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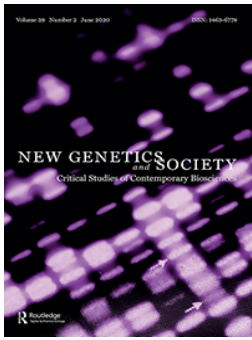
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Genome editing: the dynamics of continuity, convergence, and change in the engineering of life

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Genome editing enables very accurate alterations to DNA. It promises profound and potentially disruptive changes in healthcare, agriculture, industry, and the environment. This paper presents a multidisciplinary analysis of the contemporary development of genome editing and the tension between continuity and change. It draws on the idea that actors involved in innovation are guided by “sociotechnical regimes” composed of practices, institutions, norms, and cultural beliefs. The analysis focuses on how genome editing is emerging in different domains and whether this marks continuity or disruption of the established biotechnology regime. In conclusion, it will be argued that genome editing is best understood as a technology platform that is being powerfully shaped by this existing regime but is starting to disrupt the governance of biotechnology. In the longer term it is set to converge with other powerful technology platforms, which together will fundamentally transform the capacity to engineer life.

Keywords: genome editing; sociotechnical regime; technology platform

1. Introduction

Genome editing is a powerful new technology that enables very accurate alterations to the genetic material of all living organisms. In 2015, a feature in the scientific journal *Nature* entitled “CRISPR the disruptor” anticipated the technology having a profound impact on bench research, as well as in farming, healthcare,

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and the environment (Ledford 2015). Genome editing has been rapidly and widely diffused in research across the globe and is being actively commercialized by a wave of new start-up companies involved in creating novel plant varieties and new therapeutics. The huge potential of this technology is raising important social, ethical, and legal questions, especially the possibility of genetically modifying future human generations.

Scientifically, CRISPR and other genome editing tools are the cumulative products of incremental discoveries and advances in understanding the molecular biology of living organisms. Conceptually, genome editing is part of a longstanding “genre of technique” (Landecker 2007) in which molecular biologists add, subtract, transfer, and reorder the components of cells, genes, and tissues.

This tension between disruption and continuity is itself familiar from previous accounts of biotechnology, where it is either as old as brewing and bread-making or the very definition of a modern, technology-driven business sector (Bud 1993). These different histories, or “possible pasts,” (Morrison 2012) of biotechnology serve different ends. The latter valorizes biotechnologies as novel, exciting, and generative of future health and wealth, the better to enroll support and resources. The former naturalizes it as continuing a longstanding sphere of human activity and therefore nothing to excite undue (public or political) concern. Genome editing speaks to both these traditions. Nonetheless, there are good reasons to suggest that genome editing marks a step change in the genetic engineering of life and is indeed disrupting laboratory practices, innovation processes, and regulatory regimes.

The contemporary emergence of genome editing must be understood as taking place in a radically different context from the early development of recombinant DNA in the 1970s. In the twenty-first century biotechnology, first questions attending any scientific breakthrough concern how and when it will be translated, regulated, and commercialized, as well as who owns it and who might benefit from its application. Therefore, a central task is to analyze these processes of innovation and the dynamics of socio-technical change and how they are shaping this powerful technology.

This paper analyses the emergence of genome editing and the tension between disruption and continuity. To achieve this, we draw on the idea that the actors involved in a particular innovation system are guided by a *sociotechnical regime* constituted by a specific set of *practices, institutions, norms, and cultural beliefs*. The focus is on the nature of the sociotechnical regime in which genome editing is emerging and the extent to which this marks continuity or disruption of the established biotechnology regime. Specifically, we ask:

- How and where is genome editing emerging and what regime of practices, institutions, norms, and cultural beliefs is enabling and guiding its development?
- To what extent does this represent continuity or disruption in the established sociotechnical regime associated with biotechnology?
- Which elements of this regime and what other factors are shaping its future trajectory?

This paper first sets out the conceptual framework for thinking about sociotechnical regimes and describes the methods used. The following sections analyze the key features of the technology and the core elements of the regime it is developing within: its applications, how it is being patented, commercialized and regulated, and its broader cultural meaning. In conclusion, an assessment will be made of how genome editing is related to processes of continuity and change within the sociotechnical regime associated with biotechnology, the prospects for more fundamental change as it converges with other technology platforms, and where genome editing is likely to be disruptive in the future.

2. Conceptual framework

The analysis of technological change has a long history in the social sciences, drawing on various disciplinary traditions. In this paper, we seek to describe the early development of a potentially disruptive technology arising within an established domain (i.e. biotechnology). While “disruption” may be cast as a negative term, a positive framing of “disruptive innovation” has gained considerable currency in the last decade in both business studies and technology policy, following the resurgence of interest in Joseph Schumpeter’s work on the creative destruction brought about by new technology and Clayton Christensen’s book *The Innovator’s Dilemma: When New Technologies Cause Great Firms to Fail* (Christensen 1997). For Christensen, disruptive innovation describes “a process by which a product or service takes root initially in simple applications at the bottom of a market and then relentlessly moves up market, eventually displacing established competitors” (Christensen 2018).

Within social studies of science and technology, this concept has been recently applied to the analysis of system transitions, such as energy production and the adoption of electric cars. However, it has been widely criticized in a burgeoning literature on this topic for placing too much emphasis on novelty, individual technological applications, and impact at the firm rather than the industry or system level (Winskel 2018). Analysts such as Geels have instead focused on *sociotechnical systems* (the multi-level perspective), which “... consist of an interdependent and co-evolving mix of technologies, supply chains, infrastructures, markets, regulations, user practices and cultural meanings” (Geels 2018, 225). Here, the system is marked by the interaction between material elements and social structures, such as policies, culture, technologies, or markets, which form stable relationships to enable the production and use of knowledge. Within this framework, technological change requires the alignment of different system elements through processes of mutual shaping. This is guided by a particular *sociotechnical regime*, constituted by a set of semicoherent rules and institutions, which orient and co-ordinate the actions of the social groups that reproduce the system. These form the “grammar” of a system and might include shared beliefs, values, expectations, routines, regulations, institutionalized practices, and capabilities (Fuenfschilling and

Truffer 2014). The biotechnology regime is marked by several key features: appropriation based on the patenting of living systems and processes; commodification and commercialization via dedicated research-intensive firms; governance built on institutions regulating pharmaceuticals and food and shaped by ethical principles and soft law; and cultural understandings drawing on a grammar of frames and metaphors associated with the engineering of life.

Different forms of sociotechnical disruptions may therefore occur within various elements of a system, affecting which actors and material elements are involved and the relationship between organizations and institutions. This paper explores the extent to which disruption is occurring in the regime of *practices, institutions, norms, and cultural beliefs* that guides action within the system.

Recent theoretical and empirical work has looked at important aspects of the development of biotechnology and genomics (see Franklin 2006; Thompson 2013; Jasanoff, Hurlbut, and Saha 2015; Reardon 2017), leading to important insights into the dynamics of change in these domains. However, surprisingly little research has used the multi-level systems or sociotechnical regimes approach. Our choice of topics is therefore defined by the key features of the biotechnology regime listed earlier. In the following sections, we briefly outline the key actors, organizations, and institutions that constitute the emerging regime associated with genome editing, how they relate to the established sociotechnical system built around biotechnology, and where disruption is (or is not) occurring in the associated regime of applications, intellectual property, commercialization, governance, and cultural framing.

3. Methods

Our analysis draws on multiple data sources derived from a series of discrete projects that used a range of methods. These data have been carefully integrated and cross checked to ensure a robust picture of the recent development of genome editing. The technical introduction drew on a detailed review of the academic and policy literature undertaken as part of a study of biomodifying technologies (Morrison *et al.* 2019). Data on the commercial development of the technology involved a comprehensive online survey of firms working on genome editing using industry databases and web directories (e.g. GenomeWeb). Data were then collated on individual firms from their web sites, news releases, annual reports, and stock exchange (e.g. SEC) filings. Analyses of legal and ethical governance of genome editing, and of the patent landscape involved desk-based retrieval and analysis of key legal, policy, and civil society documentation, as well as a comprehensive literature review. The scientific, clinical, and ethical aspects raised by the National Academies of Science, Engineering and Medicine's Human Gene Editing Initiative were analyzed for themes and framings, using publicly available materials (including video of keynotes, panels and audience Q&A, and presentation slides from the 2015 Human Gene Summit). The data

on cultural framing emerged from qualitative thematic and metaphor analysis of a range of media and texts including newspapers, popular science books, and blogs. For details of methods, see Cameron and Masten 2010. In addition, the authors have attended many national and international scientific and policy meetings related to gene editing between 2016 and 2018 and have drawn on observational data and informal interviews carried out at these events in writing this paper.

4. Introduction to the technology

Currently, there are three main genome editing tools: zinc fingers (ZFN), transcription activator-like effector nucleases (TALENs), and CRISPR-Cas based systems. Each of these tools works in a similar way. They contain a binding domain that can recognize specific DNA sequences and an enzyme capable of cutting DNA. This targeting capacity is not absolute, meaning that a genome editing tool may cause unintended changes known as “off target” effects (Koo, Lee, and Kim 2015).

Zinc finger nucleases were the first of this type of gene editing tools but are widely regarded as difficult to make and use. The number of translational applications of ZFN currently in development is limited. TALENs are easier to use, but most sources agree that CRISPR-Cas9 has driven the real take-off in genome editing (Ledford 2015). TALENs and CRISPR tools are available at relatively low cost through the not-for-profit Addgene repository, while CRISPR components are now routinely included in the kits of “biobricks” distributed by the International Genetically Engineered Machines (iGEM) competition. CRISPR’s accessibility and widespread distribution have thus been facilitated by building on the “installed base” of existing infrastructure set up to distribute established genetic engineering tools.

For CRISPR Cas9 in particular, the relative ease of application means it can be readily incorporated with the equipment, skill sets, practices, and routines of a wide variety of research groups, to open up new experimental possibilities. Thus, it makes more sense to regard genome editing as a platform technology akin to polymerase chain reaction (PCR) or cell culture rather than thinking of it as, for example, a “medical technology” (cf. Keating and Cambrosio 2003; Landecker 2007). Another reason for the widespread uptake of CRISPR is its considerable adaptability. Researchers have modified the Cas9 protein to give it novel properties, such as editing RNA instead of DNA, making epigenetic modifications, changing one base to another, and silencing or boosting the expression of specific genes, with further options under exploration. Other CRISPR variants, from different strains of bacteria (e.g. CRISPR-Cpf1) offer a further range of properties such as smaller size, varying efficacies in plant, animal, or human cells, and different degrees of on and off target effects. In this sense, CRISPR-Cas genome editing systems are still being studied to adapt and modulate their properties. As a result, the scope of genome editing is changing rapidly and looks likely to continue to do so for the foreseeable future as new tools, techniques, and capacities emerge.

CRISPR has been widely and rapidly adopted in laboratories across the world in the last few years and has transformed the genetic manipulation of many living systems. It is notable in its relative simplicity, ease of use, low cost, and speed. Although “disruptive” to many laboratory practices, this work has largely developed within the established cultural, institutional, and practice regimes of contemporary laboratory-based molecular biology.

5. Clinical, agricultural, and industrial applications

Genome editing tools can be used in the cells of any organism that has DNA – humans, animals, plants, bacteria, fungi, etc. Possible or planned applications include, but are not limited to the following:

5.1. Human healthcare

Genome editing tools are being developed for multiple human therapeutic applications. Most interventions are still at the preclinical stage, but some have been experimentally applied in humans. As of April 2019, some 25–30 clinical trials were underway worldwide recruiting ~1,000 patients. These mainly use blood cells that are extracted, genetically modified *ex vivo*, and re-applied by transfusion. For example, white blood cells modified with ZFN have been designed to resist infection by HIV or edited using CRISPR-Cas9 to increase their efficiency in attacking tumor cells. Of these, chimeric antigen receptor-modified T (CAR-T) cells (such as Novartis’ Kymriah) are the most translationally advanced products. The traditional model of treating genetic disease by correcting or replacing “faulty” gene variants in monogenic disorders such as cystic fibrosis is also being studied with contemporary genome editing. These approaches build directly on the long history of gene therapy and the use of modified viruses as delivery vehicles. However, the safe and effective delivery of CRISPR or the other editing tools remains an issue with a range of different approaches being investigated.

By far the most controversial use of CRISPR to date has been the modification of human embryos to produce two genetically altered children. The birth of the world’s first “CRISPR babies” was reported by Chinese scientist He Jiankui in November 2018 and provoked an international outcry and calls for a moratorium on such applications (see below).

Demonstrating their adaptability, CRISPR-based systems are also being developed for health applications that do not involve directly modifying human genetic material. Genome-editing nucleases are being designed to attack infectious agents or detect genetic material from invading pathogens such as the Zika virus. Genetically modified animals are being configured to present new models of human disease for preclinical experiments or make animal tissue more suitable for xenotransplantation into humans.

5.2. *Transgenic plants and animals*

Genome editing has the potential to create new varieties of modified animals and plants for agricultural, “pharming”, and other nonmedical applications. Already the technique has been applied to a number of crop breeding programs, including herbicide resistance, improved nutrition (e.g. soy beans with reduced trans-fat), improved shelf life (e.g. nonbrowning mushrooms), pest resistance (e.g. virus resistant cucumber), and improved yields (e.g. rice) (SAM 2017). Animal applications under development include hornless milk cows, improved milk quality and muscle growth, and disease resistance (e.g. TB resistant cattle (SAM 2017)).

Various organisms may also be genome edited for environmental and health reasons, for example, modified bacteria to clean up contaminated land. One of the more prominent applications is in the production of “gene drives” where pest animals are engineered to produce sterile offspring, with the intention of reducing breeding populations to tackle Zika or malaria spread by mosquitoes (SAM 2017).

5.3. *DIY genome editing and biosecurity*

CRISPR systems do not require sophisticated equipment or expertise, and thus, access has extended beyond formal laboratories and into the preexisting “garage labs” and “hackspaces” of DIYbio. For example, the Open Discovery Institute (ODIN) sells DIY Bacterial Gene Engineering CRISPR kits for just \$159, accompanied by a guide that suggests a novice will be able to run the same experiments as a PhD student within 6 months.

It should also be noted that there are broader biosecurity issues raised by the development of genome editing that go beyond biohacking. The Editing Biosecurity project suggests that with respect to genome editing, “Scientific, technical, economic, and social trends are increasing the range of potential biological hazards, diversifying the sources of these hazards, multiplying the routes of exposure, expanding the populations that may be exposed, and increasing these populations’ level of susceptibility.” (Kirkpatrick *et al.* 2018) These include concerns about dual use technologies, biosafety issues associated with gene drive and breaches of biological containment, and biosecurity threats from bioweapons developed by state actors, terrorist organizations, reckless individuals, and groups. How these are responded to is still emerging.

With the exception of DIYbio, almost all these approaches involve integrating genome editing into existing research trajectories, aiming for markets that, if not always extant, have at least been previously anticipated. While human and agricultural applications are seen as an incremental innovation whose new capabilities have so far been shaped by the existing grammar of biotechnological innovation systems, in contrast, DIYbio and some biosecurity applications open up genetic engineering to entirely new groups and applications.

6. Intellectual property and commercialization

One of the dominant features of the sociotechnical system that has enabled the development of biotechnology has been the commodification of knowledge through the creation of intellectual property (IP) and its commercialization by dedicated firms. The early development of genome editing has drawn heavily on these processes and institutions and has been powerfully influenced by the existing biotechnology regime.

6.1. *A contested patent landscape*

The patent landscape for genome editing has been highly contested. One of the most high-profile patent disputes involved Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (now Max Planck) who filed a US patent application in May 2012 for the use of CRISPR-Cas9 as an editing tool in any cell type and Feng Zhang (Broad Institute of MIT and Harvard) who filed in December 2012 for uses of CRISPR-Cas9 in eukaryotic cells. Zhang was awarded a patent before Doudna and Charpentier, leading to US litigation. Both the Broad's patents and UC Berkeley's patent claims were found to be sufficiently distinct to be valid (King & Wood Mallesons 2018). The complexity of the US CRISPR patent landscape was increased, when in April 2019, the US Patent and Trademark Office (USPTO) awarded UC Berkeley's patent for uses of CRISPR Cas-9 in the "cellular or non-cellular environment" (Pierson 2019). In Europe, this patent dispute has played out somewhat differently; the EPO granted Doudna and Charpentier a patent for uses of CRISPR/Cas 9 in any cell type, and although the Broad Institute also acquired some patents, disputes have arisen over the priority dates of inventions, which could lead to these being limited or revoked. Other CRISPR European patent holders include MilliporeSigma, ToolGen, Vilnius University, Harvard College, and Cellectis. In February 2019, it was estimated that over 1,700 patents had been filed by 100s of companies on CRISPR-related technology and/or uses (Cynober 2019).

The patenting of CRISPR technologies has reignited several ethical debates, as patent holders are able to control *who* uses the invention and for *what purposes* (McMahon 2019). Patents on controversial uses of CRISPR, e.g. for gene drives, could control such applications (Sherkow 2017). Conditions can also be attached to licenses to promote "ethical" uses of technologies. For example, the Broad Institute's license with Monsanto for agricultural uses of CRISPR-Cas9 requires Monsanto to allow farmers to save and use seeds in the next season (Sherkow 2017). However, patents on CRISPR technologies, if exercised in a restrictive manner, could impede access to technologies for the public and research community by refusing licenses or driving up costs.

Finally, the European patent system has morality provisions excluding patents for inventions whose commercial exploitation is against morality/ordre public, including "processes for modifying the germline genetic identity of human

beings.” If CRISPR technologies are defined as such, they would be unpatentable in Europe (San Martín and Smith-Willis 2015). To date, “germline” is undefined in this context, and this will be an important interpretive question if raised in a European challenge to the patentability of gene editing technologies. Overall, the patenting of genome editing technologies appears to fit, sometimes uncomfortably, within the existing regime for the creation of intellectual property within biotechnology.

6.2. *The commercial development of genome editing*

Very high levels of commercial interest have been shown in genome editing since the emergence of CRISPR systems. Prior to that, only a small number of companies pioneered TALEN (e.g. Calyxt) or zinc fingers (e.g. Sangamo), the latter emerging in the 1990s. As with commercialization of nearly all emerging biotechnologies, genome editing has been led by start-up companies established by the scientific pioneers of the field. The competing research groups mentioned above with patent claims on CRISPR (e.g. Broad Institute and UC Berkeley) have been active in establishing new firms to exploit these inventions. Other institutions with IP in this area, such as the University of Vienna, have also licensed this to new companies (e.g. CRISPR Therapeutics) (Cohen 2017).

Table 1 gives details of the main firms involved in the commercialization of genome editing. There are several notable features of this rapidly expanding sub-sector. First, nearly, all are US based and very young, with most formed between 2011 and 2015. They are extremely well financed, raising over \$1.2bn between them by the start of 2018, with the CRISPR-based firms winning almost \$1bn of this total. Second, they have adopted a range of business strategies. The majority are developing products in the human healthcare and agricultural areas, but several are selling research tools and services, such as enzymes. There has been an active collaboration between these small firms and much larger integrated pharmaceutical and agricultural biotechnology companies, as few start-up firms have the resources or expertise to take products all the way to market without investment and support from larger partners.

Companies working on human therapeutics focus on two main areas: genetic diseases, such as haemophilia, and CAR-T cell therapy (using engineered immune cells) for cancer. Historically, there has been a lack of interest from large pharmaceutical companies in the treatment of genetic disease, but this is changing. For example, CRISPR Therapeutics formed a \$335M joint venture (Casebia) with Bayer in 2015 to develop cures for blood disorders, blindness, and congenital heart disease (Weisman 2016) and in the same year established a collaboration with Vertex to develop therapies for sickle cell disease and β -thalassemia (BusinessWire 2015). Huge investment from pharmaceutical companies in CAR-T cell therapy has anticipated FDA approval of the first medicine of this sort in 2017. In the field of crop improvement, Precision Biosciences has partnered with Cargill to develop genetically modified canola oil. Interest also

Table 1. Leading genome editing companies (January 2019).

Name	Public/ private	Country/ year founded	Funding	Technology (licensed from)	Application area	Services/ Products in development	Major collaboration
Caribou Biosciences	Private	USA 2011	\$46M private	CRISPR (UC Berkeley)	Antimicrobials; animal health; bioproduction	Research services (drug screening; agriculture; animal)	Novartis; DuPont Pioneer; Genus
Calyxt	Public	USA 2010	\$64M IPO	Talens (Minesotta Uni)	Agricultural biotech	Speciality ingredients; food crops;	Was spun-out from Collectis; Bayer
CRISPR Therapeutics	Public	USA 2013	\$127 private \$56 M IPO	CRISPR (Vienna University)	Therapeutics inc CAR-T Cell therapy	Sickle cell & beta thalassaemia; various cancers; liver disease	Vertex; Casebia (joint venture with Bayer)
Editas	Public	USA 2013	\$210M private \$94M IPO	CRISPR (Broad Institute)	Therapeutics inc CAR-T Cell therapy	Various cancers; eye diseases; rare genetic diseases	Juno
Horizon Discovery	Public	UK 2005	\$50M private \$75M IPO	CRISPR (Broad Institute; ERS)	Tools	GE enzymes, cell lines, animal models	AstraZeneca; Roche Diagnostics; Novartis
Inscripta	Private	USA 2015	\$86M private	CRISPR (own IP)	Tools	GE enzymes	
Intellia	Public	USA 2014	\$85M private \$108M IPO	CRISPR (UC Berkeley)	Therapeutics inc CAR-T Cell therapy	Various cancers; rare genetic diseases	Was spun-out from Caribou Regeneron; Novartis
Precision Biosciences	Private	USA 2006	\$26M private	ARCUS – CRISPR variant	Food; therapeutics inc T Cell immunotherapy	GM plants; various cancers	Cargill; Baxalta
Sangamo Therapeutics	Public	USA 1995	\$85M private \$49M IPO \$73M public	Zinc fingers	Therapeutics	Various cancers; haemophilia; thalassaemia; rare genetic diseases	Pfizer; Gilead Sciences; Shire

remains in other non-CRISPR technologies with Sangamo forming a \$3 billion partnership with Gilead Sciences in 2018 to work on zinc fingers for cancer therapy (Reuters 2018).

Although young, the genome editing industry is already extensive. In rapidly reaching this point, it has drawn heavily on a well-established sociotechnical infrastructure of funding, institutions, and expertise for the exploitation of novel biotechnologies. At the same time, genome editing technology has started to be rapidly integrated into the mainstream pharmaceutical and agbiotech industries.

7. Metaphors, cultural framing, and enrolling public

One of the key processes involved in the construction of new sociotechnical systems and regimes around emerging technology is the enrolment of public. Central to this are processes of cultural framing in which a novel technology is rendered familiar through the use of well-established metaphors and discursive frames.

Genome editing is the latest in a long line of advances in genetics and genomics where powerful metaphors play a central role in the constitution of these technologies. Examples include the metaphor of the “code” in genetics, of “the book” in genomics, and of “engineering” in synthetic biology (McLeod and Nerlich 2017). The first popular science book on genome editing exploits two of these metaphors: *Hacking the Code of Life: How gene editing will rewrite our futures* (Carey 2019).

To convey hopes and fears surrounding genome editing, longstanding Western myths, and narratives and book titles are used, including “Brave New World” and “Frankenstein”, “Opening Pandora’s Box” or “Prometheus” (Kozubek 2016), as well as religious references, such as “Playing God” or “a crack in creation” (Doudna and Sternberg 2017).

Gene or genome “editing” is both a constitutive and communicative framing, having its roots in letter, book, and word processing metaphors for DNA and genomes. Editing can involve “cutting and pasting” and “finding and replacing,” which involves the use a “guide molecule,” sometimes compared to a GPS system and “molecular scissors.” The main action is that of “targeting” parts of the genome. Explanations of genome editing using such metaphors also talk about its dangers in terms of “off-target effects” (O’Keefe *et al.* 2015).

Fears about off-target effects now mingle with increasing anxieties about the “germline” genome editing or heritable genome editing. Such fears have recently been exacerbated after the birth of gene-edited babies in China. It is also the most closely associated with eugenics, “designer babies,” and other longstanding moral concerns. However, hopes and fears of control always encounter the reality of biological complexity (Ball 2017).

Ethical and social issues around genetics and genomics have been discussed in novels, films, TV series, and so on for a very long time. This continues in the context of genome editing with Sci-Fi thrillers like *Change Agent*, films like *Rampage*, TV series like *Orphan Black*, and much more (Nerlich 2019).

Those fostering public engagement with genome editing will have to take this shifting cultural landscape into account together with the complexity of ethical and social issues surrounding this new technology. Efforts are now being made to engage wider public with gene editing, efforts that also look at language and culture (Burall 2018).

A range of civil society organizations are actively criticizing the development and use of genome editing in a number of countries, including ones specifically focused on the impact of biotechnology such as the *Center for Genetics and Society* in the USA and *Human Genetic Alert* in the UK. These groups have raised important concerns about the development of genome editing, its governance, and the future imaginaries associated with it. This reflects a longstanding cultural unease with the prospect of human genetic modification. As a consequence, advocates remain concerned that public support for genome editing is not deeply rooted and resistance to the technology may emerge, framed by dystopian narratives about biotechnology, both old and new.

Currently, genome editing for medical purposes, including germline editing, seems to evoke more hope than fear in the public sphere, both in the United States and the United Kingdom, as recent research has shown (Scheufele *et al.* 2017; Royal Society 2018). The US survey found that people only drew a line when editing, especially germline editing, was for “enhancement” purposes rather than treating disease. This situation may change after the birth of the first genome edited babies, which has triggered a worldwide debate about the governance of germline editing (Rosemann *et al.* 2019).

The cultural framing of genome editing has drawn heavily on established metaphors used in the biotechnology regime. These have played an important performative function when used by state and professional actors to enroll public and win support for research. As genome editing moves from the laboratory to the clinic, emerging attitudes to the technology will be shaped not only by tropes and stories but also by the existing regime of narratives about IVF, preimplantation genetic diagnosis, and other reproductive technologies, as well as the national and international cultures of ethics surrounding them.

8. Ethics, regulation, and governance

Another key element of the biotechnology regime has been the creation of a robust framework to regulate the work of scientists and shape the creation of new products and services. This includes the design of formal regulatory frameworks and the establishment of softer forms of governance based on ethical norms as well as attempts to “invent around” ethical roadblocks by scientists (Thompson 2013, 3)

8.1. The legal regulation of human genome editing

Most applications of gene editing mimic existing gene therapies, in targeting somatic “adult” body tissues. As such, they are likely to be governed within

established regulatory frameworks, such as the Advanced Therapy Medicinal Products Regulations in the EU. However, as of July 2019, the exact framework had yet to be determined.

In contrast, there has been a great deal of controversy about the possibility of using genome editing to alter future generations (Lander 2015). The boundary separating “somatic” cell and “germline” genetic modification was created in the 1980s following the report of the President’s Commission on Bioethics. In the 1990s, this was reinforced by various international conventions and treaties that prohibited germline modification even for therapeutic purposes (Council of Europe 1997; UNESCO 1997; EU 2000). With the advent of CRISPR, some international statements have been updated to reaffirm this prohibition (e.g. UNESCO 2015).

However, this consensus has recently come under pressure. For example, the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations (2015) permit genetic modification to enable the conception of children without the mitochondrial disease, making the UK the first jurisdiction in the world to legally permit human germline modification. In justifying this, the UK government concluded that mitochondrial replacement techniques (MRT) would not affect the “genetic identity” of the resulting child (Turkmendag 2017).

While some commentators praised the UK’s approach for being “consequential in its impact and ground breaking in its regulatory evaluation process” (Adashi and Cohen 2015, 832), others claimed that the techniques provide a “quiet way station” in which to develop other human germline interventions (Baylis 2017). This concern is not unfounded: in February 2016, after the passage of MRT regulations, the HFEA granted the first license permitting gene editing of human embryos for research purposes. A range of professionals, public interest, and religious groups have opposed this liberalization and campaigned for sustaining the ban on germ line engineering.

Despite this opposition, it seems likely the UK’s MRT regulations will become a model for other jurisdictions (Adashi and Cohen 2015). Having examined the national policy framework of 16 countries, Isasi, Kleiderman, and Knoppers (2016) found that vagueness in distinctions between clinical and research applications, as well as in basic definitions, has led to legal uncertainty, which allows for different interpretations or practices to circumvent or hinder the intent of policy (Isasi, Kleiderman, and Knoppers 2016). Furthermore, as observed during the International Summit on Human Gene Editing, cultural differences between countries are likely to extend the diversity of regulations (Reardon 2015). International harmonization through “soft law” (e.g. private standards, guidelines, codes of conduct, and forums for transnational dialogue) is proposed as a possible solution. However, such an approach may depend on reaching greater international consensus on the ethics of germline modification.

8.2. *Ongoing ethical and policy debates*

The absence of international harmonization for human germline engineering has mobilized a number of initiatives. Some prominent bioethicists and genetic scientists, including Doudna, have called for a moratorium on such research pending a broad debate and the development of appropriate oversight of the field (Baltimore *et al.* 2015). Citing the 1976 Asilomar conference on regulating recombinant DNA, this group helped launch a series of debates at the US National Academies of Science, including two international Gene Editing Summits in 2015 and 2018. Framed as a consensus statement, the report of the 2015 Summit accepted that in certain cases where there was no other treatment and no possibility of selecting unaffected embryos, human germline engineering (HGE) might be permissible once considered safe, if carefully regulated (NAS 2017). These self-imposed restrictions by the scientists were criticized for being an undemocratic trust-building exercise to show the public that scientists are behaving in an ethically responsible manner, thereby “avoiding premature legislative intervention” (Jasanoff, Hurlbut, and Saha 2015; Sarewitz 2015).

By 2017, growing numbers of scientists and policy makers were advocating the cautious development of human germline genome editing. In some countries, this took the form of increasing pressure to relax restrictions to avoid “falling behind” international competitors and to prevent scientists and researchers moving to more permissive jurisdictions. In this context, prohibitive laws are perceived as an obstacle to innovation and scientific progress. For example, Canada’s criminal ban on human genome editing has been criticized for not being a suitable instrument to regulate scientific research (Knoppers *et al.* 2017). Similar concerns have been expressed by German scientists, who are forbidden by law from engaging in research projects that use human embryos (Bonas *et al.* 2017).

The clearest sign of a push for a more permissive approach was the publication in July 2018 of a major report by the UK Nuffield Council on Bioethics (Nuffield Council 2018). It concluded that germline genome editing:

could be ethically acceptable in some circumstances, so long as: it is intended to secure, and is consistent with, the welfare of a person who may be born as a consequence of interventions using genome edited cells; and it is consistent with social justice and solidarity, i.e. it should not be expected to increase disadvantage, discrimination, or division in society. (Nuffield Council 2018)

Recommendations were also made to ensure tight regulation of the technology and broad public engagement and societal consensus. This marks a major break with previous ethical frameworks, which stress the key difference between genetic enhancement and therapy and instead argued that a stable and principled boundary of this sort was not sustainable. This new, more permissive, ethical framework based on welfare, justice, and solidarity is highly significant given the UK’s leading international role in establishing regulatory standards in reproductive technology.

Despite this apparent consensus that human applications were premature, particularly for heritable changes, the 2018 Gene Editing Summit was overshadowed by the announcement by the Chinese scientist, He Jiankui, that he had used CRISPR to edit the genomes of two recently born twin girls to confer resistance to HIV (Lovell-Badge 2019).

In the wake of global criticism of He's action, and further calls for a temporary moratorium, a group of Chinese bioethicists also published a response, rejecting the assumption that there is a scientific and ethical divide between the East and the West and suggesting that Jiankui's actions can be better explained by the "prevailing international science culture that puts a premium on sensational research and being first" (Zhai *et al.* 2019). Shortly after, China's health authority announced draft regulations providing stricter oversight of human genome editing (Bloomberg News 2019). Despite these moves to prevent the germ line editing of humans in the short term, there remains a strong current of international policy and professional support for this as an option in the longer term, something that is certain to provoke fierce opposition from many groups.

8.3. *The governance of agricultural and environmental applications*

In the US it initially appeared that the Food and Drugs Administration (FDA) would tightly regulate products created using genome-edited plants and animals. However, in April 2018, the US Department of Agriculture (USDA) ruled that innovators would be allowed to use genome editing technologies to create novel crop varieties without regulatory oversight (McKie 2018). This marked a significant break from previous regulations controlling genetically modified organisms (GMOs), which have historically been less permissive and is likely to stimulate rapid testing of various agricultural and environmental applications. The key argument made in support of this change was that stringent regulation should only apply to organisms "... where novel DNA can actually be detected and not to those which could have arisen by natural mutation (such as those involving manipulation of a single base)" (POST 2016, 4). As a consequence, advocates hoped that the technology would be seen as more "natural" than the transgenic intraspecies transfer of DNA that characterized GMOs prior to recent advancements in genome editing. In contrast, in July 2018, the Court of Justice of the European Union ruled that genome-edited crops should be subject to the same regulation as more conventional GMOs, placing Europe in direct opposition to the US on this key issue (Callaway 2018).

Despite this apparent shift in policy, the FDA has continued to govern the use of genome editing in animals. The FDA Plant and Animal Biotechnology Innovation Action Plan remained committed to "a comprehensive framework for the development and regulatory oversight of animal biotechnology products, including intentionally genetically altered animals and the food and drug products derived from them" (FDA 2019). This suggests that the Agency will retain formal oversight of

some gene-edited animal products, creating tension at the heart of US policy. Under these proposals, all new animals produced using genome editing will be regulated as a new animal drug. This places a much greater regulatory burden on innovators in terms of safety and has been criticized by industry as being too stringent.

8.4. *The governance of DIYbio*

The risks of DIYbio have been taken seriously by security agencies for some time before CRISPR emerged, with the FBI convening a conference in 2012 and the EU Non-Conventional Threat Briefing taking place in 2014. The possibility of genome editing being conducted in kitchens and garages has also rung warning bells. In late 2017, in response to the availability of kits offered by the ODIN and YouTube videos showing advocates experimenting on themselves, a number of official and scientific bodies, such as the American Society of Gene and Cell Therapy (ASGCT), warned against the dangers of DIY genome editing (ASGCT 2017). In addition, the FDA asserted that the sale of the kits was illegal and the German consumer protection agency, the BVL, warned that importing them could incur a fine of up to EUR 50,000 (BVL 2017).

However, some have welcomed the “democratization” of molecular biology. Kuiken (2016), for example, argues that the culture of responsibility, transparency, and collaboration seen in DIYbio “community labs” ought to be a model for institutionalized science. Furthermore, some involved in DIYbio communities argue that DIYbio, including gene editing, will be the only way to realize the promise of personalized medicine, moving advanced therapies out of commercial and institutional laboratories. Genome editing offers to transform this area, making it easier for nonexperts to routinely undertake the genetic engineering of life, thus redrawing the boundaries between science and society.

9. Discussion and conclusion

In this section, we focus on issues of continuity and change, the extent to which genome editing is usefully conceived of as being “disruptive” and the likely pathway of its future development. We have illustrated above how genome editing can be usefully understood as a “biomodifying” technology that transforms living biological tissue in novel and increasingly customized ways (Morrison *et al.* 2019) and as a generic platform technology with multiple potential human, animal, plant, environmental, military, and industrial applications spanning many areas that have historically been considered discrete within scientific, policy, ethical, and public debates.

9.1. *What is stable and enduring?*

Picking-up on the theme of continuity and change within the biotechnology regime, we might start by asking what aspects of genome editing represent business as usual? First, in the realm of sociotechnical expectations, the enduring hopes

invested in the engineering of life continue to provide both a guiding set of technical principles and a powerful imaginary increasingly linking fundamental science to the growth of the bioeconomy. Genome editing is closely entangled in the continued reproduction of futures in which the engineering of life is seen as a source of economic value, as exemplified by the rapid capitalization of the technology by start-up companies.

There is also considerable stability in the organizations and institutions constituting the sociotechnical system being assembled around genome editing. In this sense, the emergence of genome editing builds on the established institutional, technical, and social infrastructures that have provided the foundation for biotechnology over many decades. These include research funding programs, scientific and commercial support infrastructure (e.g., reagents, manufacturing), the apparatus for commercial development (creation of start-ups, venture finance), clinical and agricultural development and testing (translational research institutes), and the protection of IPR (well-established patent systems). None of these were in place when genetic engineering first became possible in the 1970s, making it far easier for the rapid growth and diffusion of genome editing to occur.

Scientific and public narratives around genome editing also demonstrate strong continuity, with their cultural framing drawing on well-established tropes surrounding earlier biotechnologies. These include both utopian and dystopian discourses about the potential power of genome editing to revolutionize medicine or create monsters. The strong link to the hope for a cure for rare genetic diseases and the sociocultural embedding of biotechnology may contribute to what appears to be greater public acceptability of some aspects of genetic engineering. Here, processes of normalization may work over time, so that new technological possibilities gradually get less “disruptive” (Marvin 1990). In this sense, ethical debates on germline engineering can be seen as running ahead of the science in an attempt to establish new norms and are playing a key role in moves to clear the way for technologies that were previously socially unacceptable.

Seen from this perspective, genome editing is growing within an existing sociotechnical regime and its emergence and applications are being powerfully shaped by what has gone before. Its early development has therefore not proved to be very disruptive, at least not immediately and not everywhere.

9.2. *What is changing and what is being disrupted?*

Even as the emergence of genome editing illustrates the obduracy of the expectations, institutions, and cultural framing built around genetic engineering, it is also important to analyze what is different or changing (materially, politically, ethically, culturally, procedurally) from previous technologies? In particular, where is regime “disruption” occurring and for whom?

At a scientific level, new tools to improve gene editing are rapidly being developed and the technology is set to become ubiquitous, pervasive, and mundane

through its low cost, high speed, and ease of use. These quantitative improvements may ultimately bring about major qualitative changes as genetic engineering of cells, tissues, and whole organisms becomes cheap, quick, and routine. This has strong similarities with the earlier development of polymerase chain reaction (PCR), a technology platform for amplifying very small amounts of DNA, which transformed genetic research and became the foundation for many key developments in biotechnology, such as genetic testing and forensics. In particular, genome editing is altering both the scale and scope of genetic engineering practices. The scale is growing dramatically as a result of the huge increases in the speed and volume of genetic manipulation made possible by CRISPR. For example, genome editing makes it much easier to create large libraries of genetically modified laboratory animals. The scope is also dramatically increasing as the ability to alter a much greater range of organisms at a large number of different sites (DNA, RNA, epigenome) matures. Although the full impact of this shift in scale and scope made possible by this powerful technology platform is still to be felt, its outline is becoming visible.

First, the boundaries between organisms are being further eroded as it becomes easier to transfer and manipulate genes across species and between generations. While this has always been part of recombinant DNA technology, genome editing is increasingly challenging existing categories and distinctions between the “natural” and “synthetic,” as well as creating novel forms of hybrid life. This further transgresses traditional social (and legal/regulatory) categories through which everyday life is ordered and rendered meaningful and is highly disruptive to the collective understandings and governance of living things.

Second, there is increasing convergence among related technology platforms, with next-generation sequencing (NGS), and synthetic biology vastly increasing the capacity to custom synthesize large stretches of DNA. This combination of the ability to rapidly “read,” “write,” and “edit” the genome opens-up many new technical possibilities that may have profound consequences in the long term. Already these tools are being used in combination in a major international initiative to construct the first synthetic eukaryotic organism (the Synthetic Yeast Genome Project – see <http://syntheticyeast.org/>). The creation of a powerful integrated platform for genetically engineering life will enable an acceleration in the (re)production of life in biological time, marking a break with natural cycles of organismic reproduction and a shift to postgenomic temporalities. Genetic changes that would have taken generations of selective breeding will become possible in a single generation. Already, genome editing is commercially available to rapidly speed-up and customize the production of inbred mouse lines for drug testing (Taconic 2018).

The growth of genome editing also has important geospatial implications as it makes genetic modification much more accessible to a wide range of groups and countries not traditionally involved in biotechnology, especially in the Global South. Therefore, it falls within Christensen’s notion of disruptive innovation by

making a product, service – or in this case, a technology platform – accessible to completely new groups of users, in ways which may ultimately force older, major players to adapt or be forced from the field. This is visible in DIYbio, but also in the diffusion of genome editing to Africa (Mudziwapasi, Ndudzo, and Rutendo Patricia Nyamusamba 2018). This shift to a postgenomic spatiality raises key questions for the governance of genome editing by both professional and state actors. Taken together, the compression of biological time and the globalization of genetic manipulation may prove to be highly disruptive of existing institutions, scientific practices, and cultural norms. However, the analysis presented here has mainly focused on the UK and the USA and the sociotechnical regimes in these countries. Therefore, it must be stressed that while there are strong similarities between such regimes in many advanced economies and the existence of a globalized biotechnology sector, there are important differences between countries. These are most significant with respect to the scale of public bioscience research, the structure of the biotechnology industry, and the history and culture of governance debates that are informed by religious traditions and legal systems. As a consequence, the scale of adoption and disruption may differ in time and space depending on cultural, technical, and geopolitical contexts, fostered, acceptance, or resisted. This might lead to friction and complications in attempting to establish global regulatory standards, as well as in creating international markets for genome edited products.

Thirdly, perhaps the most immediate disruptive effect of genome editing is in terms of governance. Existing regulatory frameworks play an important function in enrolling support for genome editing and are shaping its early development in a familiar fashion. However, the ability to more readily manipulate embryos and ultimately the germ line is putting pressure on the *de facto* international moratorium on human germline engineering. New coalitions of actors, especially those families and patients suffering from rare genetic disorders, are placing great hope in the possibility of this technology to develop new therapies. In the short term, this may lead to genome editing tourism, but in the longer term, there are likely to be increasing calls for experimental embryo and germline modification following the testing of mitochondrial transplants and the maturation of gene therapy for rare diseases. This will stoke demand for young women willing to donate ova for research, a practice already subject to its own long-standing ethical conflicts and track record of poor regulation at a global level. In other areas, such as the regulation of agricultural GMOs, there are already signs of less stringent regulation and the unravelling of regulations preventing the widespread cultivation of GM crops in some countries.

Thus, while the field of genome editing is still very much in the making and taking place within the established biotechnology system, there are clear signs of disruption to the underpinning regime of technical capabilities, scientific practices, ethical norms, and regulations, especially in relation to the possibility of germline editing. At the same time, the emergence of a new postgenomic regime dominated

by the convergence of key technology platforms – genome editing, next-generation sequencing, and synthetic biology – is occurring. The outline of this is still only partially visible, but the direction of travel seems clear as the capacity to engineer life dramatically increases. This may herald an intensification in the commodification and capitalization of life, the establishment of new cultural values that normalize synthetic organisms, and the resurgence of a neo-eugenics biopolitics centered on germline engineering.

How the tension between integration into existing sociotechnical networks, institutions, and practices and disruption of the established regime is resolved over time is important for several reasons. The development of genome editing within existing structures enables rapid diffusion and adoption at low cost across a range of sectors and applications, easier commercialization, and more robust regulation, as well as higher levels of public acceptance. The ease of use and adaptability of the technology makes this possible. However, integration may also lock genome editing into a more domesticated role prescribed by established governance arrangements. While this may limit its more radical potential in the short term, a range of powerful actors remain committed to exploiting its disruptive potential across a much wider range of applications. The balance of political and economic forces supporting or opposing these options will be critical in deciding how disruptive genome editing is in particular settings and spaces. Further research will be needed to provide greater detail of how changes to specific elements of the regime are occurring in different domains, institutions, and geographies. Many features of this new landscape have still to be negotiated and will be powerfully influenced by public and professional opposition and the social, ethical, and biopolitical debates about the governance of life. The social sciences must remain fully engaged with these vitally important questions.

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