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Mind the lag: appreciating and accelerating the timescale of engineering biology research

Executive summary

- Compared to other science and technology fields, engineering biology is significantly more reliant on tacit knowledge and needs more 'debugging' through the 'Design-Build-Test-Learn' cycle, which often involves months or years of work.
- Tacit knowledge acquisition occurs mostly during the first 6-12 months of a project, creating a 'lag phase' in scientific or commercial output.
- Engineering biology thus strongly benefits from long-term vision and resourcing. We propose that the UK's research investment should focus on medium (2-3 years) and long (>3 years) projects and grants rather than shorter programmes that aim to create novel technologies in 1 year or less.
- Facilitating information sharing across research institutions, as well as supporting open-source and community-developed laboratory hardware, could significantly reduce this 'lag phase' and accelerate the progress of engineering biology research across the UK.
- A revision of patent regulations would also significantly enhance collaboration and information sharing. Meanwhile, the development and encouragement of basic reproducible standards would greatly contribute to the popularisation of useful community-developed laboratory hardware.

Introduction

This report was submitted by the University of Oxford's Engineered Biotechnology Research Group members in response to the following questions raised by the inquiry:

- What are the possible barriers and limitations to good and effective use of engineering biology?
- How can Government policy support the development of engineering biology?

As a group of researchers in various career stages, we aim to highlight common inefficiencies and challenges in the field, particularly with relation to the timescale of engineering biology research, and suggest how to address them. While our comments primarily pertain to academic work, with which we have the most experience, we believe that many of them may extend to commercial contexts, particularly technology development in early-stage start-ups.

With increasing international competition, the UK's window of opportunity to become a leader in engineering biology is brief, which calls for decisive action to secure the nation's advantageous position in the field. As a smaller country with fewer funds to spare on unproductive efforts compared to the US or China, the UK cannot afford a time-inefficient strategy. The timeliness of HM Government's support for engineering

biology research is thus a key consideration, which should be informed by the particularities of this nascent field rather than extant assumptions about the science and technology sector as a whole.

We argue that misunderstanding the timescales of engineering biology R&D may cause inefficiencies and hinder the translation of public investments into economic and social outputs. We therefore make two suggestions: first, to adapt the timescales of research funding to those of engineering biology; and second, to enact measures that can accelerate these timescales and help the UK outrace its competitors.

Engineering biology research operates over medium-to-long time scales

Engineering biology combines scientific knowledge of biology and engineering design methods to edit or create new biological systems with useful functions. As outlined in the UK's National Vision for engineering biology[1], its applications span multiple key sectors, including but not limited to medicine, agriculture, or manufacturing. The unique potential of engineering biology stems from using biological molecules and systems, which through millions of years of evolution have specialised to perform diverse tasks and functions. Like basic parts or systems that form the basis of other engineering fields – for instance, a screw of a standard size or an electronic circuit component with specific features – biological engineers have been working to standardise the biological parts and systems they work with at various levels.

Despite this standardisation, the immense complexity of biological parts and systems often means that their features and performance may be affected by contextual or environmental variables in an unpredictable manner. This unpredictability is a direct consequence of how the living cell is organised. As opposed to the modular, well-defined responses to inputs characteristic of man-made control systems, cells process inputs through complex biomolecular networks, and only a fraction of each network can be accurately measured or forecast using even the most cutting-edge techniques. Moreover, biochemical reactions comprising these networks are stochastic, i.e. their behaviour is influenced by randomness. Therefore, when biological engineers assemble new systems from standard parts, they rarely perform as expected. Even an already functional biological system may fail when tested in an institution different than the one which created it for reasons as trivial as changes in the local chemical composition of tap water. This contrasts with other engineering fields, where standard parts – like screws and electronic circuit components – can be used to predictably assemble new systems.

Whenever biological engineers begin developing a new technology, they may thus spend a great deal of time debugging their designs, which can take from one week to several years (Box 1); yet, overcoming this inertia is necessary to realise the potential of engineering biology applications. Part of this debugging is the acquisition of tacit knowledge, which can be broadly understood as nuances in protocols, materials, or conditions that improve a biological system's performance, predictability, and ease of experimental characterisation. Hurried by deadlines for delivering results, experimentalists must by necessity settle on the first 'adequate' approach or setup which achieves a desired output, without rigorously testing how every parameter or decision impacts the outcome. This approach may be imagined as 'fiddling' with a system until a working setup is found – with such ad-hoc nature of the approach embedding a large degree of chance in the engineering process. Unlike

major changes in design or methodology that have a clear and explained effect on performance, the unclear nature of tacit knowledge (and the vast number of variables it can encompass) makes it challenging to transfer knowledge across institutions or laboratories. A nation-scale strategy to address this reproducibility challenge, e.g. by developing novel research techniques and equipment, could give the UK an outsized advantage in the next era of engineering biology.

Box 1 One PhD student in our lab needed to implement a system of genes that could be switched on and off using light signals. Despite this system being reported functional in several other publications, the system was found to be non-functional under the conditions tested. Untangling the many possibilities for the negative result has been a laborious process. Every new hypothesis required another experiment of several days' work, overall resulting in a 6-month delay before the system could actually be *used*. Such troubleshooting is not an uncommon experience in engineering biology research.

The debugging and tacit knowledge acquisition are mostly concentrated at the initial stages of an engineering biology project, usually the first 6-12 months. Starting a new engineering biology project often involves training, risk assessments, and obtaining permissions such as biosafety certifications or, if required, licenses for animal testing. Acquisition of biological parts and systems or machinery associated with engineering biology is also a slow process, ranging from days for the simplest building blocks to months for specialised equipment or systems bound by material transfer agreements. Together, all these factors result in the first 6-12 months of an engineering biology project being in the 'lag phase' of relatively low output, only after which the most relevant valuable scientific or commercial results are produced.

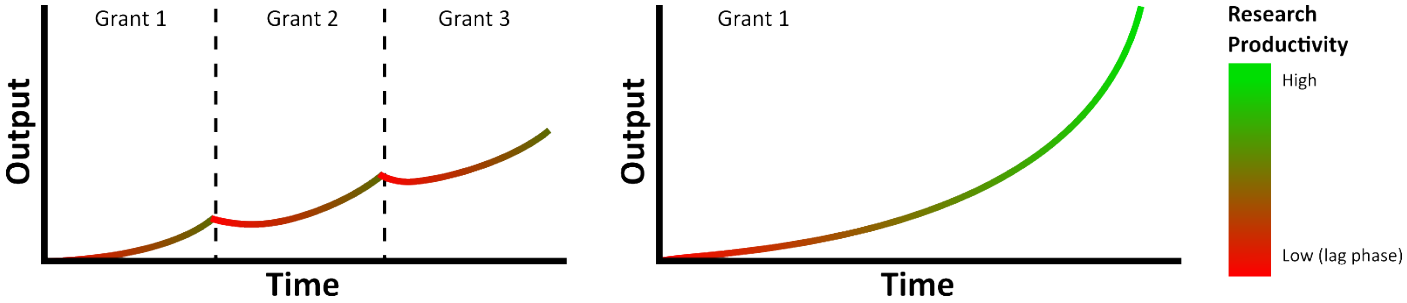

Figure 1. The impact of different grant time scales on engineering biology research output. Short-term grants are spent acquiring materials and tacit knowledge, with a lag phase of low research productivity at the start of every new project. Without continuity in people and expertise, a research programme's output regularly drops from the end of one grant to the beginning of the next. In contrast, long-term grants capitalise on accumulated knowledge and resources, enabling highly productive research.

Because this 'lag phase' takes place every time a project starts or moves location, short-term projects waste significant effort on debugging and tacit knowledge acquisition, being left with little time to produce valuable outputs (Figure 1). Whilst present research support mechanisms do not always display awareness of these timescale limitations, taking them into account could maximise the impact of engineering biology funding. For example, especially when aiming to explore novel ideas in the field, we believe that funding should be allocated to projects of medium (2-3 years) or long (>3 years) duration, which provides enough time to produce valuable outputs after the initial lag phase of debugging and acquiring tacit knowledge. In contrast, short (i.e. <24 month) schemes which call for initiation of

entirely new research directions have from our experience been more difficult to translate to success due to a combination of the challenges described above, as well as logistical hurdles in project set-up, staff recruiting, and beyond.

While an ill-suited launchpad for new research directions, short-term grants can still find their place in the academic ecosystem as spin-offs or continuations of existing longer-term research endeavours. Building on the tacit knowledge and expertise already accrued by their parent projects, programmes like the UKRI Impact Acceleration Accounts[2] can skip the 'lag phase' of research and time-efficiently extend an ongoing project's benefits to novel scientific fields and commercial applications.

Accelerating engineering biology research

Incentivising information sharing in engineering biology

The 'lag phase' of tacit knowledge acquisition could be shortened by facilitating information exchange between researchers, letting them effectively build on each other's findings to accelerate engineering biology research. We propose several strategies for fostering a UK-wide collaborative environment.

Platforms for sharing information (e.g. research protocols, DNA sequences) do exist, for instance SynBioHub[3] and JBEI-ICE[4], however the scientific community does not widely engage with them. This poses a question of incentivisation, in which the government could play a role. This incentivisation challenge is compounded by current decision-making models for allocating research funding (both to individuals and institutions) that significantly rely on publication-related statistics, such as citations, which dissuades researchers from sharing information for fear of being 'scooped' before publication. We thus propose to investigate ways to also reward – or possibly require – the pre-printing of experimental result and engagement with platforms for sharing DNA sequences and/or lab protocols.

In addition to sharing information through pre-prints or publications, person-to-person communications are essential to keeping the UK research base at the cutting edge. Here, conferences are an ideal environment; however, funding to attend such events is often limited, especially for graduate students who could benefit the most from the insights and tacit knowledge of more experienced researchers. Greater support for students to attend these discussions on the global stage would be of great national utility, as would the consideration of a nationally sponsored UK Engineering Biology conference, potentially with free attendance for those presenting their work as an explicit policy.

The sharing of knowledge should be encouraged not only among academic researchers, but also between academia and industry which, despite having many aligned goals, currently have different work practices and incentives. The resulting reluctance to communicate can be particularly harmful to engineering biology. Indeed, with the field's knowledge- and resource-intensiveness best addressed by researchers and private entrepreneurs respectively, rapid advances are only possible when these forces act in synergy. A key alignment of incentives would be to reconcile the researchers' need to publish their findings and the industry's requirement for protecting intellectual property. Any consideration of US-style grace periods for patenting would therefore be welcomed, and could deliver benefits to engineering biology and innovation more broadly. Indeed, the lack of a time window for publishing

scientific findings with no harm to the patenting prospects has been repeatedly identified as harming the commercialisation of university-based academic research[5,6]. Alternatively, academic funding considerations could include patents as acceptable deliverables for a project, fostering a more applied approach for research and encouraging entrepreneurial roll-out. At the same time, to prevent hindrances to knowledge exchange, HM Government could facilitate access to patented technologies for other researchers and start-ups, potentially by subsidising licensing of patents that have emerged from publicly funded research, with the return of increased research outputs and further entrepreneurial successes.

Supporting open-source and community-developed laboratory hardware

The 'lag phase' of engineering biology research could also be minimised by facilitating the procurement and construction of the equipment used to test and characterise designs and experimental conditions. As a highly interdisciplinary research field, engineering biology requires specialised laboratory hardware that combines a diverse set of parts, including optical, fluidics, and bioprocess components. However, many conventional scientific instruments are not built with modularity and customisability in mind and are typically not amenable to co-development by the scientific community. Hence, researchers often spend much time adapting extant commercial solutions to the needs of the project at hand, which exacerbates the associated delays.

In this regard, open-source hardware has been highlighted as a valuable opportunity for accelerating research and development in the field[7]. Open-source hardware can enable a lab or a company to build instrumentation fit to their needs by reusing previously developed parts. The inherent modularity of most open-source hardware solutions facilitates cost-effectively adaptation of existing designs. For example, upon the need for better performance or precision, an instrument’s component can be substituted for a more expensive alternative without having to buy a new higher price-band model. Broader accessibility and distributed manufacturing of open-source equipment can also accelerate the acquisition of instrumentation necessary to scale-up engineered biotechnologies. As an example, this can address the typical 6-to-18-month lead times for commercial bioreactors, which are incompatible with short projects or fast-moving needs of start-ups. Finally, research projects that use open-source hardware can output more reproducible results and protocols, enabling more efficient exchange of tacit knowledge.

The use of open-source hardware in engineering biology, while still limited, has notable success cases. Opentrons pipetting robots are widely used across engineering biology labs to streamline and automate complex Biodesign workflows. Similarly, Chi.Bio (Box 2) is an open-source, cost-effective bioreactor designed specifically for engineering biology applications. Finally, fully 3D-printable open-source devices like OpenFlexure[8,9] or OpenScope[10] provide highly modular, easy-to-customize microscopy platforms.

Box 2 The Chi.Bio[11] is an open-source bioreactor platform enabling *in situ* characterisation and manipulation of biological systems. Originally developed to make up for the lack of cost-effective, programmable bioreactors for engineering biology applications, it combines heating, stirring, liquid handling, spectrometry and light actuation into a single easy-to-use device for less than £1,000. Since 2020 the Chi.Bio has been adopted by over 100 labs across the world, including more than 40 companies and start-ups. The user-base has deployed the platform in application domains ranging from carbon capture to cellular agriculture to development of microbial vaccine systems. This adaptability has been made possible owing to the system's open-source software and hardware which – unlike commercial off-the-shelf offerings – means it can be easily customised and re-programmed, or integrated into automated laboratory workflows, to suit diverse use-cases.

The development of open-source laboratory hardware that can enhance research accessibility in engineering biology should therefore be a priority. In this context, researchers should be encouraged to ensure that open hardware developed through publicly funded research conforms to basic reproducibility standards, such as those set by the Open-Source Hardware Association[12], to amplify this technology's impact on the wider community. Notably, the emergence of journals[13] and standardised documentation formats[14] tailored to open-source hardware can facilitate adherence to (and assessment of) these practices.

To incentivise development and distribution of open-hardware designs, these contributions and their impact on the wider engineering biology community must be appropriately recognised. Finally, the conversion of pre-existing custom-designed hardware into open-source shareable designs could be supported through *ad hoc* funding schemes, providing the financial support required to standardise parts, compile the necessary documentation, and ensure the reproducibility of such devices.

Whilst engineering biology is still in its infancy, its enormous potential to improve life quality, healthcare and the economy's performance and sustainability justifies its place as a pillar of the UK's national technology strategy. We believe government could play a vital role in supporting this development with a combination of the right investment strategies and incentivisation of knowledge sharing.

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