Information System and Smart City 2023; 3(1): 294.
Review Article

Quantum computing in drug discovery

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ARTICLE INFO

Received: 6 November 2023
Accepted: 6 December 2023
Available online: 11 December 2023

doi: 10.59400/issc.v3i1.294

ABSTRACT: Quantum computers are recently being developed in wide varieties, but the computational results from quantum computing have been largely confined to constructing artificial assignments. The applications of quantum computers to real-world problems are still an active area of research. However, challenges arise when the limits of scale and complexity in biological problems are pushed, which has affected drug discovery. The fast-evolving quantum computing technology has transformed the computational capabilities in drug research by searching for solutions for complicated and tedious calculations. Quantum computing (QC) is exponentially more efficient in drug discovery, treatment, and therapeutics, generating profitable business for the pharmaceutical industry. In principle, it can be stated that quantum computing can solve complex problems exponentially faster than classical computing. Here it is needed to mention that QC will not be able to take on every task that classical computers perform—at least not now. It may be classical and quantum-coupled computational technologies combined with machine learning (ML) and artificial intelligence (AI) will solve each task in the future. This review is an overview of quantum computing, which may soon revolutionize the pharmaceutical industry in drug discovery.

KEYWORDS: quantum computing; qubits; drugs; algorithms; machine learning

1. Introduction

The fundamentals of the pharmaceutical industry are to formulate drug designs to treat or cure diseases. In 2020, the FDA has approved only 53 drugs, which is still higher in number than within the past 20 years[1]. It shows that there is a distinct lack of "hit" drugs in these years. The drugs with their exceptional therapeutic properties are used for 93% of global net drug spending growth as compared to small molecules in recent years[2]. Drug development takes approximately 13 and more years with an exceptionally high budget (£1bn) to develop a new drug[3]. Moreover, with many identified medicines in the lab, only one drug might be able to ever reach patients, while the others fail along the way. Once the search for a potential drug is over, it is developed to provide maximum benefit with minimal side effects for patients. Computational resources made the drug discovery process faster so that it could produce more effective drugs with fewer side effects in an accurate manner.

Quantum computers use the laws of quantum mechanics, such as superconducting loops (microwave radiation) or ions drifting in ion traps within electromagnetic fields (lasers). QC uses quantum behaviour to solve the problems. This "quantum advantage" helps and motivates organizations to solve problems that cannot be realistically solved by classical computers. So "universal quantum computing" is applied

with large fault-tolerant quantum computers or hybrid classical/quantum computers to do a wide range of computational tasks[3].

Quantum Information Science and Technology (QIST) has been used to transform and develop novel algorithms using machine learning techniques for technological developments. Quantum computers have more advantageous features than classical systems for molecular simulations of drug design and discovery[4]. Cloud computing, AI, and ML are using quantum computing to carry out efficient and remarkably less expensive calculations. Quantum algorithms provide exponential speedups as compared to their classical counterparts[5]. Modern quantum calculations are finding approximate solutions with the following methods, such as Ab initio methods[6], semi-empirical methods[7], density functional methods[8], density matrix methods[9], algebraic methods[10], quantum Monte Carlo methods[11], and dimensional scaling methods[12]. These systems are accurate only for larger systems and are quite expensive. It is anticipated that the exponential speedup of quantum computers can complete the simulation tasks within only a polynomial amount of time. Quantum computers use "qubits", unlike classical computers, which use "bits". Qubits can either be on or off, or both (superposition). The difference between classical bit and qubit is given in **Table 1**. Quantum gates operate on a system of qubits. Qubits and quantum gates are found to be the basic components of any algorithm, as the basic components of programming language are variables and functions. The combination of great speed with probabilistic solutions to multiple calculations with higher accuracy at one time fits well in applications such as optimization, simulation of chemicals, and AI. Today, quantum computers are known as "Noisy Intermediate Scale Quantum" (NISQ), which have limited computational resources. NISQ assists with the first level of drug discovery, which involves molecular simulations, wave function optimization, and ML. It is observed that even smaller simulations result in accurate predictions of potential drugs long before clinical trials, with reduced time and cost[4].

Table 1. Comparison between a classical bit and qubit.

Classical bit	Qubit
State 0 or 1	$\|0\rangle$, $\|1\rangle$, or superposition.
Measurement does not change the state of the bit	Measurement changes the system.
Deterministic result	Quantum state itself remains the same and it is deterministic. Different results only occur with measurement when the quantum state collapses.
Can make a copy of bi (eavesdrop)	Cannot clone the qubit (security).
One number for a string bit	A qubit can represent a state vector with 2 degrees of freedom; thus, it can store one complex number.

2. Methods

The pharmaceutical industry has developed molecular formulations to treat diseases in the form of drugs. The industry has made huge investments, which is more than 20% of total R&D industries at the global level[3]. Various computational chemistry's digital tools with AI have been opted to predict and simulate the structures, physicochemical and biological properties, pharmacokinetics, and pharmacodynamics of drugs accurately. But either accuracy or speed are affected; force fields are quick but offer generalized answers, whereas the exact solution O(n!) is called factorially, n being the number of electrons. These computational tools are not easily manageable by standard computers, and for atomic-level calculations, the methods used are not sufficiently accurate. QC can accurately predict the interactions at the atomic level. A quantum algorithm (quantum annealing) can shift the probability distribution of the superimposed states so that the state or states corresponding to the global optimum become intensely probable on measurement[13]. Massive parallelism is an advantage of QC that

can be attained by modelling many solutions simultaneously. As expected, the number of simultaneously measured solutions doubles with the addition of each additional quantum bit, or qubit. This allows for exponential scaling, which is not achieved by classical computers. The exponential scaling helps to search for and solve certain classes of problems.

Two computational methodologies have been used for drug discovery, which are (a) annealing-based quantum computation and (b) gate-based quantum computation. The larger problems are easily handled by the quantum computers. Currently, MD simulations and DFT approaches with computer-assisted drug discovery (CADD) are used to predict the behaviour of drug molecules. Quantum computers are used to shorten the screening time and make the CADD approach more effective so that the molecular properties of drugs can be predicted accurately. The modelling process of target-drug interaction can also be predicted in an effective way, as QC is capable of searching multiple possible target structures from virtual screening from compound libraries in parallel[14]. The limitation of classical approaches is the structural flexibility of the target molecule due to a lack of limited time and resources, which reduces the chance of identifying the best drug candidates. Improvements in QC have substantially decreased the requirements for simulation. For example, in 2017, 200 million physical qubits at a 10^{-3} error rate were reduced to 4 million physical qubits in 2020[3]. Several new theoretical tools have been developed to perform the simulations. Statistical methods and ML are used in drug discovery, estimation of molecular and ADMET properties of drugs, and prediction of protein-ligand binding[13]. Deep neural networks are used to predict molecular interactions[14], secondary structure[15] and 3D protein structures[16] in structural biology. These computationally intensive models with general-purpose graphical processing units (GPUs) and exponentially faster algorithms speed up the calculations to train ML models. These ML models and various algorithms of QC are used for applications in drug delivery. Variational quantum eigen-solver (VQE) methods enhanced with sophisticated state preparation methods and measurement reduction techniques are used to calculate the binding affinity between small active pharmaceutical ingredients (APIs) and a target receptor. Many quantum ML algorithms are used for quadratic or exponential speedup processes[16].

Several techniques are used to extract information from unlabelled datasets in unsupervised learning. Various ML tools are applied in next-generation sequencing (NGS) to extract and analyse the output data of biomolecules[17] or annotate genomes[18]. Principal component analysis (PCA) is used to reduce the high-dimensionality datasets of RNA microarray and mass spectrometry (MS) data[19] by searching for linear combinations of features that maximize the variance[20]. In quantum computers, quantum algorithms are used to build the covariance matrix of the data and use quantum phase estimation[20] to compute the eigenvectors in an exponential time span[21–24].

Supervised learning is used to predict the binding affinity of a ligand to a protein[21] and computer-aided disease diagnosis (CADD)[25]. Gaussian process (GP) regression[26] is used to build surrogate models, MD simulations, and predictions of the drug properties of quantitative structure-activity relationship (QSAR) models[27,28]. Another statistical method, hidden Markov models (HMM), is used for computational gene annotation and sequence alignment[27]. ML[28] and deep learning (DL) have been used for accurate contact prediction in proteins[17], precision medicine[29], molecular design[30], and simulation[30,31]. QC is extended to biomolecular[32] and biological systems as the quantum annealing (QA) method is used to investigate the coarse-grained folding landscape of a six-amino acid peptide within a 2D lattice framework[33]. QA is used to search for the transcription factor binding of DNA sequence[34]. Quantum effects have the potential to accurately model energy transport (in photosynthetic complexes)[35–39] and electron transport (redox sites of metalloproteins)[40] in biological molecules[41]. Various

combination methodologies are used for understanding the function of the brain at the genetic level with global structural/functional networks[29]. The initial step in genetics and genomics is the sequence matching of nucleotides and amino acids to the reference databases, for which various algorithms such as Needleman and Wunsch[42], Smith and Waterman[43] are used. In genomic read mapping, algorithms such as the Burrows-Wheeler transform are efficiently used to perform DNA sequence alignments[44]. The seed-based approaches[45] are used to confront the mapping of RNA reads to the boundaries between exons separated by large genomic distances. Hidden quantum Markov models (HQMMs)[46–48] can simulate classical HMMs on quantum circuits[47], as well as develop model space beyond classical HMMs[45]. Possible models such as Bayesian Networks, Boltzmann Machines[49], and variational autoencoders (VAEs) are used to predict genetic risk for particular traits, which can be partitioned across "intermediate" phenotypes, leading to insights into disease etiology[50–52]. QC simulated systems[53] are used to study the active sites of many enzyme-transition metal interactions[54].

These algorithms are useful to design drug[55–57], supervised learning (e.g., protein binding affinity), unsupervised learning (e.g., genome clustering), and generative modelling (e.g., de novo drug design). The problems related to protein structure prediction are now being tackled by gate-based quantum computers, as earlier optimisation studies were carried out by annealing methods[58]. The classical algorithms are able to provide solutions for the sampling of the conformation space of small proteins, whereas they cannot handle the intrinsic NP-hard complexity of the problem, even if it is reduced.

QC can benefit the entire value chain, but its prime focus lies in the research and development process. The pharma value chain includes research and development, production, logistics and supply chain, and access to the commercial market and patients. The research includes the understanding of disease and developing the hypothesis, target identification, hit generation and identification, lead generation, optimization of drug candidates with ADMET prediction, and dose and solubility optimization. ML and AI techniques are used to find structure-property relationships and potentially predict the 3D structure of target proteins. QC is able to create novel types of drug-candidate libraries with peptides and antibodies. An advanced-level approach by QC can be used to automatically screen structurally relevant targets against drug-like molecules via next-generation sequencing (NGS) approaches. QC increases the modelling accuracy of target-drug interactions, reduces the number of development cycles, and increases the quality of the optimized lead compounds. New molecules are synthesized, and their physicochemical and biological properties are predicted in a faster manner. QC can be used to reliably identify the 3D structure of targets. Drugs are often developed without even knowing the structure of a protein, accepting the risk of a trial-and-error approach because of their high commercial uses and profits in the pharma business. Researchers "Demis Hassabis" and "John Jumper" were recognized for creating the AI tool, which has easily predicted the 3D structures of almost every known protein[59]. The prediction of template-free protein structure is one major problem in molecular engineering and drug discovery. The folding funnel hypothesis assumes that the native state of a protein corresponds to its free energy minimum under the solution conditions usually encountered in cells[60,61], although many counterexamples exist. The quantum computing focus is on the protein lattice model, where the peptide can be modelled by self-avoiding walking on a lattice[60]. The residue is correlated to each node of the lattice, and the energy function is contributed by the interactions between spatial neighbours. Two main model schemes are used for protein structure prediction, among several other models. These are hydrophobic-polar model[62] (considering only two classes of amino acids) and Miyazawa and Jernigan[63] (containing interactions for every pair of residues). These models provide understanding for protein folding mechanism[64] and have been considered as a coarse-grained substitute to search conformational

space before further refinement[65,66] with a large number of qubits. D-Wave quantum annealers and the Quantum Approximate Optimization Algorithm (QAOA) algorithm both share identical features for the protein lattice problem encoded as a Hamiltonian operator. Rotamer sampling in the Rosetta energy function[67] and conformer sampling[68] are performed by the quantum annealing method. QC-associated AI tools will be able to resolve the formation of protein complexes, protein-protein interactions, and protein-ligand interactions. QC can apply a hit generation and validation approach to deliver optimized potential lead molecules with an easier and quicker approach. Other properties, such as ADMET properties, dose and solubility optimizations, and other safety issues, can be solved with QC. Using the ML algorithms, QC can generate a type of fake data, which can be specifically useful where there is a scarcity of data, such as in rare diseases, where the missing information through artificial data sets can be mitigated[3]. Here, QC will speed up the training of ML models, the amount of required initial data, and the accuracy level. The development includes patient identification and stratification, pharmacogenetic modelling, site selection, and side effects analysis for drugs used by the concerned patients. Recently, many features were studied for Alzheimer's drug research[69] with ML applications, which has given insights to identify cancer treatment biomarkers from genomics data analysis. The application of expected QC for hit generation, hit-to-lead, and lead optimization is given in **Table 2**.

Table 2. Expected QC for hit generation, hit-to-lead, and lead optimization.

CADD approaches	**Hit generation and hit-to-lead**		**Lead optimization**	
-	Method (virtual screening/docking)	Lead identification	Optimize ADMET	Optimize drug activity
Multiomics	-	-	-	-
Reverse protein blocking	-	-	-	-
De novo modelling/ protein folding	-	-	-	-
Comparative modelling	-	Grid-based pocket probes, surface alignment	Supervised machine learning for ADMET	-
BE calculations	Classical MD, quantum-inspired SM, QM/MM approach	Classical MD, absolute BE, thermodynamic integration, free-energy perturbations, QM/MM approach, fragmentation approaches	Simulation methods	Synthetic biology approaches, absolute BE calculations, thermodynamic integration, free-energy perturbations
Conformational analysis	-	Classical MD, QM/MM approaches, fragmentation approaches	-	-
Reaction path simulation/kinetic predictions	-	Fragmentation approaches with QM calculation (synthetic routes)	-	-
QSAR	Supervised and unsupervised ML	Supervised ML to derive empirical evidence, fragmentation approaches	Quantum-inspired ADME descriptor calculation, supervised ML for ADMET	-
Molecular docking	-	Fragmentation approaches	-	Classical MD, QM/MM approaches
Automated retrosynthesis	-	Unsupervised ML with supervised ML (synthetic routes)	-	Supervised ML

Abbreviations: CADD (computer aided drug design); MD (molecular dynamics); QM/MM method (quantum mechanics/molecular mechanics); QSAR (quantitative structure-activity relationship)[5].

3. Discussion

The profile of drugs is developed for a specific disease and selected for a specific protein target of

that disease. Further, all desired properties of the drug are considered, such as specific protein binding sites, oral/IV insertion, brain permeability, dose usage, target group, similar and combination drugs, administration (timings and time span), package and delivery, marketing strategies, and so forth. Various databases can be created for these drugs, which can generate a large chemical space with a larger number of molecules. Quantum algorithms such as the Quadratic Unconstrained Binary Optimization (QUBO) algorithm are used to search for specific properties of the drug profile in a large chemical space[70]. These results can be used to filter the desired drugs and preferred binding site(s). Once the chemical space is reduced, it greatly reduces the extensive benchwork, which includes tests for toxicity, appropriate dosages, and potential costs, among many others. This shortened path eliminates inappropriate molecules and helps in the experimental design of a few complexes, so that the production cost is also reduced. The clinical phase 1 trials took several months, with only 70% of the initial passing of the experimental drugs. QC can treat many more diseases in a smaller number of cases as compared to a few years ago. QC will improve drug efficacy in cases of drug shortages. QC will help find small drug molecules to improve delivery methods. QC can also help prepare asset portfolios that will have great potential as life-changing medicines in the future. These drugs, when obtained in the early stages, can shorten the production time at a later stage. The supply of drugs will be faster with hybrid quantum computing incorporating developed methodologies such as cloud computing, AI, and ML. QC will also help in searching for the smallest possible drugs with the desired properties of the selected drug profile, and simulations will become easier with QC. Further repurposing of drugs becomes faster with pre-existing clinical data as the clinical trial phases 1, 2, and 3 take several years, with only 20%–30% of drugs passing all three phases. QC brings great hope for drug discovery as it can reduce the time of clinical trials, provide accuracy, and increase safety in an effective manner. In quantum technology, quantum annealers and "quantum-inspired" annealers will be used in much larger spaces to work for billions of molecules if and when needed.

At present, there are no commercial gate-based quantum computers that can support over 90 qubits to develop variational quantum Generative Adversarial Networks (GAN) algorithms, except for quantum annealers. However, a hybrid GAN using fewer qubits can be exploited for the benefits of quantum computing[71].

Drug discovery with QC is fast, safe, and effective. It is anticipated that gate-based universal quantum computers, quantum annealers, and quantum-inspired digital annealers will be able to transform drug discovery in the future. Quantum methods are linear, and high-performance computing (HPC) is not cost-effective. Supercomputers with many GPUs are slow, expensive, and not environment- and user-friendly. The threefold advantage of QC is that it can solve larger problems, discover new drugs at a faster rate, and be used in multiple ways. These features will improve and transform drug discovery in the near future. Quantum algorithms using appropriate quantum hardware can solve significant problems. Quantum processors are built by including trapped ions[72], superconducting circuits[73] and photonic devices[74]. However, these processors face errors during computation, which can destroy the computational process. Though these errors can be reduced by quantum error-correcting codes, these codes demand a large increase in the number of qubits, which further requires advanced methodologies. There are many other resources that affect quantum computing, such as decoherence. Small fluctuations can change the quantum gate to produce a different output than expected, and the imperfect control mechanisms will always cause some errors. With the maturity of quantum computers, quantum circuits will be designed to solve meaningful problems in the future. The main challenge in QC is that designing quantum circuits on a small scale requires preparation for quantum algorithms. Though the cost and time for drug

discovery are reduced as compared to the traditional methods, with the testing of a large number of molecules, it is reduced to a few to be synthesized and measured. QC is associated with significant risk, as quantum capabilities are important for the privacy of information and national security. Extracting exact information from quantum computers is also very difficult. Though obtaining energy is simple, recovering the entire wave function is hard. So, these quantum computers are not fit for those chemical applications where the insights are taken from the electronic structure calculations. Still, quantum simulation will be one of the useful applications of QC[75].

Interestingly, the hybrid approach of ML with quantum computing is now used as a powerful tool in predictive analysis. Although the reversibility of the quantum gates is guaranteed, the lower power consumption is not a bonus that comes along with reversibility[76]. Only specific designs of quantum circuits allow you to save some energy[77]. Quantum circuits perform quadratic, polynomial, or exponential tasks in a faster manner[78–80]. Hybrid quantum ML uses QC to perform ML algorithms or acquire the processing of quantum information into ML[81–83]. It includes supervised[84], unsupervised[85], and RL[86] for drug discovery. An open-access quantum ML framework for Python by Google LLC is available to use hybrid quantum ML[87] for varied applications. Various hybrid-quantum MLs are likely to be released soon for pharmaceutical applications.

4. Conclusion

In theory, the QC algorithm with many qubits is powerful and fast. But whether the practical QCs in the next few decades can do so is still questionable. Various pharmaceutical companies or start-ups are collaborating to develop beneficial quantum computing-based drug development contracts. The recruitment of skilled technicians and professionals is needed to develop QC-based algorithms to enhance pharmaceutical research in drug design and discovery. Currently, there are only a few examples of proven quantum advantages, such as Shor's algorithm[88]. In addition, there is a lack of explanation as to why the accuracy level can be increased with QC. Multinational companies, such as IBM, are conducting various workshops on quantum computing interfaces. Qiskit and other alternative sources will be helpful in the development of specialized programs internally to train the staff in QC. QC in drug discovery is outperforming even the best supercomputers for certain tasks, promising to make difficult problems easy in the biological sciences. Though huge progress has been made on the hardware side, there are still limitations in scaling and implementing better-quality qubits. The smart players in QC have come up with excellent solutions to work with the noise. These improved and more noise-resilient algorithms have generated impact and are being adopted on a large scale. With the deeper collaboration of pharma and QC companies, great creativity-enabling solution development will be seen in the future. Still, in its infancy, the capacity of QC to drastically accelerate and optimize trials and predictions for the drug discovery space and the life sciences can flourish the pharma industry in the future.

Data availability

Not required.

Acknowledgments

RS acknowledges the financial assistance provided by the DST WOSA project (SR/WOS-A/CS-69/2018). RS is thankful to her mentor Shrish Tiwari, Bioinformatics, CSIR-Centre for Cellular and Molecular Biology, and G. Narahari Sastry, Director, CSIR-NEIST, for the technical support.

Conflict of interest

The author declares no conflict of interest.

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