

THE SYNTHETIC YEAST PROJECT AS A TOPIC FOR SOCIAL SCIENTIFIC INVESTIGATION

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The synthetic yeast project (Sc2.0) is a visible example of the recent rise in prominence of eukaryotic synthetic biology. Drawing on an analysis of news stories, scientific papers, and our involvement with the scientific community, we describe the synthetic yeast project and some of its precursors, and we identify the technical, social and conceptual issues that we find particularly salient as researchers in Science and Technology Studies. We discuss the 'design principles' that are central to the project, and how these align Sc2.0 with the mainstream engineering agenda in synthetic biology. We identify the project's preference for openness regarding intellectual property, and compare this to ownership approaches in other branches of synthetic biology. We also argue that a study of yeast encourages us to consider more explicitly the spatial and temporal dimensions of the organisms used in synthetic biology. We conclude that social scientific investigation into the synthetic yeast project raises important questions that will help us better understand the movement of synthetic biology into more complex organisms and systems, and assist us in further exploring the tensions between engineering and biology that are central to this emerging field.

I INTRODUCTION

Yeast is a familiar microorganism. It is central to the production of everyday foods like bread and beer, and it is scientifically well understood. The familiarity of yeast makes the decision to build a synthetic 'designer' version of the entire yeast genome all the more significant. The goal of the synthetic yeast project (known as Sc2.0) is to create a novel, rationalised version of the genome of the yeast species *Saccharomyces cerevisiae* ('*S. cerevisiae*').¹ In March 2014, the complete synthesis of one of the chromosomes of *S. cerevisiae* was announced,² and received widespread scientific and media coverage. In this commentary we discuss the Sc2.0 project, paying attention to those features of the project, and of the synthetic organism, that we find particularly distinctive or noteworthy.

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¹ The National Science Foundation, *Synthetic Yeast 2.0, Building the world's first synthetic eukaryotic genome together* (2015) Synthetic Yeast 2.0 <<http://syntheticyeast.org/>>.

² Narayana Annaluru et al, 'Total synthesis of a functional designer eukaryotic chromosome' (2014) 344(6179) *Science* 55.

Synthetic biology is a field concerned with the design of new biological parts, devices and systems, and the re-design of existing biological systems for useful purposes.³ The majority of synthetic biology research to date has been conducted on prokaryotic organisms (particularly bacteria) but there is growing interest in eukaryotic synthetic biology, with attention turning to yeast, plants, and even mammalian systems. For example, one of the research testbeds of the US Synthetic Biology Engineering Research Centre ('Synberc') focuses on mammalian systems.⁴ Also, the UK Research Councils have recently made large investments in eukaryotic synthetic biology, including the establishment of OpenPlant,⁵ a joint initiative of the University of Cambridge and the John Innes Centre, as well as the SynthSys-Mammalian research centre at the University of Edinburgh.⁶

We are social scientists in the field of Science and Technology Studies ('STS'), and we have been studying the emergence and formation of synthetic biology for the past seven years.⁷ Our earlier work implicitly revolved around prokaryotic synthetic biology, because this was the focus of the scientists and engineers we were interacting with. But we have recently become involved in two large-scale synthetic biology projects: a multinational project titled 'Induced Evolution of Synthetic Yeast genomes',⁸ and a UK research centre focused on mammalian synthetic biology.⁹ As the research focus of scientists and engineers expands from prokaryotic systems to include yeast and multicellular mammalian systems, we reflect on how our own research questions are also being revised and expanded. In what follows, we show how recent activities, particularly in yeast synthetic biology, relate to our existing interests while also re-directing our attention to a somewhat different set of questions.

As STS researchers, we ground our work in empirical investigation of our subject matter, usually conducting interviews and extensive participant observation. This commentary piece marks the beginning of our investigations into synthetic yeast. It is not intended to provide a comprehensive overview of all the relevant issues, but instead highlights topics and themes that we identify as valuable to explore further. We draw on our previous research on synthetic biology, building on this through preliminary engagement with members of the yeast synthetic biology community and a survey of recent scientific publications on yeast synthetic biology. We have also conducted a thematic analysis of news stories (approximately 35 articles) accompanying the 2014 *Science* publication that reported successful construction of a synthetic version of yeast chromosome III.¹⁰ Combining these different sources allows us to identify themes that we intend to pursue through further investigation of yeast synthetic biology.

After introducing yeast and describing the Sc2.0 project and its precursors, we outline some of the technical, social and conceptual issues we intend to explore in our future work. We end by asking how these different dimensions of the synthetic yeast project could help us to

³ This is a commonly used definition of synthetic biology. See, eg, <<http://syntheticbiology.org/>>.

⁴ Synthetic Biology Engineering Research Centre, *Synberc building the future with biology* (2015) <<http://www.synberc.org/content/research-thrust-and-testbed-leaders>>.

⁵ OpenPlant <<http://openplant.org/>>.

⁶ The University of Edinburgh, *SynthSys Mammalian* <<http://www.synthsys.ed.ac.uk/research/funded-research/synthsys-mammalian>>.

⁷ See, eg, Jane Calvert and Emma Frow, 'Social Dimensions of Microbial Synthetic Biology' in Colin Harwood and Anil Wipat (eds), *Microbial Synthetic Biology, Volume 40 (Methods in Microbiology)* (Burlington: Academic Press, 2013) 69.

⁸ Projektträger Jülich (Germany), *ERASynBio 1st joint call 2013: 8 proposals selected for funding* (2015) ERASynBio <<https://www.erasynbio.eu/joint-calls/1st-call>>.

⁹ University of Edinburgh, above n 6.

¹⁰ Narayana Annaluru et al, above n 2.

deepen our understanding of the relationship between biology and engineering in synthetic biology.¹¹

II THE SIGNIFICANCE OF YEAST

Yeast is of great cultural importance for human societies, since it is essential to the brewing of alcohol and the baking of bread. The ancient relationship between yeast and humans is well known, and was frequently alluded to in several of the media stories we analysed (often with reference to the geographical origins of this relationship in the Fertile Crescent).¹² Indeed, the Latin name *Saccharomyces cerevisiae* means ‘beer sugar mould’, showing that even the name for this organism is inseparable from its common cultural use.¹³ With its ability to ferment at industrial scale, yeast has been an essential part of the biotechnology industry from its beginnings,¹⁴ and is currently in widespread use for the production of medicines, vaccines and biofuels. Thanks to its history of safe use in food products, yeast as an organism is categorised as ‘generally recognised as safe’ or ‘GRAS’ in the US, which streamlines its regulatory approval process.¹⁵

Given this longstanding relationship with human culture, yeast is a familiar everyday entity, and the news stories we analysed often transferred this sense of ‘domestication’ to their discussion of the synthesis of chromosome III. There were frequent associations made between yeast and consumer products (including Vegemite, in the Australian media),¹⁶ with some sources also suggesting that synthetic yeast might lead to the production of ‘better beer.’¹⁷

Yeast is not only the object of widespread domestication, but scientifically it is ‘one of the most important model organisms for studying eukaryotic genetics.’¹⁸ It was the first eukaryotic organism to have its full genome sequenced in 1996, and is described as well-suited to scientific investigation because it has a ‘relatively compact and stable genome’¹⁹ and is simple compared to most eukaryotes. These features make yeast ‘an ideal candidate to extend synthetic genomics beyond bacteria.’²⁰

¹¹ The relationship between engineering and biology is a central focus of a social scientific research project we are both involved with. See, European Research Council, *Engineering life: ideas, practices and promises* (2014) <<http://erc.europa.eu/engineering-life-ideas-practices-and-promises>>.

¹² See, eg, David Shukman, ‘Scientists hail synthetic chromosome advance’ *BBC News* (online), 27 March 2014 <<http://www.bbc.co.uk/news/science-environment-26768445>>.

¹³ Anna Krzywoszynska, “*We produce under this sky*”: *making organic wine in a material world* (PhD Thesis, the University of Sheffield, 2012).

¹⁴ Robert Bud, ‘Molecular biology and the long-term history of biotechnology’ in Arnold Thackray (ed), *Private Science: Biotechnology and the Rise of the Molecular Sciences* (University of Pennsylvania Press, 1998) 3.

¹⁵ US Department of Health & Human Services, *Microorganisms & Microbial-Derived Ingredients Used in Food (Partial List)* (2013) US Food and Drug Administration <<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/MicroorganismsMicrobialDerivedIngredients/default.htm>>.

¹⁶ Chris Pash, ‘Australia Has Joined the Global Effort to Create the First Synthetic Complex Organism, A Yeast to Make a Better Wine’, *Business Insider Australia* (online), 27 May 2014 <<http://www.businessinsider.com.au/australia-has-joined-the-global-effort-to-create-the-first-synthetic-complex-organism-a-yeast-to-make-a-better-wine-2014-5>>.

¹⁷ William Herkewitz, *Scientists Create Synthetic Yeast Chromosome (And Unlock the Future of Beer)* (27 March 2015) *Popular Mechanics* <<http://www.popularmechanics.com/science/health/a10289/scientists-create-synthetic-yeasts-and-open-the-door-to-the-future-of-beer-16637455/>>.

¹⁸ Stephen George Oliver et al, ‘The complete DNA sequence of yeast chromosome III’ (1992) 357 *Nature* 38, 38.

¹⁹ Dejana Jovicevic, Benjamin Blount and Tom Ellis, ‘Total synthesis of a eukaryotic chromosome: Redesigning and SCRaMble-ing yeast’ (2014) 36(9) *Bioessays* 855, 856.

²⁰ *Ibid.*

III THE SYNTHETIC YEAST PROJECT AND ITS PRECURSORS

To date, the highest-profile genome synthesis project has been the synthesis of the complete bacterial genome of *Mycoplasma mycoides* ('*M. mycoides*'). This was carried out by a team of researchers at the J Craig Venter Institute ('JCVI') and published in the journal *Science* in 2010.²¹ The article describes how a synthetic copy of the natural *M. mycoides* genome was inserted into an already existing cell, where it was able to switch the cell from its original *Mycoplasma capricolum* phenotype to the new *M. mycoides* phenotype. This ambitious genome synthesis and assembly project is often invoked as a precedent to the synthetic yeast project.²²

However, the Sc2.0 yeast genome synthesis project is an order of magnitude larger than the 1.08 million base-pair bacterial genome synthesised by the JCVI.²³ At 11 million base pairs, the synthesis of the *S. cerevisiae* genome is a considerably more challenging task. Because of its size, the Sc2.0 project is an internationally distributed effort, with different yeast chromosomes being synthesised simultaneously in different institutions around the world. For example, Macquarie University is synthesising chromosomes XIV and XVI in collaboration with the Australian Wine Research Institute, and the University of Edinburgh is working on the synthesis of chromosome VII and the 'neo-chromosome'. A commentary accompanying the 2014 *Science* publication includes an image illustrating the global distribution of the project, with each chromosome associated with the national flag of the country leading on its synthesis.²⁴

This image is reminiscent of the Human Genome Project ('HGP'), which was a large-scale international genome sequencing project that ran from 1990 to 2003.²⁵ The HGP is often invoked in discussions of the synthetic yeast project.²⁶ Although the HGP's focus was on sequencing, not synthesis, it was a similarly ambitious, internationally distributed project that required coordination of tasks, milestones and timelines. In his analysis of how the HGP was governed, Hilgartner notes that special attention had to be paid to the division, organisation and peer recognition of work so as to ensure longer-term career viability of participating researchers, particularly postgraduate students and junior staff scientists.²⁷ To date, the yeast synthesis project has been relying heavily on undergraduate student contributions, which raises questions about how project allocation and authorship credit are being determined among the students contributing to this collective effort.

The geographical dispersion of the Sc2.0 project seems to be a key motivation behind the creation of a statement on ethics and governance, which has been agreed to by the Sc2.0 consortium participants and is published on the project's website.²⁸ The statement explains that 'this is a massive, collaborative project involving diverse scientists from academic and

²¹ Daniel Gibson et al, 'Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome' (2010) 329(5987) *Science* 52.

²² See, eg, Ewen Callaway, *First synthetic yeast chromosome revealed* (27 March 2014) Nature International Weekly Journal of Science <<http://www.nature.com/news/first-synthetic-yeast-chromosome-revealed-1.14941>>.

²³ Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

²⁴ Elizabeth Pennisi, 'Building the Ultimate Yeast Genome' (2014) 343 *Science* 1426.

²⁵ Stephen Hilgartner, 'Constituting large-scale biology: Building a regime of governance in the early years of the Human Genome Project' (2013) 8(4) *BioSocieties* 397.

²⁶ See, eg, Elizabeth Pennisi, above n 24.

²⁷ Stephen Hilgartner, above n 25.

²⁸ Synthetic Yeast 2.0, *Sc2.0 Statement of Ethics and Governance* (24 November 2013) <http://syntheticyeast.org/wp-content/uploads/2014/04/Sc2_EthicsAndGovernanceAgreement_131124final.pdf> ('Statement').

commercial institutions across the globe.’²⁹ It goes on to say: ‘with scientists with such different backgrounds working together on this single project, it is essential that everyone involved is well informed and conscientious with regard to the ethics and related policy issues.’³⁰ It is notable that the size and geographical spread of the project is seen to demand that particular attention is paid to governance. This necessity for coordination, not only scientific but also ethical, may well be a feature of eukaryotic genome synthesis projects in the future. The Sc2.0 statement recognises this, saying: ‘we hope that this effort can serve as a model for other similarly collaborative, global endeavours in synthetic biology.’³¹

IV DESIGNING THE SYNTHETIC YEAST GENOME

To examine the technical features of the synthetic yeast genome project, it is helpful to return to the comparison with the JCVI’s synthesis of the *M. mycoides* genome. A key difference between the two projects is in the scope of genome (re-)design. The JCVI researchers created a synthetic version of an existing bacterial genome (adding a few unnatural, noncoding ‘watermarks’ to distinguish the natural and synthetic versions).³² In contrast, the aim of the synthetic yeast project is not to produce a synthetic version of the wild-type *S. cerevisiae* genome, but rather to create a ‘designer genome’. The changes being made are described as ‘much more drastic alterations than those demonstrated by Venter and his team in 2010.’³³

The synthetic yeast genome can be described as a ‘refactored’ genome. ‘Refactoring’ is a widely used approach in synthetic biology. The term is borrowed from software engineering and it means rationalising or cleaning up software code. Synthetic biologists have taken this idea and are applying it to *genetic* code, attempting to make it more ‘rational’ and streamlined.³⁴ Naturally occurring DNA³⁵ sequences, with their many repeats and redundancies, are rearranged in a way that is perceived of as ‘better’ (or perhaps ‘sleeker’).³⁶ The synthetic yeast project is an attempt to refactor the entire yeast genome.

The Sc2.0 project team is working to refactor the yeast chromosomes *in silico* before synthesising them. They are following three core (yet arbitrary) design principles: maintaining genomic stability, increasing genetic flexibility, and maintaining the fitness of the yeast.³⁷ These principles were applied to the redesign of chromosome III, and will be adhered to in the synthesis of the other chromosomes. Chromosome III was the first to be synthesised in the Sc2.0 project, and is described as a ‘sentimental favourite of yeast geneticists’³⁸ because it is one of the shortest, and it is also the chromosome containing the genes responsible for yeast sexual behaviour. It was also the first chromosome to be

²⁹ Ibid 1.

³⁰ Ibid.

³¹ Ibid.

³² Daniel Gibson, above n 21.

³³ Ewen Callaway, above n 22.

³⁴ Karsten Temme, Dehua Zhao and Christopher Voigt, ‘Refactoring nitrogen fixation gene clusters from *Klebsiella oxytoca*’ (2012) 109(18) *Proceedings of the National Academy of Sciences of the United States of America* 7085.

³⁵ Deoxyribonucleic acid.

³⁶ Ian Sample, ‘Designer’ chromosome for brewer’s yeast built from scratch’, *The Guardian* (online), 28 March 2014 <<http://www.theguardian.com/science/2014/mar/27/designer-chromosome-brewers-yeast-eukaryotic-saccharomyces-cerevisiae>>.

³⁷ Jessica Dymond et al, ‘Synthetic chromosome arms function in yeast and generate phenotypic diversity by design’ (2011) 477 *Nature* 471.

³⁸ Jef Boeke quoted in David Biello, ‘Baker’s Yeast Gets a Genetic Makeover’, *Scientific American* (online), 27 March 2014 <<http://www.scientificamerican.com/article/bakers-yeast-gets-a-genetic-makeover/>>.

sequenced in 1992, and at that time was the first complete sequence of an entire chromosome from any organism.³⁹

In an attempt to improve the genomic stability of the synthetic chromosome III, all known genome-destabilising elements were deleted, including small stretches of DNA called transposons and introns.⁴⁰ The ends of the chromosomes, called telomeres, were also removed and replaced by shorter, synthetic versions.⁴¹ All told, the deletions have resulted in a synthetic chromosome that is 14% smaller than the original.⁴² Another major change is that all of the yeast's transfer RNAs,⁴³ which are essential for making proteins from DNA, have been extracted from their original locations and will be combined to make a 'neo-chromosome'. This is because transfer RNAs can be sites of genomic instability, and it is predicted they will cause less damage if separated from the rest of the genome.⁴⁴

The researchers have attempted to increase genetic flexibility in the synthetic genome by building in so-called 'SCRaMbLE' sites,⁴⁵ which 'will make it possible to reshuffle the genome at will.'⁴⁶ This will allow the researchers to evolve the yeast on demand, and to use evolution as a laboratory tool for obtaining new functionality,⁴⁷ which may prove to be an industrially relevant approach. Another aim is to find out more about biology, because it is hoped that the SCRaMbLE system 'will allow direct testing of evolutionary questions.'⁴⁸ Jef Boeke, the scientist leading the Sc2.0 project, says that he sees the synthetic yeast primarily 'as a learning tool.'⁴⁹ This tension between obtaining a greater understanding of biological systems and using this understanding in pursuit of industrial application runs through much of the current activity in synthetic biology.⁵⁰

The intentional application of three 'design principles' shows that the synthetic yeast project, like much of synthetic biology, is strongly influenced by an aspiration to apply ideas from engineering to biology.⁵¹ But the features that are being designed into the synthetic yeast compel us to think in new ways about the place of engineering in biology. For example, to what extent can we call the synthetic yeast genome a 'designer' genome if the SCRaMbLE system will yield unpredictable mutations? Evolution may be 'induced' in this project, but it is the power of the evolutionary process, not rational design, that is being harnessed. This raises questions about the relationship between evolution and rational design, questions that are becoming increasingly important to synthetic biology.⁵²

³⁹ Stephen George Oliver et al, above n 18.

⁴⁰ Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

⁴¹ Elizabeth Pennisi, above n 24.

⁴² Helen Thompson, *Scientists Build a Yeast Chromosome From Scratch. Next Up? Designer Genomes* (27 March 2014) *Smithsonian* <<http://www.smithsonianmag.com/science-nature/scientists-build-yeast-chromosome-scratch-next-up-designer-genomes-180950281/?no-ist>>.

⁴³ Ribonucleic acid.

⁴⁴ Elizabeth Pennisi, above n 24.

⁴⁵ Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

⁴⁶ Elizabeth Pennisi, above n 24.

⁴⁷ Dejana Jovicevic, Benjamin Blount and Tom Ellis, above n 19.

⁴⁸ Narayana Annaluru et al, above n 2.

⁴⁹ William Herkewitz, above n 17.

⁵⁰ Maureen O'Malley et al, 'Knowledge-making distinctions in synthetic biology' (2008) 30(1) *BioEssays* 57.

⁵¹ Pablo Schyfter, Emma Frow and Jane Calvert, 'Guest Editorial: Synthetic biology: Making Biology into an Engineering Discipline' (2013) 5(1) *Engineering Studies* 1.

⁵² Jane Calvert, 'Evolution or design?' in Ginsberg et al, *Synthetic Aesthetics: Investigating Synthetic Biology's Designs on Nature* (Cambridge, MA: MIT Press, 2014) 259.

In contrast with much of the synthetic biology literature (particularly that from the 'BioBricks' school),⁵³ reporting about the synthetic yeast project discusses engineering mainly at the genomic or systems level⁵⁴ rather than focusing on standardised genetic 'parts', refactored genetic 'circuits',⁵⁵ and individual engineered 'devices' with specific functions.⁵⁶ In previous work, Calvert and colleagues distinguished between approaches to synthetic biology that focus on making standardised biological parts ('DNA-based device construction'), and those concerned with 'genome-driven cell-engineering', where the genome as a whole is regarded as the causal engine of the cell.⁵⁷ The synthetic yeast project is more strongly aligned with the latter approach. The ways in which engineering at the level of whole genomes might be considered similar to or different from engineering focused on parts (such as BioBricks), is a topic that would benefit from further investigation.

Interestingly, in our analysis of the media coverage surrounding the synthetic yeast chromosome, we find that some of the language departs from that typically associated with systematic engineering. For example, there are also many craft-like metaphors associated with the project — several sources use the language of 'stitching' and 'sewing' to describe the construction of the synthetic chromosome.⁵⁸

V OPENNESS AND OWNERSHIP

One area of strong similarity between the synthetic yeast project and the parts-based approach to synthetic biology is in their emphasis on openness and the sharing of synthetic biological constructs. The BioBricks approach has from its outset promoted the growth of a community of contributors who make their standardised biological parts freely and openly available for others to use. However, developing legal mechanisms to facilitate this has not been straightforward, given the strong emphasis on appropriation in biotechnology.⁵⁹ Similarly, those involved in the synthetic yeast project have decided that they will not claim intellectual property rights on the synthetic sequence. The Sc2.0 Statement of Ethics and Governance states this explicitly:

'We are committed to facilitating innovation and maximising beneficial use of Sc2.0. As such, no intellectual property rights will be exercised on the clones used to generate novel strains, intermediary strains, or the final Sc2.0 strain.'⁶⁰

This has led to the synthetic yeast project being called 'the academic, open-source reply to what Venter did.'⁶¹

As this quotation suggests, the approach of the Sc2.0 consortium is very different from that taken in the JCVI's synthetic genomics work. The JCVI filed 13 patents in association with its synthetic *M. mycoides*, and their website maintains that:

⁵³ Drew Endy, 'Foundations for Engineering Biology' (2005) 438 *Nature* 449.

⁵⁴ Priscilla Purnick and Ron Weiss, 'The second wave of synthetic biology: from modules to systems' (2009) 10(6) *Nature Reviews: Molecular Cell Biology* 410.

⁵⁵ Karsten Temme, above n 34.

⁵⁶ Although there is a passing reference to modularity in Dejana Jovicevic, Benjamin Blount and Tom Ellis above n 19.

⁵⁷ Maureen O'Malley et al, above n 50.

⁵⁸ Ewen Callaway, above n 22.

⁵⁹ Jane Calvert, 'Ownership and sharing in synthetic biology: a 'diverse ecology' of the open and the proprietary?' (2012) 7(2) *BioSocieties* 169.

⁶⁰ Statement, above n 28. It should be noted that intellectual property is allowed on derivatives of the yeast.

⁶¹ Tom Ellis quoted in Ewen Callaway, above n 22.

'Intellectual property is important in the synthetic genomics/biology space as it is one of the best means to ensure that this important area of basic science research will be translated into key commercial products and services for the benefit of society'.⁶²

Across the Sc2.0 project and JCVI's work, we thus see contradictory understandings of the relationship between intellectual property protection and innovation for 'beneficial use'.⁶³ More broadly, these two initiatives are grounded in different funding structures and institutional frameworks for supporting research and innovation, and draw different conclusions for how benefits (whatever they may be) are best derived.

The open norms we find in the yeast project may also owe something to the norms of the 'traditional' (non-synthetic) yeast research community. This is something we plan to investigate further. There may well also be parallels with other model organism research communities, such as the *Drosophila melanogaster* (fruit fly) community, which has traditionally adopted strong norms of 'sharing and free exchange',⁶⁴ and the *Caenorhabditis elegans* (worm) community, 'often celebrated as a model of scientific cooperation.'⁶⁵

A striking feature of the synthetic yeast consortium is its emphasis on 'togetherness'. The tagline of the Sc2.0 website is 'Building the world's first synthetic eukaryotic genome together' (emphasis added), and the project has been called 'a great example of "do it together" biotechnology'.⁶⁶ Undergraduates in a popular 'build-a-genome' course at Johns Hopkins University carried out significant portions of the chromosome III synthesis.⁶⁷ The Sc2.0 project also officially involves a group of LA-based bio-hackers, and a class of high school students in New York.⁶⁸ With its language of togetherness, the Sc2.0 project undertakes a subtle but potentially meaningful shift away from the common 'do-it-yourself' description of synthetic biology activities involving bio-hackers and the lay public.⁶⁹ Social scientists have previously noted how 'do-it-yourself' communities are fundamentally dependent on the general infrastructure of science and engineering in order to operate,⁷⁰ but in the language chosen by the synthetic yeast project, the collaborative nature of synthetic biology endeavours becomes more explicit.

VI SPATIALITY AND TEMPORALITY

Moving from the social organisation of the project to more conceptual issues, our preliminary discussions with scientists on the synthetic yeast project reveal the importance being placed on the spatial configuration of the yeast chromosome. For example, a key strand of the work in the 'Induced Evolution of Synthetic Yeast Genomes' project⁷¹ will be to

⁶² J. Craig Venter Institute, *First self-replicating synthetic bacterial cell* <<http://www.jcvi.org/cms/research/projects/first-self-replicating-synthetic-bacterial-cell/faq/#q11>>.

⁶³ Stephen Hilgartner, 'Novel Constitutions? New Regimes of Openness in Synthetic Biology' (2012) 7 *BioSocieties* 188.

⁶⁴ Robert Kohler, 'Moral Economy, Material Culture, and Community in *Drosophila* Genetics' in Mario Biagioli (ed), *The Science Studies Reader* (New York: Routledge, 1999) 243, 345.

⁶⁵ Rachel Ankeny, 'Fashioning Descriptive Models in Biology: Of Worms and Wiring Diagrams' (2000) 67 *Philosophy of Science* 260, 262.

⁶⁶ Drew Endy quoted in David Biello, above n 38.

⁶⁷ Jessica Dymond et al, 'Teaching synthetic biology, bioinformatics and engineering to undergraduates: the interdisciplinary Build-a-Genome course' (2009) 181(1) *Genetics* 13.

⁶⁸ Statement, above n 28.

⁶⁹ DIYbio, *An Institution for the Do-It-Yourself Biologist* (June 8 2015) <<http://diybio.org/>>.

⁷⁰ Alessandro Delfanti, 'Tweaking genes in your garage: Biohacking between activism and entrepreneurship' in Theo Hug and Wolfgang Sützl (eds), *Media Activism and Biopolitics: Critical Media Interventions in the Age of Biopower* (Innsbruck: Innsbruck University Press, 2012) 163.

⁷¹ Projektträger Jülich (Germany), above n 8.

produce 3D images of the synthetic genomes to show how spatial organisation affects the design of new chromosomes, since ‘exactly how DNA is packaged up and put away is vitally important for the functioning of the organism.’⁷²

This explicit attention to genome topology challenges the ‘flattened’ representations of genes and genomes that are often presented in circuit diagrams of gene regulation widely adopted in molecular biology and in parts-based synthetic biology.⁷³ Once we start conceptualising the yeast genome (in both its synthetic and non-synthetic forms), as an entity that is arranged, coiled, and packaged in 3D space, it becomes much harder to imagine it as ‘flattened’ and abstracted from its cellular context. This simplification is challenged even further by an acknowledgement of the temporal dimensions of this organism, which the scientists on the project also plan to address. They talk about wanting to conduct a 4D study of synthetic yeast (where the fourth dimension is time).⁷⁴

We are not suggesting that spatiality and temporality are unique to yeast. They are of course essential features of all living systems and processes. Indeed, some maintain that it is their dynamic, processual nature that makes living things what they are — alive. As the philosopher of biology John Dupré puts it: ‘a static cell is a dead cell.’⁷⁵ We do see discussions of morphology and topology in other areas of both prokaryotic and eukaryotic synthetic biology, and there seems to be growing attention to exploring the physical constraints under which biological systems operate.⁷⁶ But spatiality and temporality are features of synthetic biology that are brought to life in our study of yeast. Growing attention to these characteristics might over time challenge dominant engineering approaches in synthetic biology, which tend to represent biological circuits as relatively static and flat. It seems that space and time are more easily ignored, eliminated or suppressed in some branches of synthetic biology than in others.

VII THE PERSONALITY OF YEAST

A final feature of yeast to emerge from our analysis of the media coverage associated with chromosome III synthesis is that there was much discussion of its ‘personality’. For example, emphasis was placed on the familiar, ‘humble’ nature of brewer’s yeast, and there was also much talk of yeast as being ‘pliable’,⁷⁷ ‘tolerant’,⁷⁸ ‘robust’,⁷⁹ a ‘domesticated servant’,⁸⁰ and a ‘workhorse’.⁸¹

⁷² Gregory E. Kaebnick, *Synthetic Chromosomes*, The Hastings Center (28 March 2014) <<http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6853&blogid=140>>.

⁷³ Nikolas Rose, ‘Molecular Biopolitics, Somatic Ethics and the Spirit of Biocapital’ (2007) 5(1) *Social Theory & Health* 3.

⁷⁴ Jef Boeke, personal communication. See also National Institutes of Health, *4D Nucleome* <<http://commonfund.nih.gov/4Dnucleome/index>>.

⁷⁵ John Dupre, ‘Living Causes’ (2013) 87(1) *Aristotelian Society Supplementary Volume* 19.

⁷⁶ Timothy Rudge et al, ‘Cell Polarity-Driven Instability Generates Self-Organized, Fractal Patterning of Cell Layers’ (2013) 2(12) *American Chemical Society Synthetic Biology* 705.

⁷⁷ Narayana Annaluru et al, above n 2.

⁷⁸ Dan Vergano, ‘Scientists Move Closer to Inventing Artificial Life’, *National Geographic* (online), 27 March 2014 <<http://news.nationalgeographic.com/news/2014/03/140327-functional-designer-chromosome-synthetic-biology/>>.

⁷⁹ Alan Boyle, ‘Gene Gurus Create Synthetic Yeast Chromosome From Scratch’, *NBC News* (online), 27 March 2014 <<http://www.nbcnews.com/science/science-news/gene-gurus-create-synthetic-yeast-chromosome-scratch-n63316>>.

⁸⁰ Jessica Dymond et al, above n 37.

⁸¹ *Ibid.*

There seem to be attempts to preserve the character and ‘personality’ of yeast even in its synthetic form. This connects to one of the project’s three design principles: that the fitness of the yeast should be maintained. After publishing the synthesis of chromosome III, Boeke is reported as saying: ‘We checked everything by sequencing the whole chromosome and we also tested the “yeastiness” and saw essentially no difference with normal yeast.’⁸² In another interview he explains: ‘we’ve actually got a yeast that looks like a yeast, smells like a yeast, and makes alcohol like a yeast’, adding ‘We can’t really tell it apart, and yet it’s so different.’⁸³

Given the radical changes being made to the synthetic yeast genome (including the creation of a ‘neo-chromosome’), the extent to which preservation of ‘yeastiness’ is understood is an issue we hope to explore further. We speculate that such refactoring of existing genomes may challenge traditional species distinctions and give rise to questions about species identity and taxonomy.⁸⁴ This may, in turn, raise broader ethical questions about, for example, our responsibilities towards different ‘natural’ and ‘synthetic’ species of yeast or other refactored species (both prokaryotic and eukaryotic). Krzywoszynska⁸⁵ argues that we should see yeast as a ‘matter of concern’;⁸⁶ as a subject with its own ‘telos’ independent of human intentionality. Questions arise here about the telos of the *synthetic* yeast, a tool for understanding and manipulation, purposely designed to evolve on demand.⁸⁷ We plan to explore in more depth what is implied by the researchers’ attempt to ensure they have created a ‘happy, healthy yeast.’⁸⁸

VIII CONCLUSION

In closing, we reflect on how the relationship between biology and engineering — one of our key research interests in synthetic biology⁸⁹ — plays out in the synthetic yeast project, technically, socially and conceptually.

Technically, the synthetic yeast project is a large-scale refactoring exercise driven by intentional design principles, so to this extent it is well aligned with an engineering agenda. However, the media reporting about the project suggests that the drive for standardisation is not as strong as in other branches of synthetic biology. And the emphasis on the whole genome, rather than discrete ‘parts’, in the synthetic yeast project may lead to a different conception of biological engineering, which might require a greater recognition of the importance of context. Additionally, the attempt to harness the powers of evolution that we

⁸² Jef Boeke quoted in James Urquhart, *Synthetic yeast chromosome is fully functional* (27 March 2014) Royal Society of Chemistry <<http://www.rsc.org/chemistryworld/2014/03/synthetic-yeast-chromosome-fully-functional>>.

⁸³ Jef Boeke quoted in Helen Thompson, above n 42.

⁸⁴ Carrie Friese notes taxonomic conundrums facing zoo professionals creating interspecies ‘chimeric’ offspring of endangered species; the speculative designer Daisy Ginsberg has also drawn attention to possible challenges to current taxonomic practices with the advent of genome synthesis. See Carrie Friese, ‘Classification conundrums: categorizing chimeras and enacting species preservation’ (2010) 39(2) *Theory and Society* 145.

⁸⁵ Anna Krzywoszynska, above n 13.

⁸⁶ Bruno Latour, ‘Why Has Critique Run out of Steam? From Matters of Fact to Matters of Concern’ (2004) 30(2) *Critical Inquiry* 225.

⁸⁷ Gregory E. Kaebnick, above n 72.

⁸⁸ Jef Boeke quoted in Arielle Duhaime-Ross, *Scientists just took a major step toward making life from scratch* (27 March 2014) The Verge <<http://www.theverge.com/2014/3/27/5553044/first-functional-eukaryotic-chromosome>>.

⁸⁹ See, eg, Emma Frow and Jane Calvert, ‘Can simple biological systems be built from standardized interchangeable parts?’ (2013) 5(1) *Engineering Studies* 42.

see in this project perhaps gives away some of the control that we normally associate with engineering approaches.⁹⁰

With respect to its social dimensions, we see that the large-scale, international synthetic yeast project is perceived to require specific guidelines and oversight precisely because of its distributed nature and size. Issues concerning the division of labour, credit, and reward also become more pertinent. 'Big science' as a term was originally associated with the physical sciences and engineering, with the HGP being one of the first 'big biology' projects.⁹¹ The synthetic yeast project looks set to continue this trend. 'Scaling-up' is a key aspiration of engineering,⁹² but this may take on novel forms and characteristics when the focus is biological.⁹³

We have also mentioned the synthetic yeast project's preference for openness with regards to intellectual property, and compared this to similar norms in the BioBricks school of synthetic biology, and the more proprietary approach adopted in the JCVI's work on synthetic bacteria. The BioBricks approach explicitly draws on computer engineering, and is inspired by open-source software. The synthetic yeast project is influenced by this agenda, but its orientation towards openness may also be something that is carried over from the traditional yeast research community, since openness is often a feature of model organism communities.

More conceptually, we have shown how the synthetic yeast project encourages us to think explicitly about the spatial and temporal dimensions of the organisms used in synthetic biology — dimensions that are perhaps more easily ignored or overlooked in work on simpler organisms. Arguably, it is the dynamic and processual nature of living things that distinguishes them from engineered artefacts. We asked about the extent to which the organism's 'yeastiness', and perhaps even its telos, might be preserved in its synthetic form. The attempts to keep synthetic yeast 'happy' may go beyond the instrumentalisation that we expect of engineering approaches.

As researchers in STS, our primary concern is not with regulation, nor in attempting to draw a line between permissible and prohibited research. Instead, in this commentary we have highlighted key themes, issues and topics of investigation that the synthetic yeast project encourages us to think about, particularly with respect to the relationship between engineering and biology that is central to this emerging field. We hope that this brief foray into eukaryotic synthetic biology via the synthetic yeast project will prove useful in guiding our understanding of, and reflections on, the development of synthetic biology as it moves into more complex organisms and systems

⁹⁰ That being said, directed evolution approaches are becoming increasingly widespread in synthetic biology, and are not limited to synthetic yeast. See Ryan Cobb, Tong Si and Huimin Zhao, 'Directed evolution: an evolving and enabling synthetic biology tool' (2012) (16) *Current Opinion in Chemical Biology* 285.

⁹¹ Stephen Hilgartner, above n 25.

⁹² Emma Frow, 'Making big promises come true? Articulating and realizing value in synthetic biology' (2013) 8 *BioSocieties* 432.

⁹³ Gail Davies, Emma Frow and Sabina Leonelli, 'Bigger, faster, better? Rhetorics and practices of large-scale research in contemporary bioscience' (2013) 8 *BioSocieties* 386.