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Review

Computer-aided chemical engineering research advances in precision fermentation

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Precision fermentation is a promising food production technology that uses micro-organisms to produce specific proteins, fats, and vitamins, offering a more sustainable alternative to animal agriculture. This review explores recent advances in computer-aided chemical engineering research within precision fermentation, focusing on process systems engineering (PSE), process control, and artificial intelligence. PSE offers important process synthesis and process optimisation tools for fermentation, helping evaluate environmental impacts and economic feasibility during design. Advanced control strategies, such as soft sensors, can improve productivity and yield. Artificial intelligence methods, such as surrogate modelling, enable rapid experimentation, process optimisation, and scale-up, accelerating development. These advances pave the way for precision fermentation to play a greater role in the food production system of the future.

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Introduction

Fermentation can be defined as the use of micro-organisms to produce value-added products in the presence of an organic carbon source [1]. It is an important industrial process used in the production of food, biochemicals, and pharmaceuticals [2]. The carbon source, often referred to as a substrate, is most commonly a carbohydrate, such as glucose, although simpler substrates such as methane can also be used [3]. While fermentation has a long history, with evidence for wine-making stretching back at least 7000 years [4], this review will focus on modern, precision fermentation, rather than traditional fermentation or biomass fermentation.

Precision fermentation systems are biologically optimised to produce specific high-value biomolecules, such as proteins, vitamins, enzymes, natural pigments, and fats using naturally occurring or genetically modified organisms as microbial 'factories' [5]. Because of this, precision fermentation lends itself to the production of food components that mimic those obtained in traditional animal agriculture, such as animal fats and proteins [6]. It can be distinguished from biomass fermentation as the desired product is a metabolite, rather than the microbial biomass itself. Interest in precision fermentation, and the related term 'cellular agriculture' has increased exponentially in recent years. This can be seen as being driven by the application of methods developed in the pharmaceutical industry to optimise fermentation-based drug production, such as metabolic engineering, to the food industry. Examples of products currently produced by precision fermentation include rennet, an enzyme used in cheese-making; whey and casein proteins, components of milk; and soy leghemoglobin, a haem analogue used to improve the taste of plant-based burgers [7].

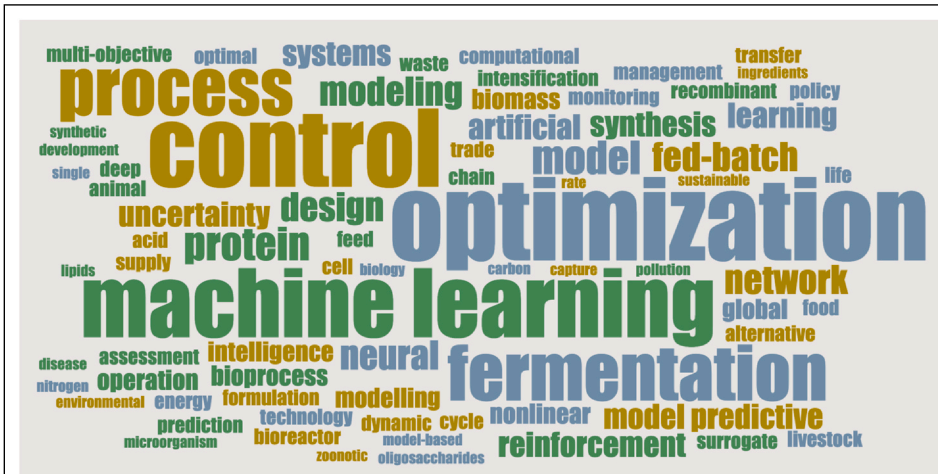
Relative to conventional methods of food production, fermentation-derived food has several advantages as a source of dietary fats and proteins, particularly when compared with animal agriculture. On a per-unit protein basis, relative to meat, eggs, and dairy, fermentation-derived protein has significantly lower carbon and nitrogen emissions [8], reduced land use [9], and lower water use [7], largely as a result of microbial fermentation being more efficient than livestock at converting carbohydrate-based feedstocks into protein. Fermentation also has advantages in terms of food and health security by decoupling food production from animal husbandry. By avoiding use of livestock, fermentation-based protein production reduces the risk zoonotic infections pose to human health [10] and avoids the problems of antibiotic pollution [11]. Additionally, fermentation can produce vastly more protein per unit area than animal agriculture [9], potentially allowing small, densely populated areas to be more self-sufficient in protein supply.

An important distinction in the design, operation, and control of fermentation processes is between batch, fed-batch, and continuous fermentations. In batch fermentation, all the nutrients available to the micro-organisms during the course of the fermentation are present in the reactor vessel at the point of inoculation. The system is partially closed, with no feeding or discharge [1]. In fed-batch operation, the substrate concentration in the reactor is controlled over the course of the batch fermentation by varying the rate at which a substrate solution is added to the reactor. This avoids substrate inhibition of growth and can improve productivity [1]. In continuous fermentation, the reactor is fed with a substrate solution, as in fed-batch, but product is also drained from the reactor on an ongoing basis. Precision fermentation can, in theory, be run in any of these three configurations. However, research to date has focused on the operation and control of batch and fed-batch precision fermentation, often to produce pharmaceutical products.

Despite widespread adoption of precision fermentation to produce high-value products such as vitamins and antibiotics, for precision fermentation to become a significant part of the food production system, several challenges will need to be addressed. Process improvements and scale-up are needed to enable fermentation to be cost competitive with conventional alternatives at scale; food products such as fats and proteins are much less valuable, gram for gram, than pharmaceuticals and vitamins, leading to a greater need for cost-efficient operation. Indeed, it has been estimated that food fermentations require production titres several orders of magnitude higher than those for pharmaceuticals in order to be cost competitive with conventionally produced alternatives [12]. Product development, including selection and engineering of novel variants of target molecules, is also important to allow fermentation-derived ingredients to compete with a wider set of conventional foods. These challenges may be addressed in many different ways, with cost reductions possible through improvements in strain development, feedstock optimisation, and bioprocess design and operation.

Currently, the majority of precision fermentations rely on a small number of legacy hosts, fed on a refined sugar substrate, in a continually stirred tank reactor. However, strain selection and development could result in higher titres and yields, greater robustness, and faster growth, making precision fermentation more cost-efficient. Strain selection and improvement could be accelerated by combining computational modelling, design of experiments, and high-throughput screening to efficiently explore the design space. Equally, the use of alternative substrates such as agricultural waste products and by-products could significantly reduce feedstock costs, one of the main costs of manufacture [7], but this relies on research and design tools to model the trade-offs of different host–substrate–product combinations. This cross-disciplinary review provides an overview of recent research relevant to precision fermentation. Figure 1 shows common keywords in the range of literature reviewed. The perspectives of three different research disciplines are considered: process systems engineering (PSE), process control, and artificial intelligence (AI). Some of the tools and methodologies associated with each of these areas are shown in Figure 2. In each

Figure 1



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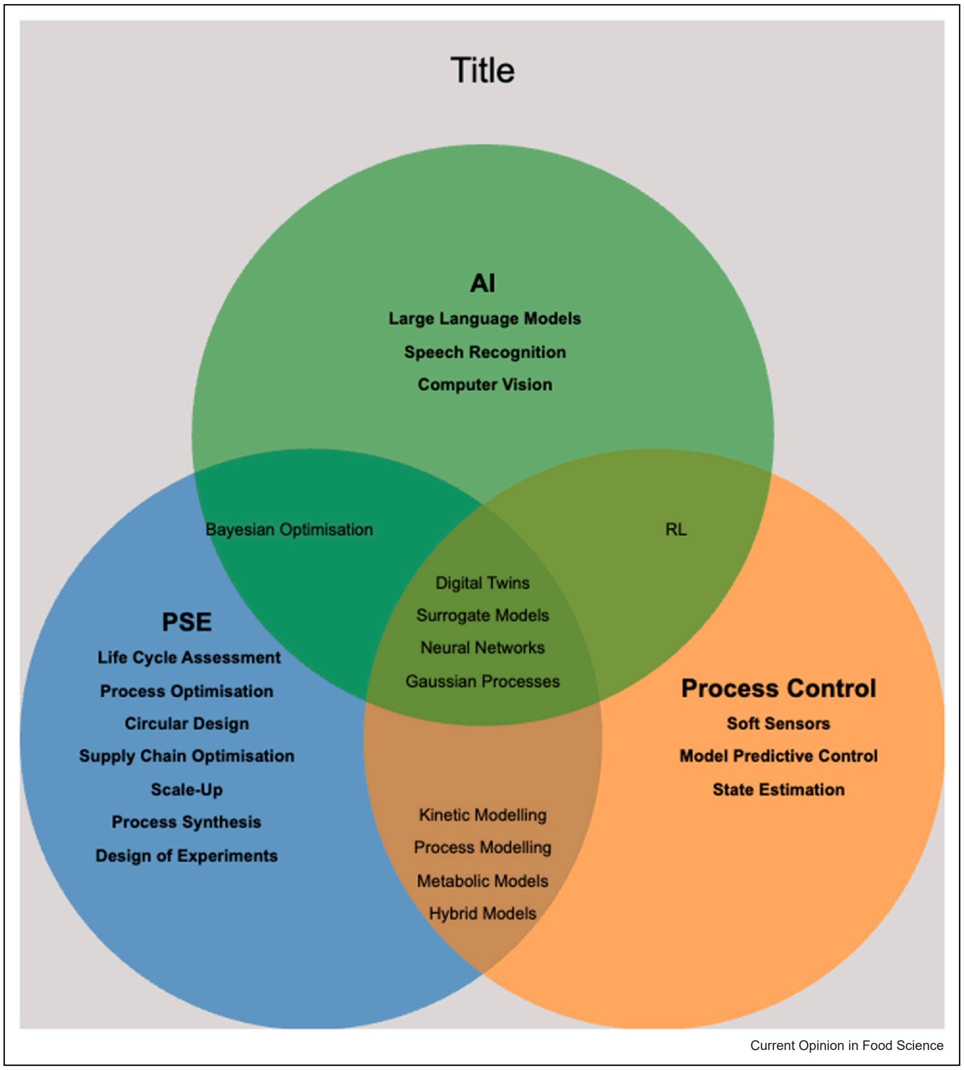
Visualisation of keywords from cited works. The frequency of words and phrases in this corpus is indicated by their size. Created using wordclouds.ethz.ch.

Figure 2



Research methodologies/tools relevant to precision fermentation and associated research disciplines.

section, research frontiers are highlighted that can ultimately enable a step change in precision fermentation in the food industry.

Process systems engineering

Bioprocess design and optimisation is key to both development of new fermentation products and improvement of existing fermentation processes. Traditional process synthesis and design provides an established set of methodologies founded on heuristics driven by chemical engineering expertise. These heuristics often separate product design from process synthesis. Product design focuses on consumer demand, which in the context of precision fermentation may consist of identifying specific desirable biomolecules, such as proteins, while process synthesis involves planning and optimisation of the operations required to produce efficiently at scale.

Sustainable design considering multiple objectives, such as sustainability and profitability, is challenging, as it requires comprehensive assessment of the alternative biosynthetic pathways and the wider process systems. To address these challenges, rigorous methodologies that can embed sustainability metrics into product and process design are needed. Heuristic process synthesis (HPS) and process optimisation (PO) are key strategies in conceptualising a process flowsheet. HPS aims to find a pathway for converting raw materials into useful products, combining multiple unit operations [13]. It defines the topology of the process and outlines the design strategies that solve the desired objectives. While HPS is fast, simple, and provides good solutions to process design problems, it requires extensive heuristic rules that are sensitive to the emergence of new technologies. On the other hand, PO is a more systematic tool to deliver optimal solutions to multiobjective problems by using mathematical programming in the process and product design [14].

Life cycle assessment (LCA) offers a useful tool to quantify the environmental impacts of products and processes and highlight potential improvement spaces for precision fermentation. LCA is now commonplace, having been standardised in technical standards such as ISO14040/44 [15], and the systems thinking that it has brought about has led to reductions in the environmental impacts of many processes. Previous studies have highlighted that products produced via precision fermentation result in environmental benefits due to the increased yields and increased efficiency particularly when the synergies between fermentation and other parts of the process are considered [16]. Additionally, new market mechanisms may be able to finance novel fermentation processes that deliver significant carbon reductions but would not otherwise be financially viable [17]; if LCA can be used to demonstrate that fermentation can produce environmentally preferable substitutes for foods such as meat, carbon credits could offer a way of monetising this advantage.

To facilitate sustainable design and operation, LCA and technoeconomic analysis [18] can be incorporated into the process optimisation. More sophisticated algorithms have increased the speed and robustness of PO, enabling solutions to process design that simultaneously solve both the process flowsheet and the operating conditions. However, PO does come with shortcomings such as oversimplification of complex process designs and high computational cost. Additionally, optimal solutions can only be found if the design space allows for an optimal pathway. In some cases, heuristic and mathematical approaches can be hybridised, yielding a reduced process design space that can be optimised more easily [19]. The process can be split into two phases, the first providing early stage elimination of unacceptable process designs and the second solving for an optimal design of the resulting superstructure.

While PO and HPS methods have been used extensively in chemical engineering for decades, several challenges lie ahead for new products and processes, including precision fermentation. Process synthesis and optimisation will be important in enabling the use of new substrates and alternative reactor designs, as well as the systematic incorporation of economic and environmental objectives into decision-making [20]. The current drive for greater sustainability and circularity in design has motivated the development of robust and adaptive PS and PO methods that can optimise multiple objectives throughout the process and product design life cycle [21]. Furthermore, newer, more sustainable technologies are being developed that utilise greener supply chains, renewable energy, and low-carbon feedstocks. However, these technologies have their own limitations [20], such as increased complexity in design of unit operations and separations, low yield and conversion, and difficult scaling-up considerations. The use of modelling tools that employ both mechanistic [22] and data-driven methods [23] can significantly improve the process design of these technologies.

Fermentation process control

In recent years, there has been significant innovation in fermentation process control, with advances in sensing, process modelling, and machine learning being used to improve productivity, sustainability, and efficiency. While the bounds for many process operating parameters are set by the reactor, process design, and the choice of host species, within these bounds improved control can result in increased output, higher titres, and improved yields at lower capital costs when compared with modifications to the reactor design.

The dynamics of fermentation control depend on whether the fermentation is run in batch, fed-batch, or continuous operation. Table 1 gives an overview of common state and manipulated variables in each operational mode, partially based on a literature review conducted by Chai et al. [1]. Batch operation has traditionally been favoured by the pharmaceutical industry, as this minimises the risk of contamination. It typically also has a smaller number of manipulated variables. However, batch productivity is much lower than for continuous fermentation, as the time-average biomass concentration will be much lower in the batch fermentation. In continuous fermentation, the biomass concentration can be maintained at the productivity-

Table 1

Common state and manipulated variables in fermentation based partially on works reviewed by Ref. [1]. T: temperature; S: substrate concentration; X: biomass concentration; P: product concentration; DO: dissolved oxygen concentration; N: nitrogen concentration; V: broth volume; EtOH: ethanol concentration.

Type	Common state variables	Common manipulated variables
Batch	T, pH, DO	Cooling water flow rate acid flow rate base flow rate oxygen-source flow rate
Fed-batch	T, pH, S, X, P, DO, N, V, EtOH	As above + substrate feed rate nitrogen-source feed rate stir rate
Continuous	As above	As above + outlet flow rate

maximising level. Indeed, Anand and Srivastava [24] found the productivity of the continuous fermentation of mycophenolic acid was more than four times higher than the productivity of the batch fermentation. Fed-batch offers a compromise, with some additional complexity resulting in higher productivity than is possible for batch, while still lower than that obtained in continuous fermentation.

Model predictive control (MPC) combines a model and mathematical optimisation to control a plant. It is based on a receding-time horizon and aims to find the optimum sequence of control actions to maximise the objective function over the chosen time window. While the method itself is not new, having originally been developed in the 1970s, research on its application to the control of bioprocesses is ongoing. MPC can either be used to track a reference or to calculate its own reference based on the cost function and constraints of the problem. Jorgensen and Petersen successfully applied MPC to set the inlet and outlet flow rates in a single-cell protein fermentation to maximise the value of the output [25]. More recently, Wang et al. [26] employed a nonlinear MPC, in combination with a support vector machine predictor, to control product concentration in a lysine fermentation.

Reinforcement learning (RL) is emerging as a control approach in fermentation. While RL is, in theory, a model-free technique, often a model-based emulator will be used to train the RL controller. After this initial training, the controller will be applied to a plant. Li et al. [27] and Pandian et al. [28] explored the application of RL to computational models of batch and fed-batch fermentations, while other authors have examined the use of RL to control microbial cocultures [29]. Oh et al. [30] combine RL and MPC to control the substrate feed rate in a fed-batch fermentation of penicillin, finding that the hybrid outperformed various RL strategies. Panjapornpon et al. [31] investigated the use of a deep deterministic policy gradient algorithm for pH-controlled processes, including fermentation, but this was limited to the control of pH and liquid level. Future work will likely widen the number of variables controlled using RL methods, although this is complicated by the curse of dimensionality, which makes learning much harder in higher dimensional decision spaces.

Increasing application of machine learning methods, particularly neural networks, to control is another clear trend. Khaleghi et al. [36] provide an excellent review of machine learning methods for fermentation optimisation and control. They identify synergies and challenges in implementing machine learning in combination with mechanistic modelling for fermentation processes, highlighting the potential for these hybrid methods to improve predictability. Shah et al. [32] developed a hybrid predictive model for fed-batch fermentation using a neural network trained on plant data to predict critical time-varying parameters in a complex kinetic model based on the current state and control action. The hybrid model has better predictive accuracy than the fixed mechanistic model and, when used as the model in MPC, is found to result in higher product concentrations. A similar hybrid predictive approach was developed by Winz et al. [33] to describe the growth and sporulation of *B. subtilis*, with a neural network trained to predict the specific growth rate as a function of cell concentration and temperature, with biological knowledge incorporated to this function using a penalty term. This model is found to describe the process dynamics sufficiently well, fitting experimental data well. Time series–based machine learning methods have also been applied in fermentation control, such as by Wang et al. [37], who used a recurrent neural network to accurately predict glucose and ethanol concentrations from electronic nose signals in an ethanol fermentation.

Another area of advance is in fermentation sensors and soft sensors. Increasingly, the line between online and offline sampling is being blurred, with chemical analysis techniques such as High-performance liquid chromatography, Raman spectroscopy, and infrared spectroscopy used to estimate product and substrate concentrations for process control purposes, as well as quality control [1]. Another emerging alternative to estimate these concentrations is to use soft sensors [2] based on an accurate process model that may be mechanistic, data based, or hybrid.

Another control approach looks at deriving insights from metabolic models. Dynamic flux balance analysis (dFBA) combines a flux balance model that describes known intracellular reaction pathways with substrate uptake kinetics and extracellular mass balances on substrates and products [34]. A linear programming model is then used to determine the fluxes associated with each reaction. This can be combined with MPC to optimise fermentation control in real time. Within precision fermentation, methods combining MPC and dFBA have been demonstrated in the control of fed-batch fermentations of *Saccharomyces cerevisiae* to produce ethanol [34] and Chinese Hamster Ovary cells to produce antibodies [35], with both studies finding improved production titres relative to simpler comparison controllers. An overview of the fermentation process control research reviewed here is provided in Table 2.

Artificial intelligence in precision fermentation

The hype generated around AI and digital twins has led to renewed industrial interest in use modelling and data-driven insights to support modelling new technologies, pathway selection and bio-process design. Precision

Table 2

Summary: recent research on fermentation process control. Variables — V: volume; t: time; S: substrate concentration; S_{in}: substrate feed concentration; X: biomass concentration; P: product concentration; T: temperature; DO: dissolved oxygen concentration; I: intermediate product concentration; Q_N: nitrogen-source feed rate; Q: substrate feed rate; Q_{out}: outlet flow rate; Q_{O_2}: oxygen-source feed rate; Q_C: catalyst feed rate; Q_{Base}: base feed rate; ω: stir rate. Methods — NL-MPC: non-linear model predictive control; SVM: support vector machine; RL: reinforcement learning; ANN: artificial neural network; DDPG: deep deterministic policy gradient.

Mode	Method	State variables	Manipulated variables	Process	Ref
Fed-batch & continuous	Economic NL-MPC	X, S, V	Q, Q_{out}	Biomass fermentation	[25]
Fed-batch	NL-MPC w/ SVM	T, pH, DO, P	Q_N, Q_{O_2}, ω	Precision fermentation of lysine	[26]
Fed-batch	RL	X, S, P, V	Q	Precision fermentation of lysine	[27]
Fed-batch	RL-ANN hybrid	X, S	Q	Yeast fermentation	[28]
continuous	RL	X_A, X_B	Q_A, Q_B	Microbial coculture	[29]
Fed-batch	RL-MPC hybrid	X, S, P, V, t	Q	Precision fermentation of penicillin	[30]
Continuous	RL (DDPG)	pH_{out}, pH_{in}, V	Q, Q_{Base}	pH treatment	[31]
Batch	MPC w/ ANN parameter estimation	X, S_1, S_2, P, I, DO, V	Q_C, Q_{S_2}	Precision fermentation	[32]
Batch	ANN and polynomial regression for parameter estimation	$X_{vegetative}, X_{spore}, S, X_{unstable\_spore}$	T	Spore production	[33]
Fed-batch	NL-MPC w/ metabolic flux balance analysis	X, S, P, V	Q, DO	Ethanol fermentation	[34]
Fed-batch	NL-MPC w/ metabolic flux balance analysis	Glucose flux	Q, Q_{out}, S_{in}	Antibody production	[35]

fermentation has been an early adopter of machine learning and advanced statistical methods, with metabolic engineering requiring sequencing, high-throughput screening, and 'omics' to optimise metabolic pathways, strains, and yields [5].

Machine learning techniques such as Gaussian process regression, support vector machines, and neural networks have all been shown to be effective for modelling complex relationships between experimental parameters and performance [38]. To screen for experimental designs, Pensupa et al. [39] developed machine learning models by data mining existing literature to find the key experimental parameters for maximising biomass concentration in a fermentation of *Yarrowia lipolytica*, with Gaussian processes providing the most accurate predictive capability. Similarly, Packiam et al. [40] developed PERISCOPE-Opt for predicting optimal fermentation conditions using XGBoost, random forest, and support vector machines, demonstrating the potential for these approaches.

Another recent trend is use of AI techniques to speed up the solving of physics-based models [41]. By using machine learning and data-driven modelling to obtain faster input–output relations, ML-assisted CFD makes it possible to simulate larger models by using computational resources more efficiently [42]. These approaches have yet to see widespread use in the fermentation community but could be helpful in addressing current challenges around scale-up, in which gas transfer is often a key problem.

With the rise in importance of renewable feedstocks, there has been increased interest in low-carbon feedstocks and waste valorisation to create circular processes. A core challenge of modelling these systems is the complexity of the biological system [43] and the complexity and variability of the feedstock composition [44]. New approaches, tools, and techniques are required to address this, as often the traditional approaches are inaccurate or inapplicable. Data-driven approaches to modelling, improved experimental design via Bayesian optimisation, and application of tools from synthetic biology were suggested to hold the key to unlocking higher productivity from such systems [45].

In the last 5 years, the major trend in engineering modelling research has been development of predictive surrogate models, for complex processes that are either poorly understood with large amounts of experimental data or are computationally intensive to simulate mechanistically. Embedding surrogate models into larger optimisation problems is now commonplace [46], including for the modelling of complex physical processes [47]. A major challenge in this area is the accuracy of such models, particularly when there is limited data availability, or when extrapolating outside the domain of the training data [48]. Recent advances in Bayesian optimisation [49] and physics-informed [50] AI may unlock the benefits of both traditional modelling and modern data-driven approaches.

Conclusion

In conclusion, recent advances in AI, from optimisation to machine learning and reinforcement learning, are being employed widely in precision fermentation, with applications in process synthesis, process optimisation, control and state estimation (see Figure 2). This is accompanied by increased use of predictive surrogate models and complex metabolic models, leading to powerful multiscale models that capture the relationships between metabolism and process control. Another development is the increased role of LCA in process design, driven by the greater importance of sustainability. Together, these approaches are accelerating the development of sustainable fermentation technologies, by facilitating experimentation, process optimisation, and scale-up, paving the way for a increased role for precision fermentation as part of a more efficient, sustainable, and resilient food system.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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