

# Omics and the bioeconomy

*Applications of genomics hold great potential for a future bio-based economy and sustainable development*

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In the wake of the worst financial crisis since 1930, many countries face the challenge of creating a new economy model that relies less on financial services but more on production. Science therefore plays an increasingly important role to generate the knowledge that will eventually give rise to these new products. This coincides with the grand challenges of the 21<sup>st</sup> century: dealing with the effects of global climate change, energy security and producing enough food for a growing human population. By 2050, nine billion people are expected to live on this planet, who will need access to food and clean water while the area of fertile land for agricultural is decreasing owing to overgrazing, salinisation, desertification and urban development.

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One promising strategy to meet these challenges is the bioeconomy, a sustainable model based on biological production, which has the potential to decouple economic growth and greenhouse gas (GHG) emissions, increase food production, and help to preserve the environment. The OECD published a policy agenda for developing a bioeconomy in 2009 and interest has been growing since. In 2012, the USA published its bioeconomy blueprint, and the EU elaborated a similar strategy.

Several other nations, including Belgium, Canada, Germany, the Netherlands and South Africa, have also developed their own bioeconomy strategies. Generally, these strategies rely on more efficient agriculture to increase the production of food, biofuels or complex compounds for the chemical industry. However, if a future bioeconomy is seen as the major solution to achieve all these goals, it will be necessary to reconcile agricultural and industrial needs for biomass and land. It is clear that there is much capacity for improving agricultural productivity and industrial production through the application of science; here, we highlight the progress and potential value of genomics and associated technologies for several key sectors that a future bioeconomy will rely on.

The past decade has seen a growing middle class in formerly developing countries in Asia, South America and Africa. Their increasing wealth goes along with consumption and, in particular, a growing demand for meat consumption, which stresses agricultural production. The production of meat, in particular beef, requires large amounts of feed and/or pasture, large amounts of water and it thereby contributes to deforestation. Genomics therefore holds potential to increase production efficiency. One of the greatest challenges to successfully apply genomics, however, is the wide diversity of breeds used across the industry and the fact that cattle functional genomics is still in its infancy.

Beef cattle breeding to increase protein production requires selection of economically relevant traits (ERTs), most of which are quantitative traits such as early life growth or

carcass quality. These are output traits that impact revenue. There are many other ERTs though that are not breeding objectives—such as disease resistance, feeding efficiency—because the capacity to collect data in the field does not exist or the cost of collecting data is too high. Many of these ERTs affect input costs of production and these are fertile ground for the application of genomics. Efforts to sequence the genomes of important animal breeds for the beef industry are being made to identify variants and to associate those variants with genetic variations across beef populations with the aim to improve the selection of desirable traits in breeding programmes.

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In the near future, artificial reproductive technologies combined with genomics might become available for cattle breeding. This could enable verification of favourable traits in embryos and make breeding faster and much more accurate. The development of specific “genomic-audited” lineages may offer opportunities for the livestock industry to produce the animal required for each type of application, thereby improving quantity and quality.

Another cause for the expansion of cattle production is the increasing global demand for milk, particularly in Asia. Again, genomics

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could help to improve both quantitative and qualitative traits in breeding cattle for milk production. A very important economic factor is protein content, which has a linkage to heritability. Lesley-Ann Raven and colleagues from the Department of Primary Industries Victoria in Australia demonstrated a role for the RNASE5 (*angiogenin ribonuclease, RNase A family 5*) pathway, indicating that sequence polymorphisms might explain some of the observed differences in protein content [1]. Their methodology contributes to the fundamental science of lactation, with practical implications for milk production. A related issue with particular relevance to human health is microbial spoilage of milk. Raw milk can contain a variety of human pathogens that have been associated with serious food-borne illnesses such as diphtheria and brucellosis. Other, non-pathogenic species can produce off-flavours, unwanted acidification, and thereby contribute to lower shelf life. Pasteurised milk is not completely risk-free either. The indigenous strains found in the dairy vary significantly from type strains, thus necessitating a better understanding of how they survive in milk, and how to take measures to ensure their eradication.

**R**uminant production is notoriously costly in terms of water and land, and it is also a major contributing factor for GHG emissions. Seafood could provide a more sustainable alternative to meat; indeed, seafood is already the highest value globally traded food commodity. However, many wild fish populations are over-exploited or in precipitous decline. Many wild fisheries should therefore be regarded as “not necessarily renewable” and the remaining ones need to be carefully managed to avoid unsustainable exploitation. There are many potential applications of genomics to fish production. Many difficulties associated with wild fisheries are related to mis-identification. Incorrect identification can lead to errors in estimating the actual magnitude of fish stocks, with consequences for fisheries management and fishing communities. Standardised DNA barcodes that are unambiguous, widely applicable and globally accessible to the non-expert could therefore address this and other problems such as traceability, illegal fishing and fraud [2].

Aquaculture is a viable and sustainable alternative to wild fish and production has been growing annually at around 6–8%. Today, farmed seafood—around 60 million

tonnes each year—exceeds the yield of wild fisheries and has significant potential for future growth. High priorities for genomics research to improve fish farming are the development of single-sex populations and improving disease resistance. Production of single-sex stocks—either male or female, depending on the species—helps to cut costs: In any commercial fish species, one sex usually reaches maturity and market size more quickly than the other; for instance, male Nile tilapia grow faster than females while it is the other way around in halibut. Genomics research is now contributing to understanding the sex determination mechanism, as illustrated by two recent papers applying restriction-associated DNA (RAD) sequencing analysis to tilapia and halibut. Christos Palaiokostas from the University of Stirling in the UK and colleagues developed assays for sex-associated DNA markers from RAD sequencing analysis to help implement single-sex female halibut production [3]. They used the same technique to identify a candidate region for sex-determining gene(s) and sex-linked single nucleotide polymorphisms in male Nile tilapia, with no ambiguity in assigning sex [4].

**F**eeding all humans on this planet remains a major challenge, which is further exacerbated by the growing demand for bio-based fuels, chemicals and plastics and the effects of global climate change. Arable land is the critical resource and it is dwindling. Estimates vary, but arable soil is being lost between 13 and 40 times faster than its rate of renewal [5]. About 2.5% of arable land in China is too contaminated for agricultural use [6]. In the face of soil destruction and pollution, more crops will have to be grown more efficiently. There are many applications of genomics to crop production with great potential to improve yields: pest resistance; more “efficient” use of water; resistance to environmental stress; tolerance of contaminants; and nitrogen fixation to replace synthetic fertilisers.

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The 1988 drought in the USA caused in a 30% reduction in US corn production and

cost about US\$39 billion. The USA has again just experienced its most widespread drought in more than half a century, and the 2014 drought in California is perhaps the worst ever recorded. As agriculture accounts for around 70% of all water use, measures to conserve water are of great social and economic importance. Moreover, heat and drought stress together can cause disproportionate damage to important crops compared with either stress individually [7]. Therefore, understanding dual stress tolerance in crop plants in multiple locations over multiple seasons has become a top priority in research. Transgenic plants with dual stress tolerance could enable farmers to maintain higher yield and productivity over variable and adverse environmental conditions.

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While many areas face the problem of too little water, other important food producers suffer from too much of it. Rice is an important staple crop well adapted to wet, monsoon climates and grows well in flooded landscapes; however, 18% of the global supply of rice is vulnerable to flash flooding [8]. Most rice varieties can tolerate only a few days of submergence and die after about a week. The SUBMERGENCE 1 (SUB1) trait has already been introduced into several varieties of rice through marker-assisted backcrossing without apparent adverse effects on the plants [8]. Under submergence for 7–14 days, such tolerant cultivars have an average yield advantage of 1.5 tonnes per hectare over intolerant cultivars, with no reduction in yield under non-submerged conditions. SUB1 is gradually being introduced to all varieties developed for lowland ecosystems by the International Rice Research Institute.

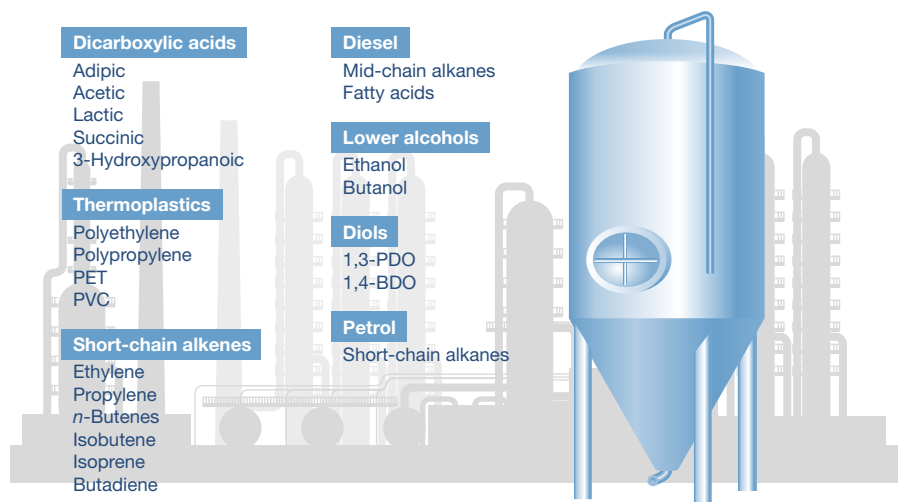
Nitrogenous fertilisers are major contributors to waterway eutrophication and GHG emissions, and the Haber-Bosch process, for synthesising ammonia from atmospheric nitrogen is very energy intensive. When the price of Brent crude oil rose from \$50 per barrel to about \$110 by January 2013, the prices for ammonia in

Western Europe and the Mid-Western Corn Belt in the USA roughly tripled over the same period (<http://marketrealist.com/2013/02/brent-oil-moves-nitrogenous-fertilizer-prices/>). Again, genomics could have a major impact here and synthetic biologists have already made important progress towards inserting microbial genes into the cells of crop plants that would enable these plants to fix nitrogen from the atmosphere. This opens up the possibility of creating plants that make their own fertilisers, which could revolutionise agriculture, and significantly decouple it from the oil industry.

While genomics could significantly affect agriculture and aquaculture, it has even more potential for industrial biotechnology and the bio-based production of fuels, chemicals and plastics. Most of these products are still made from fossil resources. Given that most crude oil is used for fuel production and that there is currently no shortage of fossil oil or gas, there is no pressing need for the chemical industry to replace the oil barrel with renewable resources. However, increasing political pressure and societal awareness over climate change and energy security may necessitate changes long before crude oil becomes scarce. In fact, genomics and synthetic biology have made considerable advances in generating “microbial factories” that produce important compounds for the chemical industry including plastic monomers, synthetic fuels or drug precursors.

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One of the questions is about how many fossil-derived chemicals and other products can eventually be replaced with bio-based equivalents (Fig 1). There is now early evidence that even completely unnatural compounds can be manufactured using microbial cells. The list is increasing, while the time from conception to production (the innovation cycle) is decreasing. However,



**Figure 1. Examples of chemicals and fuels that can be synthesised through metabolic engineering of microbes.**

what is achievable in the laboratory may never see commercial mass production. Bio-based production of aromatics, an extremely important class of industrial chemicals, is still a major challenge, partly because of their toxicity to microbial cells.

Another major challenge for synthetic biology is synthesising fuels and other compounds from lignocellulose. For now, most microbial factories and biofuel production require crop plants as biomass source, which directly competes with food production. Lignocellulose from non-food crops, and agricultural, forestry and food wastes would significantly resolve this problem and open a whole new resource for biotechnology. Yet, before the dominance of the petrochemicals industry, wood refineries existed in significant numbers to produce fuel and other products, while lignocellulose is a potential source of aromatic compounds. The combination of wood or “green” chemistry with microbial metabolic engineering could eventually become economically and technically feasible to replace food crops as the major resource for the biochemical industry. The ultimate goal is the integrated biorefinery that synthesises multiple classes of bio-based products from multiple sources of biomass. Yet, bio-based production is still in its infancy with a preponderance of single substrate, single product biorefineries. Moreover, the translation from a proof of principle in the laboratory to industrial-scale processes is not easy and a costly undertaking. Public-private partnerships

will be required to decrease the risk for private investments.

Perhaps the most controversial issue regarding bio-based production is indirect land use change (ILUC) when land used for food production is converted to grow non-food crops. This problem was first highlighted in 2009 [9], and it has since become an increasingly perplexing political issue. One route to avoid ILUC, and spin-off issues such as the food versus fuel debate, is to use industrial waste gases, such as CO<sub>2</sub> and CO, as feedstocks for fermentation. A good example is the use of steel mill off-gases, especially highly toxic CO, to produce chemicals [10]. Photosynthetic and non-photosynthetic biocatalysts are being developed that could improve yields and titres. The first solid waste biorefineries have also been built, which address another societal challenge, namely the diminishing supply of suitable landfill sites. It again highlights that environmental and economic aspirations need not contradict each other.

We are just at the start of developing bio-manufacturing and it is still a long way to a new energy model. It also requires developing new policies to support and guide these developments. Several bioeconomy-related policies are emerging such as green growth strategies, bioeconomy strategies, biomass R&D programmes, industrial biotechnology, bio-refinery and synthetic biology roadmaps. Clearly there is scope for policy overlaps, conflicts and contradictions. As different

ministries and departments are involved, they need to coordinate their policies and investments. Indeed, a crucial message from industry is the need for policy consistency and stability: most of the investments for this new future will have to come from the private sector, but policy stability is needed to decrease the risk of private investments.

One of the toughest issues, particularly in Europe, relating to the role of -omics technologies is public acceptance and support. Many applications of genomics technologies, for instance in breeding programmes or aquaculture, may not require genetic modification or synthetic biology. Industrial production usually takes place in contained bioreactors under strict regulation to diminish environment risks. However, the greatest hurdles in terms of public opposition are related to the deliberate release of genetically modified crops. Negative public reaction is not monolithic, however: many opponents are not against the technology *per se*, but are concerned about monopoly positions by large companies.

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To turn the aspirations of genomics, synthetic biology and biotechnology into real products will need a qualified workforce. The bioeconomy therefore poses a long-recognised conundrum for higher education:

the need for both breadth and depth and multi-disciplinarity. Yet, science and engineering still tend to be taught by discipline. Biologists who understand engineering are few but increasing in number. Adding business skills may also be necessary. Bioinformatics is rapidly becoming a major bottleneck, given the progress in high-throughput technologies and the need to analyse the data. New educational programmes would need careful design, but also careful monitoring to avoid over-estimating need or teaching young students the wrong skills.

In the wake of the human genome project and high-throughput genome sequencing, the major focus of genomics research and public attention has been human health. Of course, this is an important factor given the ageing populations in most advanced countries and the associated challenges to health care. According to the International Monetary Fund, the ratio of working people-to-elderly will change from currently 4:1 to 2:1 by 2050 with serious economic consequences. However, the trinity of food, energy and chemicals is also vital to the future bioeconomy. Food production, energy and chemicals are highly dependent on fossil fuel resources, and that will inevitably change. Many countries have already embarked on the journey to sustainable energy production, which is, without doubt, a long and expensive process that will have yet unknown impacts on our lifestyles. A society with drastic reductions in chemical products will trigger even larger lifestyle changes. With sufficient political and societal will and support, research could help make the necessary transitions easier to manage.

#### Conflict of interest

The authors declare that they have no conflict of interest.

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