Quantum Computing at the Frontiers of Biological Sciences

Prashant S. Emani[1,2]*, Jonathan Warrell[1,2]*, Alan Anticevic[3], Stefan Bekiranov[4], Michael Gandal[5], Michael J. McConnell[4,6], Guillermo Sapiro[7], Alán Aspuru-Guzik[8,9,10,11], Justin T. Baker[12,13], Matteo Bastiani[14], John Murray[15,16], Stamatios N Sotiropoulos[14], Jacob Taylor[17,18], Geetha Senthil[19], Thomas Lehner[19,20,#,†], Mark B. Gerstein[1,2,21,22#], Aram W. Harrow[23#]

[1]Program in Computational Biology and Bioinformatics, Yale University, New Haven, Connecticut, USA.

[2]Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut, USA.

[3]Yale School of Medicine, Department of Psychiatry, New Haven, Connecticut, USA.

[4] Department of Biochemistry and Molecular Genetics, University of Virginia School of Medicine, Charlottesville, Virginia, USA.

[5]Department of Psychiatry, Semel Institute, David Geffen School of Medicine, University of California–Los Angeles, Los Angeles, California, USA.

[6]Department of Neuroscience, Univ. of Virginia School of Medicine, Charlottesville, Virginia, USA.

[7]Department of Electrical and Computer Engineering, Duke University, Durham, North Carolina, USA.

[8]Department of Chemistry, University of Toronto, Toronto, Ontario, Canada.

[9]Canadian Institute for Advanced Research (CIFAR), Toronto, Ontario, Canada.

[10]CIFAR Artificial Intelligence Research Chair, Vector Institute, Toronto, Ontario, Canada

[11]Department of Computer Science, University of Toronto, Toronto, Ontario, Canada.

[12]Schizophrenia and Bipolar Disorder Program, McLean Hospital, Belmont, Massachusetts, USA.

[13]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA.

[14]Sir Peter Mansfield Imaging Centre, School of Medicine, University of Nottingham, Nottingham, UK.

[15]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA

[16]Department of Physics, Yale University, New Haven, Connecticut, USA.

[17]Joint Center for Quantum Information and Computer Science, University of Maryland, College Park, Maryland, USA.

[18]National Institute of Standards and Technology, Gaithersburg, Maryland, USA

[19] New York Genome Center, New York, New York, USA

[20] National Institute of Mental Health, Bethesda, Maryland, USA.
[21]Department of Computer Science, Yale University, New Haven, Connecticut, USA.
[22]Department of Statistics and Data Science, Yale University, New Haven, Connecticut, USA
[23]Center for Theoretical Physics, Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
† Present Address: Neuropsychiatric Disease Genomics, New York Genome Center, New York, New York, USA.
* These authors contributed equally.
# Corresponding authors.

Abstract

Computing plays a critical role in the biological sciences but faces increasing challenges of scale and complexity. We evaluate the potential for quantum computing algorithms to aid in the merging of insights from genetics to neuroscience.

Introduction

In an era of increasingly collaborative efforts towards unravelling the complexities of biology, one may posit the existence of two broad tendencies: first, an approach towards greater depth in particular fields, whether relying on intensive technological, theoretical or computational development, that aims to comprehensively explore a specific aspect of biology; and second, a recognition of the need to knit together the disparate experimental and conceptual threads across the vast spectrum of length, time and system-size scales inherent in biology into a coherent framework. Addressing both sources of complexity necessarily requires research-area-specific experimental and theoretical advances, but there is also the possibility of outsourcing some of the analytical burden to high-throughput computing resources. The significant interest in large-scale computing infrastructure evinced by governmental and private entities underscores the importance of the scientific community exploring new ways of interfacing with cutting-edge computing technologies. These include expansions of current super-computing and other massively parallel computing facilities, but also considerations of entirely new computing paradigms. Here, we consider the potential of quantum computing (QC) to address complex biological questions. Recent technological developments have carried QC capabilities from the realm of academic exploration to commercial opportunities[1,2]. While the scale is not currently competitive with classical technologies, there is substantial excitement in its eventual promise, and we hope to provide an entry point for biologists to certain aspects of the discussion surrounding QC. This effort is especially timely given recent policy efforts at a national or international level, such as the U.S. National Quantum Initiative Act 2018[3]

(implementation of a National Quantum Initiative for quantum information science and technology[4]), the European Quantum Technologies Flagship, and efforts in the UK and China[5].

We first present a primer on quantum computation to familiarize the reader with the basic concepts and language of QC. The remainder is focused on the study of the human brain through genetics, genomics, neuroimaging, and deep behavioral phenotyping, a multidisciplinary effort that falls under the term 'convergent neuroscience'. We highlight these areas as they exemplify the two aforementioned sources of complexity: separately, each field presents an incredibly rich set of problems that often push the limits of classical computational capability; in combination, they offer a multi-scale challenge leading from the molecular scale through the cellular and tissue levels, to brain architecture and, eventually, to complex human behaviors and disorders. The study of the emergent properties of the brain, such as cognition and behavior, is a uniquely challenging multi-level endeavor that demands pioneering approaches in computation. Accordingly, we discuss how quantum algorithms that map onto methodological issues in neuroscience may provide much needed improvements in computational efficiency, and posit open questions for eventual development of new computational solutions.

Classical versus Quantum Circuits: State of the Art

Quantum computers (QCs) promise a new form of computing that would be qualitatively different from any previous ("classical") form of computation[10]. While QCs are technically more difficult to build, and the best current general-purpose quantum computers have only 50-100 qubits, they can solve some problems with a time that grows more slowly as a function of the input size. The term "qubit" refers to a quantum two-level system, such as the spin of a spin-1/2 particle. Qubits can be thought of as a generalization of classical bits (cbits), in that cbits can be in states 0 or 1, while the state of a single qubit is described by complex numbers α_0 and α_1 satisfying $|\alpha_0|^2 + |\alpha_1|^2 = 1$. The power of quantum computers comes from scaling. A system of n cbits can be in one of 2^n possible states at any time, while the state of n qubits is described by a complex unit vector of dimension 2^n (Fig. 1A and B). These vectors (also called wavevectors or wavefunctions) can be transformed by multiplying them by unitary matrices, and in many cases this can be done efficiently. For example, the wavevector can be Fourier transformed using $O(n^2)$ elementary quantum gates. However, not all transformations can be done efficiently. The laws of quantum measurement also limit the amount of information that can be extracted from a quantum state. A full measurement of the state yields outcome x with probability $|\alpha_x|^2$, destroying the state in the process. Thus, even though describing the quantum state of n qubits requires an amount of information that scales exponentially with n, measurement can only extract n bits of information. Finding a way to benefit from the exponential state space of quantum computers despite this and other limitations is the central challenge of quantum algorithm design[11].

The challenges in building quantum hardware and mitigating noise are considerable and are not addressed in this paper, since our focus is principally on algorithm development. Large-scale quantum computers are likely to rely on error-correcting codes and other error mitigation

strategies which will result in additional overheads, e.g. needing to use many physical qubits to store one logical qubit. However, quantum algorithms can be built out of a universal set of quantum gates in a way that does not depend on the underlying hardware, just like classical algorithms.

Given the ubiquity of classical computers, the natural way to understand the strengths of quantum computers is by comparing their run-time scaling with the best-known classical algorithms. In some cases, these speedups are exponential: a QC with a few thousand error-corrected qubits could factor numbers that could not be factored using existing classical computers and currently known algorithms in time less than the age of the universe. In other cases, provable polynomial speedups are known: for example, given the ability to compute a function $f(x)$ where x takes on N values, a QC can find the minimum value of $f(x)$ in only $O(\sqrt{N})$ evaluations of $f(x)$ while a classical computer would require $O(N)$ steps (assuming that $f(x)$ has no other structure we can exploit)[13]. On the other hand, for some problems, QCs are known to be no stronger than classical computers. And in many other cases, plausible heuristic algorithms have been proposed for QCs, whose performance is only incompletely understood.

The source of quantum speedup. There is not a simple description of what accounts for speedups, although the most plausible explanation is the difference between interference of amplitudes and addition of probabilities. For example, a qubit can have states $|0\rangle$ and $|1\rangle$, which correspond to cbit values 0 and 1, and, in the representation of Fig 1A, are the north and south poles. Qubits can also be in superpositions (see Box 1) such as $\frac{|0\rangle+|1\rangle}{\sqrt{2}}$ and $\frac{|0\rangle-|1\rangle}{\sqrt{2}}$, which lie on the equator in the figure. To see that these differ from each other, and also from a random mixture of $|0\rangle$ and $|1\rangle$, consider the $\sqrt{NOT}$ gate, which maps $|0\rangle$ and $|1\rangle$ to $\frac{|0\rangle+|1\rangle}{\sqrt{2}}$ and $\frac{|0\rangle-|1\rangle}{\sqrt{2}}$, respectively. Starting with the $|0\rangle$ state, applying $\sqrt{NOT}$ once yields $\frac{|0\rangle+|1\rangle}{\sqrt{2}}$. This state could be thought of as analogous to a random mixture of 0 and 1, as we would expect if $\sqrt{NOT}$means applying NOT with probability ½. However, applying $\sqrt{NOT}$ twice yields $|1\rangle$, just as we would expect from a NOT gate, whereas applying the randomized version twice would yield the same uniform mixture of 0 and 1. More generally, quantum computers and randomized computers can both be thought of as taking different paths through the 2^n possible bit strings, but for randomized computers we sum the nonnegative-valued probabilities of these paths to get the final output distribution, while for quantum computers we sum the complex-valued amplitudes of these paths. Adding complex numbers of roughly the same phase corresponds to constructive interference while opposite phases correspond to destructive interference, analogous to the way that light and other waves can exhibit interference.

While we often do not know how to take advantage of the rich possibilities offered by quantum interference, in some cases we can use them to achieve asymptotic speedups. Algorithms like Grover's are simple examples of this, making use largely of the fact that probabilities are obtained by taking the square of quantum amplitudes, so that a subroutine with a small success probability p needs to be repeated only $O(1/\sqrt{p})$ times instead of $O(1/p)$ times[14]. The quantum Fourier transform (used in period finding and Shor's factoring algorithm (Fig. 1C)) is a more sophisticated example of how complex-weighted transitions can be useful, and in some

cases this can give rise to exponential speedups. On the other hand, some problems are known to not admit any quantum speedup, e.g. taking the parity of N numbers requires time $O(N)$ on either a quantum or classical computer[15]. It is a major open research problem to determine when quantum speedup does or does not exist, and it is unlikely to ever be fully resolved, just as there is still no single theorem describing which problems can be solved by efficient classical algorithms. We next discuss some examples of potential quantum speedups.

Exponential speedup. The main exponential speedups known are for cryptanalysis (dramatic but unlikely to be relevant here) and quantum simulation of molecules or other large quantum systems. If the properties of a molecule are not well captured by simple classical approximations then there is a good case to be made for using a quantum computer to make a better-quality approximation computationally tractable. The advantage of a QC here arises from the exponentially growing dimension of quantum states. As a result, some promising cases for quantum advantage involve molecules with large numbers of active electrons, such as organometallic compounds[16].

Polynomial speedup. Typical polynomial speedups can be thought of as direct improvements of some classical algorithms. The best known of these is Grover's square-root search speedup[17], which is a quadratic improvement of classical brute-force search: given a search space of size N, brute-force search requires evaluating N points, while Grover search requires the equivalent of evaluating $O(\sqrt{N})$ points on a quantum computer. Other, more sophisticated, algorithms also admit provably quadratic improvements. For example, a classical algorithm might search over a tree of possibilities in a manner that can improve over brute-force search by sometimes being able to quickly prune entire subtrees. Such searches can also be quadratically improved quantumly, i.e. if the classical search process explores N nodes, then the quantum algorithm requires effort roughly equal to $\sqrt{N}$ times the effort to evaluate one node[18]. The strength of these algorithms is that they apply under extremely general conditions, such as needing to minimize an easily computable function. They also do not usually need more qubits than are already needed to compute the function.

Heuristic speedups. Many of the most important algorithms for classical computers either lack formal proofs of correctness or are often run outside of the regime in which these proofs of correctness apply. These include Markov chain Monte Carlo (where rigorous upper bounds on mixing time are usually not known) and gradient descent applied to non-convex problems such as deep neural networks. For quantum computers, heuristic algorithms include adiabatic optimization[19], or more generally, quantum annealing (QA)[20], and the quantum approximate optimization algorithm (QAOA)[21]. The level of speedup provided by these algorithms over classical algorithms is in general unknown, and may be anywhere from an exponential improvement to no speedup. It is expected that as quantum computers are built, our understanding of the performance of these heuristics will improve, just as much of our understanding of the performance of classical heuristics comes from empirical evidence and not only theory. In the following sections, we refer to this class of methods as “quantum heuristics”.

Interfacing with classical algorithms. There is an important caveat about quantum algorithms. Suppose for concreteness that we are minimizing a function $f(x)$. Then a quantum computer would need to compute $f(x)$ in superposition over many different values of x, i.e. the computation could not leak any information about x to any outside system. This would limit its

ability to share the computation with a classical computer. Suppose, for example, that the evaluation of $f(x)$ were a memory- and time-intensive calculation for which quantum speedups were not known. Then using quantum computers to improve the minimization of f would need to use qubits to perform this evaluation and could not offload the computation to a classical computer. This means that the overall speedup would be less than quadratic.

Big data and quantum RAM. A related limitation of current models of quantum computers is that they cannot access large classical datasets in superposition. This means that they may be able to speed up complicated calculations on small datasets (e.g. finding the best Bayesian network) but have less advantage in solving problems on large datasets. One way to address this is with filtering or data reduction techniques, which select a small but hopefully representative sample of the data and use that as input to the optimization problem[22]. Or the quantum computer could be used for "small data" problems where the difficulty comes from the complexity of the analysis. A more speculative possibility is a quantum hardware solution known as a qRAM (quantum RAM)[8], which would give a quantum computer the ability to coherently query a large classical dataset as a superposition of qubits: a superposition of input memory addresses would yield an output consisting of a superposition of memory cell contents (see Box 2). A qRAM would enable powerful quantum algorithmic primitives[8] but there are no proposals for scalable error-corrected qRAM, and it is not clear if it would ultimately be easier than making a large quantum computer[23].

Potential applications for Quantum Computing in Biology

Genetics and sequence analysis

We first consider QC algorithms implementable on near-term quantum processors. An essential initial step in genetics and genomics is the matching of sequences of nucleotides and amino acids to organism databases, and, more specifically, the mapping of sequencing reads from experimental assays to reference genomes. Any approach needs to contend with both memory (holding a representation of the reference, and information on the mapping) and speed concerns. Dynamic programming methods, such as the Smith-Waterman algorithm[30], enable queries of sequence strings against immense databases, and could be cast as Hidden Markov Models (HMMs). The recent development of Hidden Quantum Markov Models (HQMMs)[9,31] opens the possibility of simulating classical HMMs on currently available quantum circuits[31], as well as extending model space beyond classical HMMs[9]. Hybrid approaches are attractive prospects: the iteration through hyperparameter space in HMMs could be classical, with quantum optimization of the maximal trajectory through state space. Given that dynamic programming methods have mostly been supplanted by the approximate but faster k-mer-based BLAST algorithm[30] for database searches, a QC-based improvement in efficiency could reopen the case for their utility. A similar problem occurs in the *imputation* of individual-specific mutations, especially single-nucleotide polymorphisms (SNPs): given shared sets of haplotypes across subpopulations, a relatively sparse set of SNPs can be expanded by inferring additional SNPs that co-occur with the original set with high probability. This imputation usually involves an HMM-based likelihood maximization[32], which could be cast as HQMMs.

While imputation depends on inherited SNPs within populations (germline mutations), cells also contain post-conception *de novo* variants, called "somatic variants". Every neuron in the human brain is likely to contain private somatic variants, including single nucleotide variants, and large structural variants that alter allelic diversity for dozens of genes. Identifying their functional impact is essential. Machine-learning classifiers have been trained on case/control datasets to identify psychiatric disorder-associated variants[33]. However, given the large-dimensional parameter search space for the classification problem, classical computation frequently runs into search efficiency issues. These issues could possibly be ameliorated using near-term implementable QC machine learning methods[34], discussed in subsequent subsections.

Another important category of genetic analyses is the construction of optimal trees that describe the relative proximity of genetic sequences, including: ancestral recombination graphs (ARGs)[35], depicting ancestral relationships between individual genomes while accounting for genetic recombination; pathogen evolutionary trees in epidemiological studies; tumor cell mutational lineages, as could be relevant to malignancy and medical response. Tree reconstruction algorithms optimize across the similarity constraints between genomic segments, mainly involving sampling from the space of possible genealogies with heuristics and simplifications[36]. For smaller input sequence sets, the massive tree-search space makes this an open candidate problem for speed-up using available quantum heuristic optimization methods[19–21].

We next explore problems whose QC solutions may depend on the availability and storage in memory of superpositions of qubits (qRAM). For genomic read mapping, state-of-the-art classical algorithms include the exploitation of the Burrows-Wheeler transform to efficiently perform DNA sequence alignments[37], and seed-based approaches to map RNA reads to exon boundaries separated by large genomic distances[38]. Both methods rely on lexicographically sorted suffixes constructed from the reference genome, followed by scanning for matches of the query read. The classical complexity of sequence-matching depends on whether exact ($O(n+m)$; n = number of reads, m = query read length) or inexact matches ($O(nm)$), including gaps, are considered. Grover's algorithm-based improvements in string-matching speeds[39] could be exploited ($O\left(\sqrt{n}+\sqrt{m}\right)$ for exact matches) to aid the scanning process. Recent work has demonstrated the potential for even further QC speed gains under the assumption of unique membership of a query string within a reference database[40]. The scaling of the problem is such that a reduction in complexity of even simpler mapping problems would be highly beneficial, although the need to generate superpositions of the entire reference string also creates potential problems: given the need for storing a large reference database in superposition, the current lack of qRAM is an issue. Furthermore, speed gains from Grover's algorithm-based methods could be reduced by the cost of evaluating the function being searched, if done classically.

SNP association and heritability analyses are problematic for near-term quantum approaches, given the need to manipulate large matrices to solve systems of linear equations. In association

studies, SNPs can be statistically associated with individual-level phenotypes (genome-wide association studies (GWAS)) or to quantitative molecular traits (cell/tissue gene expression, methylation, epigenetic markers, cell fractions (QTL studies)). The evaluation of total SNP heritability often involves linear mixed effects models, with genetic variance estimations carried out through techniques such as the restricted maximum likelihood (REML) method[41]. With qRAM, algorithms such as Quantum Least Squares[42,43] could offer up to exponential speed-ups through the ability to perform fast linear-algebraic operations, under certain assumptions of sparseness and condition number, although it is unclear how any advantages would be undercut by the time cost of querying the qRAM. For lower-dimensional regression problems, there is some potential for near-term quantum heuristic optimizers to tackle these tasks[26].

Functional Genomics

The causal chain by which genetic variation leads to expression in higher-level behaviors such as cognitive traits involves multiple intermediate molecular-to-cellular-to-system steps, governed by complex developmental processes and gene-environment interactions. Despite this complexity, recent studies have shown that genetic risk for particular traits can be partitioned across 'intermediate' phenotypes, such as gene expression or chromatin binding profiles; a direct approach to such analysis is to impute intermediate molecular phenotypes first, and link the imputed phenotypes to high-level traits[44]. However, intermediate molecular phenotypes are typically high dimensional and interdependent, such as bulk transcriptome expression profiles (≈22K dimensional). Possible models which can learn joint probability distributions over such levels of analyses include Bayesian Networks, undirected models such as Boltzmann Machines[45], and recent deep-learning approaches such as Variational Autoencoder (VAEs). Exact optimization of such models however is intractable: structure learning in Bayesian Networks requires optimization over a search space of all directed acyclic graphs, which is super-exponential ($O\left(n!\, 2^{\frac{n!}{(2!(n-2)!)}}\right)$, where n is the dimensionality[46]). On the other hand, inference in Boltzmann machines requires a search over $O(2^n)$ states after binarization to calculate a gradient, and training VAEs requires the optimization of a non-convex objective function. Such problems may be potential candidates for quantum approaches: for smaller input sizes, near-term approaches without qRAM may be developed to perform exact searches across the space of Bayesian networks, while for moderate-sized problems, approximate quantum analogues of Boltzmann machines and VAEs have been tested in simulation and experimentally[6,7], with the optimization being conducted through QA. We note also that for all these models, prior knowledge of molecular interactions may be used during training to suggest causal network interpretations.

In contrast to direct imputation of molecular phenotypes, intermediate phenotypes may be derived at the level of sets of genes (such as functional pathways), and cell-type proportions. For instance, Weighted Gene Correlation Network Analysis (WGCNA) performs a version of hierarchical clustering to derive co-expression modules, which are enriched in gene pathways[47],

and non-negative matrix factorization (NMF) based on 'marker-gene' profiles can be used to decompose bulk transcriptome data into components corresponding to cell-type fractions[45]. Exact optimization of these models is again intractable, where exact hierarchical clustering would require a search over a large space of trees, and NMF is a non-convex optimization problem. The former may be a candidate for an exact quantum solution for small-scale problems, while both may benefit from quantum heuristic approaches (a QA approach to NMF is found in ref. [48] and quantum speedups for approximate clustering are described in ref. [22]). While clustering ~1000 - ~20,000 features is common in genomics, there are a number of applications where a relatively small number of features, ~100, are clustered across samples (e.g., protein-array data). Clustering associated with global minimization of objective functions is of great interest in these small feature number cases. More generally, comparison of clusters (and solutions to other genomic algorithms) derived from exact and approximate greedy minimization would inform the nature of the errors associated with applying greedy algorithms to large numbers of features and samples, as well as suggest possible approaches to improving the greedy algorithms in the short term. Application of these methods at full genomic scale, however, would require further technical developments in qRAM or quantum processor size.

Mapping Neuro-Behavioral Variation via Neuroimaging and Deep Phenotyping

The overarching goal of 'convergent' neuroscience is to link cellular-level mechanisms to system-level observations and ultimately behavior. Multi-modal neuroimaging provides rich high-dimensional data that can map neural and behavioral mechanisms in humans. While many quantitative optimizations remain to be done, one of the core challenges is accurate identification and alignment of brain anatomy across people to reference atlases. For instance, one widespread approach implemented in FreeSurfer software[49] employs a sequence of registration steps involving the minimization of an energy functional over the spatial transformation field. Here, potential quantum heuristic approaches could be brought to bear for images of moderate resolution if the corresponding energy function (Hamiltonian) can be mapped to an Ising-type model. A related challenge involves training statistical models to rapidly and accurately quantify neuro-behavioral variation. For instance, the presence of active psychotic symptoms in previously unseen individuals diagnosed with schizophrenia and bipolar illness can be predicted using dynamic functional connectome features derived from fMRI[50]. Quantum analogues (such as HQMMs[9,31], see 'Genetics and Sequence Analysis') may help train such predictive models more efficiently.

Computational neuroscience has used circuit models to inform and constrain experimental observations. Dynamical neural models operate at the local circuit or global level, and use parameterizations based on known constraints (e.g. biophysical parameters) or learned *de novo*. Local and global neural dynamics are typically highly nonlinear, producing difficult optimization problems in the case of parametric model fitting[51], and requiring a rich model-class for *de novo* learning methods. Fluctuations at equilibrium exhibit complex inter-dependencies. Additionally, the hierarchical relationships between genetics, anatomy, function and the equilibrium connectivity neural state are, in general, highly nonlinear, and only partially captured by available computational models. Current classical models relate such simulations to equilibrium distribution features (or to resting state characteristics): for instance, Ising

models and second-order mean-field regional models of resting-state fMRI observations[52,53]. These differential equation-based analyses of global brain dynamics represent regional firing rates using a mean-field approximation[52]. Such models can be fitted to functional neuroimaging data, by linearizing the initial stochastic nonlinear system of differential equations around a fixed point using the method of moments[52], and using methods such as Approximate Bayesian Computation to fit parameters[51]. In the QC domain, quantum algorithms have been developed which have the potential to offer exponential speed-ups in the solution of linear differential equations[54,55]. Furthermore, models such as the Quantum Boltzmann machine (QBM)[6] and Quantum VAE[7], as discussed in the previous subsection, may be naturally applied to model complex distributions as found in neurodynamics datasets.

General-purpose quantum solvers for nonlinear systems of differential equations have also been proposed[56], although currently these seem unlikely to offer speed-ups over classical methods. Efficient general-purpose solvers would eliminate the need for linear approximations, and allow more accurate fitting of neural dynamical models, particularly out of steady state (for example, transitions between resting-state and task-based fMRI). This application may help motivate finding better quantum algorithms for nonlinear differential equations.

The computational challenge in human neuroscience is particularly acute in the case of 'deep' behavioral phenotyping (e.g. digital 'real time' measures), which can generate massive amounts of continuously measured dynamical behavioral variables with varied granularity. In this situation, there is clear potential for 'very deep' optimization and the opportunity for massive state-space exploration. Relevant use-case scenarios include 'in-the-moment' clinical decisions that may require rapid computation. This becomes challenging for longitudinal real-time digital phenotyping, which may require rapid and precise data reduction. For instance, rich individualized phenotypic characterization using high-resolution video and audio datasets have yet to be leveraged since they are identifiable in raw form and present operational challenges to data reduction and protection of participant privacy.

Collectively, the complexity of human neuro-behavioral data tests the boundaries of learning algorithms, which have to deal with the high-dimensionality of data needed to robustly link nonlinear dynamics of brain states (e.g. fMRI) and the influence of time-related variables relevant to behavioral mapping. Recent deep learning approaches using interpretable recurrent networks have provided a powerful means of learning such brain-state/behavior associations de novo by jointly modeling fMRI and behavioral data[57]. Quantum analogs of neural network frameworks (such as QBMs[6] and QVAEs[7]) have the potential to discover novel structure in these datasets. Models such as HQMMs provide alternative dynamical models with intrinsically quantum representations[31], which have been shown to have comparable or possibly improved performance relative to classical methods on small-scale problems through classical simulations. Further, there is evidence that HQMMs allow complex dynamics to be modelled with a reduced state space[9] compared to classical models. The application of such methods to behavioral data, though, is a long-term goal, since reliable qRAM appears necessary to handle large dataset sizes.

Integration across disciplines

Stitching together insights across fields and levels of analyses, to yield a complete picture of brain function, is an ongoing challenge. While the extent to which quantum processes are relevant across these levels is unclear, quantum machine learning may help elucidate the interdependencies between levels through its ability to learn and simulate nonlinear, potentially classically intractable, models. One promising avenue involves mechanism-agnostic machine learning methods like deep neural networks, where biological insights are gained by interpreting the model *a posteriori*. Such an interpretable framework would involve connections between modules such as gene regulatory networks on the one hand, and structural/functional neuroimaging parameters (e.g. cortical thickness, white matter integrity, dynamic functional connectivity, etc.) on the other. The exact nature of these connections could be altered in competing hypotheses. One could imagine a hierarchical network with molecular phenotypes at the base, emergent neuroimaging-based parameters at a higher layer, and behavioral phenotypes as prediction targets. An alternative framework would treat the molecular and neural system-level components as parallel factors in determining behavior, with the latter having been influenced at a developmental stage, and not directly emerging from the molecular phenotypes per se but rather operating in dependent lock-step. Thus, different architectures of relationships between levels of analysis may be constructed. The NIMH has recently supported efforts at building such multi-scale, convergent neuroscience approaches (https://grants.nih.gov/grants/guide/pa-files/par-17-176.html). Such an analysis could be aided by quantum neural networks (QNNs)[58] and quantum variational classifiers[59], designed for use on non-qRAM, gate-based quantum computers. Quantum variational classifiers have been shown to be able to successfully classify states that were designed to be hard to simulate classically[59]. This hints at the greater generality of such circuits than their classical counterparts. Here the challenge lies in scaling up the available number of qubits.

Epilogue

While the field of QC is undergoing notable development and progress in both hardware and software, a number of significant knowledge gaps and challenges remain. To surpass classical computers, quantum computer architectures will need to improve numbers of and connectivity between qubits, reduce error rates both for operations and storage, as well as expand algorithmic development into all areas where classical computing faces inherent bottlenecks. These challenges are all significant and are partially conflicting; indeed, the central experimental QC challenge is to create quantum systems that are both highly decoupled from unwanted environmental degrees of freedom yet subject to fast and precise control and measurement. While there has been steady experimental progress over the past two decades, it is not easy to predict the rate of future improvements in QC. A recent consensus study on the progress and prospects of QC from the National Academies of Sciences, Engineering and Medicine estimates that to find a private key in a 1024-bit RSA encrypted message using Shor's algorithm requires building a quantum computer that is five orders of magnitude larger and has

error rates that are two orders of magnitude better than existing machines[60]. More than 100 academic and government laboratories around the world are working to address these challenges with a variety of hardware solutions[60]. These include ion-trap quantum computers with 20-100 qubits that are likely to become available by the early 2020s[60]. Leveraging the power of lithographic technology, superconducting quantum computers hold great promise, and 5-, 16- and 20-qubit machines are currently available to users via the web. Other promising approaches include developing quantum computers based on photonic, neutral-atom and semiconductor qubits[60].

As mentioned above, many algorithmic quantum speedups depend on qRAM, but there is no practical implementation of this technology. In fact, this reliance on qRAM, in part, stems from attempts to arrive at algorithms that are essentially quantum versions of classical algorithms. An alternative approach is to design intrinsically quantum algorithms which take advantage of quantum features such as interference. This alternative approach offers the additional benefit that small-scale versions of problems are readily implementable on existing hardware. Indeed, recent advances in "near-term" quantum machine learning algorithm development exploit the exponentially large quantum state space to estimate kernel functions[59,61] as well as the natural ability of quantum computers to execute kernel-based classification[62,63]. Generalizations of these algorithms for genomics applications hold great promise and will allow assessment of the current capabilities of publicly available quantum computers[34]. Given the potential of quantum computers to efficiently explore a vast state space, the natural applications to neuroscience problems are largely associated with optimization and machine learning as detailed above. However, yet another path is to identify computational problems that can be naturally cast into a quantum framework. For example, the minimum free energy among all possible protein folds is an important problem with an exponentially large search space and thus a compelling target. Another natural set of problems are those associated with quantum biology – the study of chemical processes including formation of excited electron states within molecules (e.g., proteins) in living cells, and their functional effects[64]. These processes are inherently quantum mechanical and may involve an exponentially vast set of excitation states, which can only be efficiently modeled by applying transformations to an exponentially large state-space afforded by a quantum computer. It is unclear whether such processes can be relevant to higher-levels of brain function (and consciousness[65]); the algorithms used by the brain at David Marr's algorithmic/representational level may ultimately be classical[66], although the advent of quantum machine learning means that increasingly this need not be the case for artificial agents. While a cautious albeit optimistic estimation associated with steady progress of quantum hardware development (e.g., applying Moore's law) puts the availability of sufficiently powerful, universal quantum computers years in the future, sudden, orders-of-magnitude breakthroughs in resolution, noise reduction, etc. are not unprecedented in experimental physics. Such unforeseen breakthroughs would unleash the power of quantum computing to address pressing computational challenges in biology.

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Author Contributions

All authors contributed to discussions on the design of the manuscript. G.S. and T.L. led the NIMH workshop and subsequent discussions. P.S.E., J.W., A.A., S.B., M.G., M.J.M., J.T.B., M.B.G. and A.W.H wrote the manuscript. P.S.E., J.W., A.A., S.B., M.G., M.J.M., G.S., J.M., J.T.B., G.S., T.L., M.B.G. and A.W.H edited the manuscript. A.W.H. contributed to the Quantum Computing section. P.S.E., J.W., S.B., M.G., M.J.M., M.B.G. contributed content to the genetics and genomics sections, and A.A., G.S., J.T.B., and J.M. to the imaging and behavioral phenotyping subsections.

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Figure Legends

Figure 1. Concepts in Quantum Computing. A. Conceptual illustration of bit vs. qubit. The state of a qubit can be represented by a point on the unit sphere with the North and South poles corresponding to the states 0 and 1 of a classical bit. **B.** The state space of 3 qubits is a 2^3-dimensional complex vector. **C.** Classical (Number Field Sieve (NFS) algorithm) and quantum (Beckman-Chari-Devabhaktuni-Preskill (BCDP) implementation of Shor's algorithm) runtimes for factoring integers. Shor's algorithm for quantum computers yields an exponential speedup over the best-known classical algorithm (Panel C from ref [12]).

Figure 2. Complexity of linking levels of analyses from genomics to human behavior. The challenge consists, in part, of the need to interrogate the enormous search space for determining the mapping across levels, which constitutes a many-to-many probabilistic problem. Computational innovation will be a key effort to help close these gaps. Figure adapted with permission from ref. [29].

Boxes

Box 1: Glossary of Terms

Biological:

- *Single nucleotide Polymorphisms (SNPs)*. Germline (inherited) mutations in a genome where the identity of a single nucleotide is changed relative to a reference genome, and whose prevalence in a population is dependent on the pattern of their inheritance.
- *Genetic recombination.* Exchange of segments between separate genomes or chromosomes, or different regions of the same chromosome, by the creation of single- (eg. viruses) or double-stranded (eg. humans) breaks and subsequent ligation of the crossed segments.
- *Genome-Wide Association Study (GWAS).* Identification of mutations in a population with statistically significant associations to the occurrence of a studied phenotype.
- *Quantitative Trait Loci (QTL).* Mutations in a genome or population with statistically significant association to the occurrence of a studied endophenotype, i.e. a phenotype at the sub-organism level, for example, cell- or tissue-level gene expression.

Machine Learning:

- *Hidden Markov Models (HMMs).* Stochastic latent state method to model a linear sequence of observations as a probabilistic sequence of underlying state transitions and state-to-observation emissions.
- *Boltzmann Machines.* Generative classical neural network model, based on an energy function containing local (unary) and pairwise terms over an underlying undirected graph. Recently, the model has been extended to replace the classical energy with a quantum Hamiltonian to form a Quantum Boltzmann Machine (QBM)[6].
- *Variational Auto-Encoders (VAEs).* Generative neural network model, incorporating a latent space which is mapped to observed variables by a learned feedforward classical neural network. Latent space can be a classical (Gaussian) or quantum (QBM)[7] distribution.

Quantum Computing:

- *Quantum Superposition.* A fundamental principle of quantum mechanics whereby the overall state of a system (e.g., electron in an atom, qubit, etc.) is in a linear combination of orthogonal basis states (e.g., lowest energy state, next excited state, etc.). For example, if $|0\rangle$ denotes the lowest energy state of a qubit and $|1\rangle$ an excited state of a qubit, the state of the qubit, $|\psi\rangle$, can be in a superposition of basis states: $|\psi\rangle = \alpha_0|0\rangle + \alpha_1|1\rangle$.
- *Quantum Random Access Memory (qRAM).* In analogy with random access memory (RAM) which uses n bits to address 2^n distinct memory cells, qRAM uses n qubits to address any quantum superposition of 2^n memory cells[8].
- *Quantum Annealing (QA).* A technique for minimizing a function f using a low-temperature quantum system whose energy corresponds to f, along with an auxiliary field which is slowly turned off. The auxiliary field attempts to create superpositions between nearby qubit strings, similar to equally weighting possible solutions, and facilitates "quantum tunneling" (i.e. transition of a quantum state between nearby low-energy strings even through regions of higher energy) to arrive at a minimum of f relatively efficiently once turned off.
- *Hidden Quantum Markov Model (HQMMs).* The quantum analogue of HMMs, where the sequence of quantum operations is such that information of the state transition and emission probabilities of the qubits can be retained even after partial measurement of the system (i.e. measurements do not collapse the entire system)[9].

Box 2: Computational Opportunities for the Future

Existing quantum algorithms, for example, function minimization, are often written in terms of abstract and highly general functions. If biological applications can help motivate specific, mathematically well-posed tasks, then it may be the case that targeted quantum algorithm development can lead to improvement. While this promise is discussed at length in the following section in the context of the study of the human brain, here we briefly introduce some of the key areas of ongoing research in quantum computing, related to and providing the context for applications in biology.

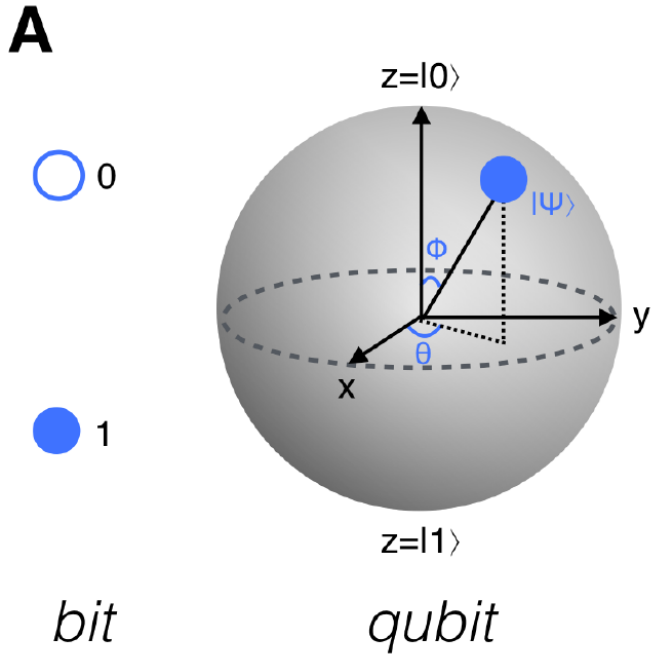
Optimization in biomolecular problems. There has also been considerable interest in extending QC to biomolecular and biological problems[24]. In several cases, small examples of biological

problems have been mapped to combinatorial optimization problems. A QA approach was employed in the exploration of the coarse-grained folding landscape of a six-amino acid peptide, within a 2D lattice framework[25]. QA was also evaluated against a set of classical methods on an optimization problem involving the search for the consensus DNA sequence motif of transcription factor binding[26]. In this instance, the authors trained a classifier (sequence is binding or non-binding) and a ranking algorithm (ranking sequences by binding affinity), finding a slight improvement of QA over classical approaches in the classification problem, and similar performance for the ranking task.

Simulation of classical and quantum systems. There have been successful demonstrations of the application of quantum computation to problems in chemistry. A Variational Quantum Eigensolver (VQE) approach was used[27] to estimate the ground state energies of small molecules as a function of their component atomic separations. Briefly, short quantum circuits define a variational ansatz of trial solutions for the ground state and the circuit parameters are varied to minimize the energy using algorithms such as gradient descent. While the complexity of simulating quantum dynamics on quantum computers is well understood and is usually tractable, the success of VQE will depend on the quality of the ansatz and is an active area of ongoing research.

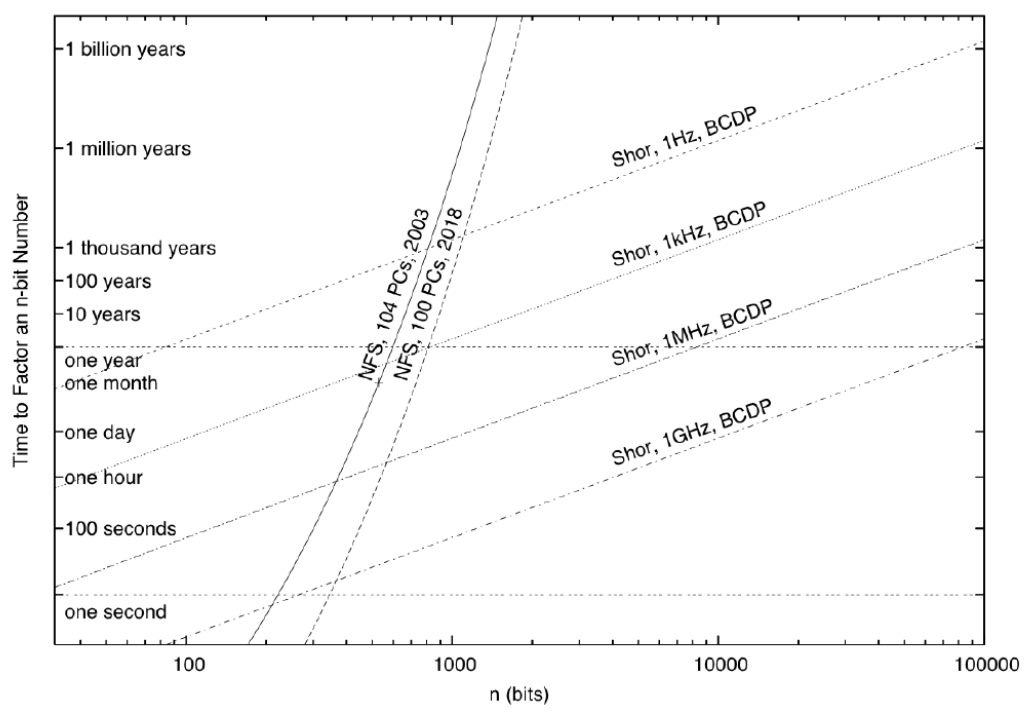
Quantum simulation of chemical reactions is known in principle to be possible on a quantum computer and as the practical details are fleshed out, this is expected to be an important application of quantum computers for applications both inside and outside of biology. One particular strength is in modeling dynamics, and there is evidence that energy transport and electron transport in biological molecules involves quantum effects that could potentially be more accurately modeled by a quantum simulation[28].

Competing interests statement: The authors declare that they have no competing financial interest.

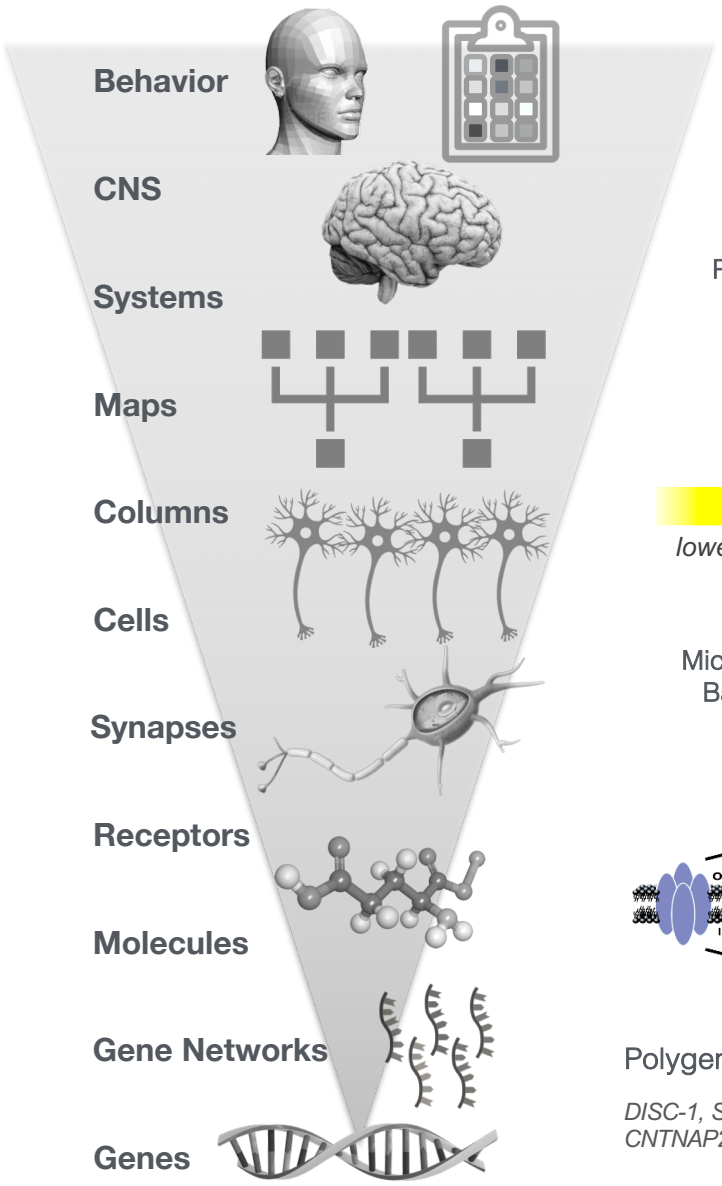


B

$$\begin{pmatrix} \alpha_{000} \\ \alpha_{001} \\ \alpha_{010} \\ \alpha_{011} \\ \alpha_{100} \\ \alpha_{101} \\ \alpha_{110} \\ \alpha_{111} \end{pmatrix}$$



Computational Complexity Across Level of Analysis: Many-to-Many Mapping Problem



Psychosis Spectrum

ASD Spectrum

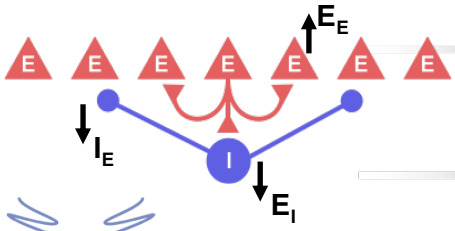
Pervasive Synaptic Disruption

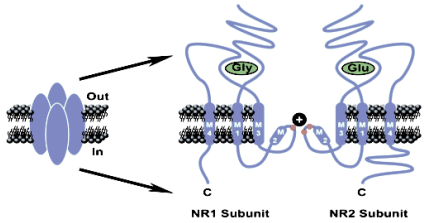
Localized 'Hotspots' of Dysfunction

Intensity of Perturbed Regional Computation

lower *higher*

Microcircuit Balance





Receptor Function

Polygenic Interactions

DISC-1, SHANK3, MECP2, GAD, CNTNAP2, NLGN, NRXN1

Rare Variants

1q21.1, 15q11.2, 16p11.2, 22q11.2, 22q13.3

Mapping not known