CellPress
OPEN ACCESS

Trends in
Biotechnology

Review

Bioinformational trends in grape and wine biotechnology

Thomas A. Dixon [1,*,@] Thomas C. Williams [2,@] and Isak S. Pretorius [2,3,*]

The creative destruction caused by the coronavirus pandemic is yielding immense opportunity for collaborative innovation networks. The confluence of biosciences, information sciences, and the engineering of biology, is unveiling promising bioinformational futures for a vibrant and sustainable bioeconomy. Bioinformational engineering, underpinned by DNA reading, writing, and editing technologies, has become a beacon of opportunity in a world paralysed by uncertainty. This article draws on lessons from the current pandemic and previous agricultural blights, and explores bioinformational research directions aimed at future-proofing the grape and wine industry against biological shocks from global blights and climate change.

Highlights

Uncertainty caused by pandemics, global blights, and climate change, tends to heighten the focus on how biotechnological advances can mitigate challenges to public safety, cyberbio resilience, environmental sustainability, and bioeconomic security.

Convergence of cyberbio technologies and high-throughput automation in biofoundries offers future-shaping bioinformational engineering opportunities with transformational potential to the wine industry.

Consumer preferences, biosecurity, and bioethical considerations, must guide research directions and adoption of new bioinformational engineering technologies at the levels of both problem selection and experimental design.

The shock and awe of the pandemic's creative destruction

The years of global pandemic outbreaks, 1346, 1918, and 2020, loom large in history because these low-probability, high-impact disasters have devastating impacts on people's lives with tranquilising effects on society as a whole. In this regard, the 2020 coronavirus outbreak was no less damaging than previous once-in-a-century pandemics, **global blights** (see Glossary), and other catastrophes. This paper explores the future of grape and wine biotechnology with future global biological shocks in mind. These shocks include both the potential for global blights but also the disruptive potential of climate change. It is important to note that these two shocks combine in a layered manner; temperature change combined with existing land use patterns can contribute to the likelihood of a new global blight emerging.

COVID-19 exemplifies the power of a global biological shock. The virus has infected millions of people and reset the trajectory of macro political, economic, sociological, technological, legal, and environmental (PESTLE) forces that shape the modern world. Such powerful forces are of course not solely the province of human biological shocks, and global blights harbour similar levels of disruptive potential. This paper explores the emerging science and technologies that might mitigate the risks of a global blight in the grape and wine sector.

In every crisis there is opportunity and as the COVID-19 pandemic's **creative destruction** vaults the world 5–10 years forward in business and consumer digital adoption, it is important to review the new technological behaviours that are propelling all economic sectors into a new normal. COVID-19 triggered an unparalleled scientific mobilisation and collaboration to understand the biological fundamentals of coronavirus and to find responses, treatments, and vaccines. Crucial contributions have come from seemingly unrelated areas of expertise. Inventing and delivering a vaccine within record time would not have been possible without the many years of investments in basic research across, for example, areas such as informatics, genomics, and recombinant DNA technology. Such basic bioinformational research contributions might have been considered as pointless amusements a few decades ago. However, the world has now reaped the benefit of many basic research investigations at the lower end of the technological readiness scale. When researchers, practitioners, and business leaders take a goal-

[1]Department of Modern History, Politics and International Relations, Macquarie University, Sydney, NSW 2109, Australia
[2]Department of Molecular Sciences and ARC Centre of Excellence in Synthetic Biology, Centre Headquarters, Macquarie University, Sydney, NSW 2109, Australia
[3]Chancellery, Macquarie University, Sydney, NSW 2109, Australia

*Correspondence:
thom.dixon@mq.edu.au (T.A. Dixon) and sakkie.pretorius@mq.edu.au (I.S. Pretorius).
@Twitter: @thomdixon (T.A. Dixon) and @Dr_Tom_Williams (T.C. Williams).

 https://doi.org/10.1016/j.tibtech.2021.05.001

oriented, multidisciplinary approach alongside policymakers, and when scientific evidence is respected and multilateral collaboration fostered, solutions come faster. Similarly, such collaboration was essential in the 19th century during the Great Wine Blight that so severely afflicted European agriculture (Box 1).

The shock and awe of the crisis of 2020 and its creative destruction, have demonstrated the value of sustained investment in basic research and putting scientific evidence at the heart of decision-making and policy setting. The pattern behind **innovations** across time and academic discipline demonstrates that one invention can lead quite unexpectedly to a slew of others. Rigorous trans-disciplinary research, scientific excellence, robust data, and **collaborative innovation networks** across multiple sectors, will be essential to the world's societal and economic recovery and its building-back-better endeavours. This article draws on the cross-sectoral lessons of creative destruction and innovation stemming from the current pandemic, as well as previous agricultural epidemics and blights, to chart new **bioinformational engineering** and biotechnological trends aimed at securing a sustainable future for a resilient grape and wine industry. This paper explores both the opportunities and challenges available to the grape and wine industry and these are summarised in Table 1.

Computer aided design

Computer aided design (CAD) has progressed significantly since the mid 1990s to enable biological engineers to design new functions with greater precision. Within the grape and wine industry CAD products extend across the production cycle (Figure 1), but here we focus on CAD applications that can support grape growing, fermentation, and maturation. Some of the earliest and most widely adopted CAD tools focused on metabolic networks, where constraint-based stoichiometric

Box 1. The forces of innovation that shape the global wine industry

Across the history of grape growing and winemaking [50–53] the sector has had its fair share of existential challenges. A small yellow root-feeding **phylloxera** aphid (*Daktulosphaira vitifoliae*) arrived as an unwanted import from America in Europe in 1863 [54]. In France alone, the phylloxera soil louse destroyed approximately 2.5 million hectares of manicured vineyards, threatening the very existence of the French wine industry.

As with the invention of a vaccine against the current COVID-19 pandemic, the global wine industry had to cooperate across local, regional, and national boundaries, to find a solution to what has become known as the *Great Wine Blight* of the 19th Century [55]. These experts discovered that phylloxera is native to the east coast of the USA and hypothesised that native American vine species (*Vitis aestivalis, Vitis berlandieri, Vitis labrusca, Vitis mustangensis, Vitis riparia, Vitis rotundifolia, and Vitis rupestris*) have generally evolved with resistance against *D. vitifoliae* [56,57]. Following successful demonstrations of the ability of American vines to withstand phylloxera, experts recommended large-scale grafting of the noble *Vitis vinifera* cultivars (e.g., Chardonnay, Riesling, Sauvignon Blanc, Cabernet Sauvignon, Pinot Noir, Shiraz, etc.) on to phylloxera-resistant American rootstocks.

Would the availability of the genome sequence of *Vitis vinifera ssp. sylvestris* (*V. sylvestris*), the ancestor of domesticated cultivars of *Vitis vinifera ssp. vinifera* (*V. vinifera*) [58,59], and the genome sequences of several widely-cultivated *V. vinifera* noble varieties (e.g., Cabernet Sauvignon, Carménère, Chardonnay, Nebbiolo, Pinot Noir, Syrah, and Tannat) enable the wine world to find effective solutions to disease and pest outbreaks faster? It is reasonable to suggest that the clonal diversity revealed by comparative genome sequence analyses within, for example Chardonnay vines [60], is likely to assist with future blights and adaptation to climate change.

From clonal diversity among noble grape cultivars [61] to microbial strain variation among malolactic bacteria (e.g., *Oenococcus oeni*) [62] and *Saccharomyces cerevisiae* [63–71] and non-*Saccharomyces* (e.g., *Hanseniaspora vineae*, *Hanseniaspora guilliermondii,* and *Torulaspora delbrueckii*) [71–74] wine yeasts, comparative genome data could help solve challenges with sluggish and stuck wine fermentations, and the reshaping the aroma profile and alcohol levels of wine when consumer preferences change [75,76]. Similarly, the genome sequence of three strains of the main wine spoilage yeast, *Brettanomyces bruxellensis*, revealed the gene responsible for the unpleasant 'medicinal' off-flavour in wine, as well as the genes involved in sulphite tolerance [77]. These insights into the genomics of *B. bruxellensis* are likely to provide wineries with clearer diagnostic tools and new 'weapons' against outbreaks of sulphite-resistant contaminants in wineries [78].

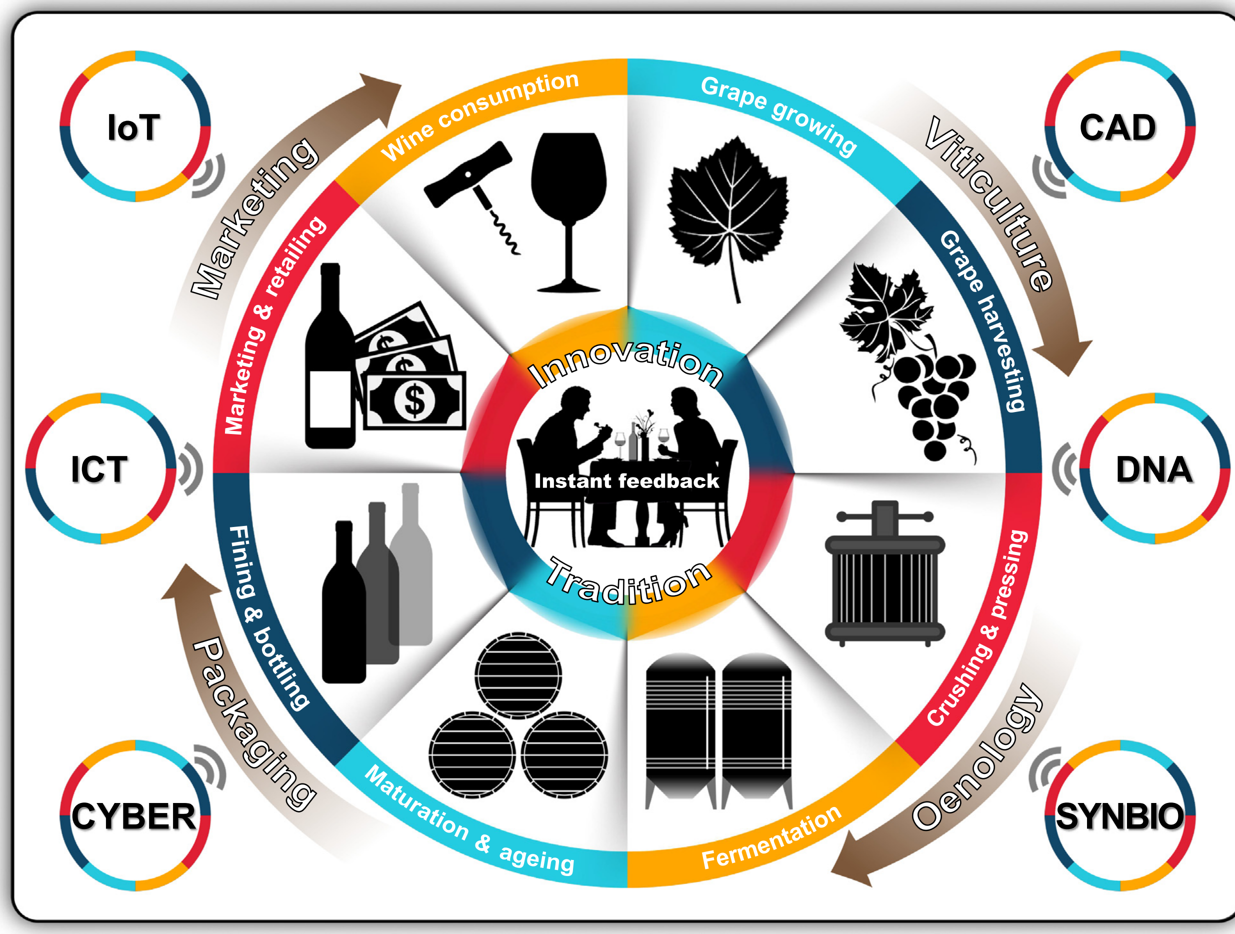
Glossary

Bioeconomy: the bioeconomy is the knowledge-based production and use of biological resources to provide products, processes, and services, in all economic sectors within the frame of a sustainable economic system.
Bioinformational engineering: the confluence of life sciences and information sciences that enables the engineered integration of biological and digital information structures.
Collaborative innovation networks: self-organizing emergent social systems of multiple stakeholders, cooperating to innovate and cope with external change and challenges.
Creative destruction: the process by which emerging ideas, technologies, innovations, and industries continuously supplant existing ones, thereby catalysing economic change.
Engineering biology: the set of methods for designing, building, and testing engineered biological systems, which have been used to manipulate information, construct materials, process chemicals, produce energy, provide food, and help maintain or enhance human health and environment.
Global blight: a botanical 'pandemic' whereby plants are damaged by disease and pests.
Innovation: the creation, development, and implementation of a new product, process, or service, with the aim of improving efficiency, effectiveness, performance, or competitive advantage.
Phylloxera: a root-feeding aphid-like insect (*Daktulosphaira vitifoliae*) and vine pest responsible for an epidemic in the late 1800s that destroyed European vineyards planted with *Vitis vinifera* wine grapes.
Synthetic biology: the design and construction of new biological parts (genes), devices (gene networks), and modules (biosynthetic pathways), and the redesign of biological systems (cells and organisms) for useful purposes.

Table 1. Challenges and opportunities for grape and wine bioinformational research

Research area	Current state	Key challenges	Future state	Application to mitigating global biological shocks	Application to vine growers and winemakers	Refs
Computer aided design (CAD)	Genetic circuit and metabolic network design at increasing degrees of complexity. Machine learning integration into design space exploration and combinatorial testing protocols.	Achieving robust and rational computer based design of higher-level bioinformational abstractions based on agreed data standards.	*In silico* biodesign becomes a 'design build deploy' process instead of 'design build test'. CAD provides digital mirrors of natural, engineered, and agricultural ecosystems.	Deep simulation capacity to design biological interventions that enable agricultural and ecosystem resilience in the face of novel adverse biological events.	Mapping metabolic and physiological pathways critical to vine growing and winemaking can ensure these critical inputs are understood well enough that solutions can be designed as climate change continues tomorrow. Precision engineering of yeast fermentation is where CAD tools are likely to make the most immediate impact.	[1]
Internet of biological things (IoBT)	Basic research into the extraction and conversion of living system information structures into digital information instantiations.	Developing and proving commercial readiness of information substrate conversion technologies (e.g., robust and long-lived sentinel plant monitors).	Digitally interoperable living systems and networked ecosystems facilitating low-latency monitoring that trigger precision interventions.	Molecular-level early warning systems for novel biological shocks that monitor living system stress levels and trigger follow-up investigation by drones and humans.	Monitoring sentinel plant signals for grape must development after rains and water stress during droughts will reduce crop spoilage and increase water efficiency in the production process.	[2]
Beverage manufacture for a changing climate	Proof-of-concept for engineered yeast strains with reduced carbon dioxide production, engineering hop flavours from yeast, and carbon waste stream recycling via co-located brewing.	Alignment of grape growing and winemaking producer and consumer preferences with next-generation biotechnology adoption.	Complex alcoholic beverage fermentation from non-grape carbon sources enabling distributed production via locally sourced carbon waste streams.	Engineered redundancy of carbon sources, enabling superior vintages to be replicated synthetically in the event of a catastrophic biological event in the grape and wine sector.	Today, yeast can be engineered to re-assimilate CO_2. In the future, it is likely that yeast will be engineered to produce complex beverages directly from CO_2 feedstocks.	[3–5]

and now thermodynamic models enabled prediction of gene knockouts and environmental conditions for enhanced metabolite production [5]. Design and analysis of genetic sequences has been assisted by software such as Benchling, Geneious [6], TeselaGen, and J5 [7]. At higher levels of abstraction, entire genetic circuits can be designed using tools such as Cello [8], novel proteins designed using Rosetta [9], and retrosynthetic metabolic pathways suggested by RetroPath [10], BNICE [11], and a range of other tools [12]. Most recently, machine learning (ML) is emerging as a critical part of the biological design–build–test–learn (DBTL) cycle. Initially ML was used to suggest superior designs of simple genetic motifs such as ribosome binding sites [13,14] and promoter variants [15] but has now progressed to more complex tasks, such as metabolic network/pathway design iteration [16–18]. The future of CAD will likely involve more complex integration of all current tools to enable higher levels of design abstraction. Critical to this process will be the standardisation of biological design at all levels. In particular, standardised reporting of biological system design and function will be important for the effective implementation of ML across larger design scales. Standardisation has been a key pursuit in the field of **synthetic biology**, but until recently, has largely been an idealised concept lacking broad implementation. The Synthetic Biology Open Language (SBOL) provides a framework for standardised descriptions of biological part design and function [19], and the Global Biofoundry Alliance [20] aims to share biological automation protocols, projects, and data. Open source projects such as these provide the opportunity to



Trends in Biotechnology

Figure 1. Cyber–biological systems from grape to glass. Engineered bioinformational feedback loops on the nano- and micro-scale will allow vintners to receive instant feedback on the progress of their production line, from vine to table. The digital properties of a superior vintage may be just as, if not more, valuable than the physical properties of that vintage, as they will ensure the vintage can be replicated year after year. Abbreviations: CAD, computer aided design; ICT, information communication technology; IoT, internet of things; SYNBIO, synthetic biology.

implement standards in biology that will facilitate more accurate and powerful CAD for rational design. Ultimately, due to the complexity and context specificity of biological components, it may be necessary to engineer simplified chassis cells with modular genomes for higher-level CAD and standardisation to reach its full potential.

Though we may solve today’s urgent problems based on yesterday’s scientific discoveries, we cannot solve today's problems with yesterday's thinking. To be forward-thinking, we have a responsibility to imagine future challenges and potential solutions alongside new opportunities and possible benefits to producers and consumers alike [21–23]. In this context, our contention here is that the convergence of information technology and synthetic biology will enable the translation of bioinformational data into practical applications that would assist with the mitigation of future risks, finding solutions to unforeseen challenges and creating new opportunities for the global grape and wine industry.

No conceptual framework in the life sciences better encapsulates the application of engineering thinking than DBTL [23–25]. Similarly, the bioeconomics of high-throughput automation and mass production are made real in the biofoundry (Figure 2). Biofoundries signify the transposition of engineering thinking and expertise from semiconductor foundries to the biological world [23,26]. Indeed, the American trajectory of industrial policy for semiconductors and **engineering biology** follow very similar paths, albeit 50 years apart in levels of advancement. From the semiconductor manufacturing technology (SEMATECH) program in the 1980s to the Engineering Biology Research Consortium (EBRC) today [27], the tools and techniques of public–private research and development coordination remain the same. This has important correlatives when it comes to thinking about and planning research and development into mitigating future biological shocks at an industry level.

Transforming winemaking and grape growing with bioinformational research

The short-to-medium term directions shaping bioinformational research in this sector are characterised by the increasing availability of biological information across varying length scales

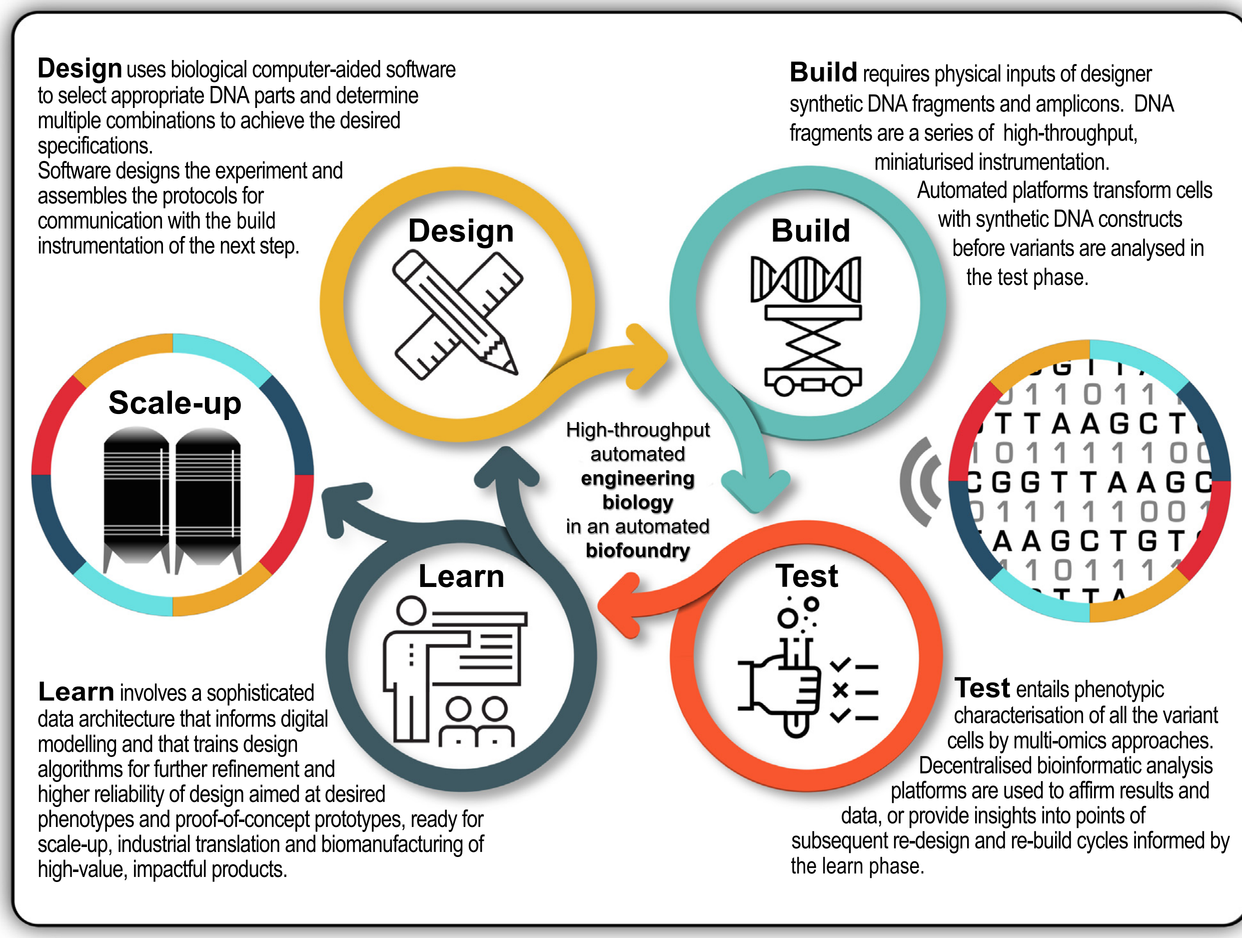
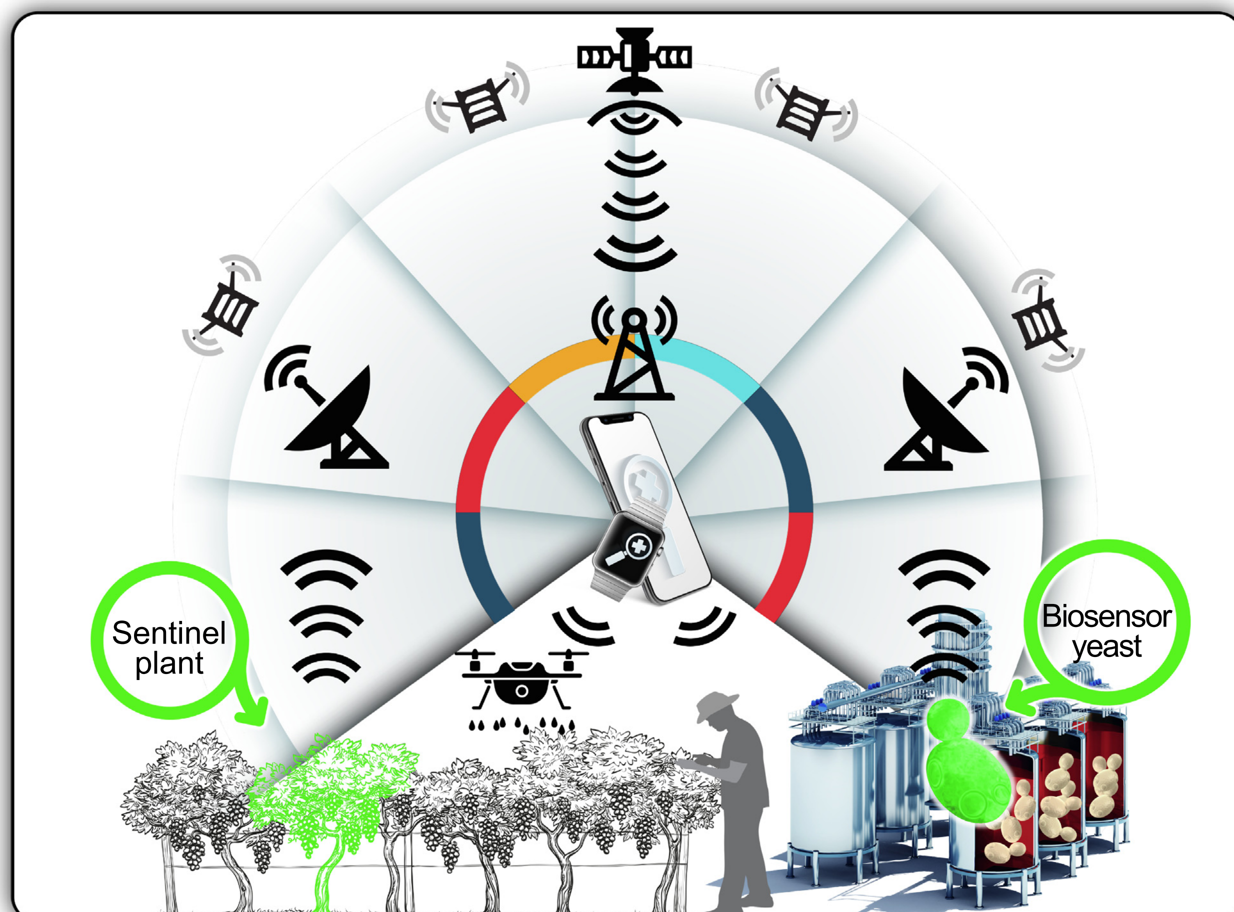


Figure 2. A biofoundry's design–build–test–learn cycle for industrial scale up. The information-managed design–build–test–learn cycle is a well understood route for undertaking the information-managed engineering of biology. Industrial scale up of validated designs is supported by a rapidly growing upstream and downstream ecosystem of commercial players.

for digital consumption (Figure 3). Multiscale sentinel agriculture is one of these promising research and development avenues [23,28–30]. The integration of cyberbio technologies in 'multiscale' designs can enable bidirectional communication across organic and inorganic information systems, such as biological devices and computer systems. For example, biosensor-enabled sentinel vines could facilitate information transfer from within an engineered vine in a vineyard and the surrounding *terroir* to a nearby 'smart farm' via satellite constellations or fifth generation telecommunications infrastructure. Sentinel viticulture is likely to render visible an array of bioinformation above and below ground at the micro through to the nano scale at varying degrees of complexity and abstraction [31,32]. Once this information is available, it can be integrated within decision-making and control loops that actuate autonomous robotic interventions on the vine or in the vineyard. Increasing the real-time availability of bioinformation in digital systems is the first step in reducing the latency of autonomous robotic interventions and implementing next-generation precision viticulture. Over time, vintners that use these kinds of monitoring technologies are likely to discover the bioinformational footprint for superior



Trends in Biotechnology

Figure 3. The internet of biological things for the vintner. The internet of biological things (IoBT) is a concept describing the cyber-networking of biological organisms and processes. This will facilitate low-latency monitoring and precision interventions both in the vineyard and in the winery. Sentinel vines can report stressors via satellite constellations and interventions can be made via drone. Yeast strains equipped with a biosensor can report culture condition ensuring controlled fermentation.

vintages. Though this may displace some of the 'magic' behind making a superior bottle of wine, it will allow those who understand and reinforce each element of a superior vintage to outperform their competitors. At the core of this is a rarefication of the myths and magic behind making and tasting wine, and the understanding that each element in a biological process creates bioinformational metadata that can be monitored, analysed, and evaluated with contemporary technology. For instance, the company Aromyx makes digitally enabled olfactory biosensors that can rationalise wine taste and fragrance characterisation. The digital shadow of a superior wine will come to be just as valuable, perhaps even more so, than the actual vintage, because that digital shadow will ensure a vintner can continue to maintain their superior production quality and is ultimately a bioinformational property of the vintner's work. Perhaps more importantly, that digital shadow may soon be synthetically replicable in the sense that the chemical composition of a superior vintage can be manufactured without grapes or fermentation. For example, the San Francisco start-up Ava Winery is beginning to achieve this by analysing the chemical composition of wines and recapitulating that composition without grapes or fermentation. This would facilitate the mass synthesis of superior quality vintages, allowing the technologically-enabled vintner to fully capitalise on their biophysical and bioinformational assets in any given season, thus allowing them to offset the risk of a biological shock in a later season.

Similarly, a vineyard with a sentinel vine that deploys a synthetic biosensor may be able to rationally engineer electrical pulses from the vine via satellites to a smart viticultural station nearby to alert when the vines are under water stress and automatically switch on the irrigation system (Figure 3). This could solve challenges with under- and over-watering, and in so doing optimise both water use and crop yield. Similarly, the same sentinel vine could also 'report', in real-time, when the vineyard experiences mould-induced stress and other biotic stresses.

Autonomous fermentation tanks (bioreactors) may be able to offer smart culture-condition control and the targeted actuation of engineered gene expression in malolactic bacteria and wine yeast strains without the intervention of the winemaker (Figure 3). Bioinformational systems involving optogenetic control of gene expression and biosensor-mediated output of intracellular physiological states of wine yeasts and malolactic bacteria could be integrated within a wine tank to facilitate optimal production and quality [23,33–35]. Synthetic biology applications for alcoholic beverages are promising a number of development branches that the industry will need to keep a close watch on over the coming decade (Box 2).

Across the longer term, the data availability heuristic could facilitate bioinformation being stored and accessed in biological substrates. With the building of the first synthetic yeast genome nearing finalisation [36], a key example here is the idea of a synthetic metagenome, or the concept of a ready-to-use 'ecosystem in a cell' [21]. A synthetic yeast metagenome could theoretically store a representation of the yeast ecology of a local *terroir* within a single synthetic organism, *Saccharomyces cerevisiae*. Time series sampling and storage of the local yeast ecology within multiple metagenomes would provide an efficient and effective method for identifying changes in the local ecology over time, changes that might be detrimental to the productivity of the vines or the taste of wine. The metagenome concept highlights the fact that in the longer term, complex biological information may best be stored and accessed from synthetic biological substrates.

Synthetic biology for future alcoholic beverages

As climate change affects traditional winemaking regions [37], the tools of synthetic biology may be used to maintain desired wine characteristics and enhance flavour profiles. For example, as climates warm, there is a greater chance that grapes will have higher sugar content, leading to undesirably high alcohol content in wine. To counter this problem, yeast strains have been

Box 2. Cyberbio convergence for high-throughput automation

Cyber–biological convergence has manifested across: (i) the application of engineering thinking and the design–build–test–learn (DBTL) framework to biological functionality [7]; (ii) the multiscale digital abstraction of biological functionality via computer aided design (CAD) tools [7,23]; and (iii) the creation, development, standardisation, and maintenance of bioinformational libraries for different length–scale abstractions such as proteins, antibodies, genomes, genetic parts, biological devices, and their associated metadata [20,23]. It is timely to review the contribution of cyber–biological convergence to the COVID-19 pandemic response as the development trajectory for these capabilities will contribute to global pandemic preparedness (in crops, animals, and humans) throughout the 21st century and beyond.

Twenty years of research and development enabled biofoundries to pivot when the COVID-19 outbreak manifested [79,80]. Several member foundries of the Global Biofoundries Alliance (GBA) and the International Gene Synthesis Consortium (ISCG) pivoted in response to COVID-19. They developed high-throughput testing protocols to mitigate testing bottlenecks in rural and urban scenarios, and they developed viral-like particles to validate the research and development of new testing protocols. The scale of the biofoundry response to the COVID-19 outbreak suggests these facilities should now be conceptualised as pandemic preparedness capabilities that support the wider **bioeconomy** when they are not dedicated to emergency response [79,80].

Biofoundries could not function without their supporting CAD toolsets. Again, these toolsets trace their research and development back at least a decade and are inextricably linked to the birth of synthetic biology as a discipline. The University of California Berkeley hosted their inaugural Critical Assessment of Genome Interpretation (CAGI) competition in 2010. From there the DBTL software market has grown to include cloud computing, browser-based applications, and machine learning. Commercial services exist in a large and growing ecosystem that shares space with open-source researcher-developed code. Yet, neither of these services could exist today if not for the brute force work of fundamental biochemistry and genetics research [81–83] which continues to make critical contributions to the characterisation of biological functionality. This research has painstakingly catalogued biological functionality at varying degrees of information abstraction, length, and time scales for the past 2 decades. Indeed, the fact that many biopharmaceutical companies had selected a vaccine candidate before many people even knew there was a virus outbreak is indicative of the scale and power of engineering biology's contemporary CAD solutions.

engineered to produce less alcohol by diverting carbon flux towards glycerol, a tasteless metabolite [38]. Yeast strains have also been engineered to enhance wine flavour by producing a variety of molecules, such as thiols and raspberry ketone [39,40]. A prominent example in the brewing industry was the engineering of yeast to produce hop flavours [41]. In practice this would mean that hop plants are not required for beer, reducing the land, water, fertiliser, and associated greenhouse gases required for brewing. The company Berkeley Yeast is currently commercialising engineered wine and beer yeasts for enhanced performance, flavour, and environmental sustainability, while LanzaTech is capturing carbon waste streams and recycling them via co-located brewing processes. The environmental impacts of winemaking and brewing will become significant as the world moves to a net-zero carbon emission economy by 2050. Recent examples of how agriculture and fermentation can be engineered for reduced carbon footprints include rewiring of photosynthesis in crops to increase the efficiency of CO_2 incorporation to biomass [42], and the re-assimilation of CO_2 produced by bioethanol yeast to increase ethanol yields [43]. An extreme extension of sustainable alcoholic beverage production would therefore be to engineer strains of yeast that are capable of fermentation from more sustainable carbon sources, such as sugars or greenhouse gases, so that resource intensive grains or grapes are not required. Utilisation of greenhouse gas derivatives is within reach, as *S. cerevisiae* has recently been engineered to metabolise methanol and formate [44,45], and the methylotrophic yeast *Pichia pastoris* was recently engineered to grow on CO_2 as the sole carbon source [46]. Producing complex alcoholic beverages from simple industrial carbon sources would involve extensive metabolic engineering of yeast to recapitulate the flavour and mouth feel components that are normally derived from grapes or grains in the yeast metabolic network, while maintaining ethanol production. In theory this approach could enable the production of complex alcoholic beverages from carbon sources such as sugarcane, CO_2, or even sugars derived from photosynthetic bacteria growing on CO_2. Alcoholic beverage production from simple carbon sources would have a smaller environmental footprint relative to traditional practices, and could open up the possibility of production in remote locations on Earth and beyond [47]. Across the medium term, however, grape and wine experiments in space are likely to be focused on optimising agricultural yield back on Earth. The company Space Cargo Unlimited received a return shipment of 320 snippets of Merlot and Cabernet Sauvignon grapevines from the International Space Station in January 2021. These experiments seek to activate functionally useful genetic and epigenetic changes via the stressors of cultivation in space. The ultimate aim of activating these genetic and epigenetic changes is to redeploy them for the benefit of grape growing and winemaking under Earth's changing climate.

The anchors of bioethics and the wings of bioinformation in the wine sector

All of the previously stated advances aimed at mitigating future biological shocks must also occur within the current ethical context of winemaking and grape growing [48]. For much of wine's long history, this ethical context has been set in Europe by Europeans. Indeed, there is much research available on how bioethics debates of previous decades have been shaped in part by European political concerns [49]. The salience and prominence of European bioethics in determining the standards of grape growing and winemaking will necessarily need to accommodate global changes in production and consumption patterns. That said, the adaptation of European winemaking to 19th century disruptions indicate that the European wine sector can respond in an agile manner to selection pressures that require a continual evolution of manner and method. The course of winemaking over the next few decades will necessarily be born from the political, ethical, and mythical discourses that underpin the growing of grapes and the fermenting of wine in different *terroirs* and different markets around the world, and further into the future, in off world scenarios and habitats.

Concluding remarks

Finding certainty in an uncertain world poses a massive challenge to every person, company, industry, and nation. The grape and wine industry is not alone in its craving for certainty and stability on one hand, and its fascination with uncertainty and adventure on the other (see Outstanding questions). Yet, as political and ethical processes in the grape and wine industry have shown before, strong selection pressures can either induce change or inertia in production processes. This makes sense in an industry that is thousands of years old: such an industry not only needs to display high levels of resilience but also requires a careful and selective approach to adaptation.

This article contends that the global trend of biotechnology is to render biological information visible in digital systems, and that there will be an advantage for those grape growers and winemakers that adapt to and take advantage of this development. From the colorimetric output of fragrance and flavour through to digitally enabled biosensors or the crop-integration of sentinel plants and precision agriculture, the paths and ways of grape and wine production are becoming informationally-enabled. Companies like Aromyx are already offering products in this space. The savvy grape grower and winemaker will be undertaking pilot projects incorporating these types of bioinformational products within the next 5 years. Similarly with sentinel plants, if producers undertake initial work today with companies like Planet that specialise in space-based observation with a daily refresh rate, they will be ready for next-generation commercial solutions deployed at decreasing time- and length-scales. At their simplest, sentinel plants are grown specifically to place early warning triggers across a field. Contemporary sentinels do not need to be bioengineered if they express desired early warning signs appropriately. Whether a sentinel is bioengineered or not, the monitoring tools that will track that plant are the same. These technologies, such as space-based observation, drone-based observation, and co-located biosensor technologies, are all at varying degrees of maturity and companies today can deliver these capabilities for various applications. Future-ready grape growers and winemakers should at the very

Outstanding questions

How can we integrate sentinel plants with precision agriculture for improved vineyard management?

Can autonomous bioreactors deploy engineered gene expression pathways and biosensor-mediated output to facilitate optimised production and quality?

Can digitally interoperable olfactory biosensors rationalise wine taste and fragrance characterisation and contribute to production quality control?

How will producers and consumers adopt climate change mitigation efforts that deploy engineered yeast strains, to counter higher alcohol content due to the higher sugar content in grapes arising from warmer temperatures?

What is the future for computer-assisted design as an enabler of grape and wine biotechnology?

How will producers use the bioinformational production profile of superior vintages of wine to ensure ongoing production quality?

least be thinking about experimenting with these companies and their products in the next 5 years in order to customise targeted sentinel agriculture pilot projects for their needs.

Previously, grape growing and winemaking operated on a timescale of validation that required an entire season or longer, before claims of quality could be made. Bioinformation on the nano- and micro-scale will bring minute daily fluctuations of biological processes from the field and the fermenter to the laptop. These technologies are likely to become critical to providing resilience to future environmental and economic disasters from climate change, pests, or pandemics, as well as unpredicted and unpredictable biological shocks of unknown origins. This trend is well underway, and it will gradually accelerate across the industry. There will be a first mover advantage for those producers that upskill today and develop bioinformational expertise by incorporating space observation, sentinel plant monitoring, and commercial biosensors into their production processes. Similarly, this will be true for those winemakers that spend time today characterising the vine and yeast physiology and molecular biology most important to their operations. The ability to mitigate the impacts of a changing climate comes first from mapping those unique biological pathways on which one relies for sustainable profit. It is currently difficult to estimate how much the industry might change, or how the validation of quality and the mitigation of risk might evolve. One thing is certain: it is unlikely the convergence of information and biology can be ignored forever.

Acknowledgements
External support for Macquarie University's Synthetic Biology initiative is acknowledged from Bioplatforms Australia, the New South Wales (NSW) Chief Scientist and Engineer, and the NSW Government's Department of Primary Industries. Australian Government funding through its investment agency, the Australian Research Council, towards the Macquarie University-led ARC Centre of Excellence for Synthetic Biology is gratefully acknowledged. Bronte Turner from Serpentine Studio is gratefully acknowledged for the artwork used in the Figures.

Declaration of interests
No interests are declared.

References
1. Vickers, C.E. (2016) The minimal genome comes of age. *Nat. Biotechnol.* 34, 623–624
2. Goold, H.D. *et al.* (2018) Emerging opportunities for synthetic biology in agriculture. *Genes* 9, 341
3. Gleizer, S. *et al.* (2019) Conversion of *Escherichia coli* to generate all biomass carbon from CO2. *Cell* 179, 1255–1263
4. Gassler, T. *et al.* (2020) The industrial yeast *Pichia pastoris* is converted from a heterotroph into an autotroph capable of growth on CO_2. *Nat. Biotechnol.* 38, 210–216
5. Wang, L. *et al.* (2017) A review of computational tools for design and reconstruction of metabolic pathways. *Synth. Syst. Biotechnol.* 2, 243–252
6. Kearse, M. *et al.* (2012) Geneious basic: an integrated and extendable desktop software platform for the organization and analysis of sequence data. *Bioinformatics* 28, 1647–1649
7. Hillson, N.J. *et al.* (2012) DNA assembly design automation software. *ACS Synth. Biol.* 1, 14–21
8. Nielsen, A.A.K. *et al.* (2016) Genetic circuit design automation. *Science* 352, aac7341
9. Leaver-Fay, A. *et al.* (2011) In *Computer Methods, Part C. Methods in Enzymology* (Vol. 487) (Johnson, M.L. and Brand, L., eds), pp. 2–637, Academic Press
10. Delépine, B. *et al.* (2018) RetroPath2.0: a retrosynthesis workflow for metabolic engineers. *Metab. Eng.* 45, 158–170
11. Finley, S.D. *et al.* (2009) Computational framework for predictive biodegradation. *Biotechnol. Bioeng.* 104, 1086–1097
12. Lin, G.-M. *et al.* (2019) Retrosynthetic design of metabolic pathways to chemicals not found in nature. *Curr. Opin. Syst. Biol.* 14, 82–107
13. Groher, A.-C. *et al.* (2019) Tuning the performance of synthetic riboswitches using machine learning. *ACS Synth. Biol.* 8, 34–44
14. Jervis, A.J. *et al.* (2019) Machine learning of designed translational control allows predictive pathway optimization in *Escherichia coli*. *ACS Synth.Biol.* 8, 127–136
15. Kotopka, B.J. and Smolke, C.D. (2020) Model-driven generation of artificial yeast promoters. *Nat. Commun.* 11, 2113
16. Karim, A.S. *et al.* (2020) *In vitro* prototyping and rapid optimization of biosynthetic enzymes for cell design. *Nat. Chem. Biol.* 16, 912–919
17. Radivojević, T. *et al.* (2020) A machine learning automated recommendation tool for synthetic biology. *Nat. Commun.* 11, 4879
18. Zhang, J. *et al.* (2020) Combining mechanistic and machine learning models for predictive engineering and optimization of tryptophan metabolism. *Nat. Commun.* 11, 4880
19. McLaughlin, J.A. *et al.* (2020) The Synthetic Biology Open Language (SBOL) version 3: simplified data exchange for bioengineering. *Front. Bioeng. Biotechnol.* 8, 1009
20. Hillson, N. *et al.* (2019) Building a global alliance of biofoundries. *Nat. Commun.* 10, 2040
21. Belda, I. *et al.* (2021) Seeding the idea of encapsulating a representative synthetic metagenome in a single yeast cell. *Nat. Commun.* 12, 1599
22. Dixon, T.A. *et al.* (2020) Bio-informational futures: the convergence of artificial intelligence and synthetic biology. *EMBO Rep.* 21, e50036
23. Dixon, T.A. *et al.* (2021) Sensing the future of bio-informational engineering. *Nat. Commun.* 12, 388

24. Way, J.C. *et al.* (2014) Integrating biological redesign: where synthetic biology came from and where it needs to go. *Cell* 157, 151–161
25. Heinemann, M. and Panke, S. (2006) Synthetic biology—putting engineering into biology. *Bioinformatics* 22, 2790–2799
26. National Research Council (2004) *Productivity and Cyclicality in Semiconductors: Trends, Implications, and Questions. Report of a Symposium*, The National Academies Press, Washington DC
27. Aurand, E. *et al.* (2019) *Engineering Biology: a research roadmap for the next-generation bioeconomy*, Engineering Biology Research Consortium
28. Vettraino, A. *et al.* (2015) Sentinel trees as a tool to forecast invasions of alien plant pathogens. *PLoS One* 10, e0120571
29. Mansfield, S. *et al.* (2019) The value of sentinel plants for risk assessment and surveillance to support biosecurity. *NeoBiota* 48, 1–24
30. Felsot, A.S. *et al.* (1996) Using sentinel plants as biomonitors of herbicide drift and deposition. *J. Environ. Sci. Health* 31, 831–845
31. Ma'ayan, A. (2017) Complex systems biology. *R. Soc. Interface* 14, 20170391
32. Schwille, P. (2017) Biology and the art of abstraction. *Biophys. Rev.* 9, 273–275
33. Carpenter, A.C. *et al.* (2018) Blueprints for biosensors: design, limitations, and applications. *Genes* 9, 375
34. Williams, T.C. *et al.* (2016) Synthetic evolution of metabolic productivity using biosensors. *Trends Biotechnol.* 34, 371–381
35. Williams, T.C. *et al.* (2017) Positive-feedback, ratiometric biosensor expression improves high-throughput metabolite-producer screening efficiency in yeast. *Synth. Biol.* 2, ysw002
36. Pretorius, I.S. and Boeke, J.D. (2018) Yeast 2.0-Connecting the dots in the construction of the world's first functional synthetic eukaryotic genome. *FEMS Yeast Res.* 18, foy032
37. Van Leeuwen, C. *et al.* (2019) An update on the impact of climate change in viticulture and potential adaptations. *Agronomy* 9, 514
38. Goold, H.D. *et al.* (2017) Yeast's balancing act between ethanol and glycerol production in low-alcohol wines. *Microb. Biotechnol.* 10, 264–278
39. Lee, D. *et al.* (2016) Heterologous production of raspberry ketone in the wine yeast *Saccharomyces cerevisiae* via pathway engineering and synthetic enzyme fusion. *Microb. Cell Fact.* 15, 49–55
40. Van Wyk, N. *et al.* (2019) The whiff of wine yeast innovation: strategies for enhancing aroma production by yeast during wine fermentation. *J. Agric. Food Chem.* 67, 13496–13505
41. Denby, C.M. *et al.* (2018) Industrial brewing yeast engineered for the production of primary flavor determinants in hopped beer. *Nat. Commun.* 9, 965
42. Guadalupe-Medina, V. *et al.* (2013) Carbon dioxide fixation by Calvin-Cycle enzymes improves ethanol yield in yeast. *Biotechnol. Biofuels* 6, 125
43. Li, Y.J. *et al.* (2017) Engineered yeast with a CO_2-fixation pathway to improve the bio-ethanol production from xylose-mixed sugars. *Sci. Rep.* 7, 43875
44. Espinosa, M.I. *et al.* (2020) Adaptive laboratory evolution of native methanol assimilation in *Saccharomyces cerevisiae*. *Nat. Commun.* 11, 5564
45. Gonzalez de la Cruz, J. *et al.* (2019) Core catalysis of the reductive glycine pathway demonstrated in yeast. *ACS Synth. Biol.* 8, 911–917
46. Gassler, T. *et al.* (2020) The industrial yeast *Pichia pastoris* is converted from a heterotroph into an autotroph capable of growth on CO_2. *Nat. Biotechnol.* 38, 210–216
47. Llorente, B. *et al.* (2018) The multiplanetary future of plant synthetic biology. *Genes* 9, 348
48. Sliva, A. *et al.* (2015) Freedom and responsibility in synthetic genomics: the synthetic yeast project. *Genetics* 200, 1021–1028
49. Herring, R. and Paarlberg, R. (2016) The political economy of biotechnology. *Annu. Rev. Resour. Econ.* 8, 397–416
50. Chambers, P.J. and Pretorius, I.S. (2010) Fermenting knowledge: the history of winemaking, science, and yeast research. *EMBO Rep.* 11, 914–920
51. Dixon, T. and Pretorius, I.S. (2020) Drawing on the past to shape the future of synthetic yeast research. *Int. J. Mol. Sci.* 21, 7156
52. Jagtap, U.B. *et al.* (2017) Synthetic biology stretching the realms of possibility in wine yeast research. *Int. J. Food Microbiol.* 252, 24–34
53. McGovern, P. (2004) *Ancient Wine: The Search for the Origin of Viticulture*, Princeton University Press
54. Robinson, J. (1999) *The Oxford Companion to Wine*, Oxford Press
55. Ordish, G. (1987) *The Great Wine Blight*, Sidgwick & Jackson Ltd.
56. Lewin, B. (2010) *Wine Myths and Reality*, Vendange Press
57. Vivier, M.A. and Pretorius, I.S. (2002) Genetically tailored grapevines for the wine industry. *Trends Biotechnol.* 20, 472–478
58. Badouin, H. *et al.* (2020) The wild grape genome sequence provides insights into the transition from dioecy to hermaphroditism during grape domestication. *Genome Biol.* 21, 223–247
59. This, P. *et al.* (2006) Historical origins and genetic diversity of wine grapes. *Trends Genet.* 22, 511–519
60. Roach, M.J. *et al.* (2018) Population sequencing reveals clonal diversity and ancestral inbreeding in the grapevine cultivar Chardonnay. *PLoS Genet.* 14, e1007807
61. Jaillon, O. *et al.* (2007) The grapevine genome sequence suggests ancestral hexaploidization in major angiosperm phyla. *Nature* 449, 463–467
62. Mills, D.A. *et al.* (2005) Genomic analysis of *Oenococcus oeni* PSU-1 and its relevance to winemaking. *FEMS Microbiol. Rev.* 29, 465–475
63. Borneman, A.R. *et al.* (2008) Comparative genome analysis of a *Saccharomyces cerevisiae* wine strain. *FEMS Yeast Res.* 8, 1185–1195
64. Borneman, A.R. *et al.* (2013) Comparative genomics: a revolutionary tool for wine yeast strain development. *Curr. Opin. Biotechnol.* 24, 192–199
65. Borneman, A.R. *et al.* (2013) At the cutting-edge of grape and wine biotechnology. *Trends Genet.* 29, 263–271
66. Borneman, A.R. and Pretorius, I.S. (2015) Genomic insights into the *Saccharomyces sensu stricto* complex. *Genetics* 199, 281–291
67. Dunn, B. *et al.* (2012) Analysis of the *Saccharomyces cerevisiae* pan-genome reveals a pool of copy number variants distributed in diverse yeast strains from differing industrial environments. *Genome Res.* 22, 908–924
68. Hyma, K.E. *et al.* (2011) Divergence in wine characteristics produced by wild and domesticated strains of *Saccharomyces cerevisiae*. *FEMS Yeast Res.* 11, 540–551
69. Legras, J.L. *et al.* (2018) Adaptation of *S. cerevisiae* to fermented food environments reveals remarkable genome plasticity and the footprints of domestication. *Mol. Biol. Evol.* 35, 1712–1727
70. Novo, M. *et al.* (2009) Eukaryote-to-eukaryote gene transfer events revealed by the genome sequence of the wine yeast *Saccharomyces cerevisiae* EC1118. *Proc. Natl. Acad. Sci. U. S. A.* 106, 16333–16338
71. Peter, J. *et al.* (2018) Genome evolution across 1,011 *Saccharomyces cerevisiae* isolates. *Nature* 556, 339–344
72. Giorello, F. *et al.* (2019) Genomic and transcriptomic basis of *Hanseniaspora vineae*'s impact on flavour diversity and wine quality. *Appl. Environ. Microbiol.* 85, e01959–e02018
73. Seixas, I. *et al.* (2019) Genome sequence of the non-conventional wine yeast *Hanseniaspora guilliermondii* UTAD222 unveils relevant traits of this species and of the *Hanseniaspora* genus in the context of wine fermentation. *DNA Res.* 26, 67–83
74. Tondini, F. *et al.* (2018) Genome sequence of Australian indigenous wine yeast *Torulaspora delbrueckii* COFT1 using nanopore sequencing. *Genome Announc.* 6, e00321–e00328
75. Pretorius, I.S. (2020) Tasting the *terroir* of wine yeast innovation. *FEMS Yeast Res.* 20, foz084
76. Pretorius, I.S. and Bauer, F.F. (2002) Meeting the consumer challenge through genetically customised wine yeast strains. *Trends Biotechnol.* 20, 426–432
77. Curtin, C.D. *et al.* (2012) *De-novo* assembly and analysis of the triploid genome of the wine spoilage yeast *Dekkera bruxellensis*. *PLoS ONE* 7, e33840
78. Curtin, C.D. and Pretorius, I.S. (2014) Genomic insights into the evolution of industrial yeast species *Brettanomyces bruxellensis*. *FEMS Yeast Res.* 14, 997–1005

79. Crone, M.A. *et al.* (2020) A role for Biofoundries in rapid development and validation of automated SARS-CoV-2 clinical diagnostics. *Nat. Commun.* 11, 4464
80. Kitney, R.I. *et al.* (2021) Build a sustainable vaccines industry with synthetic biology. *Trends Biotechnol.* Published online January 8, 2021. https://doi.org/10.1016/j.tibtech.2020.12.006
81. Radler, F. (1986) Microbial biochemistry. *Experientia* 42, 884–893
82. Moreno-Arribas, M.V. and Polo, M.C. (2005) Winemaking biochemistry and microbiology: current knowledge and future trends. *Crit. Rev. Food Sci. Nutr.* 45, 265–286
83. Gómez-Plaza, E. and Gil-Muñoz, R. (2021) Biochemistry of Wine and Beer. *Biomolecules* 11, 59