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Exploring Hybrid Quantum-Classical Algorithms for Multi-Scale Bioprocess Optimization

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Abstract

Bioprocess optimization spans multiple scales, from molecular interactions to plant-wide operations, presenting challenges due to non-linearity, high-dimensionality, and computational intractability. Traditional methods, such as Mixed-Integer Nonlinear Programming (MINLP), often fail to efficiently solve these problems. This work explores Hybrid Quantum-Classical (HQC) algorithms as a promising alternative. By integrating quantum solvers for discrete combinatorial optimization with classical solvers for continuous variable refinement, HQC approaches overcome computational bottlenecks inherent to classical techniques. The application of HQC algorithms enhances efficiency, scalability, and decision-making in bioprocess optimization, particularly in metabolic pathway selection, real-time fermentor control, and plant-wide resource allocation. This perspective outlines the theoretical foundation of HQC methods, their applications across bioprocess scales, and future research directions.

Keywords: Hybrid Quantum-Classical (HQC), Quantum Computing, Bioprocess Optimization, Multi-scale optimization, Industrial Biotechnology

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1 Nomenclature

Acronym	Definition	Variable	Definition
HQC	Hybrid Quantum-Classical	H	Hamiltonian of the system
QAOA	Quantum Approximate Optimization Algorithm	θ	Vector of variational parameters
QNN	Quantum Neural Networks	E	Energy
QUBO	Quadratic Unconstrained Binary Optimization	C	Cost function
NISQ	Noisy Intermediate-Scale Quantum	γ	Classical parameter for the cost operator
QSVM	Quantum Support Vector Machines	β	Classical parameter for the mixing operator
GEO	Generator-Enhanced Optimization	σ_z	Pauli-Z operators acting on the i -th qubit
VQE	Variational Quantum Eigensolver	σ_x	Pauli-X operators acting on the i -th qubit
		$\mathbf{x}$	Vector of decision variables
		y	Discrete variable
		α	Learning rate
		$\nabla C(\theta)$	Gradient of the cost function at θ
		$\mathbf{X}(t)$	State variables of the plant at time t
		$\mathbf{u}(t)$	Control inputs at time t
		$\mathbf{f}(\mathbf{X}(t), \mathbf{u}(t), t)$	Nonlinear function describing plant dynamics

1. Introduction

Computational approaches have become indispensable in modern scientific and engineering disciplines, particularly in material design and bioprocess optimization¹. In materials science, computational techniques accelerate the discovery and optimization of novel materials by predicting molecular interactions, reaction mechanisms, and thermodynamic properties. Similarly, in bioprocess engineering, advanced computational frameworks enable the design, control, and optimization of biochemical reactions, metabolic pathways, and large-scale production systems^{2,3}. Despite these advancements, the inherent multi-scale complexity of biological systems ranging from enzyme kinetics to plant-wide operations poses significant challenges for classical optimization methods.^{1,4-6}

Bioprocesses span multiple organizational levels, each with distinct yet interconnected optimization challenges^{7,8}. At the molecular level, enzyme activity and reaction energetics shape overall metabolic efficiency⁹. At the cellular level, gene regulation^{10,11} and flux distributions¹² govern productivity, while fermentor-scale variables such as pH, agitation, and nutrient flow demand continuous control¹³⁻¹⁵. At the plant-wide level, decisions on scheduling, energy use, and resource allocation determine the overall economic and environmental performance¹⁶.

Traditional computational techniques, such as deterministic modeling, process simulation, and heuristic methods, have been extensively applied to improve process performance across these scales¹⁷. For instance, mathematical modeling approaches, including kinetic modeling¹⁸⁻²⁰, flux balance analysis (FBA)²¹⁻²³, and computational fluid dynamics (CFD)^{24,25}, have been widely used to describe bioprocess behavior. In addition, dynamic simulation tools like KT-Biologics I (KTB1) have been developed to model time-dependent behavior in continuous biologics manufacturing, supporting better decision-making and process control²⁶.

However, as optimization extends from intracellular pathways to industrial-scale production, the associated computational cost increases exponentially, making large-scale optimization increasingly challenging²⁷. Conventional techniques, including Mixed-Integer Nonlinear Programming (MINLP)²⁸, Nonlinear Programming (NLP)²⁹, evolutionary algorithms³⁰, and metaheuristics, often struggle with high-dimensional search spaces, strong nonlinearities, and the stochastic nature of biological systems and their operation. In this context, multi-objective optimization frameworks have gained relevance, enabling the simultaneous consideration of competing objectives, such as maximizing yield while minimizing energy consumption or environmental impact³¹. Likewise, stochastic optimization approaches, including Monte Carlo³² and probabilistic modeling³³, provide a means to account for uncertainties in biological systems, improving robustness in process optimization and decision-making.

Due to the dynamic nature of bioprocesses marked by fluctuating parameters and intricate interdependencies, traditional solvers often fall short of delivering robust solutions. This gap has led to interest in emerging paradigms such as Artificial Intelligence (AI), including Machine Learning (ML) and Deep Learning (DL), which offer adaptive and data-driven strategies to enhance predictive performance and process control. For instance, AI-driven surrogate mod-

els can effectively approximate complex bioprocess behavior³⁴, allowing for rapid evaluation of potential optimization scenarios. Furthermore, reinforcement learning approaches³⁵ enable adaptive learning and continuous improvement of bioprocess strategies by dynamically adjusting to real-time data inputs. Furthermore, hybrid data-driven methods integrate historical data with ML to enhance accuracy and reliability³⁶. These developments reflect a broader shift in modeling paradigms, where classical model-based approaches are increasingly enhanced by AI and ML to address complexity, uncertainty, and data integration challenges³⁷.

However, despite these advancements, these methods remain constrained by computational limitations when tackling large-scale, highly dynamic, and multi-scale biological systems. These constraints highlight the urgent need for novel computational paradigms capable of efficiently handling nonlinear, high-dimensional, and multi-objective optimization problems beyond the reach of conventional solvers. In this context, recent developments in quantum computing offer a promising alternative. Quantum algorithms exploit the principles of superposition and entanglement, allowing them to explore large combinatorial spaces more efficiently than classical approaches. However, current quantum hardware remains constrained in its ability to process continuous decision variables and large-scale industrial problems. To bridge this gap, Hybrid Quantum-Classical (HQC) algorithms have emerged as an advanced computational paradigm, integrating quantum solvers for discrete optimization with classical solvers for continuous decision-making³⁸.

The HQC framework provides a structured methodology for partitioning complex optimization problems. Quantum algorithms such as the Quantum Approximate Optimization Algorithm (QAOA)³⁹, Variational Quantum Eigensolver (VQE)⁴⁰, and Quantum Neural Networks (QNNs)⁴¹ efficiently handle discrete decision-making tasks, such as pathway selection, reaction mechanism design, and process scheduling. These approaches are increasingly being explored for applications in chemical and biomolecular product design, where the search space is inherently combinatorial and benefits from quantum speedup⁴².

Meanwhile, classical solvers address continuous variables through established nonlinear programming techniques, ensuring a scalable and computationally efficient optimization process. By leveraging the strengths of both paradigms, HQC algorithms mitigate computational bottlenecks and enhance the optimization of high-dimensional, nonlinear, and combinatorial problems in bioprocess engineering.

Figure 1 illustrates the hierarchical structure of bioprocess systems, emphasizing the interactions between different scales and the need for optimization strategies that capture these dependencies. Molecular interactions dictate cellular metabolism, which in turn influences fermentor performance and ultimately impacts large-scale production efficiency. Classical optimization approaches often fail to account for these complex dependencies simultaneously, reinforcing the necessity of hybrid computational frameworks such as HQC.

This work presents a perspective on the integration of HQC algorithms as a means to overcome the computational

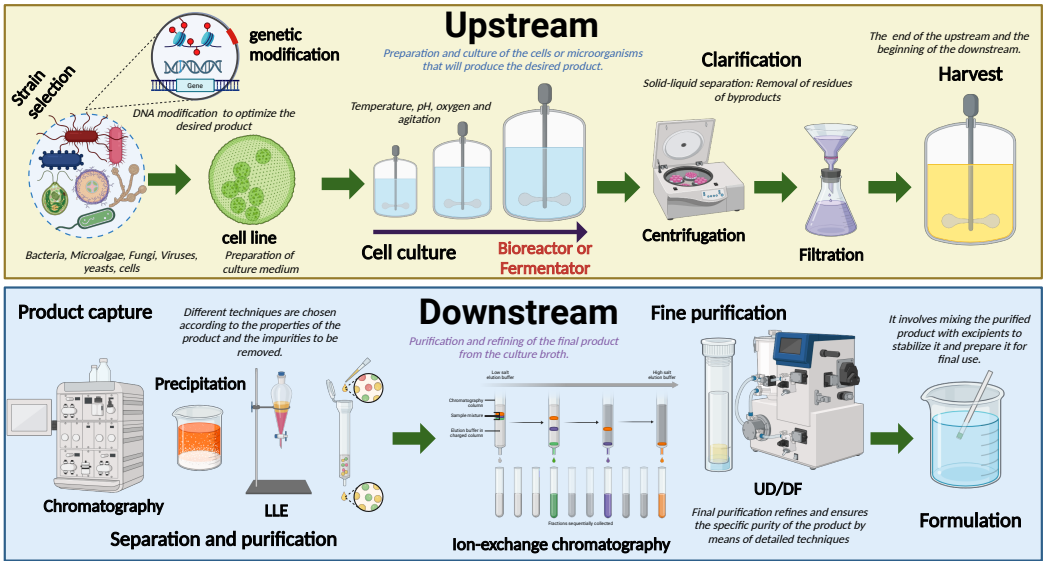


Figure 1: Diagram of a typical bioprocess, including strain selection, genetic modification, and bioreactor cultivation (upstream), followed by product separation, clarification, and purification (downstream). Each stage faces significant complexities, with operational, control, economic, and energy challenges at the cellular, molecular, fermenter, and plant levels, reflecting the need for advanced optimization strategies to improve the efficiency and quality of the final product.

difficulties associated with large-scale bioprocess optimization. Specifically, it makes the following three contributions:

- 1. Conceptual Framework for HQC in Bioprocess Optimization.** This manuscript provides a critical perspective on how HQC algorithms can reshape bioprocess optimization by integrating quantum solvers for discrete combinatorial problems with classical methods for continuous variable optimization. By exploring their potential in addressing high-dimensional, nonlinear, and computationally intensive challenges, this work highlights the transformative role of HQC approaches in advancing bioprocess modeling and decision-making.
- 2. Multi-Scale Relevance of HQC Approaches.** A structured discussion is presented on the molecular, cellular, fermentor, and plant-wide levels, examining how HQC methodologies could facilitate reaction mechanism optimization, metabolic pathway regulation, process control, and large-scale production strategies. By analyzing the computational feasibility and scalability of HQC frameworks, this work underscores their potential to improve efficiency, sustainability, and adaptability in industrial biotechnology.
- 3. Future Directions for Quantum-Enhanced Bioprocess Engineering.** This perspective article outlines key challenges and opportunities for the adoption of HQC algorithms in industrial bioprocesses, emphasizing scalability, computational trade-offs, and integration with existing optimization paradigms. By positioning HQC as a strategic computational tool, this work provides a roadmap for future exploration, encouraging further research into practical implementation, algorithm refinement, and experimental validation in quantum-enhanced

bioprocess optimization.

These contributions are developed in detail throughout the manuscript: the conceptual framework for HQC in bioprocess optimization is discussed in Section 3, the multi-scale relevance of HQC approaches is analyzed in Section 5, and the future directions for quantum-enhanced bioprocess engineering are explored in Section 6.

This paper is organized as follows: Section 2 presents the challenges associated with multi-scale bioprocess optimization, highlighting computational bottlenecks at the molecular, cellular, fermentor, and plant-wide levels. Section 3 introduces the HQC framework, providing an overview of its theoretical foundations and explaining its role in addressing complex decision-making problems. Section 4 expands on the broader applications of HQC algorithms in industry and science, contextualizing their impact beyond bioprocesses. Section 5 focuses on the perspectives for HQC in multi-scale bioprocess optimization, discussing feasibility, implementation strategies, and potential trade-offs. Section 6 explores the quantum-specific challenges and opportunities that must be addressed to advance HQC methodologies in bioprocessing. Finally, Section 7 presents the conclusions, summarizing key insights, emphasizing the potential of HQC algorithms, and outlining future research directions.

2. Challenges in Multi-scale Optimization of Bioprocesses

Optimizing bioprocesses across different scales, from cellular mechanisms to industrial-scale production systems, presents significant computational challenges (see Figure 2).

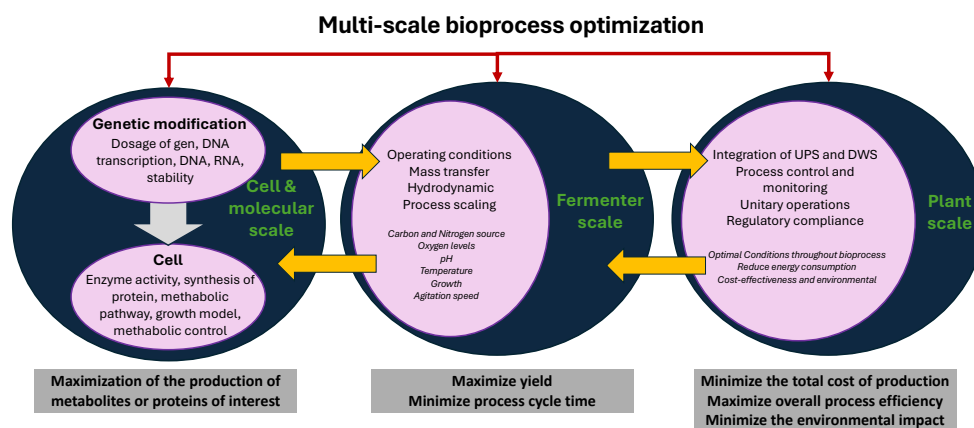


Figure 2: Multi-scale optimization of bioprocesses involves addressing challenges at three different modeling levels: 1. At the molecular/cellular level, the focus is on optimizing the genetic and metabolic processes. 2. At the fermentor level, the goal is to identify optimal operating conditions and maximize mass transfer. 3. At the plant scale, the goal is to integrate the process most efficiently and sustainably while minimizing operating costs to ensure economic efficiency.

This work focuses on microbial fermentation-based production systems, where metabolic pathways are engineered to maximize the yield of target biochemicals. These challenges span multiple levels: optimizing metabolic fluxes at the cellular level, controlling bioreactor conditions at the fermentor level, and coordinating large-scale production strategies at the plant-wide level. The overarching objective is to enhance the efficiency and sustainability of bioproduction while managing trade-offs among productivity, energy consumption, and economic feasibility. To highlight the general nature of these computational challenges, we focus on mathematical formulations rather than detailed mechanistic models. This choice allows us to emphasize the structural complexity common to various fermentation-based systems, without relying on case-specific kinetic parameters or experimental assumptions. Instead, we identify the key mathematical features that make these problems difficult to solve and justify the relevance of HQC optimization strategies. The intractability of multi-scale bioprocess optimization stems from the exponential growth in decision variables and constraints. While conventional optimization techniques may perform adequately on small-scale or simplified systems, they often struggle to identify global optima in large-scale, nonlinear settings. This challenge is compounded by non-convex objective functions, strong nonlinear interactions, and the coupling of discrete and continuous variables across different scales. In this context, quantum computing offers a promising computational alternative. Quantum algorithms are able to explore high-dimensional combinatorial spaces more efficiently than classical methods. This capacity may accelerate the discovery of optimal pathways and configurations in complex bioprocess models, particularly in discrete decision layers. When integrated within HQC frameworks, quantum solvers can complement classical methods, enabling more scalable and effective optimization of multi-scale bioprocess systems.

2.1. Cellular and Molecular Scale

Cellular function is driven by complex networks of interacting chemical reactions, precisely coordinated in space and time. These biochemical networks are responsible for observable cellular behaviors. Network reconstruction identifying and cataloging all reactions in a metabolic system has been applied across multiple organisms, offering critical insights into cellular metabolism. The hierarchical organization of these pathways is depicted in Figure 3, illustrating the increasing granularity of cellular metabolism as modeling moves from whole-cell function to individual biochemical reactions. Understanding this hierarchy is essential to appreciating the challenges inherent in optimizing metabolic pathways.

As we progress through the levels of this metabolic hierarchy, the complexity of optimization increases substantially. A major computational bottleneck arises from the combinatorial explosion in pathway selection. For a network with k possible pathways, the number of feasible configurations scales as 2^k , rendering exhaustive search strategies impractical. Moreover, reaction dynamics are governed by nonlinear differential equations, as shown in Equation 1:

$$\frac{dC_i}{dt} = S_{ij}v_j \quad (1)$$

where C_i represents metabolite concentrations, v_j the reaction fluxes, and S_{ij} the stoichiometric matrix. These relationships introduce feedback loops and nonlinear regulatory dependencies that significantly burden computation. The resulting nonconvex optimization space hinders the performance of gradient-based methods, while heuristic algorithms often demand substantial computational effort to explore high-dimensional landscapes.

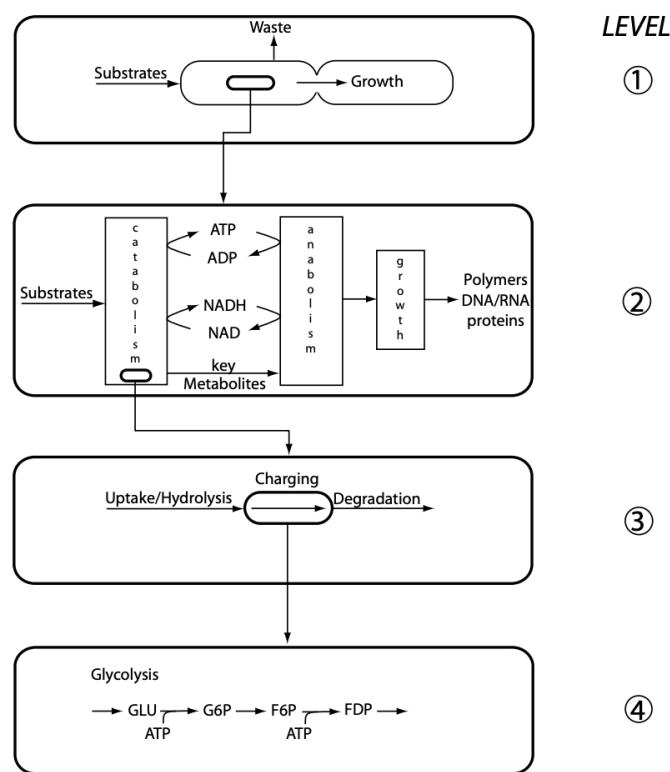


Figure 3: Hierarchical structure of metabolic processes. Level 1 represents the entire cell, level 2 breaks metabolism down into metabolic sectors (catabolism and anabolism), level 3 provides details about specific metabolic pathways, and level 4 focuses on individual biochemical reactions. This hierarchy captures the complexity of metabolic function from the cellular to the biochemical levels. Reproduced with permission from reference⁴³. Copyright 2006 Cambridge University Press.

At the highest level (Level 1), metabolism is viewed as a global conversion of inputs into products and by-products supporting cellular maintenance and growth. While this perspective simplifies modeling, it lacks mechanistic detail and limits its usefulness for optimization. At Level 2, metabolism is divided into functional sectors, catabolism, and anabolism, revealing how energy and resources are allocated for different cellular processes. Yet, even this level aggregates processes that obscure individual regulatory elements.

The complexity deepens at Level 3, where specific metabolic pathways are analyzed. These pathways are composed of numerous reactions with intricate regulatory and kinetic mechanisms. Since pathways are interconnected, the activity of one can significantly influence others, introducing additional layers of feedback and interdependence. At Level 4, we focus on individual biochemical reactions, each shaped by kinetic properties, enzyme concentrations,

thermodynamic feasibility, and regulatory mechanisms like feedback inhibition and enzyme modulation through conformational changes. Small perturbations at this level can ripple through the network, amplifying the difficulty of identifying robust optimization strategies.

As illustrated in Figure 3, each level introduces factors such as enzyme availability, substrate concentration, and reaction regulation that affect metabolic flow and system efficiency. The exponential growth in possible pathway configurations, each consisting of numerous reactions, makes identifying optimal routes a combinatorial challenge. The goal is to maximize the production of desired metabolites while minimizing resource consumption and the formation of undesirable by-products.

The complexity of metabolic optimization arises from the interdependence of thousands of reactions, each subject to nonlinear kinetics, thermodynamic constraints, and layered regulation. Although MINLP provides a unified framework to capture both discrete (e.g., pathway selection) and continuous (e.g., flux) decisions, classical solvers often fail due to the size and nonconvexity of the solution space. In many applications, traditional methods either require prohibitively long computation times or converge to suboptimal solutions. Quantum optimization offers a promising alternative by enabling more efficient exploration of combinatorial search spaces particularly for discrete decisions where classical approaches struggle.

2.1.1. Formulation as MINLP

The increasing complexity of metabolic networks, as shown in Figure 3, requires advanced mathematical frameworks to model both discrete decisions and continuous relationships. MINLP is widely adopted for this purpose, capturing the interplay between binary variables representing pathway activation or deactivation and continuous variables, such as reaction fluxes and metabolite concentrations. Nonlinearity in metabolic systems emerges from interactions among fluxes, stoichiometric constraints, enzyme kinetics, and regulatory loops. As more pathways and regulatory elements are integrated into a model, the number of variables and constraints grows rapidly, leading to exponential expansion of the solution space. Specifically, if k binary variables are used to represent pathway inclusion, the search space scale as 2^k , making exhaustive search infeasible. On the other hand, kinetic relationships often introduce nonconvex constraints, as illustrated by Equation 2, which represents the Michaelis–Menten kinetics governing enzyme-catalyzed reaction

$$v_j = v_{\max} \frac{C_i}{K_m + C_i} \quad (2)$$

This equation represents a class of non-linear expressions that can create multiple local optima. These features severely limit the effectiveness of gradient-based methods and increase the computational burden for classical solvers.

A general MINLP formulation for optimizing the metabolic pathway is given in Equation 3, where both discrete

and continuous decisions are integrated.

$$\begin{aligned}
 &\text{Minimize or Maximize: } f(\mathbf{x}, \mathbf{y}) \\
 &\text{Subject to: } g_i(\mathbf{x}, \mathbf{y}) \leq 0, \quad i = 1, \dots, n, \\
 &\quad h_j(\mathbf{x}, \mathbf{y}) = 0, \quad j = 1, \dots, p, \\
 &\quad \mathbf{x} \in \mathbb{R}^m, \\
 &\quad \mathbf{y} \in \{0, 1\}^k
 \end{aligned} \tag{3}$$

Here, $\mathbf{x}$ represents the continuous variables, such as reaction fluxes and metabolite concentrations, while $\mathbf{y}$ represents the binary variables, such as the activation state of pathways (on/off decisions). The objective function $f(\mathbf{x}, \mathbf{y})$ could represent a goal like maximizing the production of a desired metabolite or minimizing resource consumption. The constraints $g_i(\mathbf{x}, \mathbf{y})$ and $h_j(\mathbf{x}, \mathbf{y})$ capture nonlinear inequalities and equalities that reflect stoichiometric balances, thermodynamic feasibility, and enzyme capacity limitations.

As more metabolic pathways are incorporated, the size of the variable sets $\mathbf{x}$ and $\mathbf{y}$ increases exponentially. This expansion not only adds more binary and continuous variables but also introduces additional nonlinear constraints, reflecting the complex interactions among network components, including mass balances and thermodynamic constraints.

The integrated multiscale nature of metabolic networks further reinforces the need for MINLP formulations, particularly at finer biochemical levels where feedback regulation and nonlinear kinetics dominate. The challenge lies in simultaneously optimizing discrete decisions such as pathway selection and continuous process variables like flux distributions. The exponential growth in binary variables $\mathbf{y}$, combined with the inherent nonconvexity of kinetic models, creates a highly complex solution landscape with numerous local optima.

These challenges persist across biological scales, from cellular-level metabolic control to large-scale bioprocess design and operation. In such high-dimensional, nonconvex, and combinatorially large search spaces, classical solvers often fail to converge to global optima or require excessive computational time. This complexity motivates the exploration of alternative computational paradigms, including hybrid quantum-classical strategies capable of efficiently managing the discrete-continuous structure of MINLP problems.

2.1.2. Issues in Metabolic Pathway Optimization

As detailed in Figure 1, optimization becomes increasingly complex at the deeper levels of the metabolic hierarchy, particularly Levels 3 and 4, where optimization must account for specific pathways and individual biochemical reactions. At these scales, the interplay between kinetic behavior, thermodynamic feasibility, and regulatory mechanisms introduces high levels of system interdependence and sensitivity. A key issue at these levels is the emergence

of nonlinear behaviors and feedback regulation that distort the solution landscape, making it rugged and filled with local optima. This nonconvexity severely limits the reliability of classical solvers, which often converge to suboptimal solutions. Moreover, the dynamic nature of biochemical networks means that small changes in a single reaction or regulatory mechanism can cascade throughout the system, affecting the performance of entire pathways. The optimization task is further complicated by the hierarchical structure of the network, where modifications at one level can propagate upward or downward, disrupting local and global balances. This system wide coupling increases not only computational cost but also the difficulty of designing robust interventions. As models are extended beyond the cellular level to include fermentor scale dynamics and integrated bioprocesses, the number of variables, constraints, and interactions escalates. The compounded complexity underscores the limitations of classical methods and motivates the use of HQC frameworks, which offer a principled way to decouple and solve the discrete and continuous aspects of the problem more efficiently.

2.2. Fermentor Scale

At the fermentor scale, bioprocess optimization involves managing a range of operational parameters, including temperature, pH, agitation, oxygen transfer, and nutrient concentrations. These variables, while external to the cell, are closely tied to metabolic activity at the molecular level. Nonlinear behaviors present in cellular metabolism are amplified at this scale, where physical and biological factors interact to influence microbial dynamics⁴⁴.

The complexity arises from the number of interacting variables and the system's dynamic nature. When cellular-level regulation is translated into a fermentor system, new phenomena such as heat and mass transfer, aeration, and shear effects must be considered. These interactions are highly nonlinear: for example, microbial growth is influenced by temperature and nutrient availability in ways that produce multiple local optima. Moreover, time-dependent effects and feedback mechanisms such as oxygen limitations affecting growth rate require continuous adjustments, complicating control and optimization. Mechanistic modeling at this scale is particularly difficult. First-principles models often become impractical due to the volume of interacting variables and the uncertainty in biological responses. Consequently, empirical and hybrid models based on experimental data are frequently used to quantify parameter relationships and guide optimization.

2.2.1. Intricacy of the Optimization Problem

The general optimization problem on this scale can be expressed as a multi-objective problem, where the goals might include maximizing the product yield, minimizing production costs, and reducing the time to complete the fermentation process.

Minimize/Maximize: $f(\mathbf{x}) = \{f_1(\mathbf{x}), f_2(\mathbf{x}), \dots, f_k(\mathbf{x})\}$

Subject to: $g_j(\mathbf{x}) \leq 0, \quad j = 1, \dots, m$ (4)

$h_l(\mathbf{x}) = 0, \quad l = 1, \dots, p$

where $\mathbf{x} = (x_1, x_2, \dots, x_n)$ represents the continuous decision variables, $f_i(\mathbf{x})$ are the objective functions, which might include maximizing product yield, minimizing production time, and reducing costs and $g_j(\mathbf{x})$ and $h_l(\mathbf{x})$ represent inequality and equality constraints, respectively, reflecting physical, biological, and operational limitations.

2.2.2. Nonlinearity and Dynamic Behavior

Scaling metabolic optimization to the fermentation level introduces additional complexity due to interaction between biological regulation and the parameters of the physical process. External factors such as mass transfer, agitation, and nutrient flow interact with internal metabolic states, creating a tightly coupled, dynamic system. The fermentation process is governed by non-linear differential equations that describe microbial growth and product formation:

$$\frac{dC_i}{dt} = \mathbf{r}(\mathbf{C}(t), \mathbf{u}(t), t) \quad (5)$$

where $\mathbf{C}(t)$ represents the concentrations of various species (e.g., cells, substrates, and products) at time t , $\mathbf{u}(t)$ denotes the control inputs (e.g., temperature, pH, agitation speed), and $\mathbf{r}(\mathbf{C}(t), \mathbf{u}(t), t)$ is a nonlinear function defining reaction kinetics. These equations capture how small fluctuations in operational conditions can propagate through the system, altering metabolic activity and productivity.

The time-dependent nature of these interactions necessitates real-time optimization. However, classical approaches such as nonlinear programming (NLP) rely on iterative simulations and numerical integration, which are computationally intensive particularly for large-scale fermentor systems with stiff equations and multiple feedback loops. Further challenges arise from the presence of multiple local optima due to the nonlinear dependence of microbial growth on environmental factors. Delayed responses and cascading effects such as shifts in oxygen transfer rates or nutrient depletion can destabilize the process if not addressed dynamically. For this, HQC algorithms provide a promising alternative. Quantum solvers can efficiently explore combinatorial spaces for discrete control decisions (e.g., feed timing or step changes), while classical solvers fine-tune continuous parameters in real time. This division of labor improves computational efficiency and robustness, enabling scalable optimization under complex, dynamic bioprocess conditions.

2.3. Plant-wide Scale

At the plant-wide scale, bioprocess optimization involves coordinating multiple interconnected upstream and downstream operations across the entire production facility (see Figure 1). This level builds upon the complexity of cellular and fermentor scales, introducing new challenges as the number of units, variables, and interdependencies increases. Operational aspects such as heat and mass transfer, mixing efficiency, and energy use become more difficult to manage, requiring integrated strategies to maintain consistency and efficiency. As bioprocesses are scaled from laboratory or pilot setups to full-scale industrial systems, nonlinearities intensify. Factors that were manageable at smaller scales, such as mixing, transfer rates, and environmental stability, often behave unpredictably at larger volumes. These scaling effects, combined with unit-to-unit variability, can propagate across the system and disrupt overall performance. Traditional modeling approaches, struggle to capture the combinatorial and dynamic nature of large-scale operations. Interventions that work well locally may have unintended global consequences, making system-wide optimization particularly difficult. Ensuring stable, synchronized performance across all units becomes a central challenge at this level, especially when minor deviations in one section can cascade throughout the plant.

2.3.1. System Integration and Interdependencies

At the plant-wide scale, optimization involves coordinating a complex network of interconnected units, spanning both upstream production and downstream purification. Each unit contributes its own set of decision variables, yet their interactions create strong interdependencies across the entire system. As in earlier scales, disturbances in one part, such as nutrient fluctuations affecting fermentation, can propagate downstream, impacting operations like filtration or chromatography. Managing these interactions requires an integrated view of the plant as an integrated system.

The general optimization problem at this scale can be expressed as:

$$\begin{aligned} \text{Minimize/Maximize: } & F(\mathbf{X}) = \{F_1(\mathbf{X}), F_2(\mathbf{X}), \dots, F_k(\mathbf{X})\} \\ \text{Subject to: } & G_j(\mathbf{X}) \leq 0, \quad j = 1, \dots, M \\ & H_l(\mathbf{X}) = 0, \quad l = 1, \dots, P \end{aligned} \quad (6)$$

where $\mathbf{X} = \{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_n\}$ represents the combined set of decision variables across all units and processes (e.g., flow rates, temperatures, pressures, equipment states), $F_i(\mathbf{X})$ are the global objective functions, such as minimizing energy consumption, maximizing production efficiency, reducing operational costs and $G_j(\mathbf{X})$, $H_l(\mathbf{X})$ represent the overall inequality and equality constraints, reflecting the physical, chemical, and operational limits across the plant. This formulation illustrates the need to consider the entire plant as an integrated system, where the decision variables $\mathbf{X}$ span multiple units, and the objective functions $F_i(\mathbf{X})$ reflect the overall goals of the plant. The coupling between

different units introduces interdependencies, where the performance of one unit directly impacts others, creating a highly complex and interdependent optimization problem.

Classical methods often struggle with such complexity, especially when real-time responsiveness is required. HQC approaches offer a scalable alternative: quantum solvers can efficiently explore discrete decision spaces such as batch scheduling or equipment assignment while classical solvers fine-tune continuous parameters to meet dynamic constraints. This integration enhances decision-making capacity, offering new possibilities for improving economic performance and sustainability in industrial bioprocesses.

2.3.2. Dynamic Behavior and Real-Time Optimization

Plant-level optimization is further complicated by the dynamic behavior of the system. The state of the plant $\mathbf{X}(t)$ changes over time due to fluctuations in inputs, changes in operating conditions, and other time-dependent factors. This dynamic behavior can be modeled by a system of time-dependent differential equations:

$$\frac{d\mathbf{X}(t)}{dt} = \mathbf{f}(\mathbf{X}(t), \mathbf{u}(t), t) \quad (7)$$

where $\mathbf{X}(t)$ represents the state variables of the plant at time t , $\mathbf{u}(t)$ represents the control inputs, $\mathbf{f}(\mathbf{X}(t), \mathbf{u}(t), t)$ is a nonlinear function that describes the plant dynamics. The need for real-time optimization arises because the optimal operating conditions may change over time. The optimization algorithm must be able to continuously adjust decision variables to maintain efficiency under varying conditions.

Plant-wide bioprocess optimization presents challenges associated with high-dimensional decision spaces, dynamic system constraints, and multi-objective trade-offs. The number of possible system configurations grows exponentially with the number of decision variables, making exhaustive evaluation infeasible. Process scheduling, energy management, and supply chain integration introduce additional layers of complexity. Existing classic process optimization frameworks, which become computationally infeasible when handling large-scale industrial datasets. HQC frameworks provide an opportunity to address these limitations by leveraging quantum-based combinatorial search algorithms for high-dimensional decision-making, coupled with classical optimization techniques for refining continuous operational parameters.

In summary, while each scale, cellular, fermentor, and plant-wide poses distinct optimization challenges, these levels are deeply interconnected. Decisions made at one level, such as pathway activation at the cellular scale, can propagate through the system, altering fermentor dynamics and ultimately affecting plant-wide performance. As a result, optimizing each scale in isolation can lead to suboptimal or conflicting outcomes. This complexity underscores the need for a unified optimization strategy that can simultaneously manage discrete and continuous decisions across all scales. Traditional solvers struggle with the combinatorial and nonlinear nature of such large, multi-scale systems

particularly under dynamic conditions. HQC algorithms offer a powerful alternative: quantum components efficiently explore large combinatorial spaces, such as pathway configurations or scheduling options, while classical solvers refine continuous process parameters in real time. By leveraging this complementary architecture, HQC frameworks enable scalable, integrated optimization of the entire bioprocess, ensuring that decisions made at one scale align with system-wide objectives. This integrated approach is essential for advancing the efficiency, adaptability, and sustainability of next-generation biomanufacturing systems.

3. An Overview of HQC Algorithms

HQC approach emerges as a solution to the computational intractability of multi-scale bioprocess optimization problems. These problems involve both discrete and continuous decision variables, covering molecular, cellular, fermentor, and plant-wide levels, making them computationally intensive. This approach combines quantum solvers for discrete optimization tasks (e.g., metabolic pathway selection, scheduling) with classical solvers for continuous variable optimization (e.g., reaction fluxes, fermentation kinetics, process control). This hybrid strategy enables efficient exploration of high-dimensional decision spaces, overcoming the limitations of classical solvers in navigating combinatorial complexity, non-linearities, and real-time dynamic constraints.

HQC algorithms are characterized by a highly iterative process that efficiently integrates the capabilities of quantum and classical computing (see Figure 4). A classical computational system is initially responsible for setting the initial parameters based on a problem-specific ansatz, a crucial step that shapes the quantum circuit approach to exploring the solution space. This initial configuration is crucial as it determines the structure and dynamics with which the quantum processor will approach the solution space of the problem at hand. Once these parameters are established, the quantum processor executes the circuit, performing quantum operations that allow for a parallel exploration of many possible solutions. This ability to simultaneously evaluate various potential solutions is one of the main advantages of quantum computing and is fundamental to the effectiveness of hybrid algorithms in tackling challenging problems from which an optimal discrete solution will be drawn.

After completing the quantum computational phase, a series of measurements of the qubit states are made. These results are interpreted to draw the discrete solution and are integrated into the classical computational environment. At this stage, classical optimization algorithms come into play, analyzing the data drawn from the quantum computing framework to identify patterns, evaluate the effectiveness of the used parameters, and adjust them accordingly. This parameter analysis and adjustment are based on advanced continuous optimization techniques, which may include gradient methods, evolutionary algorithms, or other heuristic search methods, depending on the problem-specific nature and the hybrid algorithm design. This iterative cycle of configuration, quantum execution, and classical optimization is repeated several times, with each iteration refining the parameters of the quantum circuit to hopefully approach an

optimal solution.

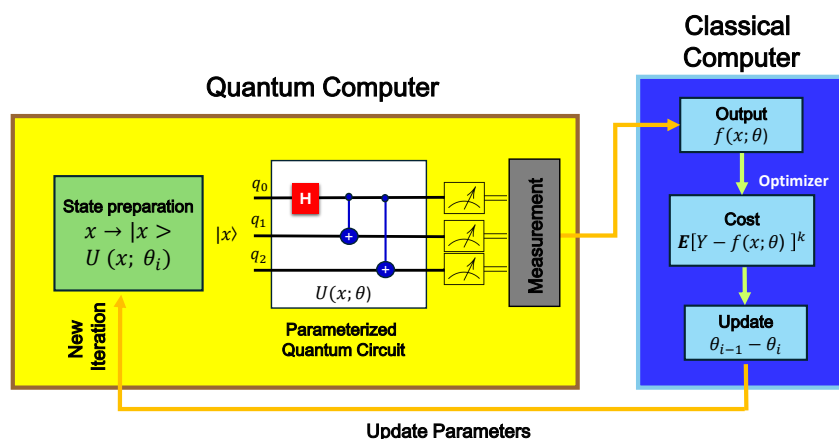


Figure 4: Schematic representation of a hybrid quantum-classical algorithm for the optimization of mixed-integer continuous systems. It is composed of the quantum computation components, including quantum circuits and quantum gates, deployed for handling the optimization of integer variables through a measurement process. The classical computing components handle the optimization of continuous parameters, and the feedback loop, with an iterative process indicated by arrows flowing between the quantum and classical systems.

In quantum computing, the term "ansatz" refers to an initial, educated guess or hypothesis for a quantum state or a quantum circuit that is used as a starting point for further optimization or exploration. The ansatz is a crucial concept in variational quantum algorithms, where the goal is to find the quantum state that minimizes a given objective function, often related to the energy of a system or the solution to a computational problem. The followings are key points about the Ansatz state in Quantum Computing.

- **Initialization of Parameters (Classical Processing):** The optimization process begins with a problem-specific ansatz, which serves as an initial approximation for the quantum circuit. This ansatz defines the structure of the quantum state and establishes the initial parameter values, guiding the exploration of the solution space.
- **Quantum Computation:** The quantum processor executes the parameterized circuit, leveraging quantum parallelism to evaluate multiple solution candidates simultaneously. This parallelism enables the efficient exploration of discrete decision variables, such as pathway selection or process scheduling.
- **Measurement and Interpretation:** Upon completion of quantum computations, qubit states are measured, yielding a set of discrete solutions. These results are processed to determine optimal decision variables, which will be further refined through classical optimization.
- **Classical Optimization:** The measured quantum outputs are fed into classical solvers, which optimize the continuous variables (e.g., reaction fluxes, fermentation kinetics) using gradient-based methods, evolutionary algorithms, or nonlinear solvers. This step ensures the feasibility and fine-tuning of the hybrid solution.

- **Iterative Iterative Refinement:** The optimized parameters are fed back into the quantum circuit, and the process repeats iteratively. Each iteration improves solution accuracy, dynamically adjusting both discrete and continuous variables until convergence to an optimal solution is achieved.

Within the realm of HQC algorithms, some stand out for their differing approaches to complex computational challenges and their applicability to specific problems: the VQE specializes in tackling quantum chemistry problems, the QAOA addresses combinatorial optimization problems, and Quantum Machine Learning Algorithms (QMLAs) such as Quantum Neural Networks (QNNs), enhance the capabilities of traditional machine learning models and neural networks by integrating quantum computing principles.

For VQE, which is adept at finding the lowest energy states of a particular system, the addressed problem should be framed in terms of finding ground state energies of molecular systems. This involves representing the molecular structure and interactions within a quantum circuit in the typical Hamiltonian approach. The challenge lies in designing a variational ansatz that is both expressive enough to capture the ground state and efficient for quantum computation. The precision of the result will be contingent on the quality of the quantum hardware and the chosen ansatz.

When employing QAOA for combinatorial optimization problems such as routing or scheduling, the problem must be formulated as a cost function that QAOA can minimize. This cost function is then encoded into a Hamiltonian on which the quantum circuit can operate. The algorithm iteratively adjusts quantum circuit parameters to find the solution that minimizes the cost function. The depth of the quantum circuit (number of layers in the algorithm) plays a critical role in the solution quality, balanced against the computational resources available.

QMLAs are best suited to address machine learning problems where traditional machine learning models might struggle with the dataset size or complexity. For tasks such as classification and regression, data features are mapped onto quantum states in a process known as quantum embedding, then processed by a quantum circuit. For generative modelling tasks, the quantum circuit can be trained or programmed such as the quantum state represents the data distribution. The quantum algorithm should be selected based on its ability to handle the specific machine learning task and the dataset characteristics, considering the computational limitations of current quantum hardware.

In the case of QNNs, the problem should be compatible with neural network approaches, such as pattern recognition or system simulations. The neural network architecture must be adapted to a quantum framework, which involves defining quantum neurons and the entanglements between them. This quantum neural network uses superposition and entanglement to process information, potentially offering significant computational advantages. However, the design and training of QNNs are constrained by the noise levels and error rates in current quantum systems, as well as the nascent theoretical foundations for quantum deep learning.

In conclusion, the evolution of HQC algorithms is not just a response to the limitations of classical computation

environments. In fact, it marks the beginning of a new era in challenging problem-solving. As we explore applications in the optimization of biological processes, these algorithms emerge as key tools capable of navigating the inherent complexity of biological systems, as well as leveraging datasets derived from experiments and observations in this field. Furthermore, by incorporating quantum principles into machine learning and neural networks, new possibilities open up for understanding and modeling biological processes. It includes everything from genetic engineering to the optimization of metabolic processes, as well as the improvement of production techniques, process control, and methods of extraction and purification of biological products. We will now examine each of these topics in detail and provide further information on the associated computing algorithms.

3.1. VQE- Variational Quantum Eigensolver

VQE is a HQC algorithm designed to find the ground-state energy of molecules or, more generally, the lowest eigenvalue of a quantum operator, typically the Hamiltonian of a quantum system (see Figure 5). It is particularly useful for solving the eigenvalue problem, a fundamental task in quantum chemistry and materials science. However, with a proper restructuring of the problem, extensions to typical Engineering problems should be feasible. For instance, imagine a chemical reaction system where the reactants are in a specific molecular configuration. The VQE algorithm can be used to calculate the ground-state energy of this molecular configuration. This energy is crucial in understanding the reaction dynamics and predicting the optimal reaction outcome. By calculating the ground-state energy, this approach can identify the most stable molecular configuration.

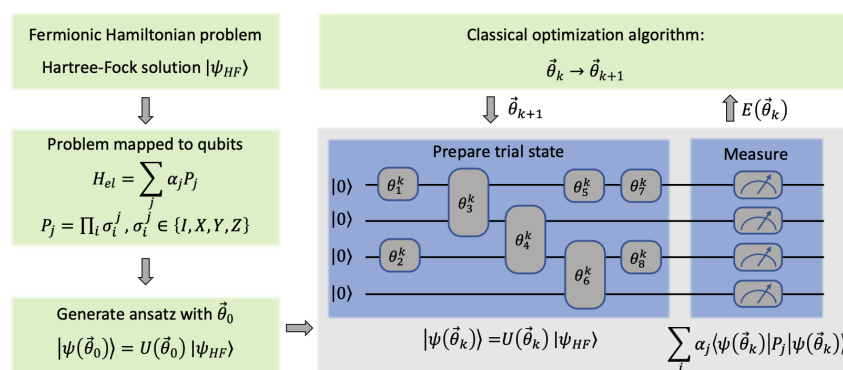


Figure 5: Schematic of the Variational Quantum Eigensolver (VQE) algorithm. Reproduced from reference⁴⁵. Available under a CC-BY 4.0 license. Copyright 2021 Dmitry A. Fedorov, Bo Peng, Niranjan Govind, and Yuri Alexeev.

3.1.1. Mathematical Formulation

Let H denote the Hamiltonian of the system, ψ denote the trial wave function, and θ represent the vector of variational parameters. The cost function C is defined as the difference between the calculated energy E and the target

energy E_0 :

$$C(\theta) = E(\theta) - E_0 \quad (8)$$

where $E(\theta)$ is calculated using the wavefunction ψ and the Hamiltonian H . Given a Hermitian matrix H , the goal is to find the smallest eigenvalue λ_{min} and its corresponding eigenvector $|\psi_{min}\rangle$. Ensuring that the Hamiltonian is a Hermitian matrix prevents the occurrence of complex-valued eigenvalues. The VQE algorithm uses a parameterized quantum circuit $U(\theta)$ to prepare a trial state $|\psi(\theta)\rangle$, which is then measured to estimate the expectation value of the energy:

$$E(\theta) = \langle \psi(\theta) | H | \psi(\theta) \rangle \quad (9)$$

next, the θ parameters are adjusted using a classical gradient descent optimizer to implicitly minimize the energy level as represented by $E(\theta)$. This process is mathematically represented as:

$$\theta^{k+1} = \theta^k - \alpha \nabla C(\theta^k) \quad (10)$$

where k is the iteration number, α is the learning rate, and $\nabla C(\theta^k)$ is the gradient of the cost function at θ^k .

The VQE algorithm is a powerful tool for calculating the ground-state energy of quantum systems, particularly in quantum chemistry. By leveraging the computational power of quantum computers and the optimization capabilities of classical computers, the VQE algorithm can efficiently solve challenging problems in Engineering, such as predicting reaction rates and identifying stable molecular configurations.

3.2. QAOA- Quantum Approximate Optimization Algorithm

QAOA is an HQC algorithm that addresses the optimal solution of highly combinatorial optimization problems. Beyond a certain problem size, such problems become unsolvable by traditional computing methods. However, the solutions to these problems now appear attainable through the use of quantum computing environments. In particular, this approach looks effective in tackling problems characterized by many local optima, such as MaxCut³⁹ and Max2SAT⁴⁶ problems, and the large number of binary decision variables. In simple cases, the MaxCut problem is easy to solve. However, for large scale systems, it is an NP-hard combinatorial optimization problem. In this section we discuss a way to deal with large scale combinatorial optimization problems by formulating the problem as a quadratic binary optimization problem (QUBO).

3.2.1. QUBO Problems and the Ising Model (IM)

The QUBO framework allows for formulating combinatorial optimization problems in a way that maps directly into the quantum perspective for exploring optimal solutions⁴⁷. QUBO problems are of the form:

$$\text{Minimize } \Omega(x_0, x_1, \dots, x_m) \quad (11)$$

where $x_j \in \{0, 1\}$. Moreover, $\Omega(x_0, \dots, x_m)$ is a quadratic polynomial on the x_j variables. This should make the name QUBO obvious. We are attempting to optimize quadratic problems with binary variables without other types of constraints.

In quantum computing, an IM, also known as an objective function in optimization settings, is a mathematical function used to describe systems of interacting binary variables, which can be in one of two states, often represented as +1 or -1 (or equivalently, "up" or "down" spins). In quantum computing, the IM is significant because it can be mapped to quantum optimization problems, enabling the use of quantum algorithms to find optimal solutions. The IM originally describes a lattice of spins in a magnetic field, where each spin can interact with its neighbors. The energy of the system depends on the alignment of these spins, with certain configurations being more energetically favorable.

The energy of a configuration in the IM is given by the Hamiltonian:

$$H = - \sum_{i,j} J_{ij} z_i z_j - \sum_i h_i z_i \quad (12)$$

where z_i and z_j represent the spins at sites i and j (each spin can be +1 or -1), J_{ij} represents the interaction strength between spins i and j , h_i represents the external magnetic field acting on spin i . In the above equation, the first term represents the interaction energy between spins, and the second term represents the energy due to the external magnetic field. In quantum computing, the IM can be extended to include quantum effects, where spins can exist in superpositions of states, and the system evolution can be described by a quantum Hamiltonian. This leads to the following quantum IM:

$$H = - \sum_{i,j} J_{ij} \sigma_i^z \sigma_j^z - \sum_i h_i \sigma_i^z - \sum_i \Gamma \sigma_i^x \quad (13)$$

where σ_i^z and σ_i^x are Pauli matrices representing spin components in the z and x directions and Γ represents a transverse field that induces quantum tunneling effects, allowing the system to explore different spin configurations. Hence, the IM is used in quantum computing for solving optimization problems, particularly those that can be framed as finding the ground state (minimum energy configuration) of the Ising Hamiltonian⁴⁸. Algorithms like the QAOA and Quantum Annealing leverage the IM to solve combinatorial optimization problems. In summary, the IM is applicable to various optimization problems, including the traveling salesman problem, portfolio optimization, and machine learning tasks such as classification.

For instance, in a chemical reaction scenario, the QAOA algorithm can be utilized to enhance the parameters for a chemical reaction related to the synthesis of a particular compound⁴⁹. The objective function in this scenario

would symbolize the energy necessary for the reaction, while the quantum circuit would transform the initial state into a superposition of states that signify the most efficient reaction conditions. Therefore, we obtain a combinatorial optimization problem we would like to solve. We then encode it into an Ising Hamiltonian. Now, in order to solve for its ground state, we need to apply a quantum evolution to the initial state using a quantum circuit.

3.2.2. Mathematical Formulation

The QAOA algorithm can be mathematically represented as follows.

Cost Operator: The cost operator is defined as:

$$C = \sum_i c_i \sigma_i^z \quad (14)$$

where c_i are the coefficients of the cost function and σ_i^z are the Pauli-Z operators acting on the i^{th} qubit.

Mixing Operator: The mixing operator is defined as:

$$B = \sum_i b_i \sigma_i^x \quad (15)$$

where b_i are the coefficients of the mixing operator and σ_i^x are the Pauli-X operators acting on the i^{th} qubit.

Quantum Circuit: The quantum circuit is composed of the cost operator and the mixing operator, which are applied to an initial quantum state:

$$U(\gamma, C) = e^{-i\gamma C} \quad (16)$$

$$U(\beta, B) = e^{-i\beta B} \quad (17)$$

where γ and β are the classical parameters controlling the quantum circuit.

Classical Optimization: The classical optimizer adjusts the parameters γ and β to minimize the cost function:

$$C(\gamma, \beta) = \langle \psi(\gamma, \beta) | C | \psi(\gamma, \beta) \rangle \quad (18)$$

where $\psi(\gamma, \beta)$ is the quantum state evolved by the quantum circuit.

The QAOA algorithm is a powerful tool for solving large-scale combinatorial optimization problems in Engineering. By leveraging the capabilities of quantum computers and classical optimization techniques, QAOA can efficiently optimize reaction conditions to achieve the maximum yield or minimize the energy required for the reaction, among other applications.

3.3. QML- Quantum Machine Learning

QML is a subfield of machine learning that explores the intersection of quantum computing and machine learning^{50–52}. It aims to develop new algorithms and models that can leverage the power of quantum computing to solve challenging machine-learning problems.

3.3.1. QNN- Quantum Neural Networks

QNNs represent a novel class of neural networks using quantum computing for computational tasks^{53–55}. Their architecture is specifically designed to overcome challenges that classical neural networks are not well suited to manage. For example, consider a chemical reaction in which the reactants are arranged in a particular molecular configuration. The QNN algorithm may be employed to forecast the reaction yield through an examination of the molecular structure and the reaction processing conditions. Hence, within an Engineering context, QNN may be employed to forecast the most favorable reaction parameters for a given chemical process flowsheet.

3.3.2. Mathematical Formulation

A QNN consists of multiple layers of quantum gates, each applying a unitary transformation to the input state. The output of the QNN is measured to obtain the result. In Quantum Circuit Learning, the parameters of the QNN are adjusted using a classical optimizer to minimize a loss function. The loss function is typically defined as the difference between the desired output and the actual output of the QNN. In a HQC framework, the training process involves iteratively updating the parameters of the QNN using a classical optimizer while the quantum circuit is executed on a quantum computer. This hybrid approach allows for leveraging the strengths of classical and quantum computing.

The QNN algorithm can be mathematically represented as follows:

Quantum Circuit:

$$U(\theta) = e^{-i\theta H} \quad (19)$$

where

$$H = \sum_i h_i \sigma_i^z \quad (20)$$

and

$$\sigma_i^z = \begin{bmatrix} 1 & 0 \\ 0 & -1 \end{bmatrix} \quad (21)$$

are the Pauli-Z operators acting on the i^{th} qubit.

Quantum State:

$$|\psi\rangle = \sum_i c_i |i\rangle \quad (22)$$

where $|i\rangle$ are the basis states of the qubits and c_i are the coefficients of the quantum state.

Quantum Measurement:

$$|\psi\rangle \rightarrow |i\rangle \quad (23)$$

where $|i\rangle$ is the outcome of the measurement.

Classical Post-processing:

$$y = f(|i\rangle) \quad (24)$$

where y is the final output, and f is a classical function that processes the outcome of the measurement.

4. Broader Applications of HQC Algorithms in Industry and Science

HQC algorithms have demonstrated considerable potential across diverse fields, effectively addressing complex optimization problems that often challenge traditional computational methods. While this study focuses on their application in optimizing multiscale bioprocesses, it is important to recognize that the utility of HQC algorithms extends well beyond this domain. These algorithms have shown promise in areas such as drug discovery, energy systems optimization, industrial process control, logistics, and more underscoring their versatility across both scientific and industrial applications.

The advancement of quantum computing, which harnesses entanglement, superposition, and other core quantum principles, holds the promise of significant processing advantages over traditional computing⁵⁶. These quantum attributes enhance the resolution of numerous complex problems in comparison to conventional computing methods, including quantum optimal control⁵⁷, electrical power system monitoring⁵⁸, drug design⁵⁹, sustainable energy development^{60,61}, banking enhancements⁶², quantum chemistry⁶³, and healthcare⁶⁴. In recent years, substantial progress in quantum software, algorithm development, and hardware research has brought us closer to the realization of functional quantum computers. Research in this field is rapidly expanding, with frequent breakthroughs in areas such as hardware, software, algorithms, and error correction on Noisy Intermediate-Scale Quantum (NISQ) devices. Initially driven by academic researchers, the field attracts industry experts focused on practical applications⁵⁶. The combination of quantum and classical computing is particularly promising, as HQC algorithms capitalize on both strengths to address complex problems in novel ways. Following some of the recently developed works using HQC algorithms are described.

⁶⁵ propose the use of Quantum Support Vector Machines (QSVM) to enhance Human Activity Recognition (HAR) in Industry 4.0. Sensor integration and data processing make tracking and optimizing human activities crucial for performance improvement. However, the surge in wearable sensor usage has led to a data explosion that conventional

technology may struggle to handle by 2030. Quantum computing emerges as a promising solution. The QSVM, deployed using the Qiskit library and quantum simulator, outperforms state-of-the-art machine learning algorithms with 98 percent accuracy. The study suggests future extensions for classifying complex activities and explores industrial applications like packaging and heavy industry operations using multimodal sensors. In another work, Quantum-Inspired Genetic Programming (QIGP) was deployed for optimizing crude oil scheduling in real-world refineries⁶⁶. It integrates linear and grammar-guided genetic programming with a quantum-inspired approach to generate scheduling solutions. Testing on five real refinery scenarios showed promising results, with success ratios ranging from 36 percent to 100 percent. QIGP contributions include the development of a domain-specific language, the integration of various GP approaches, and the ability to handle diverse scheduling scenarios.

Recently a Generator-Enhanced Optimization (GEO) framework was proposed by⁶⁷, which uses generative models like Generative Adversarial Networks, Variational Autoencoders, and Quantum Circuit Born Machines for optimization problems. Focusing on a quantum-inspired version called TN-GEO, the study demonstrates its effectiveness in portfolio optimization problems, where it outperforms classical solvers by proposing lower cost function values. TN-GEO can enhance classical solvers using prior data or act as a standalone solver with no prior observations. Comparisons with state-of-the-art algorithms show TN-GEO as a top performer, highlighting the practical potential of quantum-inspired generative models in real-world applications. In another work, the TN-GEO method was employed for optimizing a BMW assembly line based on their manufacturing schedule⁶⁸. By employing the TN-GEO method, which utilizes quantum-inspired modeling based on tensor networks, the study compares optimization techniques and finds that quantum-inspired methods can discover lower-cost solutions in specific contexts when combined with conventional black-box methods. The research highlights the significance of problem representation, demonstrating that parameter groupings based on correlations and problem-motivated encoding of assembly line parameters lead to improved results compared to naive representations. Combining these techniques, the study shows that quantum-inspired generative model-based solvers match or surpass conventional optimization methods in most tested cases, particularly in intermediate solution space sizes. Overall, TN-GEO ties or outperforms conventional optimization methods in 31 out of 45 tested cases, showcasing the effectiveness of these optimization methods in industrially-relevant settings.

A quantum-inspired optimization strategy for solving the optimal dispatch problem in Combined Heat and Power (CHP) systems is proposed by⁶⁹. In this work, the algorithm explores a larger search space by combining quantum mechanics principles with classical optimization. It achieves superior solution quality and computational efficiency performance compared to other techniques. The implemented Quantum Particle Swarm Optimization (QPSO) algorithm effectively minimizes total operating costs with enhanced near-global optimal solutions and minimal computing time. Future research aims to explore quantum-inspired optimization in other energy systems and validate practical implementations in real-world scenarios to enhance understanding and utility. The quantum mechanic principles

have been used in addressing the computational challenges associated with simulating turbulent flows in complex geometries⁷⁰. Utilizing matrix-product states, a compressed representation of quantum states, the framework achieves memory and runtime scaling logarithmically with mesh size. It offers a complete solution for flows around immersed objects of arbitrary geometries, incorporating non-trivial boundary conditions. Moreover, it enables the direct retrieval of solutions from compressed encoding, bypassing the expensive dense-vector representation. This framework sets the stage for more efficient solvers for realistic fluid problems, promising significant advancements in Computational Fluid Dynamics (CFD) research and industry applications.

⁷¹ proposed a generative model that addresses the longstanding challenge in chemistry and biology of discovering small molecules with therapeutic potential. Leveraging a HQC generative model, the researchers integrate the computational power of quantum algorithms trained on a 16-qubit IBM quantum computer with the reliability of classical methods to design new KRAS inhibitors crucial for cancer therapy. KRAS is a gene often mutated in cancers, driving tumor growth. This innovative approach resulted in synthesizing 15 promising molecules, with two effectively engaging with KRAS. This work marks the first instance of a quantum-generative model producing experimentally confirmed biological hits, demonstrating the practical potential of quantum-assisted drug discovery. Comparative analysis with classical generative models revealed that the quantum approach enhanced distribution learning from established datasets and suggested a correlation between the efficacy of distribution learning and the number of qubits used.

In another work, a transport robot scheduling problem has been used to compare the performance of D-Wave quantum-classical hybrid framework, Fujitsu quantum-inspired digital annealer, and Gurobi classical solvers⁷². The three models in question stem from a pertinent industrial scenario, each following distinct design philosophies. The benchmark assesses solution quality and end-to-end runtime across model and solver combinations. Promising results have been noted for the digital annealer, while some potential opportunities have been identified for the hybrid quantum annealer compared to Gurobi.

5. Perspectives on the Application of HQC Algorithms in Multiscale Bioprocess Optimization

The HQC algorithms addresses the computational limitations of classical solvers in multi-scale bioprocess optimization, which involves a mix of discrete and continuous decision variables across different hierarchical levels. Classical approaches struggle due to the combinatorial explosion of possible solutions, nonlinear regulatory constraints, and real-time decision-making requirements. HQC algorithms offer an integrated solution by leveraging quantum computing for discrete optimization tasks while using classical solvers for continuous variable refinement.

Figure 6 presents a schematic representation of this computational workflow, explicitly illustrating how quantum and classical solvers interact iteratively across these levels. While each optimization scale (molecular, cellular, fer-

mentor, plant-wide) can be solved independently, the full HQC framework integrates them dynamically, ensuring that interdependencies across scales are efficiently managed. This section provides perspectives on how HQC algorithms tackle challenges and offer flexible and scalable solutions at various bioprocess scales.

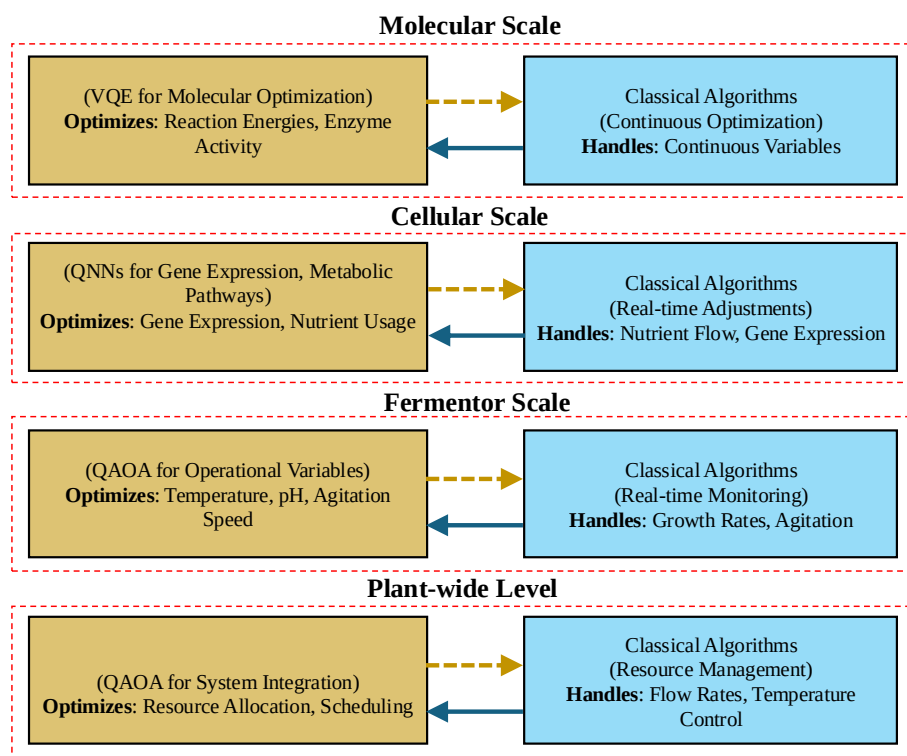


Figure 6: Schematic representation of the Hybrid Quantum-Classical (HQC) computational workflow for multiscale bioprocess optimization. While each level, cellular, fermentor, and plant-wide, can be optimized independently, decisions made at one scale often propagate and impact others, making isolated optimization insufficient for achieving global performance. The HQC framework addresses this challenge by coordinating quantum and classical solvers through an iterative feedback loop. Quantum algorithms handle discrete, combinatorial decisions (e.g., pathway selection, scheduling), while classical solvers manage continuous variables and real-time adjustments (e.g., metabolic fluxes, process control). This loop enables simultaneous, cross-scale optimization under dynamic conditions.

- Molecular Level.** At the molecular level, optimization focuses on solving quantum mechanical problems related to enzyme configurations and reaction energetics, where electronic structure calculations scale exponentially with system size. Classical solvers (e.g., DFT, Coupled Cluster) struggle with large biomolecular systems due to high computational costs. The intricacy here arises from the need to solve Hamiltonians representing molecular interactions, which grow exponentially in size as the system becomes more complex. Classical algorithms find it difficult to efficiently explore these configurations because of computational bottlenecks. VQE is especially well-suited for this task because it leverages quantum hardware to efficiently find the ground-state energy of molecular systems. VQE encodes molecular states as quantum circuits, enabling it to explore multiple configurations in parallel, which classical methods cannot achieve. This parallel exploration allows VQE

to quickly identify optimal enzyme conformations that maximize catalytic activity. By accelerating molecular optimization, VQE improves the design of enzymes and reaction conditions, enabling faster and more efficient biocatalyst development. The improvements lead to higher metabolic efficiency, minimizing the costly and time-consuming trial-and-error methods often needed in classical molecular modeling.

- **Cellular Level.** At the cellular level, the challenge lies in managing non-linear interactions within metabolic pathways and gene expression networks, which are highly sensitive to environmental changes. QNNs address these challenges by encoding metabolic states as quantum states, enabling the simultaneous exploration of multiple regulatory scenarios. QNNs are particularly suited for this task because cellular processes often involve highly coupled, dynamic systems with multiple interdependencies. In contrast, classical machine learning models tend to get trapped in non-convex spaces. QNNs capture these relationships through quantum entanglement, which enhances predictive accuracy and optimization. Unlike classical algorithms, QNNs explore multiple metabolic configurations in parallel, allowing them to identify optimal gene expression patterns and nutrient flows more efficiently. QNNs are especially well-suited at this stage, as the cellular level offers a wealth of experimental data to train models and refine predictions, allowing the quantum-classical approach to take full advantage of both exploration and real-time adjustments. This makes QNNs ideal for optimizing dynamic cellular systems, where adaptive control and accurate predictions are essential to maintaining productivity. As shown in Figure 6, the quantum-classical interaction at the cellular level captures the exploration of potential configurations and the real-time management of critical process variables.

- **Fermentor Level.** Fermentor systems require continuous optimization of operational parameters. These variables interact dynamically, and small changes in one parameter can significantly impact microbial performance, creating a highly non-linear solution space. Classical algorithms often fail to escape local optima, limiting their effectiveness in optimizing these processes. The QAOA is particularly well-suited for this scale because it encodes operational configurations as quantum states and explores them in parallel. The QAOA's ability to leverage quantum tunneling allows it to escape local optima efficiently, identifying the best combination of parameters for maximum yield and minimum energy consumption. The dynamic tuning of fermentor conditions ensures consistent microbial performance while reducing the need for manual adjustments. As a result, QAOA enhances both productivity and sustainability by lowering process cycle times and resource consumption.

- **Plant-wide Level.** At the plant-wide level, the challenges increase due to the need to coordinate multiple interdependent units, including upstream reactors, downstream processing, and energy management systems. Classical algorithms become computationally inefficient when solving such large-scale scheduling and resource allocation problems. QAOA again proves advantageous by encoding scheduling tasks as QUBO problems,

which it can solve efficiently using quantum hardware. The QAOA's ability to evaluate multiple scheduling configurations simultaneously enables it to identify optimal resource distribution and synchronize operations across units. This ensures smooth transitions between production stages, reduces downtime, and minimizes energy consumption. By optimizing plant-wide operations, QAOA aligns production processes with sustainability goals, contributing to both economic efficiency and environmental performance.

5.1. *HQC Feedback Loop and Implementation*

The success of the HQC framework in capturing the full complexity of bioprocess optimization lies in the feedback loop that integrates quantum exploration with classical real-time control. At each scale, quantum algorithms are responsible for exploring high-dimensional, discrete decision spaces, while classical algorithms handle continuous process variables and refine quantum-generated solutions in real-time. This continuous exchange between quantum and classical systems allows for iterative optimization, where real-time data informs quantum adjustments, and quantum results guide classical process control. This interaction ensures optimal solutions are maintained across all scales, even as conditions evolve.

5.2. *Broader Implications and Future Directions*

The potential applications of HQC extend beyond theoretical research into practical, real-world scenarios. In areas such as pharmaceutical manufacturing, biofuel production, and precision biomanufacturing, HQC algorithms can enable more sustainable, efficient, and flexible production processes. Their ability to dynamically optimize challenging systems opens new possibilities for resource-efficient production, reduced waste, and enhanced product quality. Future work should focus on implementing HQC algorithms on emerging quantum hardware platforms and validating them through experimental trials, bridging the gap between theory and real-world applications. The convergence of quantum computing with biotechnology offers exciting opportunities for developing next-generation production systems that are both resource-efficient and environmentally sustainable.

6. **Quantum Challenges and Opportunities Solving Bioprocess Problems**

HQC offers promising solutions for addressing the complex optimization challenges inherent in bioprocesses, but they also bring significant technical obstacles. A primary concern is the scalability of current quantum hardware. Most quantum computers are constrained not only by the limited number of qubits but also by qubit quality, coherence time, and gate fidelity. Furthermore, quantum systems are susceptible to high error rates and noise, which can degrade the accuracy of computations. Although quantum error correction techniques are being developed, these techniques increase overhead and require additional qubits, limiting the size of problems that can be solved efficiently.

Another critical challenge is integrating and ensuring seamless communication between quantum and classical systems. The efficient data transfer between quantum algorithms optimized for discrete decision-making and classical algorithms handling continuous variables and stability remains a bottleneck. Establishing robust interfaces is essential to ensure that classical systems can refine quantum-generated solutions in real time. Without efficient communication, delays in data exchange can disrupt real-time control, which is crucial in time-sensitive bioprocesses. This interplay is fundamental to realizing the full potential of HQC algorithms in dynamic, time-sensitive bioprocessing environments.

Developing quantum algorithms aimed to bioprocess optimization poses a significant challenge. While algorithms such as VQE, QAOA, and QNNs provide a foundation, adapting them to multiscale bioprocess environments requires new methodologies. This customization demands collaboration between quantum computing experts, bioprocess engineers, and industry stakeholders to ensure effective and practical solutions. Despite these challenges, HQC holds transformative potential in bioprocess optimization, combining the scalability of quantum computing with the reliability of classical control mechanisms to achieve breakthroughs in efficiency and precision.

Quantum algorithms could potentially offer advantages in combinatorial optimization problems, including those that grow exponentially with the number of variables, such as resource allocation, process scheduling, and the optimization of operating conditions across scales. However, whether they provide a distinct advantage in addressing NP-hard problems is not yet definitively known. Quantum methods explore solution spaces differently than classical methods, potentially leading to more efficient pathways for certain problem types, but this does not imply “parallel exploration” in the way classical parallel computing does. Moreover, quantum computing is not well-suited for problems requiring significant data throughput, which can limit its applicability in certain data-intensive bioprocess optimizations. Furthermore, integrating HQC into bioprocessing can foster innovation by enabling the development of optimization methods that extend beyond the current reach of classical computing. Combining quantum and classical systems facilitates approaches that balance exploration and stability, unlocking new possibilities for resource-efficient production. The technical challenges that arise from implementing HQC also create opportunities for interdisciplinary collaboration, accelerating the development of tailored quantum solutions that can reshape the field of bioprocess optimization.

7. Conclusions

This study has discussed the potential of HQC algorithms as a robust solution for the optimization challenges found in multiscale bioprocess systems. HQC combines the capabilities of quantum algorithms to explore discrete, combinatorial problems with the strengths of classical algorithms in managing continuous variables and ensuring real-time process control. Unlike classical approaches, HQC can process large volumes of data and dynamically adjust system parameters, responding to real-time changes. This hybrid approach provides a framework for optimizing

processes across multiple scales, from molecular to plant-wide systems, addressing the limitations of classical methods in solving high-dimensional, non-linear problems.

The work highlights the main optimization challenges inherent in bioprocesses, ranging from system complexity to non-linearity, and demonstrates how HQC are well suited to overcome these obstacles. Combining quantum and classical computers offers a pathway to addressing the dynamic and large-scale nature of bioprocess optimization. In addition, the exploration highlights HQC's potential to solve intractable problems in bioprocesses, such as resource allocation, process scheduling, and metabolic pathway optimization, as system complexity increases.

In the near future, as quantum computing technology continues to grow and improve in terms of qubit coherence, quantum error correction, and scalable algorithms, HQC will become even more powerful. These advancements will enable HQC to solve even more challenging optimization problems, providing innovative solutions in areas such as metabolic engineering, bioprocess design, and industrial-scale operations. As a result, bioprocess optimization will become more precise, efficient, and sustainable, with significant implications for the biotechnology industry. Finally, while this paper focuses on theoretical exploration, future research should explore experimental applications and scaling the algorithms to emerging quantum hardware platforms.

8. Author Contributions

Ilse María Hernández-Romero: Conceptualization, Methodology, Visualization, Investigation, Writing – original draft, Supervision. **Shawn M. Gibford:** Formal analysis, Writing – review and editing. **Antonio Flores-Tlacuahuac:** Project administration, Supervision, Writing – review and editing. **William Clements:** Manuscript improvement during revision and response to reviewers. **Christopher Savoie:** Manuscript improvement during revision and response to reviewers. **Seyed Soheil Mansouri:** Conceptualization, Supervision, Writing – review and editing.

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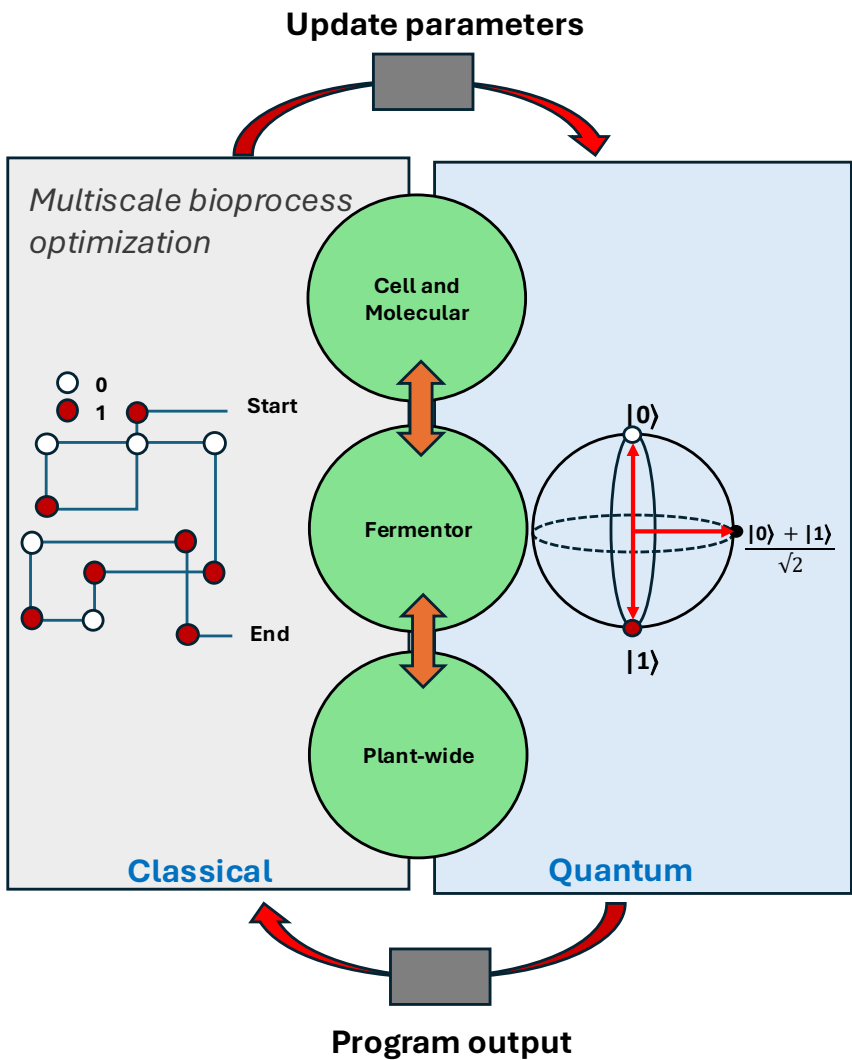
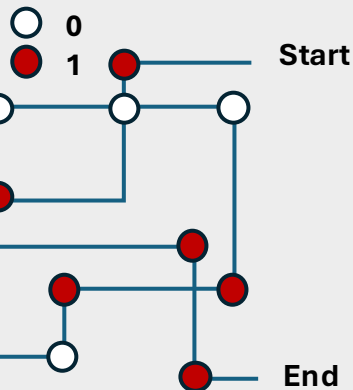


Figure 7: *

Update parameters

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*Multiscale bioprocess
optimization*



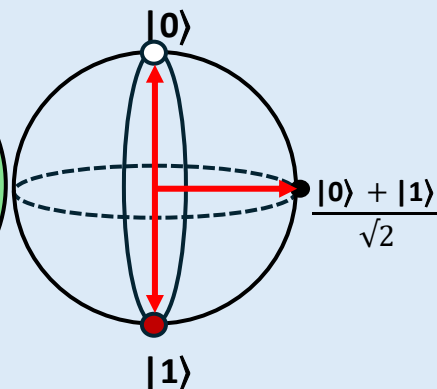
Cell and
Molecular

Fermentor

Plant-wide

Classical

Quantum



ACS Paragon Plus Environment

Program output

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