialisation; (2) Maximising the capability of the innovation pipeline; (3) Building an expert workforce; (4) Developing a supportive business environment, and (5) Building value from national and international partnerships.

Both the 2012 roadmap and the 2016 strategic plan stress the importance of RRI in the context of synthetic biology. However, there is clearly a tension between accelerating research and development for economic benefits and fostering a culture of responsible innovation (which should include time for anticipation and reflection). The authors of the 2016 strategic plan see 'entrepreneurship' as a bridge between the two and state: "A good understanding of stakeholder interests and potential future market value needs to continue to influence the selection of research topics and to inspire the development of innovative applications. Doing so within a responsible framework ensures effective balancing of societal benefits and commercial value. For synthetic biology entrepreneurship and the principles of responsible research and innovation can, and indeed should, be complementary." Can such balance and complementarity be achieved?

Acceleration and autonomy

As Filip Vostal has made clear in a recent blog post entitled 'In search of scholarly time', a "commitment to speed" is nothing new in the academy and indeed in science and industry in general. A focus on speed and rapid progress has been with us for at least two centuries. However, Vostal points out that "the positive virtues of speed have metamorphosed into a new form of social evil in the present conditions of oppressive 'acceleration society'", which "results in the experience of time-shortage and hurry sickness".

Vostal asks whether slowing down is the answer, as advocated for example by the 'slow science' movement. He is not entirely convinced that this is the right way to go. Instead, he considers another option "akin to scholarly time autonomy, enabling them [academics] to determine how temporal resources should be used."

This is a nice thought, but can it work in a context where academic and professional autonomy is being gradually eroded? As Vostal says "one wonders whether anyone at all can resist the oppressive nature of late modern fast time. In order to resist academic hurry sickness, it would perhaps have to be those academics holding senior administrative positions who need to legislate the principle of scholarly time autonomy as an explicit political demand – and perhaps as an ethical principle integral to the education and science governance."

Acceleration and responsibility

This brings us back to RRI. Can RRI and some of the governance and ethical principles that it entails be made entirely compatible with a culture of speed and acceleration? Can the circle be squared between RRI-inspired reflection,

dialogue, engagement, inclusion and so on (activities that demand time) and bringing products rapidly to market? In a way RRI seems to be at the eye of an accelerating time vortex. Can it withstand being swept away by it? One way to prevent this might be more explicit reflection on the issues of both time/acceleration and autonomy within RRI.

Should respect for academic time and respect for academic autonomy be part of RRI? Both in terms of scholarly time autonomy, and, perhaps even more importantly, scholarly research autonomy - in particular autonomy over the 'selection of research topics'? At the moment both are endangered not only by the arrival of an 'accelerated academy', but also by the emergence of an industrialised and 'marketised academy'. These developments make it even more important to re-examine a persistent tension within the RRI agenda which was noted as early as 2012, when the first synbio roadmap was being written, namely "that there is still a tendency to present these issues as matters of promoting public acceptance, accelerating innovation and maximising economic growth and too little attention is given to the complexities and uncertainties of the innovation process".

The question for social scientists and natural scientists working together under the banner of RRI is: Are social scientists trying to engage in RRI with their natural science colleagues just (perceived as) "time thieves" slowing down the synbio "productivity ninjas", to use some of the wonderful metaphors created in Vostal's blog post? Or can we find a more collaborative rhythm? We shall find out over the next few years, as social scientists continue working with their natural science colleagues, stakeholders, students and members of the public in the six synthetic biology research centres that have been established in the UK. Only time will tell.

6. MORE GENERAL REFLECTIONS ON RRI

Responsible innovation: Great expectations, great responsibilities

I recently (February 2014) happened to click on a website providing advice to researchers working on 'medical technologies'. It starts by pointing out that: "Researchers in cutting edge fields are increasingly being asked by funders and regulators to conduct responsible innovation in order to increase the social and economic benefits and effectively manage the risks of their work."

Since around the start of the millennium research proposals submitted to physical, engineering, biological and medical science funders in the UK have to contain a section in which researchers explore how their research engages with the wider public sphere and more recently how it would lead social and economic impact in the wider world. Over the last couple of years or so reflections on public and stakeholder engagement have begun to be replaced by reflections on 'responsible innovation' or 'responsible research and innovation' (RRI), which tries to embed public participation earlier and more deeply into the research process and combines it with scientific and technological (risk) assessment.

Definitions of responsible innovation vary. However, this one comes up first when one puts 'responsible innovation definition' into Google: "*Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products(in order to allow a proper embedding of scientific and technological advances in our society)*" (René von Schomberg, 2011) Responsible (research and) innovation is becoming a new language for thinking about relations between science and society, science in society, science with society and science for society. This is observable not only in the UK but also, and

perhaps even more so in Europe, especially as part of Horizon 2020, and now also in the US.

Funders hope that, through 'responsible innovation', innovations can happen on a moral basis and that one can steer innovations to the 'right' impacts in an ethical and democratic way. They also hope that one can do this while staying economically competitive during times of financial crisis and while societies are grappling with a number of great socio-economic challenges that demand "the development of new, interdisciplinary, innovative and impact-oriented solutions".

In principle, responsible innovation seems to be a 'good idea' and a 'good thing'. Why would one object to it? In the following I'll first chart a very short history of responsible innovation, summarise some recent work on buzzwords like responsible innovation, and then point to some possible fault-lines that need to be monitored in the future.

Big

There have always been efforts to make the science and innovation process more ethical and responsible through codes of conduct, codes of ethics, corporate social responsibility programmes, public consultations, public participation and so on. However, the new 'responsible innovation' agenda began to emerge only quite recently in around 2010/2011 in a variety of shapes and forms, when people like René von Schomberg, Jack Stilgoe, Richard Owen, and Phil Macnaghten started to write and blog about it. This new push for responsible innovation has some of its roots in debates about the responsible use of emerging technologies, such as nanotechnology in around 2007, and reflections on how this fitted in with established frameworks of ethics, governance, public engagement and risk assessment (more information here). In the current round Horizon 2020 Error! Hyperlink reference not valid.around €14 million to responsible innovation projects.

In a very short time responsible innovation has become an important part of the European and UK funding and research scene. Like older enterprises, such as public engagement, dialogue, participation and so on, it has the support of both the scientific elite (funders and industry) and of those who see their task as critically engaging with science and technology from the perspective of 'science and technology studies'. Interestingly, responsible innovation is now becoming itself an object of study for sociology and the social study of science. It even has its own journal. Responsible innovation, at least as an academic enterprise, seems to be unstoppable. It's a bit of a steamroller; it's big; there is a lot of buzz about it; but … there may be issues we have to think about.

Buzz

In a recent article for *Public Understanding of Science*, the philosopher and historian of science Bernadette Bensaude Vincent discusses the 'politics of buzzwords', focusing in particular on 'public engagement'. She also mentions in passing a number of other buzzwords, such as 'responsible innovation'.

She points out that buzzwords have their roots in marketing and are "hollow terms, with more hype than substance" (p. 3), or as the online edition of the *Oxford English Dictionary* puts it: "a term used more to impress than to inform" (OED). Could it be the case that responsible innovation is such a term? But if it's hollow and hype how can it attract so much attention and so many followers? There are various reasons for this. Responsible innovation comes as part of a cluster of phrases, which all reinforce each other. These are: responsible innovation, sustainable development and, of course, public engagement. Together they convey a message that is easily remembered, albeit vague. Such buzzwords are especially potent when they appear in times of crisis and seem to show a way out of the crisis. The concept responsible innovation emerged in the middle of the world's latest financial crisis, which is also a crisis in innovation.

As Bensaude Vincent points out, buzzwords spread, like rumour, from mouth to mouth, paper to paper, institution to institution. In the case of responsible innovation this happened through academic papers, blogs, briefing documents and, most importantly, 'frameworks' for and by funders both in the UK and in Europe, and now also in the US. Once widely spread, buzzwords establish something like a 'trading zone' in which people from different backgrounds, such as funders, natural and social scientists, policy makers and industrialists, can communicate without however having to be too explicit about what they are saying.

The success of responsible innovation as a buzzword, the speed with which it has spread and established itself, is quite astounding. Another reason for this, apart from the flexible way with which it can be used, may be that it links up with and reinforces prominent cultural values and also promises to enable a way of innovating and creating wealth without destroying such values. Responsible innovation promises to deliver innovations that are ethically acceptable, safe, sustainable and socially desirable, for example. That's all 'good', isn't it?

But

Buzzwords like 'responsible (research and) innovation' seem to have an almost magical force, especially if used ritualistically and repeatedly, as they seem to be in the context of current research funding applications. But should one perhaps question this magical power a bit more?

Are there some chinks in the magical armour of responsible innovation that need to be discussed? Here are some questions that one might want to ask, some of which have been asked already by Hilary Sutcliffe, one of the champions but also critics of responsible innovation (for some more questions see p. 9 of this article by Nikolas Rose, HT @SujathaRaman2):

- Does responsible innovation slow down research and innovation? And is that good or bad in a competitive market situation?
- Horizon 2020 is supposed to increase competitiveness. May responsible innovation impede competition?
- Is responsive innovation just a perfunctory tick-boxing exercise that one has to go through to get funding

- Should one think more about the responsibility of funders in setting research and impact agendas in the context of responsible innovation
- May responsible innovation lead to alienation and disengagement rather than integration and collaboration between workers in the social and natural sciences, as they might feel they are just cogs in a huge responsible innovation machine that needs to be fed?
- Is responsible innovation merely 'academic', in the pejorative sense of that word? That is to say, is it just one of those key words you have to use in your funding application to press the right buttons, or does it have real world relevance in industry, in businesses and for people in enterprise, people who actually do the 'innovation'?
- And, of course, does it have real value for those living with and through those innovations, that is 'real' people?
- Can responsible innovation actually achieve its intended goal or this goal intrinsically elusive? And finally:
- Is responsible innovation perhaps not as big as the buzz suggests, or only big in parts?

'Responsible innovation' creates great expectations that 'mobilise the future into the present', while at the same time trying to anticipate and assess the impacts that possible futures may have on the present. This is a complex task that needs more scrutiny than it has so far received, and not only in academic circles. We might need a responsible innovation approach to responsible innovation itself.

RRI and impact: An impossiblist agenda for research?

Richard Jones has written a long, profound and thought-provoking blog post on (ir)responsible innovation (stagnation). I read his post (in February 2014) alongside a recent post on the social impact of research, its challenges and opportunities. This made me think that we are witnessing a confluence of agendas which are generally only looked at separately but that should really be scrutinised together; namely, what it means for us academics to live in a world increasingly governed by *both* demands for *Responsible Research and Innovation* (RRI) and demands for *Impact* as part of the Research Excellence Framework (REF). All this reminded me of a blog post on the REF which highlighted its 'impossiblist' discourse.

In this context I want to ask: Are RRI and impact, separate or together, an 'impossiblist' agenda for academic research and might they have negative rather than positive effects on the way we carry out research and translate it into products, services, innovations? I have no answers to these questions but will point out some paradoxes and also come to one relatively positive conclusion.

What are RRI and Impact?

First RRI: Richard Jones points out: "responsible innovation is a term of art in science policy. Richard Owen, Jack Stilgoe and Phil Macnaghten, writing for the UK research council EPSRC, define it as *'a commitment to care for the future through collective stewardship of science and innovation in the present"*, while

Rene von Schomberg, in the context of the EU's Framework program, writes that *"Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society)."*

Now Impact: The *Economic and Social Research Council* points out that: "Research Councils UK (RCUK) defines research impact as 'the demonstrable contribution that excellent research makes to society and the economy'. Research impact embraces all the diverse ways that research-related skills benefit individuals, organisations and nations. These include: fostering global economic performance, and specifically the economic competitiveness of the United Kingdom'; increasing the effectiveness of public services and policy; enhancing quality of life, health and creative output.

A key aspect of this definition of research impact is that impact must be demonstrable. That is to say, impact must be auditable. And here we are getting into the realm of paradoxes…

Pathways to a better future?

Both RRI and impact deal with the future. Both are supposed to lead to innovations for and impacts on society that are 'beneficial' to society. Both are supposed to steer research from its inception to its application and beyond in a certain direction, on a certain pathway towards … a desirable good or better future (for all) that is compatible with or even inextricable linked to economic growth.

These entailments of the RRI and Impact agenda lead to certain challenges and even paradoxes highlighted in the two blog posts I cited at the start of this post.
With respect to RRI, Jones points to one paradox when he writes: "We need to innovate responsibly, and yet, we do need to innovate. If it's irresponsible to innovate without a reflexive process of alignment with widely held societal priorities, it's irresponsible not to innovate in the face of pressing societal challenges. This necessary innovation is not happening."

With respect to impact, Peter A.G. van Bergeijk, Shyamika Jayasundara-Smits, and Linda Johnson point out that when it comes to generating and auditing impact, especially in the context of development studies and the social sciences: "social scientists often have to deal with specific and sensitive types of data, have limited budgets available for impact assessments to track (long run) social impact and are confronted with the ambiguity of whose intervention actually produced a particular impact on a particular situation, when many stakeholders from diverse sectors are involved (so that the question arises to whom to give credit for a certain policy outcome when the research has been carried out with a variety of stakeholders including government officials, NGOs and private sector representatives.)."

This hints at another overall paradox hidden in RRI and Impact: How can one *steer* a *hugely* complex system towards a better future, a future that we 'all' (or at least most of us) want? This complex system comprises what one may still call basic science, applied science, the private and public sector (which are increasingly intermingled), people (let's not forget people, and people do lots of things for very different and unpredictable reasons), markets, (unpredictable) natural, social and political events and much more

Is it really possible in this context to audit Impact and to audit Responsibility? Is it possible to push for Impact (and Innovation) in a Responsible Way? Or are we not getting quite dangerously entangled in a deeply 'impossiblist' enterprise?

Maxims

All this needs to be discussed in more detail. However, this does not mean that one should not keep some of the 'maxims' (in the Kantian sense) of RRI and Impact in mind when undertaking academic research. That's my *positive* message. And yet, I believe that we would be deluding ourselves if we thought we could guide humanity to a 'better' future for 'all', whatever that may mean. In the context of RRI and Impact intentionality meets complexity and all that this entails.

7. MISCELLANEOUS

Advanced fermenters

I recently (April 2015) dipped my blogging toe into the microbiome, lured there by Jon Turney's book *I, Superorganism*. A few days ago, while trying to find an old email on a completely unrelated topic, I came across a comment by Denis Noble that he had sent me when we were corresponding about the microbiome in around 2008. He said: "I was amused to see Nicholson proposing that we are 'advanced fermenters'". That made me think. Are we just advanced fermenters and what does that mean?

I, advanced fermenter

When I tried to find the article by Nicholson et al. on gut microorganisms again (which turned out to be behind a pay-wall here at the University), I stumbled upon a paper by Maureen O'Malley. Some of what she wrote about the microbiome project and the human genome project is worth repeating: "Microbiomic research encourages the conceptualization of any multicellular organism as a composite of all three domains (bacteria, archaea and eukaryotes) and the fundamental genome as a metagenome of microbial and other DNA …. It is even suggested that humans and other animals could be regarded as 'advanced fermenters', the main role of which is to house, nourish and assist the reproduction of an enormous array of microbes (Nicholson et al. 2005). The original human genome sequencing projects were, from this perspective, about only a tiny and unrepresentative complement of our genes, but this limitation is rapidly being remedied by the human microbiome project ….".

So what about advanced fermenters? After finally getting access to the article, I can now tell you what Nicholson, Holmes and Wilson, rather than other people, said in the 2005 paper: "The average human should be regarded as a complex ecology or '**super-organism**' rather than an individual. Indeed, it is tempting to suggest that the role of the host is to function as an **advanced fermenter**, carefully designed to maximize the productivity of the microbiome." (p. 7, bold by me).

Selfish genes and selfish microbes

When thinking about this and Denis Noble's work, especially his 2006 book *The Music of Life*, which tries to provide a counter-point to Richard Dawkins' work on the 'selfish gene', I began to wonder … Are we 'just' the products and replication vehicles for selfish genes or are we 'just' advanced fermenters, the products and replication vehicles of 'selfish microbes'? What does this make us? Are these the only two choices? Where would 'we' be located in either scenario? I am not totally sure!

And what about synthetic biology in this context, or microbial engineering? Are we perhaps on the way to becoming 'just' our own 'biofactories'? Ok, this is a bit of a stretch! At the moment we are just trying to build so-called biofactories that work for us; indeed here at Nottingham, at the BBSRC/EPSRC funded Synthetic Biology Research Centre, we are synthetically engineering microorganisms to work as what one might call 'advanced fermenters' in order to produce useful molecules, useful for us and the planet!

So, thinking about the microbiome makes us think about our'selves' in new ways and, as we shall see, it also makes us think about the world we live 'in' in new and quite surprising ways. I found that out, yet again, when trying to find the Nicholson article and reading another paper by John Dupré and Maureen O'Malley on metagenomics and biological ontology from 2007. I'll just quote the questions they ask, which, eight years later are becoming even more urgent.

Ocean warming, melting ice-caps and antibiotic resistance

"It is becoming increasingly clear that a range of fundamental questions about life on this planet will find their answers only with advances in system-based understandings of microbial communities in global environments …. Will warming oceans disturb the world's primary oxygen producers, the marine cyanobacteria *Prochlorococcus* and endanger oxygen dependent lifeforms (everything apart from prokaryotes)? Will the thawing of the polar icecaps lead to intensified global warming as dormant methanogenic prokaryotes become active and release more methane (a contributor to global warming)? Will global changes in human habitat and diet modify the microbiome in human bodies and have significant health consequences? Will antibiotics still be effective in twenty years or will we see the return of high fatality rates from infections such as tuberculosis and pneumonia with the worldwide circulation of antibiotic resistant genes in the microbial metacommunity?"

Antibiotic resistance in particular is becoming an urgent problem, as Nicholson et al. pointed out ten years ago: "Given the enormous biological success of our own species in terms of colonizing the planet, this has certainly been a success story for our microbiomes and parasites. One important realization must be that the reckless and largely uncontrolled use of antibiotics might not only change human society through the increased risks associated with multiple antibiotic resistance in pathogens but also through irreversibly altering the microbiome with which we have co-evolved." (p. 7)

Life, talk to me about life!
Microbiomics, metagenomics, synthetic biology, microbial engineering…. These sciences and technologies are more important to life, the universe and everything than one might think! And they are worth thinking about!

If you want to know more about the future of microbiome research, you can read this recent article by Jon Turney!

Synthetic biology or the modern Prometheus

When waiting for a plane, I was randomly musing about synthetic biology, responsible innovation and stories – this is the result.

Once upon a time there were Mary Shelley and her husband Percy Bysshe Shelley. Mary wrote *Frankenstein; or The Modern Prometheus* (first published in 1818; now available in twitter-form, as tweeted by Katie Reeves); Percy wrote *Prometheus Unbound*, a rather complex adaptation of Aeschylus's tale with the same title (drafted in 1818 but only published in 1820, after the couple had lost a daughter and a son). She wrote a tale of moral agonizing over whether it was a good idea to create artificial life; he wrote a poem about defying a tyrannical god (actually I am not totally sure). Both the novel and the poem link back to the Greek myth of Prometheus who stole fire/power of thought/knowledge from the Gods and was cruelly punished for his 'hubris'.

Both *Frankenstein; or The Modern Prometheus* and *Prometheus Unbound* have been used/alluded to in modern discussions of advances in genetics, genomics and synthetic biology, although *Frankenstein* much more so than *Prometheus Unbound*. *The Economist* in particular seems to like Prometheus: it talks about unbinding Prometheus when reporting on synthetic biology and it evokes Prometheus Unbound when talking about regenerative medicine.

Both the novel and the poem deal with hugely challenging topics, but only the novel still speaks directly to modern concerns about science and society, as Mary tried to fathom the depth to which the life sciences could plunge before hitting the rock of moral revulsion. We are now reaching, yet again, a Frankensteininan moment, as we grapple with the power we are developing to design and redesign life. Fears are emerging yet again that Prometheus may be unbound.

Bounding Prometheus

In the past, we tried to reign in the presumed Promethean powers of science by writing stories and poems. More recently, we have created 'frameworks' that are supposed to do a similar job. First, we created ELSI or ELSA (Ethical, Legal and Social Aspects/Issues) programs whose job it was to constrain or bound science in ethical and legal ways. More recently, we have created Responsible Research and Innovation or RRI, whose task it is to make science work for what Percy Shelley would have called perhaps the 'betterment of humankind', to bind science to social values and, in the process, create 'peace and prosperity for all'. Most importantly, the dream of RRI is that science and society, scientists and members of the public can work together towards these goals. Can such 'frameworks' really achieve these tasks? Can they really engage both both researchers and members of the public and make them think and work together rather than apart, or … do we also need stories and poems for that?

Houston, we need a narrative

When thinking about these issues, I came across a tweet by Carmen McLeod announcing a new book by Randy Olson entitled *Houston, We have a Narrative*, in which he argues that scientists need to tell stories and tells them how to do it. This again made me think that in the case of synthetic biology the old stories of Frankenstein and Prometheus still do a good job of making us think about 'responsible innovation', while new stories about synthetic biology as modern-day Lego might be less suitable to do so. I also thought that there must be modern stories already out there talking both about the promises and perils of synthetic biology. When scientists start to tell stories about synthetic biology, they might want to know what's already being told.

Houston, we have some narratives

So I started to look around, I asked some people and I asked 'Google'. According to a very useful webpage, it seems that a small sub-genre of science fiction in general and biopunk in particular is emerging around synthetic biology, which one might call, I suggest, synbio fiction. It all began, perhaps, in the 1980s, with 'Tales of a biotech revolution'; and the genre's most iconic modern incarnation seems to be The Windup Girl. If you want to explore the merger of the novel's plot with reality, you should also read this article on the Corn Wars. Interestingly, protagonists in the novel are not only genetically modified humans like the windup girl, but also megacorporations like AgriGen. I'll come back to that.

Alongside novels, films/movies are also beginning to deal with synthetic biology. Some of these have been explored in a 2013 article by Angela Meyer, Amelie Cserer and Markus Schmidt (who works at Biofaction and organises biofiction festivals), entitled "Frankenstein 2.0.: Identifying and characterising synthetic biology engineers in science fiction films".

Science and culture tend to go hand in hand, inspire each other, and, in a way, egg each other on. The authors of the article point out that only a few weeks after Craig Venter announced his creation of the first synthetic bacterium, on 20 May 2010, the film Splice was released in the United States. "The film tells the story of

two young scientists who engineer new synthetic creatures in the lab by combining DNA from different organisms." Interestingly, towards the end of their article, when the authors discuss issues of ethics and responsibility, they remark: "Discussing in June 2010 the breakthrough made by the Craig Venter Institute and its possible consequences, the German newspaper Die Zeit started its article with illustrations from the film Splice and the question "What happens if the bio-industry succeeds in re-programming the human body?"."

Synbio fiction seems already to be a fertile ground for ethical, social and public reflections on our current Frankensteinian moment. RRI researchers might want to take note of these developments.

From Prometheus to profit

Our Frankensteinian moment is quite different to that explored by Mary Shelley in her 1818 novel. Here the focus was on a lone genius/mad/megalomeniac scientist; today the focus is shifting to megalomaniac mega-corporations as objects for ethical reflections. As the authors of the article "Frankenstein 2.0." remark: "images and characteristics used to depict SB [synthetic biology] scientists in modern science fiction films particularly emphasise a shift from a purely academic to an increasingly industry-oriented and entrepreneurial spirit. […] Involved in market-oriented research, he or she is more reflecting the image of a scientific entrepreneur than that of a weird megalomaniac professor. Taking this idea one step further, film makers also tend to see a powerful company, political regime or army as main driver of SB research."

Who takes responsibility?

This shift means that, in the context of synthetic biology, film makers (and sci-fi authors) have begun to think about novel aspects of responsibility and ethics, going beyond, but also taking stock of, two centuries of ethical reflection in modern literature and film, while also engaging strongly with developments in modern science. This means that while most scientists working by themselves are portrayed as striving for the 'betterment of mankind' but unleash some sort of evil instead, which they then regret and want to bring to a halt, sometimes by killing themselves, scientists working in large teams and/or for huge industrial companies are portrayed as not assuming responsibility for their actions. Responsibility is distributed and diluted. This is a real problem, also in the real world. Can Corporate Social Responsibility help here? Can Responsible Research and Innovation help here? These are important questions for those interested in responsible innovation!

Natural/artificial

The Nuffield Foundation on Bioethics will soon report on a project that critically explores "how current public and political bioethics debates are affected by ideas about naturalness and how this correlates with academic discussions relating to the concept". (The findings are now available here) This made me think, especially as I am working now as a social scientist with a team of people engaged in 'synthetic biology'. Some definitions of synthetic biology say that one

group of synthetic biologists "uses unnatural molecules to mimic natural molecules with the goal of creating artificial life" and another group "uses natural molecules and assembles them into a system that acts unnaturally".

Thinking with categories

Human beings are thinking beings. Thinking needs some sort of scaffold to happen. For a long time one of the scaffolds has been our ability to sort things into categories and in particular to make binary distinctions. That seems only logical and indeed natural. As Claude Levi-Strauss told us "culture is organized around pairs of fundamental polarities", such as nature and culture, and "its myths (we would say its value system also) attempt to mediate those polarities" (Veatch, 1971, 1).

For a long time we have been happy thinking and living with or, if you like, cursed by what appear to be ready-made (natural) categories with hard and fast boundaries. They enabled us to distinguish clearly between life and death, male and female, humans and machines, Gods and humans, good and evil, nature and culture, the natural and the artificial…. This type of thinking scaffold has served us quite well. Up until now.

Advances in science, especially the biological sciences, seem to be blurring these categories and one can even venture to say that these categories have now gone. But this also means that a particular kind of logic has gone. We live in a world of artificial intelligences and technologically enhanced bodies, one even where Barbie has artificial intelligence and tries to make (artificial) friends….. To be able to live in this 'brave new world' of ever-blurring boundaries and categories, people might have to master 'fuzzy' (non-categorical, boundaries-blurring) thinking. That can be quite frightening and disturbing.

The problem is that human beings are still better at traditional logic based on (hard) categories than at fuzzy logic. They want to hang on to categories and binaries, even when they dissolve under their feet. They still want things to be either dead or alive, male or female, natural or artificial, and so on.

Of course, there have also always been people who have strayed beyond the boundaries or tried to subvert them. Art is full of hybrids, chimeras and monsters and so is our literature. The problem is that nowadays these mixed up beings are appearing in science (and reality) instead of in fiction and in art and are therefore seen as much more threatening.

Thinking beyond categories

As soon as science began to emerge and challenge the constraints imposed by traditional thinking during the Enlightenment, philosophers began to dream about artificial bodies and artificial minds and to ask questions about the 'unnatural'. And so did in fact many early 'science fiction' writers who began to question and probe the artificialisation of nature. These discussions and speculations should be revisited as they laid the foundations for modern debates about similar issues – and structure them all the time, whether we want to or not. Creating an awareness of pervasive metaphors, images and scripts and

about where they came from and how they shape our thinking and acting, may help overcome some still existing barriers of communication between 'experts' and 'lay people' – another binary we think with.

In 1769, Denis Diderot, the famous editor of the *Encyclopédie* and paragon of the Enlightenment, speculated about the origins of life and the creation of 'artificial life' in his essay *The Dream of d'Alembert*. As Gordon Rattray Taylor summarised it in his 1968 book *The Biological Time Bomb*, Diderot "described how one day human embryos would be artificially cultivated and their hereditary endowment predetermined. His hero saw 'a warm room with the floor covered with little pots, and on each of these pots a label: soldiers, magistrates, philosophers, poets, potted courtesans, potted kings….'" (Taylor, 1968: 9). Taylor predicted that this vision would come true in the year 2000. We are not quite there yet (fortunately).

Of course, Diderot was not the only one who dared to dream beyond established categories. He had predecessors in medieval alchemists and the clay Golem of Jewish folklore and he had followers in Frankenstein's monster and the babies in jars of Huxley's Brave New World – a topic explored in depth by Philip Ball in his 2011 book *Unnatural: The Heretical Idea of Making People*. Surprisingly, Ball points out that "the idea that making life is either hubristic or 'unnatural' is a relatively recent one". I am looking forward to the Nuffield report to tell us when it became natural to think such ideas were unnatural.

Embracing ambiguity

It's interesting to note that ever since such philosophical or fictional speculations are turning into scientific realities, there has been what Robert M. Veatch called in 1971 "a cultural stampede back to the wilderness" (1971: 1) and people have tried to cling to the "simplistic ethical notion that if something has been artificially processed it is intrinsically evil" (ibid.). In his insightful article "Doing what comes naturally", Veatch asks us whether it might not be "better to face these technological breakthroughs for what they are: ethically complex and ambiguous phenomena, simultaneously offering great hopes and great threats to mankind" (p. 2). He exhorts us to avoid dichotomisation and polarisation, especially between 'humanist' and 'scientist', as well as between 'scientist' and 'non-scientist'. He warns us that "when roles are stereotyped and polarized, the ethicist is limited to criticizing dubious intervention, while the scientist can only defend his realm against onslaught." (p. 2) These are insights and warnings we should take to heart.

Provocative question

I'll end with a provocative (and probably silly) question. Walking through town the other day, I saw a poster in front of a café which said: "Fresh, made from scratch, natural". This made me think. Would cells freshly made 'from scratch' by synthetic biologists therefore be natural, even more natural than natural ones?? (If you put in 'from scratch' and 'synthetic biology' into Google you get 42,600 results; if you put in 'life from scratch' you get 440,000 results; 18 September)

The colours of biotechnology

I have recently been musing about images used to make science public and wondered what images are out there for synthetic biology. I knew that in the past cloning was visually represented by 'Dolly the sheep' or 'armies of little Hitlers', nano found its visual incarnation in nanobots and fantastic voyage, but what images would synthetic biology conjure up, I wondered? To investigate in a quick and dirty way, I searched Google Images (on 19 October, 2015).

I first did a test run on nanotechnology and found that Google Images now do what one might call a 'thematic analysis' of prevailing images! So for nanotechnology we have groups of images related to medicine, robots, electronics, products and car (the Tata 'nano' car, which is obviously not nano-seized). Nanobots are still there it seems, even the ubiquitous 'Nanolouse', but most of the images depict nano structures, such as carbon nanotubes and buckyballs. The colour schemes are still what they were when I first looked at nano images, namely red (inside the body) and blue (evoking outer space). So, it seems to me that Google Images captures pretty well what one might call collective visual representations of various types of science.

Synbio – between art and applications

Then I tried 'synthetic biology'. Here the themes covered are applications, art (congratulations to Jane Calvert and her colleagues!), circuit, food, comic (congratulations to Drew Endy!), and, finally biofuel. The first two images underneath these thematic groups are beginning to be quite ubiquitous. I have seen them in powerpoint presentations and I have used them myself. The first shows a little diagrammatic image of the expected journey from using genes to program cells that become cellular factories to make high value products. This certainly represents the dream of many synthetic biologists, including those working at our Nottingham Synthetic Biology Research Centre. The second (although a couple of days later this was the first) is perhaps the most evocative, as it depicts electrical circuits inside a cell. Biofactories inside cells and circuits are, it seems, becoming symbolic for synthetic biology, which brings an engineering approach to biology.

The rest of the images are mixtures of hands holding vials, more cells and circuits and the odd double helix. The prevailing colour scheme is blue, but blue doesn't dominate.

Crisper images

What about other fields associated with synthetic biology but currently more topical, such as CRISPR, gene editing and genome engineering? CRISPR, a gene editing tool, is attracting a lot of attention, increasingly so from social scientists who are demanding a public debate about the issues related to editing genes or genomes. Some are carrying out a "pilot survey to gauge what different members of the public think about genome editing". In an article accompanying the survey, Siliva Camporesi and Lara Marks point out that the "survey also aims to capture what images, ideas or associations people have when they think about CRISPR/Cas9. Capturing this aspect of the public response is important as it can

shape the boundaries of the ethical debate and the thinking of policy-makers." So, I thought my Google Images 'method' might be a good starting point to study such public associations.

Google has thematically grouped images relating to CRISPR as: genome editing, knockout, genome engineering, mechanisms, review, knockin – nothing much popular here yet. The images underneath are all abstract diagrams and there is no colour scheme emerging yet. It's still a black and white issue, so to speak.

When we turn to 'gene editing' things become a bit more concrete. We can see images of double helixes being snipped by scissors or knives, for example. Interestingly, and rather surprisingly to me, things get even more concrete with 'genome engineering'. There are only three rather abstract themes listed: editing, zinc finger nuclease and CRISPR. The images are rather concrete though. Scissors figure heavily alongside the more abstract diagrams that characterise CRISPR images. Amongst the most popular representations are one stark image of an unzipping double helix against a blue background and another rather futuristic one of two hands snipping a red double helix held in a type of transparent vice, again against a brooding dark blue background. A further image shows a yellow pencil with a rubber used to erase parts of a double helix, against brown background. This is an advert for a conference on genome engineering and synthetic biology. This links up with one of the core images of genomics, namely that of reading, or in the case of synthetic biology, writing or rewriting the 'book of life' – a connotation that is otherwise absent from our 'cutting' (but not pasting) images.

One tomato, two tomato, three tomato, four

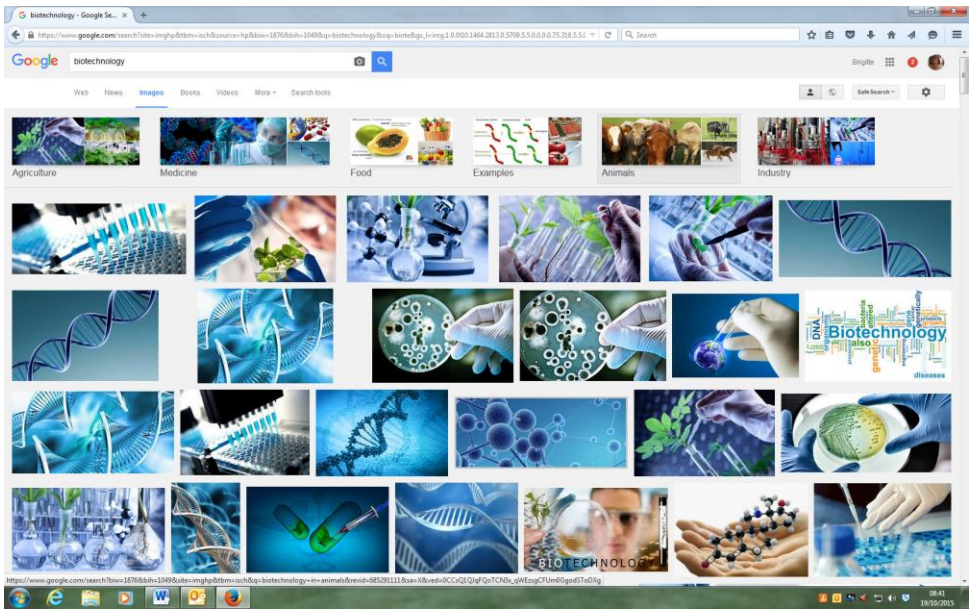
I then thought, ok, so this is the state of affairs with the 'cutting edge' stuff. But what about genetic engineering – the old stuff – have images settled down there a bit more? When looking at the images for 'genetic engineering', we still find quite a mixture of images used with one or two showing tomatoes. When we look at 'genetic modification' we get more tomatoes and some piglets, but strangely no pictures of crops and no pictures of Frankenstein. When we finally get to GMOs, a lot of the images depict tomatoes (a veritable sea of red), especially tomatoes being injected with something. This image has history!

As Wolfgang Wagner says in a classical article on the social representations of GM foods from 2002 (here summarised in 2012): "Genetically modified organisms (GMOs), for example, were gradually introduced during the 1990s.This signalled the beginning of a heated dispute between opponents and supporters of biotechnology in many European countries, the course of which illustrates exceptionally well the steps in the emergence of a social representation. As long as GMOs were not an issue, the intensity of the media's reporting about biotechnology as a novel scientific achievement was low and insignificant. During this period a significant number of people felt free to answer questions in surveys about technology with the response: 'don't know.' At a certain point, when the technology became a topic of relevance, the media intensity increased significantly and correlated with a simultaneous increase of debates in some countries. This was the time when images of tomatoes being

injected with genes through a syringe were circulated and began to be recognized by virtually all citizens as an iconic metaphor for genetic engineering." Surprisingly this still seems to be the case today, despite the fact that genetic engineering has moved from tomatoes to, mainly, corn/maize and soy.

Yes, we have no tomatoes

So to the final part of my image survey, 'biotechnology', a word that has been around since 1921 (according to the Oxford English Dictionary; according to others since 1919) and should therefore have accrued some popular visual connotations. Google images lists the following themes: applications, medicine, food, examples, animals, industry. Now, with medicine I'd have expected some reddish colour scheme; with food, some green and with animals, various colours. However, what we find instead is a sea of blue images, mainly of double helices, hands holding vials or petri dishes, some automated pipetting, and not much more.



GMOs are red
Biotech is blue
Why should that be?
I ask you!

Synthetic biology comes to Nottingham

On Monday (9 November, 2015) we are convening a public debate about synthetic biology and responsible research and innovation as part of the *ESRC's Festival of Social Science*. You are all welcome to join us! Us means: Adam Rutherford as chair, Hilary Sutcliffe, Andrew Balmer, Klaus Winzer and Peter Licence on the panel (see brochure) and myself as organiser. (Lakeside Arts/Djanogly Art Gallery, Lecture theatre A30)

What is synthetic biology? There have been many definitions but the one we used on the website of the Synthetic Biology Research Centre here at the University of Nottingham is the following one: "Synthetic Biology has the potential to create new products and processes by engineering biological systems to perform new functions in a modular, reliable and predictable way, allowing modules to be reused in different contexts."

Synthetic biology: Up on Mars
What does this mean concretely? I think the best way of making abstract synthetic biology concrete might actually be to look up into the heavens, in particular at Mars. Synthetic biology has recently been drafted into 'space science' and visions of future missions to Mars. As people know, going to Mars is difficult, as astronauts and, even more so, future (futuristic) settlers would need a sustainable flow of foods, materials and medicines which cannot all be taken 'up there' in one go. So scientists are thinking about creating, indeed, engineering, foods, fuels, plastics, and medicines 'biologically' using synthetic biology. One such proposition can be found in an article by Amor Menezes for the journal *Interface* published by the Royal Society and entitled "Towards synthetic biological approaches to resource utilization on space missions". In a recent post about this article for the blog 'Berkeley Engineer' it has been pointed out that: "The researchers identified microbes that can be engineered to convert gases from the Martian atmosphere or a spacecraft's waste stream into useful supplies. A methane-oxygen fuel blend can be produced by harnessing *Methanobacterium thermoautotrophicum,* a single-celled organism common in sewage treatment plants and hot springs; cyanobacteria, such as *Arthrospira* or *Synechocystis,* can make spirulina food or the painkiller acetaminophen; and construction-grade biopolymers needed for 3-D printing replacement parts can be engineered from a soil bacteria, *Cupriavidus necator."*

Synthetic biology: Down in Nottingham
What has this to do with us here down on earth? Quite a lot actually! Take *Cupriavidus*. The aim of many projects within the SBRC here in Nottingham is to use this and other bacteria for the production of chemicals, pharmaceuticals or

enzymes which are needed for sustainable and biotechnology focussed industries here on Earth.

This means, as explained on our SBRC's website: "The Nottingham SBRC will use Synthetic Biology to engineer microorganisms that can be used to manufacture the molecules and fuels that modern society needs in a cleaner and greener way. We will harness the ability of organisms, to 'eat' single-carbon containing gases, such as carbon monoxide (CO), carbon dioxide (CO2) and methane (CH4). When these gases are injected into the liquid medium of fermentation vessels they are consumed by the bacterium and converted into more desirable and useful molecules. Fortunately CO, our initial target, is an abundant resource, and a waste product of industries such as steel manufacturing, oil refining and chemical production. Moreover, it can be readily generated in the form of Synthesis Gas ('Syngas'), by the gasification (heating) of forestry and agricultural residues, municipal waste and coal. By allowing the use of all these available low cost, non-food resources, such a process both overcomes concerns over the use of land resources that could be used for food production. Furthermore, capturing the large volume of CO (destined to become CO2 once released into the atmosphere) emitted by industry for fuel and chemical production provides a net reduction in fossil carbon emissions."

Responsible Research and Innovation

And what has social science to do with all this? Over the last two years, six synthetic biology research centres have been created in the UK, funded by the public purse via Research Councils, with investment currently over £60 million. The centres are located at the Universities of Nottingham, Cambridge, Bristol, Manchester, Warwick and Edinburgh. In addition there is a Synthetic Biology Innovation and Knowledge Centre at Imperial College London.

All six research centres have been tasked with exploring a new approach to connecting science with society called 'Responsible Research and Innovation'. By adopting this approach, research funders here in the UK, in Europe and in the United States hope that scientific research can be opened up at an early stage, allowing a wide range of societal issues and concerns to steer or shape innovation pathways. In doing so, it is also hoped that new technologies and products will be socially desirable and undertaken in the public interest. (A brief summary of of this approach can be found in this Nottingham report)

Thinking about the challenges of marrying synthetic biology with RRI, the following quote from Shakespeare comes to mind: "*There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy*." (Hamlet (1.5.167-8), Hamlet to Horatio).

As you have seen already from my descriptions of synthetic biology up in the heavens and down on earth, developing synthetic biology responsibly poses many challenges, some as yet undreamt of, for natural and social scientists, policy makers and members of the public. Some of these will be explored on Monday. We hope you can join us!