FORUM: Synthetic biology

Engineering explored

Synthetic biology involves the creation of biological systems for new applications by modifying and reassembling biological components. Two views are presented here on the best way to engineer these components so that they reliably generate organisms with desired traits.

THE TOPIC IN BRIEF

- The aim of synthetic biology is to predictably bioengineer organisms that perform beneficial functions — from producing antibiotics to purifying contaminated water.
- One approach is rational design, which involves characterizing many biological components to generate a library of modules that can be assembled within an organism to give predictable, reliable outcomes (Fig. 1a).
- An alternative approach is called directed evolution, in which genetic mutations of unknown impact are introduced into a target of interest, generating a library of mutants that is screened for desired characteristics. Iterative rounds of the process produce mutants with optimized traits (Fig. 1b).
- Opinions differ on which of these methods is the more effective.

Rationalizing nature

PAMELA A. SILVER & JEFFREY C. WAY

Rational design is a mainstay of synthetic-biology ideology. What does this term actually mean? As proponents of the rational-design approach, we believe that human designers can use nature to inform the creation of genetic circuits, proteins and even life forms. A human designer can learn from failures, which should ideally inform future designs. By contrast, evolution can be seen as a series of makeshift solutions, in which each change must work at some level for survival — non-working intermediates are not permitted.

Rational design relies on the idea that biological systems are fundamentally modular. The gene was originally defined as the basic biological unit. But the advent of technology allowing manipulation of DNA has revealed tantalizing levels of modularity that extend to many other cellular regulatory elements, including promoters, which control gene expression, and binding sites for the ribosome (the cellular machinery responsible for translation), which stimulate protein production. The dream of the rational designer is to understand these modular parts in sufficient detail to be able to assemble them logically, much as an engineer would build a machine for a certain purpose. There are already success stories — for example, assembly of simple genetic circuits that rely on the existence of two stable states in a system[1]. Recently, we used these principles to design a bacterium that can sense whether or not an animal has been exposed to antibiotics as it travels through the gut[2].

We are aware, however, that rational design alone is unlikely to be a valid strategy for synthetic biology. Instead, we see it as an overarching approach that will use many tools, including knowledge of physical principles and natural biological systems, computer simulations and more. The synthetic biologist's toolbox will probably contain some level of directed evolution or random variation, but such strategies are often limited by throughput: sometimes animal testing or clinical trials, which can be inherently low throughput, are the most interesting tests of the outcomes.

Ideally, in designing a biological system, synthetic biologists would understand (and apply) all of the phenomena that nature manipulates. This would require a detailed mastery of gene expression, protein structure, enzyme kinetics and so on. But although many of these are well understood, the data are generated by specialists who often do not interact with each other and who frequently do not speak a language that can be understood by bioengineers.

Moreover, most of the scientific literature has been written with the goal of making natural phenomena less mysterious, rather than providing guidance for a bioengineer. Practical facts and principles are diffusely scattered, and buried in an excess of documentation. One immediate challenge is to consolidate these data into information that engineers can use.

The past 50 years has seen an explosion of biological knowledge, funded mainly at public expense. People might assume that such knowledge is wasted if it cannot be used to rationally design biology for real-world applications. Now is the time to make good on the public's investment.

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Evolving with purpose

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Genomes are great books of instructions on 'how to': how to extract materials and energy and convert them into self-repairing, self-reproducing machines; how to function in an extraordinary range of environments; even how to adapt over the long term. Evolution has accumulated a vast library of instructions. We argue that it is also a great tool for writing new ones. The results of directed evolution are rational and predictable, even if the underlying genetic changes follow an uncharted course.

How good are synthetic biologists at writing useful biological instructions? We are getting better at synthesizing long stretches of DNA that can be inserted into a variety of organisms in which they will be read and — sometimes — acted on. But most of our writing merely rearranges passages lifted from the few genomes that we have read. We are plagiarists, poor crafters of original literature. We cannot yet create an enzyme or a biosynthetic

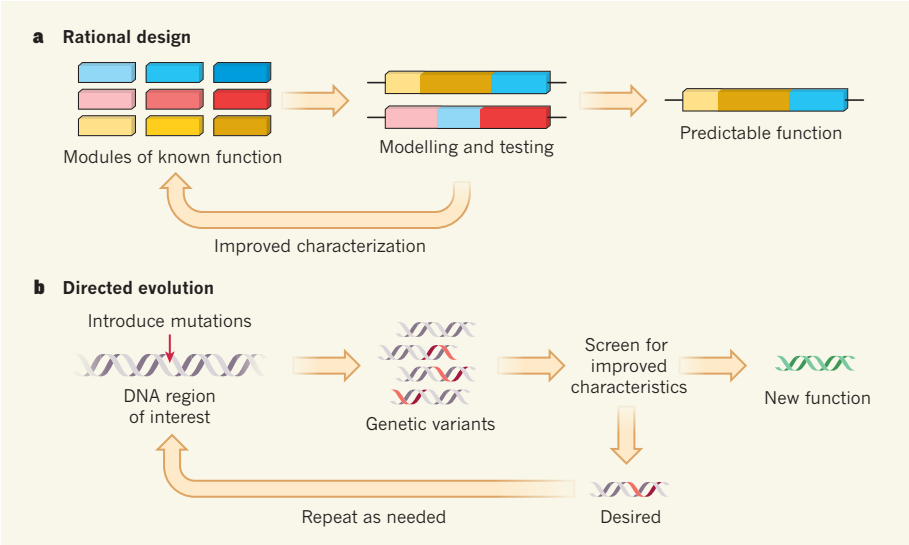

Figure 1 | Two methods for the synthetic engineering of organisms. **a**, In rational design, biological 'parts' (such as genes, gene regulators and proteins) are studied through modelling and testing such that their behaviour is understood. This produces libraries of well-characterized parts — or modules consisting of multiple parts — that can be rationally assembled in cells in different combinations, resulting in predictable functions. **b**, An alternative approach is to harness the power of evolution to direct the design of synthetic organisms. A region of interest (in this example, a gene) is randomly mutated, producing cells that harbour a variety of mutations. The cells are then screened to find those with mutations that result in or improve a desired function. Cells that do not harbour such mutations are eliminated from the pool; those that do can be cultured and then subjected to new rounds of mutation and screening, to achieve a desired end product.

pathway that compares favourably with nature's engineering outputs. Nature's writing is intricate (some say convoluted and opaque), but it is effective. We are just learning to hold the pencil.

The reason is simple: in biology, details matter a lot, and we don't understand the details. Rational design is hard when one cannot even predict the effects of a single mutation in a single enzyme, or the full impact of adding a single gene to the thousands already present in an organism. It is fine to hope that 'modular' biology is possible, but our ham-fisted attempts at assembling biological components usually show that biology is anything but modular. The engineering of systems that tackle real-world problems, such as producing an antimalarial drug or an alternative fuel through a new microbial pathway, involves years of trial and error[3]. Realizing the potential of synthetic biology requires dealing with the details.

Rational design will not move beyond these problems until our understanding of the details of biology has improved dramatically. Luckily, we do not have to wait. Evolution is a time-tested tool for engineering the details, and we can use it in the lab to circumvent our profound ignorance of how sequence encodes function. Accumulating beneficial mutations over multiple generations is a general algorithm for turning a poor copy-and-paste job into effective writing, and it works at all levels of complexity. From creating a DNA-editing enzyme that excises HIV from the host genome[4], to optimizing multi-enzyme biosynthetic pathways[5], directed evolution has produced results with purpose[6].

Evolutionary engineering is not incompatible with 'rational' design; in fact, the two are highly complementary. Directed evolution requires a starting design, and the better the design, the easier the evolution. Evolution also requires a rational search strategy. Where should mutations be targeted, and how many of them? How do we measure success along the way? Directed evolution and rational design are even claiming common ground, for example in mutant libraries that have been designed with input from computational processes, accelerating the evolutionary process[7].

With a good starting point in hand, evolution is the most direct approach to engineering the biological world, and it is uniquely effective with biological substrates, the products of that same process. Biology is highly evolvable, and we should exploit that feature to the fullest, as we have for thousands of years with everything from rats to racehorses. The writer's best friend is a good editor — the synthetic biologist's should be directed evolution. ■

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CLIMATE SCIENCE

The origin of regional Arctic warming

Observational data and modelling show that the rapid warming of the northeastern Canada and Greenland sector of the Arctic over the past three decades has been strongly driven by cooling in the tropical Pacific Ocean. SEE LETTER P.209

JÜRGEN BADER

Over the past 30 years, Earth has become a warmer place. One of the most striking examples of surface-temperature warming is the polar regions in the Northern Hemisphere (Fig. 1). The greater warming in the Arctic[1], compared with the global mean, is associated with a reduction in sea ice[2] and dynamical and radiative feedbacks[3], and is widely attributed to anthropogenic climate change. But the fact that the warming is not spatially uniform raises the question of whether natural climate variability has a role in driving it and causing regional climate change. On page 209 of this issue, Ding *et al.*[4] show that the most prominent Arctic warming has occurred in northeastern Canada and Greenland, and that cooling in the tropical Pacific Ocean forced half of the warming in these two regions. The findings indicate that a substantial part of regional Arctic climate change is therefore a result of natural climate variability.

Much of the interannual and decadal variability in atmospheric climate can be described by the evolution of the leading modes of climate variability, such as the North Atlantic Oscillation (NAO). The NAO consists