Advancing Gas Fermentation Technologies: A multi-disciplinary challenge

This document summarises the outcome of a workshop on microbial systems with gaseous feedstocks run jointly by the Environmental Biotechnology Network (EBNet, www.ebnet.ac.uk) and the Carbon Recycling Network (https://carbonrecycling.net). The goal was to identify key questions and knowledge gaps, R&D needs for technology progression and transfer, and actions that should be undertaken to promote progress and alleviate any obstacles.

Outcomes - Main research and implementation issues

Microbial: Our understanding of fundamental systems biology in this area lags behind that in other fields, with some major knowledge gaps to be addressed.

There is significant untapped potential for the use of non-model organisms: very few strains have been investigated or had cultivation protocols developed, and much of the prokaryotic tree of life is unexplored. As an example, the entire domain of *Archaea* is under-represented in gas fermentations and in industrial biotechnology generally.

The potential of mixed cultures and microbial communities warrants more extensive investigation. Key questions include, what opportunities can they offer and when is the added complexity inherent in such systems of value? What are the trade-offs (ecological, technological, economic, regulatory) between synthetic biology and wild-type organisms, and between open and closed systems.

To unlock these opportunities will require the development of new tools for genetic characterisation and manipulation of non-model organisms and for mixed culture/community engineering.

Metabolic: Primary needs include a better overall grasp on the impact of external conditions on microbial metabolism, and on community structure where relevant. Key metabolic aspects include the role of electron transfer, electron donor selection, and electron bifurcation systems; the effect of microbial metabolites; and the prevention or mitigation of inhibition. More work is needed to explore spatial structure in microbial cultures, and how to manipulate and exploit it. Development and maintenance of biofilms is particularly relevant for many gas fermentations, given potential gains in mass transfer and volumetric throughput.

Mass transfer and hydrodynamics: Limitations in gas-liquid mass transfer are a critical factor in the design of most gas fermentation systems, and work is needed both to improve fundamental understanding of relevant factors and to develop better hydrodynamic models and design tools.

Experimental assessment is needed to clarify how fermentation broth properties (viscosity, surface tension etc) affect gas-liquid transfer and hydrodynamic behaviour. Better understanding of the rheological characteristics of these complex liquids is essential as a basis for engineering solutions with improved mixing and distributed biokinetics.

Improved insights into gas-liquid-biomass interactions in these complex multi-phase systems will elucidate how system design and operation can be used to modify the local micro-environment, and will also enable better design of scale-down experiments, allowing targeted investigation before transition to more expensive pilot-scale studies.

Process monitoring and control: Monitoring of fermentation parameters is vital for effective operation, and further advances in development of sensors and monitoring tools are needed to support this, with real-time in situ measurement of dissolved gas concentrations a particular priority.

Modelling: Multi-scale mechanistic modelling approaches have a critical role in this field. Simulation of bioreactors with integrated biokinetics offers a powerful tool for elucidation of microbe-microbe and microbe-environment interaction. The task is to bring together all levels from genetic, cellular and community through to bulk physical and chemical parameters. This will require liquid culture models covering cells and biofilms/flocs/granules and incorporating thermodynamics (metabolism) and hydrodynamics (flows and mass transfer) across scales relevant to the microbial environment.

Scale-up: One major topic requiring attention is scale-up, including the impact of scale effects on mixing and mass transfer and their repercussions for microbial metabolism and performance. To progress our understanding in this area will require both further development of open access facilities for gas fermentation, with investment in additional infrastructure; and more targeted support for scale-up and demonstration to move technology/integration readiness levels upwards.

Empirical and theoretical studies are needed to enable the development of high mass-transfer scalable gas phase bioreactors, and to allow understanding and exploitation of hydrodynamic and concentration gradients at full scale.

Other topics related to scale-up for technology progression include methods for hygienic operation of biofilm reactors; cost-reduction strategies where sterile or pure culture operation is required; and the development of cost-effective standard designs for gas fermentation reactors.

Feedstock, process and product: Several interlinked issues were identified concerning feedstock, process and product selection and diversification. There is a need for open and honest discussion of which bioprocesses/products to focus on. This could be supported by cost-benefit analysis of bioproduction methods for different classes of bioproducts e.g. bulk chemical, high-value and pharmaceutical.

Other factors to consider are the impact of gas quality and any purification requirements; and in the case of H_2 production, the need to accommodate intermittent renewable energy production while matching CO_2 supply conditions.

Significant work remains to be done on process selection for targeted products, and on recovery methods. One key aspect is recovery of non-volatile products from fermentation broths liquors, and its effects on system biology, either directly via in situ extraction or in downstream processing and recycling. Technology innovations in this area must be closely linked to overall process optimisation, with tools for effective integration of up, down and sidestream processes a critical requirement.

Modelling, including AI and machine learning approaches, again has a key role to help answer '**what-if**' questions in process control and operational decisions.

Mapping the location, scale and composition of gaseous and other feedstocks and linking this to logistics and markets is an essential step, both to identify specific process applications, and to assess the overall contribution of gas fermentation technologies to national and international net zero and sustainability targets.

Consideration should be given to the relative advantages of two-stage processes in which gaseous feedstocks are first converted into soluble form (e.g. formate, methanol) by physico-chemical means, before microbially-mediated conversion. This idea is attractive as it can reduce or eliminate some of the difficulties associated with gaseous feedstocks, such as mass transfer limitations and safety (flammability risks etc); although fermentation of these liquid feeds also has its challenges. Many of the key issues identified in the workshop - from systems biology to mixing and mass transfer, and from scale-up to process optimisation and investor confidence - also apply to systems of this type, however; and indeed are relevant to the development of a much wider range of industrial biotechnologies.

Actions for implementation

The multi-disciplinary nature of the subject has led to a perceived lack of holistic overview and knowledge integration in this area. Better understanding and communication is vital to create a generation that can engage effectively across disciplines and specialisms.

Staff recruitment can also be problematic, with current UK policies limiting access to the global talent pool. Talent acquisition and retention will be facilitated by initiatives to promote trans-disciplinary work and training.

Funding is key to progressing this area, via targeted cross-disciplinary, cross-sectoral funding opportunities. Open competitive challenges are an effective way to ensure progress, as is support for collaborative projects between industry and academia. Industrial engagement is also essential to enable informed appraisal and techno-economic assessment.

Many of the R&D needs identified above are also directly relevant to other microbially-mediated systems, and will offer performance benefits in a wide range of industrial biotechnology: progress in these areas thus adds value across the whole sector. Funding can be fragmented or subject to cross-Council remit issues, however, so targeted support is needed focusing on the interactions between physico-chemical, biological and engineering factors and on scale effects.

There is a clear need for dedicated funding streams to support scale-up, and for improved mechanisms to access such facilities. R&D and demonstration funding with a longer horizon for planned returns is also needed, to ensure the UK's place as an innovation leader rather than a follower.

Transparent reporting that facilitates comparison and sharing of data, models and practices is essential for rapid progress. There is a need to develop and promote agreed formats that allow 'anonymised' results to be collated for process data-mining on a wide variety of fermentations. Recent moves requiring accessibility of data and other outputs have been effective, and should be continued and strengthened.

Access to equipment and instrumentation at laboratory level is dispersed across Universities nationally. Safe working is essential even at small and pilot scale, and further initiatives to share expertise in H&S, HazID and HazOps should be promoted.

There is a lack of agility in contracts procedure and IP management in Universities. IP arrangements at University level could and should be simplified by development and sharing of sample agreements and templates.

Lack of trust by investors is an issue for all new technologies, perhaps especially in this area due to its relative novelty. Increased investor confidence could be promoted by identifying or creating new business cases with real positive societal, environmental and economic impact; as well as by raising the profile of gas fermentation technologies in general and by more focused support for technology translation and commercialisation.

For similar reasons the policy framework and investment climate are not fully supportive in this area. Initiatives are needed to inform policymakers and regulators on the potential contributions of these technologies, to promote their inclusion in broader policy assessments, and to facilitate the development of appropriate regulatory environments.

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