Design in synthetic biology

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Abstract

Significant transformations in biological technique and biological work are taking place in the aftermath of genomics. While existing accounts of genomics and biotechnology contend that species differences and evolutionary histories have undergone 'flattening' by molecular techniques and concepts, analysis of design practices in synthetic biology suggests that vertical aggregations of biological technique, substance and work are occurring. The paper analyses the movement of design processes into biology by examining software, diagrams and forms of collaboration intersecting in the production of biological constructs such as metabolic pathways, minimal genomes and biological standard parts. In characterising the design processes taking shape in synthetic biology, it develops the concepts of 'meta-technique' and 'meta-material.' The notion of design as a meta-technique shows how synthetic biology assembles techniques and renders them available via practices of collaboration and standardisation. The notion of meta-material suggests ways of thinking about the dynamism of living things infused by models, constructs and layered work-processes. The practical re-deployment of biological techniques we see in the design software, the development of increasingly extensive and interlinked biological constructs assembled by design, and the shifting enrolments of biological work associated with design as a de-coupled work process alter what counts as biological work and what counts as biological substance. The increasing salience of biological design has significant implications for how we conceptualise participation in biotechnology and biomedicine more generally.

Design in synthetic biology

In the series of momentous changes associated with molecular biology, recombinant DNA biotechnology, genomics and systems biology, synthetic biology can be seen as altering how people work on biological substance. Proponents of synthetic biology advocate 'engineering design principles' – abstraction, modularity or 'decoupling', and standards (e.g. (Forster & Church, 2007; Kitney, 2007; Marshall, 2008; R. Weiss, 2007; Andrianantoandro, Basu, Karig, & R. Weiss, 2006)) – in order to re-fashion molecular biology as biological engineering, thereby economising the time, effort and skill needed to create biological constructs with desirable properties. Numerous review articles and nearly all of the major public pronouncements concerning synthetic biology cite design principles. The principles mould the structure of workshops, conferences, funding, publications and patents. Synthetic biology design principles have been adopted and reiterated by policy analysts, funding bodies, science journalists and social scientists. For instance, in perhaps the first social science monograph on synthetic biology, Paul Rabinow and Gaymon Bennett use the terms 'design' or 'designing' close to 300 times without discussing it explicitly (Rabinow & Bennett, 2008).

This paper seeks to problematise the practice of design in synthetic biology. This is not to say that design cannot be done in biology, or that it should be done in some ways and not others. Rather, the paper departs from the question of how biological *work, techniques* and *materials* are being re-configured under the rubric of *design* in synthetic biology. The significance of this re-configuration is multiple. Firstly, synthetic biology epitomises what Kaushik Sunder Rajan, following Michael Fischer, has described as 'new emergences in the life sciences'

(Sunder Rajan, 2006, pp. 279-280). Whatever else synthetic biology might do, its emergence has rapidly enrolled large numbers of scientists and garnered substantial public and private funding. Design, I will argue, is an important vector of the contagious intensity of synthetic biology. Secondly, the rapid emergence of synthetic biology can be read as another symptom of the 'end' of molecular biology as a twentieth century life sciences discipline (Rheinberger, 2008, p. 304). While many working biologists remain somewhat sceptical about or adopt pragmatic attitudes to the advent of synthetic biology, treating it mainly as a useful funding possibility and a potential vector of science legitimation or popularization, the practices of design rapidly developing in synthetic biology bring heterogeneous changes in the way biological work is organised and imagined, especially amidst proliferating genomes and other 'omes'. Finally, changes in the organisation and practice of biological work in turn affects what counts as biological substance, and affects how biological substance exists as such. Potentially, different ways of doing design imply different materialisations of the living. Importantly, different ways of doing design entail different patterns of connection, relation and participation running across science, technology, institutions and cultures. Across each of these facets – rapid emergence, transformation in how biological work is done, multiple materialisations of the living – design is writ large.

On the basis of engineering design principles such as abstraction, decoupling and modularity, many descriptions of synthetic biology divide it into three related, partially overlapping construction strategies (Balmer & P. Martin, 2008; Lentzos, Bennett, Boeke, Drew Endy, & Rabinow, 2008; O'Malley, Powell, Davies, & Calvert, 2008; Rinie van Est, 2007):

1. device-based standardised construction
2. mid-range problem-focused re-engineering of microbes as biotechnologies
3. whole genome engineering or cellular 'chassis' production

(Some analysts include other categories such as artificial cells or artificial DNA. They also fit synthetic biology.) These three design strategies are often aligned with the three principal North American public scientific spokespersons for synthetic biology: Drew Endy, Jay Keasling and J. Craig Venter respectively. The most prominent instance of device-based synthetic biology is probably the annual iGEM undergraduate synthetic biology competitions held at MIT, Massachussets, a competition that serves also to publicise the development of standards and libraries for biological parts or BioBricks. The most commercially and concretely promising problem-focused synthetic biology project would most likely be Keasling's work on the anti-malarial compound artemisinin (Dae-Kyun Ro, Kimberly A. Ho1, & Yoichiro Shiba2, 2006; V. J. Martin, Pitera, Withers, Newman, & Keasling, 2003). Finally, the most publicly visible event in the whole genome engineering approach to synthetic biology to date is arguably the publication by researchers of the first synthesis of an entire genome, an artificial genome labelled JCVI1.0 (Gibson, 2008, p. 1216).

Many existing definitions and characterisations of synthetic biology take at face value the claim that *design* can be done and is done according to *principles*. The fact that design is also an aggregate of practices, spanning a highly variable set of techniques, processes, materials, abstractions and sensations, and often standing on shifting economic and organisational ground is barely recognised. Actual biological design techniques and the practices of design are seldom discussed, even though they differ significantly from the already well-established practices of experimental design (usually focused on statistical validity) found in many scientific settings. Moreover, the instabilities and tensions within the very idea of 'designing things' that have been explored in other settings – especially in relation to the design of software and human computer interfaces – hardly figure in the many invocations of design in synthetic biology. The rather flat and neatly packaged descriptions of synthetic biology that pivot around broad and abstract engineering design principles normalize the direction and

aspirations of synthetic biology. Certainly, design principles can be found in the introductory pages of many engineering textbooks, especially those associated with software, electrical and electronic engineering (for example, a textbook on the structure of computer programs (Abelson, 1996) has been cited by several synthetic biologists). However, the widespread affirmation of these engineering design principles does not address the question of how such principles would practically, conceptually, materially and semiotically depend on a reorganisation of the techniques of molecular biology and genomics (cloning, sequencing, restriction enzymes, mutagenesis, RNA interference, etc) and hence a reorganisation of biological work. The principles cover over a multitude of heterogeneous dynamics and connections, and above all, conceal the strong connections between conceptions of design and ethical framings of action. If social scientists and analysts of synthetic biology or other versions of biological engineering ignore the grounding of design techniques in software, documents, databases, diagrams, and many textual, graphical and calculative devices, they skew analysis of synthetic biology in particular ways.

Above all, unquestioning acceptance of the principles offers little insight into how synthetic biology becomes credible and contagiously desirable as a way of working with biological substance. Arguably, the very term 'design' carries much weight here. It is freighted with many resonances and values in relation to contemporary products, architecture, media and services. Design techniques have, to date, been widely developed in industrial engineering, in service design, in media production, in software and hardware, in transport and infrastructure, in fashion and consumer goods, in architecture, urban spaces and landscapes (Margolin, 2002)). Moreover, as we will, design itself is particularly important in bringing particular ways of working and collaborating from network media into synthetic biology. These include the explicit imitation of the ethos of collaboration and openness of internet engineering (for instance, in the use of standards documents called RFCs (Request for Comments) first

developed by the Internet Engineering Task Force (IETF) to enrol participants in developing standards in the late 1960s); the proliferation of computer-assisted design (CAD) software for synthetic biology (e.g. GeneDesign, TinkerCell, Clotho and many others), a move that mirrors the automation of design in electronics and software engineering of the 1970s; the institution of online 'registries' and libraries for biological parts, a shift reminiscent of the boom in registries and libraries in object-oriented software design of the 1980s; the borrowing of constructs such as 'virtual machine,' 'network,' 'platform,' and 'refactoring' from software and communication engineering as a way of rendering biological processes as technological systems; the adoption of web-based collaborative platforms such as Wikis as a sign of collective openness; and the proliferation of eCommerce-style form-based websites to facilitate both design and purchase of synthetic biology products, both modes typical of the late 1990s and early 2000s web cultures. As design in the form of synthetic biology impinges on the life sciences and biotechnology, it brings with it collective imaginings of human capability from the more or less proximate practices of network media, electronic and software engineering. Under the rubric of design, practices and sensibilities coming from different places can begin to bear on biotechnology. From a critical design perspective, the examples of design software, standards for biological parts, biological chassis and platform design bear the imprint of wider design imaginings of the power to shape things across multiple scales and locations. The figure of the designer-engineer as an exceptionally decisive form of subjectivity looms large here too (see (Thackara, 2005) for a business-oriented vision of the designer).

Critical work on design principles and designer/engineers suggests that they lead very troubled lives in practice (Flusser, 1999; Margolin, 2002; Suchman, 2006). Design principles span many related activities and materials. They seek to smooth over the uneven, shifting connections between diverse practices, materials and settings using textual, graphical,

symbolic materials such as models and diagrams. Invocations of engineering design principles such as 'abstraction' or 'decoupling' function as serve as abstract, decoupled names for the more intensive processes that re-organise how, where and by whom things are made. The very separation of design and engineering from other technical skills rely on multiple practices, infrastructures, and knowledges of de-coupling, abstraction, and modularity. Design is always engaged in the development of what we might call 'meta-technique.' The widely-used 'meta-' prefix usually means something that abstracts from something else. To say 'meta-technique' in some ways only confirms what synthetic biologists themselves aspire to when they invoke design principles as a way of abstracting away the uncertainties and intricacies of biology. However, design in synthetic biology is also a meta-technical practice in the other sense of meta, what comes after or beyond. Design is a meta-technique in that it organises, groups, assembles and subsumes other techniques, practices, methods, protocols, knowledges, services, and infrastructures into specific arrangements, while at the same time, appearing to stand outside them. At the same time, because it brings new divisions of labour, a meta-technique also engenders, as we will see, processes of subjectification.

In synthetic biology, design confronts many different materials, techniques, knowledges, and forms of value (aesthetic, scientific, economic, moral-ethical). That is not unusual for design in any field. However, meta-technique in synthetic biology faces specific challenges, many of which centre on the engineering of heterologous biological substances. Borrowing a term from physics, we might say that meta-techniques in synthetic biology gives rise to 'meta-materials' (Nader & Ziolkowski, 2006). This second concept complements meta-techniques in several respects. The trans-contextual character of meta-techniques imbue biological susbstance with some profound instabilities. Meta-techniques materialize biological substance as meta-materials, materials whose properties are intensified or potentialised in ways that cannot be indexed solely either to life as inordinately complex, to mechanism as fully

designable. 'Meta-materials' characteristically take the form of constructs such as pathways, devices or networks. Yet, they mix contemporary network cultures' styles of working, collaborating and communicating with specific knowledges and practices concerning biological substance.

In the discussion below, I first discuss how attention to techniques can help situate synthetic biology more precisely than affirmation of general design principles. This section of the paper also develops the notion of design as meta-technique by tracking how extant biological techniques are currently being re-configured in a computer assisted biological design. Secondly, I explore how design as a meta-technique affects biological substance and renders it as a meta-material at the crossroads between biological and network cultures. I trace some of the borrowings of conventions, patterns of collaboration, and design practices from information and network cultures. The intense and rapid emergence of synthetic biology derives from such transcontextual movements. Design affects the mode of existence of biological substance in broader biopolitical frames. Finally, I address the question of subjectivities in synthetic biology. Design always points to the figure of a designer. Synthetic biology as a design discipline poses the question: who designs?

Techniques and the flattening of biological substance

In synthetic biology, *techniques* exist in a rather unstable state. They are at once generic, transportable, wide-ranging, and hybrid. Techniques, as we know from Michel Foucault's treatment of them in relation to formation of self (Foucault, Gros, Ewald, & Fontana, 2005), have no necessary connection to epistemological regimes, knowledge and truth. Techniques can be somewhat agnostic or generic in relation to knowledges, values, subjectivities, selfhood or personhood and even embodiment. There is something at once eminently superficial and yet precise and concrete about techniques. Because they have a fairly low-

profile, techniques often lead a polyphase existence. Less universal and abstract than concepts or mathematical functions, less fragile than the nested, interwoven structures of *technology*, techniques pass through a series of more or less temporary embodiments in individuals, groups, pedagogical systems, devices and institutions.

Techniques in the life sciences display a long history of surprise transpositions and reorderings. In her account of how cells became standard platforms for biological work in both biological research and medicine, Hannah Landecker advocates close attention to technique:

> Keeping an eye on practices, protocols, methods, technique, touch, or infrastructure provides access to the ways in which work on some life (nematodes, insects, yeast) reshapes human life by introducing systematic change into biological existence (Landecker, 2007, p. 234)

The cases she discusses drawn from twentieth century tissue culture are directly relevant to synthetic biology. Landecker's methodological emphasis on practices and techniques is premised on the fact that 'technologies of living substance' (1), as exemplified in tissue culture techniques of artificial parthogenesis, immortalisation, and cell fusion, have frequently short-circuited metaphysical debates about body, difference, time, vitality and substance. Hence, biological existence at any point in recent history can be better grasped from the perspective of technique and practice than from relatively abstract concepts of life, gene, heredity, reproduction or sovereignty. If synthetic biology too attempts to 'introduce systematic change into biological existence,' we should look for transformations in the techniques of working with living substance.

Accounts of 20th century biotechnology have usually agreed that the advent of recombinant DNA or genetic engineering technique (Cooper, 2008, pp. 31-3; Wheale & McNally, 1990,

pp. 3-4) decoupled biological substance from evolutionary processes. How did they do this? The techniques that defined biotechnology involved transfers of genetic material (as in bacterial recombination), borrowings (e.g. enzymes and other molecular constructs derived from extremophiles) and the utilisation of 'abnormal' transgenic events (transduction, horizontal gene transfer, transposons, etc.). A common trope for this dimension of biotechnology is *lateralization* or *flattening*. Versions of this trope can be found, for instance, in (Franklin, Lury, & Stacey, 2000; Parisi, 2007; Rose, 2006) as well commonly figuring in descriptions of economic globalization such as Thomas Friedman's *The World is Flat (T. L. Friedman, 2005)*. Nikolas Rose, for instance, writes:

> [I]n the interventions that proliferate in this flattened world, almost any vital element can, in principle, be freed from its ties to cell, organ, organism, or species, set free to circulate and to be combined with any other, provided certain conditions are met {Rose, 2006 #10, 16}.

The transfers and transpositions effected in biotechnology sheer away from external biological reference points such as species differences, attributes of specific organisms, ecological or physiological contexts. Lateralization is highly conditional, as the last part of Rose's formulation suggests: 'provided certain conditions are met.' There is never any complete lateralization, only partial lateralizations alongside resurgences of linearity or verticality (Pottage, 2006, pp. 143-44). Importantly, animating many of the processes of lateralization found in biotechnology, we find techniques that transpose biological elements between *in vivo* and *in vitro* settings. Transpositions between living and non-living allowed molecular biology as procedure or technique to move across many different life science settings (Rheinberger, 2008, p. 306).

A wide variety of molecular biological procedures have found their way into synthetic

biology. However, the tendency to move laterally has begun to yield vertical aggregates. The procedures or techniques of molecular biology have vertically aggregated in nested and convoluted biotechnical systems that array and concatenate techniques (for instance, in high-throughput DNA sequencing or synthesis) to produce data about biological processes. This largely *in silico* process of stacking, arraying and concatenating has allowed what seemed at the time gigantic technical feats of whole genome sequencing in the 1990s. While genomes might be seen as one of the larger flattened results of large-scale molecular biology, genomes come, as is well known , from the heavily parallelised and grid-like production processes of genome centres. Today, as genomes rapidly cycle through large-scale high-throughput sequencing, new layers of organisation further vertically aggregate techniques of molecular biology.

Meta-techniques in synthetic biology

It is possible to detect in synthetic biology some traits that both continue and diverge from this tendency to lateralize biological substance. Its dependency on commodity DNA synthesis can be seen as one such lateralisation. Synthetic biology is often presented as the inevitable consequence of fast and 'cheap' commercial DNA synthesis (Garfinkel, Drew Endy, Gerald L. Epstein, & R. M. Friedman, 2007, p. 1). Once long stretches of genetic material can be synthesised quickly and cheaply, then biologists and engineers can envisage new forms of experiment and prototyping, and can henceforth, in principle, discover and innovate more rapidly. DNA synthesis is a quite substantial biotechnology growth industry. Sponsorship of high-profile synthetic biology events such as IGEM (the annual international Genetically Engineered Machine competition) and conferences such as SB4.0 by DNA synthesis firms (e.g. DNA2.0, GeneArt, Integrated DNA and Coda Genomics) advertises these services. Commercial DNA synthesis promises 'an immediate and easy path from sequence databases

and DNA manipulation software to physical reality' (DNA2.0, 2009a). A customer enters a DNA (or sometimes amino acid) sequence into a web-based form and the gene synthesis service will deliver it in a few days or weeks (e.g. (GENEART AG, 2009)). Reliance on such services weaves synthetic biology tightly into digital economies, with all their network infrastructures, and distributed transactional arrangements.[1]

While DNA synthesis companies offer an 'easy and immediate path' (and hence, probably a flat one too) to researchers, they also usually do more than synthesise a sequence of DNA. They offer to design or help design a sequence of DNA for some purpose. DNA2.0 allows 'you to redesign entire gene sequences to maximize the likelihood of high protein expression, easy genetic manipulation, minimal promoter leakiness, and convenient protein purification by adding tags' (DNA2.0, 2009b). Here design of DNA sequences links closely to laboratory techniques and work. It makes manipulation easier, it minimises work or makes it more convenient.

Redesigning DNA is only one level of design in synthetic biology. DNA sequence design more generally brings a range of techniques to bear on the sequences. We can see sequence design software as one layer of the increasingly vertically aggregated techniques of working on biological substance. Other layers are begining to appear. For instance, *Gene Designer* is a software application that runs on PCs. The software was first described in an academic publication (Villalobos, Ness, Gustafsson, Minshull, & Govindarajan, 2006), and is now freely distributed by the Californian DNA synthesis company DNA2.0. Design here appears in several forms.

[FIGURE 1 ABOUT HERE]

The design promise of *Gene Designer* is stated clearly on the first page of the manual that comes with the software:

Gene Designer from DNA2.0 Inc. is tool [*sic*] for molecular biologist and synthetic biologist. This software enables the user to:

Design large and small DNA fragemnts [*sic*].

Optimize expression in desired hosts using codon optimization

. Build and Manupulate [*sic*] DNA from building blocks such as promoters and ORFS.

(DNA2.0, 2009a)

Again, the promise of optimized expression appears. Adding to that, it mentions 'large and small fragments,' and 'build and manipulate … from building blocks.' Practically, *Gene Designer* displays a palette of sequence elements, some proprietary to DNA2.0, others more generic, that can be dragged and dropped onto an iconic diagram of what will become a sequence. The process of design here, as in many other domains of new media work, consists in choosing elements from menus, dragging them and arranging them on screen. The list of the elements contained in the 'Design Toolbox' section of the screen include regulatory elements, codon elements, 'drug resistance cassettes,' and reporter proteins. 'Custom objects' based on any DNA sequence can easily be added. For instance, a design project might begin by finding a DNA sequence of interest in an online database such as GenBank, pasting it in a new ORF (Open Reading Frame). Alternately, it might start from a protein or enzyme amino acid sequence of interest, and then paste it in as a new amino acid (AA) sequence object that will be reversed translated back into DNA sequence. One might find a gene from a microbial database that confers resistance to some antibiotics or find a protein that could be biotechnologically or biomedically useful. In either case, the specific sequence would need to be flanked by various generic promotor, regulator, start and stop sequences. The actual codons that comprise the synthetic DNA construct can then be 'optimised' by the software to confer

optimum expression of the target protein construct in the chosen host. Once a design has been assembled using these components, *Gene Designer* can check it for errors, optimise it in various ways (for instance, for expression in different target organisms), check it for completeness, and then provide an estimate of the cost of synthesis. Finally, the software can send the sequence as an 'order' direct to DNA2.0.

In the way that it gathers different materials and spans a range of techniques, this relatively small software application mimics design software found in the software and electronics industries, but also in graphic, media and industrial design. In the layers of graphic diagrams and on-screen manipulation of DNA-based elements, *Gene Designer* differs from earlier 'gene design' software, even that of just a few years earlier such as *Gene Design*, a web-based sequence design application that first became available in 2006 (sricha11, 2006). However, *Gene Designer* itself represents a low-level design application, perhaps analogous to the assembly language programming tools common on personal computers in the 1980s. Already, research prototypes for synthetic biology IDEs (Integrated Development Environments) have started to appear. Software applications such as Genocad (Czar, Cai, & Peccoud, 2009), SynBioss (Hill, Tomshine, Weeding, Sotiropoulos, & Kaznessis, 2008) and Clotho (Clotho, 2008) range much further. They borrow visually and architecturally from software development environments such as Eclipse (Eclipse Foundation, 2009) or software such as AutoCAD for 2D and 3D design (Autodesk Inc, 2009). Like software development design platforms, or the engineering design software used for electronic circuits design (EDA – Electronic Design Automation), the objects, models, components and processes listed in the menus of these 'development environments' have been heavily de-contextualised in this software.

In *Gene Designer* everything on the palette of components is still ultimately a DNA sequence yet the classification and iconic rendering of the sequences as small icons that can be dragged

and dropped onto a 'new object' tends smooth over to how and by whom new sequences are put together. There is a certain deliberate superficiality to the design practices here. They consist in browsing lists of components, cutting and pasting, dragging and dropping components onscreen, applying various commands to selected components, and then ordering the DNA construct via a commercial web service. Their arrangement of DNA on screen as colourful iconic components connected by arrows and lines renders biological constructs as superficial in a literal sense. Design software can be seen as propagating shallow understandings of biological context, simplifications of cellular or extra-cellular interactions, and even a reductionist understanding of the dynamics of genome transcription. However, even in *Gene Designer,* each component of the 'Design Toolbox' running down the left hand side of the screen embodies a technique of combining, separating, connecting, sorting, signalling, expressing, or reporting drawn from the last four or five decades of molecular biology. For instance, *Gene Designer* displays a set of components called 'recombinases'. The different components include the sequence for enzymes such as Cre (Cyclic Recombinase) recombinase (1029 bases) and corresponding sequences for recognition sites such as loxP (Locus of Chromosomal Crossover in bacteriophage P1 -34 bases). Together the two Cre-LoxP components help deal with difficult topological manipulations of tissue in organisms. They offer the possibility of designing a construct that could perform 'site specific recombination' using Cre-Lox recombination, a technique patented by Dupont in the 1980s {Enquist, 1989 #124} itself drawing on research done in the 1970s. Subsequently, during the 1990s, Cre-Lox site-specific recombination was adapted for use in model organisms such as mice (Akagi et al., 1997, p. 3), and the technique has been useful in tissue-specific research into complex cancer and immune system. While this particular technique – Cre-Lox recombination – is not very central in current synthetic biology, the important point is that the technique embodies an attempt to deal with context, interactions, and variabilities encountered

in assessing 'role of genes in complex processes' (Akagi et al., 1997, p. 3). Almost every entry in the 'Design Toolbox' enfolds a similarly complex weave of techniques, patents, research efforts and responses to specific experimental problems (for instance, mouse models have been developed to help explore the dynamics of sporadic cancer (Willimsky & Blankenstein, 2007)). In the compressed space of the software interface, the history of molecular biology as technical accomplishments is re-rendered as an expanding tree of menu options. In the same way, graphic design or page layout software presents a palette of strokes, brushes, shapes and effects largely derived from the history of print and image cultures

Design software of this kind may seem rather trivial. The fact that such software is freely available on the web does not mean that design work is immediately transformed. Access to other resources and skills would inevitably be needed to make use of it. However, I would argue that the evident superficiality of the design software begins to differentiate the practices of synthetic biology from antecedent technical practices in molecular biology and genomic sciences with their focus on flattening of biological substance. While everything onscreen in *GeneDesigner* is still ultimately expressed as a DNA or amino acid sequence, those flat sequences are beginning to be laminated into other forms of aggregate order. The proliferation of increasingly sophisticated biological design software (see the list of current applications in (Purnick & Ron Weiss, 2009) can be regarded as migrating biological work into a process that is no longer primarily concerned with experiment or knowledge production, but with the organisation of work, production and innovation. Design software and design environments signify an effort to configure the flattened biological substance of biotechnological and molecular biology as subject to a multiplicity of techniques coordinated on an elevated surface (the screen). Each added facets of design software represents an effort to re-stage biological techniques. While not all techniques can be rendered in the software setting as components to be assembled in a model, the general tendency to reassemble the biological

techniques into a vertical aggregate collection holds sway. Alluding to synthetic biology's divergence from molecular divergence, Alain Pottage suggests, '[w]hat is significant about synthetic biology is not (just) that it suspends evolutionary genealogies, but that it collects biological elements into digital media and modes of organization' (Pottage, 2006, p. 146). The act of *collecting* is particularly significant in making meta-materials.

Collecting: pathways, platforms and chassis as meta-materials

What have the design processes appearing synthetic biology produced? In the published literature of synbio, we see an abundance of practices presented as design techniques. We also see many constructs presented as products of design. They include 'pathway,' 'platform,' 'chassis,' 'gate,' 'switch,' and 'oscillator.' For instance, a relatively early synthetic biology paper authored by Chan, Kosuri and Endy entitled 'Refactoring Bacteriophage T7' (Chan, Kosuri, & D. Endy, 2005) applies the software design technique of *refactoring* to a relatively small viral genome. The paper reports, '[h]ere, we converted the genome of a natural biological system, bacteriophage T7, to a more structured design.' In software design, the term 'refactoring' refers to

> a disciplined technique for restructuring an existing body of code, altering its internal structure without changing its external behavior. Its heart is a series of small behavior-preserving transformations. Each transformation (called a 'refactoring') does little, but a sequence of transformations can produce a significant restructuring' (Fowler, 2008)

Refactoring is an example of a design meta-technique that takes existing technical objects or materials and reorganises them. As a result, they take begin to act as meta-materials, materials whose properties are difficult to attribute to a single domain of materiality. In Chan, Kosuri and Endy's work, the result of the re-factoring process is T7.1, a version of the bacterial virus

or bacteriophage T7 first discovered in the 1940s. A very small genome is treated as a 'body of code' amenable to small transformations that render it more usable by others for other purposes. In this case, individual functional genetic elements were separated out by inserting endonuclease restriction sites (3). Without substantially altering any biological function, re-factoring readies a specific biological substance for wider participation in processes of design, modification, standardisation and experimentation. Many synthetic biology projects entail 're-factoring' processes. Judging by the design practices appearing in synbio to date, the key question is: what almagam of techniques render biological substance susceptible to further design?

Meta-material is marked by the presence of increasingly 'heterologous constructs.' Recombinant DNA techniques had already treated biomolecules such as enzymes as technical elements inside the cell rather than outside it (see (Watson, 2007, pp. 75-106)). However, the scale of the constructs beginning to appear in contemporary synthetic biology is of a different order. In the oft-cited work of Jay Keasling's group (V. J. Martin et al., 2003), the authors describe how they engineered a new metabolic pathway in the standard biological model organism, *E.coli*, to produce a precursor chemical compound, amorphadiene, for the anti-malarial drug, artemisinin, a drug currently derived from plant sources such as Chinese wormwood. Martin and co-researchers reportedly added a complete metabolic pathway to *e.coli* rather than modifying existing metabolic pathways. As they say, 'we chose to bypass this pathway [the DXP pathway that produces the precursor, amorphadiene] by engineering the expression of the *S. Cerevisiae* mevalonate pathway in *E.coli'* {Martin, 2003 #547, 797}. The engineered pathway is 'heterologous', or as software designers might say, 'orthogonal' to the existing metabolic pathways in *E.coli* because there is little correspondence or interaction between the existing and added structures. If the introduced pathway intersected with existing pathways in *E.coli.*, it might be subject to 'unknown physiological control elements' (797).

Hence, whatever else it achieves, one index of the practical outcome design in the context of synthetic biology will be the construction of increasingly extensive heterologies.

If design as meta-technique constantly corrals and aggregates traits present within biological substance, then the limit case would be a purely heterologous construct, a biological substance that has become generic meta-material, capable of indefinite variations and modifications. One version of this aspiration to such a mutable materiality can be seen in the paper published in *Science* January 2008 entitled 'Complete Chemical Synthesis, Assembly, and Cloning of a Mycoplasma genitalium Genome.' There, Daniel Gibson and co-authors including J. Craig Venter and Hamilton O. Smith described the design and assembly of a complete bacterial synthetic genome at the J. Craig Venter Institute using a combination of *in vitro* and *in vivo* methods (Gibson, 2008).[2] The key achievement of this well-publicised paper was synthesis of an entire genome. While the genome in question is one of the most compact genomes known (582, 970 base pairs), it has not been synthesised before. Given that sequencing a complete genome was a major accomplishment 20 years ago, synthesising a whole genome is significant. In order to manage the synthesis process, the genome itself had to be viewed from the perspective of design and construction. The architecture of the *M. genitalium* genome had already been the target of the question 'How few parts would it take to construct a cell?' (Glass et al., 2006). In the 2008 papers, the process of assembling rather than analyzing the genome's architecture becomes the key objective. More specifically, since it is possibly the largest 'chemically synthesized molecule of defined structure' (1219), the process of synthesis through assembly of fragments is the main focus of design. Here the concept of meta-techniques again highlights how design process brings together several different modes of production.

Whole genomes readily support further design processes. Somewhat trivially, these include 'watermarking' of the sequences with the scientists' names. More significantly, the streamlined

construction process can be set against the patent application that precede the publication by several years. The most relevant U.S. and European patent is simply titled ‘Synthetic Genomes’ (J. Craig Venter et al., 2007). The outstanding claims here is for the possibility of 'millions of genomes':

> [0011] According to one exemplary embodiment and method, a synthetic version of the Mycoplasma genitalium genome having 482 protein- coding genes and 43 RNA genes comprising a 580-kilobase circular chromosome is assembled from gene cassettes. Each cassette may be made from chemically synthesized oligonucleotides. Several versions of each cassette may be made such that combinatorial assembly into a complete chromosome results in millions of different genomes. These genomes may be tested for functionality by "genome transplantation," replacement of a cell's resident chromosome by the synthetic genome (J. Craig Venter, Hamilton O. Smith, & Hutchinson III, 2007, p. 3).

The patent envisages a combinatorial explosion on the basis of the minimal genome. The patent claim is not just for 'combinations' but 'combinatorial assembly' of 'millions of [cassette-based] different genomes.' While the *Science* paper articulates the design of an assembly process (‘synthesis’) that brings together commercial DNA services and the techniques of yeast genetics, the patents meanwhile delineate combinatorial assembly for many possible purposes: ‘[r]ational methods may be used to design the synthetic genome ... Synthetic genomes of the invention may be introduced into vesicles ... to generate synthetic cells. Synthetic genomes of synthetic cells may be used for a variety of purposes’ (1). The papers in *Science* and the patent express a vision of a specific biological material as the substrate of ongoing, open-ended design work. ‘”[D]ecoupling” the design of engineered genetic material from the actual construction of the material’ is the first ‘benefit’ of ‘synthetic genomics’ (Garfinkel et al., 2007, p. 10). This decoupling is already inherent in the very

notion of doing design. The question is how can this decoupling be achieved in the domain of biological substances.

Who designs what?

What is at stake in these tendencies, and in the emergence of design in life sciences? The term 'rational design' often appears in synthetic biology. It highlights an underlying apprehension of the inefficiency or 'irrationality' of trial-and-error approaches to creating biotechnologies and drugs. The techniques of modelling, synthesis, assembly, exchange and distribution loosely coalescing in synthetic biology are all motivated by an apprehension of the excessive complications and complexities of biological substance, and by the overwhelming work needed to collect it into manageable forms and formats. One way of parsing this question is to ask: *who* designs biological substance? At some levels, the answer to this question is obvious: scientists or biological engineers will design biological constructs fit for the many and various problems they encounter. However, at another level, the answer is not all obvious. The turn to design in biology already attests to an awareness of shifts in the organisation, distribution and responsibility for doing biology. These shifts are at once economic, intellectual, globalized and political. They deeply affect what it means today to practically participate in doing biology. In this setting, the question of *who* designs *what* remains open, and we can regard several important facets of design in synthetic biology as evidence of this.

The general problem of excess data is widely perceived in biology. The mismatch between the accelerated output of genome sequencing centres and the practical translation of this information into new therapies, diagnostics and biotechnologies is well recognised. Excess or surplus also can be understood as constitutive of biotechnology more generally. As Eugene Thacker writes: '[t]here is never too much data, only the production of an excess that serves to trigger further development of tools for the management of this excess' (Thacker, 2005, p.

128). Sometimes, this excess is deliberately induced. For instance, as Alain Pottage has argued in his analysis of Craig Venter's sampling and sequencing ocean microbe voyages in the research vessel *Sorcerer II*, synthetic biology goes hand in hand with the corralling of an abundance ('combinatorial' in scale) of genomes to be used as resources (Pottage, 2006).

It might be possible to see synthetic biology as a response to a surplus essential to life itself. It responds in divergent ways. Different figures of design vie with each other, and these design figures have significantly divergent modes of responsibility associated with them. We can see this contrast by turning to the intersection between synthetic biology and digital media or network cultures. On the one hand, as we have already seen, synthetic biology relies on networked infrastructures for DNA synthesis, as well as for the now standard day-to-day work of sequence similarity searching. On the other hand, substantial practical efforts are being made to locate synthetic biology within web and network cultures, and to mold synthetic biology in the image of the web-centric ethos of sharing, openness and collaborative distributed work. These efforts bring different senses of how design can be done and for what purposes.

The synthetic biology and biological engineering-focused website *OpenWetWare* ('Share Your Science') is perhaps the leading symptom of an awareness of the importance of the question of *who* designs. This publicly editable 'MediaWiki' (a software platform originally developed for Wikipedia) promotes sharing of practical information about techniques, protocols, materials and resources in 'biology and biological engineering' between several thousand registered users (OWW, 2009). Its pages present many of the most well-known synthetic biologists working in academic institutions, as well as the lab notebooks for some of the annual IGEM competition teams. It incorporates portals to the *Registry of Standard Biological Parts*, and to the related *BioBricks Foundation*, as well as cross-links to many of the web pages for the highly publicised annual iGEM synthetic biology competition. Not only does *OpenWetWare*

rely on the internet as an infrastructure for collaboration (as do countless other groups, individuals and institutions today), it explicitly performs models of co-operative work or 'digital labour' as a transformative element of life science research. In *OpenWetWare* (as well as in the IGEM competition, and the standard biological parts community more generally), design is understood as depending on flexible and fluctuating flows of imitation, invention, and talent co-ordinated through exchanges of knowledge and information about materials, protocols, and techniques, as well as norms and values. Hence, networks and software here are not only the practical tools of communication, coordination and control in biological work. They also represent the potential for a transformation in who does design and for what ends.

All this may seem secondary to the actual design of biological constructs (proteins, cells, actuators, sensors, platforms, vectors, models, switches, relays, programs, etc.). However, *OpenWetWare* implicitly poses the question of who designs what. By framing a practical response guided by the norms of a certain ethos of recent network culture, it also promotes a certain idea of design. In addressing the issue of participation in synthetic biology, it also materially constitutes certain practices of communication, cooperation and sometimes collaboration as part of synthetic biology. We do not yet know the consequences or ramifications of efforts like *Openwetware,* the Registry of Standard Biological Parts, or the iGEM competition (all of which maintain extensive wikis). However, we can see that they generate a quasi-public presentation of current issues, directions and trends in the field (many well known synthetic biology labs, for instance, maintain pages on OpenWetWare). It is also evident that their membership includes a far greater range of participants than many other institutional science communities (including for instance, many individuals, artists, hobbyist groups). Finally, the upsurge of standard-making efforts and the development of mechanisms of collaboration, copying, sharing and circulation of standard-based constructs in synthetic

biology embodies one of the most literal enactments of a borrowing by synthetic biology of the norms and practices of internet and software cultures.

Alterations in the mode of participation in scientific community can be regarded as a 'meta-design' issue, but such changes may inflect how design is done and to what ends. For instance, if a wave of speculative-affective attachment to biological design work grows around synthetic biology, then the dynamics of social networking websites such as *SourceForge (Geeknet, Inc., 2009)* or *FaceBook* might become more significant effects on biological design than the latest advance in the application of yeast genetics to assemble synthetic genomes. Although little discussed in the current scientific, policy and social science research on synthetic biology, the strong presence of network cultures practices in synthetic biology may well generate very different design processes and dynamics. What is at stake here is not so much the reduction of complexity, or the suppression of troubling forms of emergence, but the elaboration of design as meta-technique that renders change open-ended and potently recursive.

Conclusion: design as intensification

Where have we come to with design? Fairly obviously, invoking design principles allows synthetic biology to be named in terms of different approaches (parts and devices, problems, whole systems). It demarcates synthetic biology from genomic science and biotechnology more generally by borrowing a form of legitimation derived from the manifest success of engineering design in many domains. It promises products rather than experiments. However, design, I would suggest, does a good deal more than rhetorically boost synthetic biology. Importantly, design software marshals an array of biological techniques and connects them to infrastructurally networked services (such as DNA synthesis, but also database searches). This compresses and flattens work on biological substance into a meta-technical space of design. A

flattened space of technical operations then supports re-factored constructs such as pathways and minimal genomes, constructs that practically configure biological substance as heterologous meta-materials receptive to potentially many different forms of modification and multiplication. These materials are not flattened in the same way as the techniques and elements arrayed in the software menus and palettes of operations and components might suggest. Rather their development and production depends on re-configured patterns of biological work. Design is always done by someone. The question of how design work is coordinated, in what forms of collaboration, and according to what norms of responsibility undercuts any simple application of design principles.

Apart from opening a whole range of inquiries into how synthetic biology is being done, what does analysis of the role of design in the rapid emergence of synthetic biology contribute to understandings of contemporary life sciences and biotechnology more generally? It is widely accepted that biotechnology and contemporary neoliberal capital are co-produced (Cooper, 2008; Rajan, 2003; Thacker, 2005). As Sunder Rajan writes, 'understanding biocapital involves analyzing the relationship between materiality and modes of abstraction that underlie the coemergences of new forms of life science with market regimes for the conduct of such science' (Sunder Rajan, 2006, p. 33). The variable substance of biotechnology – life at every scale from the microbial to the ecosystem, and at extreme limits (physical, spatial and temporal), from the most objective dimensions of biochemical and physical properties through to the most sensitive, nuanced expectations and sensibilities concerning selfhood, memory, illness and mortality – contains resources and potentials for the growth of capital. Is synthetic biology's rapid emergence just another among several others – high-throughput genome sequencing, genome-wide association studies, stem cell re-programming, tissue engineering, personalised genomic medicine, etc – that have magnetised public interest in life sciences in recent years?

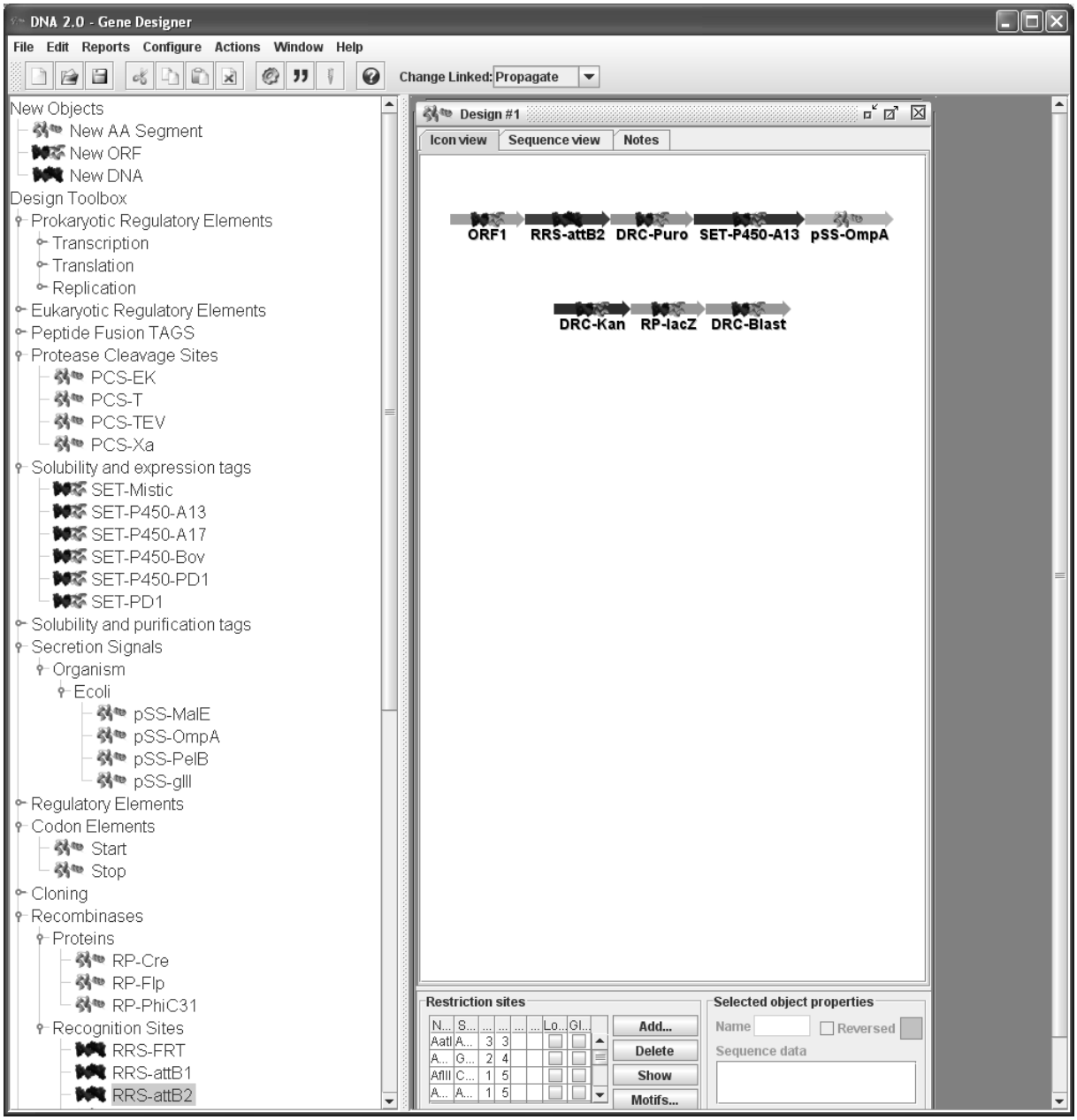
A focus on design does two things. Firstly, any life science has its own material-technical traits, genealogical affiliations and vectors of capitalisation. Design, I would argue, allows the specificity of synthetic biology to be articulated. There are good reasons to think that the streamlining and de-coupling of techniques and materials, the configuration of forms of biological work reliant on web services, standards, computer-assisted design tools (such as software, and models), and the engendering of patterns of networked collaboration might intensify work on biological substance in ways that differ from other scientific communities or innovation processes. Critical accounts of software, product and architectural design have argued that practices of design display much greater heterogeneity than the abstract principles of abstraction, modularity, and de-coupling can convey. The mobilisation of design in biotechnology means following or making new pathways of coordinated and more or less shared practice. The key cases of design software, of chassis or platform design, of standard-making efforts in synthetic biology display extensive and diverse borrowings from adjacent information, network and software cultures. The intensification of synthetic biology depends heavily on those borrowings. In understanding the specific intensity of synthetic biology, an emphasis on the flow of design technique and practices is particularly useful. It brings into view and at the same time questions the de-coupling between thinking and making, between designing and producing, that design aspirations inevitably rely on.

Secondly, focusing on design in synthetic biology raises a new set of questions and perspectives concerning vertical aggregation in contemporary biosocial settings. From the perspective of recent critical work on biotechnology and capital, the injection of design into biotechnology can be seen as a further capture of surpluses associated with biological substances. However, synthetic biology throws up new conjunctions and complications for current critical accounts of capitalism and biology. The common vein of thought running through the biocapital literature that regards recombinant DNA technologies as flattening or

lateralizing species and evolutionary differences seems only one part of synthetic biology. While synthetic biology also imagines a hyper-flattened terrain of inter-species difference, the design processes taking shape there in some ways twist and subduct that flatness. The smooth translation and global incorporation sometimes implied in biocapital contrasts with the topological boundaries, forms of closure, compaction, stickiness and path-dependency that arise as design work conjoins different materials and practices. Meta-materials and meta-techniques articulate the curious aggregates of accessibility, closure, surface and depth of biological substance in design processes.

Thirdly, and this aspect requires much further investigation, as synthetic biology gathers momentum by assembling larger, more heterologous constructs, social ramifications move into much deeper entanglements with the processes of doing biology. Rather than separating out ethical-social issues from the doing of the science, intensification of design generates concrete entanglements and partial connections (Haraway, 1999) between sciences, business, State-power, popular and media cultures. The very image of design as streamlining, as outmoding trial-and-error, experimental or otherwise inefficient approaches, here might encounter an alter-ego: design as mess-making, as vertical aggregate, as meta-stable proliferation of connections and layers. In that setting, as well as speeding up production in vertically aggregated formations, design might become much more important as a vector of imagining pluralised participation in the making and making sense of engineered biology.

Figure 1


DNA 2.0 - Gene Designer
File Edit Reports Configure Actions Window Help
Change Linked: Propagate
New Objects
New AA Segment
New ORF
New DNA
Design Toolbox
Prokaryotic Regulatory Elements
Transcription
Translation
Replication
Eukaryotic Regulatory Elements
Peptide Fusion TAGS
Protease Cleavage Sites
PCS-EK
PCS-T
PCS-TEV
PCS-Xa
Solubility and expression tags
SET-Mistic
SET-P450-A13
SET-P450-A17
SET-P450-Bov
SET-P450-PD1
SET-PD1
Solubility and purification tags
Secretion Signals
Organism
Ecoli
pSS-MalE
pSS-OmpA
pSS-PelB
pSS-gIII
Regulatory Elements
Codon Elements
Start
Stop
Cloning
Recombinases
Proteins
RP-Cre
RP-Flp
RP-PhiC31
Recognition Sites
RRS-FRT
RRS-attB1
RRS-attB2
Design #1
Icon view
Sequence view
Notes
ORF1
RRS-attB2
DRC-Puro
SET-P450-A13
pSS-OmpA
DRC-Kan
RP-lacZ
DRC-Blast
Restriction sites
Add...
Delete
Show
Motifs...
Selected object properties
Name
Reversed
Sequence data

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1 In the last ten years, the web has been heavily reconfigured as a service platform. This contrasts with the more common idea of the web as a 'new medium.' 'Web services' embody a contemporary form of attachment to complex, dynamic, distributed products.

2 The minimal genome synthesised by Daniel Gibson and others and announced in 2008 is meant to pre-emptively eliminate undesirable emergent phenomena associated with cellular environments for the production of genomes. The 'complete chemical synthesis' suggests that the genome can be purified of unwanted biological dependencies on cells. However, there are several grounds on which this claim to 'complete … synthesis' and hence the control of emergence falls short. It still 'suffers' from unwanted dependencies on the specificities of living substance. For instance, while DNA synthesis services can readily supply DNA in 20kb lengths, the assembly of the fragments into a whole genome, even the minimal 592kb genome of *m. genitalium,* still relies on other organisms, and in particular, yeast.