Remaking yeast

Remaking yeast: Metaphors as scientific tools in *Saccharomyces cerevisiae* 2.0

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Abstract

Synthetic biology appears to be moving toward engineering whole living organisms. This article addresses how *Saccharomyces cerevisiae* 2.0, a whole-genome construction project, presents an argument for a route toward that end through discursive tools it employs to construct "synthetic yeast." I analyze metaphors in recent peer-reviewed literature associated with the synthetic yeast project, asking how these metaphors shape the nature of synthetic yeast and relate the yeast to its parts and to its engineers. While chromosomes and other genome components are handled with metaphors emphasizing scientific control, the absence of these metaphors' extension to the whole organism leaves space for the synthetic yeast itself to have unpredicted and surprising emergent characteristics. I argue that examining metaphors as instruments of scientific construction in disciplinary discourse, independent of their use in science communication to lay audiences, contributes to conversations about how and what scientists construct in their movements toward 'engineering life.'

Keywords: synthetic biology, yeast, genomes, metaphors, discourse analysis

Introduction

Synthetic biology, as an umbrella for diverse approaches to "engineering biology" (Endy, 2005) calls for re-envisioning biological materials as engineerable substrates. As specific projects sitting under its umbrella, synthetic biology involves many diverse approaches for realizing that transformation. Synthetic biology has been 'emerging' as a field or collection of approaches for

at least two decades, during which its identity has been characterized as much by big promises to bring forth a bio-industrial revolution as by any particular approach to doing so (Frow, 2013; Molyneux-Hodgson and Meyer, 2009). Consequently, every new major effort in the field can be read as advocating for a particular vision of how engineering meets biology and arguing for one of many potential paths toward "making the living world engineerable" (National Academies 2016).

The *Saccharomyces cerevisiae* 2.0 (Sc2.0) project represents the largest undertaking to-date in the whole-genome mode of synthetic biology, as defined in contrast to parts-based and protocell-construction approaches historically at the field's center (O'Malley, Powell, Davies, and Calvert, 2008). This "synthetic yeast project" aims to construct the world's first synthetic eukaryotic genome assembled wholly out of laboratory-synthesized DNA. That genome takes an existing laboratory strain of the common yeast *S. cerevisiae* as a starting point for numerous large-scale modifications in an effort to make the resulting "Sc2.0" a more robust and flexible organism for future research and industry use (Richardson et al., 2017).

In some respects, the Sc2.0 project is not especially new. Many tools employed in designing and constructing Sc2.0 are well-established in molecular biology. Geneticists, and people employed in fermentation industries before the advent of genetics, have a long history of custom-designing yeast strains. What makes the Sc2.0 project distinct is the unprecedented scope and scale of genetic work undertaken to create this new strain. Because of the sheer volume of DNA being assembled, the project involves new scientific, informatics, and organizational tools. In contrast to many other synthetic biology projects focused on constructing genetic pathways or circuits – engineering small components *within* living organisms – Sc2.0 is about constructing a complete genome and is therefore closer to the long-imagined goal of engineering in the context

of complete living organisms themselves (Palsson, 2000). This article aims to identify whether assembling synthetic yeast similarly involves new *discursive* tools – elements of the scientific toolkit just as real and just as influential as restriction enzymes or fluorescent markers.

I examine metaphors in the peer-reviewed scientific literature of the Sc2.0 project as scientific tools involved in shaping what synthetic yeast becomes. The goals of doing so are two-fold. First, I consider how metaphors used in scientific discourse function as information-handling tools which participate in shaping what synthetic biologists develop. Second, I aim to understand how the Sc2.0 project, as a potential forerunner of a whole-genome approach in synthetic biology, advances an argument of how living organisms may be made engineerable. Consequently, this analysis can contribute to understanding how Sc2.0 is shaping synthetic biology as well as to how synthetic biologists are using discursive tools to shape Sc2.0. More broadly, this analysis connects the relatively impoverished literature empirically analyzing metaphor in disciplinary scientific discourse, to conversations about enacting reflexive, reflective scientific research.

Examining scientific discourse enables seeing how synthetic biologists (re)shape living systems and bring about future worlds with discursive tools – tools used to make knowledge both in and outside the lab. These tools therefore enable cross-community conversations involving the kinds of questions de la Bellacasa (2011) asks in "translating ethico-political caring into our ways of thinking and representing things:" "How does respect for concerns in the things we re-present encourage attention to the effects of our accounts on the composition of things?" Stating the case more strongly, after Mol's (2002) questions asking whether and how it is good for things to be made differently, we can ask: what are good metaphors for making life as we want it to be, and as we want to be in community with it?

Metaphors as scientific tools

Metaphors are essential to scientific discourse. As has been observed by scholars as diverse as Stanley Falkow ("Ending the War," 2006) in microbiology, Lakoff and Johnson (1980) and Elena Semino (2008) in cognitive linguistics, and Evelyn Fox Keller (1995) and Donna Haraway (1976) in science studies, among many others, metaphors do not merely make science more accessible to popular audiences but are essential to getting science done.

Kenneth Burke (1967) gives a classic formulation of how metaphors shape knowledge. For Burke, any set of discursive choices function as a "terministic screen," forming a screen or lens that inevitably colors the observations language-users make: some things become more visible, others less so, such that the screen shapes observed reality. These mediations are inevitable insofar as "we *must* use terministic screens, since we can't say anything without the use of terms; whatever terms we use, they necessarily constitute a corresponding kind of screen; and any such screen necessarily directs the attention to one field rather than another" (Burke, 1967).

Metaphors shape how language-users understand something (the target domain) by suggesting its similarity to something else (the source domain), instructing readers to apply a screen already developed in one context to pattern how a new picture takes shape. By suggesting that the preexisting screen and set of terms apply in the new situation, metaphors also locate new scientific work in the context of preexisting knowledge, instructing readers (per Stanley Fish's terminology) in how to connect newly introduced information to what they already know. Metaphors which become standard ways of thinking and communicating about scientific phenomena thus lay out patterns that suggest what may be done with new information, what

additional questions are reasonable, and how new and existing concepts relate (Brown, 2003). Thomas Kuhn makes a similar argument in *Structure of Scientific Revolutions* (1962) in presenting how paradigms influence scientific observation. Independent of Kuhn's conclusions about relationships amongst paradigms or how scientists move amongst them (robustly disputed in science studies, particularly in their applicability to biology; see, for example, Keller, 2012), his suggestion that the scope of any line of scientific inquiry is embedded in its initial choice of terms coheres with rhetorical scholarship about how language shapes thought.

The consequences of such patterning are evident in Evelyn Fox Keller's (1995) account of conflicts amongst developmental biology and genetics in the twentieth century, which traces how genetics has been shaped by "director" metaphors accepted early in its development to describe how nuclear DNA relates to the rest of the cell. Morganian genetics won wars for epistemic dominance, Keller suggests, at least in part because asking how genes produce effects as directors of cellular action was a much more readily answered set of questions than asking how "environmental signals alter what a gene does." Consequently, molecular biology has largely worked to describe linear genetic effects, seeing contributions from the rest of the cell as secondary, with long-lasting influence on synthetic biology and other derivative fields.

By suggesting appropriate images to apply in formulating questions and guiding what makes sense as knowledge in the search for a response, metaphors iteratively make their targets more and more like their own image and make seeing those targets through different screens increasingly difficult. Some of Foucault's (1989) metaphors for this phenomenon involve knowledge sedimenting like layers of silt, becoming more and more difficult to unmake the deeper they become and the more they stick together. This is not to say that metaphors can force the world into *any* physical shape. As Keller (1995) puts it, their "efficacy" relies on the

"resources" afforded by the relevant social, natural, and technical environments. Terministic screens have effects *in conjunction* with some observable reality seen through them. Metaphors can be seen as information-handling tools which, like other tools, leave marks behind.

In the synthetic yeast project, scientists employ metaphors not only to construct new knowledge about how yeast DNA works but to physically rebuild the yeast genome, remaking the physical resources of the genome in the image of the metaphors they use to conceptualize it. Understanding which metaphors scientists use with synthetic yeast and other genetic construction projects therefore becomes important to understanding how science is done and what science makes, what science *can be* done and what science is likely to make, *in addition* to understanding how explanations of that work are constructed for other audiences.

In any attempt to generalize across studies of metaphor in science, it is important to observe that the vast majority of such studies continue to concern popular science communication and implications for public understanding of science (though important exceptions include Brown, 2003; Semino, 2008). As importantly, both for studies of popular communication and less frequent studies of disciplinary discourse, diverse theoretical positionings are at play. Brown (2003), for example, argues that metaphorical reasoning underpins most scientific work and that examining scientific rhetoric can unlock underlying principles of scientific thought. Many studies in the public understanding of science literature (e.g. Christidou, Dimopoulos, and Koulaidis, 2004; Gschmeidler & Seiringer, 2011; Hellsten & Nerlich 2011) examine metaphors as framing devices in popular science news without engaging with metaphor in scientific discourse at all. Freddi, Korte, and Schmied (2013), meanwhile, introduce "developments and trends in the rhetoric of science" by claiming that science needs rhetoric "in the basic sense as a means of expression in order to inform, persuade or motivate

particular audiences in specific situations," placing science outside of and before the language used to communicate it. The present study belongs to a building line of critical STS approaches to science communication beginning from the position that rhetorical devices are necessarily constitutive of scientific knowledge as something able to travel beyond one worker at the laboratory bench, and which therefore focus attention on disciplinary discourse in addition to popular communication.

Early in 2017, the Sc2.0 consortium celebrated a major milestone with the publication of seven new scientific articles about the project in a special issue of the journal *Science*, together with two brief commentary pieces – one from the issue's editors, one about the accompanying artwork. This special issue affords an ideal corpus for investigating questions about the discourse of synthetic yeast. I employ a metaphor analysis of the seven articles in the issue to ask: what metaphors shape Sc2.0? How do these metaphors advocate for how whole organisms are made engineerable? I contextualize this textual analysis through eighteen months of experience working alongside scientists, informaticians, and designers in an Sc2.0 consortium laboratory.

Background: *Saccharomyces cerevisiae* 2.0

Synthetic biology is a field or community resistant to singular definitions, but generally characterized by a focus on "the design and engineering of biologically based parts" (Synthetic Biology Roadmap for the UK, 2012). Most synthetic biology work can be described as taking one of three general approaches: trying to create standardized genetic parts which can be linked together to form customizable pathways (the parts-based approach), building simplified whole cells from non-living components (the protocell approach), or using existing organisms as starting points for redesigning and synthesizing whole genomes (the whole-genome approach) (O'Malley, Powell, Davies, and Calvert, 2008). Previous whole-genome work has been limited to

viruses and bacteria and largely undertaken by the J. Craig Venter Institute, a California-based private research institution best known for creating a bacterium with the smallest genome known to sustain a free-living cell (Hutchison et al., 2016).

Sc2.0 is the first attempt to synthesize the whole genome of a eukaryotic organism. Eukaryotes, in comparison with prokaryotic bacteria and their single circular genomes, have substantially larger genomes organized into multiple chromosomes. The Sc2.0 project works at an order of magnitude larger than previous bacteria-based projects (approximately 12 megabases for *S. cerevisiae* versus approximately 1 megabase for *Mycoplasma*; Dymond and Boeke, 2012), and has likewise led to a larger and more complex project organization. Rather than being undertaken by a single research group, Sc2.0 construction involves a consortium of eleven laboratories located in the United States, the United Kingdom, China, Singapore, and Australia, in addition to several affiliates in continental Europe and the United States.

The design principles of the synthetic yeast genome – fitness, genome stability, and genetic flexibility (Dymond et al., 2011) and the detailed DNA sequence – were centrally determined by the project's leaders. Individual laboratories have taken responsibility for constructing one or more of the yeast genome's sixteen chromosomes and have been free to devise their own preferred means of doing so. Two laboratories are making additional contributions to the genome. At the University of Edinburgh, the Cai lab has constructed a seventeenth "neochromosome" to which all 275 recombination-prone tRNA genes have been relegated (Walker, 2017). These genes, considered "hotspots of instability" (ibid.) normally scattered across the yeast genome, are being quarantined to this separate DNA molecule in an attempt to make the finished synthetic genome more stable. At the Australian Wine Research Institute, a small team is constructing what they call a "pan genome," a non-essential add-on

module to the basic genome comprised of genes from yeast strains used in beer, bread, wine, and sake production that are *not* found in the laboratory yeast strain being used as the basis for Sc2.0. Adding this pan genome to the completed synthetic yeast will, they hope, transform the laboratory strain on which the Sc2.0 genome is based – a strain wholly unsuitable for food fermentation tasks – into a more functionally diverse organism with useful applications for wine and other fermentation industries.

The Sc2.0 project is unique not only in terms of the magnitude of DNA being designed and constructed, but in how extensively the template yeast genome is being modified. Previous bacterial projects have either made relatively minor additions to existing genomes – adding 'trademark' sequences or encoding small sections of English-language text – or have worked toward increasingly small genomes by deleting as many genes as possible, largely through trial and error, while still enabling cell survival. The Sc2.0 genome, in contrast, incorporates numerous systematic genome-wide modifications. In addition to relocating tRNA genes to the neochromosome, noncoding DNA is being deleted, making the whole genome about 8% shorter than the original. Stop codons,[ii] which normally occur in two forms (TAG and TAA), have all been changed to a single form, TAA, so that TAG can be 'freed up' to encode an additional unconventional amino acid later on. Most interestingly, the whole genome incorporates a system called SCRaMbLE that yeast biologists in and outside the project suggest may deliver the Sc2.0 project's most important contributions to that field (Dymond et al., 2011; Richardson et al., 2017).

SCRaMbLE is both a clever acronym and a metaphorical expression standing for Synthetic Chromosomal Rearrangement and Modification by LoxPsym-Mediated Evolution. In other words, SCRaMbLE is a system of short sequences distributed throughout the genome that

serve as recognition sites for an enzyme, Cre recombinase, able to catalyze rearrangement between any two of these sites. When a yeast strain bearing one or more synthetic chromosomes harbors the *cre* recombinase gene on a plasmid (a small, circular DNA molecule separate from the nuclear genome) under the control of a hormone-activated promoter, synthetic biologists can 'scramble' the synthetic chromosomes on command by introducing the appropriate hormone signal into the yeast growth media. Recombinase recognition sites have been written into the synthetic genome at the end of all putatively non-essential genes and at important chromosomal features.[iii] Inducing expression of the recombinase enzyme, by catalyzing recombination amongst any of these sites, therefore creates the possibility of large-scale rearrangements including duplications, deletions, inversions, and translocations (Shen et al., 2015). While the technologies involved in SCRaMbLE are old, this mode of implementing them is new and has potentially broad ramifications for developing new yeast strains and learning about yeast gene function.

Methods

The corpus for this study comes from a special issue of *Science* featuring Sc2.0 published on 9 March, 2017. While much has been written around the project's periphery, this special issue contains more than half of extant research articles directly describing chromosome construction, including five articles about newly completed chromosomes, one about characterizing a previously completed chromosome, and one describing the global strategy for designing the genome (table 1). Importantly, the special issue represents several years of cross-consortium collaboration during which the full genome sequence was designed *in silico* and several full chromosomes synthesized *in yeasto*[i] (Lin, 2015) such that it is reasonable, at this stage, to expect

the working metaphors of the project to have achieved some degree of stability. The issue also represents the work of laboratory teams in the United States, Scotland, and China, enabling some sense of how metaphors characterize the project at an international consortium-level. Two commentaries accompany the research articles: one from the issue's editors about the importance of the project to the scientific community, and one from the artists responsible for the cover design and the illustration for the editorial commentary about creating those images. As my interest here is in the metaphors which enable scientists' operations, I focus solely on the seven peer-reviewed research articles.

My textual analysis is informed by a year of collaboration with the consortium and close contact with one of the consortium laboratories. For one or two days each week, I worked in the laboratory office alongside PhD students and postdocs, participating in conversations and meetings and being involved as an associate member of the lab group. I have also conducted formal interviews and had informal conversations with many members of the Sc2.0 consortium about, among other things, the nature of the "synthetic yeast" under construction. This discursive immersion provides context for reading the *Science* corpus from an insider-outsider position – a position Valve and McNally (2013) liken to someone who "engages with a project as if it were a client, and who therefore takes the project's objectives very seriously while at the same time retaining his or her own normativity" and disciplinary perspectives (474). I sought to read simultaneously with an insider's understanding of how language functions in the context of the wider project and an outsider's critical eye to what else that language might do.

I read each of the seven research articles in full and in detail, focusing on the sentence level, and cataloguing all metaphors applied to DNA, chromosomes, the genome, the synthetic yeast, or other targets of the project's work. I ignored two categories of dead or conventional

metaphors which are not specially characteristic of the project. The first, metaphors conventional to general discourse, are common uses of expressions such as "this work *paves the way*" (Mercy et al., 2017). The second are metaphors conventional to specialized scientific discourses which contribute to Sc2.0 (e.g. genetics, genomics, microbiology), such as "wild type" to describe the phenotype of the unmodified parent organism or "cell debris" to describe the unfiltered results of mechanically breaking up cells in a liquid suspension. While these metaphors are interesting in their own right and indicate that synthetic biology draws working concepts from a long history of metaphors in genetics and yeast research, they are not informative in terms of what new conceptualizations the Sc2.0 project advances or how Sc2.0 sits in the special discourses of synthetic biology.

In what follows, I employ Lakoff and Johnson's (1980) convention of indicating metaphors in upper case and individual metaphorical expressions in ordinary sentence case. In all quotes illustrating metaphorical expressions, the italics highlighting the metaphor are my own.

Analysis

The single most characteristic metaphor of the Sc2.0 project is the project name itself. *Saccharomyces cerevisiae* 2.0 can be understood as metaphorical in at least two senses. First, Sc2.0 draws on the metaphor GENOME IS A COMPUTER PROGRAM, envisioning the yeast genome as an operating system which can be upgraded from 'version 1.0' to 'version 2.0.' The project's central coordinator, Dr. Jef Boeke, draws on this metaphor in communicating with the popular press, describing Sc2.0 as "essentially swapping out the code, if you will, in a living yeast cell with a sort of 21st Century version of the operating system" (Stein, 2017). This metaphor underlies other metaphorical expressions characteristic of the project, as detailed

below.

However, Sc2.0 can also be read as a metaphor in another sense which points toward a methodological problem and a theoretical question. Sc2.0 draws on the metaphor ENGINEERED YEAST IS *SACCHAROMYCES CEREVISIAE*. We could say that all species identifications are metaphorical in referring to some new organism in the same terms as a previously categorized organism, even though the two organisms are not 'really' the same thing. The species assignation patterns the target – the new organism – after the source – some already identified organism – making some features of the new organism more important and easy to see and others less important. Scientists, in treating the engineered yeast genome as *Saccharomyces cerevisiae* by naming it *Saccharomyces cerevisiae* 2.0, are indicating that the engineered genome and other *S. cerevisiae* genomes are the same thing in a particular organizational schema. Whether this and other species identifications are metaphorical requires drawing lines around the canonical meaning of *S. cerevisiae* and other species designations.

Notwithstanding their inestimable value in defining the centrality of metaphors to language, a major problem with Lakoff and Johnson's (1980) theory of metaphor is that it requires identifying a primary or canonical meaning of any potentially metaphorical term. Identifying metaphors in contrast to non-metaphorical language requires drawing boundaries around canonical uses to separate them from metaphorical ones. And yet, these core or literal meanings are both fluid and elastic – changing over time – and discourse-specific. What functions as a metaphor in one discourse community may function both as a central meaning and a literal mode of operation in another (a point explored in more detail for scientific metaphors by Semino, 2008). Identifying metaphor within a discourse community, too, requires establishing some core or more literal meaning (e.g. Pragglejaz Group, 2007).

The expression "genetic code" is a pertinent example. Genetic code has long since ceased to be a metaphor in at least three senses. One, the dominant understanding of genetics has been fashioned to make current accepted knowledge about DNA sequences fit the core definition of "code." Two, "genetic" represents a primary meaning of the word "code" widely recognized in dictionaries; the Oxford English Dictionary online, for example, lists one meaning of the verb "code" as "to be the genetic determiner of," dating the use from a 1962 paper in the *Proceedings of the National Academy of Sciences*. Three, scientists manipulate DNA sequences in ways congruent with other widespread applications of the word "code." Similarly, while "gene editing" may still be treated as a metaphor in popular media, geneticists work with DNA in ways captured by the 'ordinary' or core meaning of "editing," and "gene editing" as a standard expression in scientific discourse is largely not understood as a metaphor by scientists who use it. Scientists are, one could say quite literally, *editing* a genetic code which has been made both code and editable through the work of twentieth and twenty-first century genetics. Similarly, most of the metaphorical expressions used in these seven articles have become so naturalized to the work of genetics, genomics, and synthetic biology as to no longer be metaphors at all in those discourses, in that their primary meanings have grown to encompass the genetic use. In this respect, a more useful understanding of metaphor in this case might come from Nietzsche's (1992) argument that all language is essentially metaphorical in that we never use words to describe something entirely new but always in terms of something already seen.

To avoid the technical question of whether any given expression is or is not a metaphor and focus on the conceptual reasons for examining these metaphors in the first place, I consider them here as schema for conceptualizing synthetic yeast rather than questioning whether scientists 'really' edit or map or capture chromosomes in a literal sense. The interesting

questions in this case have much less to do with drawing boundaries between literal and figurative usages than with how metaphors function as tools for constructing Sc2.0 through the interpretive schema they invoke. The following analysis is comprehensive; excepting conventional metaphors as already noted, all metaphorical expressions in the corpus are described in the following categories. Quoting every instance of a metaphorical expression would exceed space limits, so exemplars are cited for brevity.

GENOME IS A COMPUTER PROGRAM

"Bugs" and "debugging"

The most common metaphor across the corpus, GENOME IS A COMPUTER PROGRAM, is common not only to synthetic biology but to earlier genomics discourse (Hellsten and Nerlich, 2011; Nicholson, 2013). In analyzing international newspaper articles about synthetic biology published between 2007 and mid-2010, Hellsten and Nerlich (2011) observed journalists describing "codes, booting up, software, hardware, programming, executing and tagging," extending the "codes and software" (383) language prevalent in the previous decade's discussions of the human genome project (Nerlich and Hellsten, 2009). In this corpus, the computer metaphor is extended even further via expressions involving "bugs" and "debugging."

Wu and coauthors' (2017) article describing synX, featuring "bug mapping" in its title, defines "bugs" as "fitness-reducing sequence variants" (eaaf4706). "Debugging," therefore, "is imperative for successfully building a fit strain encoding a synthetic genome" (ibid.). Thus defined, bugs and debugging are central to the Sc2.0 project because one of the three central principles guiding the synthetic genome design is to maintain wild-type fitness (Dymond et al., 2011). Depicting an organism's genome as its operating system, common in popular press

articles (Hellsten and Nerlich, 2011; Stelmach and Nerlich, 2015), also coheres with understanding the cell as oriented around a genome in direct control of its other, essentially mechanical parts (Keller, 1995). The computer program metaphor participates in recreating a version of genetic determinism that sees the genome as the director in charge of cellular operations, subordinating other parts of the cell to necessary but subsidiary positions.

In 2011, Hellsten and Nerlich pointed out that the computer programming metaphor as it is employed in synthetic biology creates an additional level of hierarchy: beyond giving the operating system control over the cell, the metaphor gives the synthetic biologist control over the operating system. The synthetic biologist becomes the programmer, the person with the capacity and expertise to write and alter the program. The synthetic biologist as programmer of the cell, however, does not work in the same fashion as the programmer of the computer. Computer programmers write new code as well as editing existing programs. Even if most programs are now constructed via standard programming libraries and patchwriting – a variant of plagiarism which Rebecca Moore Howard (1995) identifies as borrowing heavily without copying exactly – the computer programmer can and sometimes does write wholly new lines of text using component 'words' or expressions according to the logic of the programming language. The synthetic biologist as 'programmer,' however, *never* constructs wholly new genetic sequences in a cognate fashion. While genes copied from pre-existing ('natural') organisms can be edited, and while whole genes can be combined together in new ways, biologists do not yet understand enough about how DNA carries information to subdivide genes into smaller functions, or even whether genes *can* be so subdivided. Synthetic biologists can edit but not use words to write completely new sentences, a form of making text which Porcar and Paretó (2012) and others call more akin to DNA "printing" or "copying" than to "writing." The computer program metaphor

thus enables a mode of understanding which grants scientists a greater degree of scientific control over the genetic language than they exercise in physical practice.

The computer programming metaphor's extension in Sc2.0 continues overextending that sense of scientists' control over genetic systems. Debugging a computer program is a process of making changes to portions of code responsible for deviation from the desired performance of the program – of fixing errors defined in terms of the goals of the programmer. Correcting errors requires being able to recognize errors. Computer programmers recognize errors as not cohering with the grammar of the programming language, or at least not doing so with the desired effect. Debugging means rewriting code so that it *does* make the desired kind of sense.

Scientists constructing Sc2.0 define "errors" in the redesigned synthetic yeast genome as genetic modifications which are correlated with slow yeast growth. The scientists are not, however, able to identify the modification responsible for "growth defects" (as instances of sub-wild type growth are called) as deviations from accurate genetic language. Rather, scientists retrace their steps, examining strains incorporating smaller and smaller sections of synthetic DNA, until they identify the synthetic modification associated with slow growth. They then *remove that change and revert to the original wild-type sequence*. Debugging Sc2.0 is not a process of *correcting* a recognizable error by making another change, but of *removing* errors by undoing a change. The biologist-programmer has made an error in modifying a well-functioning program – the original yeast genome – and can only correct the error by undoing the modification.

Bugs and debugging appear throughout five of the seven pieces in phrases such as "after correcting nonsynonymous mutations in *MOB2*, the synVI strain still had a noticeable growth defect or 'bug'" (Mitchell et al., 2017) and "use of a competitive growth assay established that

the debugged synX strain exhibits high fitness" (Wu et al., 2017). Neither expression appears in the article describing the 3D organization of genomes containing synthetic chromosomes (Mercy et al. 2017), which is unsurprising given that this paper describes analyzing synthetic chromosomes constructed by other laboratories rather than construction itself.

More surprisingly, the authors describing the construction of synV do not use these terms even though they describe work congruent with what is called "debugging" elsewhere. Instead, these authors use the idea of building a "'perfect' designer chromosome V" to frame how they "corrected all mutations found—including duplications, substitutions, and indels" (Xie et al., eaaf4704). Working *backward* to perfectly match the synthetic chromosome sequence specified *in silico* appears, for this group, to have supplanted correcting mistakes to work *forward* toward a functional, fast-growing, "bug"-free version. The absence of the debugging metaphor highlights a difference in the orientation of this group in comparison to the other authors: rather than attempt to synthesize a chromosome which sustains wild-type growth rates, even if the sequence contains some small deviations from the original design which do not impede growth, they have attempted to precisely synthesize the specified sequence. Because bugs are defined in the project discourse as DNA sequences impairing growth rather than sequences deviating from the original specifications, bugs and debugging become less relevant to achieving "perfection."

"Refactoring"

A second programming-derived expression, "refactoring," appears in the design-focused article by Richardson and colleagues and in myriad conference and seminar presentations. According to the synthetic biologists who introduced the term to the field, refactoring aims to "improve the internal structure of an existing system for future use, while simultaneously maintaining external

system function" (Chan, Kosuri, and Endy, 2005). In a computer programming context, refactoring streamlines a program and makes it easier to manipulate without changing how the program works from a user perspective. In a synthetic biology context, refactoring similarly means maintaining the original "wild-type" behavior of an organism, changing genotype without changing phenotype, to simplify or rationalize the genome according to some logic of the biologist. Chan, Kosuri, and Endy (2005), in "refactoring bacteriophage T7," explain that in "convert[ing] the genome of a natural biological system, bacteriophage T7, to a more structured design," they were "inspired by the practice of 'refactoring,' a process that is typically used to improve the design of legacy computer software" (1). In the Sc2.0 project, refactoring work includes changing TAG stop codons to the equally functional TAA to make TAG available for encoding atypical amino acids, relocating tRNA genes from the sixteen native yeast chromosomes to a new "neochromosome" to increase the stability of the synthetic chromosomes, and eliminating suspected noncoding DNA to make the genome approximately eight percent shorter.

Refactoring does not imply that biologists perfectly understand DNA as a genetic programming language. Refactoring does, however, suggest that biologists see themselves as understanding that language fluently enough to be able to *improve* an existing program. Refactoring relies on and reinforces a theme common to the broader synthetic biology community: that biologists can improve nature, where the assessment criteria for judging improvement are held by the scientists. Synthetic biologists "improve" or "optimize" the functions of enzymes, pathways, and cells, small steps en route to larger goals of making biological systems more predictable and easier to engineer, themselves steps en route to harnessing biology to build a better future ("What's in a Name?", 2009). Refactoring participates

in this vision of biological systems as instrumental tools for serving an anthropocentric world.

Biological systems employed in laboratories have always been shaped to serve human needs, even when those human needs have been about understanding biological systems rather than about altering those systems to suit scientist-specified functions (Leonelli and Ankeny, 2013). The new move signaled by "refactoring" in synthetic biology has to do with the increased degree of scientific control in scientists' presumed ability to directly change and improve genomic DNA—that is, the system understood to directly control the operation of the organism. Beyond extending the implication of scientific mastery over the yeast genome, refactoring also extends the assumption that the yeast genome and other biological systems are materials that are better when they serve scientific interests and implies that scientists are the best arbiters of what the cell *should* need to function. Better, in this case, is a matter of making the genetic code easier for the scientist to understand and manipulate such that the primary user of the yeast genome is implied to be scientist rather than the yeast.

Looking at the array of metaphors previously documented in popular articles about synthetic biology, we can see that computer programming metaphors have become constitutive of the Sc2.0 project's work while domestic metaphors of stitching and sewing or cutting and pasting (Hellsten and Nerlich, 2011) have disappeared. It has become essentially impossible to describe the Sc2.0 project without relying on programming metaphors, not least because Sc2.0 itself is one of them. But by discussing Sc2.0 and not patchwork, collage, or piecemeal yeast, Sc2.0 becomes aligned with contemporary digital technologies and distanced from low-tech domestic labor.

Notably, while genomes are widely discussed as programmable, cells are not discussed as computers and, at least in this context, individual genes are not described as program functions.

This distinction will become important, as I address in the conclusion, in appreciating how metaphors mix, operate across biological scales, and shape what synthetic yeast becomes.

CHROMOSOME IS A LANDSCAPE

A second metaphor operating at the gene, chromosome, and genome level envisions that the CHROMOSOME IS A LANDSCAPE. *loxPsym* sites employed in the SCRaMbLE system are located at genomic "landmarks" (Mercy et al., 2017). Chromosomal regions with repetitive sequences are "nonmappable" when studying the 3D organization of genomes incorporating synthetic chromosomes (Mercy et al., 2017), while individual growth defects can be "mapped" to a "design feature" (Mitchell et al., 2017).

As with computer metaphors, landscape metaphors are prevalent in earlier synthetic biology discourse and preceding genomics discourses, with "genome mapping" the most obvious and widespread example. These metaphors made scientists behind the Human Genome Project and similar endeavors into pioneers, bravely exploring new territories, creating maps for the benefit of those who would follow, and pushing the scientific "frontier" (as Leah Ceccarelli has explored in detail in her 2013 book on the frontier metaphor). The resonance of landscape metaphors in Sc2.0, however, is slightly different. Rather than exploring new territory and creating new maps, construction workers on synthetic yeast are using maps as tools to work within the landscape they describe—they are inheritors of the metaphors which preceded them. Like a civil engineer, by having the map laid out before her, the Sc2.0 synthetic biologist is able to exercise control over the landscape and strategically operate upon it. Landscape metaphors, as with computer metaphors, reinforce the control scientists possess over the yeast genome. The kinds of control these two metaphors enable do not conflict, but contribute to how the yeast

genome is understood as a complex informational object: in addition to programming and debugging, reading and writing, scientists can locate and place "markers" within the genome.

CHROMOSOME IS A PHYSICAL OBJECT

Distinct from landscape metaphors, chromosomes are also conceptualized as physical objects and structures. Chromosomes *are* physical objects, inasmuch as any microscopic structure invisible to the human eye is imagined, invented, or brought into being as a part of the physical world through technologically mediated observation (Paxson and Helmreich, 2013). In the same sense, however, we might just as easily say that chromosomes *are* landscapes, or that DNA *is* a programming language. Read against other ways of conceptualizing chromosomes, the terminology of physical objects functions as another metaphor in activating a different conceptual schame for constructing what the chromosome is.

Chromosomes are "captured" by scientific techniques used to understand how they interact. They are "tethered" and have "trajectories" within the nuclear space (Mercy et al., 2017). Chromosomal "arms" are "capped" by telomeres, with regions that can be "cleaved" and "tagged" – expressions found across the whole corpus. Each chromosome is being constructed from "chunks," subdivided into "minichunks" and attached to each other to form "megachunks," any of which are sometimes more generally referred to as "building blocks" (Richardson et al., 2017). Significantly, unit parts of chromosomes are never described as "bricks," as the brick metaphor is conceptually associated with parts-based approaches to synthetic biology, the BioBrick standard for biological parts, and the nonprofit parts-sharing BioBricks Foundation and international Genetically Engineered Machine (iGEM) competition with which that standard is associated (Shetty et al. 2008), none of which are associated with the Sc2.0 project. "Brick," in

synthetic biology discourse, invokes a set of assumptions and way of seeing which constructors of Sc2.0 do not want to bring to bear on their work.

Physical object schema reinforce the idea that biological systems are or can be made *modular* – a common guiding principle across synthetic biology (Kendig and Eckdahl, 2017). In combination with computer and landscape metaphors, they also reinforce that genetic sequences are complex objects with characteristics that can be understood as similar to multiple distinct source domains; chromosomes are simultaneously information-carrying and physical objects which can be viewed in relation to each other from a distance or picked up, moved around, subdivided or stuck together. Again, however, while chunks might be "introduced sequentially from left to right" (Richardson et al., 2017), "assembled" or "integrated" (Zhang et al., 2017), they are not "stitched" or "sewn." Sc2.0 constructors depict themselves as high-tech programmers or engineers or builders of complex objects, but not as domestic laborers.

A visual metaphor: Sc2.0 is a jigsaw puzzle

Alongside the name *Saccharomyces cerevisiae* 2.0, the project is branded through a logo (figure 1) depicting a brightly orange-fluorescing budding yeast cell on a black background as a jigsaw puzzle with two pieces yet to be placed to complete the picture. While the jigsaw puzzle metaphor does not appear in the texts of the special issue, this image coheres with expressions that make the cell the product of assembling modular parts.

GENOME IS AN CUSTOM PRODUCT

Both chromosomes and the genome are also depicted as authentic or "designer" products, expressions that can be related to two different relevant discourses with different resonances.

"Designer" is a derivative of "design" as used in the classic design-build-test cycle of engineering, widely co-opted by synthetic biologists to describe what they do (e.g. the "'design-build-test-debug' working loop" described in Shen et al., 2017). "Designer chromosome" is a short step from "design a chromosome." But "designer" and "to design" also activate substantially different resonances in general discourse, where "designer" is associated with fashion and other forms of high-culture consumption. "Designer genome" suggests that Sc2.0 is unique, desirable, and valuable as a rare or limited authentic product. In that sense, "designer genomes" appear to challenge the trajectory of synthetic biology that drives toward making whole organisms standardized platforms, commodifying cells as products which can be mass-produced and widely used for routine purposes (Calvert, 2008). While component parts of the synthetic yeast genome may be standard modules, chunks, or building blocks, the results of assembling those parts are not presented as standardized, but as *customized*.

Bridging biological scales and whole-organism metaphors

As numerous metaphor studies have documented and theorized mixed metaphors (e.g. Ceccarelli, 2004; Condit, 1999; Kimmel, 2010), finding mixed metaphors in the literature of the Sc2.0 project is unsurprising. Perhaps more surprising, given the project's position as a "vanguard" (Hilgartner, 2015) or aspirational forerunner of whole-genome engineering, is how little work these metaphors do independently or in concert to connect characteristics of the gene, chromosome, or genome with those of the whole organism. Most operate at the level of the chromosome, conceiving of the chromosome as a landscape which can be mapped or marked, a physical object which can be captured or constructed out of building blocks, or a computer program which can be debugged or refactored. Genes are located and relocated on chromosomes.

Chromosomes are modules of the genome in the sense that debugging each chromosome contributes to debugging the genome, though it is unclear whether the whole genome will still have bugs even if all individual chromosomes are bug-free. But these metaphors do not extend to say anything about how the chromosomal landscape relates to the whole organism containing it – or enveloping it? or housing it? – or how reprogramming the cellular operating system relates to changing the cell which operates it.

Two exceptions stand out. Refactoring, understood as changing genotype without altering phenotype, creates a relationship between the thing being refactored – either the genome or any given chromosome – and its "output," that is, the whole cell's behavior which, per the refactoring metaphor, remains the same despite changes to the program. In addition, three papers (Mitchell et al., 2017; Shen et al., 2017; Xie et al., 2017) observe that synthetic chromosomes "power" or "are capable of powering" yeast cell growth, making the cell a machine or computer and the genome its engine. Yet, these metaphors are never employed at the cell or whole-organism level; the yeast cell or *Saccharomyces cerevisiae* is never described as a computer or a machine. Indeed, the whole organism is analogized only in the project's logo (figure 1), which might be read as emphasizing the modularity of the cell as a metonym for the much less recognizably depicted genome.

Together, the mixed or nested metaphors applied at the chromosome or genome level and the relative lack of whole-organism metaphors make space for the whole synthetic organism to have emergent properties not necessarily predicted by the characteristics of its parts. The cell is conspicuously *not* invoked as merely the higher structural level of its components. On the contrary, that a mixture of metaphors is useful for genomes, chromosomes, and genes suggests that it might become appropriate to bring in a new metaphor to describe the properties of a whole

organism with a synthetic genome. The implication is that the properties of that organism are not necessarily simply constrained by the properties of the synthetic genome. By leaving this space – which could have been filled by constitutive metaphors applied to the whole cell, but is not – as well as through descriptions of "designer" genomes or chromosomes, the Sc2.0 literature does not discursively construct the synthetic yeast cell as a standardized module as might be expected. Instead, it implies that while the whole cell can be anticipated to emerge from the assembly of its chromosomes, that cell will be a unique construction with features which may not yet be completely understood.

Discussion

Metaphors as arguments for engineering whole organisms

In 2000, American systems biologist Bernhard Palsson forecast that future synthetic biologists would "move from talking about genetic engineering of single genes, to what may become known as 'genome engineering,' where the whole organism is the context of the design" (Palsson, 2000). The Sc2.0 project might be easily be seen as a step in that direction. On the basis of this analysis, however, Sc2.0 seems to present a path to engineering whole organisms that does not involve designing the whole organism at all. Instead, component parts of the organism are designed with the implication that the whole will emerge from the aggregation of its components. Like the suggestion made by its jigsaw puzzle logo, assembling the chromosomes which constitute the primary unit of operation for Sc2.0 will presumably cause the complete image of the whole synthetic yeast to appear. Chromosomes, and perhaps even the whole genome itself, serve as metonyms for the whole organism—that is, parts which stand in for difficult-to-grasp wholes to "convey some incorporeal or intangible state in terms of the

corporeal or tangible" (Burke, 1945, 506). The metonym allows programming the whole organism, as an abstract 'living thing,' to become the more easily grasped problem of programming the chromosome so that grappling with engineering 'life' can be elided or deferred.

Yet, the characteristics of the whole may exceed the sum of the characteristics of the parts. The characteristics of the whole are not pre-structured by metaphors applied to the parts. The whole may therefore be surprising when it is seen, in the same sense that Ankeny and Leonelli (2011) and others point out that model organisms are useful in part because they are able to "surprise" researchers when the complexity of the organism exceeds the complexity captured in the scientist's understanding of the model. The whole organism will become an "epistemic thing" in Rheinberger's (2005) sense of a material scientific object which is "inherently polysemous" and therefore epistemically generative, a "motor of knowledge acquisition" precisely because continuing to investigate it can reveal previously unseen things. This space for surprise, together with metaphorical expressions about "designer" genomes, appears to challenge the idea that synthetic biology is necessarily extending modularity and standardization to the whole-organism level. At its current state of progress, Sc2.0 does not seem to advance a vision of engineered organisms as standardized components so much as engineered organisms as designer objects.

Metaphors and constructing life

Scientific metaphors are tools for enacting future worlds and should enter into conversations about what new worlds are desirable to create. Studying metaphors that shape synthetic biology is important for understanding how synthetic yeast and its potential future synthetic kin are being made, providing entry points for discussing how such organisms *might*, *could*, or *should* be

made. Conversations about the ramifications of communication in synthetic biology thus need to include how metaphors are employed in *disciplinary scientific discourse*. How scientific metaphors are mobilized in broader public discourse and scientific popularizations becomes an *additional* set of considerations. This same argument can be applied to science and scientific discourse in general. What makes synthetic biology worthy of special consideration are the tools synthetic biologists have at their disposal for making things through the images of their metaphors.

Conventional (understanding-focused) biology patterns its objects of study through its metaphors by making knowledge that reinforces particular terministic screens and, therefore, selective descriptions of what biological systems are understood to 'really' be. Because those descriptions are then used to construct or choose tools for further research, including cells, in iterative cycles of making things to make knowledge to make things, metaphors alter physical biological systems as well as knowledge about them. In synthetic biology, fewer intermediaries are involved because the scientific goal is itself to alter the physical biological system, not (or at least in addition) to describe it. Consequently, synthetic biologists are able to implement their conceptual understandings about biological systems more quickly, more directly, and in ways shaped by different physical tools. And, importantly, synthetic biologists are applying those tools at the level of genomes – that is, at the level to which current paradigms ascribe the most direct control over the operation of whole cells and whole organisms.

By making yeast something which can be debugged and refactored, the synthetic yeast project is changing the possibilities for human-yeast relationships. Through discourse that treats DNA sequences as code, geneticists have made it possible to decode, encode, and recode genes. Through discourse that treats cells as computers, synthetic biologists make cells increasingly like

computers and move toward a future in which cells can be programmed, loaded with applications, and used to make products and solve problems. Through discourse that treats scientists as programmers of DNA, synthetic biology positions humans ever-increasingly as controllers of and masters over biological systems. Synthetic biology is thus primed to reinvigorate and strengthen narratives of humans as masters who can and should dominate over other species, in contrast to much of the environmentally minded rhetoric of the late twentieth century.

These discursive tools for making incrementally new worlds could, so the mantra of science and technology studies goes, always be otherwise. They are contingent, not inevitable. Consequently, it is both possible and necessary to consciously consider how what we want living things to be and what kinds of relationships we want to have with them – to ask the questions Bellacasa, Mol, Tsing, and others ask about "the effects of our accounts on the composition of things" (Bellacasa, 2011).

The Sc2.0 project is positioned to be an important forward step in synthetic biology's development. As the *first* eukaryotic genome synthesis project, it invokes the possibility of *further* eukaryotic genome synthesis projects. Choices made in the Sc2.0 project can be expected to influence the structure of those future projects. The vision espoused by Sc2.0 about how to make organisms engineerable may therefore have major ramifications for the evolution of the field and, perhaps, for the evolution of synthetic life.

Limitations and conclusion

An important limitation of this study is that I can draw no comparisons with similar analyses of metaphors in the peer-reviewed literature of other synthetic biology projects. While a number of

publications have examined metaphors in popular media accounts of synthetic biology, little work appears to have dealt with the peer-reviewed literature. Remedying this deficit would be useful to scholarship in rhetoric of science, science and technology studies, and science communication. Such studies would, furthermore, help scholars in these communities identify and spend more time in their common ground. Following the discursive practices of scientists through scientific publications – the most tangible and well-travelled instantiations of scientific discourse – is a useful complement to following the physical practices of scientists in their laboratories, where the interior workings of scientific texts are more difficult to see. Rhetorical microprocesses inside these texts constitute a primary means by which scientists constitute, codify, and share new knowledge. Amongst these, metaphors are central to how scientists create shared understandings of new things, of how they indicate what is indeed seen to be new, and of how they position themselves amongst other scientists. All of these need to be ongoing questions of interest in how synthetic biology and other technosciences take and make shape.

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Notes

i *in silico* refers to symbolically designing, in a digital computer system, something which could be physically realized as a biological system. *in yeasto* refers to physically realizing something in live yeast. Both riff on terminology common in biology of performing experiments *in vitro* and *in vivo.*

ii Stop codons signal to ribosomes that the ribosome has reached the end of the portion of a messenger RNA transcript that should be translated into a protein.

iii Non-essential genes are genes which can be deleted or inactivated without killing the cell. They are putative because they have been identified as non-essential through previous experiments inactivating one or two genes at a time, but this set may not perfectly overlap with the set identified when multiple genes are inactivated simultaneously.

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Table and figure captions

Table 1. Peer-reviewed articles about *Saccharomyces cerevisiae* 2.0 in *Science* (2017), vol. 355, issue 6329.

Figure 1. The Sc2.0 logo.

Tables and figures

Table 1.

Article title	**Focus***	**First and last author**
3D organization of synthetic and scrambled chromosomes	3D genome organization	Mercy, G.,… Koszul, R.
"Perfect" designer chromosome V and behavior of a ring derivative	synV	Xie, Z.-X.,… Yuan, Y.-J.
Bug mapping and fitness testing of chemically synthesized chromosome X	synX	Wu, Y.,…Yuan, Y.-J.
Deep functional analysis of synII, a 770-kilobase synthetic yeast chromosome	synII	Shen, Y.,…Yang, H.
Synthesis, debugging, and effects of synthetic chromosome consolidation: synVI and beyond	synVI	Mitchell, L.A.,… Boeke, J.D.
Engineering the ribosomal DNA in a megabase synthetic chromosome	synXII	Zhang, W.,… Dai, J.
Design of a synthetic yeast genome	Global design	Richardson, S.M.,… Bader, J.S.

*Across the yeast genetics community, chromosomes are typically numbered in order of size and referenced as chrI, chrII, etc. Standard nomenclature across the synthetic yeast project refers to the redesigned cognate chromosomes as synI, synII, etc.

Figure 1.