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From *bricolage* to BioBricks™: Synthetic biology and rational design

Tim Lewens

University of Cambridge, Department of History and Philosophy of Science, Free School Lane, Cambridge CB2 3RH, UK

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ABSTRACT

Synthetic biology is often described as a project that applies rational design methods to the organic world. Although humans have influenced organic lineages in many ways, it is nonetheless reasonable to place synthetic biology towards one end of a continuum between purely 'blind' processes of organic modification at one extreme, and wholly rational, design-led processes at the other. An example from evolutionary electronics illustrates some of the constraints imposed by the rational design methodology itself. These constraints reinforce the limitations of the synthetic biology ideal, limitations that are often freely acknowledged by synthetic biology's own practitioners. The synthetic biology methodology reflects a series of constraints imposed on finite human designers who wish, as far as is practicable, to communicate with each other and to intervene in nature in reasonably targeted and well-understood ways. This is better understood as indicative of an underlying awareness of human limitations, rather than as expressive of an objectionable impulse to mastery over nature.

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1. Engineering nature

General accounts of the nature of synthetic biology have systematically stressed that it involves using principles of rational design for the fabrication of organic systems. This aspect of the project is repeated in a slew of definitions of synthetic biology. Here are just a few, drawn from the UK and European contexts. The UK Health and Safety executive says that synthetic biology can be described as 'the design and construction of new biological parts, devices and systems, and the redesign of existing, natural biological systems for useful purposes' (HSE, 2007). The European Commission says that synthetic biology is 'the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures… In essence, synthetic biology will enable the design of "biological systems" in a rational and systematic way' (European Commission, 2005). The UK Parliamentary Office of Science and Technology tells us that synthetic biology 'describes research that combines biology with the principles of engineering to design and build standardised, interchangeable biological DNA building-blocks. These have specific functions and can be joined to create engineered biological parts, systems and, potentially, organisms. [Synthetic biology] may also involve modifying naturally occurring genomes… to make new systems or by using them in new contexts' (POST, 2008).

There are several significant differences between the sub-varieties of synthetic biology (O'Malley, Powell, Davies, & Calvert, 2007). Some approaches aim at the 'bottom-up' construction of genetically specified components, and at their combination for the creation of novel organic devices. Others instead begin with naturally occurring organisms, and seek to remove redundant or unnecessary parts in order to produce simpler, less 'noisy' organic machines, or perhaps minimally functioning organisms. In spite of markedly different attitudes towards the centrality of the genome in organic functioning, and to the detailed methods for the production of novel biological systems, the notion that an engineering design perspective characterises a variety of synthetic biology approaches remains in very recent research articles. So, for example, synthetic biology has been described as 'the use of engineering techniques to model, design, and construct artificial biomolecular networks' (Camacho & Collins, 2009, p. 24), and even more recently we hear again that at 'the heart of synthetic biology lies the goal of rationally engineering a complete biological system to achieve a

E-mail address: tml1000@cam.ac.uk

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specific objective, such as bioremediation and synthesis of a valuable drug, chemical, or biofuel molecule' (Cobb, Sun, & Zhao, 2012, p. 1).

What is the significance of this talk of rational design methods? Is this approach entirely new, or merely a variant on a long-standing theme within biology? Does it signal some ethically troubling attitude to the natural world, perhaps drawing on the 'impulse to mastery' that Michael Sandel (in a different context) has claimed characterises various efforts at human enhancement (Sandel, 2007)? I begin in sections two and three by arguing that while humans have influenced organic lineages in many ways, and in spite of the fact that some of these have involved the intentional manipulation of organic traits for human ends, it is nonetheless reasonable to place synthetic biology towards one end of a continuum between purely 'blind' processes of organic modification at one extreme, and wholly rational, design-led processes at the other. In section four, I use an example from evolutionary electronics to explore some of the constraints imposed by the rational design methodology itself. These constraints reinforce the limitations of the synthetic biology ideal—limitations which are often freely acknowledged by synthetic biology's own practitioners. In section five, I conclude by arguing that the synthetic biology methodology reflects a series of constraints imposed on finite human designers who wish, as far as is practicable, to communicate with each other and to intervene in nature in reasonably targeted and well-understood ways. This is better understood as indicative of an underlying awareness of human limitations, rather than as expressive of an objectionable impulse to mastery.

2. Designing nature

A first attempt to articulate the notion that there might be something new about synthetic biology's engineering approach could draw on the pretensions of that school to take control of natural processes, and subject organic nature to intentional manipulation. A moment's reflection shows that in this respect, at least, synthetic biology is simply an extension of an ancient tradition whereby humans influence the makeup of the organic world. Even if synthetic biology threatens to blur the distinction between organisms and artefacts by constructing an organism, that distinction has never been exclusive. A dairy cow is an organism if anything is. And yet, dairy cows have clearly been modified by human breeders with the purpose of increased milk yield in mind. Dairy cows are organisms that have been purposefully manipulated: they are organisms and artefacts at the same time. Artificial organisms have been around for as long as intentional agents have practised artificial selection. Indeed, even before humans consciously practised artificial selection, their symbiotic relationships with plants and animals have exerted mutual evolutionary pressures on our own lineage (for example, as lactose-tolerance followed the domestication of dairy cows), and on other lineages (for example, through the domestication of the wild ancestors of dogs).

Organisms, then, have long been artefacts, too; the enlarged udders of the modern cow owe their enormous volume to the efforts of generations of humans. But the pretensions of synthetic biology are not merely to influence the organic world in line with human goals: as we have seen, synthetic biologists wish to design organic objects using rational methods. We might stop short at claiming that dairy cows have been 'designed'. Why? To say that something has been designed is to say not merely that some of its modified features are intended or desired outcomes, but that its structure has been planned. The process of design typically involves drawing up, or conceiving of, *a design*. It involves considering likely uses of the imagined artefact, and laying out an articulated structure for that artefact in the light of these potential uses, perhaps in the form of a diagrammatic specification, in advance of its construction (Cross, 2000; Houkes & Vermaas, 2010). Pioneering breeders of the eighteenth century like Robert Bakewell developed significant technical expertise regarding the most effective techniques of artificial selection. Bakewell stressed the importance of strong selection, and to some extent he pioneered the use of 'progeny testing'; that is, the evaluation of a parent's ability to transmit desired traits to offspring via an assessment of a significant number of those offspring (Russell, 1986). In the case of both sheep and cattle, Bakewell aimed at the creation of a profitable meat animal, and he even went so far as to formulate rather more specific targets for how this should be achieved: animals should grow quickly, they should transform fodder into meat in the most efficient way, the animal's mass should be given over as much as possible to saleable meat, and that meat should be of the most economically valuable kind. This adds up to a design specification for the intended outcome of the breeding project only in a highly informal sense. Nicholas Russell has argued that while some of Bakewell's stated goals may have been quite detailed, his actual methods were less refined: 'There can be no doubt that phenotypic conformation must have formed the basis of his selection programme. He chose animals which looked right, which in his terms meant those that were easy to fat, were thin-legged (since that was the place to observe the bone size in the live sheep) and conformed to the shape which he believed would reflect the best carcass for flesh and fat distribution' (1986, p. 201). This suggests that synthetic biology really does offer something new, not because it blurs the organism/artefact boundary—that has always been blurry—but because of its goal of bringing the organic within the realm of design, where design is understood to carry all the connotations of planning, diagrammatic representation of the device to be constructued, standardisation of parts to be assembled, and so forth that feature in the engineering design process.

It is quite rare to find an explicit discussion of what makes a design process rational, as opposed to irrational, but alleged exemplars of the two processes can be found with ease. In pharmaceutical discovery, 'irrational' processes include the use of vast 'libraries' of combinatorially generated molecules, coupled to high-throughput screening methods that find molecules with the desired functions. 'Rational' processes, by contrast, include efforts to construct valuable molecules using well-understood chemical principles, where the chemical knowledge in question both explains and predicts the desired functional outcome. 'Irrational' methods can be perfectly rational, in the sense that they often constitute sensible strategies for the production of an entity with the desired overall function. They are 'irrational' only because the agent who oversees the process need not understand why the resultant entity works as it does. Whether a method is 'rational' or 'irrational' is itself something that comes by degrees: an engineer may not understand why the parts of a machine work as they do, but he may still be able to predict in rough-and-ready ways how they will behave when brought together. After several moderately successful attempts he may be surprised at the makeup of the machine that works best. Here, his knowledge is partial, and some elements of irrationality are introduced into the process. Likewise, an animal breeder may have some rudimentary understanding of a desired physiological function, and he may have a good sense for which animals it is best to mate together. He is not quite in the situation of one who merely collects together a vast array of animals and picks the ones that suit his purposes best; at the same time, he falls well short of assembling parts whose combined function he predicts with forethought and accuracy.

Synthetic biology represents an effort to introduce rational design methods, in the sense that synthetic biologists attempt to produce parts with stable functions, which can then be combined in ways whose outcomes are reasonably transparent to rational prediction. We must be careful, however, not to exaggerate how sharp the break is between synthetic biology and what has gone before. I will give just two examples, the first from the early Mendelians, the second from a series of more recent breeding programmes. Some early Mendelians, in a manner evocative of some of synthetic biology's recent proponents, had a vision of animal and plant breeding as a practical endeavour whose precision would be greatly increased by knowledge of genetics (Müller-Wille, 2012). They believed that ultimately it would be possible to exert fine-grained control of the characteristics of organisms via the combinatorial manipulation of allelomorphs. William Bateson put forward such a view in an address to the New York Horticultural Society in 1902, which was published two years later. The links drawn between this proto-synthetic biology and synthetic chemistry, and the vision of rational control replacing the breeder's intuitive knowledge and luck, make it worth reproducing the quotation in full:[1]

> To use an illustration: In chemistry you may have a body, say, a simple salt, from which you can take out the base, or the acid radical, replacing the base by another base, or the acid radical by another acid radical. You can in that way decompose your substance into component parts, reforming them in various combinations. So we must imagine a plant which has one element of color, for example, another element of texture, etc., and we must conceive that when two varieties are crossed together the unit characters can be combined and recombined in the gametes of the hybrid, alternating with and replacing each other by substitution. You can take out greenness and put in yellowness; you can take out hairiness and put in smoothness; you can take out tallness and put in dwarfness, etc. The characters have their fixed possibilities of union, and hence it may be possible for us to form some mental picture of the constitution of the organism.
>
> Now when we come to the question of the significance of these things to the breeder or to the hybridist, it will be found that the significance is exceedingly great. I am afraid of saying that we have already reached a point when the practical man who is doing these things with a definite, economic object or commercial object in view can take the facts and use them for his definite advantage. But we do for the first time get a clear sight of some of the fundamentals on which he will in future work, and it cannot be now very many years, if the investigations go on at the present rate, before the breeder will be in a position not so very different from that in which the chemist is: when he will be able to do what he wants to do, instead of merely what happens to turn up. Hitherto I think it is not too much to say that the results of hybridization had given a hopeless entanglement of contradictory results. We did not know what to expect. We crossed two things; we saw the incomprehensible diversity that comes in the second generation; we did not know how to reason about it, how to appreciate it, or what it meant. We got contradictory results, and the thing looked hopeless. But with the discovery of the purity of the germ cells we have the first step, which, I think, is bound in a very short time to become a path through many of those wonderful mazes of heredity. (Bateson, 1904, pp. 2–3)

In summary, then, the aspiration to modularised, rational control over the design of artificial organisms, one of the defining themes of synthetic biology, was already present in the earliest years of genetics.

Moving to slightly more recent breeding programmes, there have long been efforts, even before the advent of synthetic biology, to draw up plans for intended organisms, and then to seek to bring these design specifications to reality, albeit through traditional programmes of selective breeding, rather than through the fabrication and juxtaposition of standardised organic elements. Some of the best known programmes of these sorts include efforts to reconstitute the now extinct aurochs. The programme begun by Heinz and Lutz Heck in the 1920s, and which subsequently enjoyed considerable support under the Nazis through Heinz Heck's friendship with Hermann Göring (Millet, 2011), is today viewed as an unsuccessful and simplistic attempt to 'breed back' an extinct species. Heinz Heck's later comments nonetheless express an ambition to combine hereditary elements in a modular manner with the aim of reconstituting the aurochs piece-by-piece, in a fashion consonant with Bateson's earlier remarks:

> No animal is ever utterly exterminated as long as some of its hereditary factors remain. The fact that these qualities may not be visible is shown by the laws of heredity to be unimportant, for what is hidden may be brought to light again and, by cross-breeding, the original component parts may be isolated. In the case of the Aurochs conditions are favourable since all its physical characteristics are still present and to be seen. They are, of course, divided between many different breeds of cattle, one having preserved a good aurochs horn, another its build, while a third has the characteristic colouring, and so on. (Heck, 1951, pp. 119–120)

Commentators today tend to regard these cattle as very unlike the aurochs, even if they may have some superficial morphological similarities. Van Vuure's verdict is damning:

> On the basis of vague criteria and without proper knowledge of the appearance of the aurochs, the two brothers made inaccurate selections among the crossbreeding products of various cattle breeds. They did not use the knowledge about the aurochs that was available at the time, nor did they take advantage of the breeding techniques others were using to create new cattle breeds in the same period. (Van Vuure, 2005, p. 366)

In spite of this apparent failure, what are now called 'Heck cattle' are still used in conservation efforts around Europe. The more recent—indeed ongoing—*TaurOs* project (http://www.taurosproject.com/) is presented as a more elaborate (and commercially oriented) attempt to first ascertain the likely genome of the aurochs, to discover its ecological setting, to reassemble an aurochs-like breed by combining genetic elements from suitable extant cattle, and to insert the resultant animal into an appropriately structured environment (Faris, 2010). The *TaurOs* project involves a more formal process of design, in the sense that it begins with a fine-grained specification for the desired genomic and ecological profile of the target breed, in spite of the fact that its breeding techniques are those of more traditional artificial selection. Whether this project will be any more successful than the Hecks' is an open question.

We can now see more generally that there is a continuum between 'pure' forms of natural evolution at one extreme, where no intentional agency influences the evolution of a lineage, and efforts at fully formalised and standardised rational design processes at the other. Lying between these extremes we have the forms of unconscious selection that Darwin (1859, 1868) pointed to, whereby merely because humans choose to preserve some varieties of cereal, say, they unconsciously end up modifying their stock. We

[1] A scholarly detail: Bateson's remarks are often significantly mis-quoted, because a short paraphrase suggested by Levins & Lewontin (1985, p. 180) has been understood by their readers as a direct quotation. The quotation has also been mis-attributed, because Levins and Lewontin erroneously reference the (1902) first edition of Bateson's *Mendel's Principles of Heredity* as the source of the comment.

have intentional efforts to modify domesticated breeds for the better, even when the principles of breeding are not well understood. We have the kind of sophisticated and targeted efforts at improving particular traits (meat quality, milk yield, and so forth) that characterised the emergence of many famed agricultural breeds during the eighteenth century. We have the clumsy design efforts of the Heck brothers and genomically assisted endeavours like the *TaurOs* project. Synthetic biology merely lies further towards the 'design' end of that continuum than anything we have witnessed before.

3. Creativity and *bricolage*

We have established that there is a 'design continuum', and that synthetic biology lies towards one end of it. We will shortly see that having acknowledged the existence of a continuum of this sort, it is possible to misplace synthetic biology at a far extreme of that continuum, by exaggerating the degree to which synthetic biology eschews more traditional methods of artificial selection, and by exaggerating the efficacy of its efforts at pure rational design. The positioning of synthetic biology towards one end of this continuum is frequently cited as a differentiating feature between it and genetic engineering (e.g. Endy, 2005). Where genetic engineering typically aims at the piecemeal modification of existing organisms via changes to the genome, synthetic biology instead aims (in some of its guises at least) either at the wholesale creation of organisms, or at the creation from scratch of a series of organic machines, via the assembly of modularised sub-parts. The aspiration to produce a set of standardised sub-units that can be combined in reliable and predictable ways perhaps reaches its clearest expression in the BioBricks™ programme: here, an 'open-source' registry of standardised genetic parts is maintained, and the BioBricks™ parts are available for use in, among other things, the annual iGEM competition, where teams submit their new biological systems. This move to a fully design-based approach is sometimes claimed not merely to be a novel transition in terms of the ambition we have to control nature, but a transition with moral weight. Boldt and Müller (2008), for example, have recently asserted that 'The shift from genetic engineering's "manipulatio" to synthetic biology's "creatio" is a shift with considerable ethical significance' (pp. 387–388).

I will return to Boldt and Müller's comment in more detail a little later. For now, note that it seems to rely on a fairly strong distinction between mere manipulation, perhaps understood as a form of piecemeal 'tinkering' with what nature happens to present to us, and full blown creation. This is a distinction we should be sceptical of. For example, there is a sense in which the process of natural selection itself is both supremely creative—for it produces novel adaptations where none were present before—and supremely constrained to tinker with the materials that natural variation happens to make available to it. In describing evolution as a form of 'bricolage', François Jacob clearly drew an analogy between the blind process of selection and the creative human *bricoleur* who fiddles with bits and pieces available to him, at the same time as he highlighted the suboptimal outputs we should expect from selective processes. Darwin (1868) tried to illustrate the creativity of natural selection itself by sketching the image of an architect who judiciously chooses and assembles rocks of diverse shapes that have fallen from a precipice: the creativity of the process is not undermined by the lack of control over the availability of the raw materials. Indeed, many theorists of engineering creativity itself have tended, in turn, to conceptualise technical innovation and technical progress in evolutionary terms, describing both in a vocabulary that stresses analogies between invention and natural selection (e.g. Vincenti, 1990; Ziman, 2000). Historians of technology and philosophers of science, too, have been attracted to an evolutionary image of scientific and technical creativity, according to which novel artefacts, or novel theories, consist in suitably reconfigured and modified combinations of elements inherited from their historical ancestors (e.g. Basalla, 1988). On such views, creation is nothing more than a series of fortunate instances of manipulation, extended over a long enough time period to produce something that seems genuinely novel compared with its ancestors.

Finally, and most significantly for Boldt and Müller's thesis, while synthetic biology might have the *ideal* of producing a series of elementary functional units that can be combined in ways that produce larger wholes with predictable and valuable functions of their own, in *practice* this remains merely an ideal. Kwok (2010) gives a sobering list of challenges facing the BioBricks™ methodology. Practitioners of synthetic biology repeatedly stress the practical need for later phases of directed evolution, whereby variants are produced using mutagens, and tested for the desired overall function, if a suitably performing molecular machine is to be constructed (see O'Malley, 2011 for further exploration of this theme). This emphasis on combinations of rational and irrational methods has persisted over several years of methodological work in synthetic biology (see, for example, Andrianantoandro, Basu, Karig, & Weiss, 2006; Cobb et al., 2012; Dougherty & Arnold, 2009; Porcar, 2010). As it is practised right now, synthetic biology does not manage to avoid an essential phase in which rational design methods are put aside in favour of a process of artificial selection of artificially generated variants. In other words, the creativity of synthetic biology itself continues to rely on processes whose efficacy may be inscrutable to the designers themselves, and which have much in common with familiar breeding techniques. In this respect, synthetic biology still has one foot in earlier traditions of artificial selection, and many recent commentators have suggested that it might always remain in this situation. In an article advocating the use of techniques of 'directed evolution' for the de-bugging and optimisation of rationally designed components, Dougherty and Arnold begin by remarking that:

> [Some] researchers advocate efforts to 'standardize' biological parts in such a way that their behavior in novel assemblies or environments becomes more predictable. The notorious complexity and context-dependency of the behavior of biological parts and their assemblies, however, make such standardization extremely challenging. It is unlikely, in fact, that biological parts can ever be fully standardized, and engineering methods that enable rapid optimization of synthetic biological systems will be very useful. (Dougherty & Arnold, 2009, pp. 486–491)

The tools of directed evolution are here described, reasonably enough, as 'engineering methods', but that should not obscure the fact that these methods do not embody rational design principles as traditionally understood. As currently practised, perhaps as it will always be practised, synthetic biology should not be placed at a far extreme of our 'design continuum'. The proper design continuum should, therefore, look something like that pictured in Fig. 1. Crucially, given the complexities of biological systems, the far right extreme of that continuum is one that may never be reached, but may instead have to serve as an aspirational goal that directs and spurs research.

4. Evolutionary electronics

There is no clear sense, then, in which the application of design methods characteristic of synthetic biology represents an entirely new way of approaching the organic world: at best it is a further development in an ongoing trend. But we can begin to see some of the more interesting features of rational design methods if we take the unusual step of looking at what happens when innovators

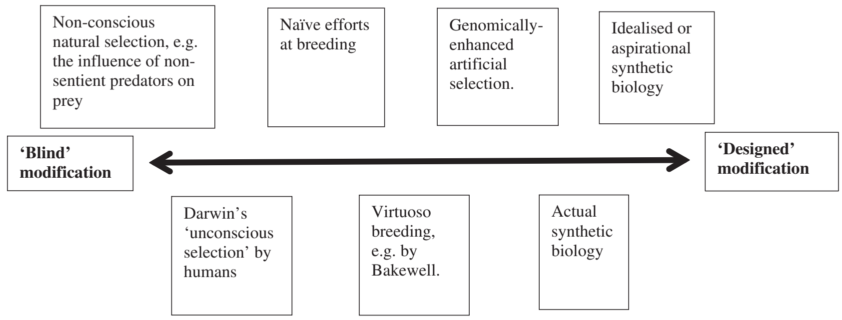

Fig. 1. A design continuum for the modification of organic nature.

explicitly throw away rational design principles, and instead use 'blind' methods of innovation similar to natural selection. It turns out that the sorts of designs that are produced are often very different to those thrown up by rational design. Indeed, some of the proponents of these evolutionary design processes claim that rational design processes—the very processes which advocates of synthetic biology wish to apply to the organic realm—can act as strong constraints preventing the exploration of significant areas of design space. If this is so, we might temper our enthusiasm (and perhaps our fear, too) for the likely ability of synthetic biology to radically re-order the biological world.

Synthetic biologists often explicitly frame their goals by analogy with electronics. They look to create organic logic gates, for example, which can be combined to produce larger components—oscillators, amplifiers, input and output devices, and so forth—in much the same way that electronic engineers can assemble electronic components. It is especially interesting, then, to consider what happens when people working on electrical devices themselves throw away attempts to design components in a rational way. Consider an example from evolutionary electronics, specifically from Adrian Thompson's group at the University of Sussex in the UK. The following case is explained in detail in Thompson (2002). The group used something called a Field Programmable Gate Array—essentially a reconfigurable chip—whose organisation was determined by a genetic algorithm. They tested a series of slightly modified configurations to the chip, preserving the circuits that were best able to discriminate between two audio tones. Although the FPGA had a 64×64 matrix configuration, the programmed section of it used only a 10×10 area of one corner of the chip. After thousands of iterations, a version of the chip that performed the task more or less perfectly was bred. The exact details of the investigation do not matter here. But the final piece of hardware had some extraordinary properties. Most striking for our purposes is the fact that some sections of the best-performing evolved chip couldn't be altered without loss of function, even though they were not electrically connected (in the usual way, at least) to the output of the chip:

> [These cells] cannot be clamped [i.e. returned to their default 'blank' state] without degrading performance, *even though there is no connected path by which they could influence the output*... They must be influencing the rest of the circuit by some means other than the normal cell-to-cell wires: this probably takes the form of a very localised interaction with immediately neighbouring components. Possible mechanisms include interaction through the power-supply wiring, or electromagnetic coupling. (Thompson, 2002)

These comments also demonstrate the important point, common in evolutionary design approaches, that when a high-performing variant is bred, investigators are frequently unable to understand why it works as well as it does. I do not wish to assert that it would be impossible for the operation of such circuits to be understood, and we have just read of some of the Sussex group's suggestions for how this might be achieved. The point, instead, is that because unconstrained pathways of evolutionary design are free to take advantage of whatever fitness-enhancing effects may present themselves, there is no reason to anticipate that such effects are easy to recover and understand by observers of the system.

We shouldn't be surprised that evolutionary processes can give rise to entities that are both highly functional and incomprehensible. In processes of rational design we begin with a general problem, and divide it into sub-problems. We then construct elements that will solve each of these sub-problems, and we stick them together. It is essential for this method to work that the functional capabilities of the sub-parts are robust across contexts, in the sense that they don't change their internal configurations when they are brought into the vicinity of other parts, that their interactions with other functional units are always predictable, and so forth. In other words, we try to ensure that sub-parts are causally isolated from each other, and from the specifics of their environments, as far as is possible. We aim to construct modularised components. This is not because causal isolation is necessarily a virtue in terms of the overall desired effect, it is simply because the design methodology of decomposition into sub-problems demands this sort of causal isolation. The end result of all this is that the operation of designed entities is comparatively easy to recover and understand through a functional decomposition of the object into constituent parts with contributory effects. This is precisely because the systems have been designed, and their parts have been assigned discrete functions during the design process itself. While such comprehensibility is likely to be a featured of designed systems, it is not guaranteed even in the realm of artefacts. Even here innovators may have unwittingly failed to reduce forms of cross-talk that, unknown to them, make an important contribution to the overall operation of the artefact.

Evolution, on the other hand, cannot literally divide a problem into sub-problems, to be tackled in isolation (Lewens, 2004). This also means that when fortuitously beneficial aspects of 'cross-talk' between elements of a system are hit upon in evolving systems, they will often be retained. There is certainly no literal effort to remove them. This result has costs and benefits. In the case of Thompson's reconfigurable chip, it turned out that when their high-performing 10×10 configuration was moved to a different part of the larger 64×64 chip, the performance was impaired or even dropped off altogether. So costs, in terms of portability, are often extreme. But as the Sussex group rightly notes, this means that evolutionary design techniques can sometimes be considerably better than standard rational design techniques, precisely because a variety of potentially beneficial effects that rely on 'cross-talk' between elements, or contingent properties of the locale, can be harnessed, rather than minimised as a result of the design methodology itself:

> Evolution has been free to explore the full repertoire of behaviours available from the silicon resources provided, even being able to exploit the subtle interactions between adjacent components that are not directly connected. (Thompson, 2002)

This form of evolutionary process unsurprisingly gives rise to systems whose overall functioning is often inscrutable to human investigators. Where no effort is made to reduce forms of 'cross-talk', to minimise the ways in which overall functioning is contingent on highly idiosyncratic properties of local material substrates, and so forth, it can become very difficult to subject these systems to typical forms of functional decomposition. These work best when components have discrete functions, whose joint actions are simple additive results of their independent contributions. In this sense, then, we can understand some of the key differences between paradigm cases of designed machines, and the much messier workings of evolved systems—whether those systems are carbon-based organisms, or inorganic circuits. John Dupré, in recent work, is right to stress the sense in which the creation of a highly modular, well-behaved system that is apt for unambiguous functional decomposition is itself a significant achievement (Dupré, 2012). It is the sort of thing that humans strive to produce via modular design methodologies.

5. Rational design and evolutionary design

Reflection on these evolved electronic systems is instructive when we begin to think about synthetic biology. Even in the biological realm, theorists have claimed significant advantages for modularity. But it is important to understand why modularity is held to be important: an evolutionary system that was very tightly connected, so the story goes, would be unable to evolve in a cumulative manner. For suppose that any modification to the eye, or to the heart, would tend to have knock-on effects on every other organ in the body. The chances are that any potential positive impact on the design of the eye would be counteracted by the countless impacts—most likely negative—on all of the connected elements of the organism. And so, the story continues, modularity is essential for cumulative complex adaptation.

Modularity may indeed be important, but on this view its importance does not lie in natural selection's methodological practice of decomposing a problem into sub-problems. As such, even if modularity is a frequent feature of organic design, we should not expect modularity to be a hard and fast feature of all evolutionary solutions. If it turns out that non-modular designs are sometimes effective, then selection knows no better than to choose them. Moreover, while theorists have often stressed the ways in which partial modularity characterises many organic systems, it remains unclear whether natural selection is able to favour modularity. Some have argued that the emergence of modularity is better explained as a result of non-adaptive processes (e.g. Lynch, 2007), while some more recent models have proposed possible routes whereby selection for modularity might proceed (e.g. Pavlicev, Cheverud, & Wagner, 2011, inter alia).

This discussion enables us to note some important rules of thumb which distinguish most organisms from most artefacts. Most artefacts will have been built in such a way that their layout reflects a prior conceptualisation, by its own architects, of the structure of the design problem the artefact addresses. This is an observation often made by engineering design theorists, and even by management theorists with an interest in innovation (Cross, 2000; MacCormack, Rusnak, & Baldwin, 2008). It has frequently been conjectured, and some evidence supports the conjecture, that the structure of a complex designed product typically 'mirrors' the organisational structure of the corporation that produced it (MacCormack et al., 2008). That is because the overall problem addressed by the artefact needs to be broken down into sub-problems of a sort that can be tackled by independent teams. The availability of such teams, and their particular expertise, is constrained in turn by the organisational composition of the company they work for.

Needless to say, there is no analogue to this phenomenon in nature. Even when organisms are modular, this sort of conceptualisation is evidently not the cause of that modularity, and in many cases departures from modularity will be favoured by natural selection. This, for example, is why distinct organic *functional* modules—that is, complexes of organic processes that combine to perform valuable developmental or physiological roles—need not be *structurally* isolated from each other, and their elements can often overlap. If a given biomolecule can be turned to useful roles in numerous different functional processes, then so be it.

Where have we got to in our discussion? There really is something rather novel in applying engineering principles to the natural world. An organism—or a sub-organic machine—organised according to the principles of rational engineering design would be far more modular, far more compartmentalised, than any natural organism. Such an organism will feature clear efforts to reduce 'cross-talk' between its functional elements. This does not mean that we should expect artificial organisms to be superior in all aspects of their performance to natural organisms: in many cases there are advantages to be had from harnessing these forms of cross-talk, as the examples from evolutionary electronics indicate.

But now recall why we should care about standardisation: synthetic biology's advocates typically do not argue that the reason to move to some form of rational design approach is because such an approach inevitably arrives at outcomes superior to those produced by natural selection. We have already seen some reasons for thinking that in restricted cases natural selection may produce more effective designs than rational agents. Natural selection is not constrained by a prior methodological commitment to rationality, and since natural selection must build traits that are effective in the face of regular internal and external insults, natural selection also needs to ensure that its products are robust against a range of environmental perturbations. The forms of redundancy and complexity that follow from blind design may often be superior in performance to the products of rational methods. Synthetic biology's advocates more usually adopt the pragmatic premise that if humans are to make efforts to alter what nature has given us, or to build new organisms, we are likely to wish to do so in ways that allow conversations between designers, the organisation of design teams, the swapping and transportation of effective elements from one design context to another, and so forth.

This is an attitude one quite frequently encounters in publications within synthetic biology. For example, a very recent paper notes that many biological functions one may wish to harness from a technological point of view are 'encoded in gene clusters', with the result that their naturally occuring genetic substrates exhibit various forms of complexity and inscrutability that make them very difficult to modify or improve upon: 'Regulation is highly redundant...regulation can also be internal to genes...Further, genes often physically overlap, and regions of DNA can have multiple functions. The redundancy and extent of this regulation makes it difficult to manipulate a gene cluster to break its control by native environmental stimuli, optimize its function, or transfer it between organisms' (Temme, Zhao, & Voigt, 2012, p. 7085). A more 'bottom-up' approach that makes use of modular synthetic components is then proposed, precisely because this offers a more tractable way to go about modifying and improving functions of biotechnological interest. These sorts of simplifications may also be of use in understanding biological complexity, because they represent a first attempt to understand simple systems, which may be overlaid one onto another in more biologically realistic, complex evolved systems (Morange, 2009). Biological complexity is here acknowledged, the barriers it presents to human intervention are explicitly admitted, and attempts are made to avoid it (in the first instance, at least) via the creation of simpler systems.

Recall that Boldt and Müller (2008) have claimed that this shift 'from "manipulatio" to "creatio ex existendo" is decisive because it involves a fundamental change in our way of approaching nature.' On my reading, synthetic biology simply recognises diverse practical reasons for aiming at various forms of modularity, standardisation, and specification of sub-problems. It is hard, then, to accuse synthetic biology of espousing an objectionable form of mastery over the feeble efforts of Mother Nature, of a wish to 'play God', or of some kind of Promethean assault on the 'given' of the natural world. These are the sorts of criticisms laid at the door of enhancement technologies by the likes of Michael Sandel (2007; see also Lewens, 2009); some commentators might have similar concerns about synthetic biology. In reality, synthetic biologists simply recognise the practical constraints imposed by the methodology of rational design. Humans *cannot* play God, because God—unlike humans—is not constrained in these ways. God, one assumes, does not need to decompose problems into sub-problems, he only makes systems modular when a modular solution is the best one, he takes advantage of all forms of noise and cross-talk when they are there to be found, he has no need to make his plans comprehensible to finite human engineers. If God is omniscient, he simply surveys all possible solutions to a design problem, and picks the best one, regardless of how complex it might be, regardless of how little modularity its elements may show, regardless of how hard it might be to understand its operations.

Maureen O'Malley (2011) has recently stressed, in a manner echoed by the comments in section three of this article, that practitioners of synthetic biology have not been able to simply put together novel biological systems from functionally isolated parts and have done with it. Instead, there is always a 'kludging' or 'debugging' phase: rational design does not suffice, because biological systems demonstrate various forms of contingency, uncertainty and context-specificity, which means that functional elements that work in one location cannot be transported without loss of function into another. Often their newly designed systems only work after considerable amounts of trial-and-error rejigging. If synthetic biologists were really trying to 'play God', the very existence of this final phase would be an embarrassment, or admission of defeat. But on O'Malley's analysis it is simply acknowledged by synthetic biology's own practitioners as a reality to be faced when dealing with the contingencies of biological systems. As she puts it:

> All of this heterogeneity and evolutionary innovation has consequences for the type of engineering that can be done in synthetic biology. Diverse sources of variability obstruct synthetic biologists from achieving the desired 'plug and play' of predictable properties. Even when it works, rational design requires multiple iterations of reconstruction and redesign. Combinatorial synthesis and directed evolution—both employing 'irrational' biological processes to improve the functioning of designed devices—are increasingly necessary complements to or even replacements of rational design. (O'Malley, 2011)

She cites numerous biological sources for this assertion, including this interesting comment from Arkin and Fletcher:

> ...unlike other engineering disciplines, synthetic biology has not developed to the point where there are scalable and reliable approaches to finding solutions. Instead, the emerging applications are most often kludges that work, but only as individual special cases. They are solutions selected for being fast and cheap and, as a result, they are only somewhat in control...(Arkin & Fletcher, 2006)

Of course, none of this means that there are no significant ethical problems that arise when we look at synthetic biology. We need to examine who shall have control of the technology, and to what ends. Some have worried that synthetic biology presents special challenges here because of the low costs of entry, and because of its potential to be translated into biological weapons or instruments of terror. We need to examine how funding should be allocated to research in the area. We need to ask all the usual questions about how to balance uncertain prospects of benefit against uncertain prospects of harm. Some have worried that synthetic biology is particularly challenging because it does not fit easily into the standard safety paradigm derived from genetic modification, whereby modified organisms are compared with their natural counterparts. General ethical approaches to synthetic biology have looked at issues relating to biosafety and biosecurity, to concerns around intellectual property, issues relating to governance and the 'exclusion' of important voices in the formulation of regulatory policies. These are serious issues, but they represent familiar ethical concerns about how to approach emerging technologies.

Synthetic biology involves something new, but only in the sense that it involves a further step towards one end of the 'design continuum': it involves an effort to apply rational design principles to the organic world. But when we understand why one might want to make that effort, and what its potential limitations are likely to be, we see that there is no special reason to worry that synthetic biology's practitioners are trying to fly too close to the Sun. Synthetic biology, in spite of some of the slogans attached to it, does not represent an intolerable hubris.

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